UNIVERSITAT POLITÈCNICA DE CATALUNYA
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Escola Superior d'Enginyeries Industrial, Aeroespacial i Audiovisual de Terrassa

DEGREE:

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STUDENT:

Xavier Sanchiz Brossa

PROJECT TITLE:

Study and use of textile substrates as a vehicle system for biomedical applications

PROJECT DIRECTOR:

Manuel-José Lis Arias. Chemical engineering department

DELIVERY TERM:

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ABSRTACT

L'eficiència de l'encapsulació i el alliberamentt de medicaments en microcàpsules de fàrmacs solubles amb quitosan estan directament influïts per molts factors durant el procés que encara no s'han estudiat.

L'objectiu d'aquest projecte és fer una primera aproximació a la influència de les variables del procés com la concentració dels components de les microcàpsules, els temps d'agitació, la temperatura del procés, les relacions molars i moltes altres variables.

En aquest projecte, diverses combinacions d'aquestes variables s'han provat i analitzat posteriorment per tal de comparar els seus resultats i tenir una primera visió de la influència de cada variable.

També s'ha estudiat i analitzat l'assaig per a l'alliberament de fàrmacs per veure l'efecte de diferents teixits en diferents mostres de microcàpsules i modelat per aconseguir un alliberament controlat de fàrmacs.

ABSTRACT

The encapsulation efficiency and the drug delivery of microcapsules of soluble drugs with chitosan is directly influenced by many factors during the process that have not been studied yet.

The aim of this project is to make a first approach of the influence of the variables of the process as the concentration of the components of the microcapsules, the stirring times, the process temperature, molar ratios and many other variables.

In this project, several combinations of this variables have been tested and analyzed afterwards in order to compare their results and have a first view of the influence of each variable.

Also the drug delivery essay have been studied and analyzed to see the effect of different fabrics in different samples of microcapsules, and modeled for achieving a controlled drug release.

ACKNOWLEDGMENTS

The project could not have been achieved without the support and constant motivation of my family, project director and of course, my couple.

I want to specially thank my teacher and project director Manuel-José Lis for all the help and support he has given during the project from the very beginning of it. To all my family, who have trusted in me, and gave me everything I needed to fulfill my goals and of course, this project.

An special thanks to my recently deceased grandmother, who always worried about the progress of my project and gave me strength to keep on going.

And last but not least, I would like to thank my couple for always trusting in me, give me all the strength I need, for coping up with my changing mood during the realization of the project, and for helping in the elaboration of the report.

Thank you all,

June 2019.

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ABBREVIATIONS

PVA:	Poly vinyl alcohol
DCM:	Dichloromethane.
UV:	Ultra-violated
TGA:	Thermogravimetric analyzer
RPM:	Revolutions per minute
W/O:	Water / Oil
EE (%):	Encapsulation efficiency

1. INTRODUCTION

The humanity desire to keep improving in every scientific field has led science and engineering to find new solutions and materials with unimaginable properties or functionalities that could not be imagined years before.

One of this fields to improve is microencapsulation, since is a relatively recent science and has still a lot of way to go in developing and improving terms, for instance, the improvement of the biocompatibility of the microcapsules inasmuch as many of the uses of microcapsules are destined to biomedicine or fields in touch with the human body, the achievement of encapsulating a vast variety of materials, as each of them has different behaviors in the encapsulation process and need specific conditions to reach a certain percentage of encapsulation.

Biocompatible polymers are a rising field since many illness or conditions require a constant level of medicaments or agents in vivo to provide the most effective prophylactic, therapeutic or diagnostic results. This dosage of medicaments have been accomplished by the use of microcapsules, and more recently using biocompatible polymers utilizing the biodegradability to improve the controlled release of the medicament and the biocompatibility to avoid any rejection from the body.

A polymer is considered biocompatible when the polymer itself or any degradation products of the polymer are non-toxic to the recipient and also present no deleterious or untoward effects on the recipient's body. (Bernstein, Zhang, Khan, & Tracy, 1999). [1]

Biocompatible polymers are being widely used in biomedical applications, and more concretely in controlled drug release. The idea of controlled drug release from polymers dates back to the 1960s with the usage of silicon rubber as coating material made by Folkman and Long. Since this polymers had a low degradability and a bad biocompatibility, the requirement of surgical removement was needed and limited their applicability. Thus, biodegradable polymers and later both biodegradable and biocompatible polymers were tested and used for microencapsulation processes as microcapsules with this polymers

mentioned will not require a surgical removement or any measure of removal since it will be degraded and absorbed by the human body with no side effects.

1.1. Background

Previously, it has been studied the microencapsulation process and the control of it, as the encapsulation efficiency, the particle size, the control of sphere porosity, and the drug release rate. [2] as well as the preparation of microspheres from linear polymers and monomers.

Regarding the encapsulation efficiency, Yang et al. [3] provided a revealing study which correlated encapsulation efficiency to sphere preparation temperature. The authors found that the highest encapsulation efficiencies occurred at the highest and lowest formation temperatures tested (50% at 4 and 38 ºC, and about 19% at 22 and 19ºC).

When considering the relation of the polymer to encapsulation efficiency Ghaderi et al. [4] found that increasing the concentration of polymer in the organic phase increased the encapsulation efficiency.

In the part concerning particle size, Yang et al. [3] reported that the size of the microsphere can be affected by the polymer concentration, temperature, viscosity, the stirring rate, and the amount of emulsifier employed. Considering the effect of polymer concentration, it has been reported that increasing the concentration of the polymer in the second emulsion increases sphere size.

In another study, Jeyanthi et al. [5] used a SEM to show that sphere size was temperature dependent; lower and higher temperatures produced larger spheres whereas intermediate temperatures produced smaller spheres.

Also, several studies reported that an increase of stirring rate produced smaller microspheres since finer emulsions were formed in the process.

Finally, the control of sphere porosity, that has an important effect on drug delivery, could be managed by regulating the amount of water in the first w/o emulsion. Less water in the first emulsion led to a porosity decrease.

1.2. Motivation

The motivation for the realization of this project comes from the introduction of the microencapsulation process by my project director, and the utility of biocompatible and biodegradable polymers in this field.

Since this is a rising field with a lot of weight several industries as pharmaceutical, textile, medical, chemical, electronics and more, a lot of interest and motivation came up to me.

As encapsulation of soluble drugs with certain biocompatible polymers have not been studied yet, this project will test the encapsulation process with caffeine as a soluble drug, and chitosan as coating polymer, adding several variables and changes to see how it effects to the process.

1.3. Objectives

In this final degree project the main objectives are to study the viability of the microencapsulation of soluble drugs with a biocompatible polymer, chitosan and to analyze the drug delivery of the system and the effect of the tissue when it is impregned by the mentioned microcapsules.

For the study of the microencapsulation viability, various surfactants and cross-linking agents have been tested to see their effect on the process.

Since there is no feedback in the field, a first approach of the encapsulation of soluble drugs with chitosan will be done without totally affirming the results obtained, at least until more research is done.

Other secondary objectives are taken in this project, as the accomplishment of proper calibration curves for the caffeine system in order to calculate the encapsulation efficiency, or understand and apply the knowledge of surfactants and cross-linking agents in order to achieve the best encapsulation process.

2. THEORETICAL FRAMEWORK

2.1. Microencapsulation

Microencapsulation is a process in which active substances are coated by extremely small capsules. It is a new technology that has been used in the cosmetics industry as well as in the pharmaceutical, agrochemical and food industries, being used in flavors, acids, oils, vitamins, microorganisms, among others. The success of this technology is due to the correct choice of the wall material, the core release form and the encapsulation method.

The polymer acts as a protective film, isolating the core and avoiding the effect of its inadequate exposure. This membrane dissolves itself through a specific stimulus, releasing the core in the ideal place or at the ideal time. [6] There are different types of microcapsules referring to their structure and terminology.

Table 1 Terminology of microencapsulation products [7]

Terminology	Description	Size range	Schematic illustration
Microcapsules (narrow sense of meaning)	Products of coating liquid nuclei with solid walls.	µm	
Nanocapsules	Same structure as microcapsules, but smaller.	nm	
Microspheres or microparticles	The cores and walls are both solid. Often, there is no clear distinction between them: the thick solid wall functions as a porous matrix where active substances are embedded.	µm	
Nanospheres or nanoparticles	Same structure as microspheres, but smaller.	nm	
Liposomes **Niosomes**	Lipid wall, often made of phospholipids and cholesterol. Subtypes: unilamellar (one lipid layer) and multilamellar (several lipid layers). Similar to liposomes but their membranes are made of synthetic amphiphylic molecules (detergents).	µm to nm	

The microcapsules also can be classified by their morphology in three basic categories as monocored, poly cored or matrix type.

Monocored microcapsules have a single hollow chamber within the capsule. The poly core microcapsules have a number of different sized chambers within the shell. The matrix type microparticle has the active ingredients integrated within the matrix of the shell material. However, the morphology of the internal structure of a microparticle depends largely on the selected shell materials and the microencapsulation methods that are employed. [8]

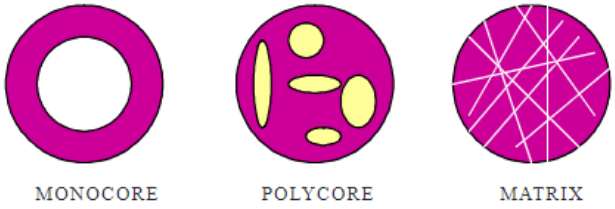


Figure 1 Types of microcapsules [8]

In the microencapsulation processes, several variables are taken into consideration to maximize the entrapment efficiency, the surface morphology, structure of the microcapsule or the size of it as is shown in the next figure

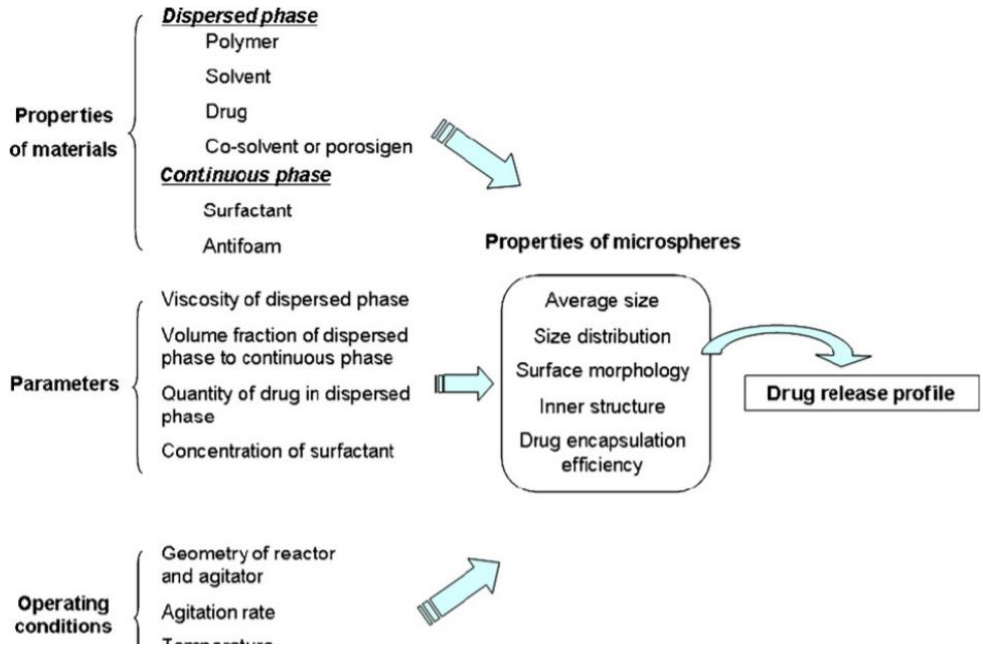


Figure 2 microencapsulation parameters [10]

2.1.1. Technics of microencapsulation

Microencapsulation techniques consist basically on the emulsion of the active compound in a solution of the coating material. The encapsulation of this active compound is achieved by modifying the continuous phase, changing parameters or with a chemical agent.

The types of emulsions are:

- w/o emulsion
- o/w emulsion
- w/o/w emulsion
- o/w/o emulsion

Generally, microencapsulation methods are divided into two basic groups, namely chemical and physical, with the latter being further subdivided into physico-chemical and physico-mechanical techniques. This article describes the most generally accepted classification of the microencapsulation methods. [9]

Chemical process	Pysico-chemical process	Physico-mechanical process
Polymerization	Coacervation	Spary-drying and congealing
Interfacial polycondensation	Solvent evaporation	Electrostatic encapsulation
	Layer-by-layer absortion	Pan coating
	Complex precipitation	Vacuum encapsulation
	Ionic gelation	Extrusion
	Supercritical fluid precipitation	Air suspension
		Multiorifice-centrifugal

Table 2 Methods of microencapsulation

In this project, the technic used is solvent evaporation method. Thus, a deeper explanation of the method is needed.

Firstly, we have to differentiate the phases of the process. The continuous phase, containing the surfactant or anti-foam agent, the disperse phase, which contains the polymer, that is in charge of the coating process, and finally the drug solution.

The basics phenomenology of the microencapsulation process is simple.

When the oil phase is formed, as is a microemulsion, the first step is taken. This microemulsion is basically little drops of the polymer with the solvent. After that, the drug solution is dispersed with the oil (or disperse) phase and the w/o emulsion is obtained, in which the polymer is mixed with the drug solution. [10]

Subsequently, the w/o phase is added to the continuous phase, and stirred at high rpm (10-20 k rpm). Thus, the surfactant, that have both a hydrophilic and hydrophobic part, surrounds the w/o phase in a certain structure called micelles because the surfactant covers the surface of the w/o drops with the hydrophobic part in the drop, and the hydrophilic part in the water.

Finally, the evaporation of the solvent is carried in continuous stirring during 8 hours. Once the solvent is completely evaporated, the polymer entrapped inside the micelle chemically interacts with the drug and is settled around the drug molecule creating a coating and consequently, forming the microcapsule.[10]

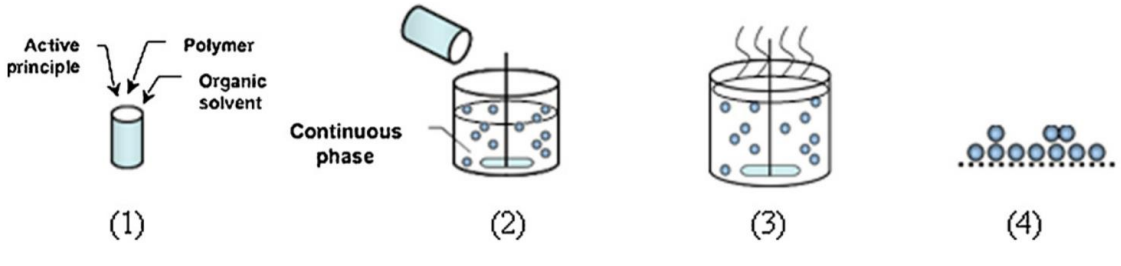


Figure 3 Steps of solvent evaporation method [10]

2.1.2. Applications of microencapsulation

The reason for microencapsulation is basically to protect the encapsulated material from the environment through which it passes without and ensuring that the encapsulated material reaches the area of action.

The main reasons for the use of this technic are the following ones:

- controlled release of the encapsulated material
- increased protection for the encapsulated material
- works as a mask for odors, taste and interactions with external elements
- protection of the environment

Due to this multiple reasons microencapsulation has been widely used in several fields. For instance, medical and pharmaceutical purposes, biotechnology, chemical materials, textile and printing industries, electronics, water treatment, construction materials and many more.

Since the introduction of microencapsulation in the 1950s in the paper industry, it has been improved, modified, researched and extended until now, and still has much way to go.
The growth of microencapsulation process is shown in the increasing number of scientific articles, patents and industrial research.

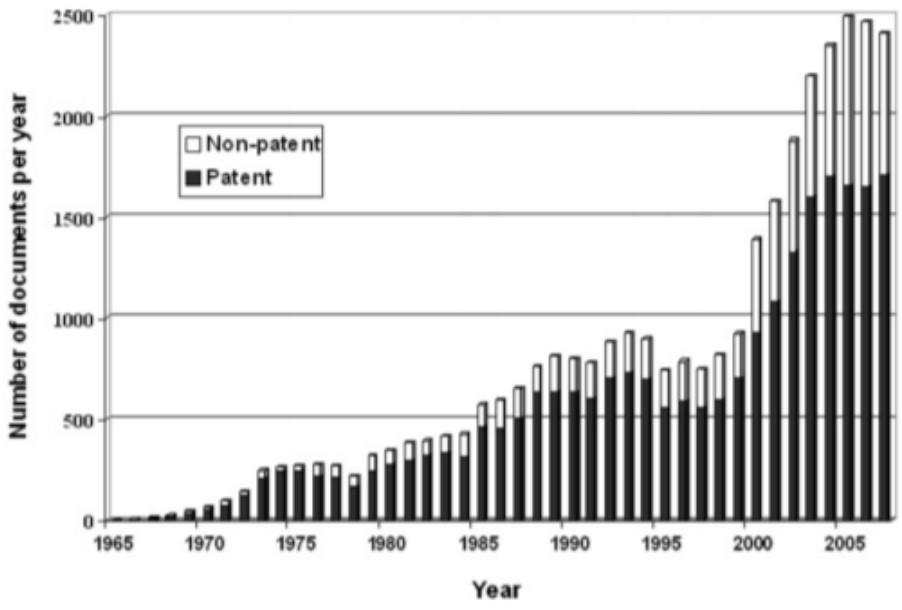


Figure 4 Growth of microencapsulation [7]

2.2. Drug release

Drug release could be described as the application of physical, chemical and biological principles for transporting drug molecules for clinical benefit.

It encompasses all the approaches, formulations, technologies and systems for the control of the temporal and spatial location of drug molecules.

When drugs are delivered using typical delivery systems as oral or injection methods, only a small part of the dose actually reaches the site of action, and the majority of the dose is wasted because it's destroyed on the way, or goes to the wrong site of action.

The aim of the controlled release is, in fact, really simple. It is based on getting the right amount of active agent in the right place, and at a certain time. It has been really useful to extend medical dosage and reduce or remove the concentrations exceeding the therapeutic requirements. [11]

In temporal control, drug delivery systems aim to deliver the drug over an extended duration or at a specific time during treatment. Controlled release over an extended duration is highly beneficial for drugs that are rapidly metabolized and eliminated from the body after administration.

Comparing concentrations in a case where a drug is delivered via injections versus a controlled release system , we can see the obvious benefits, since drug concentrations fluctuate widely during the several administrations via injection, and for only a portion of the treatment, the drug concentration is in the therapeutic range. (figure 1)

With the controlled release system, the rate of drug release equals the rate of elimination of the drug, thus, the drug concentration is in the therapeutic range for mostly of the treatment.

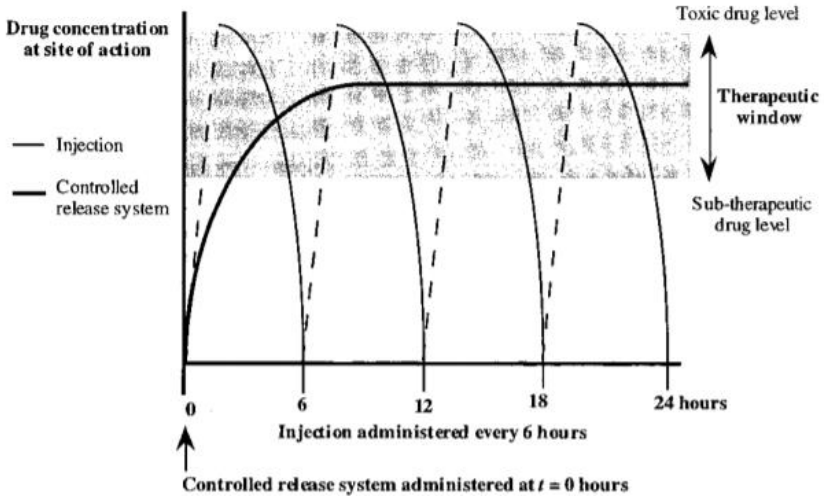


Figure 5 Drug concentration along time [12]

2.2.1. Encapsulating coating materials

The coating material should be capable to create a film around the core material/active compound, and being non-reactive and chemically compatible with it. Moreover, it has to provide some desired properties such as strength, impermeability, flexibility and sometimes, antimicrobial effects, as chitosan does.

The use of polymers for coating in microencapsulation first started back in the 1960s, firstly using silicon rubber and polyethylene, but their lack of degradability of this Systems lead to further research in obtaining better materials for this function, with a higher degradability capacity. [12]

Classification of polymers in controlled drug release can be generally divided in two groups, biodegradable or nonbiodegradable.

