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MICROFLUIDIC PRODUCTION OF DEPO-HALOPERIDOL WITH A CONTROLLED RELEASE PROFILE

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Department of Chemical & Biomolecular Engineering

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April 10, 2012

Professor Fabiano and Dr. Crocker

In November 2011, you tasked us with the problem of designing a haloperidol-loaded, poly(lactic-co-glycolic acid) (PLGA) microsphere capable of controlled drug release as a pharmaceutical product, and designing a process based on cross-flow membrane emulsification (XME) that would generate these microspheres on a commercially relevant scale. These product depo-haloperidol spheres would vastly improve the lives of patients living with schizophrenia, as the timed-release technology provides a constant therapeutic concentration of drug over the span of one month between injections. We anticipate that these drug-loaded microspheres will capture a significant portion of the anti-psychotic market due to the added consumer convenience brought about by infrequent treatment periods. The following report details the complete product and process design of the PLGA microspheres and the XME generation method.

The product depo-haloperidol spheres are designed according to a polymer molecular weight and size distribution, in order to ensure that drug is released at a constant rate over time. By ensuring constant release, we minimize potential side effects. The product is generated by emulsification of an organic phase (containing PLGA and haloperidol dissolved in dichloromethane) into an aqueous phase. The XME process allows for the generation of uniformly sized emulsion droplets, and evaporation of the dichloromethane solvent leaves a hardened drug-loaded particle.

The estimated market size of our product is $445 million, with a market price of $340.37. These parameters give a net present value of $88.8 million and an IRR of 316%. In the U.S. alone, 2.1 million patients incur an overall cost burden of 62.7 billion USD. The average patient spends 29,759 USD on their care. The microsphere formulation is projected to save each patient 8,037 USD, or 27% of their total medical spend, potentially improving the percentage of patients treated, from a dismal 19.1% The addition of controlled release and extended release features to a schizophrenia drug is unprecedented. To the 24 million people that suffer from this chronic and incurable disease, the chance to regain even a portion of their own autonomy is priceless.

Sincerely,

Gregory R. M. Cordina Abby Lee William D. Mulhearn Gurnimrat K. Sidhu

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Abstract

Haloperidol-loaded poly(lactic-co-glycolic acid) (PLGA) polymer spheres show great practical applications as pharmaceutical products. These micro scale polymer spheres can be intramuscularly injected into a patient, after which the particles reside in the patient's body and release the drug payload over the course of one month. The process of drug release into the body is controlled by diffusion of small-molecule drugs through the PLGA matrix. Over time, the aqueous environment surrounding the polymer spheres causes hydrolysis of the PLGA chains resulting in bulk matrix degradation. Such degradation facilitates the diffusive motion of small molecules such as haloperidol, and release accelerates. By controlling the size distribution of particles and the initial polymer chain molecular weight at injection, it is possible to design a timed-release product that will discharge its entire drug content at a nearly constant rate over its one-month lifetime.

To achieve the required constant release profile, we assemble product spheres using 40,000 Dalton PLGA chains in a size distribution of 5 parts by weight of 20 μm diameter spheres added to 1 part by weight of 36 μm diameter spheres. We verify by mathematical modeling that this product specification shows nearly constant release kinetics, and therefore poses minimal risk of side effects for a consumer. This formulation is predicted to remain active for 36 days before all drug content is depleted.

Product spheres are generated using the method of cross-flow membrane emulsification (XME). According to this technique, polymer and drug are dissolved into a dichloromethane solvent, which is sheared into uniformly sized emulsion droplets by cross-flow of an aqueous phase. Following generation, these emulsified droplets are collected downstream and exposed to vacuum in order to remove the organic solvent. This hardening process leaves a dry, drug-loaded polymer sphere that can be freeze-dried and sold to a consumer. The XME process has been well studied and mathematically modeled. We use this physical modeling to precisely design an array of flow-channels in which the emulsification process occurs. These channels house a thin membrane, perforated with thousands of micro-scale pores, through which the organic phase is introduced into cross-flow by the aqueous phase. The availability of a large number of emulsification pores enables the XME process to scale-up to meet the project demand. The process operates a total of 7 XME channels with a total of 12,461 pores, which enables the production of 500,000 patient doses of the PLGA sphere product over the course of a 90-day operating timetable per year.

4.6 million patients are diagnosed and treated for schizophrenia globally with two different drug classes: the atypical (2nd generation) sector and the typical (1st generation) sector, within which our product lies. The calculated sale price of the final product is $340.37 for a month-long dose. With a projected total market saturation of $445 million in the sixth year of production, and a total project lifetime of 10 years, the project is expected to generate a net present value of $88.8 million dollars, with an IRR of 316%. This is dependent on both the erosion of the atypical sector of the haloperidol market and the capture of market share from haloperidol and its equivalents in the typical sector. Beyond its application for haloperidol, the XME platform is particularly suited for development in the chronic disease market, which includes heart disease, diabetes, and cancer, the three largest disease segments in the industry. The flexibility of the segment gives access to a huge untapped source of revenue, through the convenience of dosing and dosing optimization that it facilitates.

Chapter 1: Introduction

1.0 Research Motivation

Maintaining drug concentrations within therapeutic range has long been a sought after goal in the pharmaceutical industry. This maintenance is embodied in a zero-order release profile, or constant (controlled) release. This allows for a minimization of side effects while constantly maximizing efficacy. Traditional drugs taken orally are plagued by a variety of factors that make a constant concentration nearly impossible, such as degradation in the digestive system, variability in patient metabolisms, and nonspecific targeting of a dose. Depot injections of drug allow for localized delivery, lower doses, and can ameliorate some of these variable factors, but are, on their own, still unable to address the need for a flat concentration profile. Long-acting formulations are becoming increasingly prevalent as a tool to address this need, with the added benefits of addressing patient noncompliance and simplifying treatment regimens. Long-acting formulations are most useful for the treatment of chronic conditions (e.g. heart conditions, cancer), conditions that require constant concentration in the body (e.g. vaccines, antibiotics), and conditions that affect patient compliance (e.g. schizophrenia, bipolar disorder). Many of the formulations that are currently on the market lengthen the lifetime of a dose, but few also address the issue of a consistent dosing.

Improving long-acting parenteral drug formulations allows for improved efficacy, decreased side effects, patient compliance, and reduced cost of care, making it an invaluable tool in the optimization of drug regimens.

In this paper, the application of a cross-flow membrane emulsification technique for the manufacture of combinations of monodisperse poly(lactic-co-glycolic acid) (PLGA) microspheres with haloperidol, a drug primarily used for the treatment of schizophrenia, for a zero-order, controlled release depot injection is explored. The use of a model drug allows for the demonstration of the optimization technique applicable to a wide range of therapeutic substances, both for the production process and downstream processing of the microparticles. A detailed description of the reagent, device, and processing unit specifications is discussed, and followed by an economic feasibility analysis of the platform technology and the impact of such a platform on the chronic disease management markets.

The technical specifications of the process will be tailored towards the production of 500,000 month-long patient doses of haloperidol-PLGA microspheres in the first year of production. Production occurs on a compressed 90 day schedule, which allows the plant to dedicate the remaining 75% of its operating year towards new products and leaving room for additional capacity. 500,000 doses accounts for approximately 42,000 patients treated per year, assuming a full-year regimen, which is approximately 2% of the U.S. schizophrenia market. Haloperidol itself currently accounts for 0.2% of the total U.S. schizophrenia market, but with the extended release and controlled release features of the polymer microspheres, this share is expected to increase to 4% within a six year window.

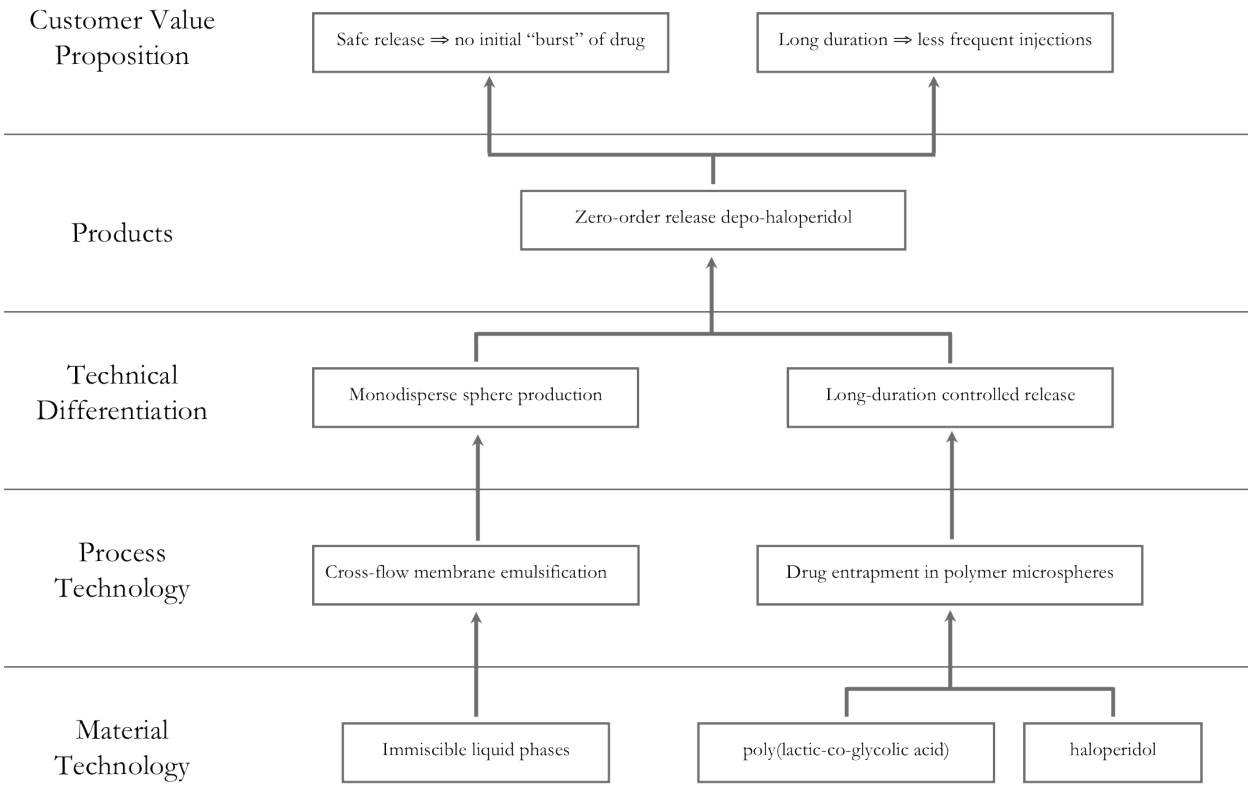
While sales of haloperidol are limited due to the increased genericization of other drugs with the same indication, the potential behind the XME technology as a platform for drug development has much greater potential. The populations and drugs that may benefits from the additional features of the XME platform include those drugs with dangerous side effect profiles (chemotherapy), diseases with poor patient compliance (mental illnesses), chronic diseases that require consistent treatment (diabetes, heart disease, oncology), and indications that have a concentration at which optimal performance is achieved (antibiotics, vaccines). The potential revenue from additional development in these areas is vast, and is an additional consideration to the optimization contained here of the model drug haloperidol.

1.1 Project Charter and Scope

Project Name	Microfluidic Production of Depo-haloperidol with a Controlled Release Profile
Project Champions	Dr. John C. Crocker, U. Penn; Robert Meyer, Merck & Co.
Project Leaders	Gregory Cordina, Abby Lee, William Mulhearn, Gurnimrat Sidhu
Specific Goals	Develop an optimized cross-flow membrane emulsification (XME) process design delivering Depo-haloperidol droplets of an optimal particle size distribution correlating to constant drug release profiles
Project Scope	<u>In-Scope</u>: • XME-based process using PLA/PLGA matrices • Produces spheres at most 100μm in size (18 gauge hypodermic needle – maximum blood entrainment size) • Continuous or batch-continuous processes • Application of process to production of other drugs <u>Out-of-Scope</u>: • Other methods of microfluidic production • Non-continuous production design
Deliverables	• Microfluidic drop formation device design • Modeled drug release profile of desired particle-size distribution • Technical feasibility assessment for commercially relevant scale of product (500,000 patient doses/year) • Capability assessment for a pharmaceutical manufacturing facility based on quality regulations and capital and operating costs
Timeline	Project feasibility and design reports to take place over the course of approximately 3 months

1.2 Technological Readiness Assessments

1.2.1 Innovation Map



1.2.2 House of Quality

								Feasible prod.
								Biodegradable
						-		Long duration
				+				Predict kinetics
				+		-		Size control
			+			-		Monodisperse
Technical Requirements	Monodisperse	Size control	Predictable kinetics	Long duration	Biodegradable	Ease of production	Dry-deliverable	
Customer Requirements								**Weight**
Safe delivery materials (FTS)					X			0.3
Long release time (NUD)				X				0.2
Constant release profile (NUD)								0.3
No initial burst		X	X					
Constant kinetics	X		X					
Hypodermic needle delivery (FTS)		X					X	0.1
Moderate cost (FTS)						X		0.1

1.3 Market and Competitive Analysis

The total prevalence of schizophrenia globally is 24 million. Of this 24 million, only 4.6 million are diagnosed and treated, which accounts for approximately 19.1% of the total population. Schizophrenia drugs comprise a $5.7 billion market.

There are two drug classes that treat schizophrenia: typical antipsychotics and atypical antipsychotics. Typical antipsychotics were the first generation of drugs developed to treat mental disorders. The class has since been overtaken by atypical antipsychotics, which were thought to have improved side effect profiles and higher efficacy. Haloperidol, the model drug used in this paper, is a typical antipsychotic. Its comparatively poor side effect profile led to it being overtaken by drugs in the atypical sector; however, recent clinical studies indicating that most side effects experienced with haloperidol were a direct result of the patient taking too much or too little of the drug.

The maintenance of an optimized concentration has been a long sought after goal in the pharmaceutical industry, and the benefits of such a dosing methodology are not limited to haloperidol alone. A drug delivery technology involving drug embedded within polymer microspheres is one way to begin the solution. Polymer microspheres have predictable drug release profiles that are dependent on size, and different sizes can be combined to deliver a constant optimized concentration, referred to as a zero-order release profile. The second advantage to these polymer microspheres is their ability to extend the lifetime of a single dose, a fringe benefit of their release profiles.

The manufacture of these microspheres must be precise to ensure a zero-order release profile. This paper explores the ability of cross-flow membrane emulsification (XME) to produce monodisperse polymer microspheres for drug delivery.

Combining haloperidol with XME technology to produce a controlled, extended release formulation would be a new generation of antipsychotics. Currently, there are several extended release formulations on the market. The products that would compete with our product are the oil-based, esterified versions of typical antipsychotics that allow for more convenient dose schedules. In particular, our economic analysis in Chapter 7 focuses on haloperidol decanoate, the extended release formulation of haloperidol. These esterified extended release formulations suffer from one

main flaw: their inability to deliver a zero-order release profile. These formulations are generally only used for mild cases of schizophrenia, due to the danger inherent in the inconsistency of drug levels, which lead to suboptimal clinical outcomes.

Other extended release formulations on the market include Seroquel XR®, an extended release formulation of quetiapine, a drug used to treat schizophrenia, bipolar disorder, mania, and depression. Seroquel XR® does not have a controlled release feature, and is more commonly used in indications outside of schizophrenia. It is a once-daily tablet, as compared to haloperidol dosing that is generally twice-daily. The finalized product specifications of the haloperidol controlled release product are for a single dose per month, which would improve the dosing convenience dramatically.

Outside of the typical sector esterified formulations and Seroquel XR®, the haloperidol controlled release profile does not have any comparable competitors, and is expected to overtake market share from both the typical and atypical sectors. The expected market share for the product is further discussed in Chapter 7.

Chapter 2: Technical Background

2.0 Chapter Introduction

The objective of this section is to describe polymer microsphere technology, the factors that influence the drug release profile from the microspheres, namely the choice of polymer and the theoretical description of degradation and drug release from microspheres, and the cross-flow membrane emulsification (XME) process. In the choice of poly(lactic-co-glycolic acid) (PLGA) as the polymer basis of this technology, three characteristics were necessary: biocompatibility, a predictable bulk degradation process, long hydrolysis half time, and compatibility with a wide range of drug conjugates. All of these characteristics are derived from unmet customer needs in the chronic disease management markets, including convenience of dosing schedule and maintenance of an optimal bioconcentration for patients, which would decrease the risk of side effects and aid in improving clinical outcomes for patients.

An analysis of the bulk-degradation process indicated size of the microparticle as the most influential characteristic of the microparticle controlled by the production process. The importance of size control to the achievement of a zero-order release (constant release kinetics) is shown, and XME as a production method that allows for the necessary precision. Finally, haloperidol is introduced as the model drug used in this paper, for its physical and chemical properties, as well as the importance of an improved controlled release formulation over the current standard, haloperidol decanoate, for schizophrenia, a chronic mental illness.

2.1 Drug Delivery Technology: Drug Embedded Polymer Microspheres

Polymer microspheres have been touted as the most promising technology to address the current deficiencies in long-acting parenteral drug formulations. An ideal microsphere would sustain itself within the body for a long period of time, have a zero-order drug release profile (constant release kinetics over time), have high drug-loading efficiency, and utilize biocompatible encapsulation materials.

Microspheres cover a wide spectrum of drug carrier technologies, including liposomes, drug polymer conjugates, and drug-embedded biodegradable polymer matrices. This paper focuses on the use of drug-embedded biodegradable polymer matrices, which boast several important advantages over other encapsulation techniques. Polymer matrices are stable, have high drug encapsulation efficiency, predictable degradation and sufficient residence time in the body (length of time between doses).[1]

2.2 Choice of Platform Polymer: poly(lactic-co-glycolic acid) (PLGA)

The most important factor in the choosing of a polymer to base a microsphere on is the type of degradation the polymer experiences. Polymer degradation occurs as a result of chain cleavage, which slowly breaks down the polymer into its constituent monomers. While there are many different catalysts that facilitate polymer degradation, for our purposes we focus only on chain cleavage by hydrolysis.

The polymer in use here is poly(lactic-co-glycolic acid), or PLGA. PLGA has been in use as a medically resorbable suture for over 40 years. PLGA has already been commercialized for number of drug delivery systems – films, matrices, microspheres, and pellets among them, and has been noted for both its biodegradability and biocompatibility in these applications.[2] Given this polymer's long history of use in biomedical applications, there is no need to engage in additional clinical trial time to approve a potentially less well-known polymer. This will be invaluable from a financial perspective, as it decreases the runway time towards approval of the overall vehicle. PLGA is compatible with a wide variety of drugs, including small molecule drugs, hormones, and proteins. This indicates a huge range of applicability for a drug delivery platform that utilizes PLGA.

PLGA is particularly well-suited for a drug carrier because of its degradation profile, which ultimately controls drug release. PLGA degradation depends on molecular weight, copolymer composition, and crystallinity, all of which can be easily manipulated during the manufacture process. For example, an increase in molecular weight of the polymer results in longer degradation times and slower release. Erosion of PLGA begins via hydrolysis of the ester bonds in the polymer backbone, which occurs upon contact with water. This hydrolysis produces acidic oligomers, which are relatively hydrophobic and therefore tend to buildup within the microsphere. This causes the microsphere to essentially degrade from the inside out due to autocatalysis. Depending on the ratio of lactic acid monomers to glycolic acid polymers as well as the molecular weight of the polymer, the hydrolysis half-life of PLGA is about 0.6 months.

The polymer microspheres mentioned in SECTION are spheres that are composed of lattices of polymer that encapsulate molecules of drug. The breakdown of these microspheres determines the rate of release of drug into the body. This breakdown is determined by the breakdown of the polymer that it is composed of, which is a function of the hydrolysis half-life of the polymer. The hydrolysis half-life indicates the approximate length of time a polymer can be exposed to water before breaking down. [3]

First, the simplest case is considered. The polymer here is defined by a chain of four monomers. Polymers tend to break the bonds between monomers at the end of the chain more easily. This chain is able to be latticed with other polymer, but upon the breakdown of the last two monomers, the polymer dissolves completely and that section of the sphere is completely decomposed. If the hydrolysis half-life of the polymer is of short duration, these bonds are broken quickly, and the difference in the duration of time that a polymer unit spends exposed to water is inconsequential. The polymer quickly 'melts', a process called surface degradation, because the polymer units on the surface degrade first.

However, if the hydrolysis half time is of long duration, then these minute differences in time that the polymer spends exposed to water become very important. As the polymer units on the outside break down, new polymers on the inside of the sphere become exposed. The uneven breakdown of the surface due to the polymer being exposed to water near the end of a chain versus the middle begins to make inroads into the sphere, creating a web of tunnels, called a pore network. This decomposition of the polymer sphere is called bulk degradation, because degradation of the polymers is not localized, but rather spread out through the entire bulk of the sphere. Bulk degradation tends to occur steadily over time in a predictable way, while surface degradation tends to occur quickly over short periods of time, resulting in bursts of drug being released into the body.

PLGA's long hydrolysis half-life indicates that it tends to bulk degrade. The distinction between bulk and surface degrading polymers and a more detailed model of bulk degradation is presented in the next section.

2.3 Polymer Degradation: Surface Degradation and Bulk Degradation Models

There are two different types of degradation: surface degradation and bulk degradation. Surface degrading polymers are generally those built primarily of functional groups with short hydrolysis half–lives. Therefore, by definition, surface degrading polymers release their drug payload very quickly, making them unsuited for long-release formulations. However, if the diffusion of water into the particle is faster than the degradation of polymer bonds, the particle undergoes bulk degradation, a process during which degradation is no longer confined to the surface of the particle. Bulk degrading polymers undergo a more variable process, whereby the degree of degradation generally increases over time.[4]

While there are various explanations for drug release from microspheres, they can be summarized in the following phases. In the initial dry state, the drug is initially localized near discrete, spherical occlusions, as well as adsorbed to the outside surface of the polymer sphere. The microsphere is then immersed in an aqueous buffer, and water quickly penetrates towards the center of the microsphere. Initial release of drug occurs due to desorption of material from the surface of the microsphere. During the hydration of the particle, pores grow in size and aggregate to form mesopores. The drug can only be released from mesopores, which have a mean characteristic radial dimension larger than the characteristic radii of the drug itself. This phase is characterized by a large pore size distribution, and is largely controlled by particle erosion. After the pores have grown to a sufficient size, drug release is largely controlled by Fickian diffusion, whereupon the drug slowly diffuses out through the pores.[5]

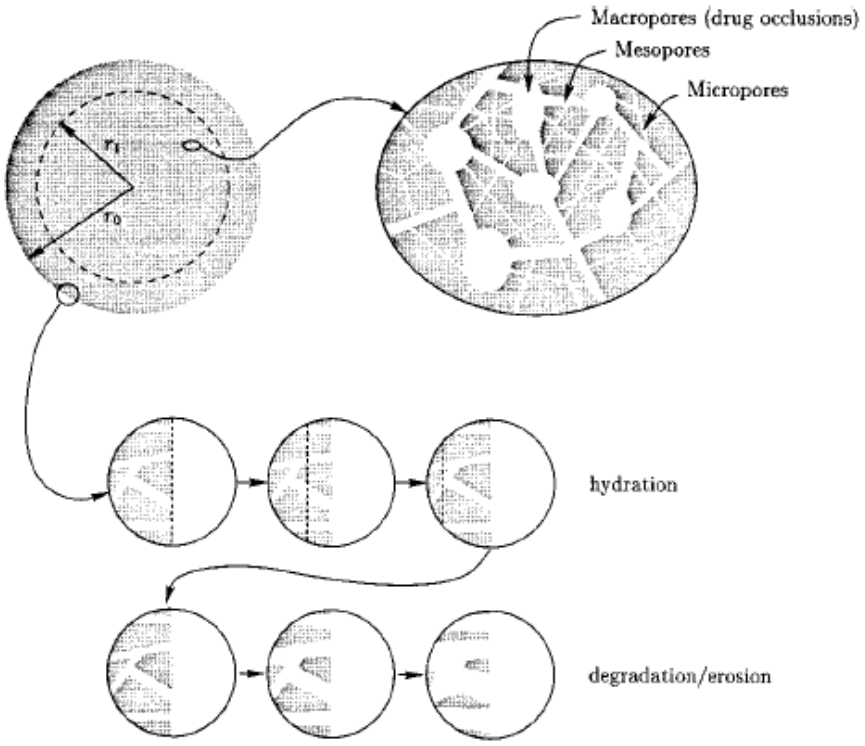


Figure 2.1. Bulk Degradation Model. This figure is adapted from the bulk degradation model presented in Batycky, Hanes, Langer, and Edwards (1997) and assumes a tri-phasic degradation process: initial burst, hydration, diffusion-controlled.[5]

2.4 Size as a Controlling Factor in Polymer Microsphere Drug Release Profile

The main transport mechanism in a bulk degradation release model is diffusion.[6] The diffusive process is controlled by the size of the particle and erosion of the polymer. Polymer chain hydrolysis begins following saturation of the polymer matrix with water.[7] The resulting degradation of the bulk polymer matrix enlarges the characteristic radius of the pore network, generally increasing the rate of diffusion. [5, 8] However, the specific impact of matrix degradation on the overall drug release profile depends on the interaction of two characteristic time scales: the time scale associated with the rate of hydrolysis versus the time scale associated with the diffusive process itself. In the case of small particles, diffusive drug release completes before significant hydrolysis has the chance to occur. Therefore, small particles show nearly constant diffusivity over their short lifetimes. In the case of large particles, the time scale associated with diffusion is longer and significant hydrolysis occurs prior to depletion. Diffusivity is a strong function of time for large particles.

Diffusivity always increases over time; while the concentration gradient between the particle and its surroundings always decreases over time. In small particles, the increase in diffusivity is less important than the decrease in concentration gradient: all drug contained within the small particle diffuses out before diffusivity has a chance to change. Diffusivity, therefore, is approximately constant for a small particle, resulting in a fairly predictable concave-down release profile as drug flux from the particle monotonically falls in time. In large particles, the converse occurs. Over the long release lifetimes of large particles, diffusivity increases exponentially and quickly outweighs the effects of falling concentration gradient. The kinetics of drug flux accelerate, giving a concave-up release profile until all drug content is depleted. The overall shape of the release profile for very large particles is therefore S-shaped, or sigmoidal. An example case of the effects of increasing particle diameter is shown in Figure 2.2. The data in Figure 2.2 were generated using the Raman et al. model[7] for drug release (see Chapter 3.1), but do not specifically replicate data reported in Raman and colleagues' paper.

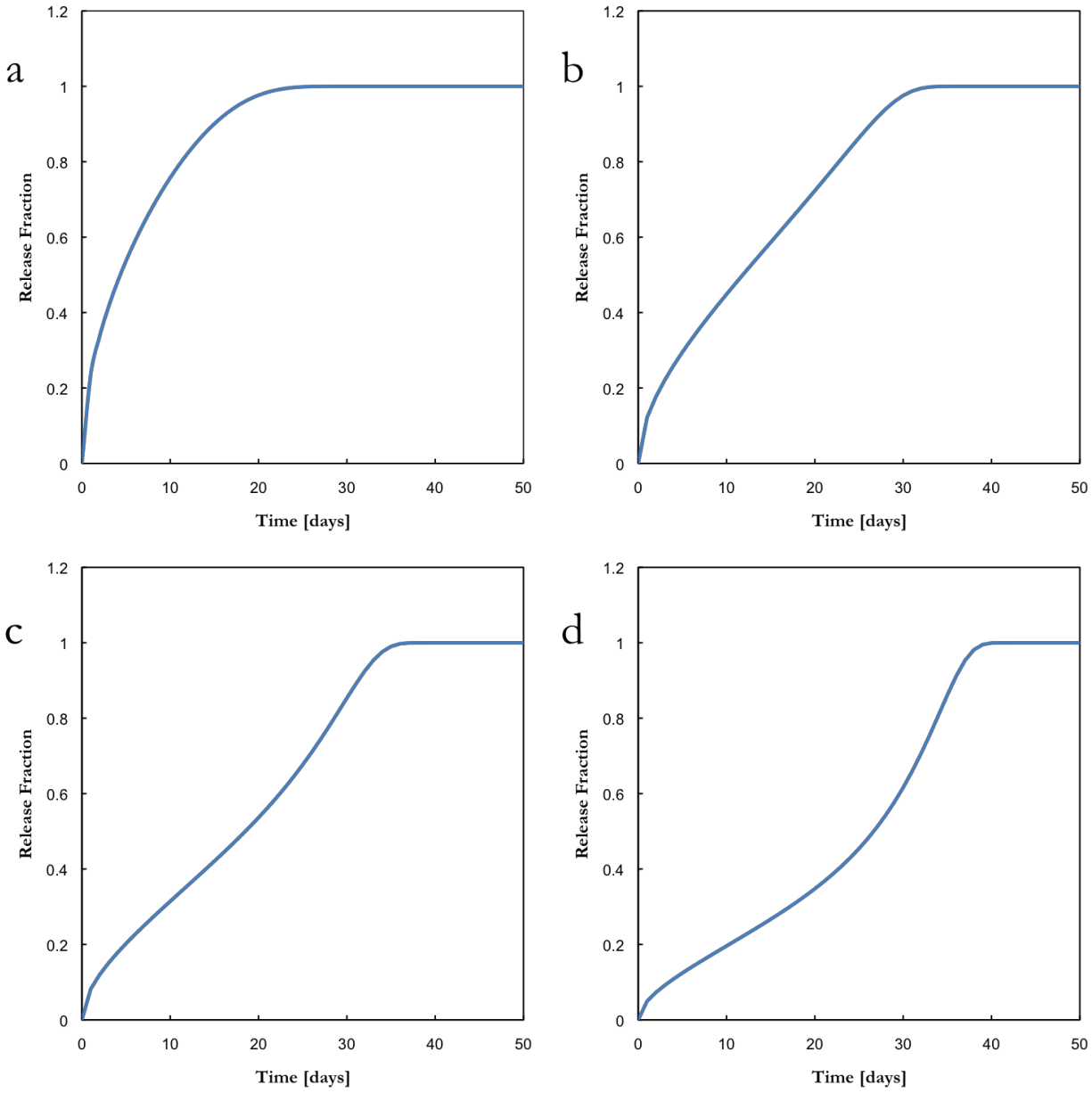


Figure 2.2. Generalized drug release profiles as a function of microsphere diameter. As the particle size increases, the release profile shifts from a concave-down shape to a sigmoidal shape. The release profiles shown were generated by the Raman et. al model (Chapter 3.1), using the following input data: 40,000 Da molecular weight polymer; radii of (a) 5 μm (b) 10 μm, (c) 15 μm, and (d) 25 μm

Both large and small particles have characteristics that are desirable in extended release microparticles: small particles for their simple and relatively zero-order release profile, and large particles for their longevity in the body. In order to best take advantage of these characteristics,

mixtures of large and small particles will be considered. An optimal mixture would have a combined zero-order release and a long lifetime in the body.

2.5 Qualitative Introduction to Cross-Flow Membrane Emulsification (XME)

Many techniques exist to manufacture drug loaded polymer microparticles, but few are precise enough to produce particles of a monodisperse size distribution. As discussed earlier, size is the single most influential feature of the microparticle's release profile. Traditional techniques simply call for physical emulsification by agitation, involving forced mixing of two immiscible liquids, one the continuous phase with the other liquid dispersed throughout, called the dispersed phase. The dispersed phase would contain the target drug and polymer in a solvent. This technique produces a wide range of different sized particles, due to the equally wide distribution of shear force experienced by the dispersed phase. In contrast, the technique explored here produces monodisperse particles by controlling shear rate, the application of which deforms and ultimately detaches a microparticle of the correct size from a dripping pore.

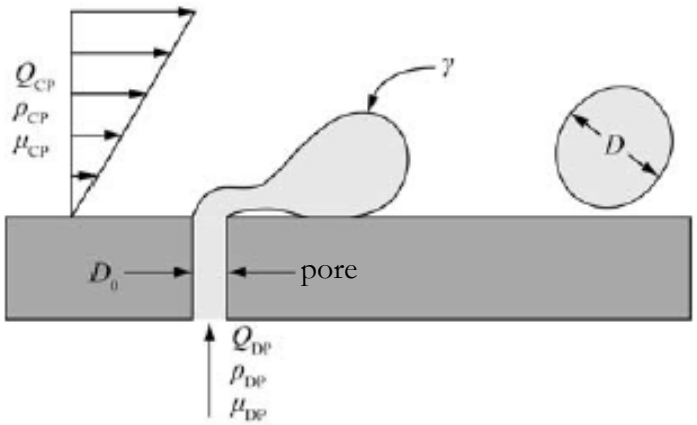


Figure 2.3. Cross-Flow Membrane Emulsification. This figure was taken from Meyer (2010) and depicts a transverse view of the XME process.[1] The continuous phase flows from left to right. The density, viscosity, and volumetric flow rate of the continuous phase can be specified. The dispersed phase exits through a pore of a set diameter, D_0, and can have its density, viscosity, and volumetric flow rate specified. The culmination of these factors results in an emulsified drop of diameter, D.

XME consists of two constituent parts: the continuous phase and the dispersed phase, which are contacted in a controlled manner, in contrast to agitation methods. These two phases

coexist in a single channel that has orifices on its bottom surface, hereafter referred to as the membrane. The figure above shows a side-view of the process, with the flow in the channel running over the orifice on the membrane. The continuous phase flows inside of the channel at a specified volumetric flow rate, which in turn controls the shear rate that is experienced by the flow out of the orifice. The flow out of the orifice is the dispersed phase, which feels the drag force exerted by the continuous phase.

As the dispersed phase is extruded through the orifice, it begins to feel the shear force exerted by the continuous phase. As the drop increases in size, the surface area that feels the force of the continuous phase increases, while the area that connects the drop to the flow out of the orifice remains constant. When the force exerted by the continuous phase overcomes the interfacial tension force connecting the drop to the orifice, the drop is detached and a new drop begins to form through the orifice. By adjusting the interfacial tension and the drag force, droplets of a monodisperse, precise size may be formed. The drops of dispersed phase that are formed are still liquid, and must be afterwards finished via processing units downstream. This technique allows for a wide array of pharmaceuticals to be used, by simply changing the choice of solvents for the continuous and dispersed phases. The relationship between the two phases must be such that the dispersed phase is denser than the continuous phase, as is standard with emulsions, and the target drug must be insoluble in the continuous phase, to prevent leaching.[1]

Haloperidol-Specific Reagent Specifications for XME Process

For the model drug haloperidol used in this paper, the continuous phase is water saturated with dichloromethane (DCM), with additional components of poly-vinyl alcohol (PVA) to aid in the prevention of aggregation of microparticles downstream. The dispersed phase, on the other hand, consists of DCM, in which is dissolved PGLA and the target drug. The PLGA and haloperidol are the components that the finished microparticles will consist of, while DCM is a solvent that is removed from the microparticles through downstream processing. The primary goal of the downstream processing is to remove excess reagents from the product, namely the PVA and DCM, harden the microparticles, and prepare them for packaging. The PLGA, drug, and DCM are

relatively insoluble in water, allowing the dispersed phase to co-exist in a separate phase within the continuous stream. The saturation of the continuous phase with DCM is an additional preventative measure to prohibit the solubilization of the dispersed phase into the continuous phase.[1]

2.6 Haloperidol as a Model Drug: Properties, Indications, Dosing Issues, Extended Release Formulation, and Optimal Dosing Analysis

Discovery and Pertinent Chemical Properties

Haloperidol is a first-generation typical antipsychotic that was first discovered on February 11, 1958 I the Janssen Laboratories, in Belgium. Its chemical designation is 4-[4-(p-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenon, and is the first of the butyrophenone series of major antipsychotics. Haloperidol is hydrophobic, with solubility in water of approximately .01 mg/L; however, it is very soluble in most organic solvents. Haloperidol has a molecular weight of 375.87 g/mol, and is therefore considered a small molecule drug.[9]

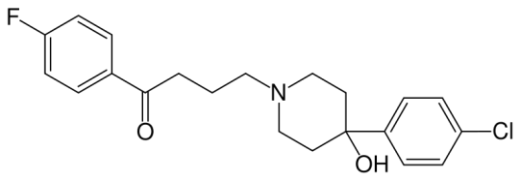


Figure 2.4. Structural Formula of Haloperidol.[9]

Indications

The precise mechanism of action is not currently known, but it is believed to block the effects of dopamine and increases its turnover rate. Haloperidol is contraindicated in depression and Parkinson disease, and can cause severe reactions in certain people, who must be switched to an alternative treatment regimen. Haloperidol is classed as a typical antipsychotic, indicated for schizophrenia and Tourette's Disorder. The drug is also indicated for the treatment of a variety of symptoms, including verbal and motor tics, and severe behavioural problems, which may or may not be symptoms of known psychotic disorders.[9]

Dosing Issues and Consequent Side Effects

Haloperidol is available in the following forms, listed below. The tablets, oral concentrate, and injection are all daily dose formulations, while the haloperidol decanote is an extended release formulation of the same drug, which will be discussed later in this section.

Available Dose Form	Available Dosages
Tablets	0.5, 1, 2, 5, 10, 20 mg
Oral Concentrate	2 mg/mL
Injection	5 mg/mL
Haldol decanoate (XR* Injection)	50, 100 mg/mL

*XR: Extended Release

Figure 2.5. Currently Available Forms of Haloperidol.[10] The tablets, oral concentrate, and injection forms of haloperidol are all once-daily doses, while the Haldol decanoate (haloperidol decanoate) injection is a once-monthly dose. The wide range of doses for the tablets is available based on a patient's ability to tolerate large doses of haloperidol at once, provided they cannot tolerate large doses at once, the smaller doses are taken throughout the day. This same flexibility can be seen in the dose range of Haldol decanoate.

Haloperidol is commonly used in acute situations as an intravenous injection, although it is not approved for that delivery method. The time to peak concentration for the oral formulation is approximately 2-6 hours, with a half-life of 21 hours. Daily dosing varies from patient to patient, but most commonly is within the window of 10-20 mg per day in the oral tablet formulation. Dosing in the upper end of that range usually necessitates twice daily dosing, as the side effects of haloperidol overdosing are very severe. Main side effects include cardiovascular effects, tardive dyskinesia, neuroleptic malignant syndrome (NMS), and reduced fertility. Haloperidol should be used with caution in pregnant or soon to be pregnant women, elderly patients, patients suffering from Parkinson's disease, patients with severe cardiovascular disorders or allergies, and patients taking anticonvulsant medications or anticoagulants.[9, 10]

Optimal Dosing Analysis

Since the side effects of the drug are potentially severe, there have been several studies that explored potential methods to reduce side effects. In several studies, the suggested rationale for side effects in haloperidol stemmed primarily from an inability to maintain an optimal therapeutic concentration, due to the bursts associated with both traditional oral forms of haloperidol and intramuscular injections. The effective, safe range of haloperidol concentration in blood serum is reported as both 5.6-16.9 μg/L and 9.2-14.1 μg/L, though most sources agree that the optimal concentration of 10 μg/L. Assuming that there is zero release, and accounting for metabolism and bioavailability, the haloperidol dose/day that results in the optimal blood serum concentration of 10 μg/L is 15 mg/day. This data, when compared with the normal dosing range of 10-20 mg/day, is well within range, and is heretofore considered to be the daily dose requirement for a schizophrenia patient.[11-13]

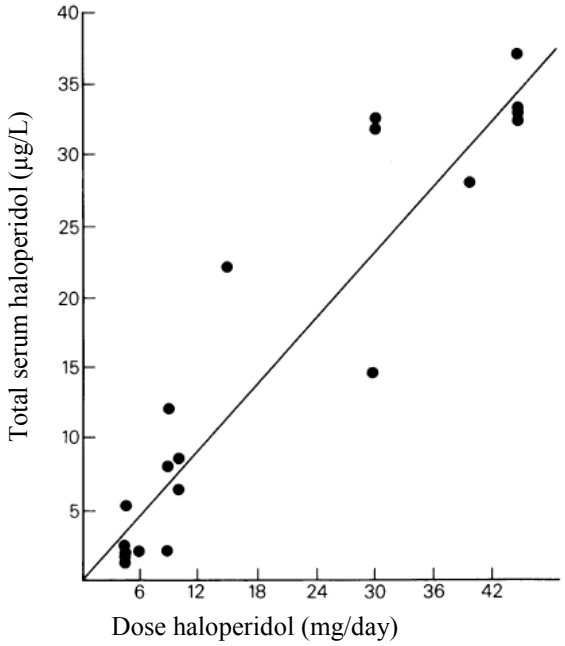


Figure 2.6. Blood Serum Concentration of Haloperidol as a Function of Dose.[13] The above graph correlates a daily dose of haloperidol with the total serum haloperidol achieved. The optimal blood serum concentration of 10 μg/L leads to an estimated optimal dose of 15 mg/day.

An Extended Release Formulation: Haloperidol Decanoate

In addition to the oral formulation of haloperidol, an esterified version called haloperidol decanoate is available, which is a depot (injectable) extended release formulation for intramuscular injection. The structural formula is shown below, with the attached ester highlighted in blue.[14]

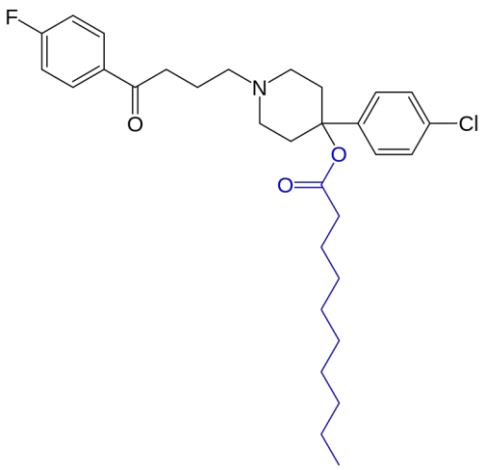


Figure 2.7. Structural Formula of Haloperidol Decanoate.[14]

Pharmacokinetics and Dosing Issues

The addition of the ester makes the compound highly oil-soluble, but sparingly soluble in aqueous solutions, like blood. The drug is injected into a large muscle, where it stays in an isolated cache, slowly dissolving out into the blood stream. Once the drug ester reaches the blood stream, it is rapidly hydrolyzed by endogenous esterase enzymes in the body, producing the parent drug haloperidol. There are a variety of issues that stem from these pharmacokinetics that contribute to the imperfect nature of haloperidol decanoate's release profile. First, is that the drug release over time is a function of diffusion of the drug through the muscle into the vein, which in turn is dependent on the distance of the drug cache to the nearest vein. Achieving unity in this metric is nearly impossible, considering the idiosyncratic anatomical makeup of a patient. Secondly, the release is also dependent on the level of activity in each individual patient. Increased physical activity hastens the diffusion of drug outwards, thereby increasing the amount of drug released.[15]

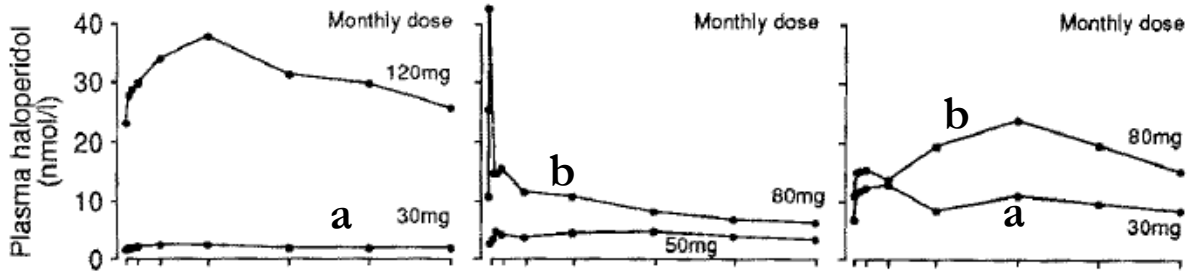


Figure 2.8. Plasma concentration over time for haloperidol decanoate. The x-axis represents time, over a time scale of 28 days.[16] Each patient group was randomly selected and there were no groups that exhibited any particular concentrations of patient type. Each data set (denoted by a connected set of points) denotes the average blood plasma concentration of haloperidol for a group of six patients. First, the two data sets marked 'a' are considered. Each of these distinct sets of patients received a 30 mg dose of haloperidol decanoate and were monitored over the same period of time. However, even though all aspects of administration were controlled for, the haloperidol plasma concentrations of each are drastically different. The same phenomenon is apparent for the data sets marked 'b', who received 80 mg doses of haloperidol. The conclusion drawn from these data is the lack of predictability, control, and consistency in drug release over time for the haloperidol decanoate product.

The graph above shows blood plasma haloperidol measurements versus time in days after the eighth injection of depot haloperidol decanoate. According to prescribing information associated with haloperidol decanoate, reaching a dosing steady-state can take up to eight months. At this snapshot in time, all patients shown have completed eight months of therapy. Each individual data set, denoted by a single connected line, is a subgroup containing six individuals. The most notable points of these graphs come when observing the differences between subgroups taking the same monthly dose – here the 30 mg (a) and 80 mg (b) groups. The variability in dose responsiveness is markedly apparent. This variability is further informed by the realization that these doses are all the low end of the scale, recalling that the calculated optimal dose per month of haloperidol is 450 mg. The variability that might be present in larger doses would theoretically be even larger, calling into question the clinical safety and efficacy of such a drug.[16]

Available Dosages and Associated Treatment Regimen

The molecular weight of this esterified formulation is 530.13 g/mol, considerably higher than daily dose formulation. Haloperidol decanoate is delivered in a sesame oil vehicle, with 1.3% benzyl

alcohol included as a preservative. Doses come in 50 and 100 mg/mL concentrations of haloperidol, which due to the increase in molecular weight, are present as 70.5 and 141 mg/mL of haloperidol decanoate. Haloperidol decanoate is injected intramuscularly every 3-4 weeks, and must be administered by a healthcare professional. The time frame of 3-4 weeks is due to the variability in release of the drug, and the precise dosing regimen must be determined on an individual basis. Haloperidol decanoate reaches a peak at approximately six days, and has a half-life of approximately three weeks. Generally, steady state blood serum levels are not obtained until the third or fourth dose, which implies 3-4 months of suboptimal treatment conditions. This variability also makes this injectable fairly unreliable for patients that require stricter dose management, such as the elderly patient population. In a recent clinical study in elderly schizophrenia populations, the risk of death was increased from 2.6% to 4.5%.[17, 18]

While this formulation was a breakthrough at the time, allowing for improved patient compliance in addition to the convenience of the dosing schedule, it also re-emphasized the necessity of a controlled release formulation that would not only extend release, but also have a zero-order release profile that would guarantee a blood serum concentration within the optimal range.

Use as a model drug

There are several advantages to using haloperidol as a model drug in this process. First, from a process perspective, its insolubility in water and high solubility in organic solvents make the choices of continuous phase and dispersed phase solvents more simple, as there is already a considerable body of work discussing the dynamics of water-dichloromethane systems. Secondly, as a small molecule, it is compatible with PLGA spheres and is relatively easy to work with in solution, unlike proteins, which are considerably bulkier and require stricter temperature control, which would simply add additional process units to control and monitor temperature. Haloperidol is a relatively small market, with approximately 44 million USD[19] in annual sales, and is a drug that would clearly benefit from the zero-order release control that is facilitated by the XME technology explored here. Additional exploration of the haloperidol market is available in Sections 5.2-5.4. While the

quantitative results of this paper are geared towards haloperidol encapsulation, tailoring the process to an alternate drug would simply require repeating the delineated steps, changing the desired optimal concentration and encapsulated dose, and adjusting the solvents to suit the solubility of the target drug in various solvents.

2.7 Preliminary Process Diagram

The overall scheme of the XME production of haloperidol encapsulated PLGA microparticles is presented in Figure 1.9. The continuous phase and the dispersed phase enter the XME channels, where the dispersed phase will be emulsified to form liquid microspheres. Two different sections of XME channels are in use to produce different sizes of microspheres. These different sizes will be combined in precise quantities during the packaging step in accordance with a calculated ratio that will give a zero-order release profile. Seventy percent of the continuous phase is diverted into the DCM waste management block in order to decrease the working volume of the particles and to make room for the addition of water during downstream processing.

The downstream processing step removes the DCM that the haloperidol and PLGA are dissolved and hardens the particles, preparing them for the packaging step. The waste from downstream processing is diverted into the DCM waste management block. This function of this block is to dispose of the DCM used in the process in accordance to environmental guidelines.

The packaging step will combine the finished particles with a quantity of dried PBS media in a single month-long dose ampoule. The ampoules will then be distributed to primary and secondary care facilities for resuspension in deionized water just prior to administration.

This chapter served to introduce the concepts of theoretical bulk degradation and size as the arbiter of drug release, cross-flow membrane emulsification, and the specifications for the model drug haloperidol. In Chapter 2, the quantitative modeling and subsequent specifications of the XME channels will be discussed. These specifications will then be translated into a scale-rendering of the channel and discuss the build material specifications in Chapter 3. Chapter 4 discusses the process units and the timing of the process. The market analysis, economic implications, and profitability assessment of the controlled release product and the XME platform are discussed in Chapter 5. Finally, Chapter 6 presents conclusions and recommendations for moving forward with the project.

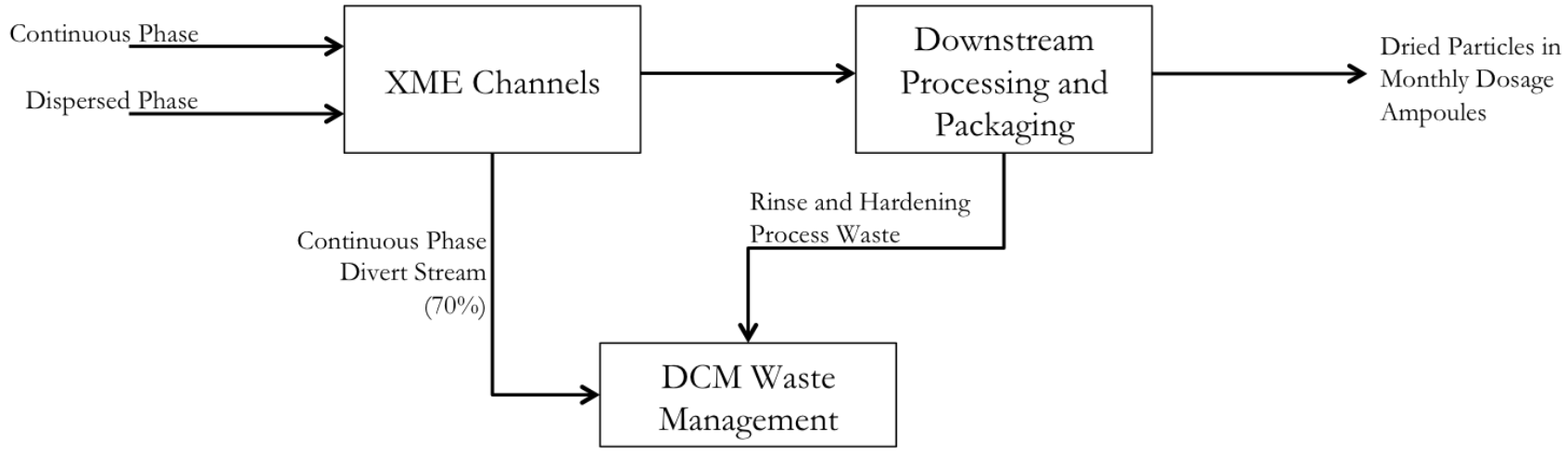


Figure 2.9. Preliminary Process Diagram.

2.8 Chapter 2 References

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Chapter 3: Depo-Haloperidol Product Design

3.0 Chapter Introduction

The design and manufacture of a timed-release haloperidol-loaded microsphere incorporates elements of both product design and process design. Chapter 3 covers the product design elements of the report, by detailing the characteristics of the polymer microspheres and how these properties meet the important customer requirements. We begin by describing a mathematical model to predict the drug release kinetics from microparticles of certain specifications. Then, the model is applied to several test cases and a collection of candidate product specifications is compiled. Finally, we study the pharmacokinetic effects of drug release and buildup inside a patient's body.

There are three essential customer requirements that the poly(lactic-co-glycolic acid) (PLGA) spheres must be able to satisfy. First, the product cannot have a very large "burst" of drug at the start of the release process. Large initial spikes in drug concentration can result in a dangerous overdose, and must be avoided. Second, the product must exhibit a nearly constant release rate (also called "zero-order" release) for approximately one month following injection. The target lifespan of this product is a full month, in order to achieve a strong advantage over the current anti-psychotic market. Third, the drug release rate should slowly taper down during the final few days of the microspheres' month-long lifetime. A gradual reduction in blood serum concentration near the end of a dosing period is logistically important, since it gives a patient a broader window during which the subsequent dose can be administered. If drug release halts abruptly after thirty days, the patient would receive an overdose if the next injection were given too early, and would suffer from a complete lack of medication if the next injection were given too late. A gradual reduction means that the patient can tolerate a fresh injection treatment during any of several days at the end of the dosing period.

In order to achieve these three design goals, we manipulate three characteristics of the PLGA microsphere product. First, we control particle size. Smaller spheres release their contents

more quickly, have larger initial bursts, and also show decelerating "concave down" release kinetics as described in Chapter 2. Larger particles have longer lifetimes, smaller initial bursts, and accelerating sigmoidal release kinetics. By varying particle size, we have some control over the release profile. Second, we can vary the PLGA chain molecular weight. The molecular weight of the polymer affects the ability of small-molecule drugs like haloperidol to diffuse through the polymer matrix. High-molecular weight PLGA shows slower release kinetics than low-molecular weight PLGA. Third, we can choose to assemble a single size of polymer microsphere or combine multiple sizes in a heterogeneous mixture. As we will demonstrate, mixtures of particles generally show smaller initial bursts and longer overall lifetimes.

3.1 Modeling Drug Release

Our central product design goal is to engineer a poly(lactic-co-glycolic acid) (PLGA) sphere loaded with haloperidol, which will release its contents after introduction into a patient's body according to three design specifications: no initial burst, constant release over one month, and a gradual reduction in drug release after one month. It has been shown that sphere diameter,[1] and average initial polymer chain molecular weight,[2] of a PLGA sphere control the kinetics by which the drug payload is released. The mechanism of release from a degrading PLGA sphere is governed by diffusion of a small-molecule drug through the surrounding polymer matrix,[3-5] and diffusion occurs more quickly through a matrix composed of short polymer chains. The aqueous environment inside a patient's body will gradually hydrolyze the bulk polymer into smaller chain lengths,[2] and as a result drug release accelerates over time provided that the PLGA sphere is not so small that all drug content is depleted before much hydrolysis occurs. Based on this physical mechanism, tuning particle size and initial chain molecular weight gives a high degree of control over the kinetics of drug release.

3.1.1 Choice of a Model

The first step in the product design analysis is to develop a workable mathematical model for drug discharge. Published experimental data covers the drug release of only a few select particle sizes; yet we must be able to predict the release profiles of any particle size within the micro-scale range in order to optimize the size selection. There are three essential criteria in a choice of a mathematical model. First, the model must be based on molecular diffusion and incorporate time-dependent diffusivity. Research strongly indicates that this is the appropriate physical mechanism for the release process.[3-5] Second, the model must have a minimum number of undetermined input parameters. Models with a large number of input constants generally become prohibitively difficult to work with, especially since report is mostly theoretical and we lack the means to gather much experimental data about the polymer system. We seek to develop a model that will simply take sphere diameter and initial chain molecular weight as inputs and return a release profile. Third, and most importantly, the model must be able to replicate the qualitative release profile behavior described in Chapter 2. We require a model that transitions between concave-down and sigmoidal kinetics as a function of particle size and initial molecular weight.

The drug release model for a spherically-symmetric system begins with the diffusion equation in spherical polar coordinates as written below.

$$\frac{\partial C}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D\{t\}\frac{\partial C}{\partial r}\right) \qquad \text{(Equation 3.1)}$$

Equation 2.1 describes the haloperidol concentration profile inside a polymer sphere as a function of radial coordinate r and time t. Here C is the local haloperidol concentration and D is the time-dependent mass diffusivity of haloperidol through the polymer matrix. There are three associated initial and boundary conditions. The concentration profile must be spatially constant at time zero, based on uniform drug loading at production. Concentration must go to zero at the surface of the sphere, since we assume that convection at the interface between the solid sphere and the liquid surrounding medium is high and therefore the haloperidol concentration at the sphere boundary is extremely small. Finally, the spatial derivative of the concentration profile must go to zero at the sphere's center to ensure differentiability and radial symmetry.

A viable model for time-dependent diffusivity must be supplied to Equation 3.1. The mathematical model developed by Raman, Berkland, Kim, and Pack (2004) is chosen for its strong experimental basis on PLGA systems, and for its simplicity. The Raman et al. model utilizes an empirical formula relating the diffusivity of small molecules through the polymer matrix with average polymer chain molecular weight. This empirical formula was found by direct measurement on PLGA spheres, and should therefore be reliable.

$$D\{MW\} = \exp\left\{-0.347\left[\ln\{MW\}\right]^3 + 10.394\left[\ln\{MW\}\right]^2 - 103.950\ln\{MW\} + 316.95\right\}$$

(Equation 3.2)

In Equation 3.2, MW is the average polymer molecular weight in Daltons and D is diffusivity reported in units of [m^2/s]. Raman and colleagues report that average polymer molecular weight decreases in time with first-order kinetics

$$MW\{t\} = MW_0 \exp\{-k\,t\} \qquad \text{(Equation 3.3)}$$

MW_0 is the average polymer molecular weight prior to any hydrolysis (i.e. lasting from manufacturing through the moment of injection into a patient). Raman and colleagues verified Equations 3.2 and 3.3 for PLGA chains in the range of 10,000 Da to 70,000 Da, so we confine our study to this range in order to ensure the model's applicability. The rate constant k is reported at 0.07 day^{-1}. Equation 3.3 was found to apply following a short "lag" period in which water saturates the polymer matrix but no hydrolysis has yet occurred. We have no way to experimentally determine the lag time of our system, and Raman and colleagues find that minimal error is introduced by assuming that the lag time is effectively zero. Therefore, this study assumes that Equation 3.3 holds for all times. This is the complete model we use in our analysis.