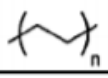
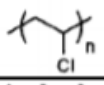
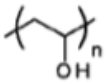
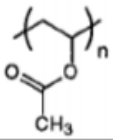
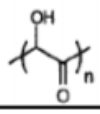
Biodegradable Systems have garnered much of the attention in drug delivery Systems since nonbiodegradable Systems need retrieval or further manipulation after introducing it into the body.

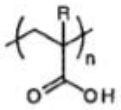
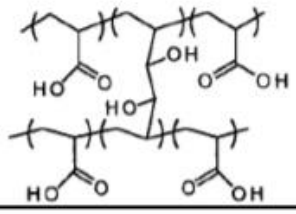
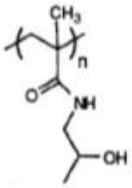
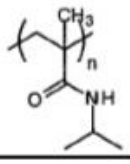
Also, polymers can be classified by their mechanism of erosion. "Degradation" refers to bond cleavage, whereas "erosion" refers to depletion of the coating material. Degradation is a chemical process, while erosion is a physical phenomenon reliant on dissolution and diffusion processes. [12]

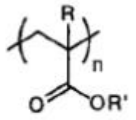
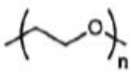
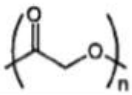
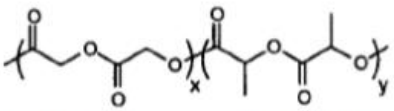
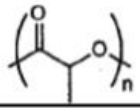
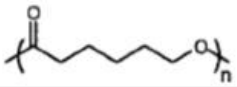
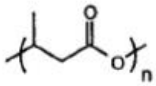
If the microcapsules are destined to a bioactivity such as medical or pharmaceutical purpose, then it is desired the biocompatibility of the polymer. This can be achieved by using natural polymers. For example, chitin (and chitosan), cellulose, lactic and glycolic acid.

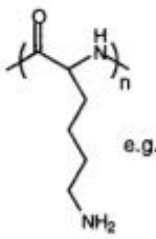
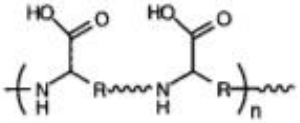
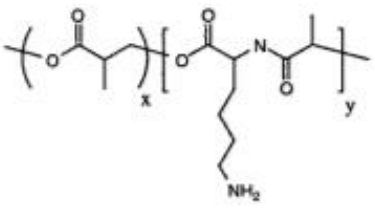
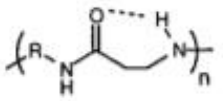
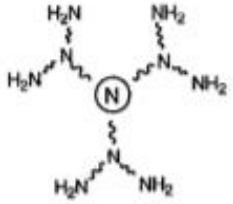
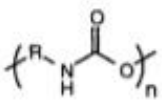
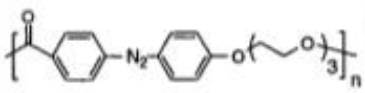
The range of polymers used in controlled drug delivery are shown in the following table based on the backbone composition.

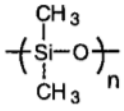
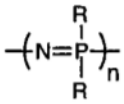
Table 3 summary of polymer structures based on backbone structures[12]

Backbone Structure	Examples	Notes
C-C	**Poly(ethylene)** (PE) 	Zero-order temporal control achieved by diffusion from matrices. Tetanus toxoid released by pulsatile kinetics. Prolonged pseudo-first order release of acetoaminophen in gastrointestinal tract.
	Poly(propylene) (PP) 	Biocompatibility improved by albumin grafting to surface. Ophthalmic drug delivery applications. Accurel® used to release agents active in vapour state.
Vinyl-based C-C	**Poly(vinyl chloride)** (PVC) 	Membrane devices formulated to release volatile agents into air and non-volatile agents into aqueous solutions.
	Poly(vinyl alcohol) (PVA) 	Water-soluble copolymer of vinyl alcohol and vinyl acetate is formed by hydrolyzing poly(vinyl acetate). Surface stabilizer in microsphere formulation. Bioadhesive hydrogels.
Vinyl-based C-C	**Poly(ethylene-vinyl acetate)** p(EVAc) 	Employed as rate controlling membrane in Ocusert®. Drug permeability tailored by ratio of vinyl acetate present. Used in magnetically controlled temporal release, ultrasound-stimulated release, subcutaneous implant for cancer pain relief, and chemotherapeutic agents.
	Poly(enol-ketone) (PEK) 	Produced by controlled oxidation of PVA.

Backbone Structure	Examples	Notes
	Poly(acrylic acid) (PAA)  R = H (acrylic) = CH_3 (methacrylic)	Bioadhesive polymer. Hydrogels of PAA reversibly swell as function of pH.
	Poly(carbophil) 	PAA-based hydrogel loosely cross-linked with divinyl glycol. Mucoadhesive properties allow temporal and distribution control.
Vinyl-based C-C	**Poly(acrylamides)** e.g., poly(N-(2-hydroxypropyl) methacrylamide) p(HPMA) 	Plasma expander used as polymer-drug conjugate for distribution control. Enzyme cleavable side chains employed to target release at colon. Hydrolytically degradable hydrogels produced by cross-linking with N,O-dimethacryloyl hydroxylamine linker. Component of photosensitive delivery system.
	Poly(N-isopropyl acrylamide) e.g., p(NIPAAm) 	Pronounced negative thermosensivity. Used in stimuli sensitive systems.

Backbone Structure	Examples	Notes
	Poly(acrylates)  R = H (acrylic) = CH_3 (methacrylic) = CN (cyanoacrylate)	Employed as surgical adhesive due to polymerization in water at room temperature. Controlled drug release applications reported in polymer-drug conjugate and topical applications. Bone cements with hydrophicility tailored to facilitate protein release.
C-O	**Poly(ethylene glycol)** (PEG) 	Also termed poly(ethylene oxide) (PEO). Used as diffusion-limited tablet formulation, cross-linked hydrogels, and polymer-drug conjugates. Employed as a component of block copolymer systems.
C-O, C=O	**Poly(glycolic acid)** (PGA) 	Copolymer: Poly(lactic acid-co-glycolic acid) (PLGA)  Biosynthetic poly(ester) often employed as copolymer with hydroxyvalerate monomer.
	Poly(lactic acid) (PLA) 	
	Poly(ε–caprolactone) (PCL) 	
	Poly(3-hydroxybutyrate) 	

Backbone Structure	Examples	Notes
C-N, C=O	**Poly(amino acids)**  **pseudo-poly(amino acids)** 	**Poly(lactic acid-*co*-lysine)** (PLAL)  **Section E.**
C-N, C=O	**Poly(amide-enamines)** 	Hydrolyzable polymer with hydrophilic and hydrophobic segments. Potential for diffusion controlled drug release.[139]
	Poly(amido amines) (PAMAM) **dendrimers** 	Complexes with DNA to form conjugates for gene therapy.[153,154]
other C-N, C-O, C=O	**Poly(urethanes)** 	Hard and soft segment polymers containing PEG for temporal controlled release.[155] Azo-containing polymers used to control site of polymer-drug conjugate degradation.[156] Anti-infectious biomaterials containing antibiotics.[10]
	Azopolymer poly(ether-ester) 	Azo bond degraded by bacteria in colon thereby generating colon-specific delivery of chemotherapeutic and other drugs.[157-159]

Backbone Structure	Examples	Notes
silicon-based Si-O	**Poly(dimethylsiloxane)** 	Temporal controlled release of rifampicin from shunt.[160] Bone infections treated with crosslinked matrix.[161]
phosphorus-based P=N, P-O	**Poly(phosphazenes)** 	Amino acid side chains generate flexible materials that degrade to amino acid, phosphate and ammonia poly[bis(glycine ethyl ester)phosphazene].[116] PEG-modified nanoparticles for site-specific drug delivery.[118] **Section F.**

The most usual polymer in microencapsulation Is PLA and PLGA, due to their biodegradability and biocompatibility, but in this project the polymer used will be chitosan, offering an appropriate biodegradability and an excellent biocompatibility and antifungal activity thanks to its natural provenance. And as long as we are working in the scope of controlled drug released for human skin, the most suitable polymer will be one that has an excellent biocompatibility.

Chitosan is produced by deacetylation of chitin, a structural element in the shells of shrimps and crabs. Chitosan is a cationic linear polysaccharide composed basically of β(1→4) linked glucosamine units together with some proportion of N-acetylglucosamine units. [13].

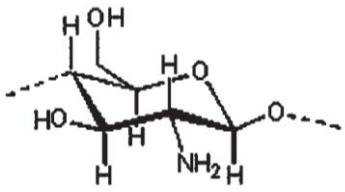


Figure 6 chitosan structure[12]

It must be pointed out that the microstructure of chitosan depends on whether the deacetylation reaction was carried out under homogeneous or heterogeneous conditions.

This structural difference is very important in determining many properties of chitosan, such as solubility. Chitosan obtained by a heterogeneous procedure is not soluble in water, whereas water-soluble chitosan can be prepared by homogeneous deacetylation of chitin.

Chitosan has an excellent film-forming ability. Chitosan films exhibit limited swelling in water. However, through the formation of blends and interpenetrated or semi interpenetrated polymer networks with highly hydrophilic polymers such as poly(vinyl alcohol), polyvinylpyrrolidone membranes with varying degrees of hydrophilicity have been obtained and used as matrices for different applications.[13].

2.2.2. Active compounds:

The active compound tested in this project is caffeine, a natural alkaloid and a soluble drug with the following chemical formula: $C_8H_{10}N_4O_2$. Is a central nervous system stimulant, and the world's most widely consumed psychoactive drug due to is found in most of our daily products and diets, such as drinks as coffee and tea, chocolate and other soft drinks. [11]

It is found in nuts, seeds, or leaves of a number of plants from Africa, Asia or South America, but the most well-known source of caffeine is the coffee bean, a misnomer for the seed of coffee plants. [11]

Concerning it chemical properties, caffeine is odorless, colorless, and bitter powder. It is very soluble in water, reaching 16 mg/mL at 25ºC.

It has a molar mass of 194,2 g/mol a density of 1.23 g/cm^3 and a melting point of 235ºC.

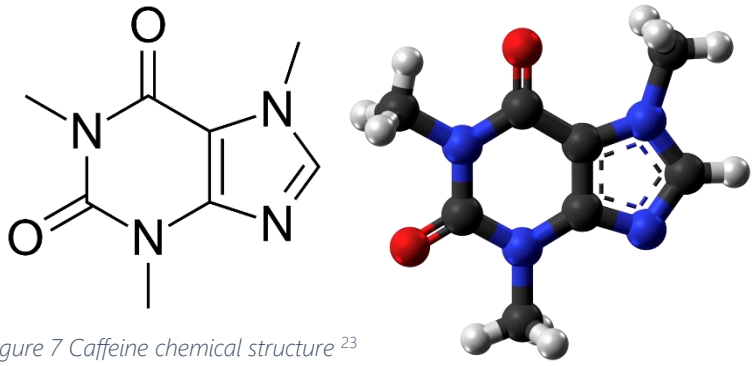


Figure 7 Caffeine chemical structure [23]

The elimination half-life time in a normal human body goes from 3-7 hours in adults, to 65-130 hours for a child, and the duration of action is held between 3-4 hours. [14]

2.2.3. Surfactants

Some compounds, like short-chain fatty acids, are amphiphilic or amphipathic, i.e., they have one part that has an affinity for nonpolar media and one part that has an affinity for polar media. These molecules form oriented monolayers at interfaces and show surface activity (i.e., they lower the surface or interfacial tension of the medium in which they are dissolved). In some usage surfactants are defined as molecules capable of associating to form micelles. These compounds are termed surfactants, amphiphiles, surface-active agents, tensides, or, in the very old literature, paraffin-chain salts. The term surfactant is now probably the most commonly used and will be employed in this book. This word has a somewhat unusual origin, it was first created and registered as a trade- mark by the General Aniline and Film Corp. for their surface-active products. The company later released the term to the public domain for others to use . Soaps (fatty acid salts containing at least eight carbon atoms) are surfactants. Detergents are surfactants, or surfactant mixtures, whose solutions have cleaning properties. That is, detergents alter interfacial properties so as to promote removal of a phase from solid surfaces. [15]

The unusual properties of aqueous surfactant solutions can be ascribed to the presence of a hydrophilic head group and a hydrophobic chain (or tail) in the molecule. The polar or ionic head group usually interacts strongly with an aqueous environment, in which case it is

solvated via dipole-dipole or ion-dipole interactions. In fact, it is the nature of the polar head group which is used to divide surfactants into different categories. [15]

In aqueous solution dilute concentrations of surfactant act much as normal electrolytes but at higher concentrations very different behavior results. This behavior is explained in terms of the formation of organized aggregates of large numbers of molecules called micelles, in which the lipophilic parts of the surfactants associate in the interior of the aggregate leaving hydrophilic parts to face the aqueous medium. The formation of micelles in aqueous solution is generally viewed as a compromise between the tendency for alkyl chains to avoid energetically unfavorable contacts with water, and the desire for the polar parts to maintain contact with the aqueous environment. [15]

A thermodynamic description of the process of micelle formation will include a description of both electrostatic and hydrophobic contributions to the overall Gibbs energy of the system. Hydrocarbons (e.g., dodecane) and water are not miscible; the limited solubility of hydrophobic species in water can be attributed to the hydrophobic effect. The hydrophobic Gibbs energy (or the transfer Gibbs energy) can be defined as the difference between the standard chemical potential of the hydrocarbon solute in water and a hydrocarbon solvent at infinite dilution. [15]

$$\Delta G_t^\circ = \mu_{HC}^\circ - \mu_{aq}^\circ$$

Equation 1 Gibbs energy equation [15]

Where the terms on the right side of the equation are the chemical potentials of the Hydrocarbon dissolved and water, respectively. [15]

2.2.4. Release mechanisms:

Several release mechanisms have been developed to achieve temporal and distribution controlled release of drug using polymers. That's because of the fact that many different drugs are used in controlled release and impose various restrictions on the type of delivery system used. Moreover, the environmental conditions or the release time directly influences on the appropriate mechanism in each case.

An important part of the drug delivery process, is to take into account the fact that the polymer is still wandering around the site of action. Here's where natural or biodegradable polymers gain weight. These polymers may be excreted directly via kidneys, or reduced into smaller molecules that are then excreted. [12]

Also, it's important to consider the number of physicochemical properties that a polymer offers, concerning the different mechanisms of controlled release. The more physicochemical properties, the more mechanisms could be carried with a certain polymer. [12]

The mechanisms can be divided in two groups, temporal controlled and distribution controlled.

- *Temporal controlled:* Polymeric devices that achieve temporal controlled release protect the active compound from the environmental conditions for an expected period of time, attaining the desired concentration of drug during this period of time.

This protection can involve delaying the dissolution of the active compound , inhibiting the diffusion of the active compound out of the microcapsule, or controlling the flow of active compound.

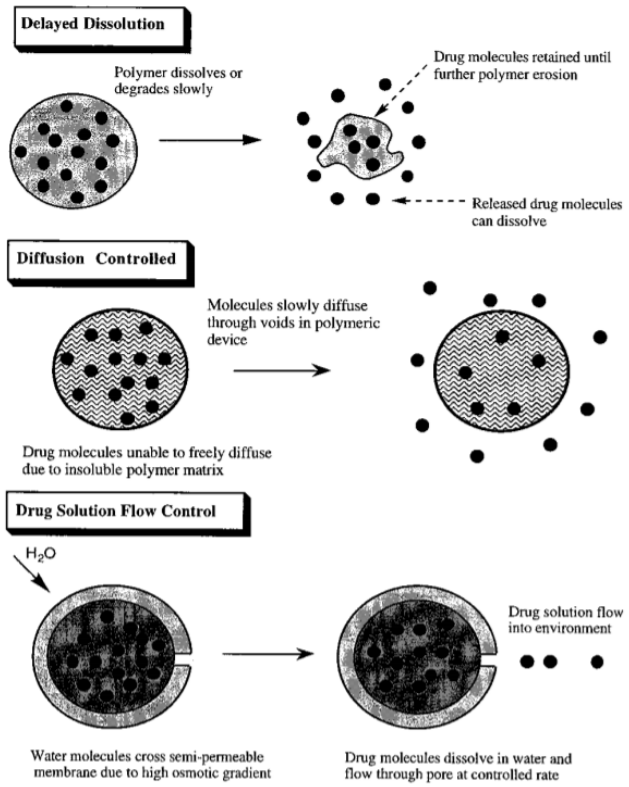


Figure 8 Examples of mechanisms of temporal controlled release[12]

-Distribution controlled:

The simplest method of distribution controlled, is to simply to directly apply the delivery device/tissue at the site of action.

For majority of diseases that require distribution controlled release of a drug, a targeting mechanism is needed for the delivery system to reach the desired target.

It exists two types of delivery systems depending on the polymer, colloidal carriers and polymer-drug conjugates.

In colloidal carrier type, encapsulation consists in the polymer encapsulating the drug within micro/nano-capsules, whether in polymer-drug conjugates the drug is coupled to the polymer.

Nevertheless, the polymer is functioning only as a carrier and is not in charge of targeting the delivery device, other biological molecules are used for targeting instead.[12]

2.2.5. Models of drug release:

In drug release, exists several kinetic models that expect to control drug release of a delivery device, and are generally governed by zero or first order.

In spite of all the models of drug release, in this project we will work with the most important three, Higuchi equation, power law, and Korsenmeyer-Peppas equation approximation.

Higuchi equation:

In 1961, Higuchi published probably the most famous and most often used mathematical equation to describe the release of drugs from matrix systems. On the beginning, it was only for planar systems, but was later improved and extended for other geometries and matrix.

The classical Higuchi equation was derived under pseudo-steady state assumptions and generally cannot be applied to real controlled release systems. [16]

The primary Higuchi equation is:

$$\frac{M_t}{A} = \sqrt{D(2c_0 - c_s)c_s t} \qquad \text{for } c_0 > c_s$$

Equation 2 Higuchi equation [16]

Mt: cumulative absolute amount of drug released at time t

A: Surface area of the controlled release device

D: drug diffusivity in the polymer carrier

Co: Initial drug concentration

Cs: solubility of the drug in the polymer

Equation 2 can be expressed as:

$$\frac{M_t}{M_\infty} = K\sqrt{t}$$

Equation 3 Higuchi equation simplified [16]

M∞: absolute cumulative amount of drug released at infinite time (equal to absolute amount of drug incorporated at time t=0)

K: constant reflecting the design variables

The simplicity of this equations is a good point for drug delivery systems, although some previous considerations must be taken into account:

- The initial drug concentration in the system is much higher than the solubility of the drug
- Mathematical analysis is based on one-dimensional diffusion. Thus, edge effects must be negligible.
- The suspended drug is in a fine state such that the particles are much smaller in diameter than the thickness of the system
- Swelling or dissolution of the polymer carrier is negligible.
- Perfect sink conditions are maintained.
- The diffusivity of the drug is constant. [16]

Power law:

Power law is an equation for drug delivery, more comprehensive and still very simple, used to describe drug release from polymeric systems. The Power law equation is:

$$\frac{M_t}{M_\infty} = kt^n$$

Equation 4 Power law [16]

Mt: cumulative absolute amount of drug released at time t

M∞: absolute cumulative amount of drug released at infinite time

K: constant incorporating structural and geometric characteristics of the device.

n: release exponent (indicative of the mechanism of drug release)

It is clear from equation 4 that when the exponent n takes a value of 1.0, the drug release rate is not linked to time. This case corresponds to zero-order release kinetics. For slabs, the mechanism that creates the zero-order release is known among polymer scientists as case-II transport. Here the relaxation process of the macromolecules occurring upon water imbibition into the system is the rate-controlling step. Water acts as a plasticizer and decreases the glass transition temperature of the polymer. Once the T equals the temperature of the system, the polymer chains undergo the transfer from the glassy to the rubbery state, with increasing mobility of the macromolecules and volume expansion. [16]

Thus, equation 4 has two distinct physical realistic meanings in the two special cases of n=0.5 (indicating diffusion-controlled drug release) and n=1.0 (indicating swelling-controlled drug release). Values of n between 0.5 and 1.0 can be regarded as an indicator for the superposition of both phenomena (anomalous transport). It has to be kept in mind that the two extreme values for the exponent n, 0.5 and 1.0, are only valid for slab geometry. [16]

Peppas and Sahlin model:

The equation developed by Peppas and Sahlin is the following one:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m}$$

Equation 5 Peppas and Sahlin equation [16]

K1, k2, m: constants

The first term on the right side of the equation 4 represents the Fickian diffusional contribution, F, whereas the other term of the right side represents the case-II relaxational contribution, R. [16] The ratio of both contributions can be calculated as follows:

$$\frac{R}{F} = \frac{k_2 t^m}{k_1}$$

Equation 6 Simplified Peppas and Sahlin equation [16]

This three models are the most commonly used in the modelling of drug release mechanisms due to their simplicity and comprehension. [16]

3. RESEARCH APPROACH

In this part, everything involved with the procedural part will be explain, including materials used, experimental methods and technics applied during the project.