3.1.2 Computational Evaluation

Equations 3.2 and 3.3 are substituted into Equation 3.1 and the partial differential equation is numerically integrated using the MATLAB function `pdepe` (partial differential equation parabolic-elliptic). First, we select the value of MW_0, average initial molecular weight, bounded between 10,000 Da and 70,000 Da. Next, the MATLAB script prompts for two input vectors: one defining the set of radial coordinates of interest and one defining the set of simulation time-points of interest. The radial "space" vector ranges from the center of the drug-loaded sphere (r = 0 μm) to the outer edge (r = R μm). The "time" vector ranges from the start of the drug-release simulation (t = 0 days) to the end of the simulation, typically 50 days (t = 50 days). The number of elements in each vector defines the precision of integration. For example, a space vector of 100 elements will evaluate the drug concentration inside of a sphere at each of those 100 radial coordinates. A time-vector containing elements [0 1 2 … 50] will report the concentration profile at each day for 50 days. Generalized input vectors are shown in Equations 2.4 and 2.5.

$$space = \left[0 \quad R/(n-1) \quad \ldots \quad (n-2)R/(n-1) \quad R\right] \qquad \text{(Equation 3.4)}$$

$$time = \left[0 \quad 1 \quad \ldots \quad 49 \quad 50\right] \qquad \text{(Equation 3.5)}$$

Here, R is the radius of the drug-loaded sphere (chosen between ~1 μm to ~100 μm), and n

is the number of entries in the space-vector. Note that the vector elements in both vectors should be evenly spaced. The units of these vector elements are understood by MATLAB to be the same as those inherited from Equations 3.2 and 3.3, which we choose to be μm and days. To consider micrometers and days, Equation 3.2 is converted from [m^2/s] to [$\mu m^2/day$], which is done with a conversion factor 8.64×10^{16}.

Finally, MATLAB requires specifications for the boundary and initial conditions of the system. The initial condition sets the time-zero concentration profile at a constant value of 1 at all radial coordinates inside the sphere. The final output of the MATLAB script is a dimensionless, fractional release profile that ranges over 0 fractional release to 1 fractional release. Since the output analysis is a dimensionless release fraction, the magnitude and units of the initial drug loading profile are irrelevant and we choose a magnitude of 1 so that the output concentration profile will be normalized to 1. The boundary conditions impose that the derivative of the concentration profile equals zero at the sphere center ($r = 0$) to ensure differentiability at the sphere center, and that the local drug concentration equals zero at the sphere surface ($r = R$) to represent the low-concentration medium around the sphere.

Given all input values, MATLAB integrates the diffusion equation and outputs a 51-by-*n* matrix of concentration values normalized by the initial concentration value of 1. The 51 rows of the matrix contain the sphere's concentration profile, at each of the 51 days of the simulation. The *n* columns track the local concentration at each of the *n* radial test points inside the sphere. It is informative to plot each row of the output matrix (a "concentration vector") against the space vector to see the concentration profile. A time-evolving concentration profile, for a 20 μm radius sphere with 40,000 Da initial polymer molecular weight, is shown in Figure 3.1.

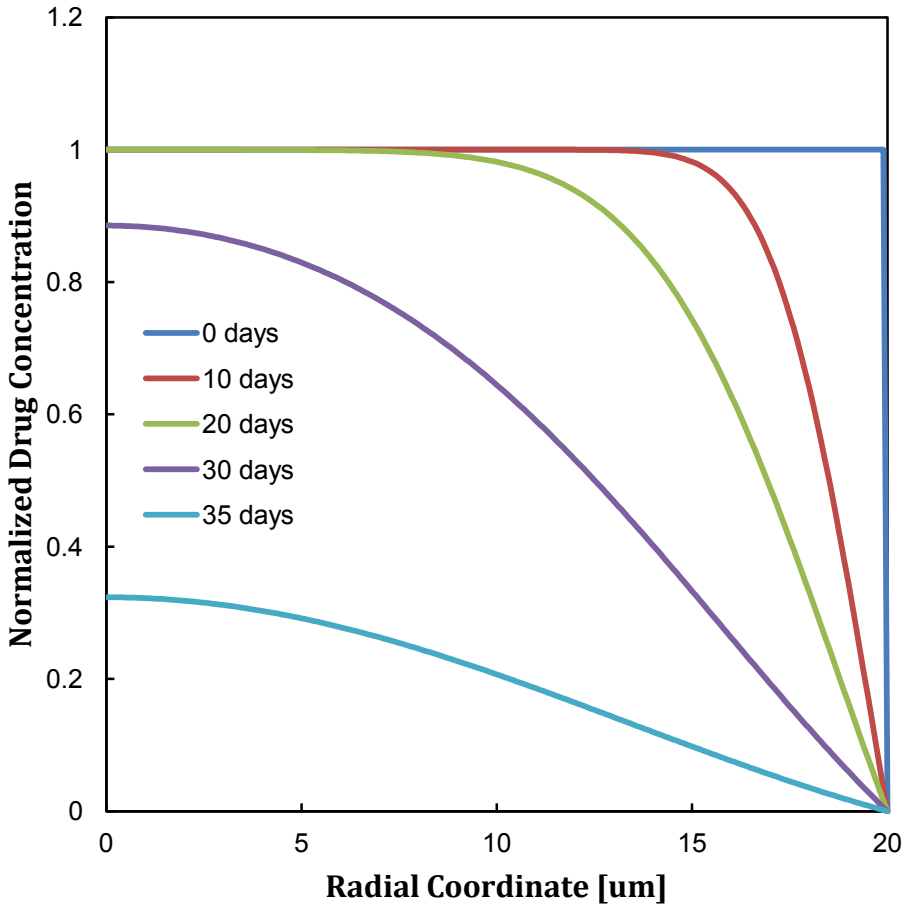

Figure 3.1. Time-Evolving Concentration Profile. Internal drug concentration profile as a function of radial coordinate for a 20 μm radius sphere with 40,000 Da polymer.

Now that the numerical solver has determined the interior concentration profile for a sphere at each of the 51 simulation-days, the computer can track cumulative drug release over time. In this spherically symmetric system, at any given time the total drug content is found by integrating the concentration profile (a single row of the output matrix) over the sphere volume.

$$Content = \int_V C\,dV = 4\pi \int_{r=0}^{R} C r^2\,dr \qquad \text{(Equation 3.6)}$$

V is sphere volume. The program applies this integral to each row-vector of the MATLAB output matrix. Since each row vector corresponds to the concentration profile at a different time,

the collection of integrals will give a time-survey of the total drug content. However, the output concentration profiles are discrete vectors, not continuous functions. So, we approximate the integral in Equation 3.6 as a trapezoidal Riemann Sum.

$$Content \approx 4\pi \sum_{i=1}^{n-1} \left(\frac{C_i + C_{i+1}}{2} \right) \left(\frac{r_i + r_{i+1}}{2} \right)^2 \Delta r \qquad \text{(Equation 3.7)}$$

Here, i is the index for each entry of the concentration row vector and n is the number of entries (the number of radial test-points). We typically consider space-vectors of 100 test-points, so $n = 100$. The C_i are the concentration values in entry i of the concentration vector (a row vector from the output matrix), and the r_i are the radial values in entry i of the space vector. Note that the number of columns in the output concentration matrix will always be equal to the number of entries in the spatial vector: n. Δr is the step-size between any two entries in the spatial vector. For the generalized vector in Equation 2.4, Δr equals $R / (n - 1)$.

The MATLAB script divides the current drug content (Equation 3.7) by the initial drug content (Equation 3.7, evaluated at time zero) to find the fraction of drug retained in the sphere. One minus the retained fraction is equal to the released fraction. We then plot this released fraction for each time-interval evaluated, giving the desired release profile. An example for 30 μm radius 10,000 Da polymer spheres is shown below in Figure 3.2.

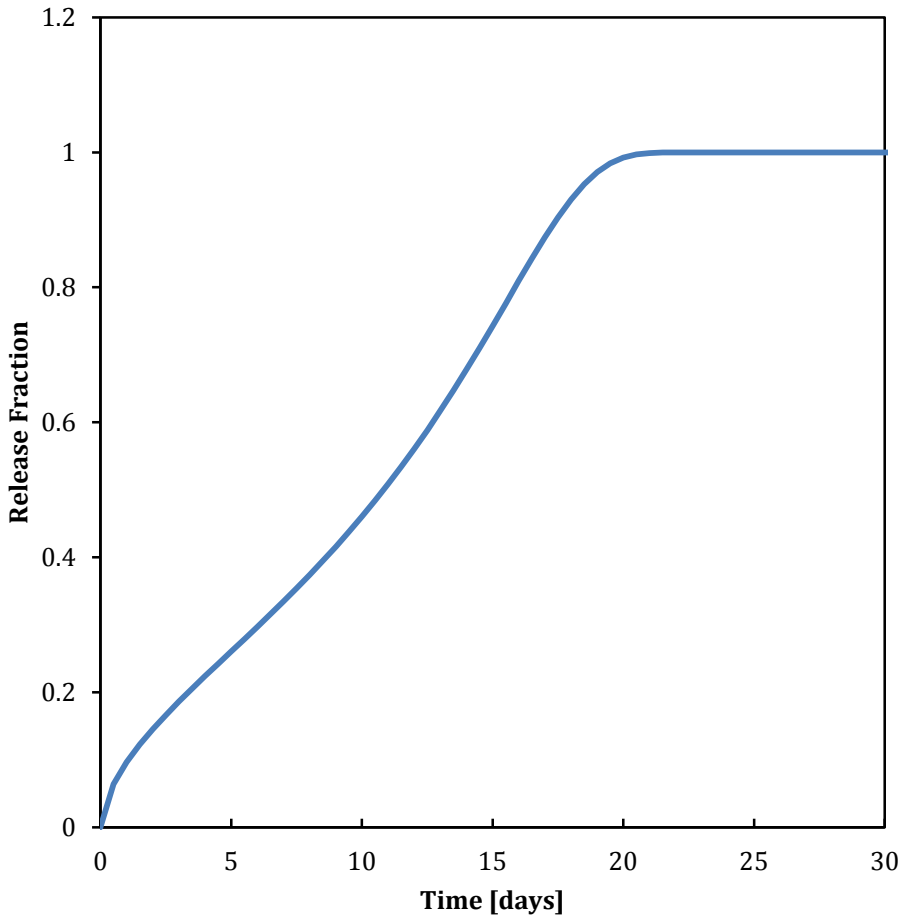

Figure 3.2. Sample Cumulative Release Profile. Cumulative fraction of drug released from a 30 μm radius sphere with 10,000 Da polymer. All drug has been discharged when the release fraction equals 1.

One final complication is the need to model a mixture of two particle sizes. An experimentally verified method to produce a zero-order release profile is to mix small and large PLGA particles.[6] The program calculates a mixture by executing the same procedure twice, over the same time-span: once for a small sphere and once for a large sphere. Integration of the two outputs gives a drug content for the small particle and for the large particle at each time point evaluated. We account for unequal mixing by multiplying the small particle drug contents by the mass ratio of small spheres to large spheres. The two drug content arrays are added together to give the cumulative retained fraction of drug.

The full MATLAB script is provided in Appendix B.

3.2 Selecting a Particle Size Distribution

In the previous section, we selected the literature Raman et al. model [2] for drug release from PLGA spheres and developed a computer program to run the model and formulate a cumulative drug release profile. The next step in the product design is to use this model to identify a PLGA sphere size or a distribution of sizes that will discharge their contents with approximately zero-order kinetics. We investigate two options: a single particle size, and mixing of two particle sizes. Finally, we leave open the possibility of using initial polymer molecular weights throughout the range of 10,000 Daltons to 70,000 Daltons in anticipation of process throughput concerns that we discuss later in this chapter.

3.2.1 Size Distribution Methods: Single Size versus Mixing

An important design consideration is to compare the performance of a single PLGA sphere size against the performance of a mixture of sizes. By iteratively applying the mathematical model developed in Chapter 3.1, it is possible to identify the single particle size that generates a release profile closest to zero-order. Consider the model case of 10,000 Da initial polymer molecular weight. For this molecular weight selection, zero-order release is most closely reached with 17 μm radius spheres. See Figure 3.3(a) for a copy of the MATLAB release profile report. The intensity of the initial burst is represented by the slope of a tangent line at the start of the release profile. A high slope represents a rapid rate of drug release.

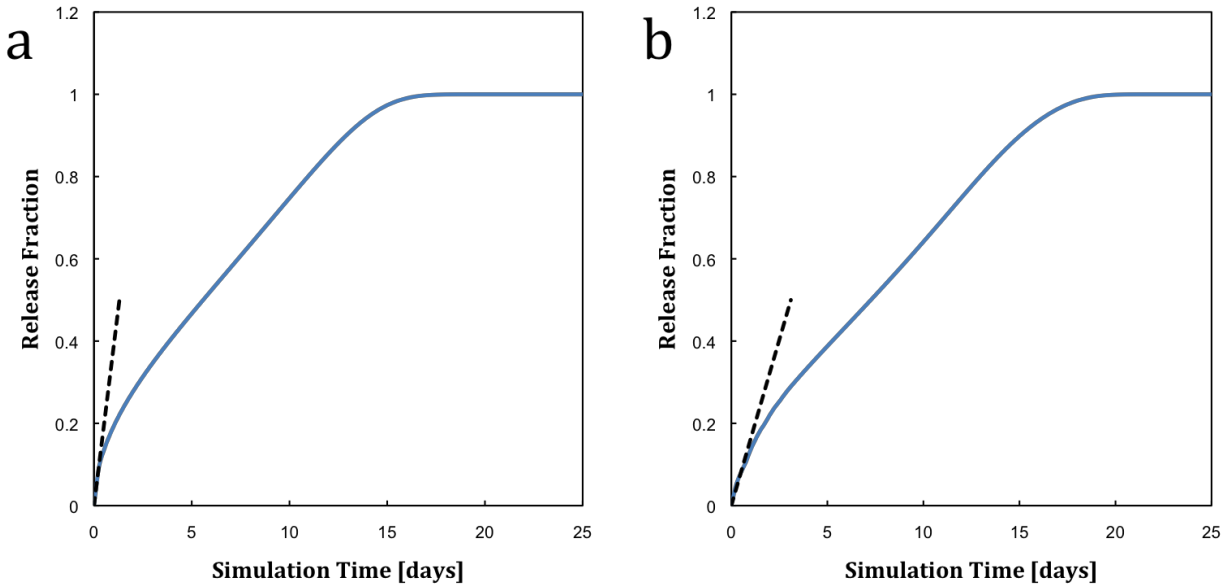

Figure 3.3. Cumulative Release from 10,000 Dalton Polymer Spheres. Cumulative fraction of drug released from 10,000 Da polymer spheres. (a) pure 17 μm radius PLGA spheres, (b) 16 μm radius and 26 μm radius spheres in a 5-to-1 volume ratio.

The release profile generated by this single 17 μm particle size is excellent from days 2 to 15, but there is an unacceptably large burst of drug near the start of release (the slope of the tangent line is much larger than the slope of the release profile's mid-section). A rapid initial release like this could cause an overdose of drug for the patient. For the same 10,000 Da system, a mixture of two particle sizes could also generate zero-order release but not show such an intense initial burst. A mixture of 16 μm radius and 26 μm radius particles in a 5-to-1 mass ratio performs very nicely. This mixture's release profile is reported in Figure 3.3(b). Mixing a few larger particles with a majority of small particles reduces the initial burst (although the burst cannot be completely eliminated). The consequences of the initial burst are further explored in Chapter 3.3. The inclusion of a few large particles also slightly increases the duration of the release profile from 15 days to 18 days. A longer particle lifetime is highly desirable for the product, since it means that a patient will not require treatment as frequently. This trend holds for all PLGA molecular weights: a mixture of particles always shows a smaller initial burst and a slightly longer lifetime than a single particle size. Therefore, we strongly recommend the mixing approach.

3.2.2 The Effects of Initial Polymer Chain Molecular Weight

The initial PLGA molecular weight must fall between 10,000 and 70,000 Daltons to remain within the bounds of Raman and colleagues' (2005) experiments. The choice of a PLGA molecular weight is complicated by two competing considerations. The first consideration is that higher molecular weight polymer chains slow the diffusion of small-molecule drugs, giving the polymer spheres a longer lifetime in a patient's body and therefore reducing the frequency of treatment. Long lifetimes are highly desirable, since the purpose of a timed-release drug delivery system is to maximize the amount of time between injections for a patient. The second consideration is that lower molecular weight PLGA spheres show accelerated release kinetics, which effectively makes the transition between concave-up and sigmoidal release profiles occur at larger particle size. Using low molecular weight polymer would enable manufacture of larger PLGA spheres while still meeting the requirement of zero-order release. As we discuss in depth later, larger particles are easier to produce by the cross-flow membrane emulsification process than small particles. Process throughput vastly improves by using low molecular weight polymer and larger particles.

Optimization analysis considers a selection of PLGA molecular weights in the range 10,000 Da to 70,000 Da and compares the tradeoff between particle lifetime and throughput feasibility. Table 3.1 reports the PLGA sphere lifetime and the mixture of sphere sizes necessary for zero-order release for a selection of polymer molecular weights. Process throughputs for each option will be discussed later in this chapter.

PLGA Molecular Weight	Small Particle (diam)	Large Particle (diam)	Release Profile Lifetime
10,000 Da	32 μm	52 μm	18 days
20,000 Da	26 μm	40 μm	26 days
30,000 Da	24 μm	36 μm	31 days
40,000 Da	20 μm	36 μm	36 days
50,000 Da	16 μm	30 μm	39 days
60,000 Da	14 μm	30 μm	40 days
70,000 Da	14 μm	28 μm	41 days

Table 3.1. Molecular Weight and Particle Size Requirements. Particle diameter requirements for zero-order release (volume ratio of 5-parts small particles to 1-part large particles), and the lifetime of the mixture's release profile for a selection of molecular weight options.

An important note is that increasing the particle lifetime does not change the total production requirement of PLGA spheres to meet the goal of 500,000 month-long patient doses per year. The daily haloperidol requirement for a patient is 15 mg/day,[7] which is independent of the dosing frequency. Using timed-release spheres with a very long lifetime will decrease the dosing frequency, but because total drug content per year remains constant the mass of drug (and therefore the mass of polymer spheres) injected at each treatment interval will increase by the same proportion. There is no production advantage for long release lifetimes, but there is significantly improved patient convenience.

In the next section of Chapter 3, we will analyze in detail how the kinetics of drug release affect the drug content inside a patient's body over the course of a month's treatment. In order to facilitate this analysis, it is convenient to fully specify the PLGA sphere product under consideration. As we discuss in Chapter 4, the optimal selection from the options in Table 3.1 is the 40,000 Dalton molecular weight sphere, with 20 μm and 36 μm diameter particles in a 5-to-1 mass ratio. This choice arises from a balance of customer demands and technical feasibility. Therefore, the entire discussion of Chapter 3.3 deals with this 40,000 Da system.

3.3 Characteristics of Release

In the previous section, we determined a set of candidate microsphere sizes and molecular weights that could satisfy the customer requirements of zero-order release for long time spans. We then skipped to the conclusion of Chapter 4 and identified the 40,000 Da polymer system as our optimal product specification. Although this chosen molecular weight and size distribution offers good zero-order release over a 36-day period, we analyze the release profile to gain insight into the initial burst phase and the final declining phase. So, Chapter 3 concludes with a deeper pharmacokinetic analysis of drug release from the mixture of 20 μm and 36 μm diameter 40,000 Da polymer spheres. For future reference, the fractional release profile of this system is shown in Figure 3.4 below.

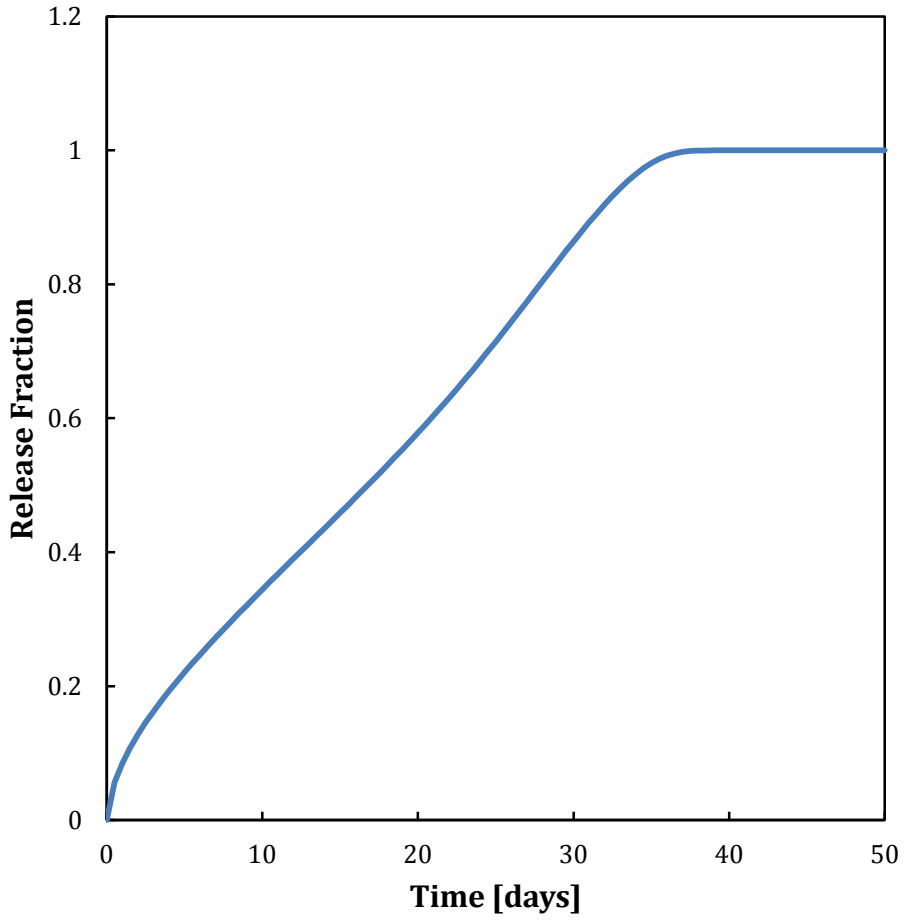

Figure 3.4. Schematic of Parabolic Flow Profile. Cumulative fractional release profile from a 5-to-1 mixture by mass of 20 μm and 36 μm diameter 40,000 Da polymer spheres.

3.3.1 Release and Blood Serum Concentration

The central deliverable feature of the timed-release product is the ability to maintain consistent blood serum concentration throughout the lifetime of the polymer particle. In the previous section, we developed the drug release profile from a 40,000 Dalton molecular weight product. The next step in the product design analysis is to extract information about blood serum concentration from the release profile. For this analysis, we assume a simplified model of the human body as a continuously stirred tank reactor (CSTR), with instantaneous and perfect mixing of haloperidol.

Before we begin, note that this pharmacokinetic model is not robust enough to quantitatively predict the blood serum concentration over time. A CSTR model fails to account for drug entrainment in various organs, passage across tissues, and many other biological subtleties. We instead use the model to predict the relative changes in blood serum concentration over time.

Analysis begins by developing a mass balance on haloperidol inside the body. Haloperidol is released from the PLGA microsphere product at a rate equal to the time derivative of the release profile (Figure 3.4) multiplied by the initial drug loading mass. We assume an initial drug loading value of 450 mg for the one-month dose, based on the common clinical oral dose of haloperidol of 15 mg/day.[7] Let the rate of haloperidol influx be $F(t)$, with units of [mg/day] The rate of haloperidol release from the PLFA spheres is shown below in Figure 3.5.

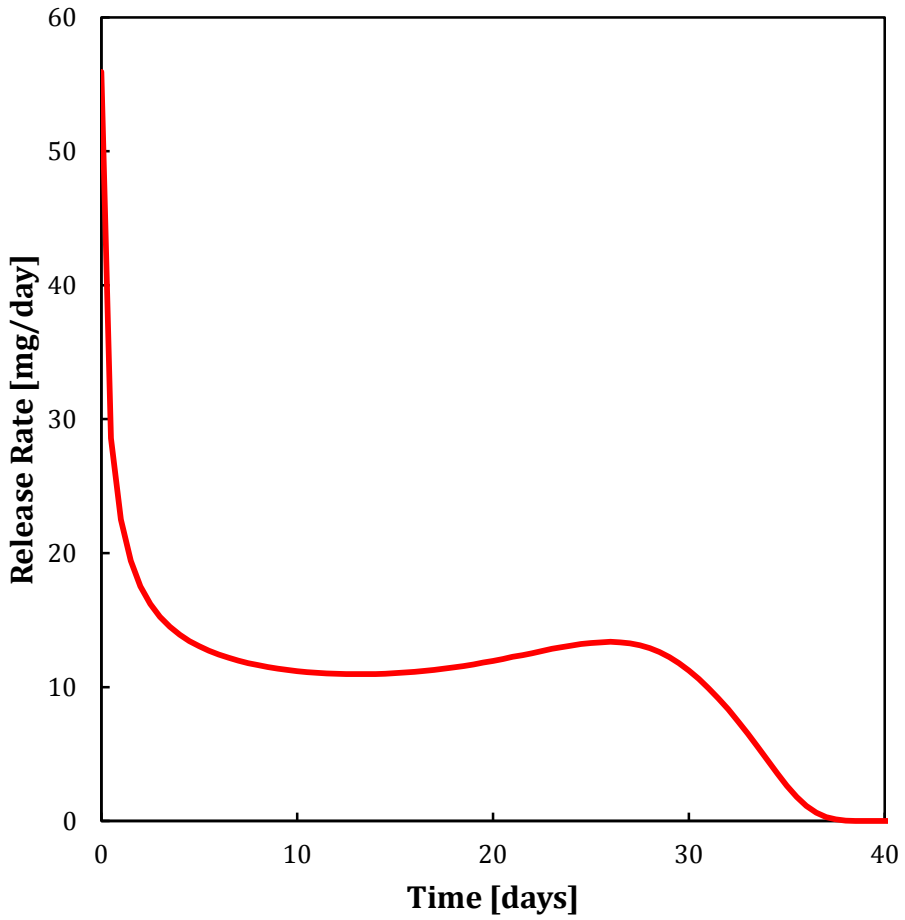

Figure 3.5. Rate of Drug Release from 40,000 Da PLGA Microspheres Over Time. The rate of drug release from the 40,000 Da PLGA system as a function of time. This profile represents the "influx" of drug to the human body.

Haloperidol has a concentration half-life in the human body of 21 hours (0.875 days).[8] The body's metabolic processes carry out this drug breakdown and we assume first-order decay kinetics. Therefore, the rate of haloperidol elimination from the body is given by $Z(t) = -k\,V\,C$, where k is a rate constant, V is the body's liquid volume (roughly 50 L for an average adult), and C is the instantaneous concentration of drug. The rate constant k can be calculated from a first-order decay function with a half-life of 0.875 days. C_i is initial concentration and t is time in days.

$$C = C_i\ \exp\left[-k\,t\right] \quad \Rightarrow \quad \ln\left(\frac{C}{C_i}\right) = -k\,t \qquad \text{(Equation 3.8)}$$

A half-life of 0.875 days gives a rate constant k = 0.792 days^{-1}. The rate of accumulation equals the rate at which material enters minus the rate at which material leaves.

$$V\frac{dC(t)}{dt} = F(t) - kVC(t) \qquad \text{(Equation 3.9)}$$

Recall V = 50 L, and $F(t)$ is found by differentiating the data in Figure 3.5, multiplied by the initial drug loading of 450 mg. We developed a short script on MATLAB to numerically integrate the concentration profile over a 40-day window. The script is given in Appendix B. The resulting concentration profile for our 40,000 Da microsphere system is shown below in Figure 3.6.

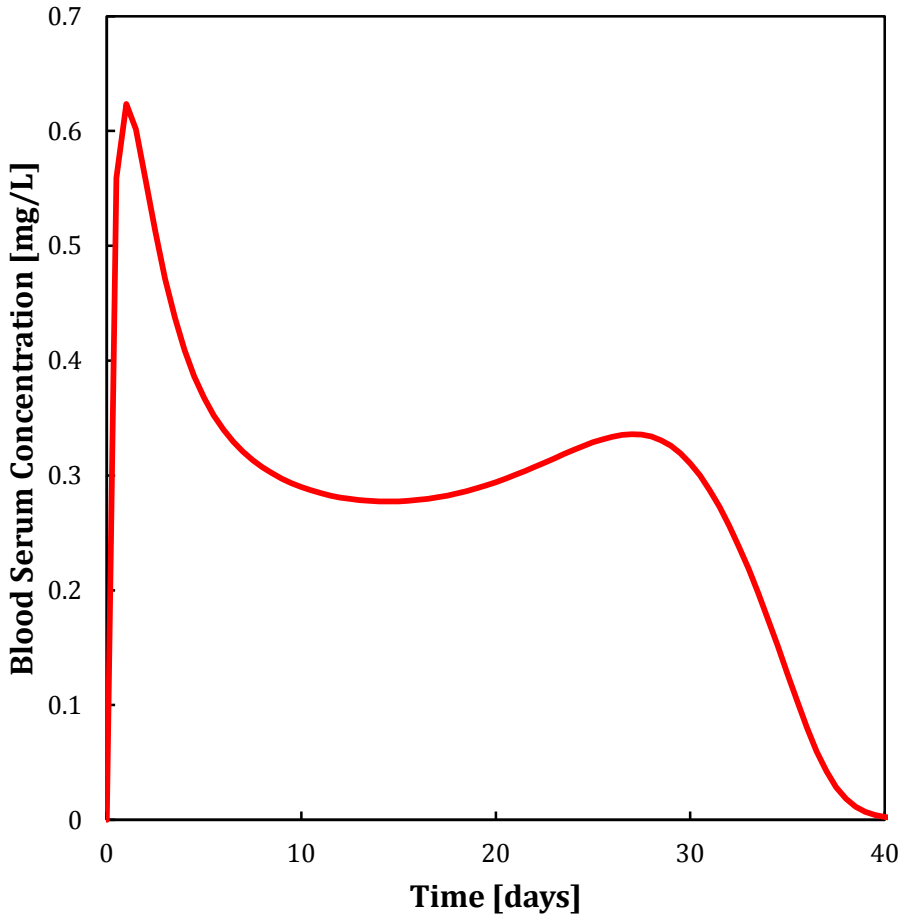

Figure 3.6. Blood Serum Concentration Over Time for 40,000 Da PLGA Microspheres. Blood serum concentration resulting from 40,000 Da polymer spheres, assuming a CSTR model for the human body.

The serum concentration profile can be divided into three phases: an initial burst phase lasting from days 0 to 3, a main phase from days 3 to 30, and a declining phase from days 30 to 36.

The main phase, which occupies the central time span of the release process, is characterized by a nearly constant serum concentration to within ±10% of an average value. This ±10% variation is acceptable, given that the therapeutic range for haloperidol blood serum concentration is 5 μg/L to 17 μg/L,[9] a window of over ±50% variation from the average value. Unfortunately, due to the shortcomings of the CSTR model for human physiology, the model dramatically overestimates the blood serum concentration for this system. The recommended therapeutic concentration of haloperidol in the blood serum is 10 μg/L (which can be achieved using a 15 mg/day oral dose).[7] However, the model predicts a main phase serum concentration of 300 μg/L, 30 times too large. A discrepancy of this size cannot simply be attributed to an overestimation of the initial drug loading, since we used a loading mass based on accepted oral dosing, and our intramuscular product should not deviate from the oral requirement by over an order of magnitude. As we mentioned at the beginning of the chapter, large quantitative errors are expected given that the human body is far more complicated than a CSTR. Still, we expect that the qualitative predictions of the serum level profile are useful. The stable concentration value throughout the main phase supports the product specification of constant treatment over a long period.

The burst phase occupies the large concentration spike near the start of release. Despite our efforts to reduce the initial burst by mixing particle sizes, the observed spike in blood concentration is unacceptably large: about twice the background main phase value. The therapeutic upper limit on haloperidol serum concentration is 17 μg/L, 70% above the optimal concentration.[9] An elevation of 100% seen in this burst phase is too high, and could cause a patient overdose. We address this problem by treating the product spheres in the production facility before shipment. In essence, we allow the first half-day of the release profile to happen in the production plant rather than in a patient's body. 6% of the total drug loading is then lost from the particles prior to shipment, but as we show later the elimination of the first half-day of the release profile reduces the burst intensity to just 20% higher serum concentration than the average value during the main phase of release.

The declining phase spans the final 6 days of release and shows gradually declining drug concentration. This gradual reduction is a highly attractive feature of the timed-release product. Patients can receive the next injection any time during the declining phase, since the body's drug content is not so high to risk an overdose with the next treatment, and also not so low that the patient is completely off medication until the very end of the 6-day declining phase.

3.3.2 Elimination of the First Half-Day of Release

Mixing small and large particles in the final product has already significantly reduced the magnitude of the burst phase. However, the reduced burst is still far too severe and effectively reaches a blood serum concentration of double the target value. A simple treatment of the PLGA spheres in-house largely eliminates the burst phase. As discussed in Chapter 6, the particles are treated after hardening so that the first 12 hours of the release profile occur in a tank in the processing facility. 6% of the total drug content, corresponding to the most intense part of the burst phase, is released and the product administered to a patient effectively begins its release profile at t = 0.5 days. It is illustrative to consider the release rate for an untreated product and a treated product side-by-side, as shown in Figure 3.7. The initial spike is much smaller for the treated sample.

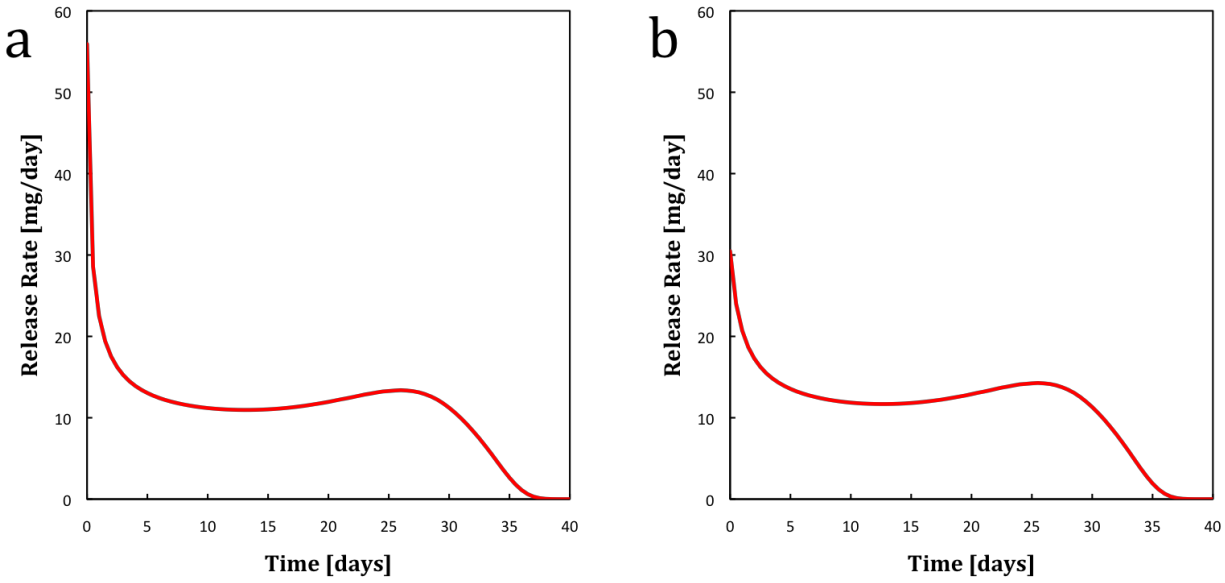

Figure 3.7. Treated versus Untreated Drug Release Profiles from 40,000 Da PLGA Microspheres. Drug release rate profiles for (a) untreated 40,000 Da PLGA spheres and (b) 40,000 Da PLGA spheres treated to allow the first 12 hours of release to occur in the processing plant. The initial drug release rate is reduced from 55 mg/day to 30 mg/day.

Following the mass balance procedure described earlier, the release rate profile for the treated 40,000 Da product in Figure 3.7b can be converted to a qualitative blood serum concentration report. The results are shown in Figure 3.8 below.

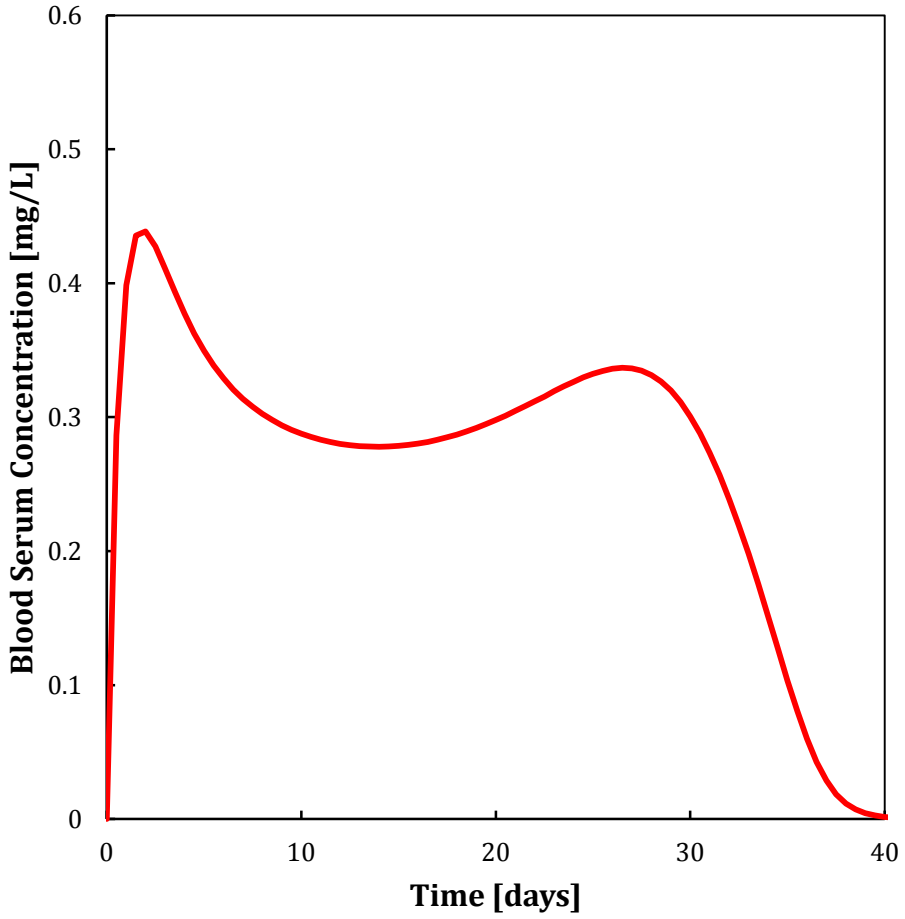

Figure 3.8. Blood Serum Concentration Over Time for Treated Microspheres. Blood serum concentration resulting from treated 40,000 Da polymer spheres, assuming a CSTR model for the human body. Elimination of the first 12 hours of the release profile reduces the magnitude of the initial burst to a peak serum concentration 35% higher than the average main phase concentration.

As shown in Figure 3.8, eliminating the first 12 hours of the release profile significantly reduces the initial burst. The peak serum concentration during the burst phase is now 40% higher than the average main phase concentration, while the peak concentration was 100% higher in the absence of treatment during processing. A burst of +35% above the target serum concentration is acceptable for a short time, as the allowable therapeutic window for haloperidol serum

concentration extends to +70% of the ideal value of 10 μg/L.[9] With this final product design, all customer requirements are fulfilled. We have developed a product capable of maintaining nearly constant drug levels in the body for one month, we have minimized the chance of an overdose by reducing the initial burst phase, and we have maintained a gradual taper-down of the drug concentration during the last 6 days of the particle lifetime to best accommodate the timing for subsequent injections.

3.4 Chapter 3 References

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Chapter 4: Optimization of Cross-Flow Membrane Emulsification

4.0 Chapter Introduction

With the product specifications completed in Chapter 3, we can now move on to the central process by which the poly(lactic-co-glycolic acid) (PLGA) polymer microspheres will be assembled. The technique we analyze is called "cross-flow membrane emulsification" (XME), and involves the formation of emulsified organic phase droplets in an aqueous medium. The process has been qualitatively described in Chapter 2, and the bulk of Chapter 4 will involve development of the necessary operating parameters for the assembly of the microparticle molecular weight and size options in Table 3.1.

As these necessary operating parameters are explored, we will begin to balance the competing demands of customer satisfaction and technical feasibility. Maximizing customer convenience tends to favor the high-molecular weight selections from Table 3.1, as these PLGA spheres have the longest effective lifetimes and therefore minimize the dosing frequency. However, we find that technical feasibility favors low-molecular weight alternatives. High molecular weight spheres with zero-order release also have small diameters, and harsh operating conditions (i.e. high flow rate of the aqueous "continuous phase") are required to achieve emulsion of very small droplets. Beyond a certain continuous phase flow velocity, the flow ceases to be laminar and the process breaks down. As we show during the course of the chapter, the optimal product selection is found by increasing polymer chain molecular weight (and therefore increasing customer convenience) until the process approaches the laminar/turbulent transition threshold at a Reynolds number of about 2000. This optimization specifies the product at 40,000 Dalton PLGA, with sphere diameters of 20 μm and 36 μm in a 5-to-1 mass ratio.

4.1 The Emulsification Model

Table 3.1 summarizes all possible choices for the product PLGA sphere sizes and polymer molecular weights. With these candidate product-specifications defined, Chapter 4 transitions to process-design and we begin application of the cross-flow membrane emulsification technique. Recall the qualitative picture of cross-flow membrane emulsification (XME) given in Chapter 2. Three papers, by Meyer (2010),[1] by Meyer and Crocker (2009),[2] and by Meyer, Rogers, McClendon, and Crocker (2010),[3] develop a powerful mathematical model to predict the size of emulsified droplets when exposed to cross-flow by an immiscible liquid phase. This section consists of an overview of the emulsification model.

4.1.1 The Dispersed Phase Liquid

Product polymer spheres are formed from a liquid material called the dispersed phase (DP), consisting of PLGA and haloperidol dissolved in a dichloromethane (DCM) solvent. The dispersed phase flows out of micro-scale circular orifices into high-velocity cross-flow of an immiscible liquid called the continuous phase. Surface tension pulls the slow-flowing dispersed phase into a bubble, temporarily attached to the formation pore, which undergoes shear stress exerted by the continuous phase. When the dispersed phase bubble grows large enough, shear force tears the DP droplet away from its pore source, generating an emulsified droplet.

We define the size of the dispersed phase droplet as the "wet diameter" or D_{wet}. Over the course of downstream processing, the dichloromethane solvent evaporates away, leaving behind a hard, dry sphere composed of 90 volume percent polymer and 10 volume percent haloperidol. We define the size of this dry sphere as the "dry diameter" or D_{dry}. The wet and dry diameters are related by the volume fraction of solid materials – PLGA and haloperidol – in the dispersed phase.

$$\left(\frac{D_{dry}}{D_{wet}}\right)^3 = dispersed\ phase\ solids\ fraction \qquad \text{(Equation 4.1)}$$

It is possible to control the composition of the dispersed phase by adding more or less polymer and haloperidol to the dichloromethane solvent, as long as PLGA and haloperidol remain in a 90% to 10% volume ratio. Meyer et al (2010) collect experimental at a maximum concentration of 10% solids by weight (close to 10% solids by volume), and indicate that very high polymer concentrations can be associated with increasingly non-Newtonian behavior. At the same time, process throughput is maximized with high solids concentrations. To ensure the applicability of the emulsification model but also ensure high throughput, we set the dispersed phase solids fraction at 10% by volume.

The densities of the dispersed phase components are: DCM = 1.33 g/mL, PLGA = 1.22 g/mL,[4] and haloperidol = 1.30 g/mL.[5] This information allows for the conversion of the solids volume fraction to a solids weight fraction. At 10% solid materials by volume (1% haloperidol by volume and 9% PLGA by volume, or 0.985% haloperidol by weight and 8.319% PLGA by weight), the dispersed phase density is 1.32 g/mL.

The addition of polymer to the dispersed phase causes the viscosity of the solution to increase. Viscosity varies with polymer concentration according to the well-established Huggins Equation.[6] We make the assumption that the small amount of haloperidol in solution does not significantly affect viscosity.

$$\frac{\eta_{sp}}{c} = [\eta] + k_H [\eta]^2 c \qquad \text{(Equation 4.2)}$$

Here, η_{sp} is the dimensionless specific viscosity of the solution (defined below). $[\eta]$ is intrinsic viscosity, an empirical constant for a given solvent-polymer system with units of dL/g. For dichloromethane and poly(lactic-co-glycolic acid), $[\eta]$ = 0.38 dL/g.[6] k_H is a dimensionless empirical constant. For dichloromethane and poly(lactic-co-glycolic acid), k_H = 0.32.[6] Finally, c is the concentration of polymer in solution with units of g/dL. The specific viscosity is defined as the fractional increase in viscosity when polymer is added.

$$\eta_{sp} \equiv \frac{\eta_{solution} - \eta_{solvent}}{\eta_{solvent}} \qquad \text{(Equation 4.3)}$$

The viscosity of pure DCM, $\eta_{solvent}$, is 0.0004 Pa-s. The viscosity of the dispersed phase with 10% solid materials by volume is 0.006 Pa-s.

4.1.2 The Continuous Phase Liquid

Dissolution of a small amount of poly(vinyl alcohol) (PVA) and dichloromethane into water forms the continuous phase (CP). PVA is an essential component of the XME process because these polymer chains adsorb onto emulsified dispersed phase droplets, acting as a surfactant to prevent coalescence downstream. The continuous phase is saturated at 13 grams DCM per liter of water to prevent DCM from the dispersed phase from bleeding out into the continuous phase during emulsification. This loss of DCM by the dispersed phase would cause emulsified droplets to have a higher concentration of PLGA and haloperidol than the dispersed phase feedstock, and it would be difficult to predict the dry particle size with Equation 4.1. Addition of polymer increases the viscosity of the continuous phase. This study uses the same continuous phase formulation as Meyer and colleagues (2009 and 2010): 1% PVA by weight in water and DCM for a viscosity of 0.0014 Pa-s. The density of PVA is approximately 1.27 g/mL.[7] The density of DCM is 1.33 g/mL, so the density of the continuous phase is 1.007 g/mL, very close to that of pure water.

Meyer et al. (2010) demonstrate that the interfacial tension γ between the continuous phase and the dispersed phase varies as a function of the frequency of droplet formation.[3] However, they find that minimal error in droplet size calculations is incurred by assuming that interfacial tension is constant. We use an experimental average interfacial tension for the system $\gamma = 8$ mN/m. Note that the performance of the polymer sphere product is a very sensitive function of particle size, and it is possible that small errors in the assumed interfacial tension will significantly affect the wet droplet diameter. If so, an advantage of the XME process is that the continuous phase flow rate can always be fine-tuned to compensate for inaccuracies in our assumption of $\gamma = 8$ mN/m. During small-scale testing and plant startup, operators would check to ensure that the proper droplet size was being generated. If any deviation were observed, the CP flow rate would be adjusted accordingly and the new, corrected CP flow rate would be maintained for the entire process.

4.1.3 Definitions of Dimensionless Quantities

The wet droplet size is calculated as a function of several dimensionless quantities. These are defined and explained below.

First, the Weber number is the ratio of inertial effects to surface tension effects in the dispersed phase. Here, ρ_{DP} is the density of the dispersed phase, Q_{DP} is the volumetric flow rate of the dispersed phase through a single pore, D_0 is the pore diameter, and γ is the interfacial tension for the chosen dispersed phase and continuous phase. Importantly, the Weber number must remain below 1.0 in order to maintain control over the process and avoid the production of small "satellite" droplets. At high Weber number, the dispersed phase flow through a pore is so rapid that the liquid chaotically "jets" as a high-velocity stream and uniformly sized droplets do not form.

$$We \equiv \frac{\rho_{DP} Q_{DP}^2}{D_0^3 \gamma} \qquad \text{(Equation 4.4)}$$

Second, the capillary number is the ratio of drag forces and interfacial tension forces acting on the forming emulsion droplet. dv/dz is the shear rate of the continuous phase flow through the channel, evaluated at the channel floor. Shear rate is a function of continuous phase viscosity, continuous phase flow rate, and channel dimensions. It is evaluated for a given channel geometry and flow condition using the computation fluid mechanics routine in the COMSOL software package (discussed in the next section). η_{CP} is the dynamic viscosity of the continuous phase.

$$Ca \equiv \frac{\eta_{CP} \frac{dv}{dz} D_0}{\gamma} \qquad \text{(Equation 4.5)}$$

Third, the Ohnesorge number is the ratio of viscous and capillary time scales, in this case considered for the continuous phase. ρ_{CP} is the density of the continuous phase.

$$Oh \equiv \frac{\eta_{CP}}{\sqrt{\rho_{CP}\ D_0\ \gamma}} \qquad \text{(Equation 4.6)}$$

There exist two characteristic Reynolds numbers for this flow geometry. The Reynolds number is the ratio of inertial forces to viscous forces, considered for the continuous phase. First is a Reynolds number to characterize bulk flow through the XME channel. Here, u is the superficial velocity of continuous phase flow through the channel and L is the characteristic length of the channel. Since the channel will be much wider than it is high, the characteristic length L is equal to the channel height. The process requires that the channel Reynolds number remains below 2000, to ensure laminar flow and parallel streamlines.

$$Re_{channel} \equiv \frac{\rho_{CP}\ u\ L}{\eta_{CP}} \qquad \text{(Equation 4.7)}$$

Second is the Reynolds number to characterize continuous phase flow around a forming spherical droplet. This droplet Reynolds number is only important at the moment of snap-off, so it is evaluated with a characteristic length equal to the final wet droplet diameter.

$$Re_{drop} \equiv \frac{\rho_{CP}\ u\ D_{wet}}{\eta_{CP}} \qquad \text{(Equation 4.8)}$$

The viscosity ratio of the dispersed phase to the continuous phase carries important information. Both of these viscosities are functions of the respective liquid compositions, as discussed earlier. Assuming that the dispersed phase is 10% polymer and haloperidol by volume the viscosity ratio equals 4.3.

$$\lambda \equiv \frac{\eta_{DP}}{\eta_{CP}} \qquad \text{(Equation 4.9)}$$

Finally, we evaluate the drag coefficient for flow past a sphere.

$$C_d = \frac{\left[\lambda\left(\frac{24}{Re_{drop}} + \frac{4}{Re_{drop}^{1/3}}\right) + \frac{14.9}{Re_{drop}^{0.78}}\right] Re_{drop}^2 + 40\,\frac{3\lambda+2}{Re_{drop}} + 15\,\lambda + 10}{(1+\lambda)\left(5 + Re_{drop}^2\right)} \qquad \text{(Equation 4.10)}$$

4.1.4 Modeling the Emulsification Process

The wet diameter of an emulsified droplet generated by cross-flow membrane emulsification is given by the following model equation. The droplet size equation is derived from a force balance on the forming droplet at the narrow "neck" just above the pore.[2]

$$\frac{D_{wet}}{D_0} = 0.8\left(\frac{3\,2}{C_d}\right)^{1/4} Oh_{CP}^{1/2}\; Ca^{-1/2} \qquad \text{(Equation 4.11)}$$

4.1.5 Simplification: Limiting Operating Parameters

The process-optimization goal is now is to find the set of operating parameters γ (interfacial tension), η_{CP} (continuous phase viscosity), η_{DP} (dispersed phase viscosity), ρ_{CP} (continuous phase density), ρ_{DP} (dispersed phase density), u_{CP} (continuous phase superficial velocity), Q_{DP} (dispersed phase flow rate per pore), L (channel height), and D_0 (pore diameter) that give each of the desired dry diameters listed in Table 3.1. These 9 parameters are the only ones that we can manipulate directly. Consulting Equations 4.1 through 4.11, there are many sets of these 9 parameters that can give a desired dry diameter. The problem simplifies greatly by placing some limits on these parameters.

Five of the operating parameters are fixed by choices and assumptions we've already made. We assume that interfacial tension is a constant for the mostly water and dichloromethane system, given by Meyer et al (2010) as 8.0 mN/m. This study considers a solution of 1.00 weight percent PVA and 1.27 weight percent DCM in water for the continuous phase, so η_{CP} = 0.0014 Pa-s and ρ_{CP} = 1.007 g/mL. Next, using highly concentrated dispersed phase maximizes process throughput. The generation rate of polymer spheres is equal to dispersed phase flow rate per pore times the number of pores times the fraction of solid materials in the dispersed phase. So, the maximum allowed solids

percent, 10% by volume, optimizes throughput. This solids fraction gives a dispersed phase viscosity of η_{DP} = 0.006 Pa-s and a density of ρ_{DP} = 1.32 g/mL.

Large-diameter emulsification pores will allow the dispersed phase flow rate to increase without violating the restriction that Weber number remains less than 1. However, Pore size D_0 cannot be arbitrarily large because the pore must remain somewhat smaller than the droplet forming out of it. The cross-flow membrane emulsification process relies on a relatively large dispersed phase droplet being held to it's formation pore by a narrow "neck" of fluid, and rupture of this neck occurs at a critical droplet size. The mathematics in Equation 4.11 do not set an explicit lower bound on D_{wet} / D_0, but some physical intuition gives an estimate on the required pore size. The smallest possible droplet size that can form from a column of liquid is dictated by the Rayleigh instability phenomenon.[8] According to Rayleigh instability, a flowing column of liquid develops surface capillary waves due to a thermodynamic drive to minimize surface area. These waves break the liquid stream down into individual droplets, whose diameters have been experimentally shown to be 1.91 times the diameter of the undisturbed liquid column.[9] In our system, the liquid column consists of dispersed phase flowing into the continuous phase medium, and the fluid column's diameter is equal to the diameter of the pore from which is emerges. Cross-flow membrane emulsification can never produce droplets smaller than this limiting case, so the wet diameter divided by the pore diameter must be greater than 1.91. We require a 25% margin above this lower limit, and establish the relationship D_{wet} / D_0 = 2.4. Since D_{wet} is a function of the target particle dry diameter (Equation 2.8), D_0 is now also a function of the dry particle size.

In order to maximize process throughput, it is critical that the dispersed phase flow rate remain fairly high. The emulsification model (Equation 4.11) indicates that Q_{DP} does not affect droplet size. The process is, however, limited by the critical Weber number of 1.0 where the dispersed phase flow transitions to jetting behavior and monodisperse droplet production is lost. We impose a significant margin below this critical limit, and therefore require that the Weber number remain significantly below the limit at 0.7. Once this assignment is made, Q_{DP} becomes a function of pore diameter, interfacial tension, and the dispersed phase composition.

Finally, we specify the channel height L. Lowering the channel height increases shear rate at the channel floor for any given continuous phase flow rate, because confining liquid flow to a

narrow channel increases superficial velocity. The emulsification process generally requires very high shear rates inside of the flow channel, since the target particle sizes in Table 3.1 are extremely small and high-shear conditions are needed to generate small droplets. However, the channel cannot become so narrow that the channel dimension approaches the wet diameter of the emulsified droplets. The continuous phase flow profile inside of the channel is approximately parabolic in the vertical axis, yet the emulsification model assumes that the shear rate (the rate of velocity change along the vertical axis) is constant across the entire face of a dispersed phase droplet. This assumption is valid only as long as the droplet is not so large that it extends into the curved portions of the velocity profile parabola. See Figure 4.1 for a schematic representation.

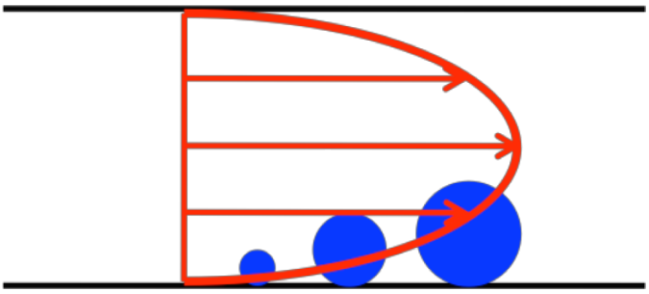

Figure 4.1. Representation of the parabolic velocity profile along the vertical axis of a flow channel. The rate of increase in fluid velocity along the vertical coordinate (shear rate) is approximately constant near the channel floor. Droplets of various sizes extend upwards from the channel floor. If the droplet's size is large compared to the channel height, the top of the droplet will extend into the curved contour of the velocity profile, where the shear rate is no longer spatially constant.

An optimal channel height is about L = 0.5 mm (500 μm). This channel is narrow enough that we can achieve the necessary shear rates for the process without excessively high flow rates, yet the channel height is an order of magnitude larger than the target emulsified droplet diameters, ensuring that the assumption of constant shear rate remains valid. It is logistically helpful to machine all channels with the same height regardless of whether they are intended to produce large particles

or small particles for the size mixture, because uniformity makes maintenance and replacement of parts much easier.

There is now only one unspecified operating parameter: continuous phase flow velocity. We leave this parameter as our independent variable, which is manipulated to tune Equation 2.11 in order to generate any necessary droplet size. The continuous phase flow rate affects both the capillary number (via the shear rate) and the drag coefficient (via the droplet Reynolds number).

4.2 Channel Operation and Throughput

A cross-flow membrane emulsification channel has nine independent operating parameters: interfacial tension, continuous phase viscosity, dispersed phase viscosity, continuous phase density, dispersed phase density, continuous phase superficial velocity, dispersed phase flow rate per pore, channel height, and pore diameter. These operating variables interact to produce secondary effects, like shear rate at the channel floor and drag coefficient at a forming droplet, but we cannot manipulate these secondary effects directly. In Chapter 4.1, we made some design selections based on a physical understanding of our system and locked in eight of these independent parameters. For a given target dry diameter for a PLGA sphere, all operating parameters except continuous phase flow rate are defined and unchangeable. To review this selection, Table 4.1 lists the specified values for each parameter.

	Operating Parameter	Value	Notes
1	Interfacial Tension	0.008 N/m	
2	Dispersed Phase Viscosity	0.006 Pa-s	10 vol% solids (PLGA and haloperidol)
3	Dispersed Phase Density	1.32 g/mL	10 vol% solids (PLGA and haloperidol)
4	Continuous Phase Viscosity	0.0014 Pa-s	1 wt% PVA 1.27 wt% DCM in water
5	Continuous Phase Density	1.007 g/mL	1 wt% PVA 1.27 wt% DCM in water
6	Pore Diameter	D_{wet} / 2.4	Limited by Rayleigh instability
7	Dispersed Phase Flow Rate (Per Pore)	$(0.5\ D_0^3 \gamma\ /\ \rho_{DP})^{1/2}$	Limited by the Weber number
8	Channel Height	0.5 mm	
9	Continuous Phase Superficial Velocity	[unspecified]	This parameter is left free

Table 4.1. Summary of operating parameter specifications.

D_{wet} represents the diameter of an emulsified droplet prior to drying, which is set by the target dry particle diameter by Equation 2.1 and our choice of a dispersed phase concentration of 10% solid materials (PLGA and haloperidol) by volume. D_0 is the pore diameter. γ is the interfacial tension between the continuous phase and the dispersed phase, 8 mN/m. ρ_{DP} is the density of the

dispersed phase, 1.32 g/mL. Superficial velocity is defined as volumetric flow rate divided by cross-sectional area of flow.

There are two objectives for Chapter 4.2. First, we calculate the dispersed phase throughput per pore for each of the molecular weight selections outlined in Table 2.1. This throughput will enable a calculation of the required number of pores in order to meet the production goal of 500,000 patient doses per year. Second, we apply the computational fluid mechanics (CFD) package contained in COMSOL Multiphysics in order to determine the value of continuous phase flow rate that will generate the required shear rates for the process.

4.2.1 COMSOL Multiphysics

This part of the study makes use of the computational fluid mechanics package with the COMSOL Multiphysics suite. COMSOL was developed from codes used by the Royal Institute of Technology (KTH) in Stockholm, Sweden. This software allows a user to predict flow characteristics for specified fluid properties and flow geometry. Numerical values of fluid shear rate along the floor of simulated channel geometry are especially important.

4.2.2 Pore Throughput

Each initial PLGA chain molecular weight option has two dry particle sizes associated with it, as described in Table 3.1. The small particles and large particles are mixed in the final product in a 5-to-1 mass ratio (equivalent to a volume ratio because the densities of the two particles are identical) in order to generate a zero-order drug release profile. Since the dispersed phase solutions consist of 10% PLGA and haloperidol by volume, the wet diameter of the corresponding emulsified droplet is given by $D_{wet} = (0.1)^{1/3} D_{dry} = 0.464 D_{dry}$. Furthermore, Table 4.2 relates the pore diameter to the wet diameter by the relation $D_0 = D_{wet} / 2.4 = 0.417 D_{wet}$. We can therefore calculate the required pore size for any given dry particle size. Finally, since interfacial tension γ and dispersed phase density ρ_{DP} are known constants, the maximum dispersed phase flow rate Q_{DP} per pore can be calculated so that the Weber equals 0.7.

PLGA MW	Size Type	D_{dry}	D_{wet}	D_0	Q_{DP} (per pore)
10,000 Da	Small Particle	32 μm	68.9 μm	28.7 μm	1.14 mL/hr
	Large Particle	52 μm	112.0 μm	46.7 μm	2.37 mL/hr
20,000 Da	Small Particle	26 μm	56.0 μm	23.3 μm	0.83 mL/hr
	Large Particle	40 μm	86.2 μm	35.9 μm	1.59 mL/hr
30,000 Da	Small Particle	24 μm	51.7 μm	21.5 μm	0.74 mL/hr
	Large Particle	36 μm	77.6 μm	32.3 μm	1.41 mL/hr
40,000 Da	Small Particle	20 μm	43.1 μm	18.0 μm	0.58 mL/hr
	Large Particle	36 μm	77.6 μm	32.3 μm	1.41 mL/hr
50,000 Da	Small Particle	16 μm	34.5 μm	14.4 μm	0.41 mL/hr
	Large Particle	30 μm	64.6 μm	26.9 μm	1.03 mL/hr
60,000 Da	Small Particle	14 μm	30.2 μm	12.6 μm	0.33 mL/hr
	Large Particle	30 μm	64.6 μm	26.9 μm	1.03 mL/hr
70,000 Da	Small Particle	14 μm	30.2 μm	12.6 μm	0.33 mL/hr
	Large Particle	28 μm	60.3 μm	25.1 μm	0.93 mL/hr

Table 4.2. Pore and Particle Specifications for Various PLGA Molecular Weights. Dry particle diameter, wet droplet diameter, pore diameter, and maximum allowed dispersed phase flow rate per pore, for a selection of molecular weight options. The dry diameters are chosen so that a 5-to-1 mixture by weight of small-to-large sizes gives a zero-order release profile. The wet diameter is linked to the dry diameter by the choice of 10% solids by volume in the dispersed phase. The pore diameter is linked to the wet diameter by the Rayleigh instability limit. The flow rate is linked to the pore diameter by the Weber number.

Given the above values of maximum dispersed phase flow rate, we calculate the required number of pores to reach the production goal of 500,000 one-month patient doses per year. For the purposes of this study, a patient dose of drug is defined as the amount of drug required to treat a

patient for 30 days. 30 days is roughly the target lifetime of a timed-release depo-haloperidol treatment, so we use this value to estimate the dosing period. A typical patient under haloperidol treatment receives about 15 mg of drug per day orally, or 450 mg per 30 days.[10] Note, as described in later chapters and in Chapter 3.3, the PLGA spheres are treated post-generation to mitigate the initial burst of drug. This treatment removes 6% of the initial haloperidol loading. The bioavailability of haloperidol delivered intramuscularly (as is the case with our product) is higher than the bioavailability of haloperidol delivered orally.[11] So, our final product should contain somewhat less drug than the ordinary monthly oral dose, but the specific dose for our novel delivery method cannot be determined without clinical testing. So for simplicity we assume that the product prior to treatment contains 450 mg of haloperidol, and that removal of 6% of the drug loading during post-processing gives roughly the desired final content, 423 mg of haloperidol. Therefore, the total annual mass of haloperidol throughput for the process is still 450 mg/dose, or:

(500,000 doses/yr) * (450 mg/dose) * (1 kg / 1,000,000 mg) = 225 kg/yr

The product depo-haloperidol spheres contain 10% haloperidol by volume (10.59% haloperidol by weight) so the total annual production requirement of dry spheres is 2,124.6 kg. Lastly, the dispersed phase is 10% haloperidol and PLGA by volume (9.30% by weight). Therefore, the total annual throughput of dispersed phase is 22,845.2 kg = 17,307.0 L.

We choose an operating time of 90 days per year, at 24 hours per day. This choice of a timetable is elaborated in later chapters. In short, the sphere-production process has a very small annual throughput requirement and it is convenient to increase production rate over a small interval rather than operate at low productivity throughout the entire year. Furthermore, operation at one quarter out of the year allows processing equipment to be used for multiple projects each year.

Each molecular weight option requires two distinct dry particle sizes mixed in a mass ratio of 5 parts small particles to 1 part large particles, equivalent to 5 mass-parts of dispersed phase throughput for small particles for every 1 part for large particles. By volume 14,422.5 L of dispersed phase pass through small pores to become small droplets while 2,884.5 L of dispersed phase pass through large pores to become large droplets, per year. Given the dispersed phase flow rates in Table 4.2, it is possible to calculate the required number of pores.

Calculated values for number of required pores are reported in Table 4.3 for each molecular weight selection. As the pore requirement becomes larger, so will the number of channels, the amount of plant-space, and the cost of operating equipment. However, recall from Chapter 3 that high-molecular weight spheres have longer lifetimes in a patient's body and are more desirable due to less frequent injections. To help consider these two competing design concerns, Table 4.3 also includes particle lifetime.

PLGA MW	Particle Lifetime	Size Type	Number of Pores (total for entire process)
10,000 Da	18 days	Small Particle	5,858
		Large Particle	564
20,000 Da	26 days	Small Particle	8,045
		Large Particle	840
30,000 Da	31 days	Small Particle	9,024
		Large Particle	948
40,000 Da	36 days	Small Particle	11,513
		Large Particle	948
50,000 Da	39 days	Small Particle	16,286
		Large Particle	1,297
60,000 Da	40 days	Small Particle	20,234
		Large Particle	1,297
70,000 Da	41 days	Small Particle	20,234
		Large Particle	1,437

Table 4.3. Particle, Droplet, and Pore Diameters, with Pore Throughput. Required number of pores for a selection of molecular weight options. For reference, the expected lifetimes of the polymer sphere release profiles are included from Table 3.1.

It is worth briefly mentioning that the small and large emulsified droplets will be generated in separate channels. Separating the process makes it easier to control the dispersed phase flow rates through differently sized pores, and will enable technicians to screen for droplets outside of a narrow target size tolerance for quality control. We elaborate the channel arrangements in Chapter 4, but for now it is sufficient to visualize two separate emulsification processes in parallel: one to produce small particles and one to produce large particles, with particle mixing in the appropriate 5-to-1 mass ratio occurring just prior to packaging.

4.2.3 Continuous Phase Flow Rate

In order to generate extremely small dry diameters, flow channels must emulsify droplets with extremely small wet diameters. We have so far constrained all available operating parameters for the channel except for the continuous phase superficial velocity u. We increase the fluid velocity to magnify shear stress acting on dispersed phase droplets forming at the channel floor, thereby generating smaller emulsified droplets. However, at very high continuous phase flow the process transitions into a turbulent flow regime at which the emulsification model (Equation 4.11) might no longer apply. At high continuous phase flow, the process also generates much more waste PVA and DCM, which must be disposed of.

To determine the continuous phase superficial velocity necessary for each target particle size, we apply the computational fluid mechanics package available with COMSOL Multiphysics. The flow channel is modeled as a rectangular prism of water with viscosity modified to 0.0014 Pa-s, obeying the no-slip boundary condition (zero flow velocity) at each of the four faces that would be in contact with the channel walls, and assuming plug-flow at the inlet. The dimensions of the simulated channel are: 0.5 mm high, 6 cm wide, and 10 cm long. We find that the specified channel width has no effect on shear rate as long as channel width is much greater than channel height. Similarly, channel length has no effect on shear rate except in a short developing-flow region extending about 1 cm from the channel inlet and a disturbance region about 1 cm from the outlet. Because flow completely develops within 1 cm of the channel inlet, we incur minimal error in the trailing 9 cm of the channel by assuming inlet plug flow. The model channel is shown in Figure 4.2, along with a sample floor shear rate profile corresponding to inlet plug flow of 1 m/s.

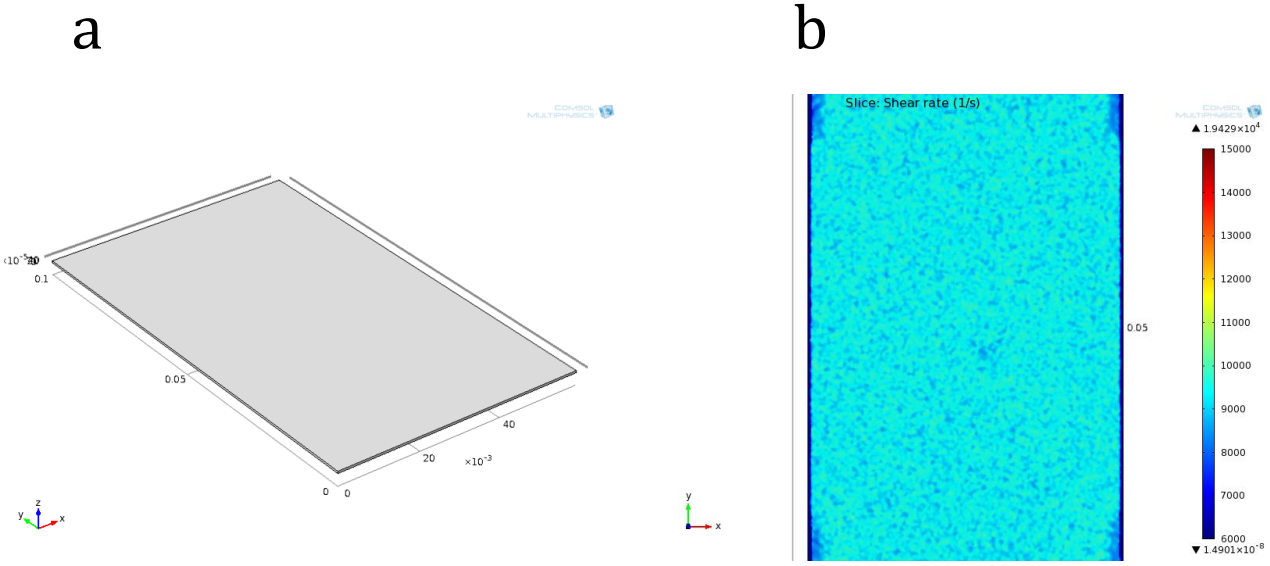

Figure 4.2. COMSOL Simulation of Droplet-Formation Region. (a) Schematic of the COMSOL simulation for the droplet-formation region of the flow channel. Channel dimensions are 0.5 mm high by 6 cm wide by 10 cm long. (b) The shear-rate map of the channel floor, with 1.007 g/mL density, 0.0014 Pa-s viscosity fluid moving at superficial velocity of 1 m/s from the bottom of the figure towards the top. The dark blue bands on either side of the shear rate map represent regions of low-shear flow, and are both about 1 mm wide through most of the channel.

This simulation was repeated for a number of continuous phase flow velocities, and the average shear rate at the channel floor was recorded for each test. The results in Figure 4.3 show a linear relationship between flow velocity and shear rate over a wide flow range.

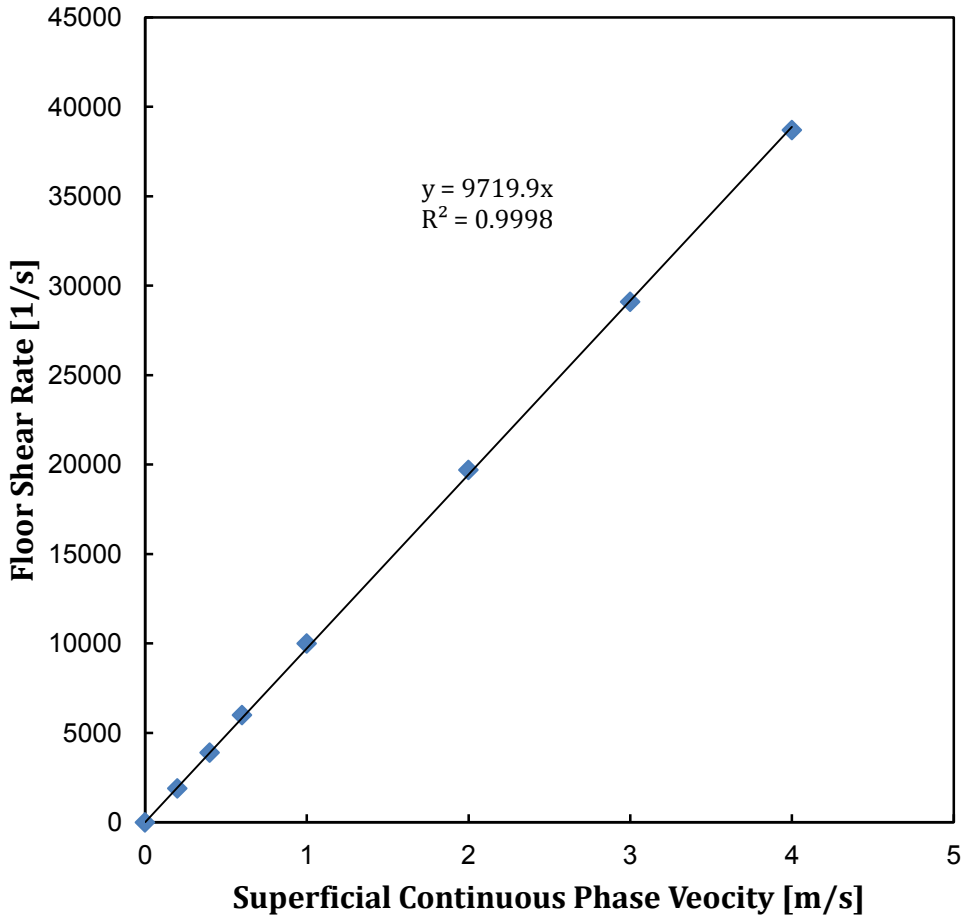

Figure 4.3. Average Shear Rate at Channel Floor vs. Continuous Phase Velocity. Average shear rate at the channel floor as a function of continuous phase velocity. Values collected for a 0.5 mm high, 6 cm wide channel containing laminar flow of a density ρ = 1.007 g/mL, viscosity η = 0.0014 Pa-s, liquid.

We now have a relationship between channel floor shear rate and the continuous phase flow velocity for our choice of continuous phase properties and channel height, dv/dz = 9719.9 u. With this relationship, and the values for the remaining 8 operating parameters given in Table 4.1, the combined mathematics in Equations 4.1 through 4.11 reduce to a single expression (albeit a very complicated one) including only D_{dry} and u.

$$\frac{2.4}{0.8} = \left(\frac{32\,(1+4.3)\left(5+\left[1.539\,u\,D_{dry}\right]^2\right)}{\left[4.3\left(\frac{24}{1.539\,u\,D_{dry}}+\frac{4}{\left[1.539\,u\,D_{dry}\right]^{1/3}}\right)+\frac{14.9}{\left[1.539\,u\,D_{dry}\right]^{0.78}}\right]\left(1.539\,u\,D_{dry}\right)^2+40\frac{3(4.3)+2}{\left(1.539\,u\,D_{dry}\right)^2}+15(4.3)+10} \right)^{1/4} \left(\frac{0.4887}{\sqrt{D_{dry}}}\right)^{1/2} \left(0.001745\,u\,D_{dry}\right)^{-1/2}$$

(Equation 4.12)

This equation has been set up with the appropriate conversion factors so that D_{dry} has units of micrometers and u has units of meters per second. The input parameters are all specified in Table 4.1. For each choice of dry diameter from Table 3.1, we substitute the dry diameter into Equation 2.19 and use a computer algebra system to solve for continuous phase flow rate u. These tabulated flow velocities are reported in Table 4.4. The required flow velocity is independent of channel width (as long as the channel width is much greater than the height). We use a channel width of 10 cm as a test case, and report the corresponding continuous phase volumetric flow rate *per channel* for each superficial flow velocity.

PLGA MW	Size Type	D_{dry}	u	$Re_{channel}$	Q_{CP} (10 cm width)
10,000 Da	Small Particle	32 µm	1.07 m/s	762	53.5 mL/s
	Large Particle	52 µm	0.47 m/s	333	23.5 mL/s
20,000 Da	Small Particle	26 µm	1.57 m/s	1119	78.5 mL/s
	Large Particle	40 µm	0.73 m/s	524	36.5 mL/s
30,000 Da	Small Particle	24 µm	1.73 m/s	1238	86.5 mL/s
	Large Particle	36 µm	0.90 m/s	643	45.0 mL/s
40,000 Da	Small Particle	20 µm	2.40 m/s	1714	120.0 mL/s
	Large Particle	36 µm	0.90 m/s	643	45.0 mL/s
50,000 Da	Small Particle	16 µm	3.50 m/s	2500	175.0 mL/s
	Large Particle	30 µm	1.20 m/s	857	60.0 mL/hr
60,000 Da	Small Particle	14 µm	4.40 m/s	3143	220.0 mL/s
	Large Particle	30 µm	1.20 m/s	857	60.0 mL/hr
70,000 Da	Small Particle	14 µm	4.40 m/s	3143	220.0 mL/s
	Large Particle	28 µm	1.37 m/s	976	68.5 mL/s

Table 4.4. Required Flow Conditions. Required continuous phase flow conditions for each molecular weight option. At or above 50,000 Da polymer, the required flow rate is so high that the flow characteristics are no longer laminar. These conditions are shaded red.

4.2.4 Project Recommendation

We now have all of the information necessary to arrive at the final product specification. Based on the channel Reynolds number calculations in Table 4.4, the process cannot manufacture particles with molecular weight equal to or above 50,000 Da without reconfiguration. These particles have such small target diameters that the process must operate under extremely high continuous phase flow and shear conditions, to the point where flow through the channel is no longer laminar. When flow starts to become turbulent, the movement of the continuous phase through the channel becomes chaotic and we lose predictable control over the emulsification process.

It is theoretically possible to reduce the Reynolds numbers for these high-molecular weight conditions by decreasing the channel height, increasing the continuous phase viscosity, or decreasing the continuous phase density, but none of these options are practical. We hesitate to lower the channel height any further, due to issues that arise if the channel height and wet droplet size are on the same order of magnitude (recall Chapter 4.1). Increasing the continuous phase viscosity requires the dissolution of additional poly(vinyl alcohol), but a highly viscous fluid is difficult to pump through the process and excess PVA could deposit in some of the process equipment and be difficult to clean out. Finally, the continuous phase density cannot be reduced without finding a new solvent other than water. However, it would be challenging to find a liquid with low density in which the solubility of DCM and haloperidol is low enough to allow emulsification.

Viable PLGA molecular weights are then 40,000 Da and below. We choose 40,000 Da polymer for the product spheres because this weight maximizes the customer requirement for long particle lifetime, while still remaining practical from a processing standpoint.

4.3 Membrane Pore Spacing

In the previous section, we compared process throughput, process operating parameters, and product sphere lifetime for a number of initial polymer chain molecular weights. By balancing these design factors, we selected 40,000 Dalton polymer as the optimal product material. Spheres manufactured from 40,000 Da material show drug release profiles lasting a full 36 days (slightly better than the target lifetime of 1 month). We treat the particles prior to shipment in order to eliminate initial any drug burst, which reduces the effective lifetime to 34 days, where the last 6 days of release comprise a gradually declining release rate as detailed in Chapter 3.3. This product requires a total of 13,264 pores operating simultaneously for 90 days per year at 24 hours per day to meet the production goal of 500,000 patient doses.

The next step is to design a close-packed arrangement of pores for the channel membranes. This packing arrangement dictates the number of pores in each channel, and therefore the number of channels that the process requires. The required channel count is an important startup cost. To arrive at a pore spacing arrangement, we look at the flow disturbances around a forming droplet using COMSOL and introduce the concept of critical shear.

4.3.1 Pore Array Scales

To begin, we select the width of the cross-flow membrane emulsification channels to be 10 cm. This value is large enough that we satisfy the important requirement that channel height be much less than channel width, but it is not so large to prevent a manufacturer from machining precise fits between parts of the channel.

An effective pore-spacing geometry is to arrange pores in diagonal lines relative to the direction of continuous phase flow. See Figure 4.4 for a schematic representation. In this diagram, we define "offset" as the lateral gap between a pore and its closest downstream neighbor. We define "pitch" as the spacing between a pore and its nearest neighbor.

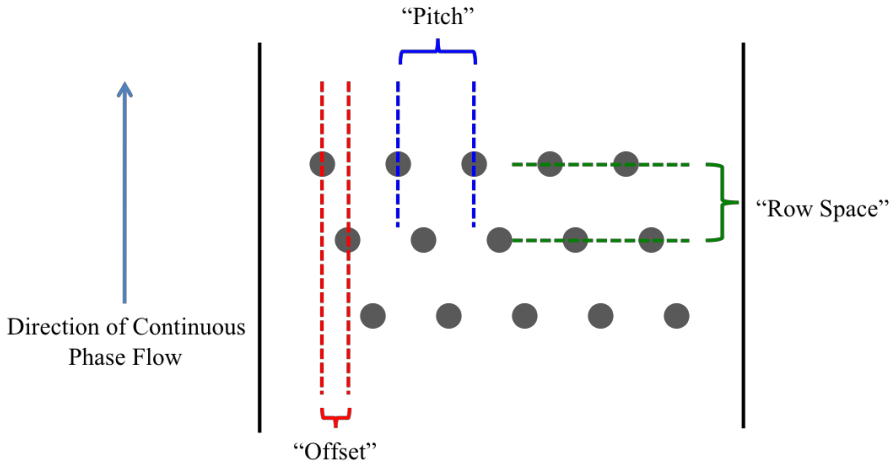

Figure 4.4. Generalized Schematic of Pore Spacing in a Channel Membrane. A diagonal arrangement allows many pores to be confined into a small area of the channel floor, without releasing droplets that will hit and disrupt a downstream pore.

4.3.2 Maximum Pore Packing Density

The maximum number of pores can be arranged into a 10 cm wide channel by minimizing pitch and offset. The offset distance must be at least as large as the diameter of the emulsified droplets formed in the channel. When an upstream droplet is pulled away from its formation pore and begins to move along the direction of continuous phase flow, it can collide with a forming droplet downstream if offset is too small. A collision would prematurely tear the downstream droplet away from its pore, producing a droplet smaller than the target diameter. For 40,000 Da polymer material, the process generates two sizes of droplets with wet diameters 43.1 μm and 77.6 μm (recall Table 4.2). Therefore, a minimum offset of 45 μm is selected for small-droplet channels and a minimum offset of 80 μm is selected for large-droplet channels.

The pitch of the pore array is dictated by continuous phase flow disturbances around a droplet still attached to its pore. In computational simulations, we observe fluctuations in the shear rate along the channel floor in the region immediately surrounding a spherical obstruction like our dispersed phase droplets. See Figure 2.8 for detailed simulations of the shear rate around 43.1 μm droplets under 2.4 m/s continuous phase flow and around 77.6 μm droplets under 0.9 m/s continuous phase flow. These are the flow conditions for our target droplets (recall Table 4.4), and

the dimensions of the wet droplet diameters. The maximum droplet size while still attached to a pore is the wet droplet diameter, and we consider this size because the wake disturbance will be the largest and we must plan for the worst-case scenario.

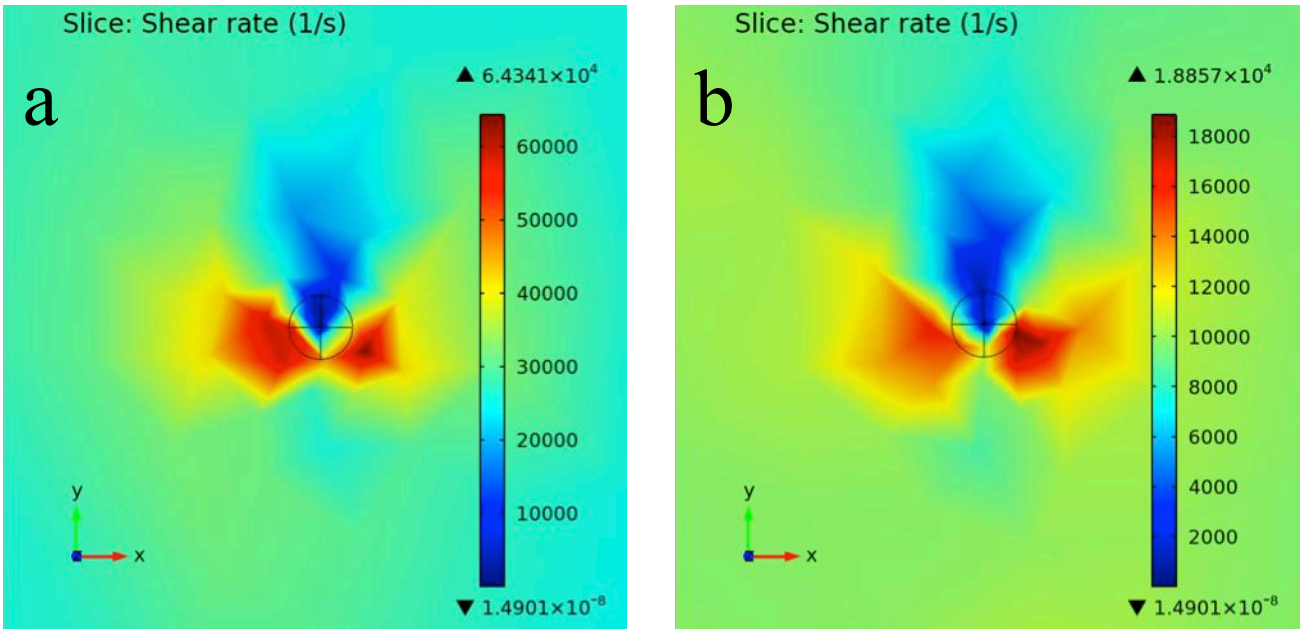

Figure 4.5. Shear rate disturbances around a forming droplet, at the droplet's maximum size. (a) "Small" 43.1 μm droplet, under 2.4 m/s continuous phase flow, (b) "Large" 77.6 μm droplet, under 0.9 m/s continuous phase flow. Droplets are shown by the wire mesh at the figure's center. Continuous phase flow moves from the bottom of the figure towards the top.

From Figure 4.5, we can see two plumes of high-shear rate flow just upstream and to the sides of the droplet obstructions, and a wake of low-shear rate flow downstream of the droplets. These characteristic disturbances sweep out an area measuring about 7 times the droplet diameter in both cases, before dying down to the ambient shear rate value further away. The primary concern with these local flow disturbances is that, if two pores are positioned too close to one another, the flow disturbance around one droplet could exert hydrodynamic stress on its neighbor. We then lose control over the shear rate acting on the affected droplet and therefore lose control over the droplet's size at detachment. To minimize any chance of droplets hydrodynamically interfering with each other, the process requires that "pitch" – the spacing between a pore and its closest neighbor –

be significantly greater than the diameter of the wake disturbance. A safe, baseline pitch value is 1~1.5 times the diameter of the wake: 450 μm pitch for the channel assigned to small (43.1 μm) droplets, and 560 μm for the channel assigned to large (77.6 μm) droplets.

Using these minimum values for pore spacing, we calculate the maximum number of pores in 10 cm wide channels. It is useful to refer back to the schematic in Figure 4.4. Begin by calculating the number of *rows* of pores. The number of rows is limited by the fact that each subsequent row must be laterally displaced by the "offset" distance. Eventually, offset brings row *N* (the furthest downstream row) back into alignment with row 1 (the furthest upstream row), but shifted one pore over. The maximum number of rows is then pitch divided by offset. We find 10 rows for the small-particle channels and 7 rows for the large-particle channels. Next, we calculate the number of *columns* of pores. The pitch distance separates adjacent columns, and we are limited by the channel width. Referring back to Figure 4.2, there are thin 1 mm boundaries against the channel walls, running the entire length of the channel, in which shear rate is significantly lower than the bulk value. We therefore subtract 2 mm from the total 10 cm channel width to arrive at a usable channel width. The number of columns is then the usable channel width (98,000 μm) divided by pitch, rounded down for fractional values. Note that we can actually fit width/pitch + 1 columns into a channel, but we must subtract 1 because row *N* is effectively displaced over one more pitch length from row 1, essentially forming an extra column. We find 217 columns for small-particle channels and 175 columns for large-particle channels. There can be a maximum of 2,170 pores for a channel dedicated to small droplets and 1,225 pores for a channel dedicated to large droplets.

4.3.3 Channel Number and Scaling Down Pore Number

For 40,000 Dalton product spheres, the process requires 11,513 pores for small particles and 948 pores for large particles (Table 4.3). A small-particle channel can contain a maximum of 2,170 pores and a large-particle channel can contain a maximum of 1,225 pores. Therefore, the process requires 5.31 channels for small particles and 0.77 channels for large particles. For practical purposes, the process runs 6 small-particle channels and 1 large-particle channel and the pore number per channel is reduced accordingly.

The 6 small-particle channels contain 11,513 pores, for 1,919 pores per channel. Keeping the previous value of 10 pore-rows, there are 192 pores in the first nine rows and 191 pores in the furthest-downstream row. Pore pitch for the small-particle channels can therefore be increased to 511 μm, well outside of the range where flow disturbances around forming droplets become problematic. Pore offset is accordingly increased to 51 μm.

The 1 large-particle channel contains 948 pores. Keeping the previous value of 7-pore rows, there are 136 pores in the first six rows and 132 pores in the furthest-downstream row. Pore pitch for the large-particle channel can therefore be increased to 721 μm, well outside of the range where flow disturbances around forming droplets become problematic. Pore offset is accordingly increased to 103 μm.

4.3.4 Pore Array Length

The length of these pore-arrays along the axis of continuous phase flow is equal to the number of rows multiplied by the spacing between rows. The number of rows is much smaller than the number of columns for both small- and large-particle channels; so generous spacing can be included between rows without taking up much space inside the channel. A row spacing value of 0.5 cm is more than large enough to eliminate the effects of any downstream disturbances between adjacent pore rows, being much larger than the low-shear dead-zone wakes downstream of each droplet in Figure 4.5 (the blue plume above the droplet). Therefore, the pore array is 5 cm long for small-particle channels and 3.5 cm long for large-particle channels along the direction of continuous phase flow. In order to house these pore arrays and include additional length to allow liquid flow to fully develop after the channel inlet, the droplet formation regions of the channels should be 10 cm long.

4.3.5 Critical Shear

The final concern for the pore arrangement is the possibility of emulsified droplet disruption downstream. It has been shown in a number of fluid mechanics studies that emulsified liquid droplets can bifurcate into two smaller droplets if they undergo sufficient shear stress. One source of increased shear is any abrupt bends or turns in the liquid flow downstream of the channel. We

address this possibility in Chapter 5. For now, we are concerned about emulsified droplets passing through the wake of another downstream pore.

Figure 4.5 shows a region of high shear rate just upstream and to the sides of a forming droplet. The elevated shear rate in this disturbance region is about 60% higher than the ambient shear rate far away from the pore, and the disturbance region spans a diameter of about 7 times the diameter of the pore. Since the pore "offset" (recall Figure 4.4) is much smaller than the disturbance wake radius, the pore arrangement forces upstream droplets to pass through the wakes of downstream disturbances. It is important to be sure that the elevated shear rates of the disturbance wake will not rupture a droplet passing through.

Numerous empirical relationships exist to predict the "critical capillary number" of a droplet. A very important note is that the capillary number we are about to discuss is different from the capillary number in Equation 4.5. This equation describes the capillary number characteristic of a droplet still attached to its formation pore, but we are now interested in the value characteristic of a free-moving droplet. The literature generally reports the critical capillary number as a function of the viscosity ratio – the ratio of the dispersed phase viscosity to the continuous phase viscosity:[12-16]

$$Ca^* = \frac{\eta_{CP}\frac{dv}{dz}\left(D_{wet}/2\right)}{\gamma} = f\left\{\frac{\eta_{DP}}{\eta_{CP}}\right\} \qquad \text{(Equation 4.13)}$$

Recall that η_{CP} is the viscosity of the continuous phase, η_{DP} is the viscosity of the dispersed phase, dv/dz is the local shear rate, D_{wet} is the diameter of the emulsified droplet, and γ is the interfacial tension between the dispersed phase and the continuous phase. In our case, the viscosity ratio is 4.3. Literature sources agree that the critical shear rate of this system, with a viscosity ratio far greater than 1, is extremely high and could never be encountered in the disturbance wakes around a forming droplet.[13, 14] The critical shear is estimated in excess of 1,000,000 s^{-1}. We can be confident that droplet disruption does not occur under any ordinary process conditions, and there is no risk in allowing passage through downstream wakes.

4.4 Summary of Particle Channel Selections

Over the course of Chapters 3 and 4, we performed rigorous optimization of the depo-haloperidol sphere products and the cross-flow membrane emulsification channel process. This optimization began by applying consumer requirements of zero-order release without an initial drug "burst" to determine a selection of possible polymer chain molecular weights and sphere sizes. From these product specifications, analysis went on to consider the operating parameters needed for our process flow-channels. These process parameters gave valuable insights on process throughout and practicality, and finally enabled the selection a molecular weight and particle size for the polymer spheres. Last, we maximized productivity by optimizing the number of droplet-formation pores inside of a flow channel.

Since important information is scattered throughout the chapter, it is useful to set a few paragraphs aside now for a concise summary of the results. These optimized results assist the later economic analysis.

4.4.1 Product Design: PLGA Spheres

Depo-haloperidol spheres consist of 10% haloperidol and 90% poly(lactic-co-glycolic acid) by volume (10.59% haloperidol and 89.41% PLGA by weight). The PLGA polymer has an average initial molecular weight of 40,000 Daltons. The average molecular weight declines during residence inside a patient's body due to continuous hydrolysis. We manufacture the product spheres in a mass-ratio of 5-parts 20 μm diameter particles to 1-part 36 μm diameter particles. A single dose of these particles lasts for just over one month in a patient's body while continuously releasing its drug content.

The mass of haloperidol contained in a dose of microparticles depends on the dosage prescribed by a doctor and rigorous clinical testing, but we consider a baseline requirement of 423 mg per one-month dose. This number arises from an initial drug loading of 450 mg of initial loading followed by a loss of 6% during treatment to eliminate initial burst (see Chapters 3 and 5).

4.4.2 Process Design: Cross Flow Membrane Emulsification

Chapter 4 only considers the flow-channel portion of the manufacturing process. The construction of the channel itself, including flow inlets and outlets are covered in Chapter 5. All downstream processing is presented in Chapter 6.

The emulsification process involves two liquid phases: the dispersed phase and the continuous phase. The dispersed phase 0.985% haloperidol by weight, 8.319% PLGA by weight, and 90.696% dichloromethane by weight. The continuous phase consists of 1.00% poly(vinyl alcohol) by weight, 1.27% dichloromethane by weight, and 97.73% water by weight. The PVA in the continuous phase coats the emulsified droplets and helps prevent coalescence downstream. The presence of DCM in the continuous phase prevents any DCM in the dispersed phase from "bleeding" out into the continuous phase during droplet formation, which would cause the resulting emulsified droplet to be more concentrated in polymer and haloperidol than we intend.

The flow channel primarily consists of a small rectangular prism dedicated to the formation of emulsified droplets. The dimensions of this droplet-formation region are: height of 0.5 mm, width perpendicular to the direction of continuous phase flow of 10 cm, and length parallel to the direction of continuous phase flow of 10 cm. The process generates small and large particles in separate channels. At the floor of each flow-channel, we position a thin membrane perforated with micro-scale orifices for cross-flow of the dispersed phase into the continuous phase stream. Small-particle membranes contain 1,919 pores each with 20.5 μm diameter, and large-particle membranes contain 948 pores each with 37.0 μm diameter. The flow rate of dispersed phase through each small pore is 0.58 mL/hr and the flow rate of dispersed phase through each large pore is 1.41 mL/hr. The flow rate of continuous phase through each small-particle channel is 120.0 mL/s and the flow rate of continuous phase through each large-particle channel is 45.0 mL/s. To meet the production goal of 500,000 thirty-day doses per year in a ninety-day operating period, the process must have 6 small-particle channels and 1 large-particle channel in operation.

The product spheres begin as emulsified droplets of dispersed phase, which consist mostly of the dichloromethane solvent. Small particles begin as 43.1 μm droplets, and large particles begin

as 77.6 μm droplets. Downstream, the solvent is drawn off by dissolution into an aqueous medium under the aid of a vacuum. The loss of the solvent leaves hard product spheres with diameters of 20 μm and 36 μm.

4.5 Chapter 4 References

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Chapter 5: Advanced Channel Specifications

5.0 Chapter Introduction

Cross flow membrane emulsification (XME) is a process where an organic dispersed phase (DP) is driven through a series of pores into transverse flow of an immiscible, aqueous continuous phase (CP), thus forming an emulsion of dispersed phase droplets which are hardened intro microparticles. The main architecture in the design of the microparticles, modeled as zero-order depot-release haloperidol loaded poly(lactic-co-glycolic acid) microparticles, is the cross-flow emulsification channel.

Chapter 5 will begin by introducing the general architecture surrounding the XME instrument and reiterating the channel specifications around the dispersed phase droplet formation region (5.1) Then the chapter will expand to talk about considerations of the continuous phase inlet and outlet (5.2), as well as considerations of the dispersed phase inlet and the emulsification membrane. (5.3). From there, we examine methods to reduce the hydrodynamic shear rate experienced by newly formed droplets (5.4). A focus on the final manufacturing process (5.5) concludes this chapter.

*SolidWorks3D CAD***.** The program used to construct and test a virtual model of the cross-flow emulsification channel referred to previously is called SolidWorks3D CAD™. SolidWorks, created by Dassault Systèmes SolidWorks Corporation, is a computer program specializing in both on-screen 3 dimensional design and numerically simulated dynamic testing scenarios. The sketches of the cross-flow emulsification channel (top, bottom, and membrane – contained within in this section were generated using the design aspect of SolidWorks, whereas stress testing of the membrane, and subsequent sketches) were calculated using the testing simulation aspect of the SolidWorks program.

5.1 XME Channel Layout

5.1.1 Overarching Design

In the broadest terms, the cross-flow emulsification (XME) apparatus refers to the machined, stainless steel construct responsible for directing fluid flow during the emulsification process. This device houses the XME channel, which refers only to the empty cavity cut out of the stainless steel. The central characteristics of the XME channel were, to some extent, specified in Chapter 2. Emulsified droplets are generated in a part of the channel called the droplet formation region which is formed in the geometry of a rectangular prism measuring 10 cm wide by 10 cm long by 0.5 mm high. At the base of the droplet formation region is the emulsification membrane. During the course of this chapter, we will elaborate on the design of the XME apparatus, the remainder of the XME channel not previously specified, and the emulsification membrane.

Before exploring the finer details of the XME device, some choices had to be made concerning the overarching design. These decisions originated from several basic design principles: building an instrument that was reliable, precisely machined, easy to maintain, and modifiable with respect to custom machined emulsification membranes. It is important to minimize the overall number of pieces and the number of contact surfaces that must be fit together, especially with regards to the XME channel itself. In order to do this, the device is composed of two parts, in-between which the emulsification membrane rests. The bottom portion, or plate, of the device contains the inlets for the continuous and dispersed phases, the outlet for the finished product stream, and a slot for the emulsification membrane. The slot is necessary to allow the emulsification membrane to be flush in plane with the floor of the channel, both to get rid of any obstacles the emulsified droplets might encounter, as well as ensure that the effective height of the channel experienced by the droplets stays consistent within the droplet formation region. The bottom plate also acts as the floor of the channel. The top plate of the device contains all of the features of the channel and a viewing portal for quality control purposes. This two-piece construction is convenient for two reasons: easy disassembly for cleaning and maintenance, as well as easy access to the emulsification membrane. This construction minimizes the number of total contacts to two areas:

contact between the top and bottom plates, and contact between the plates and the emulsification membrane.

Next, precise manufacturing and O-rings are necessary to ensure that these areas of contact do not allow for leakage or misalignment. First, the contact between the top and bottom plates is considered. This area of contact needs to be leak-proof, to prevent the CP from seeping out of the channel and potentially decreasing the volumetric flow rate, which could affect the size of the microparticles produced. In order to accomplish this, an O-ring surrounding all of the relevant features on the bottom plate is introduced into the design. This O-ring is then compressed by the weight of the top plate, which allows for a leak-proof seal.

The second area of contact to be considered is the contact between the emulsification membrane and the top and bottom plates. This is not only necessary to ensure that the channel does not experience any CP leakage, but it also ensures that the emulsification membrane is aligned exactly with the floor of the channel. This membrane alignment is accomplished by placing an O-ring underneath perimeter of the emulsification membrane. Due to the channel being much narrower than the emulsification membrane, two hemispherical sections of the membrane are in contact with the top plate, allowing for compression of the O-ring below. The area below the emulsification membrane is cut out to allow for space to insert the dispersed phase pump.

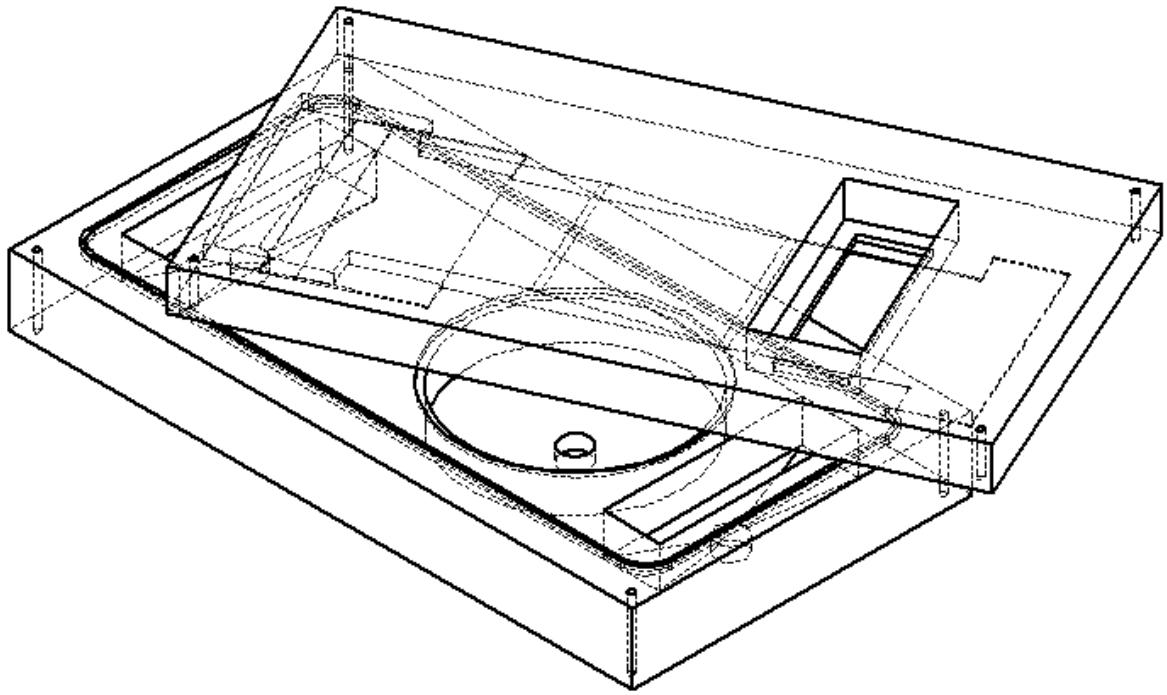

Figure 5.1. A wireframe schematic of the final assembly of the XME device. The emulsification membrane will rest in the circle shaped slot seen in the bottom section of the XME assembly. When the device is assembled, the upper and lower sections will align and be bolted together.

5.1.2 Two Separate Channels

As mentioned previously, the droplet formation region of the channel is initially specified by the determined size distribution of nascent haloperidol-loaded PLGA droplets. As these specifications are discussed in Chapter 4.1 and 4.2, they will only be briefly recapitulated here, highlighting the parts most important to the dimensions of the channel.

The creation of a zero-order release profile was best modeled by a 5-to-1 mass ratio of small to large particles, as shown in Chapter 3. This distribution of sizes allows for one to generate the final product in two ways: produce both large and small particles in the same channel, or operate two different channels in parallel, one for the small particles and one for the large particles. Initially, the thought was to manufacture a single channel that could create both large and small particles in the exact ratio needed.

This type of channel would have two distinct formation regions, one for the larger particles, and one for the smaller particles. The formation of two separate droplet sizes would be accomplished by partitioning the droplet formation region into segments with different channel heights. Given a constant inlet continuous phase flow rate, the two different droplet formation regions with distinct heights will experience different shear rates along the channel floor. By precisely tuning the two characteristic heights, and the inlet continuous phase flow rate, it would be possible to independently specify two different droplet sizes in the same channel. This design was initially chosen for its ease of use and all-inclusiveness. The ability to manufacture, in real-time, the correct ratio of large and small PLGA microparticles needed for a finished product was seen as a large selling point. It was also thought that by merely switching out the membranes one could achieve a level of flexibility that would allow the process to be adaptable to different size microparticles, different drugs, and different polymer matrices.

However, upon further consideration, a single-size single channel design provides crucial advantages over a channel built with a height step. First, the single-size single channel design provides an extra layer of quality control and robustness that the dual-size channel design lacks. If a channel produces only a single droplet size, it is very easy to screen the channel effluent for satellite fragments or other emulsified droplets lying outside of the specified size window. However, if the channel produces multiple droplet sizes, it becomes much more difficult to screen out abnormal sizes. Specifically, a dual-size channel design would have two allowable size windows, one small and one large, so a simple sieve could not be used to check for the presence of abnormal droplet sizes that fall between the small-size and large-size specifications. Hence, quality control becomes much simpler if small droplets and large droplets are generated separately. Second, the dual-height channel design is less useful as a platform technology. If it were later decided that we needed to change the sizes of the small and large droplets, it would not necessarily be possible to generate both new sizes in the same pre-existing channels. That is, we could vary the continuous phase flow rate until the shear rate was sufficient to generate the new small droplet size in the small-droplet formation region. However, at this continuous phase flow rate, the probability that the shear rate in the large-droplet formation region would be exactly correct to generate the new large droplet is extremely low. Since the channels are already machined, we cannot easily manipulate the channel height in the large-droplet formation region to adjust the shear rate any further. If, on the other hand, we used separate channels for the small and large particles, the continuous phase flow rates through each channel

could be independently controlled, and virtually any new arrangement of droplet sizes could be achieved using the pre-existing channels.

In summary, the droplet formation region of the channel itself will consist of a 0.5 mm ceiling height that can accompany the large and small droplet sizes needed for up to 40,000 Da molecular weight PLGA, a 100 mm width to allow for a plug-like transverse flow profile, and a 100 mm length to allow for full development of the flow profile before it interacts with the nascent particle droplets. A visual representation of this "single droplet formation region" channel is shown below in Figure 5.2.

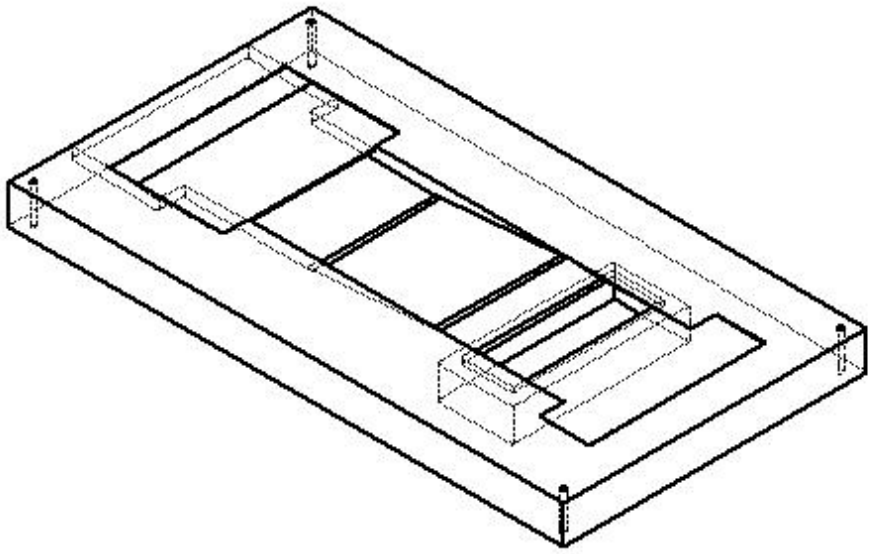

Figure 5.2. A wireframe isometric view of the upper portion of an XME apparatus that contains a single droplet formation region. The wireframe schematic is turned upside-down such that the channel machined into the steel block is located at the upper face.

5.2 Continuous Phase Inlets and Outlets

5.2.1 Location of the Inlet and Outlet

The next consideration in designing an XME apparatus was how the continuous phase enters and exits the device. The apparatus should exert minimal shear disturbance on the emulsified droplets themselves as they move downstream. Constructing an exit in the same lateral plane as the channel seems to minimize disruptive shear effects on the effluent stream. Yet if the exit were to exist on the same plane as the channel, it would be placed on the intersection of two distinct pieces of stainless steel, and it would prove impossible to achieve an adequate seal between the top and bottom plates of the XME device. Also, since the channel has a rectangular cross-section, it would be hard to find a piping fixture for the channel outlet that measures the height and width of the channel (h = 0.5 mm, w = 100 mm).

The design recommendations provided by Robert Meyer[1] indicate that continuous phase should enter and leave the XME channel through chambers bored through the bottom plate of the assembly. This way, both the inlet and outlet of the channel are located at the bottom of the device. This design allows for the insertion of an O-ring between the top and bottom plates of the XME device, preventing leakage out of the channel. Also, the inlet and outlet holes at the base of the XME device can be machined to any shape or size, making the addition of a piping fixture much easier. The bottom plate of the device – both inlet and outlet continuous phase reservoirs as well as inlet dispersed phase reservoir shown – along with a groove for an O-ring, is modeled in Figure 5.3.

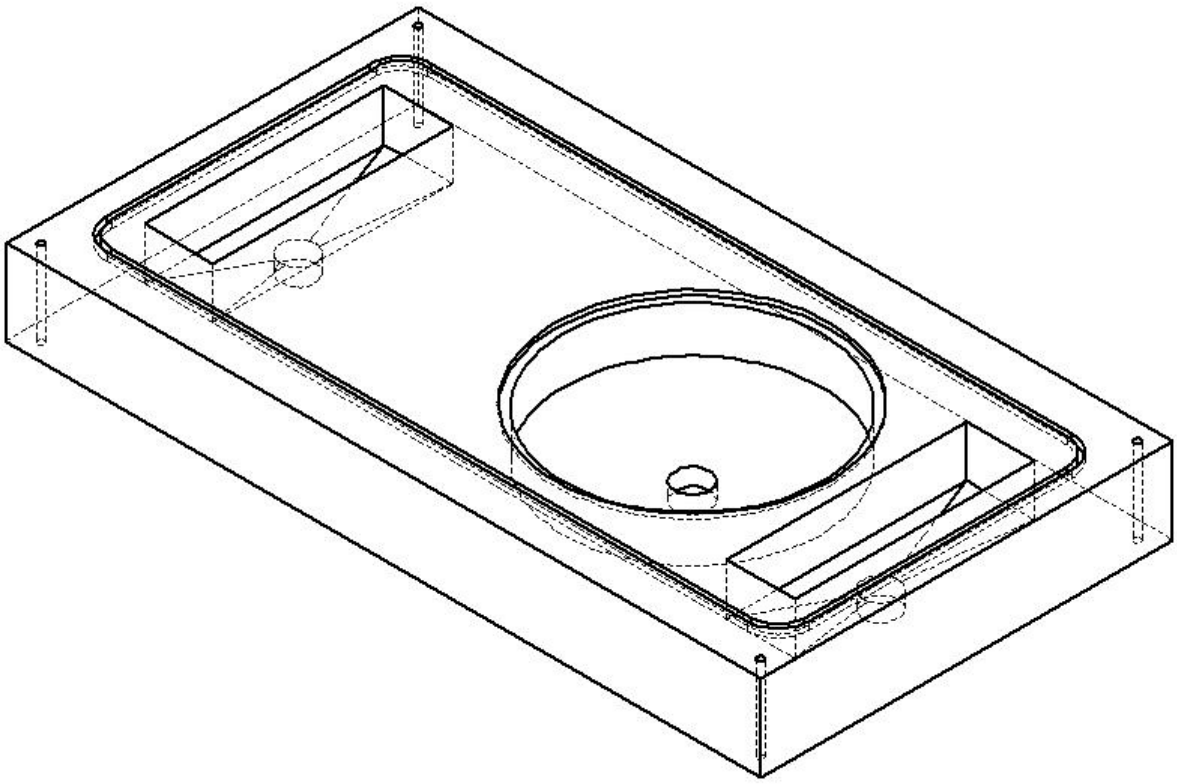

Figure 5.3. A wireframe view of the lower portion of an XME apparatus. The continuous phase entrance and exit reservoirs are the rectangular chambers on the far sides of the device, which taper down to round inlet and exit holes at the bottom of the steel block. The dark band around the perimeter of the device's upper face is a groove for an O-ring.

An initial concern for this design feature was whether a substantial shear rate at the XME channel drop-off existed. This drop-off is the 90° turn experienced by the emulsified product stream upon exit from the XME channel and entrance into the outlet reservoir. The drop-off was modeled in COMSOL, to determine whether the shear rate would increase at the 90° turn, or at any point during the drop, to levels that would shear the particles. Figure 5.4 illustrates the evolution of shear rate at the drop-off, and although there is a slight increase in shear rate, the increase is well below the maximum shear rate that can be tolerated by the microparticles. This study validates design choice to place the location of the outlet in the bottom plate.