3.1. Materials

3.1.1. Polymers and active agents

Initially, the project was willing to be carried out with an aqueous solution of a therapeutic mushroom, commonly used in Eastern countries, such as China or Malaysia, but due to the extremely late delivery of it from the associated company this aqueous solution was replaced by caffeine.

- Polymer: the polymer used in this project, as is mentioned before, is a high molecular weight chitosan. A high molecular weight chitosan is chosen in order to increase the solubility of it on DCM (dichloromethane) due to chitosan has a low solubility on organic and inorganic solvents. The chitosan used is 99% deacetylated , thus a 99% pure.

- Active agent: The active agent encapsulated is caffeine, in a 99% purity.

3.1.2. Surfactants and solvents

In this project two different surfactants are used and compared in terms of efficiency of microencapsulation of the active agent.

The two surfactants used are PVA (poly vinyl alcohol) and TWEEN 20 (or polysorbate 20). The surfactants are used in order to form the initial micelles that will become the microcapsules.

The PVA used is originally in solid form, so we first have to make a solution with water, as well as TWEEN 20, but tween is in liquid form instead.

3.1.3. Laboratory material

Concerning the material used from the laboratory, the most used materials during the experimental part were, beakers, balances, volumetric flasks, test tubes, dropper pipet, pipets, stirring rods, graduated cylinder, spatula, wash bottle with distilled water.

3.1.4. Textile substrates

The two substrates used and compared in the drug delivery are cotton and PES (polyester), since both are ones of the most commonly substrates used.

During the drug delivery, the both tissues are compared, analyzing the concentration of active agent released in a serum solution along time.

3.2. Equipment used

Since this is a basically an experimental project, many equipment were used during it.

Firstly, for the microemulsions made in the encapsulation process, an ultra turrax, a dispersing instrument that reaches 24.000 RPM, that allows the needed microemulsions, for the later microcapsules.

For the analysis of the efficiency of the encapsulation process measured by absorbances, the UV-visible spectrometry technic was used with the SHIMADZU UV2401PC UV-vis and the UVProve 2.43 software.

For the analysis of the shape and distribution of the microcapsules, an optic microscope was used. The model used is……

Also, we used a centrifuge to separate the liquid phase from the microcapsules and the remaining solids, in order to use the liquid for the efficiency analysis.

Finally,

3.3. Experimental methods and technics

All the methods and technics used in the project will be explained in this part.

3.3.1. Preparation of microcapsules

All the microcapsules were done by a double emulsion w/o/w and ending with the solvent evaporation method.

Starting by solving the polymer, chitosan in this project, with DCM (dichloromethane) at low temperature to increase solubility. Due to the bad solubility of chitosan, a mechanical agitation was needed (IKA T25) for a specific time.

Simultaneously, the active compound, caffeine, is solved in water in a magnetic stirrer and then added to the polymer emulsion, to form the first simple emulsion w1/o (using Ultra turrax T25).

Then, this simple emulsion w1/o is added to the continuous phase, that consists on PVA solved in water 2% w/w, and emulsified for several minutes to obtain the double emulsion w1/o/w2.

Lastly, the mixture was maintained under constant agitation with a magnetic stirrer until all the solvent is evaporated and, in consequence, all the microcapsules formed

3.3.2. Characterization of microcapsules

For the characterization of the microcapsules formed, several tests were done to determine, the efficiency of the encapsulation, the efficiency of the drug release, form and size of the microcapsules. The tests are the following ones: Encapsulation efficiency (via UV-Spectrophotometer), particle size distribution, optical microscope and TGA (thermogravimetric analysis) .

3.3.2.1. Encapsulation efficiency

The encapsulation efficiency of the microcapsules was measured indirectly in the liquid phase of the microcapsules mixture with the UV/vis spectrophotometer. An important previous step, is to centrifugate the solution/mixture of the liquid phase in order to minimize the interferences of remaining solids. The ratio of drug encapsulation is calculated by the following equation:

$$EE(\%) = 100 - (\frac{Cf}{Ci} * 100)$$

Equation 7 Efficency equation

Where Cf is the concentration measured in the liquid phase, and Ci is the initial concentration of drug before the microencapsulation process.

Thus, it evaluates the difference of concentration of the drug before and after the microencapsulation process.

3.3.2.2. Optical microscope

The optical microscope is used in order to have a close view of the shape and size of the microcapsules obtained. To do this test, some drops of the microcapsules solutions are deposited on microscope slide and then some time is needed to let the sample dry

Once the sample is dried it is analyzed with the microscope and thanks to the software that is attached to it, we can measure the size of some microcapsules.

3.3.2.3. Particle size distribution and zeta potential

Particle size distribution is a characterization technic that analyzes the size of nanoparticles and the molecular size form less than one nanometer to some micras with DLS dynamic light technology. [17]

The particle size distribution of microcapsules was done at Malvern Nanosizer (Nano-ZS Series). The samples of microcapsules were introduced in the zeta cells and the results were reported as an intensity size distribution.

Figure 9 Zeta sizer nano zs [18]

Zeta potential is a scientific term for electrokinetic potential in colloidal systems. This term expresses the potential difference between the dispersion medium and the stationary layer of fluid attached to the dispersed particle. [19]

3.3.3. Impregnation and Drug release

The last part of the experimental procedure consists in adding the microcapsules to a certain tissue, and then analyzing the drug delivery of the system in a serum solution.

Firstly, some pieces of the tissues are made and weight, in order to estimate the microcapsules adhered to the tissue after the impregnation.

After the weight of the tissue is taken, the impregnation of the microcapsules to the tissue is made. In this project, a rudimentary process was done that consisted in applying on the

tissue several drops (3-4) of the microcapsules solution with a droplet, and then the impregnated tissue is left in a evaporator for approximately 2 hours.

Once the tissue is dried, only the microcapsules adhered remains on the substrate. Therefore, the tissue can be weight and the difference between the weights of before and after impregnation, gives us the information of the microcapsules adhered.

Subsequently, the tissue is left inside an Erlenmeyer flask with physiological serum at 37ºC with a thermostated water bath (in order to simulate the human skin/body conditions) and several samples are taken in certain periods of time.

This samples are analyzed in the UV-spectrophotometer to evaluate the amount and the speed of release of the microencapsulated drug during the chosen period of time.

This, allows to determine the best compatible tissue for the different microcapsules obtained, and see how the drug release works in every tissue.

4. EXPERIMENTAL PROCEDURE

4.1. Preparation of microcapsules and characterization

4.1.1. Preparation of microcapsules

The preparation of the caffeine microcapsules were done under the solvent evaporation method with a double emulsion w1/o/w2. In order to compare the influence of the components, some variables were changed resulting in different microcapsules.

The changes of components in the microencapsulation process were the following ones:

- Chitosan as the coating polymer, PVA as the surfactant.
- Chitosan as the coating polymer, Tween 20 as the surfactant
- Chitosan as the coating polymer, Tween 20 as the surfactant, and tannic acid as cross-linking agent.

The type of materials and amounts used in the process and the experimental conditions and procedures are shown in the following tables [11]:

4.1.1.1. Chitosan with PVA

The encapsulation with PVA was previously tested with DCE instead of DCM, since no DCM was available at the beginning of the project, but nevertheless, in comparison the encapsulation was better with DCM.

The process followed was the solvent evaporation method with a double emulsion w1/o/w2

Table 4 Materials and amounts

Polymer	CHITOSAN	250 mg
Surfactant	PVA (Poly vinyl alcohol)	3,06 g
Active compound	CAFFEINE	83,2 mg
Polymer solvent (o)	DCM (Dichloromethane)	10 mL
Surfactant solvent (w2)	Distilled water	150 mL
Active compound solvent (w1)	Distilled water	10 mL

The experimental conditions for this essay are the following ones.

Table 5 Experimental conditions

Solutions	T (ºC)	Stirrer	Speed (RPM)	Stirring time
Active compound	Room	Magnetic	700	15 min
Polymer	4	Ultra-turrax T25	3.000-5.000	10 min
Surfactant	Room	Magnetic	700	2 h
W1/o emulsion	4	Ultra-turrax T25	16.000	15 min
W1/o/w2 emulsion	4	Ultra-turrax T25	20.000	10 min
Solvent evaporation	Room	Magnetic	400	8 h

4.1.1.2. Chitosan with Tween 20

The encapsulation with Tween 20 was done under the solvent evaporation method with a double emulsion w1/o/w2. The amount of Tween 20 used is due a 1:1 molar ratio with the active compound.

Table 6 Materials and amounts

Polymer	CHITOSAN	250 mg
Surfactant	Tween 20 (polysorbate 20)	0,225 g
Active compound	CAFFEINE	83,2 mg
Polymer solvent (o)	DCM (Dichloromethane)	10 mL
Surfactant solvent (w2)	Distilled water	150 mL
Active compound solvent (w1)	Distilled water	10 mL

The experimental conditions for this essay are the following ones.

Table 7 Experimental conditions

Solutions	T (ºC)	Stirrer	Speed (RPM)	Stirring time
Active compound	Room	Magnetic	700	15 min
Polymer	4	Ultra-turrax T25	3.000-5.000	10 min
Surfactant	Room	Magnetic	700	2 h
W1/o emulsion	4	Ultra-turrax T25	16.000	15 min
W1/o/w2 emulsion	4	Ultra-turrax T25	20.000	10 min
Solvent evaporation	Room	Magnetic	400	8 h

4.1.1.3. Chitosan with tween 20 and Tannic acid

This encapsulation process is exactly the same as the previous one with Tween 20, but with the cross-linking agent, Tannic acid.

During the addition/dosage of the tannic acid solution, a lot of care must be taken in order to not saturate the solution, otherwise the microcapsules will conglomerate and the microcapsules will become unusable and impossible to characterize.

Table 8 Materials and amounts

Polymer	CHITOSAN	250 mg
Surfactant	Tween 20 (polysorbate 20)	0,225 g
Active compound	CAFFEINE	83,2 mg
Polymer solvent (o)	DCM (Dichloromethane)	10 mL
Surfactant solvent (w2)	Distilled water	150 mL
Active compound solvent (w1)	Distilled water	10 mL
Cross-linking agent	Tannic acid	0,35 g
Cross-linking solvent	Distilled water	50 mL

Table 9 Experimental conditions

Solutions	T (ºC)	Stirrer	Speed (RPM)	Stirring time
Active compound	Room	Magnetic	700	15 min
Polymer	4	Ultra-turrax T25	3.000-5.000	10 min
Surfactant	Room	Magnetic	700	2 h
W1/o emulsion	4	Ultra-turrax T25	16.000	15 min
W1/o/w2 emulsion	4	Ultra-turrax T25	20.000	10 min
Solvent evaporation	Room	Magnetic	400	8 h
Cross-linking solvent	Room	Magnetic	400	10 min

4.1.2. Characterization of microcapsules

The conditions of each analysis process corresponding to the characterization are shown in each part, and were the same for all type of microcapsules.

4.1.2.1. Encapsulation efficiency

Encapsulation efficiency was done in order to analyze the amount of active compound entrapped during the microencapsulation process. Two steps are needed for the encapsulation efficiency. First one to centrifugate the samples, and then perform the Spectrophotometry in the UV/Vis Spectrophotometer.

The experimental conditions for the encapsulation process are the following ones.

Table 10 Centrifugation conditions

CENTRIFUGATION RATE (rpm)	1.000
CENTRIFUGATION TIME (min)	10

The UV/Vis spectrophotometer conditions are specified in the table below.

Table 11 UV/Vis spectrophotometer conditions

Parameters	PVA	Tween 20	Tween 20 + tannic acid
Wavelength (nm)	273	273	273
Cell	Quartz	Quartz	Quartz
Lightpath (mm)	10	10	10

The encapsulation efficiency of the three different microencapsulation essays are shown in the next table, where the maximum encapsulation efficiency was reached with the PVA encapsulation, and the lower encapsulation efficiency was obtained with the Tween 20 + Tannic acid encapsulation.

Table 12 Encapsulation efficiencies

Sample	Encapsulation Efficiency (%)
Chitosan with PVA	45
Chitosan with Tween 20	43
Chitosan with Tween 20 + Tannic acid	38

The encapsulation efficiencies seem low, but since there are no studies on microencapsulation of soluble drugs with chitosan, we cannot compare whether the results are meaningful or if a higher values of encapsulation efficiency should be reached.

4.1.2.2. Optical microscope

The samples were analyzed under the optical microscope in order to have a close view of the microcapsules shape and a first approach of the size of them.

The following images were taken by the microscope software. Low concentration of microcapsules are seen in the images because a little volume of microcapsules volumes were taken in order to have a clearer view of the microcapsules.

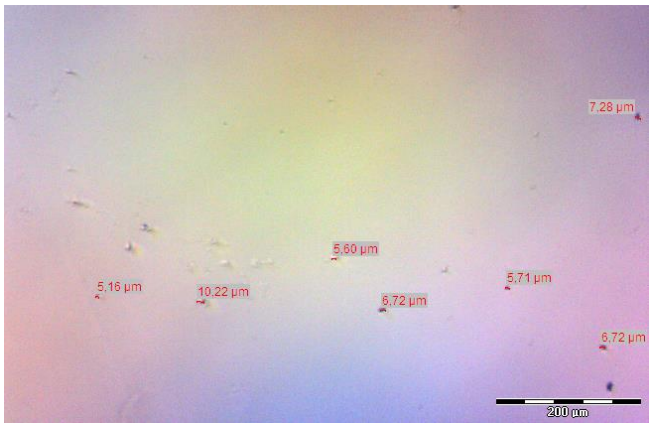


Figure 10 Microscope digital image from Chitosan with PVA microcapsules

We can see that majority of the microcapsules observed have a spherical or semi-spherical shape, although some of the microcapsules have an oval shape.

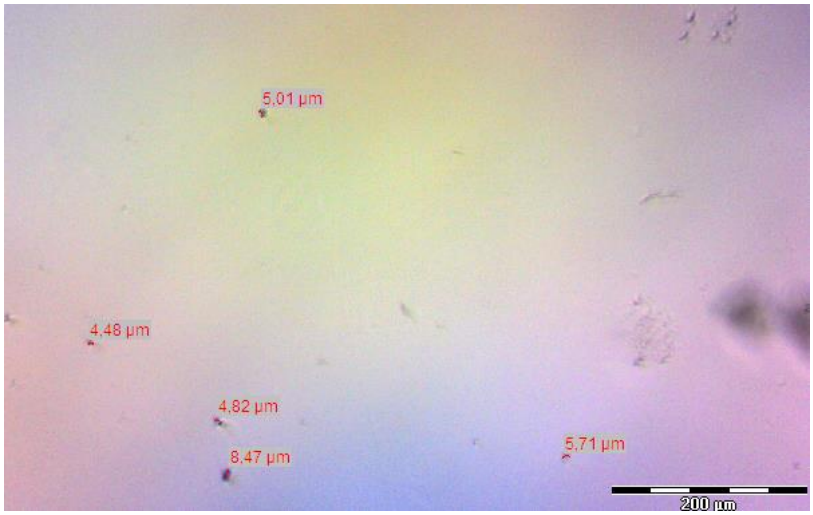


Figure 11 Microscope digital image from Chitosan with Tween 20 microcapsules

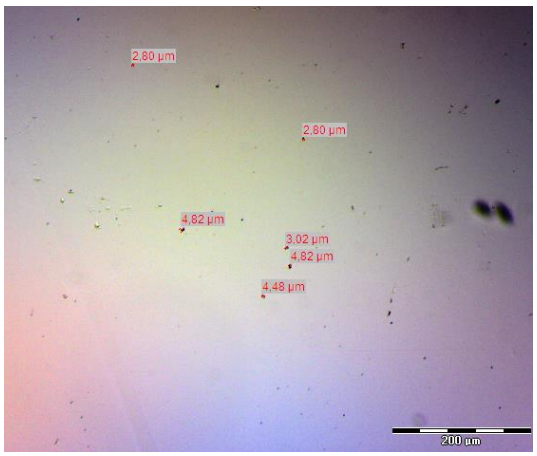


Figure 12 Microscope digital image from Chitosan with Tween 20 and Tannic acid microcapsules

4.1.2.3. Particle size distribution and zeta potential

The particle size distribution and zeta potential were done in a zeta sizer Malvern, the experimental conditions are described below.

Table 13 Zeta sizer conditions

Dispersant	Water
Cell (Size distribution)	DTS 0012 – Disposable sizing cuvette
Cell (Zeta potential)	DTS 1060 – Green disposable zeta cell
T (ºC)	25

The particle size and zeta potential of each encapsulation test are shown in the following figures.

- Chitosan with PVA microcapsules:

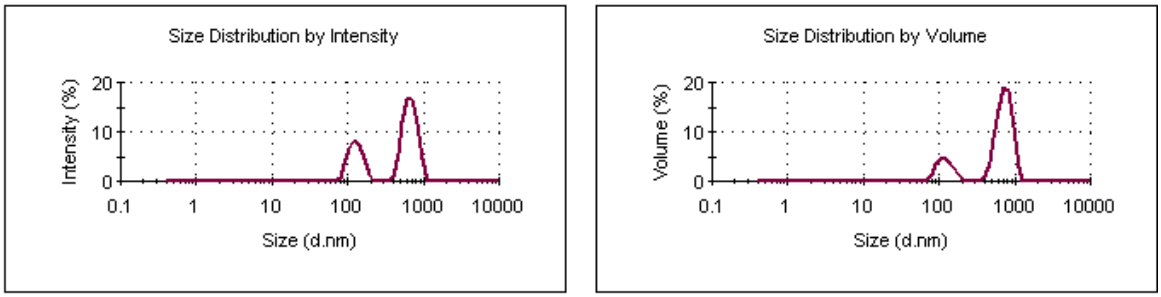


Figure 13 Size distribution by intensity and by volume of Chitosan with PVA microcapsules.

The figure above shows two peaks in both size distribution analysis in the chitosan with PVA microcapsules. One peak in 128 nm with a 32% by intensity and 20,4% by volume, and the other peak in 666 nm with a 68% by intensity and 79,6% by volume.

The average particle diameter is 666 nm, meaning that our particles are smaller than 1 micrometers. That shows, usually that there is a formation of different kind of aggregates . One of them with major proportion of PVA, due to the previous existence of nucleous of aggregation.

The polydispersity value is 0,689 which means the majority of microcapsules are not the same size.

The zeta potential of the Chitosan with PVA microcapsules are shown in the next figure.

		Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV): -3,32	Peak 1:	-3,32	100,0	4,52
Zeta Deviation (mV): 4,52	Peak 2:	0,00	0,0	0,00
Conductivity (mS/cm): 0,262	Peak 3:	0,00	0,0	0,00

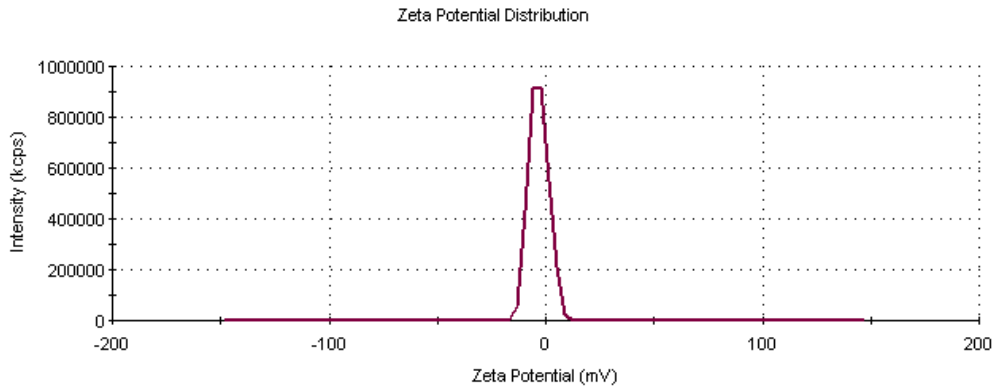


Figure 14 Zeta potential of Chitosan with PVA microcapsules

The figure 11 shows us the zeta potential of the sample, which has a peak value of -3,32 Mv.

Lightly negative, means some colloids are formed, obviously they must be microcapsules. Zeta potential in systems like these, represents the most external layer of aggregation. When the value is so little, means that there is poor stability on the system formed.

- Chitosan with Tween 20 microcapsules:

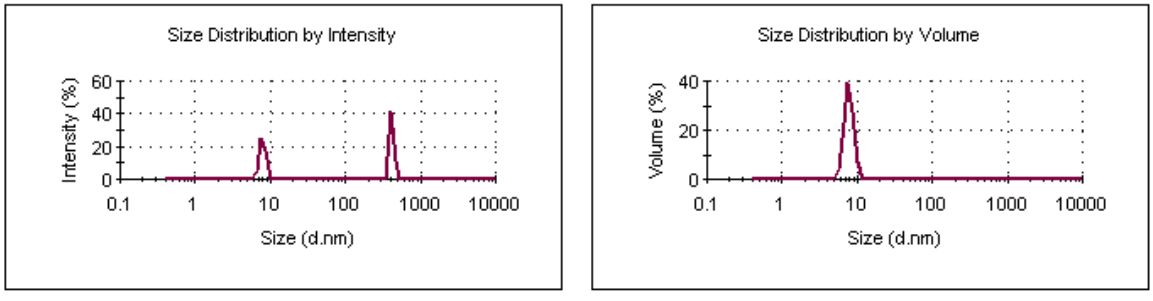


Figure 15 Size distribution by intensity and by volume of Chitosan with Tween 20 microcapsules.

In the figure 12 it is seen that two peaks appear in size distribution by intensity and only one by volume. Since Polydispersity is 1, that means that the majority of the microcapsules have a similar size, we will follow the size distribution by volume graphic.

This graphic shows a peak on 7,88 nm size with a 100% percentage.

As in the former case, there are two different structures involved into the process. As well as with PVA, there has been two colloidal species formed. One of them, very little, and the other one, reaches a size very similar that the one in which formation PVA, was used.

Effect of Surfactant, gives better distribution to the lower range of diameters, but it is still not enough to influence the second size of aggregates formed.

		Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV): 0,421	Peak 1:	0,421	100,0	5,05
Zeta Deviation (mV): 5,05	Peak 2:	0,00	0,0	0,00
Conductivity (mS/cm): 0,0730	Peak 3:	0,00	0,0	0,00

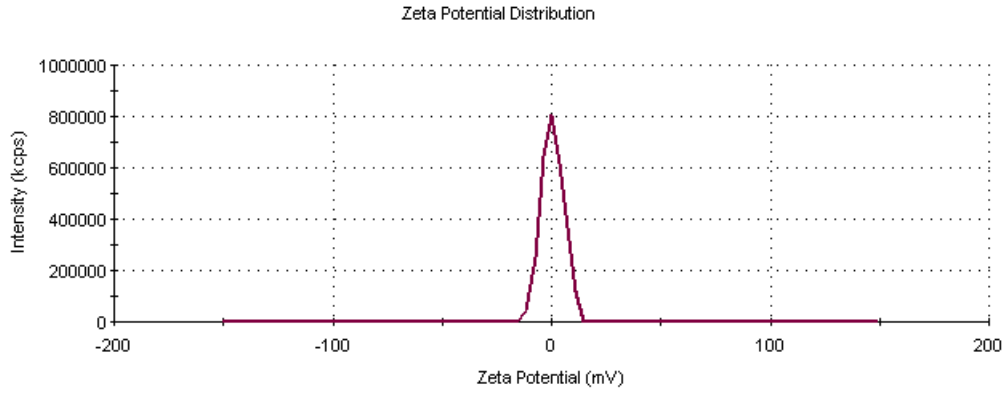


Figure 16 Zeta potential of chitosan with tween 20 microcapsules

The figure indicates a peak of zeta potential of 0,421 Mv from the sample

- Chitosan with Tween 20 and Tannic acid:

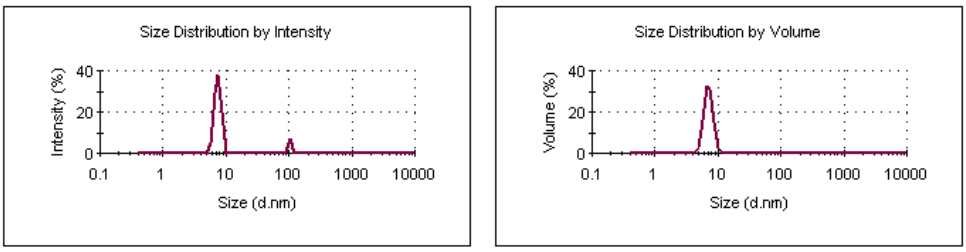


Figure 17 Size distribution by intensity and by volume of Chitosan with Tween 20 and Tannic acid microcapsules

Figure 14 shows clearly that the majority of the microcapsules are distributed in one particle size with a value of 7,34 nm. And with a polydispersity of 1, we can confirm the statement that the majority of the microcapsules have a similar size.

Here is the join effect of surfactant and a low molecular weight polymer when mixed together with Chitosan. The chemical similarity between last one and tannic acid, allows the system to be better organized. The increase in the lower range of size, allows us to consider that the final microcapsules obtained, are nearly the diameter of nano-capsules. Stability of the hybrid system formed will be better understood when TGA would be applied to these samples.

The zeta potential of the sample is represented in the next figure.

		Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV): 6,44	**Peak 1:**	2,39	90,4	7,57
Zeta Deviation (mV): 13,5	**Peak 2:**	30,5	6,7	2,74
Conductivity (mS/cm): 0,0662	**Peak 3:**	55,6	2,9	3,92

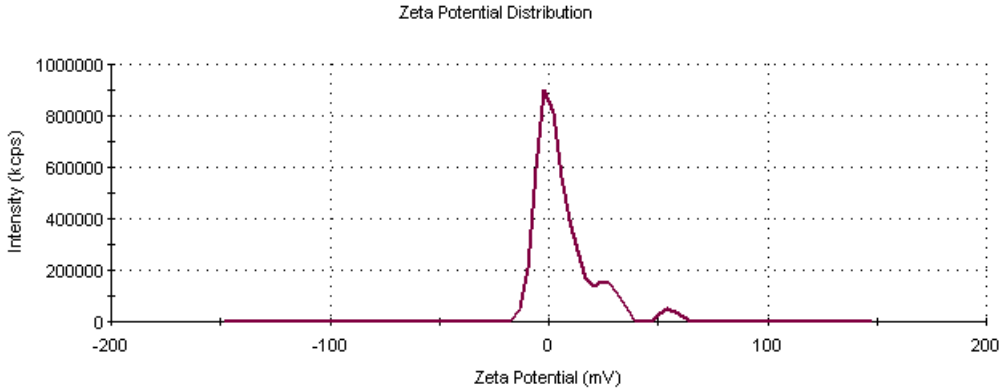


Figure 18 Zeta potential of chitosan with tween 20 with Tannic acid microcapsules

As in the other zeta potential graphics only one peak is represented, with a peak value of 6,44 Mv..

Zeta potential increases, what means that the colloids formed are much more stable than before. Clearly, not all the microcapsules formed are stable enough, but probably, the more reduced diameter would be the responsible of the positive part of the zeta potential.

4.2. Analysis of Drug delivery

4.2.1. Impregnation

The first part of the drug delivery is the weight of microcapsules attached to the tissue, that is calculated with a simple subtraction of the tissue weight before and after the impregnation of the microcapsules. The amount of microcapsules medium applied to the tissue is 5 ml. The results of the impregnation are shown below.

- Chitosan with PVA microcapsules

Table 14 Impregnation results chitosan with PVA microcapsules

Tissue	Initial weight (g)	Final weight (g)	% over weight
Cotton	0,417	0,430	3,11
Polyester	0,412	0,414	0,5

As we can see in the table above, it seems that cotton has a better affinity to the microcapsules than polyester, in which the microcapsules attached to the fabric are really low.

- Chitosan with Tween 20 microcapsules

Table 15 Impregnation results chitosan with Tween 20 microcapsules

Tissue	Initial weight (g)	Final weight (g)	% over weight
Cotton	0,488	0,497	1,84
Polyester	0,493	0,498	1,01

The results in the table 15 demonstrate that the impregnation with this sample are lower in cotton, but a bit higher in polyester.

- Chitosan with Tween 20 and Tannic acid microcapsules

Table 16 Impregnation results chitosan with PVA and Tannic acid microcapsules

Tissue	Initial weight (g)	Final weight (g)	% over weight
Cotton	0,430	0,439	2,01
Polyester	0,437	0,439	0,45

In the table above it is shown similar results as in the table 14, the sample with chitosan and PVA, but with a lower impregnation in cotton fabric.

4.2.1.1. Results

As we can see in the tables 14, 15, and 16 the impregnation on the fabric are in general really low. Also, the impregnation on cotton are higher than in polyester in all the samples tested.

One of the most important characteristic parameters controlling the affinity of the fabrics with other components is the zeta potential, which plays an important role in the electrical characterization of the fabrics in wet processing. [11]

The affinity between fabric and microcapsules are directly matched with zeta potential. If the zeta potential of the fabrics are similar to the microcapsules, then a good affinity will be ensured and vice versa.[20]

Table 17 Zeta potential of fabrics at pH 10 [2021]

Tissue	Zeta potential (mv)
Cotton	-24,5
Polyester	-60

In the table above is shown the zeta potential of the cotton and polyester fabrics at pH 10. Is clear that the zeta potentials of the fabrics are much higher than the zeta potential of the microcapsules, therefore this low impregnation results are the ones expected.

Tissue	Zeta potential (mv)
Chitosan with PVA	-3,32
Chitosan with Tween 20	0,421
Chitosan with Tween 20 and Tannic acid	2,39

As long as the chitosan with PVA microcapsules are the ones with the higher zeta potential values, we can say that it is expected that this sample obtained the higher impregnation on the fabrics.

4.2.2. Drug delivery essay

Drug delivery essay consisted on submerging the impregned fabrics into a thermostated vessel inside an Erlenmeyer filled with Physiological serum at 37ºC.

The experimental conditions of the drug delivery essay are shown below, and are the same for all the samples.

Table 18 Drug delivery essay conditions

Weight Sample (g)	0,4 – 0,5
Volume of medium (mL)	60
Medium	Physiological serum
T (ºC)	37

Once the impregnation is done, the drug delivery essay can be started. For the essay, 1 ml of the serum will be extracted in a certain period of time; 1’ 3’ 5’ 7’ 10’ 15’ 30’ 45’ 60’ 120’.

This samples are saved in test tubes in order to be posteriorly poured in an Erlenmeyer for analyzing them in the UV/Vis spectrophotometer for measuring the amount of caffeine released to the medium.

4.2.2.1. Results

The results of the drug delivery essay will be treated following two different approaches.

Experimental results, based on theoretical mechanisms of drug release and quantitative following semi-empirical equations for drug release.

4.2.2.1.1. Experimental results

From the results in the following tables (figure 15 – 20) we can observe that the behavior of the two tissues are similar, but with some differences. Cotton tissue starts releasing a big amount of caffeine at the first minutes, once ten minutes have passed, concentration of caffeine remains stable or even decreases, following a bimodal behavior. [22].

On the other hand, Polyester also has a quick release of the caffeine at the first minutes of the drug delivery, but instead of maintaining a constant concentration or even decreasing, keeps slowly increasing the amount of caffeine released to the medium or close to a constant concentration, following a bimodal behavior as well.

This behavior could be explained by a re-absorption of the caffeine released to the medium by the cotton fabric, what would explain the decrease or the constant concentration of the bath along the time.

This re-absorption happens due to the zeta potential of the cotton, since cotton has a lower zeta potential value as caffeine has, makes it easier for caffeine to be re-absorbed by the cotton tissue.

And as polyester has a higher zeta potential, caffeine has not such an affinity with the tissue and remains in the bath.

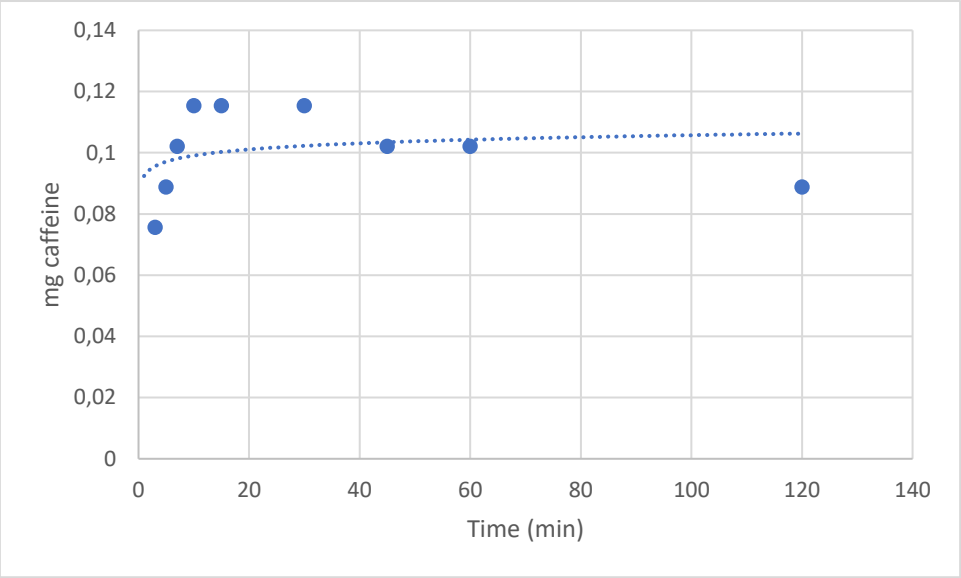


Figure 19 Kinetic release of Chitosan with PVA microcapsules with caffeine in Cotton

We can see in the figure above, that the concentration peak is found in the first ten minutes, and then the concentration starts decreasing.

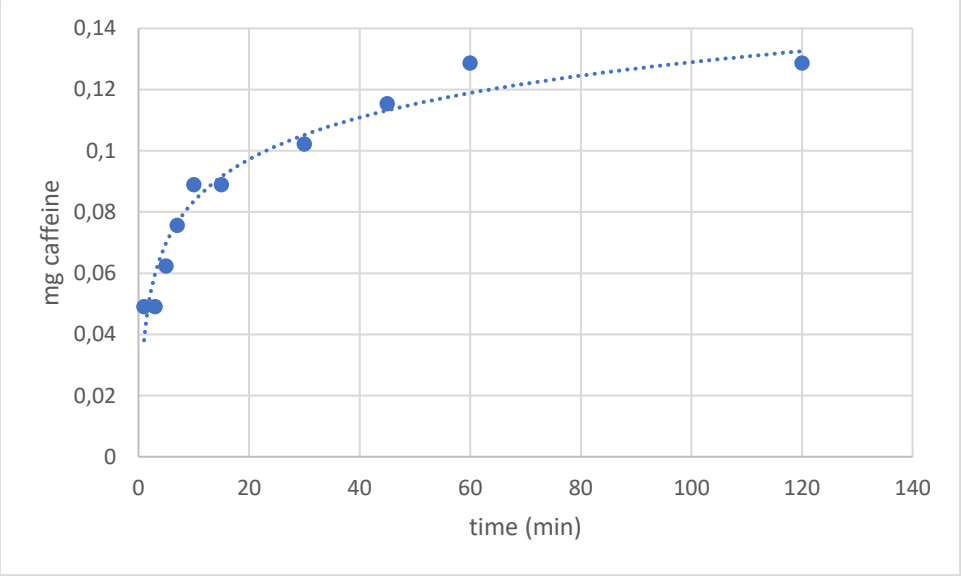


Figure 20 Kinetic release of Chitosan with PVA microcapsules with caffeine in Polyester

In figure 16 there is a clear example of what was explained before. A first part of the drug delivery where the caffeine is quickly released and afterwards a part where the concentration keeps slowly rising.

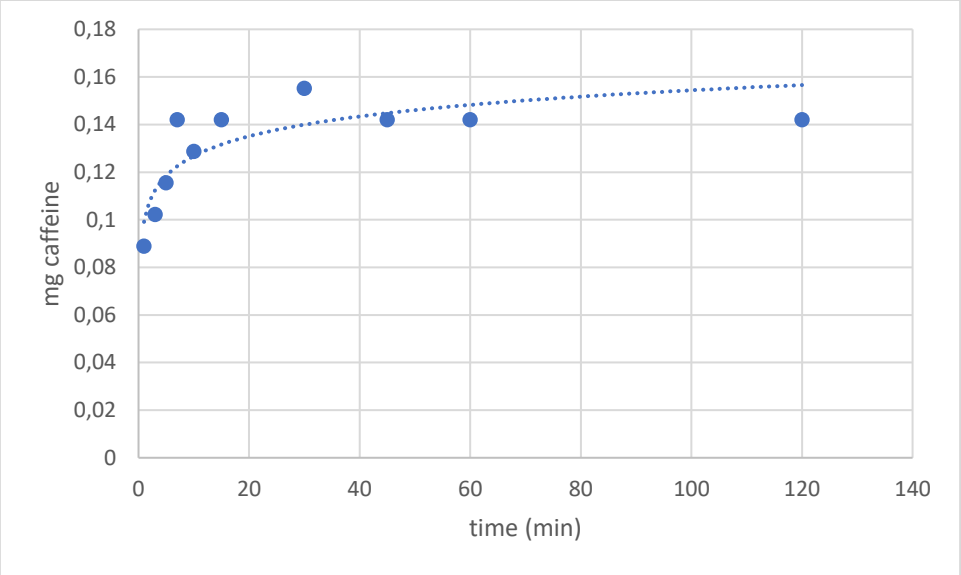


Figure 21 Kinetic release of Chitosan with Tween 20 microcapsules with caffeine in Cotton

Figure 17 follows almost exactly the same kinetic behavior as in the figure 15.

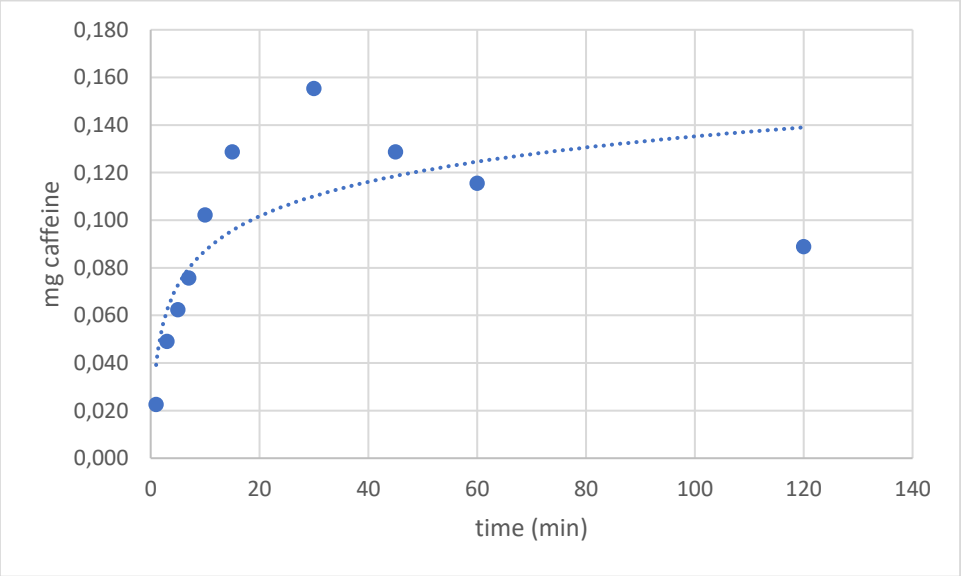


Figure 22 Kinetic release of Chitosan with Tween 20 microcapsules with caffeine in Polyester

In figure 18 we can see that the behavior is most similar to the ones with the cotton fabric, cause in the part of the drug delivery, the caffeine concentration starts to decrease. Although this could have happened because of a mistake in the measure of the concentration in the minute 30, which may be too high.