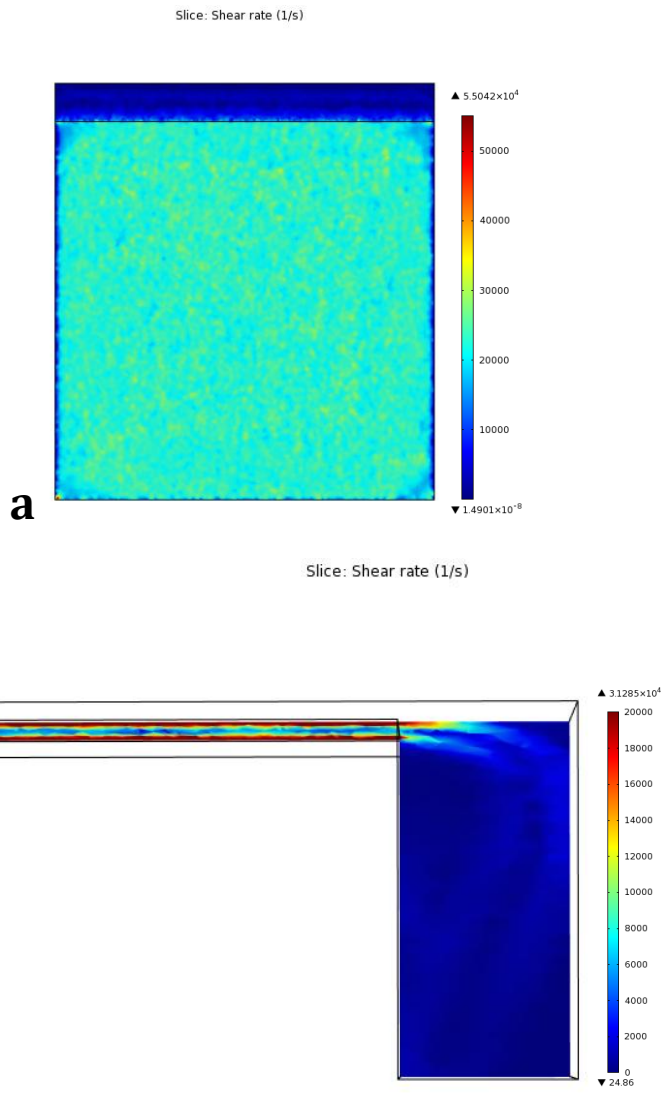

Figure 5.4. COMSOL Simulation of Shear Rate at Drop-off at Channel Outlet. Presented in this figure are two views illustrating the evolution of shear rate at the drop-off. In part a, a frontal view is presented. Upon closer analysis of the turn itself, there is evidence of a slight increase in shear rate, but this increase is well below the maximum shear rate that the microparticles can tolerate before actually shearing.

5.2.2 Development of Flow

Given many defining decisions in the XME device's architecture, two important considerations concerning the flow profile are that the continuous phase flow profile through the channel is approximately uniform across the channel width, and that the flow is fully developed before encountering the emulsification membrane and the pore array.

The first concern: uniform flow with respect to the channel's width, is accomplished by flaring out the continuous phase inlet into a reservoir. These loading reservoirs will always be filled with continuous phase, and under backpressure from the pumping process. Hence, this design gives no protection against unwanted disturbances in the continuous phase pumping pressure, due to the fact that any fluctuations in the continuous phase delivery will affect the downstream shear rate, and in turn, the droplet size. However, one can easily separate out drop size abnormalities downstream of the channel architecture. What the loading reservoirs are essentially trying to protect against is any abnormal deviation of continuous phase flow in the lateral axis by smoothing out the flow profile as liquid enters the main XME channel. The aforementioned reservoirs are designed to work as such: as the continuous phase enters the reservoir from below, it undergoes an expansion from the cross sectional area of the leading pipe to the cross sectional area of the reservoir. The continuous phase is then directed into the flow channel, perpendicular to the reservoir.

Allowing a small entrance length in the XME channel addresses the second concern: fully developed flow at the emulsification pore. As shown in Figure 5.5, COMSOL simulations indicate that continuous phase flow with properties identical to those in our process (density 1.007 g/mL and viscosity 0.0014 Pa-s) in a flow channel with height 0.5 mm becomes fully developed within roughly 1 cm of the inlet, as shown by the decaying shear rate disturbances along the channel walls.

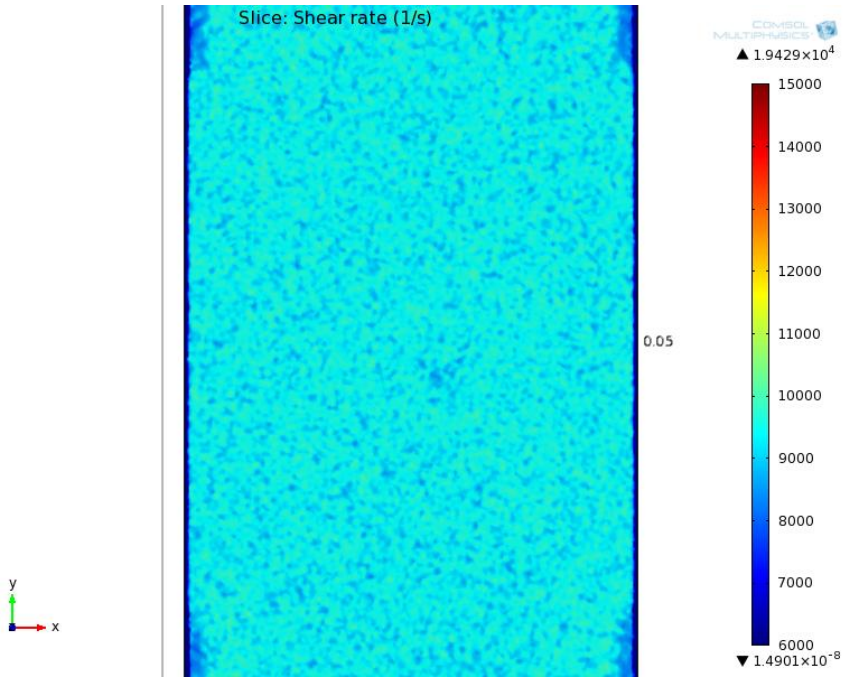

Figure 5.5. COMSOL simulation of continuous phase flow (density 1.007 g/mL, viscosity 0.0014 Pa-s) through a flow channel of width 6 cm, length 10 cm and height 0.5 mm. Flow is directed from the bottom off the figure towards the top of the figure at a superficial velocity of 1 m/s. The dark blue bands along the channel sides represent shear rate disturbances due to the no-slip boundary condition at the walls. The low-shear disturbances are wider in the bottom-most 1 cm of the schematic, indicating that flow has not fully developed.

Based on this analysis, the emulsification membrane is positioned several centimeters downstream of the start of the flow channel. This way, we can ensure that flow is fully developed at the emulsification site and maintain control over the process.

5.3 Membrane Design and Dispersed Phase Delivery

5.3.1 Review of Pore Array Spacing

Before the dispersed phase comes into contact with the continuous phase in the cross-flow emulsification process, it passes through an array of pores from which the nascent droplets form. The design of this pores array arises from a combination of physics – not wanting to let one particle interact strongly with another particle's formation region wake – and throughput calculations – the number of doses to be prepared in a year for a specific polymer chain length. The physics generally determine the pitch, offset, and row spacing of the pores, modeled below, whereas the throughput calculations determine the actual number of pores that need be manufactured. The pore spacing schematic is reproduced below as Figure 5.6.

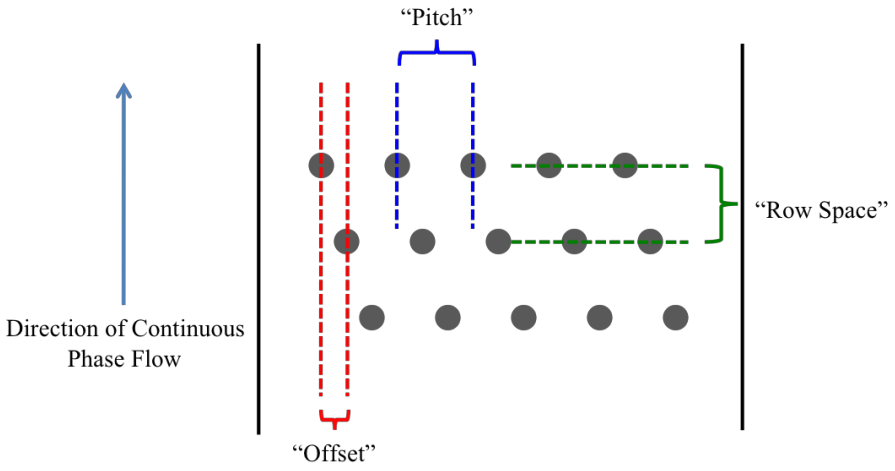

Figure 5.6. General schematic displaying a section of the diagonal pore array which allows a large number of pores to be placed close together without the forming droplets interacting. For example, given a 40,000 Da PLGA polymer with wet diameters 43.1 μm: offset = 45 μm, pitch = 450 μm, row space = 0.5 cm, number of diagonal columns = 217, maximum number of pores per 100 mm wide channel = 2170, number of pores required for throughput = 11,513, and therefore the minimum number of 100 mm wide channels = 6.

While many of these dimensions were specified through numerical means – a safe estimate of the pitch is 1~1.5 times the wake of the forming PLGA droplet – the general array was determined through a method of optimization that factors in both the channel dimensions as well as

the array dimensions. As stated in Section 3.1, the sides of the channel contain a boundary layer area where the shear is lowered drastically. Thus, a 1 mm clearance on either side of the channel was factored in to calculations about the width of the pore itself. A flow channel of width 100 mm – usable width of 98 mm due to the low-shear boundaries along the channel walls – was concluded as the most optimal solution and limited the number of required channels to a reasonable number: 6 for small particles (1,919 pores each), and 1 for large particles (948 pores). From here specifications of the membrane itself could be developed.

5.3.2 Dispersed Phase Inlet

The dispersed phase is introduced into the channel in an analogous way to the continuous phase. The bottom section of the XME apparatus is machined to include a rounded reservoir under the droplet formation region, connected to the inlet port for the dispersed phase. The emulsification membrane rests on top of this reservoir, while the interface between the reservoir and the membrane is sealed with an O-ring and held in place by the top section of the XME device when the device is secured together. The dispersed phase is then pumped from its storage vessel into this reservoir at a specified rate, given by the DP flow rate per pore times the number of pores in the membrane. Backpressure in the dispersed phase reservoir causes the DP to flow through the emulsification pores, into cross-flow of the continuous phase.

An increased or decreased flow rate of the dispersed phase will not affect the size of the droplet, as long as the Weber number (Chapter 4.7) remains less than 1, in order to avoid the onset of "jetting." We specified the emulsification process so that the Weber number remains at 0.5, and so the process can tolerate small variations in dispersed phase flow rate without exceeding the critical Weber number limit. Drawing from these conclusions, the XME channel does not need to maintain extremely precise control over dispersed phase flow rate. A schematic representation of the dispersed phase reservoir is shown in Figures 5.7 and 5.8.

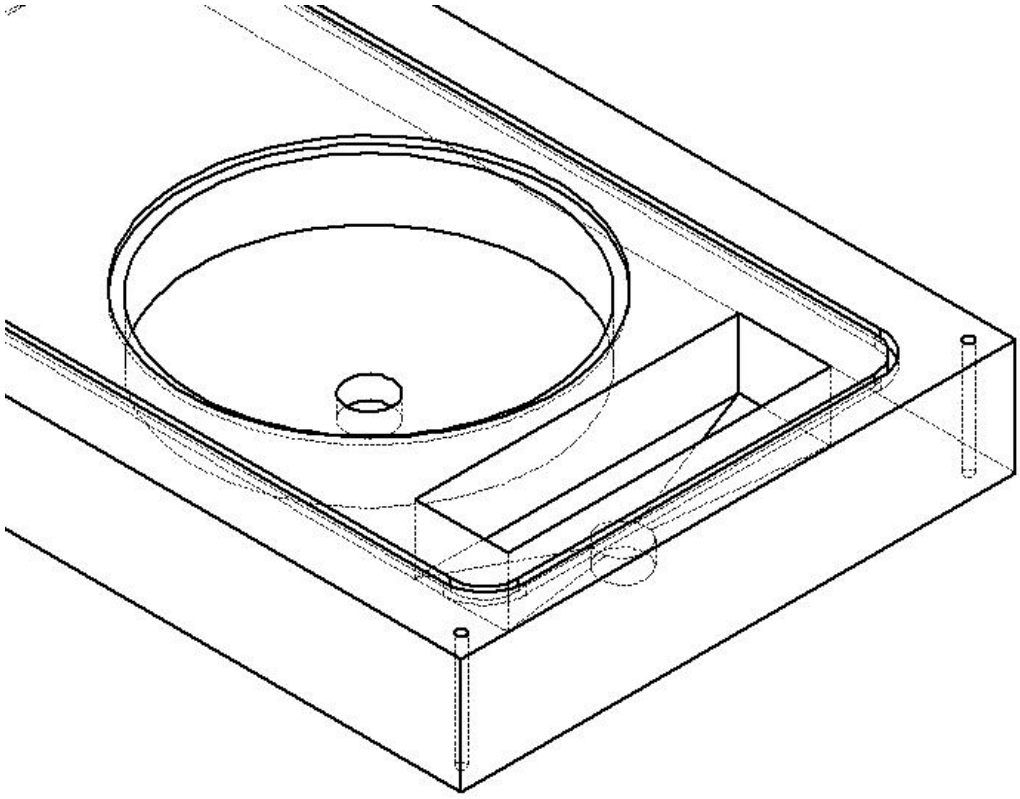

Figure 5.7. Close-up schematic of the dispersed phase inlet reservoir in the bottom section of the XME apparatus. The dispersed phase reservoir is the rounded cavity. The dispersed phase reservoir is designed to house a small O-ring at its top, which forms a tight seal with the emulsification membrane when the apparatus is assembled.

5.3.3 Membrane Deflection and Dimensions

As discussed previously, the membrane itself has to be able to contain a 98 mm wide pore array which is machined into a 100 mm wide channel. These specifications aside, the question becomes how to secure the membrane into the channel to ensure there is no movement. Given that the overarching design of the XME apparatus is already a two-plate device, including a top and bottom plate, one basic scenario becomes that of pressure fitting the membrane between the two individual plates. This design is logical, as the top and bottom pieces join on the same plane as the floor of the XME channel. Furthermore, this design allows the membrane to sit in a depression cut into the lower section and remain flush with the floor of the XME channel itself as shown below. The

membrane is designed as a thin, circle shaped piece of metal to match the upper face of the dispersed phase reservoir.

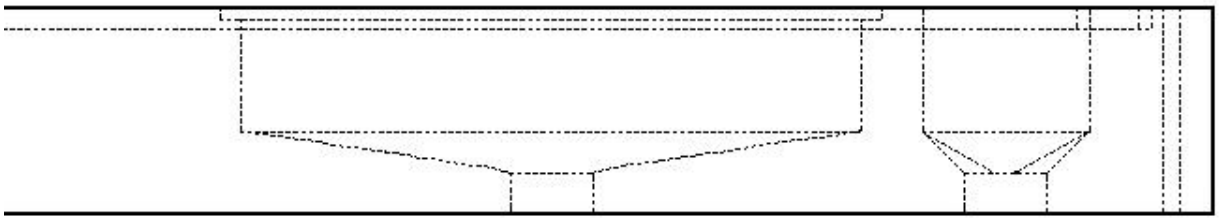

Figure 5.8. The dispersed phase reservoir, as viewed from the side. When the membrane is settled on top of an O-ring in the aforementioned depression (shown as the faint, horizontal dotted line just below the top solid line marking the upper face of the steel block) the floor of the XME channel becomes flush and continuous.

In order to make pressure-fitting possible, the lateral sides of the membrane – and in result the depression built into the lower section of the XME channel – have to extend further than the initial channel width (100 mm) by enough so that, when fully assembled, the top section of the XME channel can exert an adequate force to keep the membrane in place. For example, this means that if the channel width is 100 mm, the width of the membrane has to be greater than 100 mm by enough so that it is held in place by the top of the channel. The membrane width has been selected as 160 mm, so that the upper steel block holds down the outermost 30 mm on either end of the membrane when the XME device is assembled.

The next consideration in the design of a membrane is that of length. The length of the membrane first emerged as an issue when talking about the development of the continuous phase flow profile. Essentially, one will never be able to create a modifiable XME apparatus that does not have some discontinuity at the interface between the side of the membrane and the side of the depression. Even if the membrane is perfectly fit to the shape of the depression, at some level the two pieces are not continuous. Also, a good fit, let alone a perfect fit, is extremely difficult to

machine in any shop. Thus, a gap 20~50 μm is acceptable between the membrane and the depression on all sides. Although this might not cause a large, or even noticeable, disturbance in the laminar flow profile, the length of the membrane should still allow the continuous phase to fully return to its laminar profile before it reaches the pores. To see how long a deformation in flow profile would take to reassume its flow profile, the same COMSOL simulations similar to the one in Figure 5.5 were studied. To a close estimate, the continuous phase flow through a 0.5 mm high channel can reassume a fully-developed profile in ~10 mm downstream of a sudden change in geometry. Since the pore array proper is designed to occupy a length along the direction of CP flow of 50 mm for small-droplet membranes and 35 mm for large-droplet membranes, a membrane length of 160 mm was chosen. The pore array begins 20 mm from the upstream edge of the membrane, ensuring that any disturbances caused by flow over the gap between the leading edge of the membrane and the channel floor even out by the time the continuous phase reaches the pores.

The last consideration in designing a membrane is the thickness, which directly affects membrane deformation. If the membrane is too thin, the backpressure in the dispersed phase reservoir might cause it to bow upwards and narrow the effective height of the channel. Conversely, it is much more difficult to precisely machine micro-scale perforations into a thick membrane plate. By treating dispersed phase movement through a pore as liquid flow through a pipe with diameter equal to that of the pore and length equal to the thickness of the membrane, it is possible to calculate a pressure differential across the membrane by accounting for friction. The pressure differential is largest for the small-droplet membrane, so we study this high backpressure condition as the worst-case scenario.

$$\Delta P = \frac{\rho_{DP} f L_m v^2}{2 D_0} \qquad \text{(Equation 5.1)}$$

Here, ΔP is the pressure drop across the membrane, ρ_{DP} is the density of the dispersed phase, L_m is the length of the pore (the thickness of the membrane), v is the superficial velocity of dispersed phase through the pore, D_0 is the diameter of the pore, and f is the Darcy friction factor – equal to $64/Re$, where Re is the Reynolds number for flow through the pore ($Re = \rho_{DP} v D_0 / \eta_{DP}$ such that η_{DP} is the viscosity of the dispersed phase).

Given a pressure differential across a membrane, it is possible to predict the deflection the membrane will undergo using different stress/strain analysis tools in SolidWorks. For example, it can be calculated (using Equation 5.1) that a 0.5 mm thick membrane, with dispersed phase properties of density = 1.32 g/mL and viscosity = 0.006 Pa-s, flowing through a 20.5 μm diameter pore at a rate of 0.58 mL/hr (the specifications for a small-droplet membrane), shows a pressure differential of 16.2 psi. According to SolidWorks simulations, the maximum deformation in a membrane of the dimensions previously described, held in place on both sides by contact pressure via the upper section of the XME device, and under 16.2 psi stress is completely negligible – several orders of magnitude smaller than the height of the channel. Deflection only becomes significant when the membrane thickness dives below 0.1 mm. Therefore, we select a membrane thickness of 0.5 mm to minimize any adverse effects of backpressure.

5.4 Channel Expansion and Critical Shear

5.4.1 Review of Critical Shear

As described in Chapter 4.3, there is a value called the critical capillary number for a system of emulsified droplets. The critical capillary number (defined as the ratio of the parameters: continuous phase viscosity η_{CP}, shear rate dv/dz, droplet radius D_{wet} / 2, and interfacial tension γ) is defined in the literature as a function of the ratio of dispersed phase viscosity η_{DP} and continuous phase viscosity η_{CP}.[2-5]

$$Ca^* = \frac{\eta_C \left(\frac{dv}{dz}\right)\left(D_w/2\right)}{\gamma} = f\left\{\frac{\eta_D}{\eta_C}\right\} \qquad \text{(Equation 5.2)}$$

When this critical capillary number is exceeded, under conditions of high shear rate, the emulsified droplet will bifurcate into two smaller droplets. Based on literature correlations for our emulsification system,[3, 6] the dispersed phase droplets have a critical capillary number of approximately 10. This value gives a critical shear rate of ~2.6 x 10^6 s^{-1} for small 43.1 μm diameter droplets and ~1.47 x 10^6 s^{-1} for large 77.6 μm diameter droplets. These critical shear rates are extremely high, roughly 90 times higher than the ambient droplet-formation shear rate for small droplets and 150 times higher than the ambient droplet formation shear rate for large droplets. These theoretical critical shear rates are also higher than anything we would expect in the normal cross-flow emulsification process. However, experiments have demonstrated that under high-continuous phase flow conditions, droplet disruption does indeed occur downstream, leading to a polydisperse output. See Figure 5.9 for a sample polydisperse output, collected under a high continuous phase superficial velocity of 1.5 m/s.

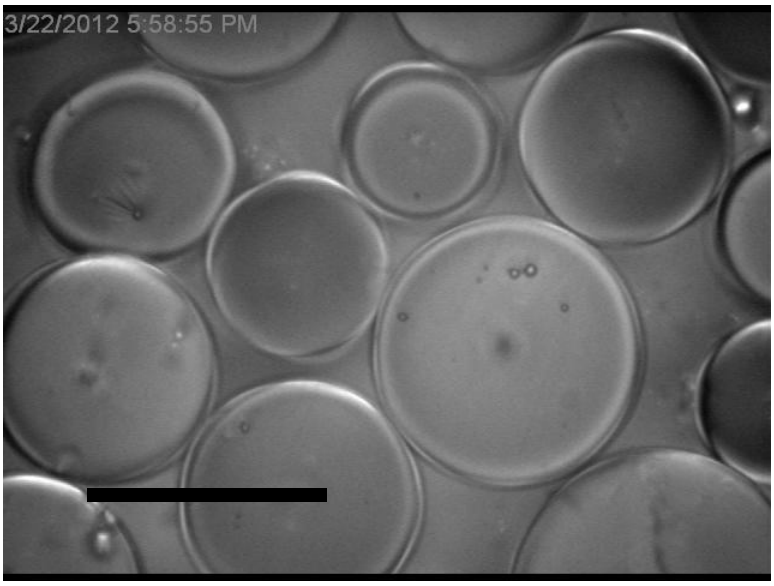

Figure 5.9. Experimental polydisperse droplet output. The dispersed phase flow rate was controlled to ensure that the Weber number remained at 0.1, so droplets should have been monodisperse at generation. Subsequent disruption may have occurred downstream due to excessive shear. Superficial continuous phase velocity was 1.5 m/s. Scale bar represents 500 μm.

From here it was initially thought that if one wants to maintain any type of reproducibility in particle size, the channel velocity must be considerably reduced after the particle formation region, thus lowering the shear at the corner where the channel meets the outlet reservoir. Assuming a constant volumetric flow rate throughout the XME channel, one can use the relation:

$$Q = u\,A_C \qquad \text{(Equation 5.3)}$$

Here Q is the volumetric flow rate, u is the superficial velocity of liquid through the channel, and A_C is the cross sectional area of the flow channel. In order to reduce the velocity of the continuous phase emulsification, the ceiling height is raised from 0.5 mm at the droplet formation region to 10 mm over a horizontal distance of 100 mm. This ceiling expansion effectively drops the effluent flow velocity by a factor of 20 and the shear rate by more than a factor of 10 as the particles travel towards the channel exit.

5.4.2 Use of a Wedge Bifurcation to Decrease Working Volume of Finished Product

The finished product stream is composed mostly of continuous phase. In the small particle channel, microparticles constitute only .34% by weight of the total flow; in the large particle channel, this improves to 1.1%. Taking off a portion of the continuous phase drastically reduces the working volume of the finished product stream, and decreases the required size of units in the downstream processing section. This is accomplished by inserting a "bifurcation wedge" – as seen below – that would effectively separate the finished product stream.

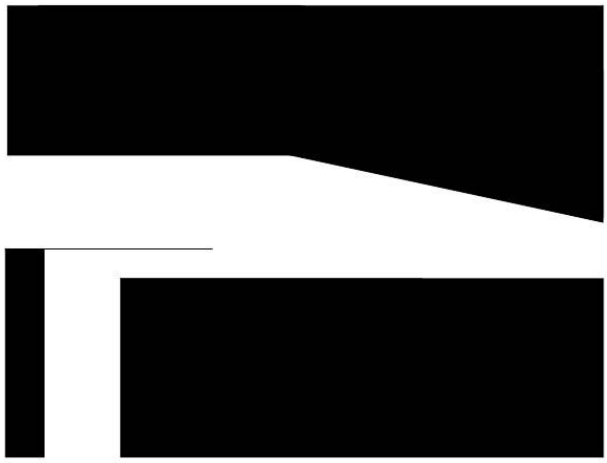

Figure 5.10. This simple schematic (not to scale) is meant to highlight the concept of the "wedge" – as seen on the left side of the picture. The continuous phase / dispersed phase emulsification will travel in – from the right – particles rumbling along the bottom of the channel. The majority of the continuous phase will be drawn off into the upper partition – exiting to the left – while the remaining CP/DP emulsification will flow into the exit reservoir – exiting bottom left.

Due to the density differences, the dispersed phase droplets will continue to travel along the floor of the channel towards the exit, and the continuous phase – diverted into the top bifurcation – will be pumped directly to the DCM waste management system. There are two positive consequences of the height expansion from 0.5 mm to 10 mm, first, that it works as a safeguard by dropping the critical shear rate experienced by the particles at the outlet. Second, it allows for easier machining, by allowing for a larger working space during the drilling of the top bifurcation.

In order to ensure that flow exits through the top bifurcation, it is necessary to overcome gravity by adding a pump. In addition to this measure, it is also important to drop the floor of the upper bifurcation below the initial ceiling height of the channel, which was 0.5 mm. This design specification helps to ensure that the continuous phase is successfully diverted into the top bifurcation. The bifurcating wedge can be seen isometrically in Figure 5.2, and in more detail as a side-view in Figure 5.10. More of the space at the outlet is dedicated to the top bifurcation, due to the large volume of excess continuous phase that needs to be drawn off. Using the wedge bifurcation, a conservative estimate of 70% of the total continuous phase is drawn off – bifurcations calculations completed using COMSOL. This percentage can be increased by increasing the power of the pump drawing fluid through the top bifurcation, or by lowering the position of the wedge further, to decrease the volumetric flow rate that can exit through the bottom bifurcation.

5.5 XME Instrument Design

Given the specifications from Chapters 4 & 5, a final bill for the manufacture of the XME product can be drawn up. The upper and lower sections of the XME instrument will be manufactured out of two blocks of highly polished grade 316L stainless steel. Of the austenitic class of stainless steel, grade 316L stainless steel has a maximum of .03% carbon – the L stands for low carbon – 16-18% chromium, and 2-3% molybdenum. Both the chromium and the molybdenum help to resist corrosion while still allowing for good machining properties. The upper portion will be cut to 440 mm long by 240 mm wide by 30 mm thick. From here the specifications of the XME channel itself will be cut into the block using a CNC (computer numerically controlled) router with both a flat head bit and a rounded head bit. The centerline of the XME channel will be positioned along the center of the stainless steel block such that the majority of the channel extends 50 mm on one half of the block and 50 mm on the other. A viewing window will be cut out directly on-top of the droplet formation site using a CNC router with a flat bit such that it extends 30 mm backwards and forwards from the center of the droplet formation region and is cut 29.5 mm down to the ceiling of the droplet formation region. The viewing window will be 120 mm wide, thus allowing a 10 mm overshoot on either side of the channel. A 60 mm X 120 mm sapphire window will sit in the viewing window frame, resting on the two 10 mm overhangs. A larger square of the dimensions 80mm long by 140mm wide by 25mm deep can be cut out concentric with the viewing window to allow for an easier viewing experience.

The bottom portion will be cut to 440 mm long by 240 mm wide by 100 mm thick. The entrance and exit reservoirs will be cut to 140 mm wide by 140 mm long by 30 mm deep, each centered 50 mm away from their respective edges. The continuous phase will flow into these channels through threaded holes cut in the center of the reservoirs. The dispersed phase entrance will consist of a circle – 160 mm in diameter – centered 160 mm from the "entrance side" of the lower block and cut deep enough into the bottom portion to support both the thickness of the desired membrane and the thickness of the desired o-ring. As this first circle is supposed to create a ledge-like structure that will support the o-ring underneath the circular membrane, a concentric circle – 150 mm in diameter – will be cut to 20 mm from the base of the block. The dispersed phase will enter this reservoir through a concentric threaded hole. In order to seal the channel in its

entirety, an o-ring slot will be cut to the rough shape of a rectangle with filleted corners. The inner dimensions of this rectangle will measure 404 mm in length by 184 mm in width, be centered on the lower block itself, and contain filleted corners with a radius of 15 mm. The outer dimensions and the depth can be specified depending on the size of the chosen o-ring.

The membrane will be cut from 0.50 mm thick 316L stainless steel sheet stock into circles of 160 mm in diameter. These circles will then have the desired array of pores cut into them using a technique called electrical discharge machining – or EDM. The advantage of EDM over other manufacturing methods, such as laser drilling and machine drilling, is that EDM is provides a much cleaner hole[1] when used. The membrane will then be coated with a non-stick polymer in order to reduce the ability for the PLGA to wet the surface of the membrane. Extensive wetting can lead to clogs that cause the machine to have to be dismantled and cleaned.

The dimensions talked about in this section can be seen visually in Appendix C in both English and metric units.

5.6 Chapter 3 References

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Chapter 6: Non-channel Processing and Design

6.0 Introduction

We have discussed in detail the design and operation of the cross-flow membrane emulsification (XME) devices in order to produce poly(lactic-co-glycolic acid) (PLGA) microparticles containing depo-haloperidol of two desired particle sizes: 20 μm and 36 μm in diameter (Chapter 5). The fluid dynamics involved in shearing the organic dispersed phase (DP) into microparticles with the aqueous continuous phase (CP) flow past channel membranes have also been investigated and reported (Chapter 4). Chapter 6 is devoted to technical aspects of the process and product design not related to the channels. This includes the preparation, storage, and delivery of inputs necessary for operation, in addition to more complicated facets of the system design.

Outflow from the XME channel arrays contains emulsified DP droplets, still containing dichloromethane (DCM), in a large volumetric proportion of CP. During downstream processing, care must be taken to avoid further shearing of the particles in order to maintain particle size such that satellite particles linked to overdose are not produced. This chapter will account for: removal of CP from the post-channel process and the separation of diverted CP using continuous distillation; hardening of the particles and removal of DCM solvent in an agitated vacuum tank with diafiltration; removal of residual poly(vinyl) alcohol (PVA) coating the particles after the hardening process stage; freeze-drying of particles; and, finally, particle storage in dose-sized vials for distribution to hospitals and doctors administering haloperidol to patients.

Unit operations involved in process stages are detailed within relevant sections to substantially describe the process design. Comprehensive equipment needs and costs are provided at the end of this report as Appendices D and E. A process flow diagram (PFD) is presented in Figure 6.1 with labels for all units by which they are referred to in this chapter. A Gantt chart and streams summary are also provided for reference as Figure 6.2 and Table 6.1, respectively.

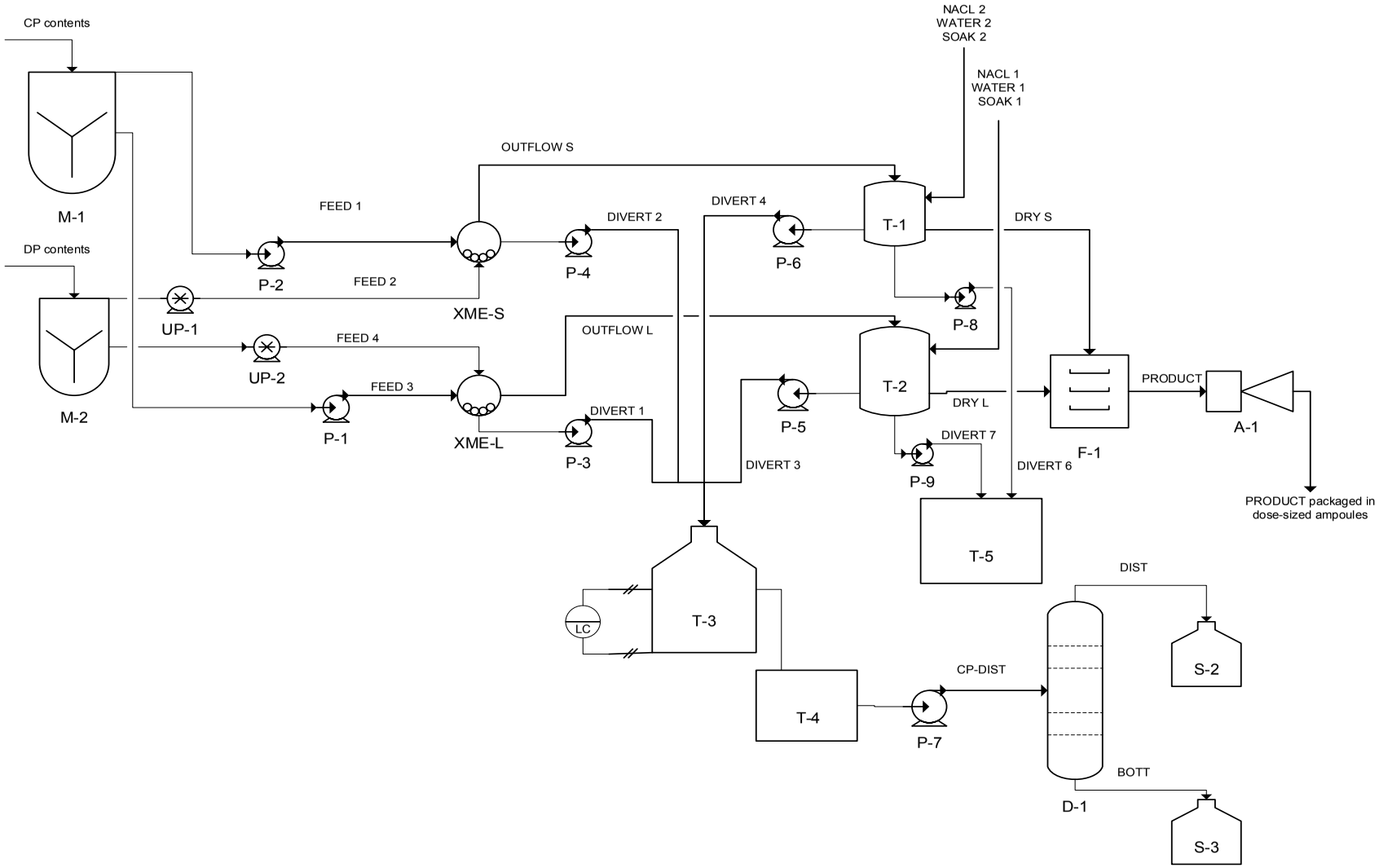

Figure 6.1. Process flow diagram (PFD) of the upstream and downstream processing unit operations and streams. The XME units refer to entire large- and small-particle producing channel arrays. Necessary units are shown for one 12 hour period of channel operation, although multiples of one unit type in use are not shown.

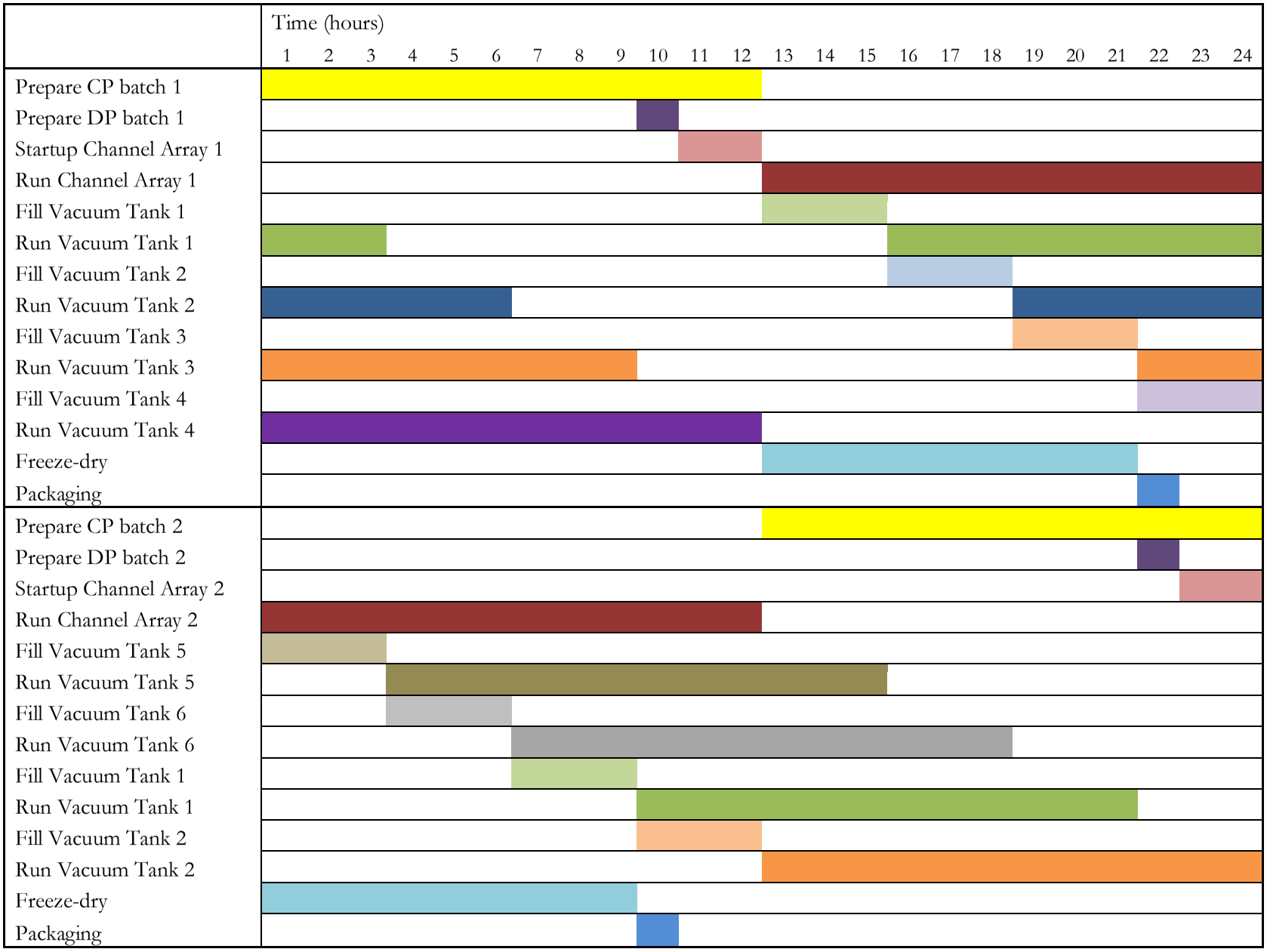

Figure 6.2. Gantt chart for 24 hours of XME channel operation. One XME channel runs for 12 hours per batch preparation of CP and DP.

6.1 Overview: Pathway of the Particle

Emulsified droplets exiting the XME channel arrays go through several stages of downstream processing. Droplets from one batch of CP and DP continuously exit the channel at a flow rate maintained by pumps introducing CP to the channel arrays. These microspheres are allowed to flow into tanks placed below the channel arrays, in which large and small spheres are collected separately, where they await hardening and DCM removal.

The same collection tanks operate as particle-hardening vessels in which increased temperature, reduced pressure, gentle agitation, and diafiltration with salt solution extracts and evaporates DCM. Droplets remain suspended as DCM is removed, and the denser hardened microparticles settle toward the bottom of the tank on a removable filter, and after 1 hour, all retentate is pumped from the bottom of the tank. Settled particles coated in ions and partially-adhered PVA are then rinsed substantially for a half hour with deionized water.

Next, drug encapsulation is reduced to eliminate the initial burst in the release profile discussed in Section 3.3. To remove the first half day of the drug release profile in Figure 3.6, the hardened particles are agitated in the same diafiltration tanks for 10 hours in circulating water at a high temperature. More precisely, the goal is to allow 6% by weight of all the haloperidol to diffuse from the particles. This diffusion occurs faster at temperatures higher than body temperature for which the 12 hour release is projected, and the ten hour period can be easily adjusted if needed during the trial process stage. Upon completion of 'soaking', retentate is drawn from the tank and particles are transferred from the filter baskets to the next process stage: freeze-drying.

Particles are freeze-dried in batches where any residual liquid phase is completely removed. After a 10 hour lyophilization period, the particles are ready for packaging. For convenience, the particles are packaged in dose-sized vials where only water must be added prior to intramuscular injection. A computerized packing system distributes specified weights of PBS buffer, large particles, and small particles to the ampoules. The vials are stored in a dark, cool, dry location before delivery. Figure 6.3 presents an overview of these process stages, to be discussed in detail in later sections.

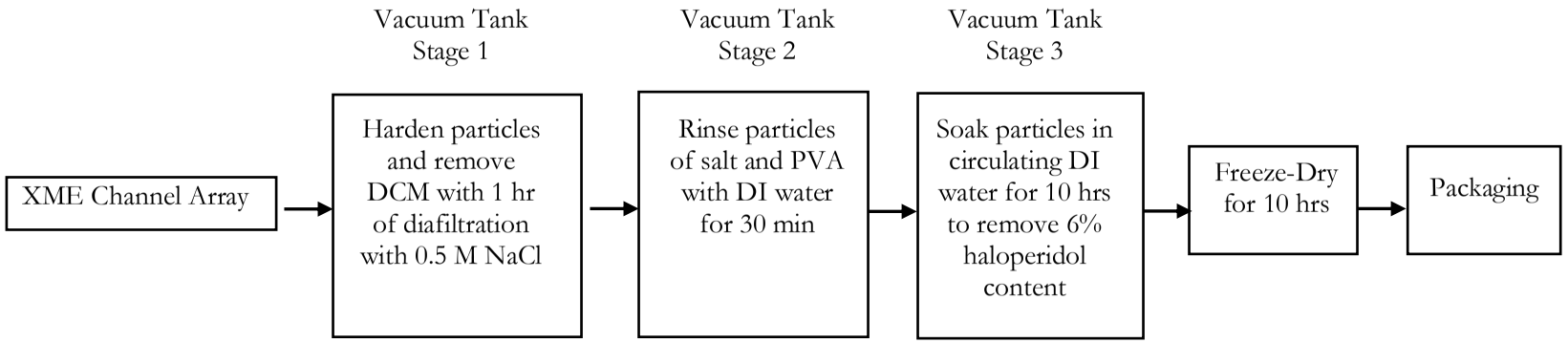

Figure 6.3. Particle Pathway Overview. Post-channel, a particle's pathway is follows: diafiltration with salt solution to promote droplet hardening and DCM removal, rinsing with deionized water to remove residual salt and PVA, soaking by diafiltration with water to remove 6% of the haloperidol per particle, freeze-drying, and then packaging in dose-sized ampoules.

6.2 The Channel as a Black Box

In this section, the XME channel is introduced as black box with specified inputs and outputs. Previous chapters have discussed channel design and the optimization of operating conditions in order to achieve the desired haloperidol production. These conditions determine pre-process preparation units and scheduling as well as the unit operations used in downstream processing. We begin this section with channel requirements and then move onto outflow exiting the channel, ending with conclusive startup and shut-down specifications. Figure 6.4 on the next page shows both channel arrays, labeled according to the PFD for easier reference.

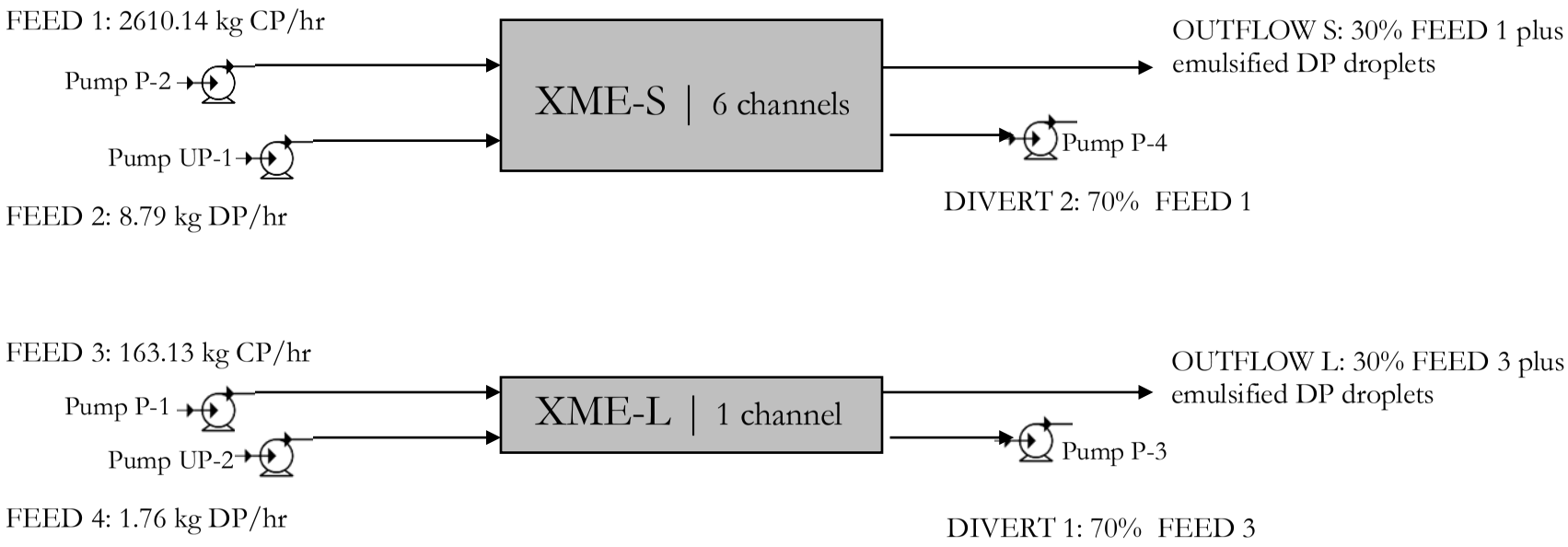

Figure 6.4. Channel Inputs and Outputs. This schematic shows both the large- and small- particle producing XME channel arrays as "black boxes" where CP and DP are both pumped into each array, and upon exit from the channel, emulsified DP droplets and CP exit to further processing while a large percent of CP is diverted for wastewater treatment.

6.2.1 Channel Input

CP flow through the large-particle producing XME channel, unit XME-L in the PFD, is approximately 162.0 L/hr, and CP flow through each of the small-particle producing XME channels, where the entire six channel array is termed XME-S in the PFD, is 432.0 L/hr. DP enters each XME-S channel at a total volumetric flow rate of 6.78 L/hr, and enters the XME-L channel at 1.34 L/hr.

In order to ensure that these deliveries of CP and DP are continuous 24 hours/day for the 90 day process cycle, two sets of equipment are required. While one set of equipment is being cleaned, another is in use. This includes all pumps, tubing, and delivery vessels for the CP and DP, in addition to channel arrays themselves. It worth mentioning early on that DCM is a hazardous organic compound that must be stored safely in equipment of proper material. While no reactions occur in this process, heavy materials such as stainless steel, aluminum, or carbon steel are required.

Seven sanitary precision pumps with high-sensitivity pressure control valves are needed per batch of CP input; six pumps (P-1) for the XME-S channel array and one for the XME-L channel (P-2). As reported on the unit specification sheets in Appendix G, pump P-1 delivers 163.13 kg/hr and each of the six P-2 pumps delivers 435.03 kg/hr as streams FEED 3 and FEED 1, respectively. The input to the six small particle-producing XME channels is aggregated as FEED 1. Both pumps are made of Stainless Steel 316 and operate with a pressure change of 25 psi and at a temperature of 20ºC. Pump P-1 operates with a power of 0.01 kW and its bare module cost is $2,900, and each P-2 pump operates at 0.20 kW and costs $3,200.

Sanitary precision pumps deliver DP to the chambers underneath the channel membranes so that DP is continuously pushed through the pores at precisely 0.58 mL/hr in XME-S and 1.41 mL/hr in XME-L. This part of the process is depicted as FEED 2 via six units of pump UP-1 and as FEED 4 via pump UP-2, respectively, on the PFD. Note that the input to the six XME-S channels is aggregated as FEED 2. UP-1 delivers 1.465 kg/hr of DP to each XME-S channel and UP-2 delivers 1.763 kg/hr DP to XME-L. Both pumps are Stainless Steel 316 and operate with power 0.01 kW, pressure change 25 psi, and temperature 20ºC. Each pump costs $1,600.

6.2.2 Channel Output

After microparticle production in the channel arrays, the continuous phase is present as an overwhelming proportion of the channel outflow volume. CP is not needed in further processing steps, so it is ideal to remove it from the particles sooner rather than later. CP cannot be recycled because all inputs in this process must be pharmaceutical grade, meaning that a CP with slightly more DCM or any other changes is an inappropriate input. For these reasons, a substantial amount of the CP solution of DCM, deionized water, and PVA is diverted immediately from downstream process units.

By means of the flared channel geometry described in Section 5.4, denser particles moving along the membrane surface remain undisturbed at the channel bottom while controlled suction pressure draws the less dense CP flowing with a laminar profile from the top of the channel. From the channel exit, 70% of the CP is drawn off via streams DIVERT 1 and DIVERT 2 in the PFD. (Refer to Section 5.4 for a discussion of the feasibility of a 70% split.)

Centrifugal pump P-3 transfers stream DIVERT 1 to surge tank T-3 at a flow rate of 113.4 L/hr. It operates at a power of .01 kW, a pressure change of 25 psi, and at 20ºC, and it costs $2,900. Similarly, six P-4 pumps transfer stream DIVERT 2 to surge tank T-3 at a flow rate of 302.4 L/hr at a power of .19 kW, and P-4 also costs $2,900. Surge tank T-3 functions to deliver CP and dilute CP to a continuous distillation column, and a discussion of this design and associated costs can be found in Section 7.7.1. A more cost-effective design is also presented such that streams DIVERT 1 and DIVERT 2 are directed to a simple storage tank.

The other 30% of the CP plus the emulsified DP from the channels is taken to the next process step continuously as streams OUTFLOW S and OUTFLOW L. These streams deliver the product to an agitated vacuum tank with diafiltration (tanks T-1 and T-2 on the PFD), which collects product for three hours before an operation stage of 12 hours as described in earlier Section 6.1. The process and operation details regarding this vessel are discussed later in Section 6.4.

Four vacuum tanks are always in use per operating XME channel array such that particles are collected and hardened simultaneously to prevent a process bottleneck. Referring to the Gantt chart, 6 of these vacuum tanks are needed for continuous XME operation. When an XME channel array finishes a batch throughput of CP and DP, it is taken out of commission for cleaning, and a second XME channel array replaces it, the four tanks used for the previous throughput are still in use for soaking the particles, and additional vacuum tanks must be used for collection during the first 6 hours of operation such that a time is available for cleaning the previously used tanks.

6.2.3 Channel Startup and Shutdown

In order to ensure proper XME operation, the channels are given a two-hour startup period. CP flows through the channels as it would during regular operation, and DP is initially jetted through the pores to ensure throughput. The latter must be addressed in the validation phase of the project, however. During startup, the channel outflow is collected in tanks, and operators involved in quality control analyze the emulsified DP droplets for monodispersity and correctness of size. The operators decide when the startup period is over, and the two hour period allotted for this accounts for time needed for potential troubleshooting. At the time of channel shut-down, when a second channel begins operation with a new batch of CP and DP, the CP is run through the first channel for two minutes longer than the batch period to ensure that all droplets produced are taken to the appropriate collection tank to await the next processing steps.

It is important to stress that a high-sensitivity control process be installed to measure particle production rate and ensure that it is consistent with desired production values. A major merit of the XME process is that particle size produced is not affected by potential pore clogging.[1] However, a slower rate of particle production rate will impact the overall process; a weight ratio of small to large particles (80:20) is required at the process end, and bottlenecks involving lags in weight produced for either particle size should be avoided. See Chapter 5 for a detailed discussion of channel design as relevant to ensure longevity and productivity of the XME process.

6.3 Pre-Process Preparation

This section addresses the XME channel input needs specified earlier in this chapter. CP and DP must be prepared at exact composition in adequate amounts for delivery to the channel arrays, and sanitary mixing tanks are scheduled to prepare and deliver inputs with startup operation in mind.

6.3.1 Continuous Phase Preparation

The continuous phase must be delivered to the XME channels at the constant rates mentioned in Section 6.2. In order to achieve the desired production requirements, the following CP properties are selected: 1.27% DCM by weight, 97.73% water by weight, and 1.00% PVA (88% hydrolyzed, MW 88.00 kg/mol) by weight. At this composition, the CP is saturated with DCM, where the solubility is 13 g/L water at room temperature and atmospheric pressure. The density of the solution is 1.007 g/mL.

PVA solutions can be difficult to homogenize because PVA becomes very sticky when first added to an aqueous phase. At least 8 hours are needed for complete mixing at room temperature and atmospheric pressure for small volumes. For larger batch volumes, it is recommended that agitators be operated at 90-98°C in order to ensure that the PVA is completely dissolved.[2] For this step, 12 hours are scheduled for mixing tank operation. Two jacketed mixing tanks will be used to prepare batches of CP in alteration, and these tanks are referred to as M-1 in the PFD and in Unit Specification Sheets. With only 8 hours needed to prepare the solution, this leaves time for a pump change from one tank to a channel array to another CP preparation tank delivering contents to another channel array, for the 2 hour startup operation, and for tank sanitization. CP from tank M-1 nears depletion after 12 hours of pump operation, and new CP from a second mixing tank takes over delivery to a new channel array.

As reported in Section 6.2, the desired flow rate of CP through the channels in order to shear small and large particles is as follows: 120 mL/s to each of the six small particle channels and 45 mL/s to the single large particle channel. At this rate, approximately 33.1 m^3 CP are required

every 12 hours. In order to account for a 2 hour period of channel startup, where operators inspect particle sizes produced in order to ensure monodispersity, 2 hours of additional CP will also be prepared for a total needed capacity of 38.6 m^3. Referring to the Gantt chart, this time occurs during the last two of the 12 hours for which the CP remains in the mixing tank as part of the preparation stage.

To accommodate reasonable volume percent for the agitation of tank contents, a 41.4 m^3 agitator/storage vessel of height 4.3 m and diameter 3.5 m is selected. For a stainless steel jacketed tank of this size operating at 95°C, the purchase cost is $82,200, according to ASPEN Process Economic Analyzer. This ASPEN program is used to price all units in downstream processing in conjunction with price quotes obtained from online suppliers to ensure up-to-date bare module costing. (See Appendix D for a table of all units evaluated using the Economic Analyzer.)

As discussed previously in Section 6.2, after mixing in unit M-1 is complete, the CP is transferred to the operating XME channel arrays via peristaltic precision sanitary pumps P-1 and P-2 as FEED 3 and FEED 1, respectively. The CP flows over the membranes in the two channel arrays, shearing large- and small- microparticles from the continuous dispersed phase flow through the membrane pores.

6.3.2 Preparation of Dispersed Phase

As discussed in Section 3.2, the molecular weight of poly(lactic-co-glycolic acid) (PLGA) used in the dispersed phase influences the achievable particle size based on desired dosage and particle degradation rate. A higher molecular weight polymer generates a sphere with a very long effective lifetime, whereas lower molecular weight spheres allow for the production of larger diameter microspheres while still maintaining zero-order release. Larger spheres allow for a much more concentrated DP and thus greater throughput. However, because lower density spheres degrade much faster, doses need to occur more frequently with lower concentrations of haloperidol. For PLGA (50:50, 40,000 Da), the following composition was selected for the DP: 0.985% haloperidol by weight, 8.319% PLGA by weight, and 90.696% DCM weight for a solution density of 1.32 g/mL.

Both PLGA and haloperidol readily dissolve in DCM, and far less DP is needed per 12 hours of channel operation than CP. DP is made in volume batches needed for 12 hours of microparticle production and 2 hours of channel startup, and this requires 96.0 L DP. Larger batches of DP could be prepared, even for the entire 90 day process cycle which requires 17.27 m^3, but because the organic DP requires precise composition, and imperfect sealing over a period of time and potential leaks must be considered, a batch preparation process for 12 hours of channel operation is selected. Stainless steel mixing tank M-2 with nominal capacity 113.6 L is scheduled for prepare DP for one hour before delivery to the channels for startup and then regular operation. After 12 hours of microparticle production and when the DP is near depletion, a second tank holding DP is connected to a new channel beginning production with a new batch of CP. Mixing tank M-2 has a height of 0.94 m, a diameter of 0.53 m, and costs $2,310.

6.4 Hardening Emulsified Droplets in a Vacuum Tank with Diafiltration

The drying of residual solvents is usually the rate limiting step in pharmaceutical production.[3] A method to achieve dry, hard microspheres without further shearing the emulsified DP droplets formed in the microfluidic channel is a major design objective. It is also important to emphasize that DCM removal from the emulsified particles present in streams OUTFLOW S and OUTFLOW L must meet pharmaceutical standards set forth by governmental organizations. DCM can pose significant health risks if ingested, and PVA adheres to the PLGA microparticles, affecting weight distribution in packaging, so quality control is considered in detail in this section.