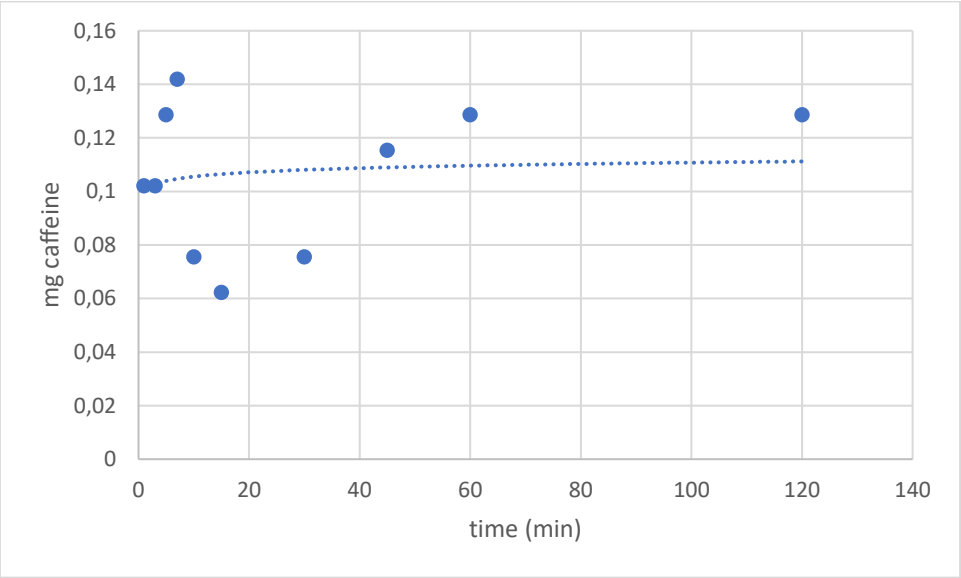


Figure 23 Kinetic release of Chitosan with Tween 20 and Tannic acid microcapsules with caffeine in Cotton

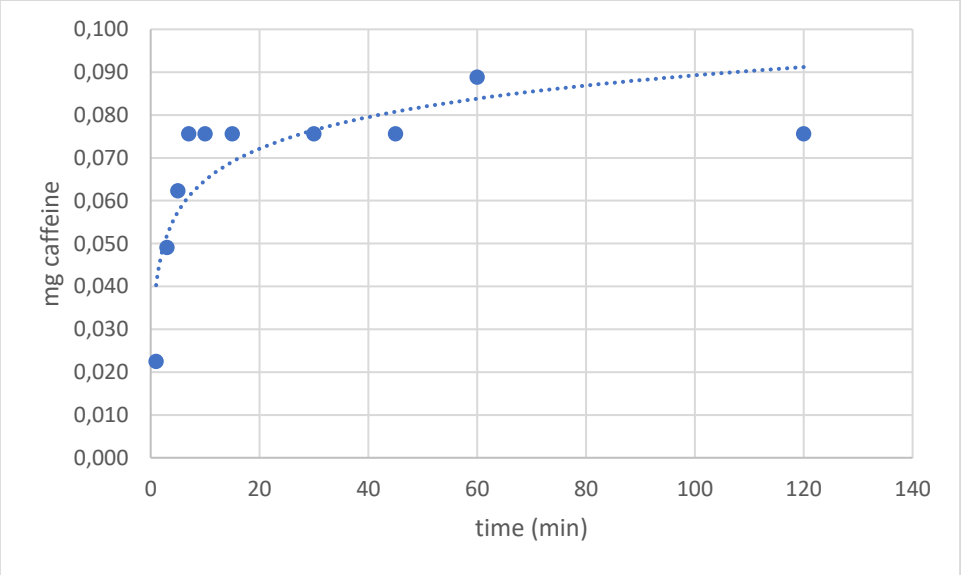


Figure 24 Kinetic release of Chitosan with Tween 20 and Tannic acid microcapsules with caffeine in Polyester

In figure 20 we can see that the behavior in this sample is almost the same as in figure 16, following the behavior described previously.

4.2.2.1.2. Power law

The results for Power Law equation for the different samples are shown in the next tables and graphics.

It has taken in considerations the two behaviors of the drug release, and will be treated different. A focus in the first step, short times, will be done.

Using the Power law equation, the value of the exponent n, indicates the type of mass transport calculated.

- Chitosan with PVA microcapsules

From equation 4. we can extract the value of the exponent n by logarithms, as shown in the following figure.

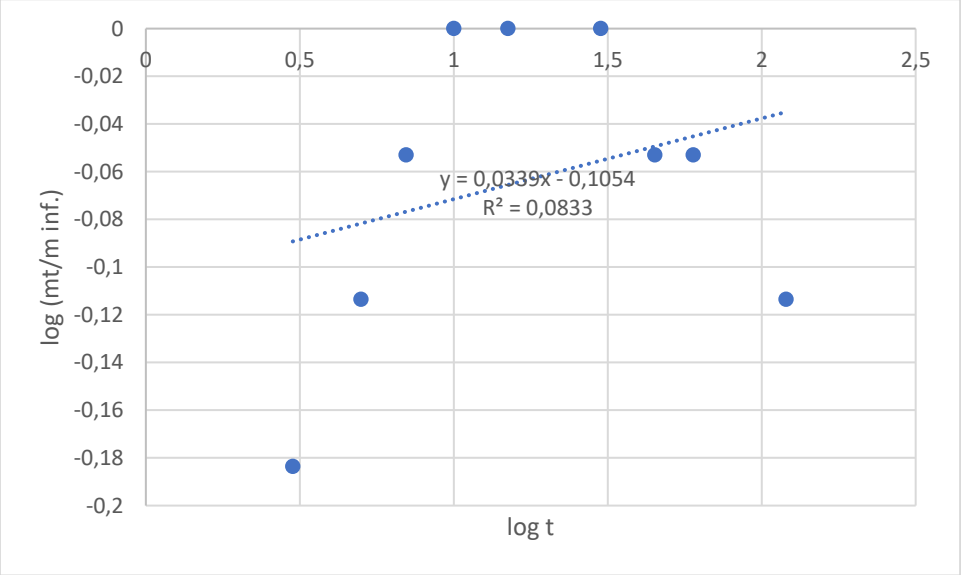


Figure 25 n value of Power law; COTTON

When log (mt/m inf.) represented vs log time, the slope of the linear regression is the value of n. in this case the n takes a value of 0,0339, being an anomalous diffusion.

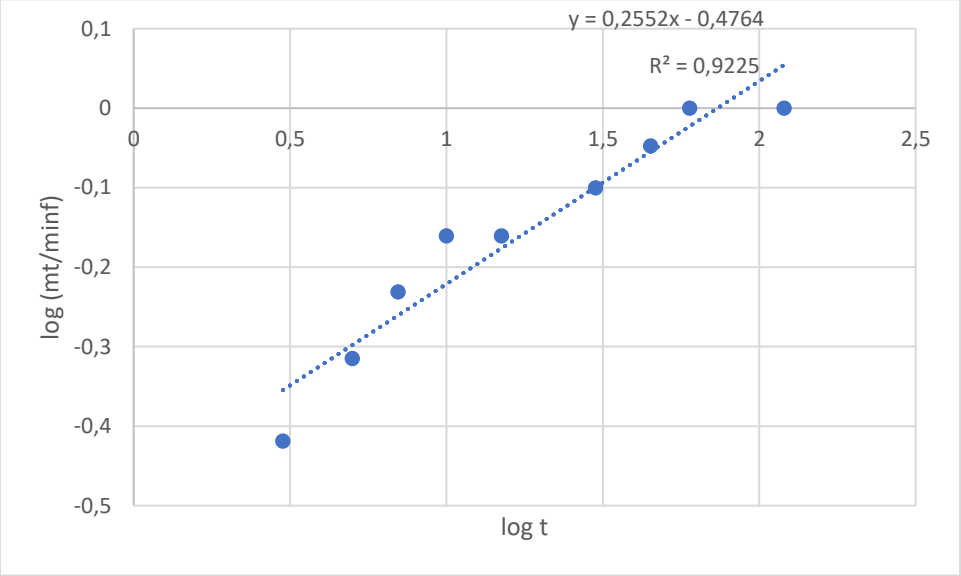


Figure 26 n value of Power law; POLYESTER

In the sample with the polyester tissue, the n has a value of 0.2552, so follows an anomalous diffusion. We can see that in polyester the n values are higher than in cotton.

Table 19 n values obtained from fitting drug release experimental data to Power Law

Fabric type	n	R^2	Drug delivery system
Cotton	0.0339	0.0833	Anomalous difussion
Polyester	0.2552	0.9225	Anomalous difussion

- Chitosan with Tween 20 microcapsules

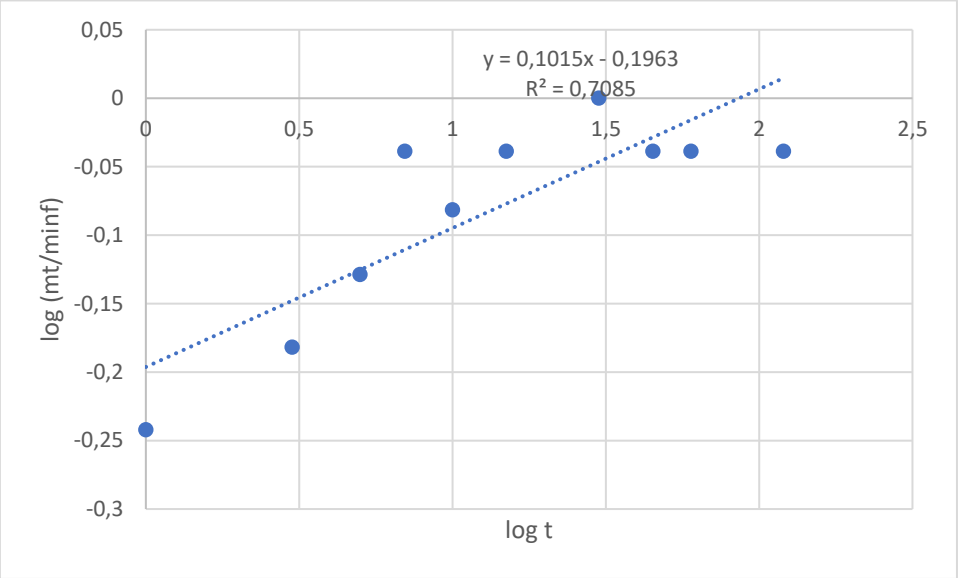


Figure 27 n value of Power law; COTTON

In this case, the n value is much higher than with the previous microcapsules sample in cotton, meaning that the chemicals interactions between tween 20 and the tissue are more favorable in the drug delivery essay than PVA.

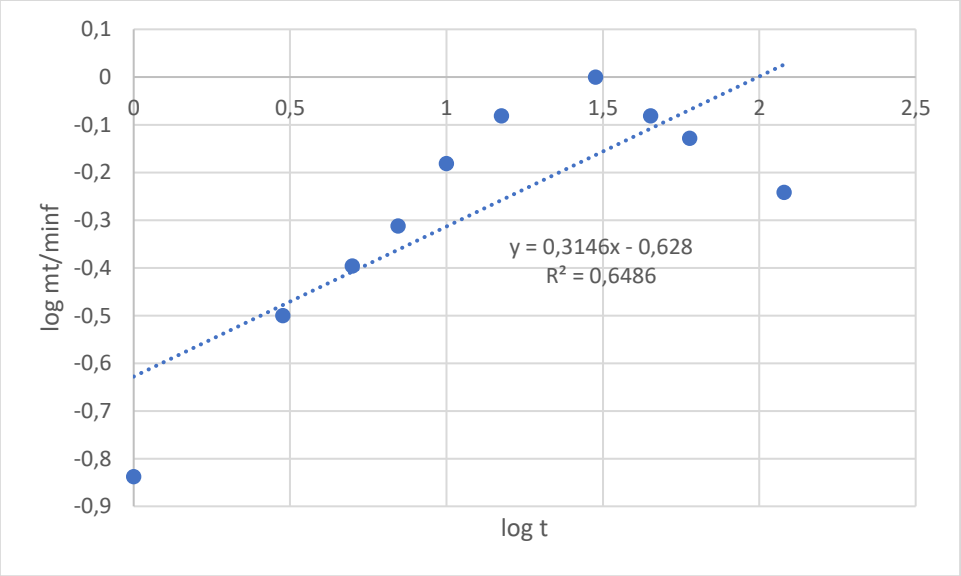


Figure 28 n value of Power law; POLYESTEr

In this microcapsules sample, as the one before, the n values in the polyester tissue are higher than in cotton. Also in figure 27, the n value is relatively close to 0.5, but lower, meaning an anomalous diffusion.

Table 20 n values obtained from fitting drug release experimental data to Power Law

Fabric type	n	R^2	Drug delivery system
Cotton	0,1015	0,7085	Anomalous difussion
Polyester	0,3146	0,6486	Anomalous difussion

- Chitosan with Tween 20 and Tannic acid

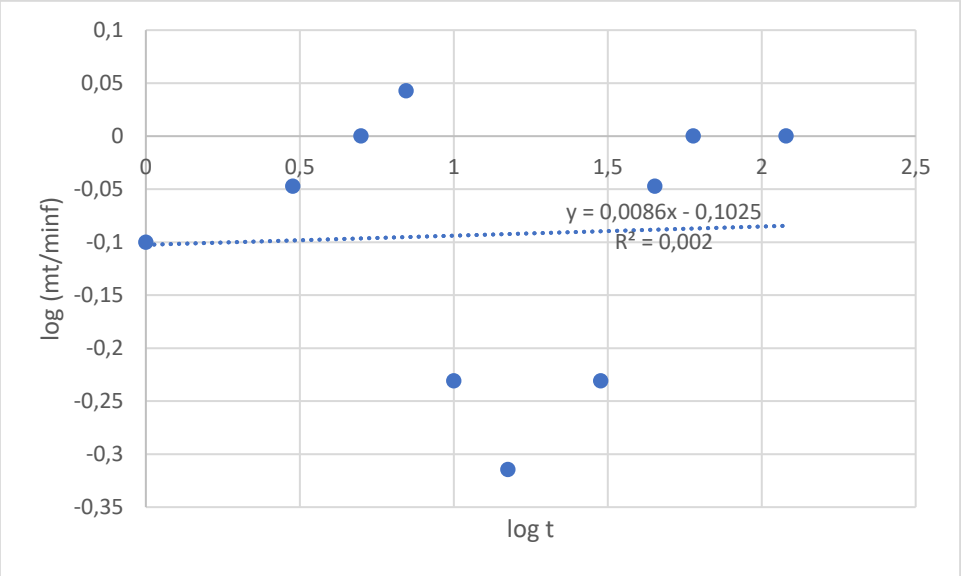


Figure 29 n value of Power law; COTTON

In this essay, both the n value and regression coefficient are really low. Therefore, this drug delivery is defined by two really different trends, and following an anomalous diffusion.

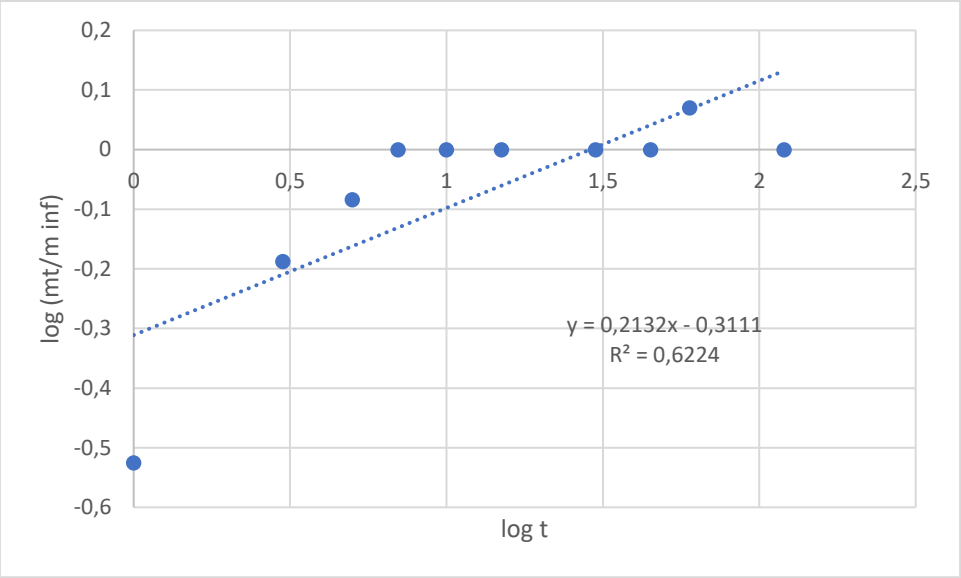


Figure 30 n value of Power law; POLYESTER

It is shown in the graphics that the regression coefficient in cotton tend to be much lower than in polyester tissues, meaning that in cotton tends to have a much more differenced bimodal behavior than in polyester, that have a similar behavior in both short and long times, as expected and explained before in the experimental results.

Table 21 n values obtained from fitting drug release experimental data to Power Law

Fabric type	n	R^2	Drug delivery system
Cotton	0,0086	0,002	Anomalous difussion
Polyester	0,2132	0,6224	Anomalous difussion

4.2.2.1.3. Higuchi model and Korsmeyer-Peppas approximation

Since the release mechanism of active compound follows a Fickian diffusion, the Korsmeyer-Peppas approximation and Higuchi model are taken.

In the Higuchi equation, equation 3., when (mt/m inf.) vs $\sqrt{t}$ is represented, the slope of the linear regression is the "K_H" value.

The K_H values of the experimental results are shown in the following tables and figures.

Once this value is obtained, the diffusion coefficient, D/δ^2 can be calculated from the Korsmeyer-Peppas approximation for planar delivery systems:

$$Kh = \frac{16\,D}{\pi \cdot \delta 2}$$

Equation 8 Korsmeyer-Peppas approximation for planar systems

- Chitosan with PVA

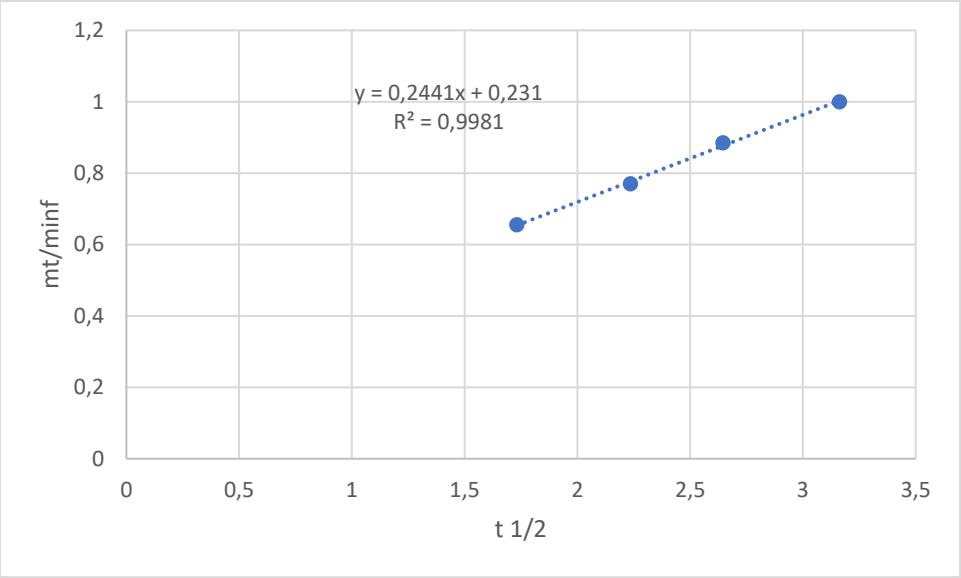


Figure 31 K value of Higuchi model COTTON

The k value of the Higuchi model is the slope of the regression line. Since the regression coefficient of the line is really close to 1, we can assume that the model fits the experimental results.

In the cotton tissue, the K value is 0,2441. Then the diffusion coefficient can be calculated.

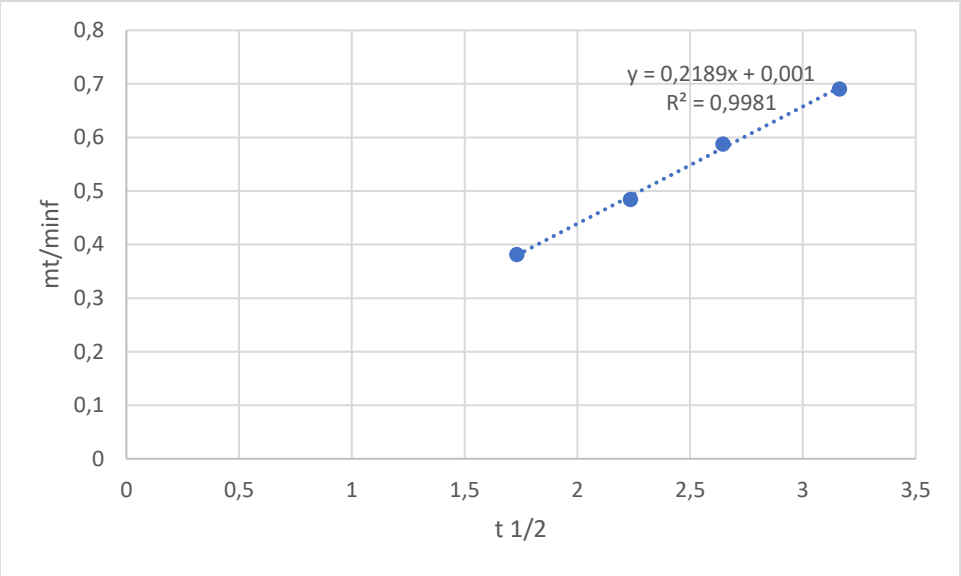


Figure 32 K value of Higuchi model POLYESTER

In the figure 9, the K value is 0,2189, in the polyester tissue, a bit lower than in cotton tissue.

Although it was said before that polyester had a more progressive release during time than cotton tissue, on short times we can see that the release is faster in cotton than in polyester in this microcapsules sample. This could be attached to the fact that higher weight of microcapsules were sticked to the tissue, so a larger concentration of caffeine could be released.

Table 22 K and D/ δ^2 values obtained from fitting drug release experimental data to Higuchi

Fabric type	Kh	D/δ^2	R^2
Cotton	0,2441	0,048	0,9981
Polyester	0,2189	0,043	0,9981

- Chitosan with Tween 20

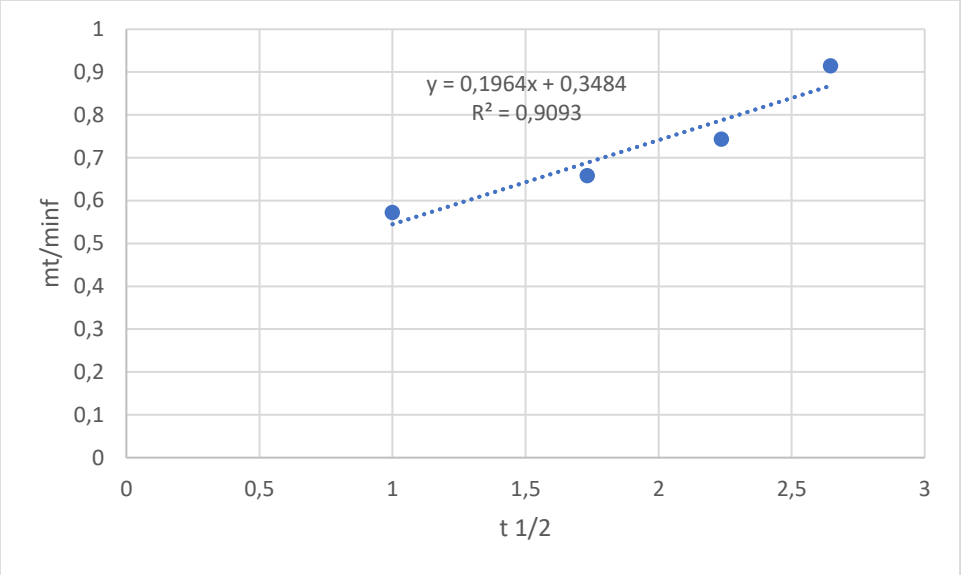


Figure 33 K value of Higuchi model COTTON

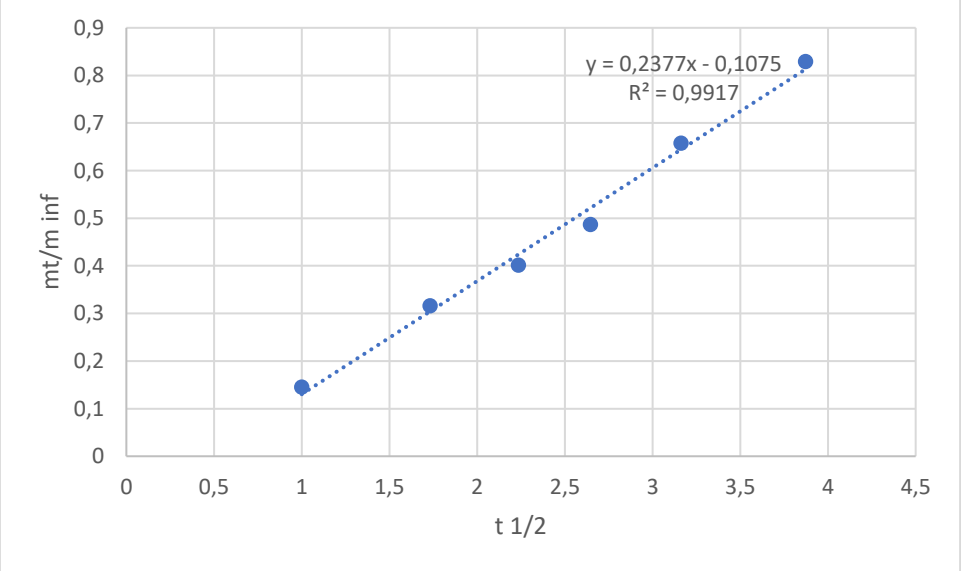


Figure 34 K value of Higuchi model POLYESTER

In this microcapsules sample we can observe that the k value, and therefore, the diffusion coefficient value is higher in polyester than in cotton, but really close one to the other.

As in the case before, this little difference could be explained because the weight attached to the tissues were more similar than in the previous case, and as far as polyester has a

faster release of the caffeine solution, made polyester had a better diffusion coefficient than cotton.

Table 23 K and D/ δ2 values obtained from fitting drug release experimental data to Higuchi

Fabric type	Kh	D/δ^2	R^2
Cotton	0,1964	0,038	0,9093
Polyester	0,2377	0,046	0,9917

- Chitosan with Tween 20 and Tannic acid

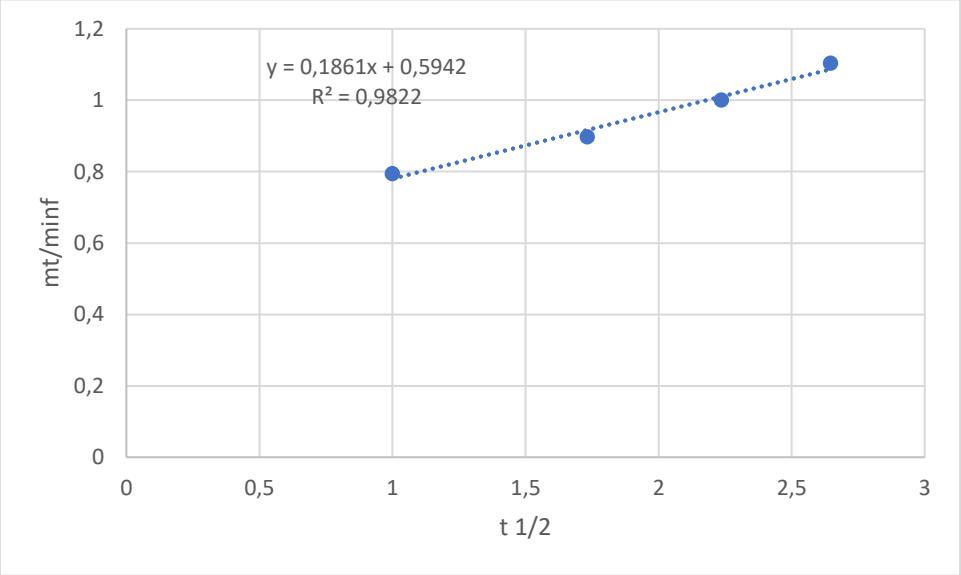


Figure 35 K value of Higuchi model COTTON

In the last sample, the graphics show that the K value is much higher in polyester than in cotton. Thus, the diffusion coefficient is higher in polyester than in cotton for this sample.

Also this reveals that the diffusion coefficient in this sample for polyester, is the higher one obtained. This could be linked to zeta potential, since this sample microcapsules have the less zeta potential value and polyester the bigger one.

Once they are in the bath system, they easily leave the tissue and start degradating0 instead of the capsules in the cotton tissue due they have a better affinity that make it more difficult for the microcapsules to leave the tissue.

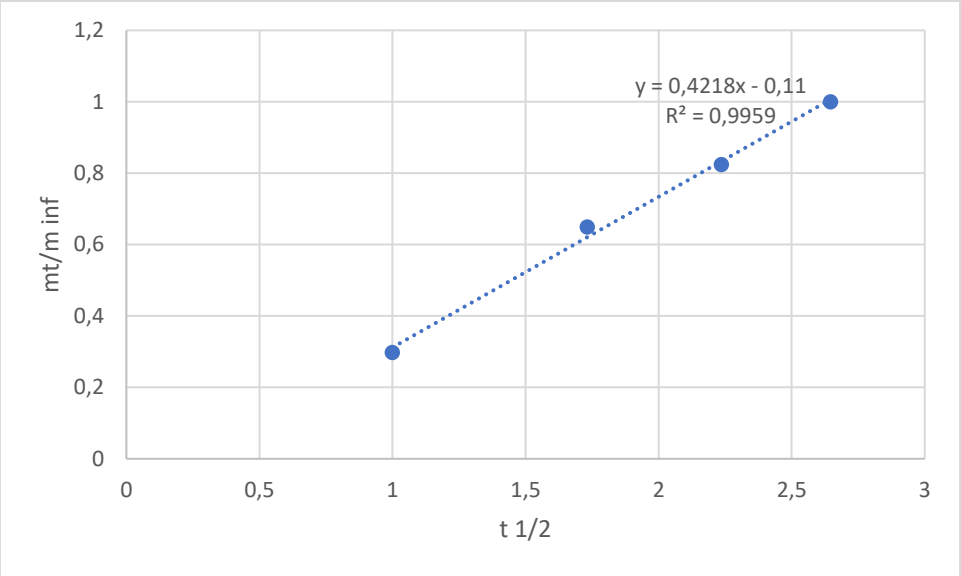


Figure 36 K value of Higuchi model POLYESTER

Table 24 K and D/ δ^2 values obtained from fitting drug release experimental data to Higuchi

Fabric type	Kh	D/δ^2	R^2
Cotton	0,1861	0,036	0,9822
Polyester	0,4218	0,083	0,9959

To conclude the drug delivery essay, we can ensure that zeta potential is an important fact to be taken into consideration, as is the most important phenomena in impregnation and has influence in drug release since rules the interaction between microcapsules and tissues.

We can see that as the zeta potential is lower, the diffusion coefficient increases, though the impregnation percentage decreases, so an equilibrium must be found in order to optimize the impregnation of microcapsules in the tissue and the diffusion coefficient.

In this samples, generally the cotton tissues release a bigger amount of caffeine to the medium but with a smaller diffusion coefficient, a choose can be made in which tissue should be used depending on the type of release needed, a fester release with less concentration will need a polyester tissue and vice versa.

5. CONCLUSIONS

This project has focused on the microencapsulation of caffeine, a soluble drug, with chitosan, the comparison of different reagents to see their effect on encapsulation efficiency, particles size, shape, affinity and impregnation to the tissues and the release in the drug delivery.

Firstly, The encapsulation efficiency of the samples are low, but since there is no feedback on the caffeine encapsulation with chitosan, we can compare the results obtained. Also, the better encapsulation efficiency was obtained in the samples with PVA, and the lower encapsulation efficiency with the tween 20 and tannic acid samples.

Nonetheless, the smaller particles were obtained by the Tween 20 with tannic acid samples thanks to tannic acid, that as a cross-linking agent wrap the molecule and compressed the particle by cross-linking chitosan and therefore reducing the particle size. Is also seen that the PVA microcapsules sample have a relatively bigger microcapsules, so we can ensure the effect of different surfactants on the particle size since the Tween 20 microcapsules had a similar particle size as the Tween 20 with Tannic acid samples. To sum up, PVA will lead to bigger microcapsules and Tween 20 to smaller ones. Adding Tannic acid will make them even smaller.

Concerning to impregnation on the tissue, it is shown in the results that, as the both tissues had a really high zeta potential, the samples with the bigger zeta potential lead to a better impregnation because the closer the zeta potential was, the better affinity between the tissue and the sample had.

Since the tissue with the lower zeta potential was cotton, this tissue lead to higher impregnation of microcapsules and therefore, polyester had lower impregnations,

Thus, the samples released different concentrations of caffeine in the medium, so concentration released can be controlled by the tissue, since the impregnation can be controlled.

In the drug delivery essay, it is clear that chitosan with caffeine microcapsules have a bimodal behavior, the first one with higher release speeds, and the second one with a lower

release of the active compound. The difference between polyester and cotton was mainly the concentration of the active compound released, due to the impregnation, and the second behavior of the drug release.

While cotton maintained an almost constant concentration of caffeine in the second behavior, polyester had an increasing concentration trend of the active compound. This is why the regression coefficients in the experimental results were much lower in cotton than in polyester. Also, cotton had a reabsorption phenomenon, that is what explains the constant concentration of caffeine in the second part of the drug release, as it reaches an equilibrium in the bath.

5.1. Future outlook

The main objective of this project is obtaining a controlled drug delivery system to release the desired drug in the right place at the right time for a desired period.

The first issue that must focus on is the encapsulation efficiency, since many factors influence the encapsulation efficiency as mentioned in the introduction part and a lot of study is needed to define the better factors for higher encapsulation efficiency in this encapsulation process.

Also, an important problem to be solved is the affinity between fabrics and microcapsules, since their zeta potentials are really different, the impregnation on the tissues are really low, and many microcapsules and tissue are not used.

Finally, I would like to recommend for future researchers the help of analysis instruments as SEM (Scanning Electron Microscopy) to have a closer view of the microcapsules, and the microcapsules on the fabric. Also a TGA (Thermogravimetric Analyzer) to see the distribution of the layers around the active compound and see their degradation with temperature.

ATTACHMENT A

BUDGET

In the Attachment A the budget of the equipment cost, material, products and service needed for the accomplishment of the project is included.

Table 25 Services budget

Budget: Services				
Service	Unity	Tariff	Nº of services	Total
UV/VIS	Hour	65,00 €	100	6.500 €
Zeta sizer	Samples	85,00 €	18	1.530 €
Optical microscope	Hour	30,00 €	15	450 €
			Total price	2.635 €

Table 26 Material budget

Budget: Material			
Material	Units	Price	Total
Lab coat	1	20 €	20 €
Graduated pipette 5 ml	5	56 €	280 €
Graduated pipette 10 ml	5	58 €	290 €
Volumetric flask 25 ml	20	9,50 €	190 €
Beaker 10 ml	3	5 €	15 €
Beaker 50 ml	2	15 €	30 €
Beaker 600 ml	1	50€	50 €
Beaker 250 ml	2	20 €	40 €
Naturflex gloves	1 box x 100	5 €	5 €
Stirring rod	3	15 €	45 €
Test tubes	40	5 €	200 €
Spatula	3	20 €	40 €
Dropper	10	2 €	20 €
Parafilm 100 X 75 mtrs	1	47,5 €	47,5 €
		Total price	1.272,5 €

Table 27 Projector budget

Budget: projector			
Projectors	Price	Hours	Total
1	15 € / h	1100	16.500 €

Table 28 Chemical reagents budget

Budget: chemical reagent			
Material	Units	Price	Total
Chitosan 500 g CAS: 9012-76-4	1	51,60 €	51,60 €
PVA 500 g CAS: 9003-20-7	1	65,34 €	65,34 €
Tween 20 1 kg CAS: 9005-64-5	1	16,07 €	16,07 €
Tannic acid 250 g CAS: 1401-55-4	1	62,90 €	62,90 €
DCM 1L CAS: 75-09-2	1	29,40 €	29,40 €
Physiological serum CAS: 7647-14-5	1	21,60 €	21,60 €
Caffeine 100 g CAS: 58-08-2	1	26,10 €	26,10 €
		Total price	273,01 €

Table 29 Total budget

Total Budget	
Services	2.635 €
Projector	16.500 €
Material	1.272,5 €
Chemical reagents	273,01 €
	20.680,51 €

ATTACHMENT B

In this Attachment B the material safety data sheet of each chemical reagent will be added.

The MSDS are all extracted from FISHER SCIENTIFIC.

https://www.fishersci.com/us/en/catalog/search/sdshome.html

ThermoFisher SCIENTIFIC

SAFETY DATA SHEET

Creation Date 22-Jun-2009 **Revision Date** 17-Jan-2018 **Revision Number** 4

1. Identification

Product Name **Sodium chloride**

Cat No. : **S271-1; S271-3; S271-10; S271-10LC; S271-5; S271-50; S271-50LC; S271-350LB; S271-500; XXS271150KG; NC1608665**

CAS-No 7647-14-5
Synonyms Halite; Common salt; Rock salt

Recommended Use Laboratory chemicals.
Uses advised against Food, drug, pesticide or biocidal product use

Details of the supplier of the safety data sheet

Company
Fisher Scientific
One Reagent Lane
Fair Lawn, NJ 07410
Tel: (201) 796-7100

Emergency Telephone Number
CHEMTREC®, Inside the USA: 800-424-9300
CHEMTREC®, Outside the USA: 001-703-527-3887

2. Hazard(s) identification

Classification
Classification under 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200)

Based on available data, the classification criteria are not met

Label Elements
None required

Hazards not otherwise classified (HNOC)
None identified

3. Composition/Information on Ingredients

Component	CAS-No	Weight %
Sodium chloride	7647-14-5	>95

4. First-aid measures

Eye Contact Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Get medical attention.

Skin Contact Wash off immediately with plenty of water for at least 15 minutes. Get medical attention immediately if symptoms occur.

Inhalation Move to fresh air. Get medical attention immediately if symptoms occur. If not breathing, give artificial respiration.

Ingestion Do not induce vomiting. Obtain medical attention.

Most important symptoms and effects No information available.

Notes to Physician Treat symptomatically

5. Fire-fighting measures

Unsuitable Extinguishing Media No information available

Flash Point No information available
Method - No information available

Autoignition Temperature
Explosion Limits
Upper No data available
Lower No data available
Sensitivity to Mechanical Impact No information available
Sensitivity to Static Discharge No information available

Specific Hazards Arising from the Chemical
Thermal decomposition can lead to release of irritating gases and vapors. Keep product and empty container away from heat and sources of ignition.

Hazardous Combustion Products
Hydrogen chloride gas Sodium oxides
Protective Equipment and Precautions for Firefighters
As in any fire, wear self-contained breathing apparatus pressure-demand, MSHA/NIOSH (approved or equivalent) and full protective gear.

NFPA

Health	Flammability	Instability	Physical hazards
1	0	1	N/A

6. Accidental release measures

Personal Precautions Ensure adequate ventilation. Use personal protective equipment. Avoid dust formation.
Environmental Precautions Should not be released into the environment. See Section 12 for additional ecological information.

Methods for Containment and Clean Up Sweep up or vacuum up spillage and collect in suitable container for disposal. Avoid dust formation.

7. Handling and storage

Handling Wear personal protective equipment. Ensure adequate ventilation. Avoid dust formation.

Storage Keep containers tightly closed in a dry, cool and well-ventilated place.

8. Exposure controls / personal protection

Exposure Guidelines This product does not contain any hazardous materials with occupational exposure limitsestablished by the region specific regulatory bodies.

Engineering Measures Ensure adequate ventilation, especially in confined areas. Ensure that eyewash stations and safety showers are close to the workstation location.

Personal Protective Equipment

Eye/face Protection Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166.

Skin and body protection Wear appropriate protective gloves and clothing to prevent skin exposure.

Respiratory Protection Follow the OSHA respirator regulations found in 29 CFR 1910.134 or European Standard EN 149. Use a NIOSH/MSHA or European Standard EN 149 approved respirator if exposure limits are exceeded or if irritation or other symptoms are experienced.

Hygiene Measures Handle in accordance with good industrial hygiene and safety practice.

9. Physical and chemical properties

Physical State	Solid
Appearance	White
Odor	Odorless
Odor Threshold	No information available
pH	5.0-8.0 @ 20°C; 5% aq.sol
Melting Point/Range	801 °C / 1473.8 °F
Boiling Point/Range	1461 °C / 2661.8 °F @ 760 mmHg
Flash Point	No information available
Evaporation Rate	Not applicable
Flammability (solid,gas)	No information available
Flammability or explosive limits	
Upper	No data available
Lower	No data available
Vapor Pressure	1 mmHg @ 865 °C
Vapor Density	Not applicable
Specific Gravity	2.165
Solubility	Partly soluble in water
Partition coefficient; n-octanol/water	No data available
Autoignition Temperature	
Decomposition Temperature	No information available
Viscosity	Not applicable
Molecular Formula	Cl Na
Molecular Weight	58.44

10. Stability and reactivity

Reactive Hazard None known, based on information available

Stability Hygroscopic.

Conditions to Avoid Incompatible products. Excess heat. Avoid dust formation. Exposure to moist air or water.

Incompatible Materials Strong oxidizing agents, Metals, Strong acids

Hazardous Decomposition Products Hydrogen chloride gas, Sodium oxides

Hazardous Polymerization Hazardous polymerization does not occur.

Hazardous Reactions None under normal processing.

11. Toxicological information

Acute Toxicity

Product Information See actual entry in RTECS for complete information.