6.4.1 Operating Conditions for Solvent Removal

According to literature, [4,5,6,7] stirring channel outflow at 300-400 rpm, in combination with a vacuum or increased temperature, is an efficient method of solvent removal in polymer microparticle production. Evaporation of solvent, as compared to spray-drying, direct freeze drying, and extraction processes, has a smaller effect on particle porosity and thus on drug release. Studies consistently show that less initial burst occurs and that subsequent drug release is more prolonged in spheres processed with accelerated evaporation.[8,9,10,11] While low temperatures are good for extraction due to increased solubility of solvent, higher temperatures are of course more practical for solvent evaporation. Additionally, the viscous boundary, or glass transition state, is achieved more quickly at higher temperatures.[12]

At atmospheric pressure, the boiling point of DCM is approximately 40°C, and at this temperature, DCM solubility in water is 27 g/L and the vapor pressure is 800 mmHg.[13] Freitas et al (2005) compared two methods, increasing temperature to the boiling point and reducing pressure below the vapor pressure, for speeding PLGA microparticle hardening and DCM removal. The study determined that under a 420 mmHg vacuum for 2 hours, DCM is removed completely. The reduced pressure does not affect drug release rate or drug encapsulation in scenarios relevant to this report. Additionally, when temperatures are increased to 40°C, drug encapsulation is not affected. Rapid temperature changes, however, cause the polymer sphere wall thickness to decrease, resulting

in more hollow microparticles where drug diffusion can occur more readily, potentially leading to a high initial burst upon intramuscular injection. (See Section 2.3 for a discussion of polymer matrix properties and effect on controlled release.) In contrast, a gradual temperature change maintains the polymer matrix.[14]

6.4.2 Function of Salt during Particle Solidification

To further harden particles, a number of studies utilize solvents that tighten the PLGA polymer matrix before complete DCM removal. In the particle, kinetics of the cross-linking reaction and the volume loss due to solvent diffusion should be balanced by the solvent extraction solution selected. Examples of solutions used include sodium oleate, 2 M $CaCl_2$ and 1 M HCl.[3,15] Some of these solvents significantly decrease the release profile lengths, especially at such high concentrations. However, salt is needed in the process to prevent particle aggregation during the hardening process.[1,3]

Salt solution helps promote the aggregation of a gel-like layer of PVA coating on the outside of the PLGA microparticle, which prevents the leeching of haloperidol. PVA conjugation to PLGA in solution strongly depends on the ionic species present and its hydration enthalpy.[16] A high hydration enthalpy implies that the salt ion is more likely to participate in hydration versus in complex with PVA.

While the aggregation of PVA prevents the leeching of haloperidol into solution during the hardening process, it can also inhibit the movement of DCM out of the particle. This highlights the importance of creating a layer of PVA that is neither too thick nor too thin; this is accomplished by choosing an appropriate concentration of salt that promotes the aggregation of PVA in a sufficient quantity. The selective quality of the PVA layer is due to the difference in characteristic radius of DCM versus haloperidol, which is a much larger, more complex molecule.[16] PLGA is assumed to have no tendency to leave the particle due to its significantly larger radius.

Studies indicate that a 0.5 M solution of NaCl is enough to prevent leeching of the target drug into solution, while still allowing for sufficient passage of DCM so as not to extend the drying

time.[16] Post-hardening, it is necessary to remove any remaining salt and PVA remaining on the particles, necessitating a rinse step.

6.4.3 Effects of Residual PVA

While the removal of salt is easily affected by simply rinsing the hardened particles with deionized water, the removal of PVA required additional analysis. There are two locations in which PVA exists in the hardened microparticle suspension: free in solution, and adhered to the surface of the particles. PVA free in solution, like salt ions, is easily removed via rinsing. The PVA itself tends to conjugate with the PLGA, making it impossible to remove completely.[17]

PVA is nontoxic to the body, and it is therefore unnecessary to remove it entirely from the finished particles. It is, however, still important to quantify the amount of residual PVA in the particles. The final packaging of doses requires a precise combination of small and large particles by weight. This precise weighing, as discussed in Section 3.2, ensures that the ratio of small to large particles is that which produces a zero-order release, and it also ensures that each dose contains an appropriate amount of drug to effect the optimal therapeutic blood serum concentration for a month-long period. Thus, the increase in weight of the particles must be used to adjust the doling out of both small and large particles by weight into single dose ampoules.

According to one study, PLGA particles that use DCM as the primary solvent retain PVA as a percentage of overall weight (weight of PVA/weight of particle and PVA) of 6.15%±0.35.[16] This indicates that an upward mass adjustment of 3.375×10^{-4} mg and 1.969×10^{-4} mg per small and large particle, respectively, during the packaging step. Originally, 4.249 g of combined particle sizes was considered one dose, and removing 6% of the haloperidol, a dose size becomes 4.222 g. Now, an additional 9.545 mg of small particles and 1300.10 mg of large particles will be weighed out per dose, for a final small particle to large particle weight ratio of 85:15 and total dose weight of 5.532 g.

The coating of PVA is inherent in the experimental drug release profiles that were used to generate the Raman model that is used here to build a drug release model, as discussed in Section 3.1. Therefore, no modification of the drug release profiles generated previously is necessary.

6.4.4 Vacuum Tank Design

We now translate the methods used in literature to a three-prong approach for solvent removal and particle hardening in which a vacuum, increased temperature, and diafiltration are combined in one step. The two OUTFLOW streams from XME-S and XME-L containing microparticles emulsified in CP enter two different vacuum tanks, T-1 and T-2, respectively, where they are gently stirred and diafiltration is performed using a cross-flow filter set up. For one hour, CP is continuously extracted from the tank bottom through a continuous flow filter and 0.5 M NaCl is simultaneously added at the same rate. Hardened particles sink to the bottom of the tank while DCM-rich particles remain in suspension above the filter. As the tank temperature is gradually increased to 40°C and at 420 mmHg, DCM in the droplets is extracted into the CP solution or evaporated. The one hour time step is selected based on studies in literature where either increased temperature or reduced pressured were used to evaporate DCM for anywhere between 2 hours to 6 hours.[14] Combining both of these stages with diafiltration implies a reduced time needed for DCM removal, although the allotted time period may be adjusted if this is found necessary during the trial process.

After DCM removal, a rinsing step follows for a half hour during which particles settled on the filter basket are washed with deionized water to remove salt and residual PVA. A soaking period of 10 hours at 40°C and high agitation removes 6% of the particles' haloperidol content to eliminate an initial burst in the release profile, as discussed in Section 6.1. Figure 6.5 on the next page shows a tank representative of the vacuum tanks used in this process with all input and output streams.

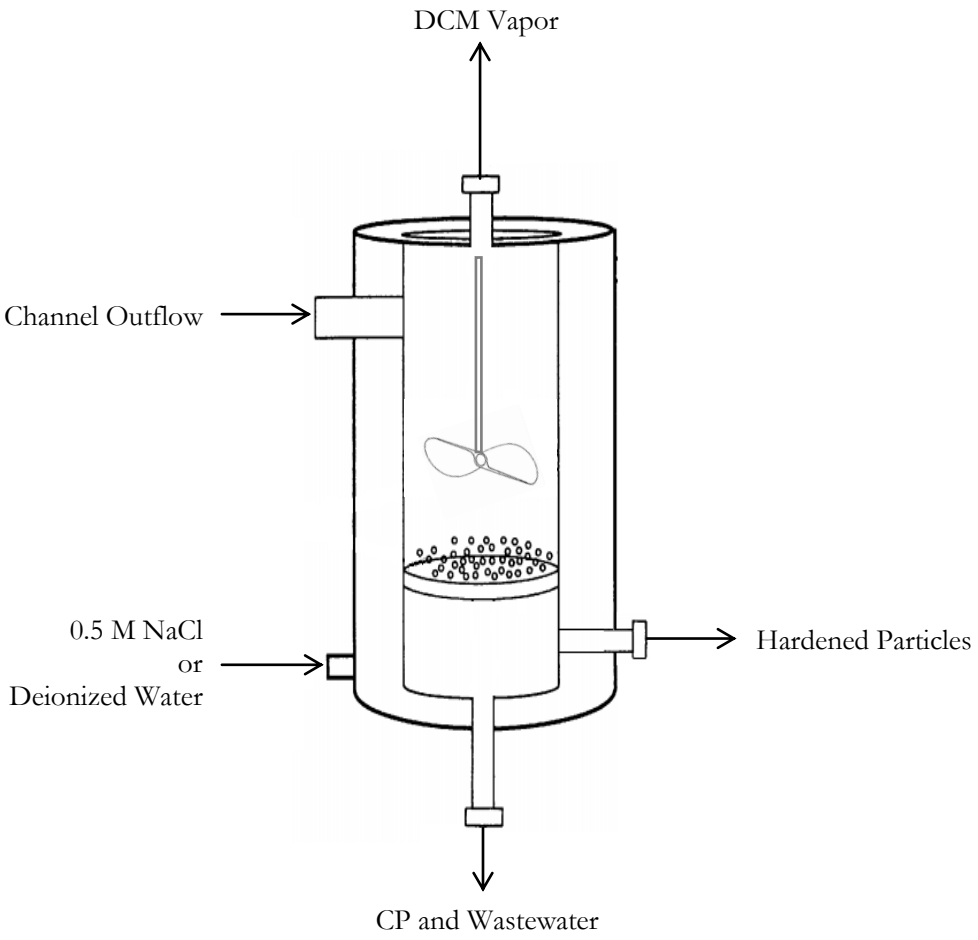

Figure 6.5. Schematic of Jacketed Mixing Tank with Diafiltration and Vacuum. At high temperature and reduced pressure, DCM vapor leaves the vessel as salt solution is used to harden the particles, which fall into the filter basket. Particles are then rinsed with deionized water and then soaked in high temperature water. Waste from is pumped from the bottom of the vessel.

The semi-batch vacuum tank is scheduled to accommodate a residence time of 11.5 hours plus an additional half hour for particle transfer from the vacuum tank filter to the freeze-drying step. Continuously produced microparticles are collected and then transferred to a vacuum tank on a 3 hour basis, and particles at the end of the soaking stage are collected per CP batch before freeze-drying. Referring to the Gantt chart, it is visible that 4 tanks are therefore needed per channel array during operation, and over a 24 hour period, at least 6 tanks are needed per operating XME channel array to accommodate time for tank sanitization.

6.4.5 Stream and Equipment Specifications

Referring now to the PFD, vacuum tank T-1 receives stream input OUTFLOW S for a three hour period, and then diafiltration with stream NACL 2 containing 0.5 M NaCl solution for one hour. After rinsing by stream WATER 2 containing deionized water for 30 minutes, and diafiltration by water stream SOAK 2 for 10 hours, the product is small particle-rich retentate ready for transfer to freeze-drying via stream DRY S. The CP and water vacuum-pulled from the tank is taken to surge tank T-3 via stream DIVERT 4 and pump P-6 for distillation. The haloperidol and water introduced during the soaking period is collected separately in collection tank T-5 as stream DIVERT 6 via pump P-8. This stream does neither contains organic phase nor does it require separation. Rather, it just needs wastewater treatment and as such, is stored in tank T-5.

Vacuum tank T-2 hardens large particles in the same fashion, with input streams OUTFLOW L, NACL 1, WATER 1, and SOAK 1, and outputs DRY L, CP-water stream DIVERT 3, and haloperidol-water stream DIVERT 5, where DIVERT 3 is delivered to surge tank T-3 via pump P-5 and DIVERT 5 is delivered to collection tank T-5 via pump P-9. The large particle-rich retentate is then taken to the lyophilization step separately. For stream flow rates and compositions, refer to Table 6.1 in Section 6.6.

Both vacuum tanks are stainless steel jacketed vessels ready for operation at primarily 40ºC and 420 mmHg. Tank T-1 has a volumetric capacity of 350 L, height of 1.25 m, and diameter of 0.60 m, and its purchase cost is $12,100. Tank T-2 has a capacity of 6.19 m^3, height of 3.5 m, diameter of 1.5 m, and cost of $35,500. All pumps used here in conjunction with these vacuum tanks are centrifugal and made of Stainless Steel 316. Pump P-5 operates at a power of 0.01 kW, delivering 97.0 L/hr to surge tank T-3 while P-6 operates at 0.38 kW and delivers 1818.7 L/hr to the same tank. P-5 costs $2,900 and P-6 costs $3,300, and both pumps operate at 20ºC and have a pressure change of 25 psi and fluid head of 9.14 m. It is important to note here that six pumps of both types are needed for continuous microparticle production, as one pump is needed for each type of the 6 vacuum tanks. Details for surge tank T-3 are given in Section 6.5 with additional stream inputs.

Collection tank T-5 has a volumetric capacity of 8.24 m^3, height of 2.7 m, and diameter of 2.0 m, and its purchase cost is $22,500. Pumps P-8 and P-9 operate continuously for the 10 hour

period for which haloperidol-water solution is removed from the vacuum tanks. Six of each of these pumps is needed as well. P-8 delivers 24.23 L/hr with a power of 0.01 kW and P-9 delivers 387.6 L/hr at power 0.19 kW. Both pumps share other temperature, pressure, and fluid head conditions with P-5 and P-6. P-8 costs $2,900 and P-9 costs $3,200.

The weight fraction of DCM in streams OUTFLOW S and OUTFLOW L is 0.013, while the weight fraction solubility of DCM in water in the vacuum tank's temperature and pressure conditions is 0.027. All DCM from the CP in the OUTFLOW streams is thus assumed to leave the tanks in the continuous retentate removal. DCM in the emulsified DP droplets leaves the tanks after evaporation through the vacuum chamber. The small amount of DCM can be condensed and sold on the market or disposed of according to environmental and governmental standards.

6.4.6 Quality Control

Particles hardened in the vacuum tanks are removed after the 11.5 hour operation process. The filter baskets on which the particles settle are removable from the tanks, and the now virtually unbreakable particles can be transferred to freeze-drier F-1. Since particles are removed from the tanks in 4 batches per 12 hour operation period of an XME channel array, particles may be stored before reaching this next step. However, before all particles are lyophilized and packaged, they must be inspected for safety and to ensure that the product meets pharmaceutical standards for good manufacturing practice.

First and foremost, the removal of DCM must be verified. As a toxic substance, certain concentrations of DCM in the particles can seriously harm a patient injected with the polymer encapsulated drug (see MSDS report in Appendix G). The maximum allowable concentration of DCM in pharmaceutical products is 500 ppm, according to the U.S. Environmental Protection Agency (EPA).[18] Particles not meeting this standard will be sent through the vacuum tank stage once more and tank operation will also be inspected for proper function.

Second, the NaCl must be completely washed from the particle surfaces. Any remaining ions add weight and detract from the quality of the product. Operators working in quality control will ensure that no substantial salt remains and that any PVA coating the particles has conjugated to the

PLGA polymer matrix. To verify proper particle distribution by weight further downstream, the weight of PVA per particle weight may be investigated for both particle sizes to meet the calculations presented in Section 6.4.3.

As this occurs, particle size will also be verified. Here, monodispersity of particles and appropriate diameter will be ensured for the dry particles. Satellite particles or aggregated particles will be investigated and a batch may be filtered to remove such deposits.

Perhaps the most important aspect of quality control is the verification of appropriate haloperidol content in the particles. The haloperidol exiting the vacuum tanks should approximate 94% of what entered the tank from an XME channel array. Each dose must contain 387 mg of haloperidol, or 10.59% weight percent of a total dose; a small particle should contain 5.453×10^{-4} mg haloperidol and a large particle should contain 3.182×10^{-3} mg haloperidol. If the drug content is not of proper concentration within a particle, then the downstream process may need further design specifications and may be altered accordingly.

6.5 DCM Removal by Continuous Distillation

In this section, we turn our attention to streams DIVERT 1-4, which transfer CP and dilute CP to surge tank T-3 toward a continuous distillation process. Originally, a separation of DCM from water waste and sale of DCM was targeted as the best manner of waste disposal from the XME process. This is not the case, however, and an alternative waste disposal method is presented.

PVA, which is highly soluble in water, is an environmentally safe compound for disposal.[18] DCM, however, has serious health and environmental effects and must be handled with care, and strict EPA standards must be followed for disposal. Concentrated DCM may be sold to paint-thinner companies or elsewhere for a profit, but at a purity of below 90% is not saleable on the market. Continuous distillation was selected as a separation process to achieve a bottoms product of water with trace DCM and containing almost all of the heavy PVA polymer and a distillate product of saleable DCM.

For reference in the following discussion, Figure 6.6 is presented as an expanded view of the portion of the PFD capturing the distillation process and all involved units and streams.

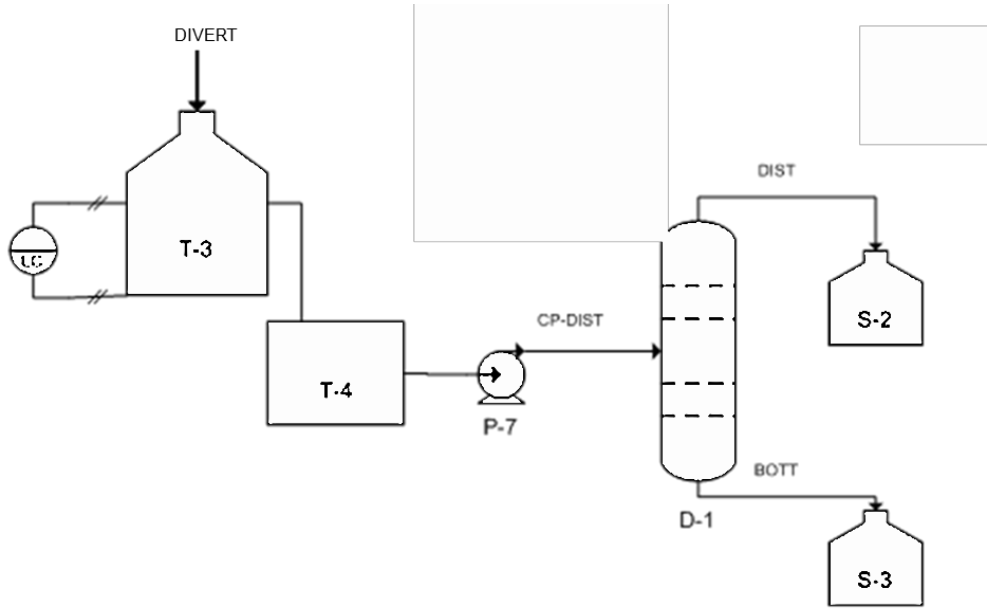

Figure 6.6. Distillation Process. This is an expanded view of the continuous distillation of diverted CP and dilute CP taken from the PFD. DIVERT streams 1-4 are indicated simply as "DIVERT" in this diagram.

The distillation was simulated in ASPEN PLUS using batches of mass flow rates on a 1.5 hour basis; streams DIVERT 1 and DIVERT 2 enter surge tank T-3 continuously for 1.5 hours, and during this period, a full volume of CP diluted with 0.5 M NaCl and water from the vacuum tanks will finish accumulating in the same tank. At 1.5 hour intervals of total volume accumulation in the tank, the contents are fed to storage tank T-4, which continuously feeds distillation column D-1 via centrifugal stainless steel pump P-7 operating at .38 kW with pressure change 25 psi for a flow rate of 5138.1 L/hr. The two tanks here allow the distillation column to be fed a constant composition and flow rate of feed. Feed from T-4 to D-1 is staggered from the surge of dilute CP from T-3 to T-4 to avoid depletion of distillation column input.

The input summary and simulation results for this scenario are reported in Appendix E. According to the results, a trace amount of DCM is found in bottoms water/PVA product stream BOTT. The DCM concentration regulation for disposal of this solution is .004 mg/L water.[19]

To yield the desired DCM-free bottoms product from the distillation column, and to operate with the desired reflux ratio of 1, the distillation column is designed to have a height of 6.40 m and a diameter of 0.85 m. Trays required for the separation is 10, and feed enters at tray 5. The unit has a purchase cost of $160,500. The additional units necessary, tanks T-3 and T-4, and pump P-7, cost $55,900, $56,800, and $3,300, respectively. Tank T-3 has a capacity of 48.11 m^3, height of 5.0 m, and a diameter of 3.5 m, and tank T-4 has has the same capacity, height, and diameter, but as a continuous vessel, costs less. The distillation tower products also require storage tanks for both the distillate and bottoms products, S-1 and S-2, respectively. S-1 has capacity 4550 L, height 4.02 m, diameter 1.20 m, and costs $17,200. S-2 has capacity 9360 L, with height 5.3 m and diameter 1.5 m, and costs $20,200. All equipment discussed here is constructed of Stainless Steel 316.

In order to achieve a higher purity DCM product, one scenario was modeled in which the distillate was condensed and then decanted at high pressure and low temperature. However, changing the temperature and pressure parameters did not make a significant difference in either water or DCM purity since DCM is miscible in water. Thus, the process was not considered financially feasible, so further processing of the distillate is not recommended. In fact, after a cost analysis of the distillation column in Section 7.7.1, and realizing that the distillate DCM product cannot easily be sold on the market, it is overall more productive to simply transport combined

waste from all the DIVERT streams to a wastewater treatment facility. This only requires a storage container similar to tank S-1 and transportation costs discussed in Section 7.7.1.

6.6 Freeze-drying and Packaging

Lyophilization of the particle-rich retentate from the vacuum tank step occurs in a semi-batch manner. Transfer of streams DRY S and DRY L to a freeze-drying unit serves to remove wash fluid adhering to the microparticles' surface. Complete drying of particles has been successful as the following conditions: -70°C under vacuum at 0.1 mmHg for 10 hours, followed by vacuum-drying at room temperature for 1 hour.[20] A 10 hour drying time is selected for the 4 batches of particles obtained from vacuum tanks collecting particles from a single XME channel array that operates for 12 hours. The Gantt chart shows that 24 hours after a channel begins producing particles for collection, lyophilization begins for that entire given production batch.

Industrial freeze-drying unit F-1 has a 60 L capacity when operating at the aforementioned temperature and pressure conditions and costs $99,950. Two of these industrial freeze-dryers are not needed to schedule cleaning, or defrosting, during the 90 day process cycle because the time during the continuous XME process for which they are not use is sufficient for this. The small and large particles will be lyophilized separately such that when completely dry, they can be mixed for packaging at the appropriate weight ratio discussed in Section 6.4.3 by an ampoule filling unit.

The particles are combined in 6 parts 20 μm diameter particles and 1 part 36 μm diameter particles by weight. They are dispensed into vials of individual dose weight, so that a single dose of 5.559 g of microparticles can be administered to a patient. Each dose requires .06125 g of dried PBS media, to be resuspended in 5 mL of water before intramuscular injection.

At the production levels described, 500,000 doses are manufactured during the process cycle, so 500,000 ampoules must also be purchased. These ampoules are filled by particle distributor A-1into dose-size vials after the freeze-drying step. Unit A-1 fills 80-150 ampoules/minute with ±3% precision and costs $1,055,000. Ampoules are vacuum-sealed and stored in a dark location at or below room temperature.

6.7 Streams Summary

This section details all streams in the process, providing all mass flow rates in and out of all process equipment with the exception of pumps. The table also serves as a mass balance check and as a check for desired overall haloperidol production per 90 day cycle.

Table 6.1. Streams Summary and Throughput Analysis.

Stream	Unit-out	Unit-in	Component	Flow rate	
FEED 1	S-1 CP Storage Tank	Small-particle channel array	*total*	2610.144	kg/hr
			DI Water	2550.894	
			PVA	26.101	
			DCM	33.149	
FEED 2	M-2 DP Mixing/Storage Tank	Small-particle channel array	*total*	8.791	kg/hr
			PLGA	0.731	
			Haloperidol	0.087	
			DCM	7.973	
FEED 3	S-1 CP Storage Tank	Large-particle channel array	*total*	163.134	kg/hr
			DI Water	159.431	
			PVA	1.631	
			DCM	2.072	
FEED 4	M-2 DP Mixing/Storage Tank	Large-particle channel array	*total*	1.763	kg/hr
			PLGA	0.147	
			Haloperidol	0.017	
			DCM	1.599	
OUTFLOW S	Small-particle channel array	T-1 CSTR - small particles	*total*	57.731	kg/hr
			PLGA	0.731	
			Haloperidol	0.087	
			DI Water	47.829	
			PVA	0.489	
	*includes emulsified smaller particles		DCM*	8.595	
OUTFLOW L	Large-particle channel array	T-2 CSTR - large particles	*total*	784.806	kg/hr
			PLGA	0.147	
			Haloperidol	0.017	
			DI Water	765.268	
			PVA	7.830	
	*includes emulsified larger particles		DCM*	11.544	

Stream	Unit-out	Unit-in	Component	Flow rate	
DIVERT 1	Large-particle channel array	T-3	*total*	114.194	kg/hr
		Surge Tank	DI Water	111.602	
			PVA	1.142	
			DCM	1.450	
DIVERT 2	Small-particle channel array	T-3	*total*	1827.101	kg/hr
		Surge Tank	DI Water	1785.626	
			PVA	18.271	
			DCM	23.204	
NACL 1	--	T-2	*total*	775.213	kg/hr
		CSTR - large particles	0.5 M NaCl	775.213	
NACL 2	--	T-1	*total*	48.451	kg/hr
		CSTR - small particles	0.5 M NaCl	48.451	
WATER 1	--	T-2	*total*	193.803	kg/30 min
		CSTR - large particles	DI Water	193.803	
WATER 2	--	T-1	*total*	12.113	kg/30 min
		CSTR - small particles	DI Water	12.113	
SOAK 1	--	T-2	*total*	387.606	kg/hr
		CSTR - large particles	DI Water	387.606	
SOAK 2	--	T-1	*total*	24.225	kg/hr
		CSTR - small particles	DI Water	24.225	
DIVERT 3	T-2	T-3	*total*	1067.386	kg/3 hrs
	CSTR - large particles	Surge Tank	DI Water	288.840	
			PVA	1.468	
			DCM	1.865	
			0.5 M NaCl	775.213	
DIVERT 4	T-1	T-3	*total*	4723.219	kg/3 hrs
	CSTR - small particles	Surge Tank	DI Water	4621.443	
			PVA	23.491	
			DCM	29.834	
			0.5 M NaCl	48.451	
DIVERT 5	T-2	T-5	*total*	387.609	kg/hr
	CSTR - large particles		DI Water	387.606	
			Haloperidol	0.002	
DIVERT 6	T-1	T-5	*total*	24.238	kg/hr
	CSTR - small particles		DI Water	24.225	
			Haloperidol	0.012	

Stream	Unit-out	Unit-in	Component	Flow rate	
CP-DIST	T-4 Storage Tank	D-1 Distillation Column	*total*	15216.178	kg/hr
			DI Water	9225.568	
			PVA	87.632	
			DCM	5902.978	
DRY L	T-2 CSTR - large particles	F-1 Freeze-dry	*total*	0.510	kg/3 hrs
			DI Water	residual	
			PLGA	0.433	
			PVA	0.032	
			Haloperidol	0.045	
DRY S	T-1 CSTR - small particles	F-1 Freeze-dry	*total*	2.542	kg/3 hrs
			DI Water	residual	
			PVA	0.159	
			PLGA	2.160	
			Haloperidol	0.223	
PRODUCT-L	F-1	A-1	*total*	2.039	kg/12 hrs
			PVA	0.127	
			PLGA	1.733	
			Haloperidol	0.179	
PRODUCT-S	F-1	A-1	*total*	10.168	kg/12 hrs
			PVA	0.634	
			PLGA	8.640	
			Haloperidol	0.894	

Total particles produced per 90 day process cycle		
Large (50 μm diameter)	367.039	kg
Small (20 μm diameter)	1830.224	kg
Total haloperidol encapsulated	193.114	kg
Total haloperidol per dose	0.387	g
Weight particles per standard dose	5.559	g
Number doses produced	500,000	per process cycle
Large:small particle weight percent ratio	15:85	

6.8 Chapter 6 References

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Chapter 7: Economic Analysis

7.0 Introduction

This chapter divides the overall economic implications of the haloperidol controlled release product and XME platform into the following segments: market analyses, profitability analysis, and sensitivity analyses. The market analysis first focuses broadly on the antipsychotic market, and then narrows to an analysis of the schizophrenia market. A comparison of the two drug classes (atypical and typical) within these sectors is presented and used to estimate a projected market share capture of the haloperidol controlled release product. This market share is derived from erosion of the atypical antipsychotic sector, and capture of share in the typical sector, where haloperidol is classed. A profitability analysis is then presented, including summaries of fixed costs, variable costs, and cash flows, and then culminates with the presentation of net present value (NPV) and internal rate of return (IRR) as profitability metrics. The robustness of these profitability metric is then analyzed in a sensitivity analysis, which examines 'worst-case' and 'best-case' scenario options for the haloperidol product.

7.1 Antipsychotic Market Analysis: Unmet Needs, Disease and Drug Classifications

The global antipsychotic market is valued at approximately 19 billion USD, and is a declining market, due to both its maturity and the increasing cost constraints brought on by generic competition. The market is expected to decrease in value significantly in the upcoming ten years, due to the patent expiry of Zyprexa and Seroquel, with annual revenues of 3.9 billion and 5.0 billion, respectively. This opens up the field considerably for new generic imitators, especially in the U.S., where the FDA, government regulation, and legal outcomes point towards increasingly receptive attitudes towards generics.[1]

The antipsychotic market is composed of four major disease classes and two antipsychotic drug classes. The disease classes are schizophrenia, bipolar disorder, depression, and anxiety disorders. There is significant cross-over between these classes, most notably depression and anxiety disorders, which are often co-morbid to other classes. The two major drug classes are typical antipsychotics (N5A9) and second-generation atypical antipsychotics. Typical antipsychotics were first introduced in the 1950s to treat a wide variety of disorders, but are often associated with poor tolerability and severe side effects like tardive dyskinesia and Parkinson-like syndromes. Atypical antipsychotics were developed with pharmacological properties in mind, and are generally active or partially active on multiple receptors. Atypical antipsychotics generally have improved side-effect profiles and higher efficacies than their first generation antecedents.[1]

$000s	*Sales, 2009*	*Sales, 2018f*	*CAGR 2009-2018*	*Market Share, 2018f (%)*
Atypical Antipsychotics	18,347	14,896	-2.3	93.4%
Seroquel	4,984	595	-21	3.7%
Zyprexa	3,861	979	-14.1	6.1%
Abilify	4,144	973	-14.9	6.1%
Risperdal	850	473	-6.3	3.0%
Risperdal Consta	1,088	384	-10.9	2.4%
Geodon	1,054	138	-20.2	0.9%
Invega	397	134	-11.4	0.8%
Seroquel XR	267	204	-2.9	1.3%
Atypical Generics	1,395	7,532	20.6	47.2%
Other Atypicals	307	3,484		21.9%
Typical Antipsychotics	668	1,049	5.1	6.6%
Haloperidol	30	25	-1.9	0.2%
Typical Generics	208	235	1.4	1.5%
Other Typicals	430	789		4.9%
Total*	19,015	15,945	-0.1	100%

2009 - 96.5% (Atypical), 3.5% (Typical)
**7MM (US, Japan, France, Germany, Italy, Spain, UK)*

Table 7.1. Top Selling Drug Brands in the Antipsychotic Category.[1]

There are several features that are important to note. First, the antipsychotics with the highest revenues are primarily indicated for schizophrenia. Second, the typical and atypical generics sectors are the sole sources of growth for the market. It is interesting to note that the typical antipsychotic market is also projected to increase, a finding that has several implications. It suggests that the pipeline for atypical antipsychotics has limited prospects, either from a price competitiveness point of view, or limited clinical improvements. The primary drivers in typical antipsychotic sales are reformulations and improvements on current drugs, such as extended release and formulations targeted at increasing patient compliance. The increasing availability of extended release formulations has increased demand for depot formulations of drugs, as a way of ensuring patient compliance. Previously, injectable formulations were used primarily for acute situations only, and were financially and logistically impractical for long-term use outside of a primary care facility. This is yet another bolster for typical antipsychotics, most of which have long since lost patent protection and are now manufactured by a variety of generics. While there are some big

pharmaceutical companies that have in-house drug delivery developments, the truly specialized technologies continue to lie outside of big pharma. These firms work with off-patent drugs due to the difficulty and reduced revenue share achieved when working with licensed products. Newer technologies also tend to work with off-patent drugs as models, giving them a headstart when it comes to accelerating to the manufacturing stage.

7.2 Schizophrenia Market Analysis: Symptoms, Prognosis, Economic Burden, Prevalence, and Impact of a Controlled Release Formulation

Within the antipsychotic market, schizophrenia is one of the single largest disease classes, valued at 5.7 billion, approximately 30% of the total antipsychotic market. Schizophrenia is a very mature market, having a variety of blockbuster drugs that draw their revenue primarily from this market. This market is subject to the same price competitiveness and draws from largely the same pipeline as the overall antipsychotic market, and therefore looks to the same sources of innovation to combat those forces.[2]

Symptoms and Prognoses. Schizophrenia is a complex mental disorder marked by a lack of normal emotional responses, reality perception, and logical thought. These symptoms occur in varying degrees for each patient, and the severity of symptoms dictates the level of care and autonomy that is recommended. The root causes of the disease are yet unknown, but it most commonly onsets in the early teen to young adult years, though there are instances of childhood-onset schizophrenia, though these are rare. There are several types of schizophrenia, including paranoid, disorganized, catatonic, and undifferentiated. Regardless of type, there are currently no medical tests to diagnose schizophrenia, and patients are examined by psychiatrists to diagnose the condition. Schizophrenia is a life-long illness, and the majority of patients need to stay on antipsychotic medication for life.[3]

The table below summarizes prognoses for schizophrenia patients. For those patients that have already completed 10 years of treatment, 25% experience a full recovery. After that mark, only 10% of that original population experiences improvement, but are still unlikely to make a full recovery. The question of whether these statistics represent only the progressive and variable nature of the disease, or rather a flaw in current treatments is indeterminate.[4]

10 Years	Time Post-Diagnosis	30 Years
25%	Complete Recovery	25%
25%	Improved: Relative Independence	35%
25%	Improved: Require Extensive Support Network	15%
15%	Unimproved: Hospitalized	10%
10%	Dead (Mostly Suicide)	15%

Table 7.2. Future Prognoses of Schizophrenia Patients.[4]

Schizophrenia Population/Prevalence. The population of people with schizophrenia is expected to increase to 5.0 million, from 4.5 million. The increase in global prevalence is estimated at roughly 31,329 new patients per year, with 24,702 of those new patients being diagnosed in the U.S. This accounts for 78% of the total influx of new patients. The U.S. also has the largest population of schizophrenia, at 2.1 million, which amounts to 46% of global incidence. The next highest incidence is dramatically lower, in Germany with 552 thousand patients, followed by Japan with 530 thousand patients. The U.S., therefore, is the market that will allow for the greatest access to patients. An entrance into the U.S. market will immediately allow for 46% of the overall schizophrenia population, pending approval of the drug from the Food and Drug Administration (FDA). Access to the remaining 54% of the schizophrenia population will be achieved upon approval from the European Medicines Agency (EMA) and the Japanese Pharmaceutical and Medical Devices Agency (PMDA), the FDA equivalents in the EU and Japan. Approval from these two agencies after FDA approval is historically guaranteed; therefore approval from the FDA can be simplistically considered as allowing access to the entire market. [5]

Global incidence of schizophrenia is estimated at approximately 24 million, according to the World Health Organization (WHO). However, of that population, only 4.6 million are diagnosed and treated, only 19.1% of the total affected. Of those 4.6 million, 99.98% live in the seven major markets (7MM), which consists of the U.S., Japan, France, Germany, Italy, Spain, and the UK. Only 0.02% of treated patients live outside of these major economic zones, implying a huge dearth of treatment in many countries. These countries fall into two archetypes: the first, countries with

underdeveloped healthcare systems and a lack of healthcare professionals and the second, countries where individuals with mental illness face intense social stigma. When the cost of schizophrenia is considered, it becomes apparent why only first-world countries can afford to extend proper care to this population.[5,6]

The Economic Burden of Schizophrenia. The cost of schizophrenia outside of the U.S. is not well-documented, as a result, the U.S. is taken as a model for costs globally, although it is likely that there is significant variation across countries. The overall cost of schizophrenia in the United States, estimated in 2002, was 62.7 billion USD. This cost is composed of three different categories: direct healthcare costs, direct non-healthcare costs, and excess indirect costs. Direct healthcare costs are broken down into outpatient care, inpatient care, long-term care, and drugs. Inpatient costs are associated with the most severe cases of schizophrenia, and severity decreases as patients shift to long-term care, still under supervision, and finally outpatient care, where patients are either living independently or under light supervision. Direct non-healthcare costs care composed of costs from law enforcement, homeless shelters, and research and training of staff for schizophrenia. Indirect costs quantify the societal impact of the disease from loss of productivity, and include the costs of increased unemployment, reduced workplace productivity, premature mortality from suicide, and family member caregiving time.[2,4,6,7]

	$ billion USD
Overall Cost	62.7
Direct Healthcare Costs	22.7
Outpatient Care	7.0
Inpatient Care	2.7
Long-term Care	8.0
Drugs	5.0
Direct Non-healthcare Costs	7.6
Indirect Costs	32.4

Table 7.3 The Economic Burden of Schizophrenia in the United States in 2002.These costs were calculated in 2002, and have increased, as a result of the worsening economy and the increase in CPI during the aftermath of the 2008 financial crisis.[4,7]

Impact of a Controlled Release Formulation. With a chronic condition such as schizophrenia, it is important to maintain consistency in order to avoid relapses, whether those come at the hands of too little, or too much, drug. Studies show that increasing numbers of episodes and relapses in schizophrenia gradually and significantly damage the brain, dramatically increasing the likelihood of permanent impairment. This increasing level of impairment is directly associated with loss of independence, and ultimately a higher cost burden per patient. Taking into account these symptoms, the merits of a controlled release formulation that effects a constant concentration of drug in the body are clear. The product explored here helps to ensure the regulation of drug concentration in the body, reducing overall relapses, side effects, and giving the patient the best chance at making a recovery and regaining some of their former autonomy. Here, an evaluation of the potential healthcare savings per patient as a result of a controlled release formulation is presented.[7]

Using the estimated cost of schizophrenia, the incidence of schizophrenia in the U.S. in 2009, and the median household income from 2006-2010, a cost per patient was calculated, adjusting for changes in the value of USD. The average cost per schizophrenia patient is 29,759 USD, which accounts for 57% of the median household income in the U.S.[8]

Incidence of Schizophrenia in the U.S.	$ 2,106,900
Overall Cost Burden	$ 62,700,000,000
Cost per Patient	$ 29,759
Median Household Income, 2006-2010	$ 51,914
Cost per Patient, % of Household Income	57%

Table 7.4. Important Cost Burden Metrics for Schizophrenia.[2,8]

Utilizing the same costs, the cost savings associated with an improvement of a patient from inpatient to long-term to outpatient are calculated. First, seven locations are presented and categorized into inpatient, outpatient, or long-term, along with an estimated percentage of the total U.S. schizophrenia population in that location. This percentage is then converted to a total population count, using the total U.S. schizophrenia population in 2009.

Percentage	Population	Location	Categorization
6%	126,414	Homeless or Shelters	Outpatient
6%	126,414	Jail	Outpatient
5%	105,345	Hospitals	Inpatient
10%	210,690	Nursing Homes	Long-term
25%	526,725	Supervised Housing	Long-term
25%	526,725	Family Member	Outpatient
23%	484,587	Independent	Outpatient

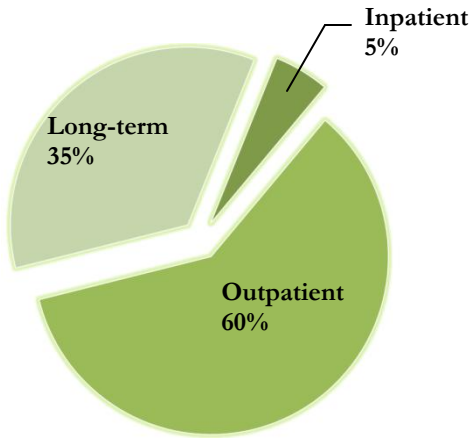

Table 7.5. Living Situations of Schizophrenia Patients. [4] This breakdown of the locations of patients was used to calculate a cost per patient based on the cost burdens presented in Table 5.3 for each of these categories.

From here, the total populations in each category are aggregated, and evaluated alongside the estimated costs of each category, to present a cost per patient.

Category	Population	Cost per Patient
Inpatient	105,345	$ 25,630
Long-term	737,415	$ 10,849
Outpatient	1,264,140	$ 5,537

Table 7.6. Estimated Population and Costs of Inpatient, Long-term, and Outpatient Categories of Patients Suffering from Schizophrenia.[2,4]

Cost savings for a patient moving from inpatient to long-term and finally outpatient are 14,781 USD and 5,311 USD for each step, respectively. The total cost savings for a move from inpatient to outpatient care is 20,093 USD. These costs will be used in Section 7.5.4.

7.3 Atypical and Typical Antipsychotic Drugs: Clinical Outcomes

There is significant debate over the effectiveness of atypical antipsychotics over typical antipsychotics. When the first atypical antipsychotic, clozapine, was discovered in the 1950s, it was lauded as having a superior side effect profile compared to typical antipsychotics. In particular, atypical antipsychotics' ability to treat mental diseases without putting patients at risk for known long-term serious side effects like tardive dyskinesia, was considered a huge step forward. Later atypicals also claimed to have improved time to onset, and were, for a time, generally accepted as the first line of treatment for illnesses like schizophrenia.[9]

However, this black and white view of atypical and typical antipsychotics does not elucidate all the relevant details. There are studies that show that atypical antipsychotics, like typicals, also cause extrapyramidal symptoms (movement disorders, characterized by uncontrollable tics or rigidity). They are also linked to weight gain, a symptom that negatively impacts the patient and is thought to contribute to relapses. A study comparing atypicals to typicals was completed in 2008, and showed similar rates of rehospitalizations and length of hospital stay. The higher cost of the atypical antipsychotics was not reflected in savings from reduced inpatient care, except in the most severe cases of schizophrenia. There is a need for further clinical studies to assess the comparative efficacy of the two drug classes.

Antipsychotics $ 000s

Molecule	Brand	2009	2010	2011	2012f	2013f	2014f	2015f	2016f	2017f	2018f	2019f	CAGR (2009-2018)
Haloperidol	Haldol	43,243	41,208	39,176	36,433	34,424	32,931	31,745	30,697	29,762	28,931		-4.4%
	Generics	4,772	4,653	4,653	4,579	4,594	4,662	4,749	4,834	4,912	4,981		0.5%
Total Haloperidol Sales		48,015	45,861	43,829	41,012	39,017	37,594	36,494	35,531	34,674	33,912		-3.8%
Total Antipsychotic Market		13,869,475	14,844,665	15,650,918	13,495,520	12,927,601	12,730,336	12,274,412	11,810,997	10,631,424	9,815,289		-3.8%
Haloperidol % of Market		0.35%	0.31%	0.28%	0.30%	0.30%	0.30%	0.30%	0.30%	0.33%	0.35%	**Average**	**0.31%**
Haloperidol % of Schizophrenia Market			0.80%	0.73%	0.74%	0.66%	0.61%	0.60%	0.59%	0.60%	0.60%	**Average**	**0.66%**

Schizophrenia $ millions

Molecule	Brand	2009	2010	2011	2012f	2013f	2014f	2015f	2016f	2017f	2018f	2019f	CAGR (2010-2019)
Haloperidol	Haldol		40,680	35,361	29,246	26,133	23,887	22,040	20,438	19,249	18,311	17,535	-8.9%
	Generics		3,858	3,662	3,330	3,165	3,023	2,825	2,660	2,504	2,347	2,195	-6.1%
Total Haloperidol Sales			44,538	39,023	32,577	29,298	26,910	24,865	23,098	21,753	20,659	19,730	-8.6%
Total Schizophrenia Market			5,722,622	6,007,297	5,509,022	5,947,407	6,158,338	6,087,307	5,998,773	5,814,110	5,670,239	5,607,808	-0.2%
Haloperidol % of Market			0.78%	0.65%	0.59%	0.49%	0.44%	0.41%	0.39%	0.37%	0.36%	0.35%	

Table 7.7. Revenue and Market Share of Haloperidol and Haloperidol Decanoate (Branded and Generic) in the Antipsychotic and Schizophrenia Markets.[1]

7.4 Projected Market Share Capture of Atypical and Typical Antipsychotic Sectors

Haloperidol is marketed both under the name brand Haldol® and as generic haloperidol. Similarly, haloperidol decanoate is sold as Haldol® Decanoate and as a generic. The revenues of haloperidol in the antipsychotic market and the schizophrenia market have been projected in Table 5.7. In this analysis, the entry of our controlled release formulation is incorporated into these data, along with market forces that have been discussed in Sections 7.1and 7.2. For the remainder of this economic analysis, the product discussed here will be referred to as the controlled release product, although it embodies features of both controlled and extended release.[11,12]

Haloperidol had overall sales of 45.9 million in 2010, with 40.7 million in the schizophrenia market alone. As is apparent from projections, the overall degradation of haloperidol in schizophrenia is anticipated to be much more significant than the degradation of haloperidol sales in antipsychotics. This is a trend generally seen in drugs that are considering new indications, but no such news exists for haloperidol. As a result, we consider the haloperidol revenues in the antipsychotic market as the relevant revenues in this report, alongside projections for the overall schizophrenia market.[2,13]

The average market capture for haloperidol over this time frame is 0.31% and 0.66% for the antipsychotic and schizophrenia markets, respectively. We now consider the expected increase in market share of haloperidol as a result of the controlled release formulation.[2] This market share will be derived from the erosion of sales from the atypical sector, and capture of market share held by haloperidol and haloperidol equivalents in the typical sector.

Atypical Market Share Takeover. As discussed in Section 7.3, the difference in clinical outcomes for atypical and typical antipsychotics may not be as wide as therapeutic choices seem to suggest.

With the expectation of an improved side effect profile for the controlled release formulation, this divide will be further narrowed. Analysis of current pipelines of the top 100 pharmaceutical companies reveals that none are planning new haloperidol products. The loss of atypical market share is attributed primarily to price competitiveness, and the increase in generics. Due to our intention to price aggressively as well as the improvement in side effect profile, we can ascribe a certain percentage of the increase in the typical antipsychotic market to the introduction of this new product. While the current projections account for the effects of pricing, this analysis will account for the switchover of patients from the atypical sector to the typical sector. The total increase in typical sales is estimated by assuming a constant average cost per patient of atypical and typical antipsychotic regimens.[14]

The current breakdown of patients on atypical or typical antipsychotic regimens is approximately 60:40. The goal of this analysis is to include revenues from patients who are expected to switch to a typical antipsychotic as a result of our controlled release formulation. This breakdown is used to calculate an average cost per customer in each sector, which is then assumed to be constant throughout the period. The total projected revenues for overall market are also assumed to remain the same. By then adjusting the breakdown of patients into the sectors as a function of the erosion of the atypical sector, as given in Table 7.1, we are able to adjust the projected revenues for each sector in 2018. These adjusted revenues can then be reverse calculated by using the constant average cost per customer assumption, and compared against a 2018 projection of the total schizophrenia population contained within the same report. If the constant average cost per customer assumption was true, the reverse calculation of the projection would have matched, but there was a 7% discrepancy, indicating that the assumption did not hold completely, but is within an acceptable range of error. This discrepancy was to be expected, as drug prices tend to increase marginally over time.[15]

The total revenues that are expected to transfer from the atypical sector to the typical sector are 220 million USD. This revenue projection, however, is an assumption based on the entire typical antipsychotic sector, as opposed to haloperidol only, which is the drug incorporated into our controlled release formulation. This 220 million USD is a projection that is significant for the

scenario in which each of the drugs in the typical sector are all augmented with the addition of the controlled release technology. For the case of our single product, however, it is necessary to isolate the portion of this larger total that is relevant to haloperidol only.

Typical Market Share Takeover. There are several drugs in the typical antipsychotic sector that we may expect a controlled release formulation of haloperidol to overtake. First, we must determine the decision drivers behind a choice of typical antipsychotic. Those drugs that are prescribed only in the event of adverse reactions associated with first-line drugs are eliminated from our analysis. Of the remaining drugs, we eliminate those drugs that have additional indications over haloperidol. Some of these additional indications include abatement of nausea and mild depression. To further validate a complete takeover of revenue for these drugs, reports of clinical studies were compiled to ensure that haloperidol was equipotent or superior to the drug. Ultimately a shortlist of four drugs was generated: chloropromazine, fluphenaxine, loxapine, and perphenazine. The projected 2018 revenues of these four drugs were aggregated with those of haloperidol and a percentage of the typical sector attributed to these revenues was generated, of 9.15%. This same percentage was used to calculate the adjusted projected revenue of haloperidol, of 116 million USD. This adjusted projected revenue implies that 95 million USD of the total revenues expected to transfer from the atypical to the typical sector are ascribed to our new controlled release product, which accounts for 43.2% of the total increase projected for the typical antipsychotic market. The remaining 126 million USD is inaccessible revenue for our product, associated with drugs in the market that are not interchangeable with haloperidol. Therefore, we adjust the different sector revenues by the 95 million USD ascribed to this product.[1,2,16]

		Revenues (millions)		Population	
	2009	2018f	2018af*	2009	2018af
Atypical Antipsychotics	18,347	14,896	14,801	2,750,160	2,232,866
Typical Antipsychotics	668	1,049	1,144	1,833,440	2,879,160
Haloperidol	45	20.7	116		
Total	19,015	15,945	15,945	4,583,600	5,112,025
				2018 projection	4,772,600
*af = adjusted future projections				Estimated % Error	7%

Table 7.8. Adjusted Projected Revenues for Haloperidol Before Price Adjustments. This figure shows the capture of additional market share from the atypical sector.[1,2,16]

The above calculations can be summarized in the following way. The original future projections of atypical and typical antipsychotics had incorporated the effects of price and generic competition. By adjusting these projections for the anticipated transfer of patients from an atypical regimen to a regimen with our controlled release formulations using the erosion of the atypical antipsychotic sector, a total projected revenue transfer from the atypical to the typical sector was calculated. This total projected revenue includes the effects of the controlled release haloperidol product, as well as the effects the addition of this technology to all products in the typical sector would have. By calculating a percentage market share of haloperidol and haloperidol equivalents in the 2018 market projections, we aggregate and apply this same percentage to the adjusted projected 2018 revenues to generate a total potential market size for our product of 116 million USD in 2018.[17]

This 116 million in adjusted projected sales occurs in 2018. The projected sales of haloperidol in 2018 were then subtracted from this total, to reveal a 95 million USD increase in sales as a result of the adjustments. In order to build up to a 95 million dollar increase in sales, a linear ramp up over the course of six years was used. Table 7.9 shows the results for adjusted projected haloperidol sales from 2013-2018.

In $000s	2013f	2014f	2015f	2016f	2017f	2018f
Current Haloperidol Sales*	29,298	26,910	24,865	23,098	21,753	20,659
Percentage of Ramp Up	17%	33%	50%	67%	83%	100%
Total Additional Sales	15,890	31,780	47,671	63,561	79,451	95,341
Total Haloperidol Sales, Adjusted Projections	45,188	58,690	72,536	86,659	101,204	116,000

*Sales figures without the release of the microsphere product. Sales of haloperidol are in decline, due to the improved clinical profiles of competitor drugs.

Table 7.9. Adjusted Projections for Haloperidol Sales Using a Linear Ramp-Up Schedule.

There are different drivers behind the total adjusted projected haloperidol sales. The two components of this figure are the projected haloperidol sales and the adjusted additional sales. Capturing the projected haloperidol sales alone simply depends on capturing haloperidol's market share, but capturing the additional sales depends on taking sales from the atypical sector, as well as sales from the four drugs identified as haloperidol alternatives.

These analyses are based on the assumption that our formulation would cost about as much as an atypical treatment regimen would. While this is a generally accepted practice, our aggressive pricing strategy makes a more rigorous sizing method. By dividing the 116 million in revenue transferred by the average cost per patient in the atypical market, a total number of patients that would be transferred over to our product is calculated as 17, 388 patients. Current haloperidol market share, plus the market share of the four drugs our formulation is expected to displace, is 1.5% of the market, or 91,729 patients. Therefore, we expect a total population of 109, 117 patients to be our total population.

Post-pricing analysis, it is more than likely that the total adjusted projections will be much higher than 116 million USD, due to cost adjusting of the patients taking haloperidol or one of its equivalents. This cost adjusting will far outweigh the additional sales that will be captured from the atypical market. Due to schizophrenia's classification as a chronic disease, patients afflicted are entitled to Medicare coverage under the Medical Scheme's Act, making them less price sensitive and more likely to change their regiment to a more expensive but more effective drug. This allows us to essentially eliminate the increase in cost of the regimen from the market share analysis.

Although our technical sections focus on optimizing the cross-flow membrane emulsification (XME) production process for haloperidol, the platform itself it not limited to that one drug. The same steps can be repeated for any number of other pharmaceuticals, based on their compatibility with poly-(lactic-co-glycolic acid) (PLGA) and altering the solvents used during the process based on the specifications discussed in Sections 1.5 and 1.6. As with the schizophrenia market, there are many other chronic disease markets that would benefit from both the extended release and controlled release features of our platform. Chronic disease exists primarily as cardiovascular diseases (heart disease and stroke), cancer, chronic respiratory diseases, diabetes, mental and genetic disorders, bone and joint disorders, and oral diseases. There are 25 diseases currently recognized by the Medical Schemes Act's Prescribed Minimum Benefits' Chronic Disease List. This list is presented in Appendix F.

Chronic diseases comprise the majority of the 875 billion USD pharmaceutical market. While we are unable to present a quantitative estimate of the market size of the XME platform here, the financial opportunities are enormous.[18,19]

This analysis has focused on identifying the potential maximum market expected from the controlled release formulation, the next section will focus on the cost of production and the price that is necessary to achieve this maximum market share.

7.5 Pricing Analysis

Two different methodologies were used to determine a price for the haloperidol controlled release product. The first method entailed using a market approach, in this case, based on the price of the haloperidol decanoate product, which was discussed in Section 2.6.

First, an average cost per mg of haloperidol was calculated from the haloperidol decanoate prices. The prices of haloperidol decanoate used here are non-branded generic doses, manufactured by the generics firm Apotex. This average cost per mg was then used to calculate the cost per dose of the controlled release product, which contains 450 mg in a single dose.[32]

Haloperidol decanoate						
5 mL vial	50 mg/mL	$144.00/vial	250	total mg	0.576	$/mg
5 mL vial	100 mg/mL	$288.00/vial	500	total mg		
Haloperidol controlled release product						
450	mg/dose					
Using the $/mg derived from the haloperidol decanote cost analysis					259.2	$/dose

Table 7.10. Market Pricing Analysis.[32]

A comparative market price of 259.20 USD per dose was then calculated. For marketing purposes, as well as ease of calculation, this estimate was rounded up to 260.00 USD for subsequent calculation. This is a baseline calculation that prices the product based only on its extended release feature, which is has in common with haloperidol decanoate.

Next, a pricing analysis was conducted to estimate the value of the controlled release feature of the product. First, as a preliminary check, a cost per dose was calculated based on the fixed and variable costs presented later in Sections 7.6.1 and 7.6.2. The total production considered was 500,000 doses. The total cost per dose was calculated to be 142.80 USD, well below the typical sector market price baseline of 260.00 USD.

The next step was to estimate the average expected cost savings of a patient taking the drug. For this estimation, patients were divided into four categories: convenience saving only, Inpatient to Long-term, Long-term to Outpatient, and Inpatient to Outpatient. The convenience saving only category was considered the largest segment at 40%, in order to maintain a conservative outlook of potential clinical trial outcomes. This segment is considered to have no cost savings, although this is, in reality, most likely not the case. In future analyses, if an estimate of cost savings for this group can be obtained, it would help to further validate this analysis.

The other groups were taken from Section 7.2, where their cost savings were calculated on a per patient per year basis. Each of these groups took an equal share of the remaining 60%. Overall, the expected savings for a patient were 8,037 USD. At this point, a percentage of this overall savings was added to the market baseline to produce a final product price. The choice of 1% was fairly arbitrary, as there is no literature detailing the rationale behind pharmaceutical pricing. In order to ensure that a wide spectrum of prices is tested, due to the potential variability in choice of price point, price was varied in a sensitivity analysis, presented later in Section 7.7.

For the purposes of calculating the profitability statistics, a final price of 340.37 USD was used, incorporating a 1% share of patient cost savings. As a broad check, we consider the cost of an atypical regimen, in this case, Seroquel XR, the only atypical drug that offers extended release on the market. A 90 day supply of Seroquel XR is 1,316 USD. For an entire year, a patient will spend 5,304 USD for a full regimen. This is compared to a yearly cost of 4,084 USD for our product, or a cost savings of 23% over the atypical regimen.

Incremental Cost/Dose		Groups		Cost Savings
Fixed	$ 17.02	Convenience saving only	40%	$ -
Variable	$ 125.78	Inpatient to Long-term	20%	$ 14,781.00
Total	$ 142.80	Long-term to Outpatient	20%	$ 5,311.00
Market Price Analysis	$ 260.00	Inpatient to Outpatient	20%	$ 20,093.00
+Cost Savings Analysis	$ 80.37	For the average patient, the expected savings are		$ 8,037.00
Sale Price	**$ 340.37**	Add 1% of the overall savings to the price		$ 80.37

Table 7.11. Pricing Analysis for Controlled Release Product: Valuation of Controlled Release Feature and Final Sale Price. [4,7,32]

7.6 Profitability Analysis

7.6.0 Introduction and Explanation of Profitability Metrics

Some justifications for metrics used in this section are based on the scenario that this project proceeds under a larger parent firm, which in this case is a large-cap pharmaceutical firm. This assumption also affects the profitability metrics presented here. The pharmaceutical industry generally expects an internal rate of return (IRR) of 30% as a threshold for project feasibility. However, firms that focus on drug delivery technology platforms, such as the XME platform presented here, regularly attain IRRs of ten times that magnitude. This is due to the large reduction in cost of both regulatory filing and approval and the reduced research and development costs as a result of using molecules and vehicles that have already gained FDA approval. Research and development costs can account for more than 25% of all total costs of a drug, in the standard scenario, and their incurrence early on further exacerbates their importance in IRR calculations.[20,21]

The IRR presented here in the final scenario is approximately 276%, which is consistent with average IRRs achieved by drug delivery firms. The net present value (NPV) of the project is 99.8 million USD, discounted at a rate of 40%.

7.6.1 Fixed Cost Summary

Fixed costs in this case consist of equipment costs and cost of land. A complete summary of fixed costs is presented below.

The first section, Equipment, tallies the total purchase costs and installation costs of the equipment in the plant. Installation costs were calculated using a 3.291 multiplier of purchase cost. This came out to a total of 11.8 million USD. The next section tallies the cost of the XME channels, which are precision machined and designed for the XME process specifically. The total cost of these channels is 168,000 USD. Due to the relative ease of installation, due to their small size, there was no associated installation cost for this section.[22]

Waste Management. All of the units compiled in the Equipment costs are essential to the process, with the exception of the distillation column (D-1). This unit is designed to effect a DCM-water separation, a mixture that constitutes the waste stream of the XME process. It is, in effect, a nonessential unit in our process, and therefore alternate schemes were considered that would eliminate this fixed cost and the cost of the land required to house it. In this alternative scheme, the cost of wastewater treatment and the cost of transportation are aggregated to get an overall cost per year for the alternative waste management scheme. The overall cost was 56,508 USD, which allowed for the elimination of the 688,705 USD required in fixed costs for the distillation column. Other factors also weighed in on the decision to undertake this alternative, primarily having to do with the flexibility gained by using the alternative. In the case of utilizing additional capacity for other target drugs, it is possible that the flow rates and compositions used to calculate the cost of D-1 will no longer be applicable. This would immediately render the current distillation column suboptimal, which would affect its efficiencies. The alternative waste management option avoids this problem altogether; however, both options were evaluated for profitability.

FIXED

	TOTAL
With Distillation Column	$11,847,883
No Distillation Column	$11,159,178

Equipment

	Bare Module	Quantity	Installation Cost per Unit	Total Cost (All Units)
Mixing Tank (M-1)	82200	2	$270,520.2	$705,440.40
Mixing Tank (M-2)	2310	2	$7,602.2	$19,824.42
Sanitary Pump (P-1)	2900	1	$9,543.9	$12,443.90
Sanitary Pump (P-2)	3200	6	$10,531.2	$82,387.20
Sanitary Pump (P-3)	2900	1	$9,543.9	$12,443.90
Sanitary Pump (P-4)	2900	6	$9,543.9	$74,663.40
Vacuum Tank with Diafiltration (T-1)	12100	6	$39,821.1	$311,526.60
Vacuum Tank with Diafiltration (T-2)	35500	6	$116,830.5	$913,983.00
Sanitary Pump (P-5)	2900	6	$9,543.9	$74,663.40
Sanitary Pump (P-6)	3300	6	$10,860.3	$84,961.80
Surge Tank (T-3)	55900	1	$183,966.9	$239,866.90
Storage/Mixing Tank (T-4)	56800	1	$186,928.8	$243,728.80
Storage Tank (T-5)	22500	1	$74,047.5	$96,547.50
Pump (P-8)	2900	6	$9,543.9	$74,663.40
Sanitary Pump (P-9)	3200	6	$10,531.2	$82,387.20
Storage Tank (S-1)	17200	1	$56,605.2	$73,805.20
Storage Tank (S-2)	20200	1	$66,478.2	$86,678.20
Freeze-Dry (F-1)	99950	1	Inclusive	$99,950.00
Ampoule-Filling Unit (A-1)	1055000	1	Inclusive	$1,055,000.00
Sanitary Pump (UP-2)	1600	1	$5,265.6	$6,865.60
Sanitary Pump (UP-1)	1600	1	$5,265.6	$6,865.60
Distillation Column (D-1)	160500	1	$528,205.5	$688,705.50
				$5,047,402

	Per Channel	Quantity	Total Cost (All Channels)
Channels*	$8,000	21	$168,000

* no installation cost

	Cost per sq. ft.	Quantity (sq. ft.)	Total Cost
Land	125	53060	$6,632,481

Table 7.12. Fixed Cost Summary: Equipment, Channels, Alternative Waste Management, and Land.

7.6.2 Total Variable Cost Summary

There are two sections that pertain to the overall total variable cost summary, which are entitled Variable and Human Resources/Operational. The section Variable accounts for reagent and utility costs (including the alternate waste management scheme), while Human Resources/Operational accounts for costs associated with staff, maintenance, and operational overhead. The utility cost consisted only of the electrical costs, and did not include utilities associated with running the distillation column.

VARIABLE

	TOTAL
With Distillation Column	$60,152,327
No Distillation Column	$60,206,791

Reagents

	Pricing		Amt (kg)/90 days	Cost
DCM	$0.50	$/kg	115532	$57,642
Pharmaceutical-Grade Water	$0.12	$/kg	8596372	$1,031,565
PVA	$0.71	$/kg	78522	$56,077
PLGA	$39,100.00	$/kg	1450	$56,696,828
Haloperidol	$10,676.00	$/kg	172	$1,832,971
Sodium Chloride	$0.13	$/kg	4209	$556.78
				$59,675,640

Utilities

	Cost
Electricity	$476,688

Alternate Waste Management Scheme

Total Wastewater Treatment Cost	$54,464
Total Treatment Cost	$38,125
Cost per kg Organic	0.33
Amount Treated	115532
Transportation Cost	$16,338
Cost (% of Shipment Value)	1.50%
Value of Shipment	$1,089,207

Table 7.13. Variable Cost Summary: Input Prices and Utilities.[22,23,24,25,26]

The Human Resources/Operational section details other variable costs, based on the assumption of 24 operators working per shift. The distribution of operators is expected to be 3:5:4 in the production of the continuous and dispersed phases, XME channels, and downstream processing sections. The combined Total Variable costs were 62.9 million USD. It is important to note that both the Human Resources/Operation section and the Variable section are based on the cost of a single cycle, defined in this case as 90 days, 24 hours/day. When the plant runs for multiple cycles, the Total Variable costs are multiplied by the number of cycles run. Running a single cycle is denoted as a capacity of 25%; two cycles, 50%; three cycles, 75%; and four cycles, 100%. Any additional capacity would require an increase in capital investment, as detailed in the Section 5.5.1.

HR/Operational/SG&A		
	TOTAL	$4,083,951
Operations	2160	hrs
Direct Wages and Benefits (24 operators)	$1,814,400.00	35 operator-hr
Direct Salaries and Benefits	$272,160.00	15% of DW&B
Operating supplies and services	$108,864.00	6% of DW&B
Technical assistance to manufacturing	$156,000.00	$52,000/(operator/shift)-year
Control laboratory	$171,000.00	$57,000/(operator/shift)-year
Maintenance		
Wages and Benefits		
Solid-fluid handling process	$533,154.74	4.5% of Ctdc
Salaries and benefits	$133,288.68	25% of MW&B
Materials and services	$533,154.74	100% of MW&B
Maintenance overhead	$26,657.74	5% of MW&B
Operating Overhead		
General plant overhead	$47,317.48	7.1% of M&O-SW&B
Mechanical department services	$15,994.64	2.4% of M&O-SW&B
Employee relations department	$33,028.94	5.9% of M&O-SW&B
Business services	$1,972.67	7.4% of M&O-SW&B
Property taxes and insurance	$236,957.66	2% of Ctdc

Table 7.14. Human Resources/Operational Costs.[22]

7.6.3 Depreciation, Working Capital, and Other Costs

There are also a number of miscellaneous costs that are standard for plant operation, as well as several that are idiosyncratic to the pharmaceutical industry. Depreciation is a method used to write down the value of an asset over the course of its lifetime. The assets that need to be written down over time are those described in the fixed cost section, excluding land and the alternative waste management plan, which was included in the final total variable cost. The lifetime of these assets was estimated at 10 years, as per pharmaceutical standard, and accordingly, the 10-year MACRS depreciation schedule was used.

Next, the working capital requirement was considered. Working capital is the value of assets needed to continue operations for a set period of time, in this case, 30 days. Working capital in the pharmaceutical industry is calculated as a percentage of overall sales. An industry average was reported as 3.60%, and this percentage was used in the analysis to calculate the working capital requirement. The working capital requirement was not added back at the end of the 10 year period. This is due to the expectation that the plant will continue to be relevant at that point in time, although this profitability analysis includes only a one year development period and a ten year ramp-up period.

There are several additional costs that must be considered. Recurring costs will be considered first. The first of the recurring costs are the distribution and sales force costs, which were reported as an industry average of 23% of sales. This percentage was used to calculate a recurring cost over the 10-year ramp-up period, during which sales are occurring. The second recurring cost was tax costs, which were held, as per U.S. corporate tax law, at 35%. There are no taxes incurred in the one year developmental period, due to a lack of revenue. Next, an appropriate discount rate was considered. Discount rates in the pharmaceutical industry tend to be magnitudes larger than discount rates used in other industries, due to the risk present in the industry. Large pharmaceutical firms tend to discount their potential projects at 20%, while smaller ventures may use a discount rate as high as 50%. For the purposes of this analysis, a high discount rate of 40% is used, to reflect the

many risks inherent in this project. The most important of these risks include proving clinical efficacy, capturing atypical sector market share, and capturing typical sector market share.

Next, initial start-up costs are considered. These costs are incurred once during the development period, but have a larger bearing on profitability measures due to the immediacy of the costs. First, the cost of plant startup is considered. Our project is intended to proceed under the umbrella of a larger pharmaceutical firm, therefore, a relatively low startup cost of 20% is used, which will take advantage of the experience of the parent firm. The remaining start-up costs are specific to the pharmaceutical industry. The first are the legal costs of a drug approval. The industry average ranges from 200,000 USD to 500,000 USD. In this case, because the two components of the haloperidol controlled release formulation are well-known by the FDA, and approval largely rests on performance at a single large clinical trial, the lower end of the spectrum is used here to represent legal costs. The second cost is the cost per clinical trial. As only a single, large clinical trial is expected to be conducted, the total cost of clinical trials rests on the cost of a single, large trial. Trials of the same scale are reported, on average, to cost 1 million USD, which is the figure that is used here. This cost does not include the cost of production, which is incorporated into the variable costs of the first year of the 10 year ramp-up period. The first year of the 10 year ramp-up period is only expected to operate at 25% capacity, leaving significant capacity for the production of clinical trial doses.

Initial Costs (during startup year)	$102,506,823
Legal Costs (Regulatory)[29]	$200,000
Cost/Clinical Trial[30]	$1,000,000
Cost of startup (20% of FIXED)[22]	$1,702,030

Sales Based Recurring Costs (incurred every year, excluding startup year)	
Working Capital (% of Sales)[27]	3.60%
Distribution and Sales Force (% of Sales)[28]	23%

Applicable Rates for Calculation of Net Income	
Discount Rate[31]	40%
Tax (on Net Income)[22]	35%

Table 7.15. Summary of Other Costs and Metrics. [22,27,28,29,30,31]

7.6.4 Cash Flow Summaries and Profitability Measures

Case 1: With Distillation Column. The first cash flow summary shows a profitability analysis of the plant with the distillation column. The NPV was calculated to be 99.2 million USD, while the IRR was 263%. Both the NPV and IRR are positive, which indicates that the distillation column, although expensive, does not harm the overall profitability of the process. Some additional costs associated with the distillation column were not considered. First, the operation of the column would require additional workers, which would then present an increase of approximately 150,000 USD in variable costs each year. There is also the question of how the outputs from the distillation column are to be disposed of. The bottoms product has a concentration of DCM well below the minimum required by the Environmental Protection Agency (EPA), but the distillate contains a mixture of DCM and water, which is not of sufficient purity to dispose of. Most likely, the distillate would have to be sent to a wastewater treatment plant in spite of being processed once already. This realization makes the distillation column an even less attractive option.

Two ramp-up schedules are presented. The first is from Section 7.4, where the linear ramp-up of additional sales from atypical sector erosion was presented. The second is a ramp of up sales from capture of the haloperidol and haloperidol equivalents in the typical sector was considered. This schedule is based on average pharmaceutical sales curves. These ramp-up schedules are identical between the analysis with the distillation column versus the analysis with the alternate waste management scheme.[33]

COSTS	
FIXED	$11,847,883
VARIABLE	$60,152,327
HR/Operational/SG&A	$4,083,951
Profitability Measures	
NPV (12/312012)	$99,229,397
IRR	262.88%

Capacity

Year	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Capacity (Quarters Occupied)	0%	25%	50%	50%	75%	75%	75%	75%	75%	75%	75%	75%
Percentage Ramp-Up (Haloperidol)		17%	33%	50%	67%	83%	**100%**	100%	100%	100%	100%	100%
Additional Patients Treated		2898	5796	8694	11592	14490	17388	17388	17388	17388	17388	17388
Capture of Haloperidol + Equiv		40%	60.0%	80.0%	**100%**	100%	100%	100%	100%	100%	100%	100%
Halo Patients Treated		36692	55037	73383	91729	91729	91729	91729	91729	91729	91729	91729
TOTAL Patients Treated		39590	60833	82077	103321	106219	109117	109117	109117	109117	109117	109117
TOTAL Patients Treated * 12 doses	0	475,075	730,001	984,926	1,239,852	1,274,628	1,309,404	1,309,404	1,309,404	1,309,404	1,309,404	1,309,404

Table 7.16. Total Costs, Profitability Measures, and Ramp-Up Schedule for Case 1: With Distillation Column.

CASH FLOWS (USD)												
Net Sales	0	161525568	248200272	334874976	421549680	433373520	445197360	445197360	445197360	445197360	445197360	445197360
	14591013	64290742	128581484	128581484	192872227	192872227	192872227	192872227	192872227	192872227	192872227	192872227
		500000	1000000	1000000	1500000	1500000	1500000	1500000	1500000	1500000	1500000	1500000
-COGS		61085874	93864586	126643299	159422011	163893560	168365110	168365110	168365110	168365110	168365110	168365110
Distribution and Sales Force		37150881	57086063	77021244	96956426	99675910	102395393	102395393	102395393	102395393	102395393	102395393
-WC	0	5814920	8935210	12055499	15175788	15601447	16027105	16027105	16027105	16027105	16027105	16027105
Gross Profit	-14591013	57473892	88314413	119154934	149995454	154202603	158409752	158409752	158409752	158409752	158409752	158409752
-SG&A	0	4083951	8167903	8167903	12251854	12251854	12251854	12251854	12251854	12251854	12251854	12251854
EBITDA	-14591013	53389941	80146511	110987031	137743601	141950749	146157898	146157898	146157898	146157898	146157898	146157898
-Depreciation	0	1115918	2008652	1606922	1285537	1028876	822431	730926	730926	732042	730926	366021
EBIT	-14591013	52274023	78137859	109380110	136458063	140921873	145335467	145426972	145426972	145425856	145426972	145791877
-Interest expense	0	0	0	0	0	0	0	0	0	0	0	0
EBT	-14591013	52274023	78137859	109380110	136458063	140921873	145335467	145426972	145426972	145425856	145426972	145791877
-Taxes	0	18295908	27348251	38283038	47760322	49322656	50867413	50899440	50899440	50899050	50899440	51027157
Net Income	-14591013	33978115	50789608	71097071	88697741	91599218	94468054	94527532	94527532	94526807	94527532	94764720
Discounted Cash Flows	-10422152	17335773	18509332	18507151	16491964	12165320	8961665	6405220	4575157	3267944	2334264	1671515

Table 7.17. Cash Flow Summary for Case 1: With Distillation Column.

Case 2: No Distillation Column. The second cash flow summary shows a profitability analysis of the plant utilizing the alternative waste management scheme presented in Section 5.5.2. The NPV was calculated to be 99.8 million USD, while the IRR was 276%, which is in line with IRR expectations established in the introduction to this section. As expected, the NPV and IRR are higher than those presented in Case 1 (NPV = 99.2 million USD, IRR = 263. Due to these performance measures, and the increase in flexibility discussed in Section 5.5.1, this case was chosen as the preferred case, and is the base case used for the sensitivity and breakeven analyses.

From a macroeconomic perspective, the cash flows and statistics presented indicate that our product will constitute 2.72% of the overall antipsychotic market (compared to 0.35% with current haloperidol products alone), and 7.64% of the overall schizophrenia market (compared to 0.60% with current haloperidol products alone).

In the next section, the sales price, reagent prices, and percentage of market share measures will be varied during a sensitivity analysis, to better understand the primary drivers behind the profitability metrics calculated here.

COSTS		
FIXED		$11,159,178
VARIABLE		$60,206,791
HR/Operational/SG&A		$4,083,951
Profitability Measures		
NPV (12/312012)	$	99,803,154
IRR		276%

Capacity

Year	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Capacity (Quarters Occupied)	0%	25%	50%	50%	75%	75%	75%	75%	75%	75%	75%	75%
Percentage Ramp-Up (Haloperidol)		17%	33%	50%	67%	83%	**100%**	100%	100%	100%	100%	100%
Additional Patients Treated		2898	5796	8694	11592	14490	17388	17388	17388	17388	17388	17388
Capture of Haloperidol + Equiv		40%	60.0%	80.0%	**100%**	100%	100%	100%	100%	100%	100%	100%
Halo Patients Treated		36692	55037	73383	91729	91729	91729	91729	91729	91729	91729	91729
TOTAL Patients Treated		39590	60833	82077	103321	106219	109117	109117	109117	109117	109117	109117
TOTAL Patients Treated * 12 doses	0	475,075	730,001	984,926	1,239,852	1,274,628	1,309,404	1,309,404	1,309,404	1,309,404	1,309,404	1,309,404

Table 7.18. Total Costs, Profitability Measures, and Ramp-Up Schedule for Case 2: No Distillation Column

CASH FLOWS (USD)												
	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Net Sales	0	161,525,568	248,200,272	334,874,976	421,549,680	433,373,520	445,197,360	445,197,360	445,197,360	445,197,360	445,197,360	445,197,360
	15,417,460	64,236,279	128,472,557	128,472,557	192,708,836	192,708,836	192,708,836	192,708,836	192,708,836	192,708,836	192,708,836	192,708,836
		500,000	1,000,000	1,000,000	1,500,000	1,500,000	1,500,000	1,500,000	1,500,000	1,500,000	1,500,000	1,500,000
-COGS		61,034,126	93,785,070	126,536,013	159,286,957	163,754,719	168,222,480	168,222,480	168,222,480	168,222,480	168,222,480	168,222,480
Distribution and Sales Force		37,150,881	57,086,063	77,021,244	96,956,426	99,675,910	102,395,393	102,395,393	102,395,393	102,395,393	102,395,393	102,395,393
-WC	0	5,814,920	8,935,210	12,055,499	15,175,788	15,601,447	16,027,105	16,027,105	16,027,105	16,027,105	16,027,105	16,027,105
Gross Profit	-15,417,460	57,525,641	88,393,930	119,262,219	150,130,508	154,341,445	158,552,382	158,552,382	158,552,382	158,552,382	158,552,382	158,552,382
-SG&A	0	4,083,951	8,167,903	8,167,903	12,251,854	12,251,854	12,251,854	12,251,854	12,251,854	12,251,854	12,251,854	12,251,854
EBITDA	-15,417,460	53,441,690	80,226,028	111,094,317	137,878,654	142,089,591	146,300,528	146,300,528	146,300,528	146,300,528	146,300,528	146,300,528
-Depreciation	0	1,184,788	2,132,619	1,706,095	1,364,876	1,092,375	873,189	776,036	776,036	777,221	776,036	388,611
EBIT	-15,417,460	52,256,901	78,093,409	109,388,221	136,513,778	140,997,216	145,427,339	145,524,492	145,524,492	145,523,307	145,524,492	145,911,917
-Interest expense	0	0	0	0	0	0	0	0	0	0	0	0
EBT	-15,417,460	52,256,901	78,093,409	109,388,221	136,513,778	140,997,216	145,427,339	145,524,492	145,524,492	145,523,307	145,524,492	145,911,917
-Taxes	0	18,289,916	27,332,693	38,285,877	47,779,822	49,349,026	50,899,569	50,933,572	50,933,572	50,933,157	50,933,572	51,069,171
Net Income	-15,417,460	33,966,986	50,760,716	71,102,344	88,733,956	91,648,191	94,527,770	94,590,920	94,590,920	94,590,149	94,590,920	94,842,746
Discounted Cash Flows	-11,012,471	17,330,095	18,498,803	18,508,523	16,498,698	12,171,824	8,967,330	6,409,515	4,578,225	3,270,134	2,335,829	1,672,891

Table 7.19. Cash Flow Summary for Case 2: No Distillation Column

7.7 Sensitivity Analyses

7.7.1 Selling Price

The first metric analyzed is the selling price of the product. This analysis skewed towards the lower spectrum, in order to incorporate more 'worse-case' scenarios than 'best-case' scenarios. This same heuristic was used when choosing sensitivity ranges for all metrics in this analysis. Bolded values in the sensitivity range indicate the value that was used in the primary profitability analysis.

The sensitivity analysis indicates a strong dependence on price, as can be seen in its effects on NPV and IRR below. The 'worst-case' scenario price is 260 USD, the market baseline price. Although there is a relatively strong dependence, the robustness of the product still propels the overall profitability measures into a positive range.

Selling Price	$260	$280	$300	$320	**$ 340**	$360	$380
NPV	$40,962,001	$55,672,289	$70,382,577	$85,092,865	$100,075,294	$114,513,442	$129,223,730
IRR	144.64%	178.20%	211.10%	243.59%	275.79%	307.78%	339.62%

Table 7.20. Sensitivity Analysis: Selling Price.

7.7.2 Reagent Prices

The next group of metrics analyzed is the prices of the reagents used in the process. None of these analyses indicated a strong dependence of profitability on reagent prices. This indicates robustness of the product with respect to input prices, which is especially important in the current economic climate, where raw materials prices are rising due to increased competitiveness. The most significant reagent was the pharmaceutical-grade water, which due to the large volume used in the process, is the most important, although one of the least expensive. This dependency is likely to be insignificant in the long-run, as the price of pharmaceutical-grade water is relatively inelastic. The project is also assumed to be housed under a large pharmaceutical company, almost all of which produce pharmaceutical-grade water in-house, due to the volume that is necessary for production of almost all drugs, making this dependence even less significant.

*Reagent Prices**

* NaCl is neglected, due to the comparatively small amount used.

DCM		0.298927423	**0.498927423**	0.698927423		[$/kg]
	NPV	$100,122,297	$100,075,294	$100,028,291		
	IRR	276.48%	275.79%	276.28%		
Pharmaceutical-Grade Water		0.09	**0.12**	0.15	0.18	[$/kg]
	NPV	$100,599,893	$100,075,294	$99,550,695	$99,026,096	
	IRR	277.52%	275.79%	275.23%	274.09%	
PVA		0.514151856	**0.714151856**	0.914151856	1.114151856	[$/kg]
	NPV	$100,106,768	$100,075,294	$100,043,820	$100,012,347	
	IRR	276.45%	275.79%	276.31%	276.24%	
PLGA		39090	**39100**	39110	39120	39130 [$/kg]
	NPV	$100,104,355	$100,075,294	$100,046,233	$100,017,172	$99,988,112
	IRR	276.44%	275.79%	276.32%	276.25%	276.19%
Haloperidol		10656	**10676**	10696	10716	[$/kg]
	NPV	$100,082,176	$100,075,294	$100,068,412	$100,061,530	
	IRR	276.39%	275.79%	276.36%	276.35%	

Table 7.21. Sensitivity Analyses: Reagent Pricing.

7.7.3 Maximum Market Share Capture

The next group of metrics analyzed is the maximum market share capture percentages. In the original analysis, both of these maximum share captures were considered 100%. While this is by no means an unrealistic assumption, in the case of suboptimal clinical trial results, it may be necessary to scale back expectations.

First, the ramp-up schedules for both the sensitivity ranges of the atypical sector share and the typical sector share were calculated. In both cases, the time to ramp-up was kept consistent, due to the lack of significant risk in that assumption.

	Ramp-Up Schedules					
Atypical 6 yr	15%	30%	45%	60%	75%	**90%**
	13%	27%	40%	53%	67%	**80%**
	12%	23%	35%	47%	58%	**70%**
	10%	20%	30%	40%	50%	**60%**
	8%	17%	25%	33%	42%	**50%**
	7%	13%	20%	27%	33%	**40%**
	5%	10%	15%	20%	25%	**30%**

Typical 4 yr	40%	57%	73%	**90%**
	40%	53%	67%	**80%**
	40%	50%	60%	**70%**
	40%	47%	53%	**60%**
	40%	43%	47%	**50%**
	40%	40%	40%	**40%**
	30%	30%	30%	**30%**

Table 7.22. Sales Ramp-Up Schedules for Maximum Market Share Capture Sensitivity Analyses.

Next, each ramp-up schedule had a specific associated NPV and IRR calculated. As expected, the market share captured from the typical sector (Haloperidol and Equivalents) is much more significant to overall profitability than that from the atypical sector (Additional Patients).

Maximum Share Capture (linear ramp-up constant)

Additional Patients (from atypical market erosion)

	30	40	50	60	70	80	90	**100**	[%]
NPV	$90,184,484	$91,597,457	$93,010,430	$94,423,403	$95,836,375	$97,249,348	$98,662,321	$100,075,294	
IRR	260.73%	262.98%	265.23%	267.47%	269.71%	271.93%	274.16%	275.79%	

Haloperidol and Equivalents

	30	40	50	60	70	80	90	**100**	[%]
NPV	$38,031,812	$53,140,829	$60,963,240	$68,785,651	$76,608,061	$84,430,472	$92,252,883	$100,075,294	
IRR	176.02%	234.53%	242.42%	249.87%	256.94%	263.69%	270.16%	275.79%	

Table 7.23. Sensitivity Analyses for Maximum Market Share Capture.

This is simply due to the larger number of patients under our treatment in the typical sector relative to the atypical sector. This is actually a much less risky proposition: acquiring market share from the typical market is much more likely than acquiring it from the atypical market, simply due to the large amount of innovation present in the atypical sector versus the typical sector. Innovation, on the part of other companies, threatens to displace the microsphere delivery technology that the XME process is based upon.

Even in the most extreme cases of 30% and 40% typical market share capture, the NPV of the project is positive. These cases are unlikely to occur, due to the elimination process inherent in the drug approval process. These lowest market share positions would most likely be a result of poor or equivalent clinical trial results in comparison to haloperidol and haloperidol decanoate. In this case, the likelihood of approval is low, and therefore these lowest market share positions would be prevented from occurring, with a complete shutdown of the project much more likely. Cases in the range of 50-90% would occur as an effect of uncontrollable factors like percentage coverage via Medicare, insufficient physician coverage, or the entrance of new competitors in the schizophrenia market. The robustness indicated here is an indicator of the project's overall strength.

7.8 Breakeven Analysis

This section is designed to analyze the compounding of 'worst-case' scenarios. First, the break even sale price given all of the conditions in the initial profitability analysis (Case 2: No Distillation Column) is 228.21 USD, which results in an NPV of 0. The likelihood of accepting a price below the market pricing analysis baseline is extremely low. A price in this range is likely a result of a poor clinical trial result, which as mentioned in Section 6.7.3, is likely to prevent the project from moving forward from the clinical trial stage.

. The Haloperidol and Equivalents market is significantly more relevant to overall profitability than the Additional Patients segment. As a result, we choose to conduct a sensitivity analysis with the typical market (the sector from which these sales are derived) when considering a compounded 'worst-case' scenario. Taking this into account, a multivariate sensitivity analysis is presented, which varies price and the Haloperidol and Equivalents Maximum Market Share.

The ramp-up schedules presented in Table 7.22 are kept consistent throughout this analysis.

The results of the analysis indicate remarkable robustness. Even with the market pricing baseline price and the lowest market share of 30% assumed here, a positive NPV and IRR results. However, there are several caveats to the most extreme cases (IRR < 160%). First, we assume a project lifetime of 10 years, which in the case of poor performance to this degree, the project would likely be cut in favor of higher NPV-generating endeavors, and therefore would not have sufficient time to generate positive NPV and IRR. Those projects that fall into this category are bolded. In the same way that these low extremes are unlikely, the high extremes also present some inherent difficulties. In the case of positive performance of this degree (IRR > 300%), there is an expectation that other competitors will find a way to compete in this market. The short approval period makes this more likely to happen within the 10 year window that these profitability metrics are calculated over. This would decrease sales in the latter half of the window, and subsequently lower both NPV and IRR. Projects in this category are underlined.

A

NPV		Haloperidol and Equivalents Maximum Market Share							
		30	40	50	60	70	80	90	100
Price	$ 260	***$12,845,885***	***$16,862,473***	***$20,879,061***	***$24,895,649***	***$28,912,237***	***$32,928,825***	***$36,945,413***	***$40,962,001***
	$ 280	***$20,926,644***	***$25,890,308***	***$30,853,971***	***$35,817,635***	$40,781,299	$45,744,962	$50,708,626	$55,672,289
	$ 300	$29,007,404	$34,918,143	$40,828,882	$46,739,621	$52,650,360	$58,561,099	$64,471,838	$70,382,577
	$ 320	$37,088,164	$43,945,979	$50,803,793	$57,661,608	$64,519,422	$71,377,237	$78,235,051	$85,092,865
	$ 340	$38,031,812	$53,140,829	$60,963,240	$68,785,651	$76,608,061	$84,430,472	$92,252,883	$100,075,294
	$ 360	$53,249,684	$62,001,649	$70,753,615	$79,505,580	$88,257,546	$97,009,511	$105,761,476	$114,513,442
	$ 380	$61,330,444	$71,029,485	$80,728,526	$90,427,567	$100,126,607	$109,825,648	$119,524,689	$129,223,730

B

IRR		Haloperidol and Equivalents Maximum Market Share							
		30	40	50	60	70	80	90	100
Price	$ 260	***96.10%***	***105.25%***	***113.29%***	***120.55%***	***127.20%***	***133.38%***	***139.18%***	***144.64%***
	$ 280	***129.14%***	***137.99%***	***145.97%***	***153.29%***	160.09%	166.46%	172.48%	178.20%
	$ 300	161.57%	170.23%	178.17%	185.55%	192.46%	198.99%	205.19%	211.10%
	$ 320	193.66%	202.18%	210.09%	217.51%	224.51%	231.16%	237.51%	243.59%
	$ 340	176.02%	234.53%	242.42%	249.87%	256.94%	263.69%	270.16%	275.79%
	$ 360	257.24%	265.57%	273.44%	280.92%	288.05%	294.88%	301.45%	307.78%
	$ 380	288.84%	297.11%	304.96%	312.46%	319.64%	326.54%	333.19%	339.62%

Table 7.24. Multivariate Sensitivity Analysis of Price versus Haloperidol and Equivalents Maximum Market Share. The sensitivity analysis presents its results in NPV in part a, and in IRR in part b. Bolded values are those projects that fall below an IRR of 160%, which would likely result only in the case of poor or equivalent clinical trial results compared to haloperidol or haloperidol decanoate. Clinical trial results in this range would result in project shutdown, and would therefore indicate a more pronounced drop-off than the numbers would suggest. Similarly, underlined values are projects that generate an IRR of greater than 300%, which would most likely result in intense competition in the latter years of the project, lowering sales in those same years. This would cause IRR to drop, making the profitability metrics that are underlined difficult to achieve.

7.9 Summary

The haloperidol controlled release product is expected to generate a net present value of 99.8 million USD and an IRR of 276%. The primary risk factor identified in the sensitivity analysis is the dependence on clinical trial results that clearly indicate an improved side effect profile. Results that indicate only equivalence or worse in the controlled release feature, regardless of the extended release feature of the product, will fail to achieve approval, and therefore result in complete shutdown. This is an unlikely scenario, and the robustness of sensitivity analyses on sale price and reagent price indicate that the project should certainly move into the clinical trial stage, during which warning signs of poor results should be closely monitored as a decisive reason to shut down the project.

Once the product moves past the clinical trial phase, the cash flow summary indicates a strong surge in market share. This, coupled with the compressed production schedule of a single quarter to produce 500,000 doses, will allow the project to quickly move into the green. However, as profitability metrics increase, so does the likelihood of competition, which will lower sales in the latter part of the 10 year project, as competitors complete development and enter the market.

The large capital investment and compressed production schedule allows for significant capacity to be dedicated to the development of new products on the platform. The platform is particularly suited to chronic disease therapeutics, which comprise the majority of the pharmaceutical market, a result of chronic disease patients being by definition 'repeat buyers'. The potential revenues from additional utilization of the platform are enormous, and these future revenues alone justify the undertaking of this first optimization for haloperidol, although they are not quantitatively presented here. However, a failure to move the haloperidol product past the clinical trial phase would serve to invalidate the platform, and effectively cut off any other potential project revenues in other disease markets. Clinical trial risk is idiosyncratic and nondiversifiable in the pharmaceutical industry, and is not specific to or overweighted in this project. All profitability metrics suggest that this platform would serve to boost a declining market, and function as a jump-off point for revenues in others.

7.10 Chapter 7 References

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Chapter 8: Experimental Section

Introduction

The cross-flow membrane emulsification (XME) process was carried out on a laboratory scale in order to verify the accuracy of the emulsification equation (Equation 2.18, Chapter 2.3) and to confirm the ability of the process to generate monodisperse droplets. Before any attempts are made to scale-up the XME process to an industrial application, it is important to test the viability of the emulsification concept on a small scale. We run the XME process under a specified set of operating parameters, and compare the sizes of the generated droplets against the theoretical size predictions based on operating conditions. In general we find that the emulsification process generates a highly monodisperse size distribution, but the resulting droplets are significantly larger than the mathematical model predicts.

Materials and Methods

Continuous phase solutions are prepared by dissolving 97.73 wt% water, 1.27 wt% dichloromethane, and 1.00 wt% poly(vinyl alcohol). The solution is moderately heated for 30 minutes to facilitate dissolution of the polymer, and then left to magnetically stir for 24 hours. Dispersed phase solutions are prepared by dissolving 0.098 wt% haloperidol, 0.860 wt% poly(lactic-co-glycolic acid), and 99.042 wt% dichloromethane. This concentration is equivalent to 1% solid materials (haloperidol and PLGA) by volume. The solution is magnetically stirred for 24 hours before use.

The XME flow device consists of a narrow rectangular channel cut into an aluminum body. The dimensions of the channel are: height approximately 1 mm, width 6.4 mm, length in the direction of continuous phase flow 6 cm. At the base of the channel is a stainless steel membrane containing a single 100 μm diameter pore.

The flow rate of the continuous phase was set at 3 mL/s, for a superficial velocity through the channel of 0.469 m/s. Based on flow simulations performed in the computational fluid

mechanics suite in COMSOL Multiphysics, this flow rate in a rectangular channel of the given dimensions generates a shear rate of 2,500 s^{-1} at the channel floor. The flow rate of the dispersed phase was set at 2 mL/hr, giving a Weber number (Equation 2.9, Chapter 2.3) of 0.051, far below the transition to jetting behavior.

Product droplets were collected in a glass dish at the channel outlet. The sample was observed using a microscope, and visual measurements of particle diameter were recorded. The sample droplets are analyzed for monodispersity, and their average diameter is compared to the predictions of the emulsification model under these operating conditions.

Results and Discussion

Based on the supplied operating parameters, the theoretical size of emulsified droplets is predicted by Equation 4.11.

$$\frac{D_{wet}}{D_0} = 0.8\left(\frac{32}{C_d}\right)^{1/4} Oh_{CP}^{1/2}\, Ca^{-1/2} \qquad \text{(Equation 4.11)}$$

Here D_{wet} is the diameter of an emulsified droplet, D_0 is the pore diameter, C_d is the drag coefficient, Oh_{CP} is the continuous phase Ohnesorge number, and Ca is the capillary number. The drag coefficient, the Ohnesorge number, and the capillary number are defined in Chapter 3.3. Based on the supplies operating parameters, the model equation predicts that the outlet droplet size will be about 220 μm.

Figure 8.1 shows a representative sample of the product droplets. The average droplet size is 353 μm with a standard deviation of 97 μm. However, if we screen out extremely small "satellite" droplets, having diameter less than 200 μm, the average size becomes 390 μm with a standard deviation of only 33 μm.

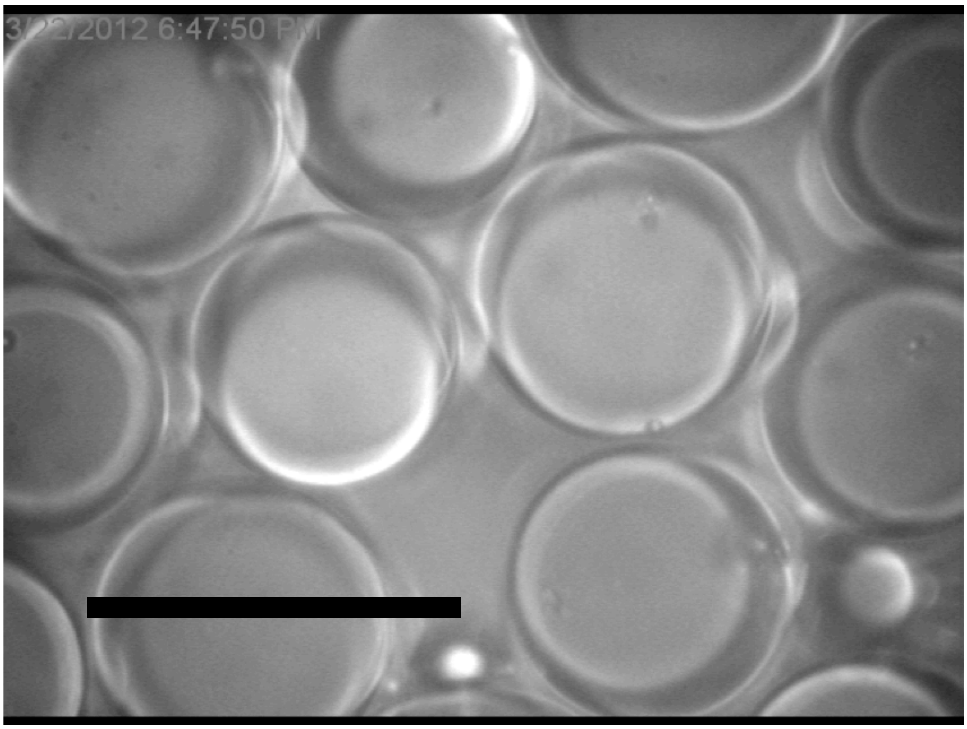


Figure 8.1. Sample photograph of emulsified droplets generated by the XME process. Included with a 500 μm scale bar.

Excluding these satellite droplets, the monodispersity of the sample is quite good given our lack of experience with the XME equipment. The standard error in droplet size, ignoring satellites, is only 8% of the average diameter. The appearance of satellite droplets can be attributed to droplet disruption and break-up in the high-shear rate environment around sharp turns inside of the flow device. A pharmaceutical-grade device would be designed specifically to avoid these sharp turns.

Despite the high level of monodispersity we observe, the mathematical model predicts that the emulsified droplets should be significantly smaller than those collected. The average collected diameter, excluding satellites, is 390 μm, 77% larger than the expected 220 μm diameter droplets. This deviation can be largely attributed to small measurement errors on channel geometry. The predicted droplet size is especially sensitive to measurement accuracy on channel height. The height of the flow channel is approximately 1 mm, but we could only resolve the measurement to roughly ±0.5 mm. A small error in the measured height, on the order of a few tenths of a millimeter, amounts to a large percent difference and would dramatically affect the actual shear rate at the

channel floor. If the height of the channel were actually 1.5 mm instead of the reported 1.0 mm, COMSOL simulations indicate that the experimental 3 mL/s continuous phase flow would actually generate a shear rate along the channel floor of 1,000 s^{-1}, rather than the expected 2,500 s^{-1} for a 1.0 mm height. With this new value for channel height, the predicted droplet size increases to 350 μm and the observed droplet diameters are only 11% too large.

Conclusions

This laboratory-scale test of the XME process supports the commercial value of the procedure. Even without long-term training and experience with the operating equipment, we were able to generate an emulsion of nearly-monodisperse droplets using similar materials to those detailed in the large-scale process design. Although the resulting droplets were unexpectedly large and we could not conclusively verify the emulsification model, the model's size prediction remains plausible given expected measurement error on the small dimensions of the flow channel.

Chapter 9: Conclusions and Outlook

The project thus described offers a comprehensive analysis of the product and process design components of time-release drug-loaded microspheres. The aim of this project was to manufacture a depot-release, zero-order haloperidol loaded poly(lactic-co-glycolic acid) (PLGA) microparticle in order to satisfy a need to overcome traditional dosing issues in the mental illness patients. These dosing issues include non-compliance (exacerbated by symptoms common in this sector), convenience of dosing schedule, and achieving an optimal concentration profile (characterized by zero-order release). The solution lies in the extended release and controlled release features of the microsphere drug delivery format. The extended release feature lies in both the choice of polymer in the microsphere, in this case PLGA, and a monodisperse combination of discrete microsphere size. The controlled release feature is expressed through the choice of large to small diameter ratio that was calculated both to achieve zero-order release, but also to maintain drug concentrations in the body at an optimal level over the course of 30 days. Achieving these product design specifications necessitated a precise and controllable manufacturing technology, as well as downstream processing methods that would preserve these characteristics and deliver them in a user-friendly format. Current manufacturing techniques do not allow for the precision of size control necessary to achieve the specifications for these features; this project explores a new technique, cross-flow emulsification (XME), that can achieve these specifications. XME flow devices allow high production throughput of monodisperse, emulsified droplets composed of polymer and drug dissolved in an organic solvent. Over the course of downstream processing, the solvent is removed, leaving behind a hard, drug-dispersed polymer sphere.

Although the basic product and process technologies were known at the outset of the project, rigorous optimization was necessary to generate a product that could satisfy customer needs and design a process that could yield the desired product at a rate acceptable to meet production demand. We began by developing a mathematical model, which would quantitatively predict the drug release kinetics of any specified depo-haloperidol sphere within the size and composition range under consideration. Modeling analysis gave a list of potential size and composition options that

would satisfy customer requirements. From here, we applied literature resources and computational fluid dynamics (CFD) analysis in order to tune the emulsification process in such a way that the process could generate particles of the specified size distribution and composition. This theoretical optimization then led to the detailed design of a flow channel. The architecture of the flow channel was considered in depth, with an eye to optimizing control over production characteristics and throughput. Finally, we developed a series of downstream processing operations that would prepare the final product for shipment to the customer.

Moving forward, we turn our attention to the company under which this platform and product should be housed. There are several options as to where this project can grow: a large pharmaceutical company, a drug delivery focused firm, a generics manufacturer, or independently. There are also several categories of advantages and disadvantages associated with each one of these options: speed of regulatory approval, intellectual property in new drugs for development, access to capital, sales and distribution capabilities, and investment return. A large pharmaceutical firm will score well on all of these metrics, and is most likely the best fir for the project, especially in terms of growth from the development of additional drugs within the platform. It is restrictive to in the sense that associations with a large pharmaceutical firm will decrease the likelihood of licensing or collaboration with other large-cap firms in the industry. Large pharmaceutical firms like Pfizer and Sanofi-Aventis also contain generic subsidiaries, which would aid in supplying a steady stream of new drugs to develop. Large-cap firms tend to specialize over a wide spectrum of disease areas, because this platform is so particularly suited for applications in chronic diseases, a firm that specializes in areas like heart disease, diabetes, or oncology will likely be able to utilize the technology in more areas. Other focuses like infectious diseases, specifically in antibiotics and vaccines, will also benefit from the controlled release and extended release features of the drug. Although this paper focuses on the optimization of haloperidol within the XME platform, the platform is easily adaptable to other drugs. This paper elucidates solvent choices for haloperidol, a hydrophobic drug, but it is important to specify these choices for other types of drugs, especially hydrophilic drugs and biologics (proteins and antibodies). The next development steps should explore applications in these two areas, which will fully specify the platform and its range. Steps should be taken to accelerate this research, and begin to establish the XME platform's flexibility. This will be a time-sensitive operation, due to the ongoing race in the pharmaceutical industry to

develop a 'go-to' drug delivery technology in-house. Each successive drug incorporated will give the research team increasing expertise, and be a step closer to realizing the potential of the PLGA-XME platform to be one of the foremost advances in the drug-delivery technology race.

Acknowledgements

To Dr. John C. Crocker,

Thank you for your guidance, undying enthusiasm, and access to your research lab (and haloperidol) over the course of this project. You have turned one of the most difficult times in a CBE senior's life into one of the most intellectually stimulating semesters we have experienced at UPenn.

To Dr. Robert Meyer,

Thank you for access to your setup and your security camera, and for sharing your expertise in the project material and in the pharmaceutical industry with us. All the help you offered was really above and beyond the call of duty, and we truly appreciate the time and effort you spent with us.

To Dr. Warren D. Seider and Professor Leonard A. Fabiano,

Thank you for the guidance and expertise that you both shared with us over the course of this project. We hope that you will bestow the same attention and time to the next generation of seniors!

Sincerely,

Greg Cordina, Abby Lee, Will Mulhearn, and Nimu Sidhu

Appendix A: Symbols and Dimensionless Numbers

Symbol	Meaning
γ	Interfacial Tension
η	Viscosity
η_{sp}	Specific Viscosity
$[\eta]$	Intrinsic Viscosity
λ	Viscosity Ratio
ρ	Density
r	Radial Coordinate
R	Polymer Sphere Radius
t	Time
C	Drug Concentration
D	Diffusivity
MW	Polymer Chain Molecular Weight
k	Polymer Hydrolysis Rate Constant
V	Product Sphere Volume
D_{wet}	Emulsified Droplet "Wet" Diameter
D_{dry}	Hardened Particle "Dry" Diameter
D_0	Pore Diameter
k_H	Huggins Equation Constant
c	Dissolved Polymer Concentration
Q	Volumetric Flow Rate
dv/dz	Shear Rate
u	Superficial Velocity
L	Characteristic Length of the Channel (Channel Height)

Weber Number: Ratio of inertial effects to surface tension effects.

$$We \equiv \frac{\rho_{DP}\, Q_{DP}^2}{D_0^3\, \gamma}$$

Pore Capillary Number: Ratio of drag effects to interfacial-tension effects, evaluated at a droplet attached to a pore

$$Ca_{pore} \equiv \frac{\eta_{CP} \frac{dv}{dz} D_0}{\gamma}$$

Free Droplet Capillary Number: Ratio of drag effects to interfacial-tension effects, evaluated at a droplet freely moving with the continuous phase stream

$$Ca_{free} \equiv \frac{\eta_{CP} \frac{dv}{dz} \left(D_{wet} / 2 \right)}{\gamma}$$

Ohnesorge number: Ratio of viscous and capillary time scales

$$Oh \equiv \frac{\eta_{CP}}{\sqrt{\rho_{CP} \, D_0 \, \gamma}}$$

Channel Reynolds number: Ratio of inertial effects to viscous effects, evaluated for continuous phase flow through a channel.

$$Re_{channel} \equiv \frac{\rho_{CP} \, u \, L}{\eta_{CP}}$$

Droplet Reynolds number: Ratio of inertial effects to viscous effects, evaluated for the continuous phase flowing around a droplet

$$Re_{drop} \equiv \frac{\rho_{CP} \, u \, D_{wet}}{\eta_{CP}}$$

Viscosity Ratio: Ratio of dispersed phase viscosity to continuous phase viscosity

$$\lambda \equiv \frac{\eta_{DP}}{\eta_{CP}}$$

Drag Coefficient: Metric of fluid dynamic resistance to motion

$$C_d = \frac{\left[\lambda \left(\frac{24}{Re_{drop}} + \frac{4}{Re_{drop}^{1/3}} \right) + \frac{14.9}{Re_{drop}^{0.78}} \right] Re_{drop}^2 + 40 \, \frac{3 \, \lambda + 2}{Re_{drop}} + 15 \, \lambda + 10}{\left(1 + \lambda \right) \left(5 + Re_{drop}^2 \right)}$$

Appendix B: MATLAB Script

The full text of the drug release model program (Chapter 3.1) is replicated here. In order to use the model, the code's text must be edited manually to enter the initial polymer chain molecular weight. The program will then prompt the user for all other input parameters once the script is initiated on MATLAB.

Script File "diffusion"

```
% Set the size and number ratio of both particles

x1_range = input('Enter small radius [um]: ');

x2_range = input('Enter large radius [um]: ');

x_1 = 0:x1_range/100:x1_range;

x_2 = 0:x2_range/100:x2_range;

ratio = input('Ratio of small-to-large: ');

% Set the time-interval

t_range = input('Enter time range [days]: ');

t = 0:t_range/100:t_range;

% Spherical coordinates are identified by MATLAB with the number 2

m = 2;

% Execute the solver for small and large particles

sol_1 = pdepe(m,@dfsnpde,@dfsnic,@dfsnbc,x_1,t);

u_1 = sol_1(:,:,1);

sol_2 = pdepe(m,@dfsnpde,@dfsnic,@dfsnbc,x_2,t);

u_2 = sol_2(:,:,1);

% SMALL PARTICLE - Integrate the output matrix

cargo_1 = zeros(1, length(t));
```

```
ind_1a = 1; %time index

while ind_1a < length(t) + 1

      ind_2a = 1; %space index

      sum_1 = 0;

      while ind_2a < length(x_1)

      sum_1 = sum_1 + 4*pi*0.5*(u_1(ind_1a,ind_2a) +
      u_1(ind_1a,ind_2a+1))*(0.5*(x_1(ind_2a) +
      x_1(ind_2a+1)))^2*x1_range/100;

      ind_2a = ind_2a + 1;

      end

      cargo_1(ind_1a) = sum_1;

      ind_1a = ind_1a + 1;

end

% LARGE PARTICLE - Integrate the output matrix

cargo_2 = zeros(1, length(t));

ind_1b = 1; %time index

while ind_1b < length(t) + 1

      ind_2b = 1; %space index

      sum_2 = 0;

      while ind_2b < length(x_2)

      sum_2 = sum_2 + 4*pi*0.5*(u_2(ind_1b,ind_2b) +
      u_2(ind_1b,ind_2b+1))*(0.5*(x_2(ind_2b) +
      x_2(ind_2b+1)))^2*x2_range/100;

      ind_2b = ind_2b + 1;

      end

cargo_2(ind_1b) = sum_2;

ind_1b = ind_1b + 1;

end
```

```
% Add the profiles

final_cargo = zeros(1, length(t));

counter = 1;

while counter < length(t) + 1

      final_cargo(counter) = ratio*cargo_1(counter) + cargo_2(counter);

      counter = counter + 1;

end

plot(t, 1 - final_cargo/final_cargo(1));
```

Differential Equation and Diffusivity Function "dfsnpde"

```
function [ c,f,s ] = dfsnpde( x,t,u,DuDx )

k = 0.07;               % polymer decay rate [1/day]
M = 10000;              % polymer MW -- between 10,000 and 70,000 Da
conv = 8.64*10^16;      % converts m^2/s --> um^2/day

c = 1/(conv*exp(-0.347*log(M*exp(-k*t))^3 + 10.394*log(M*exp(-k*t))^2 -
104.95*log(M*exp(-k*t)) + 316.95));

% c = 1/diffusivity
% This diffusivity equation comes from the Raman model. Given by
% paper in [m^2/s], convert to [um^2/day] so we can input values with
% implied units of um and days.


f = DuDx;               % MATLAB assigns a name to derivative element
s = 0;                  % No forcing term in the diffusion equation

end
```

Initial Condition Function "dfsnic"

```
function [ u0 ] = dfsnic( x )

u0 = 1;     % Initial uniform concentration profile, units and magnitude
            % are irrelevant because the concentration profile is simply
            % a fractional ratio
```

```
end
```

Boundary Condition Function "dfsnbc"

```
function [ pl,ql,pr,qr ] = dfsnbc( xl,ul,xr,ur,t )

pl = 0;       % sets derivative to zero at center (Left-Hand Side)
ql = 1;       % sets derivative to zero at center (Left-Hand Side)
pr = 0;       % sets concentration to zero at surface (Right-Hand Side)
qr = 0;       % sets concentration to zero at surface (Right-Hand Side)

end
```

The full text of the concentration integration formula is replicated here. In order to use the model, the release profile from the drug release mode (above) must be differentiated with respect to time and multiplied by the initial drug loading mass. The resulting release rate vector is passed as an input to the serum concentration model below.

Blood Serum Concentration Model "Conc"

```
R = input('Rate Vector: ');    % initial loading mult by release profile
                               % derivative

step = input('Time Step: ');   % time step must be the same as the
                               % release profile model - usually 0.5 day

C = zeros(1, length(R)+1);     % blank concentration vector

t = zeros(1, length(C));       % prepare the time vector

count = 1;

while count <= length(t)

      t(count) = (count - 1)*step;

      count = count + 1;

end

int = 1;

while int <= length(R)         % perform the integration, modify C

      C(int+1) = C(int) + (R(int)/50 - 0.792*C(int))*step;

      int = int + 1;

end

plot(t, C);
```

Appendix C: SolidWorks

The appendix as follows includes drawings – completed in SolidWorks – of the lower potion of the channel, the upper portion of the channel, and the channel assemble as imagined. The lower portion of the channel and the upper portion of the channel all include units – first in English units of "inches," then in metric units of "millimeters." For further information about the channel design and membrane design, see Chapter 5. For further information about the pore spacing analysis see Chapter 4.