Component Information

Component	LD50 Oral	LD50 Dermal	LC50 Inhalation
Sodium chloride	LD50 = 3 g/kg (Rat)	LD50 > 10 g/kg (Rabbit)	LC50 > 42 g/m³ (Rat) 1 h

Toxicologically Synergistic Products No information available

Delayed and immediate effects as well as chronic effects from short and long-term exposure

Irritation No information available

Sensitization No information available

Carcinogenicity The table below indicates whether each agency has listed any ingredient as a carcinogen.

Component	CAS-No	IARC	NTP	ACGIH	OSHA	Mexico
Sodium chloride	7647-14-5	Not listed	Not listed	Not listed	Not listed	Not listed

Mutagenic Effects Not mutagenic in AMES Test

Reproductive Effects No information available.

Developmental Effects No information available.

Teratogenicity No information available.

STOT - single exposure None known

STOT - repeated exposure None known

Aspiration hazard No information available

Symptoms / effects,both acute and delayed No information available

Endocrine Disruptor Information No information available

Other Adverse Effects The toxicological properties have not been fully investigated.

12. Ecological information

Ecotoxicity

Do not empty into drains. .

Component	Freshwater Algae	Freshwater Fish	Microtox	Water Flea
Sodium chloride	Not listed	Pimephals prome: LC50: 7650 mg/L/96h	Not listed	EC50: 1000 mg/L/48h

Persistence and Degradability Soluble in water Persistence is unlikely based on information available.

Bioaccumulation/ Accumulation No information available.

Mobility Will likely be mobile in the environment due to its water solubility.

13. Disposal considerations

Waste Disposal Methods Chemical waste generators must determine whether a discarded chemical is classified as a hazardous waste. Chemical waste generators must also consult local, regional, and national hazardous waste regulations to ensure complete and accurate classification.

14. Transport information

DOT Not regulated
TDG Not regulated
IATA Not regulated
IMDG/IMO Not regulated

15. Regulatory information

International Inventories

Component	TSCA	DSL	NDSL	EINECS	ELINCS	NLP	PICCS	ENCS	AICS	IECSC	KECL
Sodium chloride	X	X	-	231-598-3	-		X	X	X	X	KE-31387

Legend:
X - Listed
E - Indicates a substance that is the subject of a Section 5(e) Consent order under TSCA.
F - Indicates a substance that is the subject of a Section 5(f) Rule under TSCA.
N - Indicates a polymeric substance containing no free-radical initiator in its inventory name but is considered to cover the designated polymer made with any free-radical initiator regardless of the amount used.
P - Indicates a commenced PMN substance
R - Indicates a substance that is the subject of a Section 6 risk management rule under TSCA.
S - Indicates a substance that is identified in a proposed or final Significant New Use Rule
T - Indicates a substance that is the subject of a Section 4 test rule under TSCA.
XU - Indicates a substance exempt from reporting under the Inventory Update Rule, i.e. Partial Updating of the TSCA Inventory Data Base Production and Site Reports (40 CFR 710(B).
Y1 - Indicates an exempt polymer that has a number-average molecular weight of 1,000 or greater.
Y2 - Indicates an exempt polymer that is a polyester and is made only from reactants included in a specified list of low concern reactants that comprises one of the eligibility criteria for the exemption rule.

U.S. Federal Regulations

TSCA 12(b) Not applicable

SARA 313 Not applicable

SARA 311/312 Hazard Categories See section 2 for more information

CWA (Clean Water Act) Not applicable

Clean Air Act Not applicable

OSHA Occupational Safety and Health Administration
Not applicable

CERCLA Not applicable

California Proposition 65 This product does not contain any Proposition 65 chemicals

U.S. State Right-to-Know Regulations Not applicable

U.S. Department of Transportation

Reportable Quantity (RQ): N
DOT Marine Pollutant N
DOT Severe Marine Pollutant N

U.S. Department of Homeland Security
This product does not contain any DHS chemicals.

Other International Regulations

Mexico - Grade Severe risk, Grade 4

16. Other information

Prepared By	Regulatory Affairs Thermo Fisher Scientific Email: EMSDS.RA@thermofisher.com
Creation Date	22-Jun-2009
Revision Date	17-Jan-2018
Print Date	17-Jan-2018
Revision Summary	This document has been updated to comply with the US OSHA HazCom 2012 Standard replacing the current legislation under 29 CFR 1910.1200 to align with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).

Disclaimer
The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text

End of SDS

ThermoFisher SCIENTIFIC

SAFETY DATA SHEET

Creation Date 10-Feb-2011 **Revision Date** 18-Jan-2018 **Revision Number** 3

1. Identification

Product Name **Tannic acid (Certified)**

Cat No. : **A310-500**

CAS-No 1401-55-4
Synonyms Gallotannic acid; Gallotannin; Glycerite

Recommended Use Laboratory chemicals.
Uses advised against Not for food, drug, pesticide or biocidal product use

Details of the supplier of the safety data sheet

Company
Fisher Scientific
One Reagent Lane
Fair Lawn, NJ 07410
Tel: (201) 796-7100

Emergency Telephone Number
CHEMTREC®, Inside the USA: 800-424-9300
CHEMTREC®, Outside the USA: 001-703-527-3887

2. Hazard(s) identification

Classification
Classification under 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200)

Based on available data, the classification criteria are not met

Label Elements
None required

Hazards not otherwise classified (HNOC)
None identified

3. Composition/Information on Ingredients

Component	CAS-No	Weight %
Tannic acid	1401-55-4	95

4. First-aid measures

Eye Contact Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Get medical attention if symptoms occur.

Skin Contact	Wash off immediately with plenty of water for at least 15 minutes. Get medical attention if symptoms occur.
Inhalation	Move to fresh air. Get medical attention if symptoms occur. If not breathing, give artificial respiration.
Ingestion	Do not induce vomiting. Get medical attention if symptoms occur.
Most important symptoms and effects	None reasonably foreseeable.
Notes to Physician	Treat symptomatically

5. Fire-fighting measures

Suitable Extinguishing Media	Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.
Unsuitable Extinguishing Media	No information available
Flash Point	198 °C / 388.4 °F
Method -	No information available
Autoignition Temperature	Not applicable 527 °C / 980 °F
Explosion Limits	
Upper	No data available
Lower	No data available
Sensitivity to Mechanical Impact	No information available
Sensitivity to Static Discharge	No information available

Specific Hazards Arising from the Chemical
Thermal decomposition can lead to release of irritating gases and vapors. Keep product and empty container away from heat and sources of ignition.

Hazardous Combustion Products
Carbon monoxide (CO) Carbon dioxide (CO_2)
Protective Equipment and Precautions for Firefighters
As in any fire, wear self-contained breathing apparatus pressure-demand, MSHA/NIOSH (approved or equivalent) and full protective gear.

NFPA

Health	Flammability	Instability	Physical hazards
1	1	1	N/A

6. Accidental release measures

Personal Precautions	Ensure adequate ventilation. Use personal protective equipment. Avoid dust formation.
Environmental Precautions	Should not be released into the environment. Do not flush into surface water or sanitary sewer system. See Section 12 for additional ecological information.
Methods for Containment and Clean Up	Sweep up or vacuum up spillage and collect in suitable container for disposal. Avoid dust formation.

7. Handling and storage

Handling	Wear personal protective equipment. Ensure adequate ventilation. Avoid contact with skin, eyes and clothing. Avoid ingestion and inhalation. Avoid dust formation.
Storage	Keep containers tightly closed in a dry, cool and well-ventilated place. Store under an inert atmosphere.

8. Exposure controls / personal protection

Exposure Guidelines This product does not contain any hazardous materials with occupational exposure limitsestablished by the region specific regulatory bodies.

Engineering Measures Ensure adequate ventilation, especially in confined areas. Ensure that eyewash stations and safety showers are close to the workstation location.

Personal Protective Equipment

Eye/face Protection Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166.

Skin and body protection Wear appropriate protective gloves and clothing to prevent skin exposure.

Respiratory Protection Follow the OSHA respirator regulations found in 29 CFR 1910.134 or European Standard EN 149. Use a NIOSH/MSHA or European Standard EN 149 approved respirator if exposure limits are exceeded or if irritation or other symptoms are experienced.

Hygiene Measures Handle in accordance with good industrial hygiene and safety practice.

9. Physical and chemical properties

Physical State	Powder Solid
Appearance	Dark yellow
Odor	Slight
Odor Threshold	No information available
pH	3.5 100 g/L (20°C)
Melting Point/Range	218 °C / 424.4 °F
Boiling Point/Range	No information available
Flash Point	198 °C / 388.4 °F
Evaporation Rate	Not applicable
Flammability (solid,gas)	No information available
Flammability or explosive limits	
Upper	No data available
Lower	No data available
Vapor Pressure	No information available
Vapor Density	Not applicable
Specific Gravity	No information available
Solubility	soluble
Partition coefficient; n-octanol/water	No data available
Autoignition Temperature	Not applicable 527 °C / 980 °F
Decomposition Temperature	218 °C
Viscosity	Not applicable
Molecular Formula	C76 H52 O46
Molecular Weight	1701.23

10. Stability and reactivity

Reactive Hazard None known, based on information available

Stability Air sensitive. Light sensitive.

Conditions to Avoid Incompatible products. Excess heat. Avoid dust formation. Exposure to light. Exposure to air.

Incompatible Materials Strong oxidizing agents, Strong bases

Hazardous Decomposition Products Carbon monoxide (CO), Carbon dioxide (CO_2)

Hazardous Polymerization Hazardous polymerization does not occur.

Hazardous Reactions None under normal processing.

11. Toxicological information

Acute Toxicity

Product Information No acute toxicity information is available for this product

Component Information

Component	LD50 Oral	LD50 Dermal	LC50 Inhalation
Tannic acid	LD50 = 2260 mg/kg (Rat)	Not listed	Not listed

Toxicologically Synergistic Products No information available

Delayed and immediate effects as well as chronic effects from short and long-term exposure

Irritation No information available

Sensitization No information available

Carcinogenicity The table below indicates whether each agency has listed any ingredient as a carcinogen.

Component	CAS-No	IARC	NTP	ACGIH	OSHA	Mexico
Tannic acid	1401-55-4	Not listed	Not listed	Not listed	Not listed	Not listed

Mutagenic Effects No information available

Reproductive Effects No information available.

Developmental Effects No information available.

Teratogenicity No information available.

STOT - single exposure None known

STOT - repeated exposure None known

Aspiration hazard No information available

Symptoms / effects,both acute and delayed No information available

Endocrine Disruptor Information No information available

Other Adverse Effects The toxicological properties have not been fully investigated.

12. Ecological information

Ecotoxicity

The product contains following substances which are hazardous for the environment. Contains a substance which is:. Harmful to aquatic organisms.

Component	Freshwater Algae	Freshwater Fish	Microtox	Water Flea
Tannic acid	Not listed	LC50: = 37 mg/L, 96h (Gambusia affinis)	Not listed	Not listed

Persistence and Degradability Persistence is unlikely

Bioaccumulation/ Accumulation No information available.

Mobility Will likely be mobile in the environment due to its water solubility.

Component	log Pow
Tannic acid	-0.19

13. Disposal considerations

Waste Disposal Methods Chemical waste generators must determine whether a discarded chemical is classified as a hazardous waste. Chemical waste generators must also consult local, regional, and national hazardous waste regulations to ensure complete and accurate classification.

14. Transport information

DOT Not regulated
TDG Not regulated
IATA Not regulated
IMDG/IMO Not regulated

15. Regulatory information

All of the components in the product are on the following Inventory lists: X = listed

International Inventories

Component	TSCA	DSL	NDSL	EINECS	ELINCS	NLP	PICCS	ENCS	AICS	IECSC	KECL
Tannic acid	X	X	-	215-753-2	-		X	-	X	X	X

Legend:
X - Listed
E - Indicates a substance that is the subject of a Section 5(e) Consent order under TSCA.
F - Indicates a substance that is the subject of a Section 5(f) Rule under TSCA.
N - Indicates a polymeric substance containing no free-radical initiator in its inventory name but is considered to cover the designated polymer made with any free-radical initiator regardless of the amount used.
P - Indicates a commenced PMN substance
R - Indicates a substance that is the subject of a Section 6 risk management rule under TSCA.
S - Indicates a substance that is identified in a proposed or final Significant New Use Rule
T - Indicates a substance that is the subject of a Section 4 test rule under TSCA.
XU - Indicates a substance exempt from reporting under the Inventory Update Rule, i.e. Partial Updating of the TSCA Inventory Data Base Production and Site Reports (40 CFR 710(B).
Y1 - Indicates an exempt polymer that has a number-average molecular weight of 1,000 or greater.
Y2 - Indicates an exempt polymer that is a polyester and is made only from reactants included in a specified list of low concern reactants that comprises one of the eligibility criteria for the exemption rule.

U.S. Federal Regulations

TSCA 12(b) Not applicable

SARA 313 Not applicable

SARA 311/312 Hazard Categories See section 2 for more information

CWA (Clean Water Act) Not applicable

Clean Air Act Not applicable

OSHA Occupational Safety and Health Administration
Not applicable

CERCLA Not applicable

California Proposition 65 This product does not contain any Proposition 65 chemicals

U.S. State Right-to-Know Regulations Not applicable

U.S. Department of Transportation

Reportable Quantity (RQ):	N
DOT Marine Pollutant	N
DOT Severe Marine Pollutant	N

U.S. Department of Homeland Security
This product does not contain any DHS chemicals.

Other International Regulations

Mexico - Grade	Slight risk, Grade 1

16. Other information

Prepared By	Regulatory Affairs Thermo Fisher Scientific Email: EMSDS.RA@thermofisher.com
Creation Date	10-Feb-2011
Revision Date	18-Jan-2018
Print Date	18-Jan-2018
Revision Summary	This document has been updated to comply with the US OSHA HazCom 2012 Standard replacing the current legislation under 29 CFR 1910.1200 to align with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).

Disclaimer
The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text

End of SDS

ThermoFisher SCIENTIFIC

SAFETY DATA SHEET

Creation Date 14-Mar-2013 **Revision Date** 19-Jan-2018 **Revision Number** 4

1. Identification

Product Name **Poly(vinyl alcohol), 95.5-96.5% hydrolyzed, average M.W. approx. 85000-124000**

Cat No. : **AC183390000; AC183390010; AC183390025; AC183391000**

Synonyms No information available

Recommended Use Laboratory chemicals.
Uses advised against Not for food, drug, pesticide or biocidal product use

Details of the supplier of the safety data sheet

Company
Fisher Scientific
One Reagent Lane
Fair Lawn, NJ 07410
Tel: (201) 796-7100

Acros Organics
One Reagent Lane
Fair Lawn, NJ 07410

Emergency Telephone Number
For information **US** call: 001-800-ACROS-01 / **Europe** call: +32 14 57 52 11
Emergency Number **US:**001-201-796-7100 / **Europe:** +32 14 57 52 99
CHEMTREC Tel. No.**US:**001-800-424-9300 / **Europe:**001-703-527-3887

2. Hazard(s) identification

Classification
Classification under 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200)

Based on available data, the classification criteria are not met

Label Elements
None required

Hazards not otherwise classified (HNOC)
None identified

3. Composition/Information on Ingredients

Component	CAS-No	Weight %
Polyvinyl alcohol	9002-89-5	>95

4. First-aid measures

Eye Contact	Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Get medical attention.
Skin Contact	Obtain medical attention. Wash off immediately with plenty of water for at least 15 minutes.
Inhalation	Move to fresh air. Obtain medical attention. If not breathing, give artificial respiration.
Ingestion	Do not induce vomiting. Obtain medical attention.
Most important symptoms and effects	No information available.
Notes to Physician	Treat symptomatically

5. Fire-fighting measures

Suitable Extinguishing Media	Water spray. Carbon dioxide (CO_2). Dry chemical. Chemical foam.
Unsuitable Extinguishing Media	No information available
Flash Point	No information available
Method -	No information available
Autoignition Temperature	No information available
Explosion Limits	
Upper	No data available
Lower	No data available
Sensitivity to Mechanical Impact	No information available
Sensitivity to Static Discharge	No information available

Specific Hazards Arising from the Chemical
Keep product and empty container away from heat and sources of ignition. Thermal decomposition can lead to release of irritating gases and vapors.

Hazardous Combustion Products
Carbon monoxide (CO) Carbon dioxide (CO_2)
Protective Equipment and Precautions for Firefighters
As in any fire, wear self-contained breathing apparatus pressure-demand, MSHA/NIOSH (approved or equivalent) and full protective gear.

NFPA

Health	Flammability	Instability	Physical hazards
1	1	0	N/A

6. Accidental release measures

Personal Precautions	Use personal protective equipment. Ensure adequate ventilation. Avoid contact with the skin and the eyes. Avoid dust formation.
Environmental Precautions	See Section 12 for additional ecological information.
Methods for Containment and Clean Up	Sweep up or vacuum up spillage and collect in suitable container for disposal. Avoid dust formation.

7. Handling and storage

Handling	Avoid contact with skin and eyes. Do not breathe dust. Ensure adequate ventilation. Wear personal protective equipment. Avoid dust formation.
Storage	Keep in a dry, cool and well-ventilated place. Keep container tightly closed.

8. Exposure controls / personal protection

Exposure Guidelines

Engineering Measures None under normal use conditions.

Personal Protective Equipment

Eye/face Protection Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166.

Skin and body protection Wear appropriate protective gloves and clothing to prevent skin exposure.

Respiratory Protection No protective equipment is needed under normal use conditions.

Hygiene Measures Handle in accordance with good industrial hygiene and safety practice.

9. Physical and chemical properties

Physical State	Solid
Appearance	Off-white
Odor	No information available
Odor Threshold	No information available
pH	4.5-6.5 @ 20°C 40 g/l water
Melting Point/Range	230 - 240 °C / 446 - 464 °F
Boiling Point/Range	No information available
Flash Point	No information available
Evaporation Rate	Not applicable
Flammability (solid,gas)	No information available
Flammability or explosive limits	
Upper	No data available
Lower	No data available
Vapor Pressure	No information available
Vapor Density	Not applicable
Specific Gravity	No information available
Solubility	No information available
Partition coefficient; n-octanol/water	No data available
Autoignition Temperature	No information available
Decomposition Temperature	No information available
Viscosity	Not applicable

10. Stability and reactivity

Reactive Hazard None known, based on information available

Stability Stable under normal conditions.

Conditions to Avoid Heat, flames and sparks. Incompatible products.

Incompatible Materials Acids, Bases, Strong oxidizing agents, sodium hypochlorite, Powdered metals

Hazardous Decomposition Products Carbon monoxide (CO), Carbon dioxide (CO_2)

Hazardous Polymerization Hazardous polymerization does not occur.

Hazardous Reactions None under normal processing.

11. Toxicological information

Acute Toxicity

Product Information

Oral LD50 Based on ATE data, the classification criteria are not met. ATE > 2000 mg/kg.

Dermal LD50 Based on ATE data, the classification criteria are not met. ATE > 2000 mg/kg.

Mist LC50 Based on ATE data, the classification criteria are not met. ATE > 5 mg/l.

Component Information

Component	LD50 Oral	LD50 Dermal	LC50 Inhalation
Polyvinyl alcohol	> 5000 mg/kg (rat)	>7490 mg/kg (rabbit)	>20 mg/m³/h (rat)

Toxicologically Synergistic Products No information available

Delayed and immediate effects as well as chronic effects from short and long-term exposure

Irritation No information available

Sensitization No information available

Carcinogenicity The table below indicates whether each agency has listed any ingredient as a carcinogen.

Component	CAS-No	IARC	NTP	ACGIH	OSHA	Mexico
Polyvinyl alcohol	9002-89-5	Not listed	Not listed	Not listed	Not listed	Not listed

Mutagenic Effects No information available

Reproductive Effects No information available.

Developmental Effects No information available.

Teratogenicity No information available.

STOT - single exposure None known

STOT - repeated exposure None known

Aspiration hazard No information available

Symptoms / effects,both acute and delayed No information available

Endocrine Disruptor Information No information available

Other Adverse Effects The toxicological properties have not been fully investigated.

12. Ecological information

Ecotoxicity

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Component	Freshwater Algae	Freshwater Fish	Microtox	Water Flea
Polyvinyl alcohol	Not listed	Lepomis macrochirus: LC50=10mg/L 96h	Not listed	EC50=8.3 mg/L 48h

Persistence and Degradability Soluble in water Persistence is unlikely based on information available.

Bioaccumulation/ Accumulation No information available.

Mobility Will likely be mobile in the environment due to its water solubility.

13. Disposal considerations

Waste Disposal Methods Chemical waste generators must determine whether a discarded chemical is classified as a hazardous waste. Chemical waste generators must also consult local, regional, and

national hazardous waste regulations to ensure complete and accurate classification.