Figure C.1. XME apparatus assembly
(upper and lower portions) |
isometric orientation | solid view

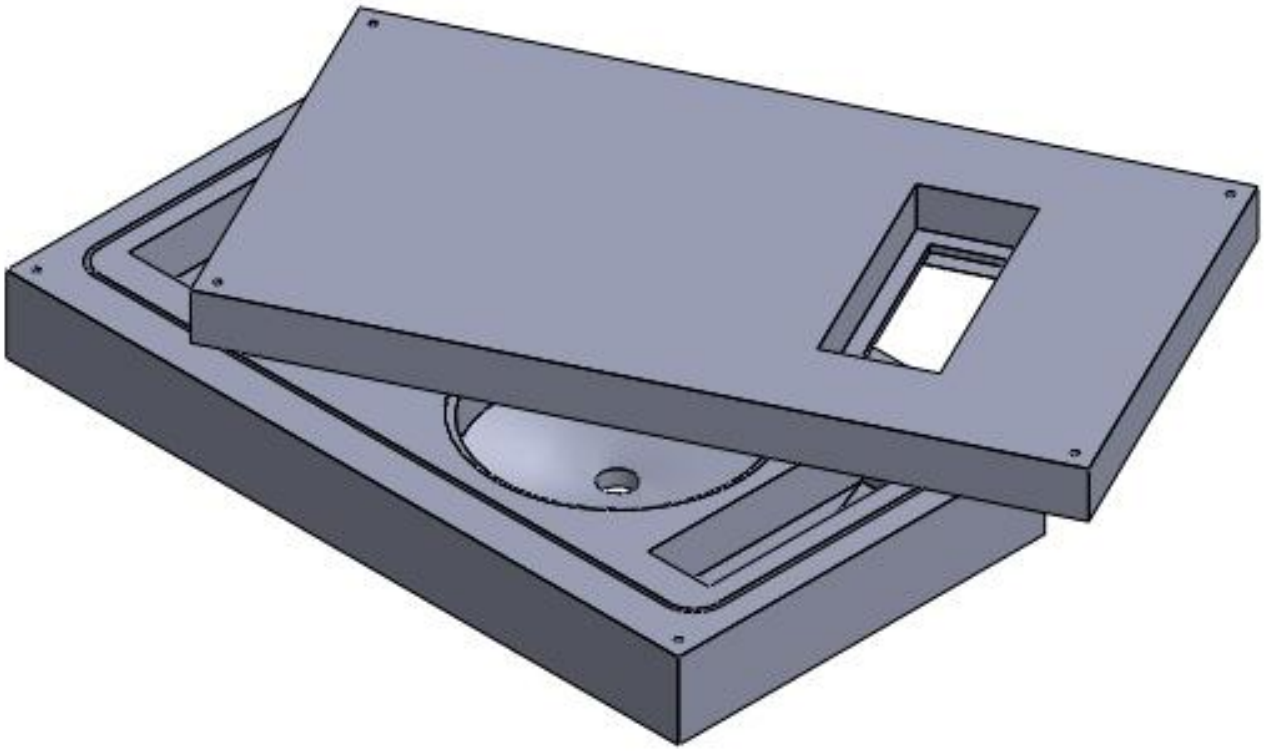


Figure C.1. XME apparatus assembly (upper and lower portions) | isometric orientation | wire-frame view

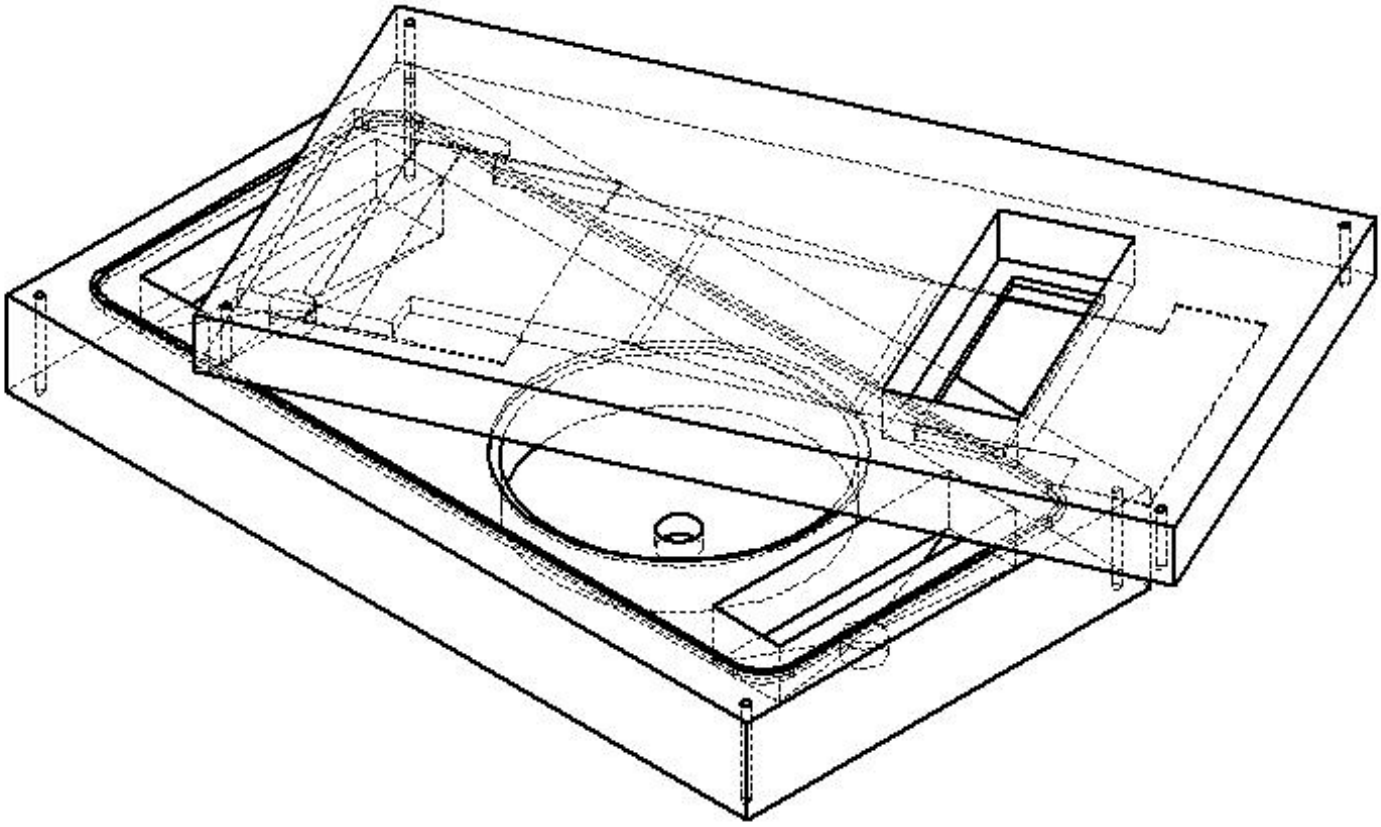


Figure C.1. lower section of the XME apparatus | isometric orientation | wire-frame view | English units “inches”

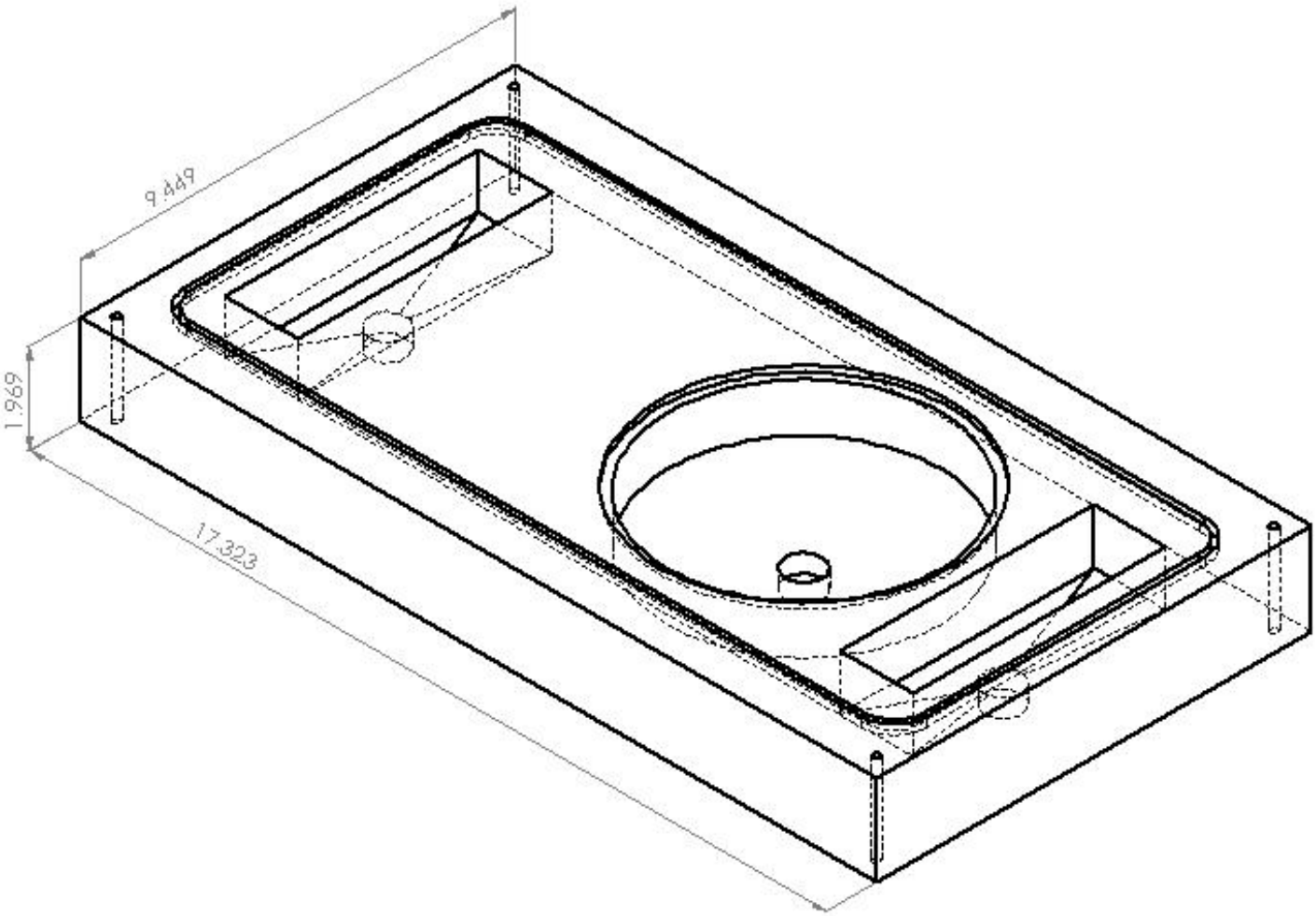


Figure C.1. lower section of the XME apparatus | isometric orientation | wire-frame view | metric units "millimeters"

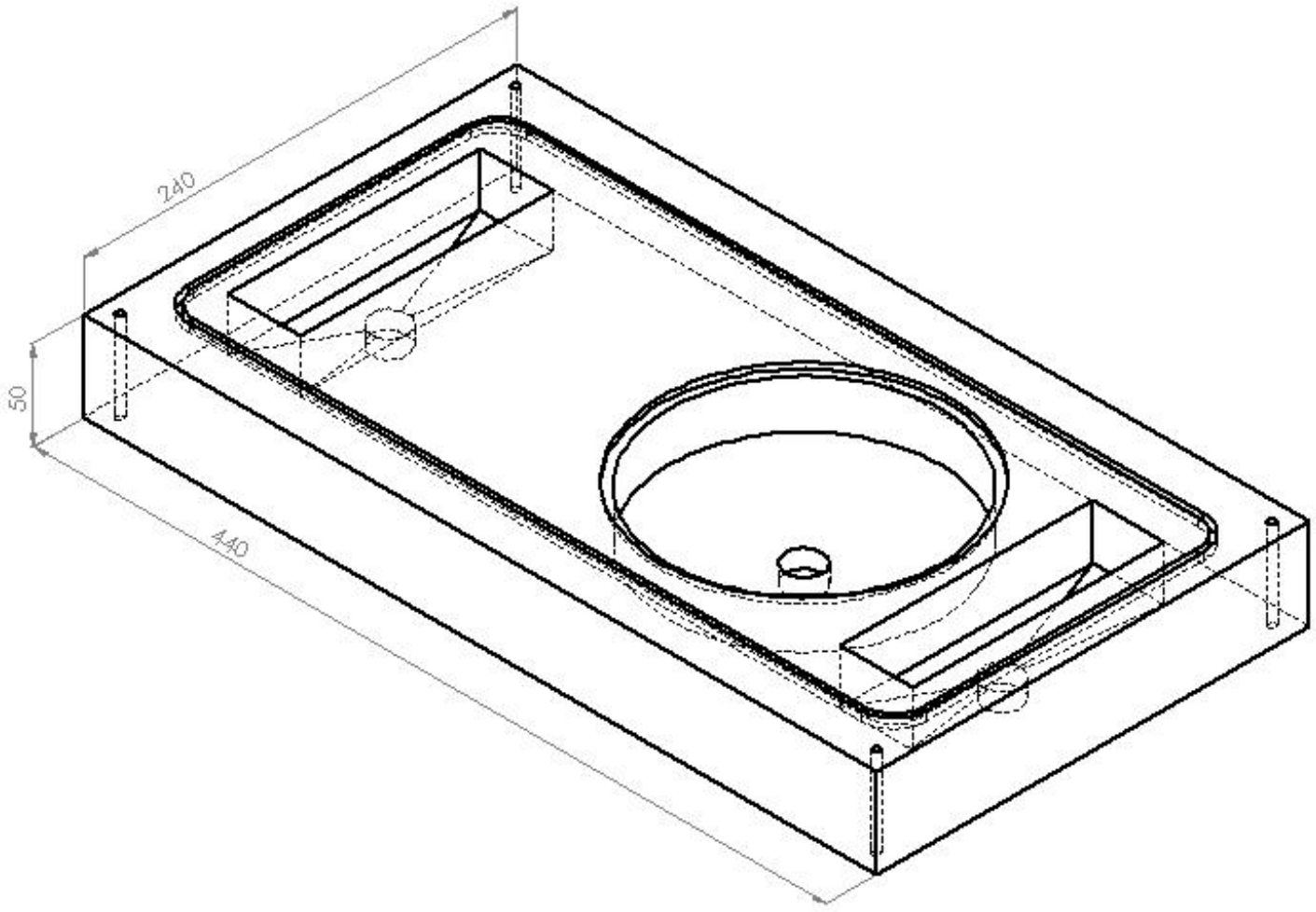


Figure C.1. lower section of the XME apparatus | side view (bottom) top view (top) | wire-frame | English units “inches”

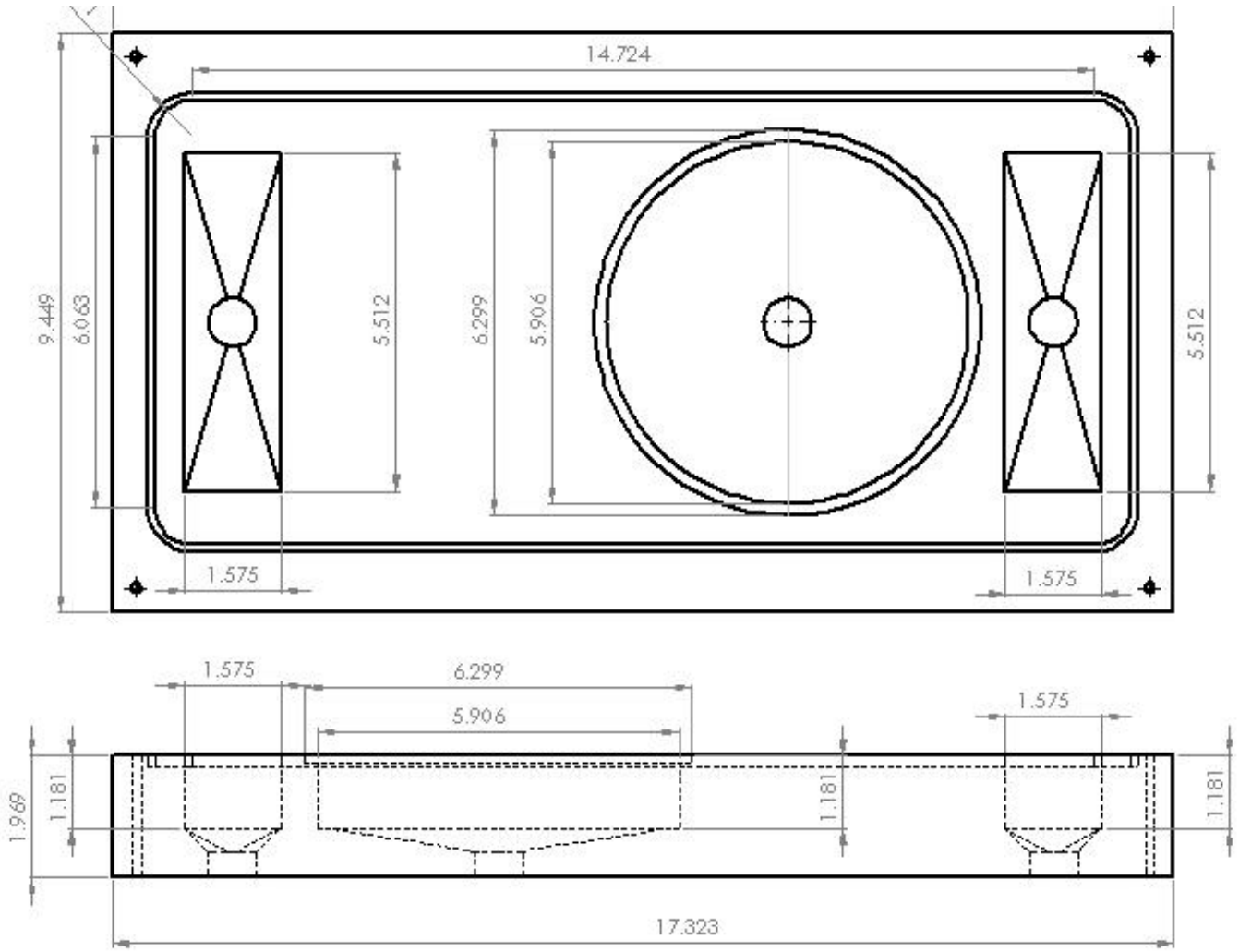


Figure C.1. lower section of the XME apparatus | side view (bottom) top view (top) | wire-frame | metric units "millimeters"

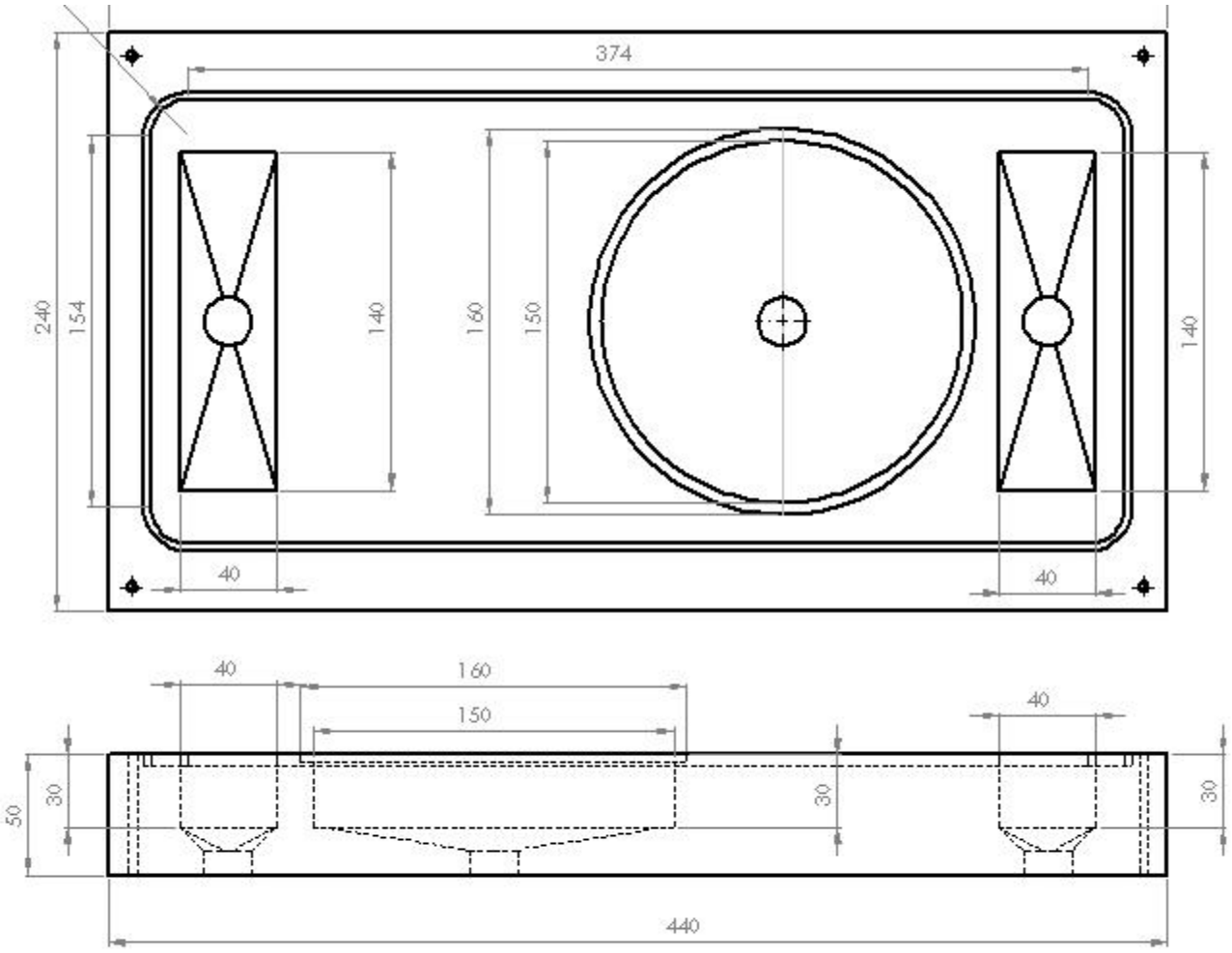


Figure C.1. upper section of the XME apparatus | isometric orientation | wire-frame view | English units “inches”

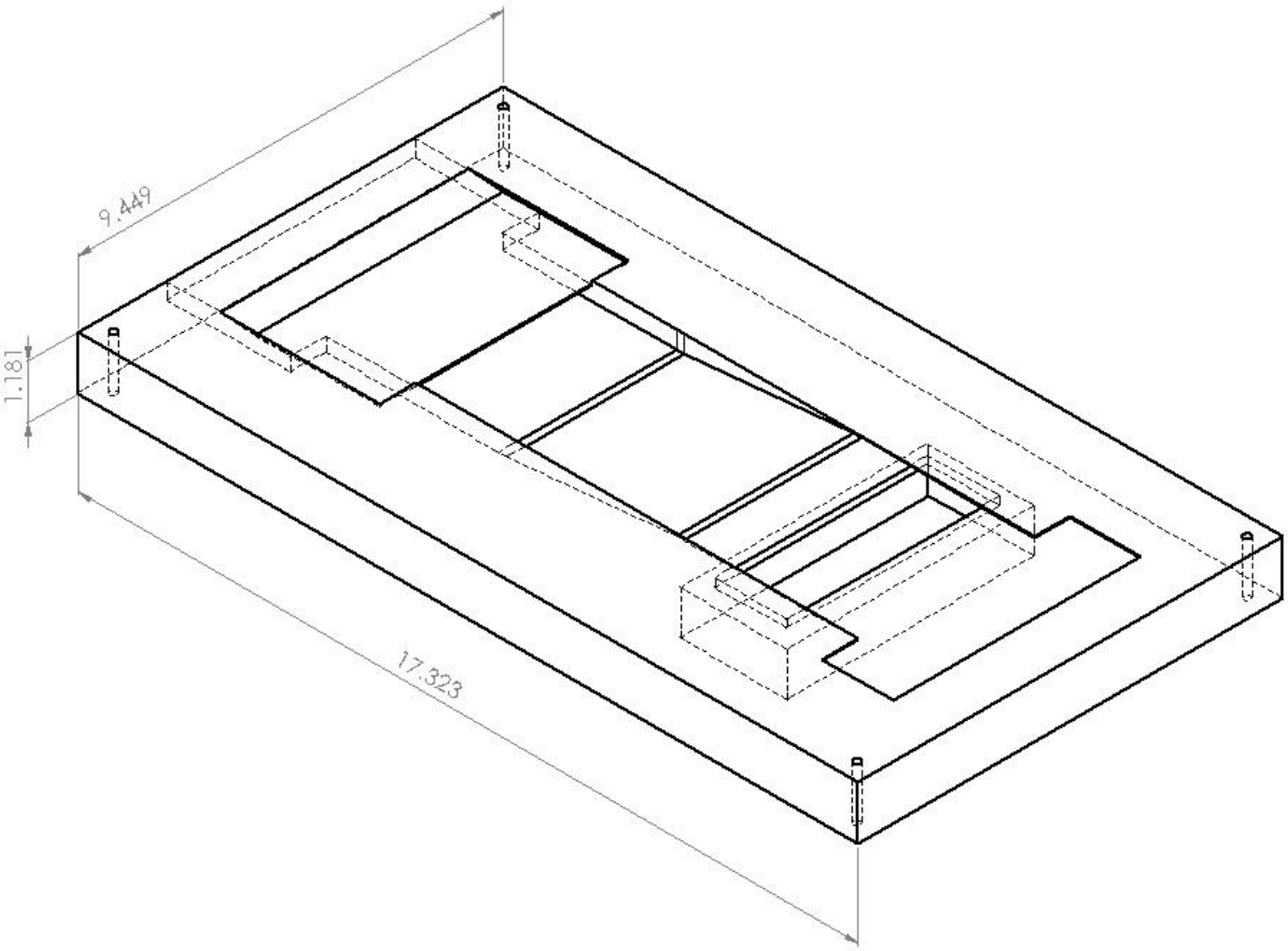


Figure C.1. upper section of the XME apparatus | isometric orientation | wire-frame view | metric units “millimeters”

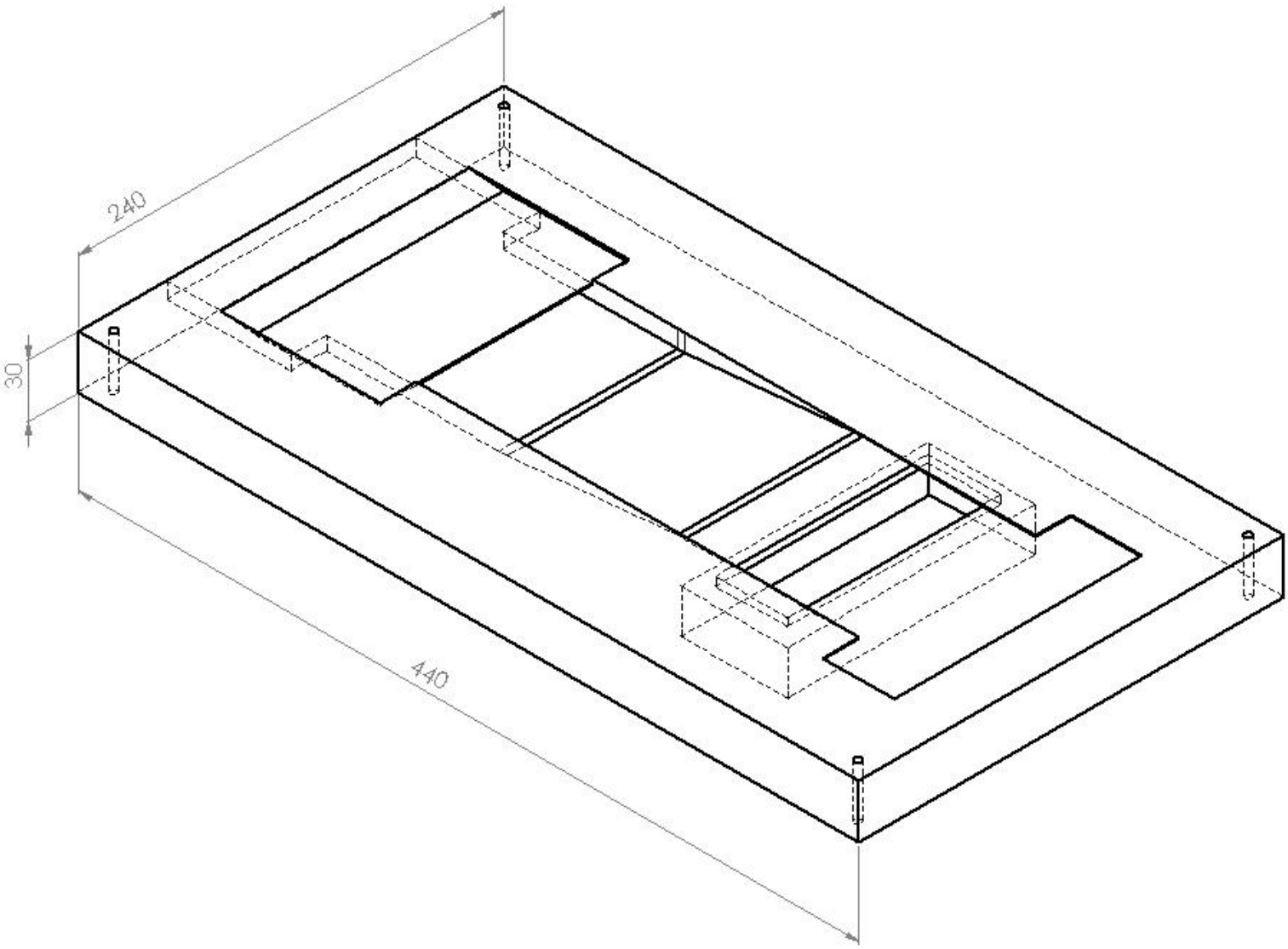


Figure C.1. upper section of the XME apparatus | side view (bottom) top view (top) | wire-frame | English units "inches"

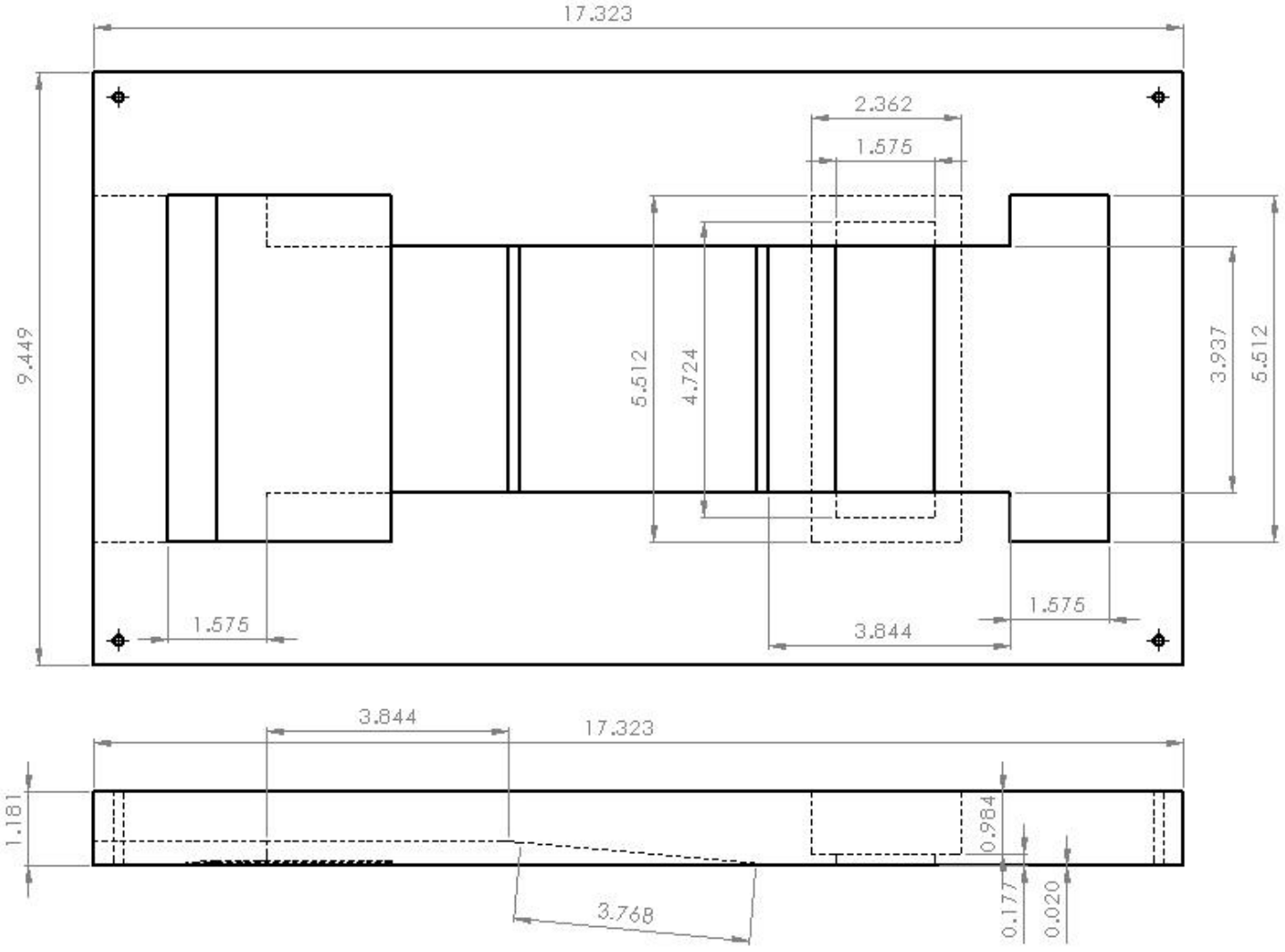
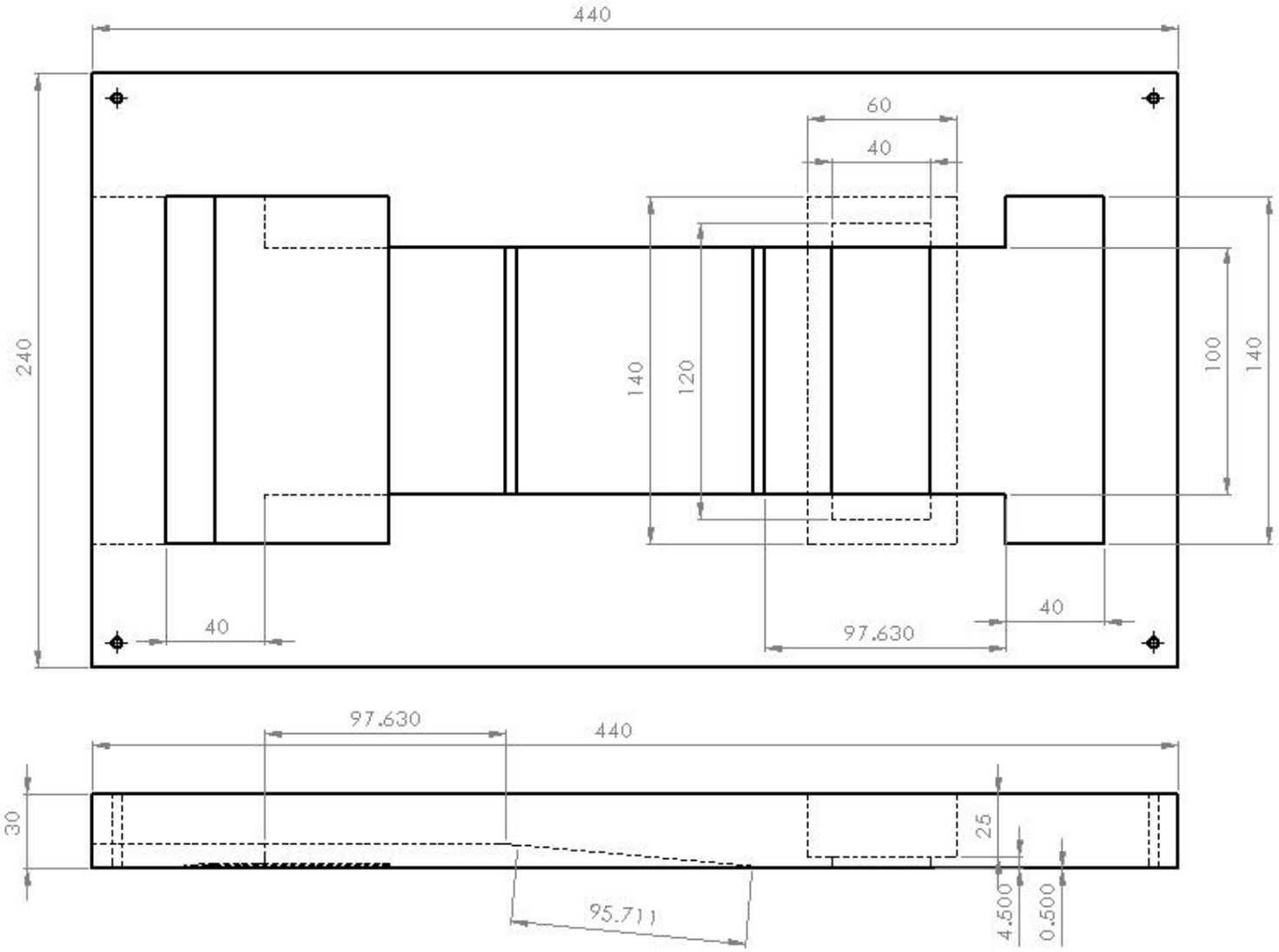


Figure C.1. upper section of the XME apparatus | side view (bottom) top view (top) | wire-frame | metric units “millimeters”



Appendix D: Unit Specification Sheets

This appendix provides unit specification sheets for all process equipment described in Chapter 4. For each piece of equipment, the following information is listed: function, operation, materials handled, equipment characteristics, and operating conditions. The function listing details streams being processed in the unit as well as other units linked by those streams. Operation is either batch or semi-continuous, and the nature of the operation schedule is also reported. 'Materials handled' includes quantities of each component entering the equipment unit. Equipment characteristics were found based on process needs (including operating conditions), and ASPEN Process Economic Analyzer was used to further specify conditions such as diameter or height of a vessel. The program was also used to price equipment, unless a vendor and model is otherwise specified.

Mixing Tank (M-1)

Function:	Tank used to mix components of continuous phase (CP) solution over the course of twelve hours to ensure dissolution of poly(vinyl) alcohol before transfer to a continuous feed storage tank

---

Operation:	Batch 12 hr preparation followed by 12 hr delivery
Quantity:	2

	Input:	Quantity (kg/batch):
Materials Handled:	Poly(vinyl) alcohol	388.26
	Deionized water	37944.55
	Dichloromethane	493.09
	TOTAL (kg/batch)	38825.90

Characteristics:	Material of Construction:	Carbon Steel
	Volume capacity:	41.4 m^3
	Height:	4.3 m
	Diameter:	3.5 m
	Working Capacity:	80%
	Sterilization:	SIP/CIP

Operating Conditions:	Temperature:	95°C
	Pressure:	1 bar

Purchase Cost: $82,200 per unit

Mixing Tank (M-2)

Function:	Tank used to mix components of dispersed phase (DP) necessary for 12 hours of channel operation plus 2 hours of startup operation. Once complete, the tank continuously delivers DP to streams FEED 2 and FEED 4

Operation:	Batch 3 hr preparation followed by 12 hrs delivery
Quantity:	2

	Input:	Quantity (kg/batch):
Materials Handled:	Poly(lactide-co-glycolide)	12.29
	Haloperidol	1.46
	Dichloromethane	134.00
	TOTAL (kg/batch)	147.75

Characteristics:	Vendor:	Mixer Direct
	Model:	SSTSC0030
	Material of Construction:	Stainless Steel
	Nominal capacity:	113.6 L
	Height:	0.94 m
	Diameter:	0.53 m
	Sterilization:	SIP/CIP

Operating Conditions:	Temperature:	20°C
	Pressure:	1 bar

Purchase Cost:	$2,310 per unit

Sanitary Pump (P-1)

Function:	Pump to transfer CP from mixing tank M-1 to the single large-particle channel array via stream FEED 3
Operation:	Continuous
Quantity:	1

	Input:	Quantity (kg/hr):
Materials Handled:	Poly(vinyl) alcohol	1.63
	Deionized water	159.43
	Dichloromethane	2.07
	TOTAL (kg/hr)	163.13

Characteristics:	Vendor:	Watson-Marlow
	Model:	520R2
	Type:	Peristaltic
	Material of Construction:	Stainless Steel 316
	Max. Flow Rate:	4.2 LPM
	Flow Rate:	2.7 LPM
	Sterilization:	SIP/CIP
Operating Conditions:	Temperature:	20°C
	Power:	.01 kW
	Pressure Change:	25 psi

Purchase Cost:	$2,900 per unit

Sanitary Pump (P-2)

Function:	Pump to transfer CP from mixing tank M-1 to the six channels in the small-particle array via stream FEED 1

Operation:	Continuous	
Quantity:	6	
Materials Handled:	Input:	Quantity (kg/hr):
	Poly(vinyl) alcohol	4.350
	Deionized water	425.159
	Dichloromethane	5.525
	TOTAL (kg/hr)	435.034
Characteristics:	Vendor:	Watson-Marlow
	Model:	620L
	Type:	Peristaltic
	Material of Construction:	Stainless Steel 316
	Max. Flow Rate:	14.0 LPM
	Flow Rate:	5.5 LPM
	Sterilization:	SIP/CIP
Operating Conditions:	Temperature:	20°C
	Power:	.20 kW
	Pressure Change:	25 psi

Purchase Cost:	$3,200 per unit

Sanitary Pump (UP-1)

Function:	Pump to transfer DP from mixing tank M-2 to each six small-particle channel via stream FEED 2

Operation:	Continuous
Quantity:	6

	Input:	Quantity (kg/hr):
Materials Handled:	PLGA	0.122
	Haloperidol	0.014
	Dichloromethane	1.329
	TOTAL (kg/hr)	1.465

Characteristics:	Type:	Peristaltic
	Material of Construction:	Stainless Steel 316
	Fluid Head:	51.8 m
	Flow Rate:	1.11 L/hr
	Sterilization:	SIP/CIP
Operating Conditions:	Temperature:	20°C
	Power:	.01 kW
	Pressure Change:	25 psi

Purchase Cost:	$1,600 per unit

Sanitary Pump (UP-2)

Function:	Pump to transfer DP from mixing tank M-2 to the single large-particle channel array via stream FEED 4
Operation:	Continuous
Quantity:	1

	Input:	Quantity (kg/hr):
Materials Handled:	PLGA	0.147
	Haloperidol	0.017
	Dichloromethane	1.599
	TOTAL (kg/hr)	1.763

Characteristics:	Type:	Peristaltic
	Material of Construction:	Stainless Steel 316
	Fluid Head:	51.8 m
	Flow Rate:	1.34 L/hr
	Sterilization:	SIP/CIP
Operating Conditions:	Temperature:	20°C
	Power:	.01 kW
	Pressure Change:	25 psi

Purchase Cost:	$1,600 per unit

Sanitary Pump (P-3)

Function:	Pump to transfer 70% CP exiting the large-particle array via a draw-off fixture within the channel end to distillation tower D-1 via stream DIVERT 1
Operation:	Continuous
Quantity:	1

	Input:	Quantity (kg/hr):
Materials Handled:	Poly(vinyl) alcohol	1.14
	Deionized water	111.60
	Dichloromethane	1.45
	TOTAL (kg/hr)	114.19

Characteristics:	Type:	Centrifugal
	Material of Construction:	Stainless Steel 316
	Flow Rate:	1.89 LPM
	Fluid Head:	9.14 m
	Sterilization:	CIP

Operating Conditions:	Temperature:	20°C
	Power:	.01 kW
	Pressure Change:	25 psi

Purchase Cost: $2,900

Sanitary Pump (P-4)

Function:	Pump to transfer 70% CP exiting each channel of the small-particle array via a draw-off fixture within the channel end to distillation tower D-1 via stream DIVERT 2
Operation:	Continuous
Quantity:	6

	Input:	Quantity (kg/hr):
Materials Handled:	Poly(vinyl) alcohol	3.05
	Deionized water	297.61
	Dichloromethane	3.87
	TOTAL (kg/hr)	304.52

Characteristics:	Type:	Centrifugal
	Material of Construction:	Stainless Steel 316
	Flow Rate:	5.04 LPM
	Fluid Head:	9.14 m
	Sterilization:	CIP
Operating Conditions:	Temperature:	20°C
	Power:	.19 kW
	Pressure Change:	25 psi

Purchase Cost: $2,900 per unit

Vacuum Tank with Diafiltration (T-1)

Function:	Hardens small particles leaving the small-particle channel array in stream OUTFLOW S with rinsing by streams NACL 2, WATER 2, and SOAK 2, and evaporates residual DCM solvent from the particles

---

Operation:	Semi-batch 12 hour operation period	
Quantity:	6	
	Input:	Quantity (kg/batch):
Materials Handled:	Poly(vinyl) alcohol	1.47
	Deionized water	288.84
	Dichloromethane	1.86
	TOTAL (kg/batch)	292.17
Characteristics:	Capacity:	350 L
	Height:	`1.25 m
	Inside Diameter:	.60 m
	Interior Construction:	316L Electropolished Stainless Steel
	Sterilization:	SIP/CIP
Operating Conditions:	Temperature:	40°C
	Pressure:	0.56 bar

Purchase Cost:	$12,100 per unit

Vacuum Tank with Diafiltration (T-2)

Function:	Hardens large particles leaving the large-particle channel array in stream OUTFLOW L with rinsing by water from stream WATER 1, and evaporates residual DCM solvent from the particles

---

Operation:	Semi-batch 12 hour operation period
Quantity:	6

	Input:	Quantity (kg/batch):
Materials Handled:	Poly(vinyl) alcohol	27.41
	Deionized water	5391.68
	Dichloromethane	34.81
	TOTAL (kg/batch)	5453.90

Characteristics:	Capacity:	6.19 m^3
	Height:	3.50 m
	Inside Diameter:	1.50 m
	Interior Construction:	316L Electropolished Stainless Steel
	Sterilization:	SIP/CIP
Operating Conditions:	Temperature:	40°C
	Pressure:	0.56 bar

Purchase Cost:	$35,500 per unit

Sanitary Pump (P-5)

Function:	Pump to transfer the remaining 30% CP exiting vacuum tank T-2 and wastewater retentate to the distillation step via stream DIVERT 3
Operation:	Semi-continuous Continuous function during each 2 hour Vacuum Tank L batch
Quantity:	6

	Input:	Quantity (kg/batch):
Materials Handled:	Poly(vinyl) alcohol	1.47
	Deionized water	288.84
	Dichloromethane	1.86
	TOTAL (kg/batch)	292.17

Characteristics:	Type:	Centrifugal
	Material of Construction:	Stainless Steel 316
	Flow Rate:	1.62 LPM
	Fluid Head:	9.14 m
	Sterilization:	CIP

Operating Conditions:	Temperature:	20°C
	Power:	.01 kW
	Pressure Change:	25 psi

Purchase Cost:	$2,900 per unit

Sanitary Pump (P-6)

Function:	Pump to transfer the remaining 30% CP exiting vacuum tank T-1 and wastewater retentate to the distillation step via stream DIVERT 4
Operation:	Semi-continuous Continuous function during each 3 hour Vacuum Tank S batch
Quantity:	6

	Input:	Quantity (kg/batch):
Materials Handled:	Poly(vinyl) alcohol	27.41
	Deionized water	5391.68
	Dichloromethane	34.81
	TOTAL (kg/batch)	5453.90

Characteristics:	Type:	Centrifugal
	Material of Construction:	Stainless Steel 316
	Flow Rate:	30.31 LPM
	Fluid Head:	9.14 m
	Sterilization:	CIP

Operating Conditions:	Temperature:	20°C
	Power:	.38 kW
	Pressure Change:	25 psi

Purchase Cost: $3,300 per unit

Sanitary Pump (P-7)

Function:	Pump to transfer CP and dilute CP from streams DIVERT 1-4 accumulated in surge tank T-3 and transferred to tank T-4 to be pumped to distillation tower D-1
Operation:	Continuous
Quantity:	1

	Input:	Quantity (kg/batch):
Materials Handled:	Poly(vinyl) alcohol	87.63
	Deionized water	9225.57
	Dichloromethane	5902.98
	TOTAL (kg/batch)	15216.18

Characteristics:	Type:	Centrifugal
	Material of Construction:	Stainless Steel 316
	Flow Rate:	5138 L/hr
	Fluid Head:	9.14 m
	Sterilization:	CIP

Operating Conditions:	Temperature:	20°C
	Power:	.38 kW
	Pressure Change:	25 psi

Purchase Cost: $3,300

Surge Tank (T-3)

Function:	Tank receives continuous and semi-continuous input from streams DIVERT 1-4, and has volumetric control such that tank contents surge into tank T-4 for continuous feed of constant composition to distillation column D-1

Operation:	Semi-batch Follows 3 hour batch cycle for filling to constant composition before surging into tank T-4
Quantity:	1

	Input:	Quantity (kg/batch):
Materials Handled:	Poly(vinyl) alcohol	266.81
	Deionized water	28446.94
	Dichloromethane	17713.91
	TOTAL (kg/batch)	46427.66

Characteristics:	Capacity:	48.11 m^3
	Inside Diameter:	3.5 m
	Height:	5.0 m
	Interior Construction:	316L Electropolished Stainless Steel
	Sterilization:	CIP
Operating Conditions:	Temperature:	20°C
	Pressure:	1 bar

Purchase Cost:	$55,900

Storage/Mixing Tank (T-4)

Function:	Tank receiving periodic input of CP from T-2 and continuously delivering through pump P-7 to distillation column	
Operation:	Continuous 90 day process period	
Quantity:	1	
Materials Handled:	Input:	Quantity (kg/hr):
	Poly(vinyl) alcohol	88.94
	Deionized water	9482.31
	Dichloromethane	5904.64
	TOTAL (kg/hr)	15475.89
Characteristics:	Capacity:	48.11 m^3
	Inside Diameter:	3.5 m
	Height:	5.0 m
	Interior Construction:	316L Electropolished Stainless Steel
	Sterilization:	CIP
Operating Conditions:	Temperature:	20°C
	Pressure:	1 bar
Purchase Cost:	$56,800	

Storage Tank (T-5)

Function:	Tank receiving semi-continuous input of haIoperidol-water solution from streams DIVERT 5 and DIVERT 6 via pumps P-8 and P-9
Operation:	Semi-continuous Filled with wastewater for a 10 hour period per vacuum tank in use Capacity for two 12 hour batches of both XME channel arrays
Quantity:	1

	Input:	Quantity (kg/hr):
Materials Handled:	Deionized water	411.832
	Haloperidol	0.015
	TOTAL (kg/hr)	411.846

Characteristics:	Capacity:	8.24 m^3
	Inside Diameter:	2.0 m
	Height:	2.7 m
	Interior Construction:	316L Electropolished Stainless Steel
	Sterilization:	CIP

Operating Conditions:	Temperature:	20°C
	Pressure:	1 bar

Purchase Cost: $22,500

Sanitary Pump (P-8)

Function:	Pump to continuously transfer the haloperidol-water solution from tank T-1 in stream DIVERT 6 to tank T-5 for delivery to wastewater treatment	
Operation:	Semi-continuous 10 hour pumping period	
Quantity:	6	
Materials Handled:	Input:	Quantity (kg/hr):
	Deionized water	24.225
	Haloperidol	0.012
	TOTAL (kg/hr)	24.238
Characteristics:	Type:	Centrifugal
	Material of Construction:	Stainless Steel 316
	Flow Rate:	24.23 L/hr
	Fluid Head:	9.14 m
	Sterilization:	CIP
Operating Conditions:	Temperature:	20°C
	Power:	.01 kW
	Pressure Change:	25 psi
Purchase Cost:	$2,900 per unit	

Sanitary Pump (P-9)

Function:	Pump to continuously transfer the haloperidol-water solution from tank T-2 in stream DIVERT 5 to tank T-5 for delivery to wastewater treatment	
Operation:	Semi-continuous 10 hour pumping period	
Quantity:	6	
	Input:	Quantity (kg/hr):
Materials Handled:	Deionized water	387.606
	Haloperidol	0.002
	TOTAL (kg/hr)	387.609
	Type:	Centrifugal
	Material of Construction:	Stainless Steel 316
Characteristics:	Flow Rate:	6.46 LPM
	Fluid Head:	9.14 m
	Sterilization:	CIP
	Temperature:	20°C
Operating Conditions:	Power:	.19 kW
	Pressure Change:	25 psi
Purchase Cost:	$3,200	

Distillation Column (D-1)

Function:	Separates the organic and aqueous phases of the CP and dilute CP delivered to tanks T-3 and T-4 via streams DIVERT 1-4. Water carries the heavy polymer in the bottoms product with trace DCM.

Operation:	Continuous 90 day process period	
Quantity:	1	
	Input:	Quantity (kg/hr):
Materials Handled:	Poly(vinyl) alcohol	87.63
	Deionized water	9225.57
	Dichloromethane	5902.98
	TOTAL (kg/hr)	15216.18
Characteristics:	Reflux Ratio:	1
	Number Trays:	10
	Feed Tray:	5
	Height:	6.40 m
	Diameter:	0.85 m
	Material of Construction:	Electropolished Stainless Steel 316
Operating Conditions:	Temperature:	20°C
	Pressure:	1 bar

Purchase Cost:	$56,800

Storage Tank (S-1)

Function:	Tank receives continuous flow of DCM-rich distillate product from distillation tower D-1 before distribution to industries utilizing low-purity DCM
Operation:	Batch
	Tank contents distributed to small vessels suitable for transport to purchasers

	Input:	Quantity (kg/hr):
Materials Handled:	Poly(vinyl) alcohol	0.00
	Deionized water	145.40
	Dichloromethane	5904.60
	TOTAL (kg/hr)	6050.00

Characteristics:	Material of Construction:	Stainless Steel 316
	Volume:	4550 L
	Height:	4.02 m
	Diameter:	1.20 m
	Sterilization:	CIP
Operating Conditions:	Temperature:	20°C
	Pressure:	1 bar

Purchase Cost: $17,200

Storage Tank (S-2)

Function:	Tank receives continuous flow of PVA-rich water bottoms product from distillation tower D-1 before transport to wastewater treatment plant
Operation:	Batch Tank contents distributed to small vessels suitable for transport to purchasers

Materials Handled:	Input:	Quantity (kg/hr):
	Poly(vinyl) alcohol	88.94
	Deionized water	9336.91
	Dichloromethane	trace
	TOTAL (kg/hr)	9425.85

Characteristics:		
	Material of Construction:	Stainless Steel 316
	Volume:	9360 L
	Height:	5.30 m
	Diameter:	1.50 m
	Working Capacity:	80%
	Sterilization:	CIP

Operating Conditions:		
	Temperature:	20°C
	Pressure:	1 bar

Purchase Cost: $20,200

Freeze-Dry (F-1)

Function:	Liquid nitrogen flash freezing of particles removed from Vacuum Tank L and Vacuum Tank S, where different-sized particles are kept separate, and drying of residual liquid phases

Operation:	Batch 10 hours freeze-drying	
Quantity:	1	
Materials Handled:	Input:	Quantity (kg/hr):
	Poly(lactide-co-glycolide)	10.373
	Haloperidol	1.248
	Water	residual
	TOTAL (kg/cycle)	11.620
Characteristics:	Vendor:	Millrock Technology
	Model:	MX85S10
	Material of Construction:	Stainless Steel 316
	Maximum volume:	30 L
	Vacuum Pump:	375 LPM
	Sterilization:	CIP
Operating Conditions:	Temperature:	(-) 70°C
	Pressure:	13.3 Pa

Purchase Cost:	$99,950

Ampoule-Filling Unit (A-1)

Function:	Dispenses precise amounts of 20 and 50 μm freeze-dried particles and dry PBS media into sealed individual dose ampoules.	
Operation:	Batch 100 dose-ampoules/min	
Quantity:	1	
Materials Handled:	Input:	Quantity (kg/hr):
	Poly(lactide-co-glycolide)	10.373
	Haloperidol	1.248
	TOTAL (kg/cycle)	11.620
Characteristics:	Material of Construction:	Stainless Steel 316
	Total power:	1.2 kW
	Filling precision:	≤ ± 3%
	Working Capacity:	80-150 ampoules/min
	Sterilization:	CIP
	Vendor:	Liaoyang Pharma Machinery Imp. & Exp. Co., Ltd.
	Model:	KH-D-Z Micro-computerized Dual Head Powder Filling Machine
Operating Conditions:	Temperature:	20°C
	Pressure:	1 bar
	Motor power:	.37 kW
Purchase Cost:	$1,055,000	

Appendix E: ASPEN Reports

This Appendix contains all ASPEN-program related information generated during the course of the project, involving either ASPEN PLUS simulations or economic analysis. The following is a list of all sections contained, in order of appearance:

1. ASPEN PLUS: Distillation Tower Input Summary
2. ASPEN PLUS: Distillation Tower Simulation Results
3. ASPEN IPE: Distillation Tower Results Summary
4. ASPEN Process Economic Analyzer: Purchase Cost Results for Select Equipment Units

ASPEN PLUS: Distillation Tower Input Summary

```
;
;Input Summary created by Aspen Plus Rel. 25.0 at 13:05:17 Sun Apr 1, 2012
;Directory C:\Users\sidhug\AppData\Local\Temp  Filename
C:\Users\sidhug\AppData\Local\Temp\~ap8f1e.txt
;

DYNAMICS
    DYNAMICS RESULTS=ON

TITLE 'dcm-water_no_decant'

IN-UNITS MET VOLUME-FLOW='cum/hr' ENTHALPY-FLO='Gcal/hr'  &
        HEAT-TRANS-C='kcal/hr-sqm-K' PRESSURE=bar TEMPERATURE=C  &
        VOLUME=cum DELTA-T=C HEAD=meter MOLE-DENSITY='kmol/cum'  &
        MASS-DENSITY='kg/cum' MOLE-ENTHALP='kcal/mol'  &
        MASS-ENTHALP='kcal/kg' HEAT=Gcal MOLE-CONC='mol/l'  &
        PDROP=bar

DEF-STREAMS CONVEN ALL

SIM-OPTIONS MASS-BAL-CHE=YES OLD-DATABANK=YES

DESCRIPTION "
    General Simulation with Metric Units :
    C, bar, kg/hr, kmol/hr, Gcal/hr, cum/hr.

    Property Method: None

    Flow basis for input: Mole

    Stream report composition: Mole flow
    "

DATABANKS PURE25  / AQUEOUS  / SOLIDS  / INORGANIC  /  &
        NOASPENPCD

PROP-SOURCES PURE25  / AQUEOUS  / SOLIDS  / INORGANIC

COMPONENTS
    WATER H2O /
    DICHLORO CH2CL2

FLOWSHEET
    BLOCK DIST IN=CP OUT=DCM H20

PROPERTIES NRTL

PROP-DATA NRTL-1
    IN-UNITS MET VOLUME-FLOW='cum/hr' ENTHALPY-FLO='Gcal/hr'  &
        HEAT-TRANS-C='kcal/hr-sqm-K' PRESSURE=bar TEMPERATURE=C  &
        VOLUME=cum DELTA-T=C HEAD=meter MOLE-DENSITY='kmol/cum'  &
        MASS-DENSITY='kg/cum' MOLE-ENTHALP='kcal/mol'  &
        MASS-ENTHALP='kcal/kg' HEAT=Gcal MOLE-CONC='mol/l'  &
```

```
        PDROP=bar
    PROP-LIST NRTL
    BPVAL WATER DICHLORO 0.0 1483.863200 .3000000000 0.0 0.0  &
        0.0 38.30000000 73.00000000
    BPVAL DICHLORO WATER 0.0 941.4288000 .3000000000 0.0 0.0  &
        0.0 38.30000000 73.00000000

STREAM CP
    SUBSTREAM MIXED TEMP=20. PRES=1. MASS-FLOW=15475.887
    MASS-FLOW WATER 9571.252 / DICHLORO 5904.635

BLOCK DIST RADFRAC
    PARAM NSTAGE=10
    COL-CONFIG CONDENSER=PARTIAL-V
    FEEDS CP 5
    PRODUCTS DCM 1 V / H20 10 L
    P-SPEC 1 1.
    COL-SPECS MASS-D=6050. MOLE-RR=1.

EO-CONV-OPTI

STREAM-REPOR MOLEFLOW
;
;
;
;
;
```

ASPEN PLUS: Distillation Tower Simulation Results

```
ASPEN PLUS   PLAT: WIN32     VER: 25.0                  04/01/2012  PAGE 1
                            DCM-WATER_NO_DECANT
                             RUN CONTROL SECTION

DESCRIPTION
 -----------
        General Simulation with Metric Units : C, bar, kg/hr, kmol/hr,
        Gcal/hr, cum/hr. Property Method: None Flow basis for input: Mole
        Stream report composition: Mole flow


ASPEN PLUS   PLAT: WIN32     VER: 25.0                  04/01/2012  PAGE 2
                            DCM-WATER_NO_DECANT
                              FLOWSHEET SECTION

 FLOWSHEET CONNECTIVITY BY STREAMS
 ---------------------------------

   STREAM     SOURCE     DEST           STREAM     SOURCE     DEST
   CP         ----       DIST           DCM        DIST       ----
   H20        DIST       ----

 FLOWSHEET CONNECTIVITY BY BLOCKS
 --------------------------------

   BLOCK        INLETS                        OUTLETS
   DIST         CP                            DCM H20

 COMPUTATIONAL SEQUENCE
 ----------------------

 SEQUENCE USED WAS:
    DIST

 OVERALL FLOWSHEET BALANCE
 -------------------------

                      ***  MASS AND ENERGY BALANCE  ***
                                    IN              OUT        RELATIVE DIFF.
    CONVENTIONAL COMPONENTS (KMOL/HR )
       WATER                     531.285         531.285        0.514189E-06
       DICHLORO                  69.5217         69.5220       -0.392942E-05
    TOTAL BALANCE
       MOLE(KMOL/HR )            600.807         600.807          0.00000
       MASS(KG/HR   )            15475.9         15475.9       -0.118122E-05
       ENTHALPY(GCAL/HR )       -37.8785        -37.0382       -0.221848E-01

                      ***  CO2 EQUIVALENT SUMMARY ***
    FEED STREAMS CO2E             51370.3      KG/HR
    PRODUCT STREAMS CO2E          51370.5      KG/HR
    NET STREAMS CO2E PRODUCTION  0.201856      KG/HR
    UTILITIES CO2E PRODUCTION     0.00000      KG/HR
    TOTAL CO2E PRODUCTION        0.201856      KG/HR
```

COMPONENTS

ID	TYPE	ALIAS	NAME
WATER	C	H2O	WATER
DICHLORO	C	CH2CL2	DICHLOROMETHANE

BLOCK: DIST MODEL: RADFRAC

INLETS	- CP	STAGE 5
OUTLETS	- DCM	STAGE 1
	H20	STAGE 10

PROPERTY OPTION SET: NRTL RENON (NRTL) / IDEAL GAS

*** MASS AND ENERGY BALANCE ***

	IN	OUT	RELATIVE DIFF.
TOTAL BALANCE			
MOLE(KMOL/HR)	600.807	600.807	0.00000
MASS(KG/HR)	15475.9	15475.9	-0.118122E-05
ENTHALPY(GCAL/HR)	-37.8785	-37.0382	-0.221848E-01

*** CO2 EQUIVALENT SUMMARY ***

FEED STREAMS CO2E	51370.3	KG/HR
PRODUCT STREAMS CO2E	51370.5	KG/HR
NET STREAMS CO2E PRODUCTION	0.201856	KG/HR
UTILITIES CO2E PRODUCTION	0.00000	KG/HR
TOTAL CO2E PRODUCTION	0.201856	KG/HR

****
**** INPUT DATA ****
****

**** INPUT PARAMETERS ****

NUMBER OF STAGES	10
ALGORITHM OPTION	STANDARD
ABSORBER OPTION	NO
INITIALIZATION OPTION	STANDARD
HYDRAULIC PARAMETER CALCULATIONS	NO
INSIDE LOOP CONVERGENCE METHOD	BROYDEN
DESIGN SPECIFICATION METHOD	NESTED
MAXIMUM NO. OF OUTSIDE LOOP ITERATIONS	25
MAXIMUM NO. OF INSIDE LOOP ITERATIONS	10
MAXIMUM NUMBER OF FLASH ITERATIONS	30
FLASH TOLERANCE	0.000100000
OUTSIDE LOOP CONVERGENCE TOLERANCE	0.000100000

BLOCK: DIST MODEL: RADFRAC (CONTINUED)

**** COL-SPECS ****

MOLAR VAPOR DIST / TOTAL DIST		1.00000
MOLAR REFLUX RATIO		1.00000
MASS DISTILLATE RATE	KG/HR	6,050.00

**** PROFILES ****

P-SPEC	STAGE 1 PRES, BAR	1.00000

****
**** RESULTS ****
****

*** COMPONENT SPLIT FRACTIONS ***

	OUTLET STREAMS	
	DCM	H2O
COMPONENT:		
WATER	.15185E-01	.98481
DICHLORO	1.0000	0.0000

*** SUMMARY OF KEY RESULTS ***

TOP STAGE TEMPERATURE	C	46.6110
BOTTOM STAGE TEMPERATURE	C	99.6491
TOP STAGE LIQUID FLOW	KMOL/HR	77.5897
BOTTOM STAGE LIQUID FLOW	KMOL/HR	523.217
TOP STAGE VAPOR FLOW	KMOL/HR	77.5897
BOILUP VAPOR FLOW	KMOL/HR	174.009
MOLAR REFLUX RATIO		1.00000
MOLAR BOILUP RATIO		0.33257
CONDENSER DUTY (W/O SUBCOOL)	GCAL/HR	-0.85656
REBOILER DUTY	GCAL/HR	1.69689

**** MAXIMUM FINAL RELATIVE ERRORS ****

DEW POINT	0.64158E-06	STAGE= 1	
BUBBLE POINT	0.28046E-04	STAGE= 1	
COMPONENT MASS BALANCE	0.33663E-05	STAGE= 2	COMP=DICHLORO
ENERGY BALANCE	0.57488E-05	STAGE= 2	

BLOCK: DIST MODEL: RADFRAC (CONTINUED)

**** PROFILES ****

NOTE REPORTED VALUES FOR STAGE LIQUID AND VAPOR RATES ARE THE FLOWS FROM THE STAGE INCLUDING ANY SIDE PRODUCT.

STAGE	TEMPERATURE C	PRESSURE BAR	ENTHALPY KCAL/MOL LIQUID	ENTHALPY KCAL/MOL VAPOR	HEAT DUTY GCAL/HR
1	46.611	1.0000	-67.779	-26.188	-0.8565
2	83.793	1.0000	-67.182	-41.464	
3	84.464	1.0000	-67.171	-41.977	
4	84.477	1.0000	-67.170	-41.987	
5	98.894	1.0000	-66.919	-56.217	
6	99.646	1.0000	-66.906	-57.150	
8	99.649	1.0000	-66.906	-57.154	
9	99.649	1.0000	-66.906	-57.154	
10	99.649	1.0000	-66.906	-57.154	1.6968

STAGE	FLOW RATE KMOL/HR LIQUID	FLOW RATE KMOL/HR VAPOR	FEED RATE KMOL/HR LIQUID	FEED RATE KMOL/HR VAPOR	FEED RATE KMOL/HR MIXED	PRODUCT RATE KMOL/HR LIQUID	PRODUCT RATE KMOL/HR VAPOR
1	77.59	77.59					77.5896
2	82.59	155.2					
3	82.69	160.2					
4	87.20	160.3		68.5979			
5	696.2	96.19	532.2089				
6	697.2	173.0					
8	697.2	174.0					
9	697.2	174.0					
10	523.2	174.0				523.2172	

**** MASS FLOW PROFILES ****

STAGE	FLOW RATE KG/HR LIQUID	FLOW RATE KG/HR VAPOR	FEED RATE KG/HR LIQUID	FEED RATE KG/HR VAPOR	FEED RATE KG/HR MIXED	PRODUCT RATE KG/HR LIQUID	PRODUCT RATE KG/HR VAPOR
1	1409.	6050.					6050.0000
2	1491.	7459.					
3	1493.	7541.					
4	1574.	7543.		5719.2722			
5	0.1254E+05	1905.	9756.6147				
6	0.1256E+05	3118.					
8	0.1256E+05	3135.					
9	0.1256E+05	3135.					
10	9426.	3135.				9425.9052	

BLOCK: DIST MODEL: RADFRAC (CONTINUED)

**** MOLE-X-PROFILE ****

STAGE	WATER	DICHLORO
1	0.99784	0.21587E-02
2	0.99944	0.56283E-03
3	0.99946	0.53902E-03
4	0.99946	0.53857E-03
5	0.99997	0.27172E-04
6	1.0000	0.11021E-06
8	1.0000	0.17971E-11
9	1.0000	0.72569E-14
10	1.0000	0.29215E-16

**** MOLE-Y-PROFILE ****

STAGE	WATER	DICHLORO
1	0.10398	0.89602
2	0.55091	0.44909
3	0.56568	0.43432
4	0.56596	0.43404
5	0.97330	0.26699E-01
6	0.99989	0.10936E-03
8	1.0000	0.17833E-08
9	1.0000	0.72008E-11
10	1.0000	0.28989E-13

**** K-VALUES ****

STAGE	WATER	DICHLORO
1	0.10420	415.06
2	0.55122	797.91
3	0.56598	805.76
4	0.56627	805.91
5	0.97333	982.61
6	0.99989	992.23
8	1.0000	992.27
9	1.0000	992.27
10	1.0000	992.27

**** MASS-X-PROFILE ****

STAGE	WATER	DICHLORO
1	0.98990	0.10096E-01
2	0.99735	0.26479E-02
3	0.99746	0.25361E-02
4	0.99747	0.25340E-02
5	0.99987	0.12809E-03
6	1.0000	0.51959E-06
8	1.0000	0.84725E-11
9	1.0000	0.34212E-13
10	1.0000	0.13773E-15

BLOCK: DIST MODEL: RADFRAC (CONTINUED)

**** MASS-Y-PROFILE ****

STAGE	WATER	DICHLORO
1	0.24023E-01	0.97598
2	0.20648	0.79352
3	0.21646	0.78354
4	0.21666	0.78334
5	0.88548	0.11452
6	0.99948	0.51535E-03
8	1.0000	0.84071E-08
9	1.0000	0.33948E-10
10	1.0000	0.13667E-12

CP DCM H20

STREAM ID	CP	DCM	H20
FROM :	----	DIST	DIST
TO :	DIST	----	----
SUBSTREAM: MIXED			
PHASE:	MIXED	VAPOR	LIQUID
COMPONENTS: KMOL/HR			
WATER	531.2852	8.0677	523.2173
DICHLORO	69.5217	69.5220	1.5286-14
TOTAL FLOW:			
KMOL/HR	600.8069	77.5897	523.2173
KG/HR	1.5476+04	6050.0000	9425.9053
CUM/HR	1681.6750	2062.7973	10.2605
STATE VARIABLES:			
TEMP C	20.0000	46.6110	99.6491
PRES BAR	1.0000	1.0000	1.0000
VFRAC	0.1142	1.0000	0.0
LFRAC	0.8858	0.0	1.0000
SFRAC	0.0	0.0	0.0
ENTHALPY:			
KCAL/MOL	-63.0461	-26.1881	-66.9058
KCAL/KG	-2447.5824	-335.8557	-3713.8348
GCAL/HR	-37.8785	-2.0319	-35.0063
ENTROPY:			
CAL/MOL-K	-37.0321	-18.6367	-34.9234
CAL/GM-K	-1.4377	-0.2390	-1.9385
DENSITY:			
KMOL/CUM	0.3573	3.7614-02	50.9936
KG/CUM	9.2027	2.9329	918.6633
AVG MW	25.7585	77.9743	18.0153

DCM-WATER_NO_DECANT
PROBLEM STATUS SECTION

BLOCK STATUS

```
*****************************************************************************
*                                                                           *
* Calculations were completed normally                                      *
*                                                                           *
* All Unit Operation blocks were completed normally                         *
*                                                                           *
* All streams were flashed normally                                         *
*                                                                           *
*****************************************************************************
```

ASPEN IPE: Distillation Tower Results Summary

PROJECT RESULTS SUMMARY		
Total Project Capital Cost	Cost	1.61E+05
Total Raw Materials Cost	Cost/period	0
Total Products Sales	Cost/period	0
Total Operating Labor and Maintenance Cost	Cost/period	491838
Total Utilities Cost	Cost/period	599168
Total Operating Cost	Cost/period	1.57E+06
Operating Labor Cost	Cost/period	482130
Maintenance Cost	Cost/period	9708.34
Operating Charges	Cost/period	120533
Plant Overhead	Cost/period	245919
Subtotal Operating Cost	Cost/period	1.46E+06
G and A Cost		116597

ASPEN Process Economic Analyzer:
Purchase Cost Results for Select Equipment Units

Unit	Bare Module	Quantity	Total Bare Module
Mixing Tank (M-1)	$82,200	2	$164,400
Mixing Tank (M-2)	$2,310	2	$4,620
Sanitary Pump (P-1)	$2,900	1	$2,900
Sanitary Pump (P-2)	$3,200	6	$19,200
Sanitary Pump (UP-2)	$1,600	1	$1,600
Sanitary Pump (UP-1)	$1,600	1	$1,600
Sanitary Pump (P-3)	$2,900	1	$2,900
Sanitary Pump (P-4)	$2,900	6	$17,400
Vacuum Tank with Diafiltration (T-1)	$12,100	6	$72,600
Vacuum Tank with Diafiltration (T-2)	$35,500	6	$213,000
Sanitary Pump (P-5)	$2,900	6	$17,400
Sanitary Pump (P-6)	$3,300	6	$19,800
Sanitary Pump (P-7)	$3,300	1	$3,300
Surge Tank (T-3)	$55,900	1	$55,900
Storage/Mixing Tank (T-4)	$56,800	1	$56,800
Storage Tank (T-5)	$22,500	1	$22,500
Pump (P-8)	$2,900	6	$17,400
Sanitary Pump (P-9)	$3,200	6	$19,200
Distillation Column (D-1)	$160500	1	$160500
Storage Tank (S-1)	$17,200	1	$17,200
Storage Tank (S-2)	$20,200	1	$20,200

Appendix F: Chronic Disease List

Chronic Disease List

Addison's disease
Asthma
Bronchiectasis
Cardiac failure
Cardiomyopathy
Chronic obstructive pulmonary disorder
Chronic renal disease
Coronary artery disease
Crohn's disease
Diabetes insipidus
Diabetes mellitus types 1 & 2
Dysrhythmias
Epilepsy
Glaucoma
Haemophilia
Hyperlipidaemia
Hypertension
Hypothyroidism
Multiple sclerosis
Parkinson's disease
Rheumatoid arthritis
Schizophrenia
Systemic lupus erythematosus
Ulcerative colitis

All of these diseases have guaranteed Medicare coverage, as per the Medical Schemes Act's Prescribed Minimum Benefits, as described in Chapter 7. [18]

Appendix G: MSDS Reports

This appendix includes Materials, Safety, and Data Sheets (MSDS) reports for all materials handled in the XME process as described within this text. Reports are found in the following order:

1. Dichloromethane
2. Distilled Water
3. Haloperidol
4. Poly(D,L-lactide-*co*-glycolide)
5. Poly(vinyl) Alcohol
6. Sodium Chloride

SAFETY DATA SHEET

DICHLOROMETHANE GR GRADE

Compilation date: 05/11/2004

Revision date: 06/10/2011

Revision No: 2

Section 1: Identification of the substance/mixture and of the company/undertaking

1.1. Product identifier

Product name: DICHLOROMETHANE GR GRADE

CAS number: 75-09-2

EINECS number: 200-838-9

Index number: 602-004-00-3

Product code: OR10007

Synonyms: METHYLENE DICHLORIDE, DCM

1.2. Relevant identified uses of the substance or mixture and uses advised against

1.3. Details of the supplier of the safety data sheet

Company name: Apollo Scientific Ltd

Units 3 & 4

Parkway

Denton

Manchester

M34 3SG

UK

Tel: 0161 337 9971

Fax: 0161 336 6932

Email: david.tideswalk@apolloscientific.co.uk

1.4. Emergency telephone number

Section 2: Hazards identification

2.1. Classification of the substance or mixture

Classification under CHIP: Xn: R22; Xn: R40

Classification under CLP: Acute Tox. 4: H302; Carc. 2: H351

Most important adverse effects: Harmful if swallowed. Limited evidence of a carcinogenic effect.

2.2. Label elements

Label elements under CLP:

Hazard statements: H302: Harmful if swallowed.

H351: Suspected of causing cancer.

Signal words: Warning

Hazard pictograms: GHS07: Exclamation mark

GHS08: Health hazard

[cont...]

Precautionary statements: P308+313: IF exposed or concerned: Get medical advice/attention.
P280: Wear protective gloves/protective clothing/eye protection/face protection.

Label elements under CHIP:

Hazard symbols: Harmful.

Risk phrases: R22: Harmful if swallowed.
R40: Limited evidence of a carcinogenic effect.

Safety phrases: S23: Do not breathe vapour.
S26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
S28: After contact with skin, wash immediately with plenty of water.
S36/37/39: Wear suitable protective clothing, gloves and eye / face protection.
S45: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

2.3. Other hazards

PBT: This substance is not identified as a PBT substance.

Section 3: Composition/information on ingredients

3.1. Substances

Chemical identity: DICHLOROMETHANE GR GRADE

Section 4: First aid measures

4.1. Description of first aid measures

Skin contact: Remove all contaminated clothes and footwear immediately unless stuck to skin. Drench the affected skin with running water for 10 minutes or longer if substance is still on skin. Consult a doctor.

Eye contact: Bathe the eye with running water for 15 minutes. Consult a doctor.

Ingestion: Wash out mouth with water. Do not induce vomiting. If conscious, give half a litre of water to drink immediately. Consult a doctor.

Inhalation: Remove casualty from exposure ensuring one's own safety whilst doing so. Consult a doctor.

4.2. Most important symptoms and effects, both acute and delayed

Skin contact: There may be irritation and redness at the site of contact.

Eye contact: There may be irritation and redness. The eyes may water profusely.

[cont...]

Ingestion: There may be soreness and redness of the mouth and throat. Nausea and stomach pain may occur. There may be vomiting.

Inhalation: There may be irritation of the throat with a feeling of tightness in the chest.

4.3. Indication of any immediate medical attention and special treatment needed

Section 5: Fire-fighting measures

5.1. Extinguishing media

Extinguishing media: Carbon dioxide, dry chemical powder, foam. Suitable extinguishing media for the surrounding fire should be used. Use water spray to cool containers.

5.2. Special hazards arising from the substance or mixture

Exposure hazards: In combustion emits toxic fumes. Carbon oxides. Hydrogen chloride (HCl).

5.3. Advice for fire-fighters

Advice for fire-fighters: Wear self-contained breathing apparatus. Wear protective clothing to prevent contact with skin and eyes.

Section 6: Accidental release measures

6.1. Personal precautions, protective equipment and emergency procedures

Personal precautions: Refer to section 8 of SDS for personal protection details. If outside do not approach from downwind. If outside keep bystanders upwind and away from danger point. Mark out the contaminated area with signs and prevent access to unauthorised personnel. Turn leaking containers leak-side up to prevent the escape of liquid.

6.2. Environmental precautions

Environmental precautions: Do not discharge into drains or rivers. Contain the spillage using bunding. Alert the neighbourhood to the presence of fumes or gas.

6.3. Methods and material for containment and cleaning up

Clean-up procedures: Clean-up should be dealt with only by qualified personnel familiar with the specific substance. Absorb into dry earth or sand. Transfer to a closable, labelled salvage container for disposal by an appropriate method.

6.4. Reference to other sections

Section 7: Handling and storage

7.1. Precautions for safe handling

Handling requirements: Avoid direct contact with the substance. Ensure there is sufficient ventilation of the area. Do not handle in a confined space. Avoid the formation or spread of mists in the air. Only use in fume hood.

[cont...]

7.2. Conditions for safe storage, including any incompatibilities

Storage conditions: Store in cool, well ventilated area. Keep container tightly closed. Store under Argon.

Suitable packaging: Must only be kept in original packaging.

7.3. Specific end use(s)

Specific end use(s): No data available.

Section 8: Exposure controls/personal protection

8.1. Control parameters

Workplace exposure limits: **Respirable dust**

State	8 hour TWA	15 min. STEL	8 hour TWA	15 min. STEL
UK	100 ppm	300 ppm	350 mg/m3	1060 mg/m3

8.2. Exposure controls

Engineering measures: Ensure there is sufficient ventilation of the area.

Respiratory protection: Self-contained breathing apparatus must be available in case of emergency.

Hand protection: Impermeable gloves.

Eye protection: Safety glasses. Ensure eye bath is to hand.

Skin protection: Impermeable protective clothing.

Section 9: Physical and chemical properties

9.1. Information on basic physical and chemical properties

State: Liquid

Colour: Colourless

Odour: Sweet-smelling

Solubility in water: Slightly soluble

Boiling point/range °C: 39.8

Melting point/range °C: -95

Flammability limits %: lower: 13

upper: 22

Part.coeff. n-octanol/water: log Pow: 1.25

Autoflammability °C: 605

Vapour pressure: 470.9 hPa at 20.0 °C

Relative density: 1.325 g/cm3

9.2. Other information

Other information: Not applicable.

Section 10: Stability and reactivity

10.1. Reactivity

Reactivity: Stable under recommended transport or storage conditions.

10.2. Chemical stability

Chemical stability: Stable under normal conditions.

[cont...]

10.3. Possibility of hazardous reactions

Hazardous reactions: Hazardous reactions will not occur under normal transport or storage conditions.

10.4. Conditions to avoid

Conditions to avoid: Heat. Hot surfaces. Flames. Direct sunlight.

10.5. Incompatible materials

Materials to avoid: Strong oxidising agents. Strong acids. Strong bases. Alkali metals. Aluminium. Amines. Magnesium.

10.6. Hazardous decomposition products

Haz. decomp. products: In combustion emits toxic fumes of carbon dioxide / carbon monoxide. Hydrogen chloride (HCl).

Section 11: Toxicological information

11.1. Information on toxicological effects

Toxicity values:

Route	Species	Test	Value	Units
ORAL	RAT	LD50	1600	mg/kg
INHALATION	RAT	LC50	52000	mg/m3

Relevant hazards for substance:

Hazard	Route	Basis
Acute toxicity (ac. tox. 4)	ING	Based on test data
Carcinogenicity	–	Based on test data

Symptoms / routes of exposure

Skin contact: There may be irritation and redness at the site of contact.

Eye contact: There may be irritation and redness. The eyes may water profusely.

Ingestion: There may be soreness and redness of the mouth and throat. Nausea and stomach pain may occur. There may be vomiting.

Inhalation: There may be irritation of the throat with a feeling of tightness in the chest.

Other information: Carcinogenicity IARC-2B: possibly carcinogenic to humans RTECS: PA8050000

Section 12: Ecological information

12.1. Toxicity

Ecotoxicity values: Not applicable.

12.2. Persistence and degradability

Persistence and degradability: No data available.

[cont...]

12.3. Bioaccumulative potential

Bioaccumulative potential: No data available.

12.4. Mobility in soil

Mobility: No data available.

12.5. Results of PBT and vPvB assessment

PBT identification: This substance is not identified as a PBT substance.

12.6. Other adverse effects

Other adverse effects: No data available.

Section 13: Disposal considerations

13.1. Waste treatment methods

Disposal operations: MATERIAL SHOULD BE DISPOSED OF IN ACCORDANCE WITH LOCAL, STATE AND FEDERAL REGULATIONS

Disposal of packaging: Dispose of as special waste in compliance with local and national regulations Observe all federal, state and local environmental regulations.

NB: The user's attention is drawn to the possible existence of regional or national regulations regarding disposal.

Section 14: Transport Information

14.1. UN number

UN number: UN1593

14.2. UN proper shipping name

Shipping name: DICHLOROMETHANE

14.3. Transport hazard class(es)

Transport class: 6.1

14.4. Packing group

Packing group: III

14.5. Environmental hazards

Environmentally hazardous: No **Marine pollutant:** No

14.6. Special precautions for user

Section 15: Regulatory Information

15.1. Safety, health and environmental regulations/legislation specific for the substance or mixture

15.2. Chemical Safety Assessment

Chemical safety assessment: A chemical safety assessment has not been carried out for the substance or the mixture by the supplier.

[cont...]

Section 16: Other Information

Other information

Other information: This safety data sheet is prepared in accordance with Commission Regulation (EU) No 453/2010.

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* Data predicted using computational software. Toxtree - Toxic Hazard Estimation by decision tree approach. http://ecb.jrc.ec.europa.eu/qsar/qsar-tools/index.php?c=TOXTREE

- Data predicted using computationanl software ACD/ToxSuite v 2.95.1 Copyright 1994-2009 ACD/labs, Copyright 2001-2009 Pharma Algorithms, Inc, Advanced Chemistry Development, Inc (ACD/Labs). http://www.acdlabs.com/products/pc_admet/tox/tox/

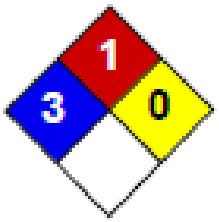
Phrases used in s.2 and 3: H302: Harmful if swallowed.

H351: Suspected of causing cancer <state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard>.

R22: Harmful if swallowed.

R40: Limited evidence of a carcinogenic effect.

Legal disclaimer: The material is intended for research purposes only and should be handled exclusively by those who have been fully trained in safety, laboratory and chemical handling procedures. The above information is believed to be correct to the best of our knowledge. The above information is believed to be correct to the best of our knowledge at the date of its publication, but should not be considered to be all inclusive. It should be used only as a guide for safe handling, storage, transportation and disposal. We cannot guarantee that the hazards detailed in this document are the only hazards that exist for this product. This is not a warranty and Apollo Scientific Ltd shall not be held liable for any damage resulting from handling or from contact with the above product.



Health	3
Fire	1
Reactivity	0
Personal Protection	E

Material Safety Data Sheet
Haloperidol MSDS

Section 1: Chemical Product and Company Identification

Product Name: Haloperidol

Catalog Codes: SLH2443

CAS#: 52-86-8

RTECS: EU1575000

TSCA: TSCA 8(b) inventory: Haloperidol

CI#: Not available.

Synonym: 4-[4-(4-Chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone

Chemical Name: Not available.

Chemical Formula: C21H23ClFNO2

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: 1-800-901-7247
International Sales: 1-281-441-4400

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Haloperidol	52-86-8	100

Toxicological Data on Ingredients: Haloperidol: ORAL (LD50): Acute: 126 mg/kg [Rat]. 71 mg/kg [Mouse]. 90 mg/kg [Dog].

Section 3: Hazards Identification

Potential Acute Health Effects:
Hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation. Severe over-exposure can result in death.

Potential Chronic Health Effects:
CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. Repeated exposure to an highly toxic material may produce general deterioration of health by an accumulation in one or many human organs.

Section 4: First Aid Measures

Eye Contact: Check for and remove any contact lenses. Do not use an eye ointment. Seek medical attention.

Skin Contact:
After contact with skin, wash immediately with plenty of water. Gently and thoroughly wash the contaminated skin with running water and non-abrasive soap. Be particularly careful to clean folds, crevices, creases and groin. Cover the irritated skin with an emollient. If irritation persists, seek medical attention. Wash contaminated clothing before reusing.

Serious Skin Contact:
Wash with a disinfectant soap and cover the contaminated skin with an anti-bacterial cream. Seek immediate medical attention.

Inhalation: Allow the victim to rest in a well ventilated area. Seek immediate medical attention.

Serious Inhalation:
Evacuate the victim to a safe area as soon as possible. Loosen tight clothing such as a collar, tie, belt or waistband. If breathing is difficult, administer oxygen. If the victim is not breathing, perform mouth-to-mouth resuscitation. Seek medical attention.

Ingestion:
Do not induce vomiting. Examine the lips and mouth to ascertain whether the tissues are damaged, a possible indication that the toxic material was ingested; the absence of such signs, however, is not conclusive. Loosen tight clothing such as a collar, tie, belt or waistband. If the victim is not breathing, perform mouth-to-mouth resuscitation. Seek immediate medical attention.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: May be combustible at high temperature.

Auto-Ignition Temperature: Not available.

Flash Points: Not available.

Flammable Limits: Not available.

Products of Combustion: These products are carbon oxides (CO, CO2), nitrogen oxides (NO, NO2...), halogenated compounds.

Fire Hazards In Presence of Various Substances: Not available.

Explosion Hazards In Presence of Various Substances:
Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available.

Fire Fighting Media and Instructions:
SMALL FIRE: Use DRY chemical powder. LARGE FIRE: Use water spray, fog or foam. Do not use water jet.

Special Remarks on Fire Hazards: Not available.

Special Remarks on Explosion Hazards: Not available.

Section 6: Accidental Release Measures

Small Spill: Use appropriate tools to put the spilled solid in a convenient waste disposal container.

Large Spill: Use a shovel to put the material into a convenient waste disposal container.

Section 7: Handling and Storage

Precautions:
Keep locked up Keep away from heat. Keep away from sources of ignition. Empty containers pose a fire risk, evaporate the residue under a fume hood. Ground all equipment containing material. Do not ingest. Do not breathe dust. Wear suitable

protective clothing in case of insufficient ventilation, wear suitable respiratory equipment If ingested, seek medical advice immediately and show the container or the label. Avoid contact with skin and eyes

Storage:
Keep container dry. Keep in a cool place. Ground all equipment containing material. Keep container tightly closed. Keep in a cool, well-ventilated place. Highly toxic or infectious materials should be stored in a separate locked safety storage cabinet or room.

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.

Personal Protection:
Splash goggles. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Dust respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits: Not available.

Section 9: Physical and Chemical Properties

Physical state and appearance: Solid.

Odor: Not available.

Taste: Not available.

Molecular Weight: 375.87 g/mole

Color: Not available.

pH (1% soln/water): Not available.

Boiling Point: Decomposes.

Melting Point: 148°C (298.4°F)

Critical Temperature: Not available.

Specific Gravity: Not available.

Vapor Pressure: Not applicable.

Vapor Density: Not available.

Volatility: Not available.

Odor Threshold: Not available.

Water/Oil Dist. Coeff.: Not available.

Ionicity (in Water): Not available.

Dispersion Properties: Not available.

Solubility: Not available.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Not available.

Incompatibility with various substances: Not available.

Corrosivity: Non-corrosive in presence of glass.

Special Remarks on Reactivity: Not available.

Special Remarks on Corrosivity: Not available.

Polymerization: No.

Section 11: Toxicological Information

Routes of Entry: Eye contact. Inhalation. Ingestion.

Toxicity to Animals: Acute oral toxicity (LD50): 71 mg/kg [Mouse].

Chronic Effects on Humans: Not available.

Other Toxic Effects on Humans: Hazardous in case of skin contact (irritant), of ingestion, of inhalation.

Special Remarks on Toxicity to Animals: Not available.

Special Remarks on Chronic Effects on Humans: Not available.

Special Remarks on other Toxic Effects on Humans: Not available.

Section 12: Ecological Information

Ecotoxicity: Not available.

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The products of degradation are more toxic.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:

Section 14: Transport Information

DOT Classification: CLASS 6.1: Poisonous material.

Identification: : Toxic solid,organic, n.o.s. (Haloperidol) : UN2811 PG: III

Special Provisions for Transport: Not available.

Section 15: Other Regulatory Information

Federal and State Regulations: TSCA 8(b) inventory: Haloperidol

Other Regulations: OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200).

Other Classifications:

WHMIS (Canada): CLASS D-1B: Material causing immediate and serious toxic effects (TOXIC).

DSCL (EEC):
R25- Toxic if swallowed. R36/38- Irritating to eyes and skin.

HMIS (U.S.A.):

Health Hazard: 3

Fire Hazard: 1

Reactivity: 0

Personal Protection: E

National Fire Protection Association (U.S.A.):

Health: 3

Flammability: 1

Reactivity: 0

Specific hazard:

Protective Equipment:
Gloves. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Wear appropriate respirator when ventilation is inadequate. Splash goggles.

Section 16: Other Information

References: Not available.

Other Special Considerations: Not available.

Created: 10/09/2005 05:41 PM

Last Updated: 11/01/2010 12:00 PM

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no event shall ScienceLab.com be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if ScienceLab.com has been advised of the possibility of such damages.

DECAGON DEVICES
We Measure the World
2365 NE Hopkins Court
Pullman, Washington 99163
phone 509-332-2756
website www.decagon.com

Material Safety Data Sheet
Distilled Water
40464

I – PRODUCT IDENTIFICATION

Issue Date: 2/28/07

Product Name: Distilled Water

Concentration: 100%

Component: Not applicable

TSCA: YES **TLV/TWA**: Not Established
STEL: N/A **PEL**: N/A **Toxicity**: N/A

II – COMPOSITION/INFORMATION ON INGREDIENTS

Chemical name:	CAS Number:
Distilled Water	7732-18-5

III – HAZARD IDENTIFICATION

This product does not contain a toxic chemical subject to the reporting requirements of Section 313 of the Emergency Planning and Community Right-To-Know Act of 1986 (40CFR372).

IV – PHYSICAL AND CHEMICAL PROPERTIES

Appearance:	Colorless liquid
Odor:	Odorless
pH:	7
Molecular Weight:	16
Boiling point:	100 °C
Vapor pressure:	3.169 kPa @ 25 °C
Vapor density:	N/A
Freezing Point	0 °C
Specific Gravity (H_2O=1)	1
Solubility:	Complete
Flash point:	Non-flammable

V – STABILITY AND REACTIVITY

Stable: Yes
Conditions to avoid: None
Incompatible: Strong acids and bases, water reactive substances
Hazardous decomposition products: Will not occur

2365 NE Hopkins Court
Pullman, Washington 99163
phone 509-332-2756
website www.decagon.com

VI – HEALTH HAZARD DATA

Inhalation: No emergency care anticipated.
Skin contact: No emergency care anticipated.
Eye contact: No emergency care anticipated.
Ingestion: No emergency care anticipated.
Medical Conditions Generally Aggravated by Exposure: None Identified
Carcinogenicity: NTP: No **IARC:** No **ZLIST:** No **OSHA Reg:** No

VII– EMERGENY FIRST AID PROCEDURES

CALL A PHYSICIAN

Inhalation: No emergency care anticipated.
Skin contact: No emergency care anticipated.
Eye contact: No emergency care anticipated.
Ingestion: No emergency care anticipated.

VIII – FIRE-FIGHTING MEASURES

Extinguishing media: Will not burn nor support fire.
Special Fire-Fighting Procedures: Not required.
Auto Ignition Temperature: N/A **Lower Explosion Level:** N/A **NFPA Rating:** N/A
Toxic Gases Produced: N/A **Unusual Fires Explosion Hazards:** N/A

IX – HANDLING AND STORAGE

Handling: Observe good industrial hygiene practices.
Storage: Store in closed original bottle. Keep container tightly closed. Store in cool and dry place.
In Case of Spillage or Discharge: In case of spillage, clean with absorbent material.
Disposal of spillage and waste: Follow Federal, State, and Local regulations for waste.
EPA Hazardous Waste #: N/A

X – EXPOSURE CONTROL/PERSONAL PROTECTION

Ventilation: Local Exhaust.
Respiratory Protection: Not required.
Personal protection: Not required.
Other: Not required.

NOTICE

The data and information as stated was furnished by the manufacturer of the product. Decagon Devices Inc products are intended for laboratory use only. All products should be handled and used by trained professional personnel only. The responsibility for the safe handling and use of these products rest solely with the buyer and/or user.

Material Safety Data Sheet

Version 3.5
Revision Date 11/04/2011
Print Date 04/01/2012

1. PRODUCT AND COMPANY IDENTIFICATION

Product name	:	Poly(D,L-lactide-co-glycolide)
Product Number	:	P2191
Brand	:	Sigma
Supplier	:	Sigma-Aldrich 3050 Spruce Street SAINT LOUIS MO 63103 USA
Telephone	:	+1 800-325-5832
Fax	:	+1 800-325-5052
Emergency Phone # (For both supplier and manufacturer)	:	(314) 776-6555
Preparation Information	:	Sigma-Aldrich Corporation Product Safety - Americas Region 1-800-521-8956

2. HAZARDS IDENTIFICATION

Emergency Overview

OSHA Hazards
No known OSHA hazards

Not a dangerous substance or mixture according to the Globally Harmonised System (GHS).

HMIS Classification

Health hazard:	0
Flammability:	0
Physical hazards:	0

NFPA Rating

Health hazard:	0
Fire:	0
Reactivity Hazard:	0

Potential Health Effects

Inhalation	May be harmful if inhaled. May cause respiratory tract irritation.
Skin	May be harmful if absorbed through skin. May cause skin irritation.
Eyes	May cause eye irritation.
Ingestion	May be harmful if swallowed.

3. COMPOSITION/INFORMATION ON INGREDIENTS

Synonyms : Lactel® BP-0100

No ingredients are hazardous according to HCS criteria.

4. FIRST AID MEASURES

If Inhaled
If breathed in, move person into fresh air. If not breathing, give artificial respiration.

In case of skin contact
Wash off with soap and plenty of water.

In case of eye contact
Flush eyes with water as a precaution.

If swallowed
Never give anything by mouth to an unconscious person. Rinse mouth with water.

5. FIREFIGHTING MEASURES

Conditions of flammability
Not flammable or combustible.

Suitable extinguishing media
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

Special protective equipment for firefighters
Wear self contained breathing apparatus for fire fighting if necessary.

Hazardous combustion products
Hazardous decomposition products formed under fire conditions. - Carbon oxides, nitrogen oxides (NOx)

6. ACCIDENTAL RELEASE MEASURES

Personal precautions
Avoid dust formation. Avoid breathing vapors, mist or gas.

Environmental precautions
No special environmental precautions required.

Methods and materials for containment and cleaning up
Sweep up and shovel. Keep in suitable, closed containers for disposal.

7. HANDLING AND STORAGE

Precautions for safe handling
Provide appropriate exhaust ventilation at places where dust is formed.

Conditions for safe storage
Keep container tightly closed in a dry and well-ventilated place.

Recommended storage temperature: -20 °C

Keep in a dry place.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Contains no substances with occupational exposure limit values.

Personal protective equipment

Respiratory protection
Respiratory protection is not required. Where protection from nuisance levels of dusts are desired, use type N95 (US) or type P1 (EN 143) dust masks. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Hand protection
Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

Eye protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

Skin and body protection
Choose body protection in relation to its type, to the concentration and amount of dangerous substances, and to the specific work-place., The type of protective equipment must be selected according to the concentration and amount

of the dangerous substance at the specific workplace.

Hygiene measures
General industrial hygiene practice.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance

Form	granules, powder
Colour	light yellow

Safety data

pH	no data available
Melting point/freezing point	no data available
Boiling point	no data available
Flash point	no data available
Ignition temperature	no data available
Autoignition temperature	no data available
Lower explosion limit	no data available
Upper explosion limit	no data available
Vapour pressure	no data available
Density	no data available
Water solubility	soluble, hydrolyses
Partition coefficient: n-octanol/water	no data available
Relative vapour density	no data available
Odour	slight
Odour Threshold	no data available
Evaporation rate	no data available

10. STABILITY AND REACTIVITY

Chemical stability
Stable under recommended storage conditions.

Possibility of hazardous reactions
no data available

Conditions to avoid
Exposure to moisture.

Materials to avoid
acids, Bases

Hazardous decomposition products
Hazardous decomposition products formed under fire conditions. - Carbon oxides, nitrogen oxides (NOx)
Other decomposition products - no data available

11. TOXICOLOGICAL INFORMATION

Acute toxicity

Oral LD50
no data available

Inhalation LC50
no data available

Dermal LD50
no data available

Other information on acute toxicity
no data available

Skin corrosion/irritation
no data available

Serious eye damage/eye irritation
no data available

Respiratory or skin sensitization
no data available

Germ cell mutagenicity
no data available

Carcinogenicity

IARC:	No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.
ACGIH:	No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by ACGIH.
NTP:	No component of this product present at levels greater than or equal to 0.1% is identified as a known or anticipated carcinogen by NTP.
OSHA:	No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by OSHA.

Reproductive toxicity

no data available

Teratogenicity

no data available

Specific target organ toxicity - single exposure (Globally Harmonized System)
no data available

Specific target organ toxicity - repeated exposure (Globally Harmonized System)
no data available

Aspiration hazard
no data available

Potential health effects

Inhalation	May be harmful if inhaled. May cause respiratory tract irritation.
Ingestion	May be harmful if swallowed.
Skin	May be harmful if absorbed through skin. May cause skin irritation.
Eyes	May cause eye irritation.

Synergistic effects
no data available

Additional information
RTECS: Not available

12. ECOLOGICAL INFORMATION

Toxicity

no data available

Persistence and degradability
no data available

Bioaccumulative potential
no data available

Mobility in soil
no data available

PBT and vPvB assessment
no data available

Other adverse effects

no data available

13. DISPOSAL CONSIDERATIONS

Product
Offer surplus and non-recyclable solutions to a licensed disposal company.

Contaminated packaging
Dispose of as unused product.

14. TRANSPORT INFORMATION

DOT (US)
Not dangerous goods

IMDG
Not dangerous goods

IATA
Not dangerous goods

15. REGULATORY INFORMATION

OSHA Hazards
No known OSHA hazards

SARA 302 Components
SARA 302: No chemicals in this material are subject to the reporting requirements of SARA Title III, Section 302.

SARA 313 Components
SARA 313: This material does not contain any chemical components with known CAS numbers that exceed the threshold (De Minimis) reporting levels established by SARA Title III, Section 313.

SARA 311/312 Hazards
No SARA Hazards

Massachusetts Right To Know Components
No components are subject to the Massachusetts Right to Know Act.

Pennsylvania Right To Know Components

	CAS-No.	Revision Date
Poly(D,L-lactide-co-glycolide)	26780-50-7	

New Jersey Right To Know Components

	CAS-No.	Revision Date
Poly(D,L-lactide-co-glycolide)	26780-50-7	

California Prop. 65 Components
This product does not contain any chemicals known to State of California to cause cancer, birth defects, or any other reproductive harm.

16. OTHER INFORMATION

Further Information

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Co., shall not be held liable for any damage resulting from handling or from contact with the above product. See reverse side of invoice or packing slip for additional terms and conditions of sale.

MATERIAL SAFETY DATA SHEET

The information contained herein is based on data considered accurate. However, no warranty is expressed or implied regarding the accuracy of these data or the results to be obtained from the use thereof.

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ELECTRON MICROSCOPY SCIENCES
1560 INDUSTRY ROAD
P.O. BOX 550
HATFIELD, PA 19440
(215) 412-8400

24 HOUR EMERGENCY PHONE NUMBER
CHEMTREC: (800) 424-9300

FOR PRODUCT AND SALES INFORMATION

CONTACT ELECTRON MICROSCOPY SCIENCES OFFICE ABOVE.

PRODUCT IDENTIFICATION

COMMON NAME: Polyvinyl alcohol
COMMERCIAL NAME(S): Not available.
SYNONYM: Ethenol, Homopolymer; PVA: PVOH
CHEMICAL NAME: Polyvinyl Alcohol
CHEMICAL FAMILY: Not available.
CHEMICAL FORMULA: (CH2CH0H)n
CAS#: 9002-89-5
RTECS: TR8100000
TSCA: TSCA 8(b) INVENTORY: Polyvinyl alcohol
CI#: Not available.

COMPOSITION AND INFORMATION ON INGREDIENTS

NAME: Polyvinyl alcohol
CAS#: 9002-89-5
% BY WEIGHT: 100

TOXICOLOGICAL DATA ON INGREDIENTS: Not applicable.

HAZARDS IDENTIFICATION

POTENTIAL ACUTE HEALTH EFFECTS:

Hazardous in case of ingestion. Slightly hazardous in case of skin contact (irritant), of eye contact (irritant), of inhalation.

POTENTIAL CHRONIC HEALTH EFFECTS:

CARCINOGENIC EFFECTS: 3 (Not classifiable for human) by IARC
MUTAGENIC EFFECTS: Not available.
TERATOGENIC EFFECTS: Not available.
DEVELOPMENTAL TOXICITY: Not available.
Repeated or prolonged exposure is not known to aggravate medical condition.

FIRST AID MEASURES

EYE CONTACT:

Immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. Seek medical attention if irritation occurs.

SKIN CONTACT:

After contact with skin, wash immediately with plenty of water. Gently and thoroughly wash the contaminated skin with running water and non-abrasive soap. Be particularly careful to clean folds, crevices, creases and groin. Cover the irritated skin with an emollient. If irritation persists, seek medical attention. Wash contaminated clothing before reusing.

SERIOUS SKIN CONTACT: Not available.

INHALATION:

Allow the victim to rest in a well ventilated area. Seek immediate medical attention. If breathing is difficult, give Oxygen. Get medical attention.

SERIOUS INHALATION: Not available.

INGESTION:

Do not induce vomiting. Loosen tight clothing such as a collar, tie, belt or waistband. If the victim is not breathing, perform mouth-to-mouth resuscitation. Seek immediate medical attention.

SERIOUS INGESTION: Not available.

FIRE AND EXPLOSION DATA

FLAMMABILITY OF THE PRODUCT: May be combustible at high temperature.

AUTO-IGNITION TEMPERATURE: Not available.

FLASH POINTS: OPEN CUP: 79.44°C (175°F)

FLAMMABLE LIMITS: Not available.

PRODUCTS OF COMBUSTION: These products are carbon oxides (CO, C02).

FIRE HAZARDS IN PRESENCE OF VARIOUS SUBSTANCES: Flammable in Presence of mechanical impact: not available Slightly explosive in presence of open Flames and sparks.

EXPLOSION HAZARDS IN PRESENCE OF VARIOUS SUBSTANCES:

RISKS OF EXPLOSION OF THE PRODUCT IN PRESENCE OF MECHANICAL

IMPACT: Not available.

RISKS OF EXPLOSION OF THE PRODUCT IN PRESENCE OF STATIC DISCHARGE: Not available.

FIRE FIGHTING MEDIA AND INSTRUCTIONS:

SMALL FIRE: Use DRY chemical powder.

LARGE FIRE: Use water spray, fog or foam. Do not use water jet.

SPECIAL REMARKS ON FIRE HAZARDS: Not available.

SPECIAL REMARKS ON EXPLOSION HAZARDS:Fine dust dispersed in air in Sufficient concentrations, and in the presence of an ignition source is a potential dust Explosion hazard.

ACCIDENTAL RELEASE MEASURES

SMALL SPILL:

Use appropriate tools to put the spilled solid in a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and dispose of

according to local and regional authority requirements.

LARGE SPILL:

Use a shovel to put the material into a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system.

HANDLING AND STORAGE

PRECAUTIONS:

Keep away from heat. Keep away from sources of ignition. Empty containers pose a fire risk, evaporate the residue under a fume hood. Ground all equipment containing material. Do not breathe dust.

STORAGE:

Keep container dry. Keep in a cool place. Ground all equipment containing material. Keep container tightly closed. Keep in a cool, well-ventilated place. Combustible materials should be stored away from extreme heat and away from strong oxidizing agents.

EXPOSURE CONTROLS/PERSONAL PROTECTION

ENGINEERING CONTROLS:

Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.

PERSONAL PROTECTION:

Safety glasses. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

PERSONAL PROTECTION IN CASE OF A LARGE SPILL:

Splash goggles. Full suit. Dust respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

EXPOSURE LIMITS: Not available.

PHYSICAL AND CHEMICAL PROPERTIES

PHYSICAL STATE AND APPEARANCE: Solid.
ODOR: odorless
TASTE: Not available.
COLOR: Off-white.
MOLECULAR WEIGHT: (44.05)n g/mole
pH (1% SOLN/WATER): Not available.
BOILING POINT: Not available.
MELTING POINT: Softens at about 200°C with decomposition.
Decomposition @ 228 deg. C.
CRITICAL TEMPERATURE: Not available.
SPECIFIC GRAVITY: 1.19-1.31 (Water=1)
VAPOR PRESSURE: Not applicable.
VAPOR DENSITY: Not available.
VOLATILITY: Not available.
ODOR THRESHOLD: Not available.
WATER/OIL DIST. COEFF.: Not available.
IONICITY (IN WATER): Not available.
DISPERSION PROPERTIES: Not available.
SOLUBILITY: Soluble in cold water, hot water. Insoluble in diethyl either, acetone, Petroleum solvents, aromatic hydrocarbons, esters. Practically insoluble in animal And vegetable oils and chlorinated hydrocarbons.

STABILITY AND REACTIVITY DATA

STABILITY: The product is stable.
INSTABILITY TEMPERATURE: Not available.
CONDITIONS OF INSTABILITY: Heat, ignition sources, flame, excess dust Generation, incompatible materials.
INCOMPATIBILITY WITH VARIOUS SUBSTANCES: Reactive with oxidizing Agents, metals acids, alkalis.
CORROSIVITY: Non-corrosive in presence of glass.
SPECIAL REMARKS ON REACTIVITY: Not available.
SPECIAL REMARKS ON CORROSIVITY: Not available.
POLYMERIZATION: Will not occur.

TOXICOLOGICAL INFORMATION

ROUTES OF ENTRY: Ingestion. Inhalation
TOXICITY TO ANIMALS:
LD50: : 14700 mg/kg {Mouse}
LC50: Not available.
CHRONIC EFFECTS ON HUMANS: Not available.
OTHER TOXIC EFFECTS ON HUMANS: Hazardous in case of ingestion.
Slightly hazardous in case of skin contact (irritant), of
inhalation.
SPECIAL REMARKS ON TOXICITY TO ANIMALS: Not available.
SPECIAL REMARKS ON CHRONIC EFFECTS ON HUMANS: Not available.
SPECIAL REMARKS ON OTHER TOXIC EFFECTS ON HUMANS: Slightly
Hazardous in case of skin contact (irritant), of ingestion, of inhalation.

ECOLOGICAL INFORMATION

ECOTOXICITY: Ecotoxicity in water (LC50) : 10000mg/196 hours {Bluegill Sunfish}
>40000 mg/1 96 hours {Fatthead Minnow}.
BOD5 AND COD: Not available.
PRODUCTS OF BIODEGRADATION: Possibly hazardous short term
degradation products are not likely. However, long term
degradation products may arise.
TOXICITY OF THE PRODUCTS OF BIODEGRADATION: The products of
degradation are not toxic.
SPECIAL REMARKS ON THE PRODUCTS OF BIODEGRADATION: Not available.

DISPOSAL CONSIDERATIONS

WASTE DISPOSAL: Recycle to process, if possible. Consult you
local or regional authorities.

TRANSPORT INFORMATION

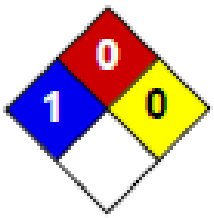
DOT CLASSIFICATION: Not a DOT controlled material (United States)
IDENTIFICATION: Not applicable.
SPECIAL PROVISIONS FOR TRANSPORT: Not applicable.

OTHER REGULATORY INFORMATION

FEDERAL AND STATE REGULATIONS:
TSCA 8(b) INVENTORY: Polyvinyl alcohol
OTHER REGULATIONS: Not available.
OTHER CLASSIFICATIONS:
WHMIS (CANADA): Not controlled under WHMIS (Canada).
DSCLA (EEC): This product is not classified according to the EU regulations.
HMIS (U.S.A.):
HEALTH HAZARD: 1
FIRE HAZARD: 2
REACTIVITY: 0
PERSONAL PROTECTION: E

NATIONAL FIRE PROTECTION ASSOCIATION (U.S.A.)
HEALTH: 0
FLAMMABILITY: 2
REACTIVITY: 0
SPECIFIC HAZARD:

PROTECTIVE EQUIPMENT:
Gloves.
Lab coat.
Dust respirator. Be sure to use an approved/certified respirator or equivalent.
Safety glasses.



Material Safety Data Sheet

Sodium chloride MSDS

Section 1: Chemical Product and Company Identification

Product Name: Sodium chloride

Catalog Codes: SLS3262, SLS1045, SLS3889, SLS1669, SLS3091

CAS#: 7647-14-5

RTECS: VZ4725000

TSCA: TSCA 8(b) inventory: Sodium chloride

CI#: Not applicable.

Synonym: Salt; Sea Salt

Chemical Name: Sodium chloride

Chemical Formula: NaCl

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Sodium chloride	7647-14-5	100

Toxicological Data on Ingredients: Sodium chloride: ORAL (LD50): Acute: 3000 mg/kg [Rat.]. 4000 mg/kg [Mouse]. DERMAL (LD50): Acute: >10000 mg/kg [Rabbit]. DUST (LC50): Acute: >42000 mg/m 1 hours [Rat].

Section 3: Hazards Identification

Potential Acute Health Effects: Slightly hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation.

Potential Chronic Health Effects:
CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Mutagenic for mammalian somatic cells. Mutagenic for bacteria and/or yeast. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. Repeated or prolonged exposure is not known to aggravate medical condition.

Section 4: First Aid Measures

Eye Contact:

Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. Get medical attention.

Skin Contact:
Wash with soap and water. Cover the irritated skin with an emollient. Get medical attention if irritation develops. Cold water may be used.

Serious Skin Contact: Not available.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention if symptoms appear.

Serious Inhalation: Not available.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. Loosen tight clothing such as a collar, tie, belt or waistband. Get medical attention if symptoms appear.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: Non-flammable.

Auto-Ignition Temperature: Not applicable.

Flash Points: Not applicable.

Flammable Limits: Not applicable.

Products of Combustion: Not available.

Fire Hazards in Presence of Various Substances: Not applicable.

Explosion Hazards in Presence of Various Substances:
Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available.

Fire Fighting Media and Instructions: Not applicable.

Special Remarks on Fire Hazards: When heated to decomposition it emits toxic fumes.

Special Remarks on Explosion Hazards:
Electrolysis of sodium chloride in presence of nitrogenous compounds to produce chlorine may lead to formation of explosive nitrogen trichloride. Potentially explosive reaction with dichloromaleic anhydride + urea.

Section 6: Accidental Release Measures

Small Spill:
Use appropriate tools to put the spilled solid in a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements.

Large Spill:
Use a shovel to put the material into a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system.

Section 7: Handling and Storage

Precautions:
Keep locked up.. Do not ingest. Do not breathe dust. Avoid contact with eyes. Wear suitable protective clothing. If ingested, seek medical advice immediately and show the container or the label. Keep away from incompatibles such as oxidizing agents, acids.

Storage: Keep container tightly closed. Keep container in a cool, well-ventilated area. Hygroscopic

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.

Personal Protection:
Splash goggles. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Gloves.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Dust respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits: Not available.

Section 9: Physical and Chemical Properties

Physical state and appearance: Solid. (Solid crystalline powder.)

Odor: Slight.

Taste: Saline.

Molecular Weight: 58.44 g/mole

Color: White.

pH (1% soln/water): 7 [Neutral.]

Boiling Point: 1413°C (2575.4°F)

Melting Point: 801°C (1473.8°F)

Critical Temperature: Not available.

Specific Gravity: 2.165 (Water = 1)

Vapor Pressure: Not applicable.

Vapor Density: Not available.

Volatility: Not available.

Odor Threshold: Not available.

Water/Oil Dist. Coeff.: Not available.

Ionicity (in Water): Not available.

Dispersion Properties: See solubility in water.

Solubility:
Easily soluble in cold water, hot water. Soluble in glycerol, and ammonia. Very slightly soluble in alcohol. Insoluble in Hydrochloric Acid.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Incompatible materials, high temperatures.

Incompatibility with various substances: Reactive with oxidizing agents, metals, acids.

Corrosivity: Not considered to be corrosive for metals and glass.

Special Remarks on Reactivity:
Hygroscopic. Reacts with most nonnoble metals such as iron or steel, building materials (such as cement) Sodium chloride is rapidly attacked by bromine trifluoride. Violent reaction with lithium.

Special Remarks on Corrosivity: Not available.

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Inhalation. Ingestion.

Toxicity to Animals:
WARNING: THE LC50 VALUES HEREUNDER ARE ESTIMATED ON THE BASIS OF A 4-HOUR EXPOSURE. Acute oral toxicity (LD50): 3000 mg/kg [Rat.]. Acute dermal toxicity (LD50): >10000 mg/kg [Rabbit]. Acute toxicity of the dust (LC50): >42000 mg/m3 1 hours [Rat].

Chronic Effects on Humans: MUTAGENIC EFFECTS: Mutagenic for mammalian somatic cells. Mutagenic for bacteria and/or yeast.

Other Toxic Effects on Humans: Slightly hazardous in case of skin contact (irritant), of ingestion, of inhalation.

Special Remarks on Toxicity to Animals: Lowest Published Lethal Dose (LDL) [Man] - Route: Oral; Dose: 1000 mg/kg

Special Remarks on Chronic Effects on Humans:
Causes adverse reproductive effects in humans (fetotoxicity, abortion,) by intraplacental route. High intake of sodium chloride, whether from occupational exposure or in the diet, may increase risk of TOXEMIA OF PREGNANCY in susceptible women (Bishop, 1978). Hypertonic sodium chloride solutions have been used to induce abortion in late pregnancy by direct infusion into the uterus (Brown et al, 1972), but this route of administration is not relevant to occupational exposures. May cause adverse reproductive effects and birth defects in animals, particularly rats and mice (fetotoxicity, abortion, musculoskeletal abnormalities, and maternal effects (effects on ovaries, fallopian tubes) by oral, intraperitoneal, intraplacental, intrauterine, parenteral, and subcutaneous routes. While sodium chloride has been used as a negative control n some reproductive studies, it has also been used as an example that almost any chemical can cause birth defects in experimental animals if studied under the right conditions (Nishimura & Miyamoto, 1969). In experimental animals, sodium chloride has caused delayed effects on newborns, has been fetotoxic, and has caused birth defects and abortions in rats and mice (RTECS, 1997). May affect genetic material (mutagenic)

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: May cause skin irritation. Eyes: Causes eye irritation. Ingestion: Ingestion of large quantities can irritate the stomach (as in overuse of salt tablets) with nausea and vomiting. May affect behavior (muscle spasicity/contraction, somnolence), sense organs, metabolism, and cardiovascular system. Continued exposure may produce dehydration, internal organ congestion, and coma. Inhalation: Material is irritating to mucous membranes and upper respiratory tract.

Section 12: Ecological Information

Ecotoxicity: Not available.

BOD5 and COD: Not available.

Products of Biodegradation:
Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: The product itself and its products of degradation are not toxic.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: Not a DOT controlled material (United States).

Identification: Not applicable.

Special Provisions for Transport: Not applicable.

Section 15: Other Regulatory Information

Federal and State Regulations: TSCA 8(b) inventory: Sodium chloride

Other Regulations: EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.

Other Classifications:

WHMIS (Canada): Not controlled under WHMIS (Canada).

DSCL (EEC):
R40- Possible risks of irreversible effects. S24/25- Avoid contact with skin and eyes.

HMIS (U.S.A.):

Health Hazard: 1

Fire Hazard: 0

Reactivity: 0

Personal Protection: E

National Fire Protection Association (U.S.A.):

Health: 1

Flammability: 0

Reactivity: 0

Specific hazard:

Protective Equipment:
Gloves. Lab coat. Dust respirator. Be sure to use an approved/certified respirator or equivalent. Splash goggles.

Section 16: Other Information

References:
-Hawley, G.G.. The Condensed Chemical Dictionary, 11e ed., New York N.Y., Van Nostrand Reinold, 1987. -SAX, N.I. Dangerous Properties of Indutrial Materials. Toronto, Van Nostrand Reinold, 6e ed. 1984. -The Sigma-Aldrich Library of Chemical Safety Data, Edition II.

Other Special Considerations: Not available.

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Last Updated: 11/01/2010 12:00 PM

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