14. Transport information

DOT Not regulated
TDG Not regulated
IATA Not regulated
IMDG/IMO Not regulated

15. Regulatory information

International Inventories

Component	TSCA	DSL	NDSL	EINECS	ELINCS	NLP	PICCS	ENCS	AICS	IECSC	KECL
Polyvinyl alcohol	X	X	-	-	-		X	X	X	X	X

Legend:
X - Listed
E - Indicates a substance that is the subject of a Section 5(e) Consent order under TSCA.
F - Indicates a substance that is the subject of a Section 5(f) Rule under TSCA.
N - Indicates a polymeric substance containing no free-radical initiator in its inventory name but is considered to cover the designated polymer made with any free-radical initiator regardless of the amount used.
P - Indicates a commenced PMN substance
R - Indicates a substance that is the subject of a Section 6 risk management rule under TSCA.
S - Indicates a substance that is identified in a proposed or final Significant New Use Rule
T - Indicates a substance that is the subject of a Section 4 test rule under TSCA.
XU - Indicates a substance exempt from reporting under the Inventory Update Rule, i.e. Partial Updating of the TSCA Inventory Data Base Production and Site Reports (40 CFR 710(B).
Y1 - Indicates an exempt polymer that has a number-average molecular weight of 1,000 or greater.
Y2 - Indicates an exempt polymer that is a polyester and is made only from reactants included in a specified list of low concern reactants that comprises one of the eligibility criteria for the exemption rule.

U.S. Federal Regulations

TSCA 12(b) Not applicable

SARA 313 Not applicable

SARA 311/312 Hazard Categories See section 2 for more information

CWA (Clean Water Act) Not applicable

Clean Air Act Not applicable

OSHA Occupational Safety and Health Administration
Not applicable

CERCLA Not applicable

California Proposition 65 This product does not contain any Proposition 65 chemicals

U.S. State Right-to-Know Regulations Not applicable

U.S. Department of Transportation

Reportable Quantity (RQ): N
DOT Marine Pollutant N
DOT Severe Marine Pollutant N

U.S. Department of Homeland Security
This product does not contain any DHS chemicals.

Other International Regulations

Mexico - Grade No information available

16. Other information

Prepared By	Regulatory Affairs Thermo Fisher Scientific Email: EMSDS.RA@thermofisher.com
Creation Date	14-Mar-2013
Revision Date	19-Jan-2018
Print Date	19-Jan-2018
Revision Summary	This document has been updated to comply with the US OSHA HazCom 2012 Standard replacing the current legislation under 29 CFR 1910.1200 to align with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).

Disclaimer

The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text

End of SDS

ThermoFisher SCIENTIFIC

SAFETY DATA SHEET

Creation Date 27-Jan-2010 **Revision Date** 17-Jan-2018 **Revision Number** 6

1. Identification

Product Name **Methylene chloride**

Cat No. : **D37-1; D37-4; D37-20; D37-200; D37-200LC; D37-500; D37FB-19; D37FB-50; D37FB-115; D37FB-200; D37POP-19; D37POPB-50; D37POPB-200; D37RB-19; D37RB-50; D37RB-115; D37RB-200; D37RS-19; D37RS-28; D37RS-50; D37RS-115; D37RS-200; D37SK-4; D37SK-4LC; D37SS-28; D37SS-50; D37SS-115; D37SS-200; D37SS-1350; D37RS1000ASME; NC1485726; D37RE200ASME; NC1568702**

CAS-No 75-09-2
Synonyms Dichloromethane; DCM

Recommended Use Laboratory chemicals.
Uses advised against Food, drug, pesticide or biocidal product use

Details of the supplier of the safety data sheet

Company
Fisher Scientific
One Reagent Lane
Fair Lawn, NJ 07410
Tel: (201) 796-7100

Emergency Telephone Number
CHEMTREC®, Inside the USA: 800-424-9300
CHEMTREC®, Outside the USA: 001-703-527-3887

2. Hazard(s) identification

Classification
This chemical is considered hazardous by the 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200)

Skin Corrosion/irritation	Category 2
Serious Eye Damage/Eye Irritation	Category 2
Carcinogenicity	Category 1B
Specific target organ toxicity (single exposure)	Category 3
Target Organs - Central nervous system (CNS).	
Specific target organ toxicity - (repeated exposure)	Category 2
Target Organs - Liver, Kidney, Blood.	

Label Elements

Signal Word
Danger

Hazard Statements
Causes skin irritation
Causes serious eye irritation
May cause drowsiness or dizziness
May cause cancer
May cause damage to organs through prolonged or repeated exposure

Precautionary Statements
Prevention
Obtain special instructions before use
Do not handle until all safety precautions have been read and understood
Use personal protective equipment as required
Wash face, hands and any exposed skin thoroughly after handling
Wear eye/face protection
Do not breathe dust/fume/gas/mist/vapors/spray
Use only outdoors or in a well-ventilated area
Response
IF exposed or concerned: Get medical attention/advice
Inhalation
IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing
Skin
IF ON SKIN: Wash with plenty of soap and water
If skin irritation occurs: Get medical advice/attention
Take off contaminated clothing and wash before reuse
Eyes
IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing
If eye irritation persists: Get medical advice/attention
Storage
Store locked up
Store in a well-ventilated place. Keep container tightly closed
Disposal
Dispose of contents/container to an approved waste disposal plant
Hazards not otherwise classified (HNOC)

WARNING. Cancer - https://www.p65warnings.ca.gov/.

3. Composition/Information on Ingredients

Component	CAS-No	Weight %
Methylene chloride	75-09-2	>99.5

4. First-aid measures

General Advice If symptoms persist, call a physician.

Eye Contact Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Get medical attention.

Skin Contact	Wash off immediately with plenty of water for at least 15 minutes. If skin irritation persists, call a physician.
Inhalation	Move to fresh air. If not breathing, give artificial respiration. Get medical attention if symptoms occur.
Ingestion	Clean mouth with water and drink afterwards plenty of water.
Most important symptoms and effects	None reasonably foreseeable. Inhalation of high vapor concentrations may cause symptoms like headache, dizziness, tiredness, nausea and vomiting
Notes to Physician	Treat symptomatically

5. Fire-fighting measures

Suitable Extinguishing Media	Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.
Unsuitable Extinguishing Media	No information available
Flash Point	No information available
Method -	No information available
Autoignition Temperature	556 °C / 1032.8 °F
Explosion Limits	
Upper	23 vol %
Lower	13 vol %
Sensitivity to Mechanical Impact	No information available
Sensitivity to Static Discharge	No information available

Specific Hazards Arising from the Chemical
Thermal decomposition can lead to release of irritating gases and vapors. Keep product and empty container away from heat and sources of ignition.

Hazardous Combustion Products
Carbon monoxide (CO) Carbon dioxide (CO_2) Hydrogen chloride gas Phosgene
Protective Equipment and Precautions for Firefighters
As in any fire, wear self-contained breathing apparatus pressure-demand, MSHA/NIOSH (approved or equivalent) and full protective gear.

NFPA

Health	Flammability	Instability	Physical hazards
2	1	0	N/A

6. Accidental release measures

Personal Precautions	Use personal protective equipment. Ensure adequate ventilation.
Environmental Precautions	Should not be released into the environment.
Methods for Containment and Clean Up	Soak up with inert absorbent material. Keep in suitable, closed containers for disposal.

7. Handling and storage

Handling	Wear personal protective equipment. Do not get in eyes, on skin, or on clothing. Avoid ingestion and inhalation. Ensure adequate ventilation.
Storage	Keep containers tightly closed in a dry, cool and well-ventilated place.

8. Exposure controls / personal protection

Exposure Guidelines

Component	ACGIH TLV	OSHA PEL	NIOSH IDLH	Mexico OEL (TWA)
Methylene chloride	TWA: 50 ppm	(Vacated) TWA: 500 ppm (Vacated) STEL: 2000 ppm (Vacated) Ceiling: 1000 ppm TWA: 25 ppm STEL: 125 ppm	IDLH: 2300 ppm	TWA: 100 ppm TWA: 330 mg/m³ STEL: 500 ppm STEL: 1740 mg/m³

Legend

ACGIH - *American Conference of Governmental Industrial Hygienists*
OSHA - *Occupational Safety and Health Administration*
NIOSH IDLH: *The National Institute for Occupational Safety and Health Immediately Dangerous to Life or Health*

Engineering Measures Use only under a chemical fume hood. Ensure that eyewash stations and safety showers are close to the workstation location.

Personal Protective Equipment

Eye/face Protection Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166.

Skin and body protection Long sleeved clothing.

Respiratory Protection Follow the OSHA respirator regulations found in 29 CFR 1910.134 or European Standard EN 149. Use a NIOSH/MSHA or European Standard EN 149 approved respirator if exposure limits are exceeded or if irritation or other symptoms are experienced.

Hygiene Measures Handle in accordance with good industrial hygiene and safety practice.

9. Physical and chemical properties

Physical State	Liquid
Appearance	Colorless
Odor	sweet
Odor Threshold	No information available
pH	No information available
Melting Point/Range	-97 °C / -142.6 °F
Boiling Point/Range	39 °C / 102.2 °F
Flash Point	No information available
Evaporation Rate	No information available
Flammability (solid,gas)	Not applicable
Flammability or explosive limits	
Upper	23 vol %
Lower	13 vol %
Vapor Pressure	350 mbar @ 20°C
Vapor Density	2.93 (Air = 1.0)
Specific Gravity	1.33
Solubility	No information available
Partition coefficient; n-octanol/water	No data available
Autoignition Temperature	556 °C / 1032.8 °F
Decomposition Temperature	No information available
Viscosity	No information available
Molecular Formula	C H2 Cl2
Molecular Weight	84.93

10. Stability and reactivity

Reactive Hazard None known, based on information available

Aspiration hazard No information available

Symptoms / effects,both acute and delayed Inhalation of high vapor concentrations may cause symptoms like headache, dizziness, tiredness, nausea and vomiting

Endocrine Disruptor Information No information available

Other Adverse Effects Tumorigenic effects have been reported in experimental animals.

12. Ecological information

Ecotoxicity

.

Component	Freshwater Algae	Freshwater Fish	Microtox	Water Flea
Methylene chloride	EC50:>660 mg/L/96h	Pimephales promelas: LC50:193 mg/L/96h	EC50: 1 mg/L/24 h EC50: 2.88 mg/L/15 min	EC50: 140 mg/L/48h

Persistence and Degradability Persistence is unlikely based on information available.

Bioaccumulation/ Accumulation No information available.

Mobility Will likely be mobile in the environment due to its volatility.

Component	log Pow
Methylene chloride	1.25

13. Disposal considerations

Waste Disposal Methods Chemical waste generators must determine whether a discarded chemical is classified as a hazardous waste. Chemical waste generators must also consult local, regional, and national hazardous waste regulations to ensure complete and accurate classification.

Component	RCRA - U Series Wastes	RCRA - P Series Wastes
Methylene chloride - 75-09-2	U080	-

14. Transport information

DOT

UN-No UN1593
Proper Shipping Name DICHLOROMETHANE
Hazard Class 6.1
Packing Group III

TDG

UN-No UN1593
Proper Shipping Name DICHLOROMETHANE
Hazard Class 6.1
Packing Group III

IATA

UN-No UN1593
Proper Shipping Name Dichloromethane
Hazard Class 6.1
Packing Group III

IMDG/IMO

UN-No UN1593
Proper Shipping Name Dichloromethane
Hazard Class 6.1
Packing Group III

15. Regulatory information

All of the components in the product are on the following Inventory lists: X = listed

International Inventories

Component	TSCA	DSL	NDSL	EINECS	ELINCS	NLP	PICCS	ENCS	AICS	IECSC	KECL
Methylene chloride	X	X	-	200-838-9	-		X	X	X	X	X

Legend:
X - Listed
E - Indicates a substance that is the subject of a Section 5(e) Consent order under TSCA.
F - Indicates a substance that is the subject of a Section 5(f) Rule under TSCA.
N - Indicates a polymeric substance containing no free-radical initiator in its inventory name but is considered to cover the designated polymer made with any free-radical initiator regardless of the amount used.
P - Indicates a commenced PMN substance
R - Indicates a substance that is the subject of a Section 6 risk management rule under TSCA.
S - Indicates a substance that is identified in a proposed or final Significant New Use Rule
T - Indicates a substance that is the subject of a Section 4 test rule under TSCA.
XU - Indicates a substance exempt from reporting under the Inventory Update Rule, i.e. Partial Updating of the TSCA Inventory Data Base Production and Site Reports (40 CFR 710(B).
Y1 - Indicates an exempt polymer that has a number-average molecular weight of 1,000 or greater.
Y2 - Indicates an exempt polymer that is a polyester and is made only from reactants included in a specified list of low concern reactants that comprises one of the eligibility criteria for the exemption rule.

U.S. Federal Regulations

TSCA 12(b)

SARA 313

Component	CAS-No	Weight %	SARA 313 - Threshold Values %
Methylene chloride	75-09-2	>99.5	0.1

SARA 311/312 Hazard Categories See section 2 for more information

CWA (Clean Water Act)

Component	CWA - Hazardous Substances	CWA - Reportable Quantities	CWA - Toxic Pollutants	CWA - Priority Pollutants
Methylene chloride	-	-	X	X

Clean Air Act

Component	HAPS Data	Class 1 Ozone Depletors	Class 2 Ozone Depletors
Methylene chloride	X		-

OSHA Occupational Safety and Health Administration

Component	Specifically Regulated Chemicals	Highly Hazardous Chemicals
Methylene chloride	125 ppm STEL 12.5 ppm Action Level 25 ppm TWA	-

CERCLA This material, as supplied, contains one or more substances regulated as a hazardous substance under the Comprehensive Environmental Response Compensation and Liability Act (CERCLA) (40 CFR 302)

Component	Hazardous Substances RQs	CERCLA EHS RQs
Methylene chloride	1000 lb 1 lb	-

California Proposition 65 This product contains the following proposition 65 chemicals

Component	CAS-No	California Prop. 65	Prop 65 NSRL	Category
Methylene chloride	75-09-2	Carcinogen	200 µg/day 50 µg/day	Carcinogen

U.S. State Right-to-Know Regulations

Component	Massachusetts	New Jersey	Pennsylvania	Illinois	Rhode Island
Methylene chloride	X	X	X	X	X

U.S. Department of Transportation

Reportable Quantity (RQ):	Y
DOT Marine Pollutant	N
DOT Severe Marine Pollutant	N

U.S. Department of Homeland Security
This product does not contain any DHS chemicals.

Other International Regulations

Mexico - Grade No information available

16. Other information

Prepared By	Regulatory Affairs Thermo Fisher Scientific Email: EMSDS.RA@thermofisher.com
Creation Date	27-Jan-2010
Revision Date	17-Jan-2018
Print Date	17-Jan-2018
Revision Summary	This document has been updated to comply with the US OSHA HazCom 2012 Standard replacing the current legislation under 29 CFR 1910.1200 to align with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).

Disclaimer
The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text

End of SDS

ThermoFisher SCIENTIFIC

SAFETY DATA SHEET

Creation Date 26-Aug-2009 **Revision Date** 23-Jan-2018 **Revision Number** 4

1. Identification

Product Name **Chitosan**

Cat No. : **AC428850000; AC428850500; AC428851000; AC428855000**

CAS-No 9012-76-4
Synonyms Poly(beta-(1,4)-2-amino-2-deoxy-D-glucose); Poly(beta-(1,4)-D-glucosamine)

Recommended Use Laboratory chemicals.
Uses advised against Not for food, drug, pesticide or biocidal product use

Details of the supplier of the safety data sheet

Company
Fisher Scientific
One Reagent Lane
Fair Lawn, NJ 07410
Tel: (201) 796-7100

Acros Organics
One Reagent Lane
Fair Lawn, NJ 07410

Emergency Telephone Number
For information **US** call: 001-800-ACROS-01 / **Europe** call: +32 14 57 52 11
Emergency Number **US:**001-201-796-7100 / **Europe:** +32 14 57 52 99
CHEMTREC Tel. No.**US:**001-800-424-9300 / **Europe:**001-703-527-3887

2. Hazard(s) identification

Classification
Classification under 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200)

Not a dangerous substance or mixture according to the Globally Harmonized System (GHS)

Label Elements
None required

Hazards not otherwise classified (HNOC)
None identified

3. Composition/Information on Ingredients

Component	CAS-No	Weight %
Chitosan	9012-76-4	>95

4. First-aid measures

Eye Contact	Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Get medical attention.
Skin Contact	Wash off immediately with plenty of water for at least 15 minutes. Get medical attention immediately if symptoms occur.
Inhalation	Move to fresh air. Get medical attention immediately if symptoms occur. If not breathing, give artificial respiration.
Ingestion	Do not induce vomiting. Obtain medical attention.
Most important symptoms and effects	No information available.
Notes to Physician	Treat symptomatically

5. Fire-fighting measures

Suitable Extinguishing Media	Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.
Unsuitable Extinguishing Media	No information available
Flash Point	No information available
Method -	No information available
Autoignition Temperature	
Explosion Limits	
Upper	No data available
Lower	No data available
Sensitivity to Mechanical Impact	No information available
Sensitivity to Static Discharge	No information available

Specific Hazards Arising from the Chemical
Thermal decomposition can lead to release of irritating gases and vapors. Keep product and empty container away from heat and sources of ignition.

Hazardous Combustion Products
Carbon monoxide (CO) Carbon dioxide (CO_2) Nitrogen oxides (NOx)
Protective Equipment and Precautions for Firefighters
As in any fire, wear self-contained breathing apparatus pressure-demand, MSHA/NIOSH (approved or equivalent) and full protective gear.

NFPA

Health	Flammability	Instability	Physical hazards
1	1	0	N/A

6. Accidental release measures

Personal Precautions	Ensure adequate ventilation. Use personal protective equipment. Avoid dust formation.
Environmental Precautions	Avoid release to the environment. See Section 12 for additional ecological information.
Methods for Containment and Clean Up	Sweep up or vacuum up spillage and collect in suitable container for disposal. Avoid dust formation.

7. Handling and storage

Handling	Wear personal protective equipment. Ensure adequate ventilation. Avoid contact with skin, eyes and clothing. Avoid ingestion and inhalation. Avoid dust formation.
Storage	To maintain product quality: Keep refrigerated. Keep container tightly closed in a dry and well-ventilated place.

8. Exposure controls / personal protection

Exposure Guidelines This product does not contain any hazardous materials with occupational exposure limitsestablished by the region specific regulatory bodies.

Engineering Measures None under normal use conditions.

Personal Protective Equipment

Eye/face Protection Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166.

Skin and body protection Wear appropriate protective gloves and clothing to prevent skin exposure.

Respiratory Protection No protective equipment is needed under normal use conditions.

Hygiene Measures Handle in accordance with good industrial hygiene and safety practice.

9. Physical and chemical properties

Physical State	Solid
Appearance	Light cream
Odor	No information available
Odor Threshold	No information available
pH	No information available
Melting Point/Range	No data available
Boiling Point/Range	No information available
Flash Point	No information available
Evaporation Rate	Not applicable
Flammability (solid,gas)	No information available
Flammability or explosive limits	
Upper	No data available
Lower	No data available
Vapor Pressure	No information available
Vapor Density	Not applicable
Specific Gravity	No information available
Solubility	insoluble
Partition coefficient; n-octanol/water	No data available
Autoignition Temperature	
Decomposition Temperature	No information available
Viscosity	Not applicable
Molecular Formula	(C6 H11 N O4)n

10. Stability and reactivity

Reactive Hazard None known, based on information available

Stability Stable under normal conditions.

Conditions to Avoid Incompatible products. Excess heat. Avoid dust formation.

Incompatible Materials Strong oxidizing agents

Hazardous Decomposition Products Carbon monoxide (CO), Carbon dioxide (CO_2), Nitrogen oxides (NOx)

Hazardous Polymerization Hazardous polymerization does not occur.

Hazardous Reactions None under normal processing.

11. Toxicological information

Acute Toxicity

Product Information
LD50 Oral VALUE >10 g/kg
Dermal LD50 Based on ATE data, the classification criteria are not met. ATE > 2000 mg/kg.
Mist LC50 Based on ATE data, the classification criteria are not met. ATE > 5 mg/l.
Component Information

Component	LD50 Oral	LD50 Dermal	LC50 Inhalation
Chitosan	> 10g/kg (Rat)	Not listed	Not listed

Toxicologically Synergistic Products No information available

Delayed and immediate effects as well as chronic effects from short and long-term exposure

Irritation No information available

Sensitization No information available

Carcinogenicity The table below indicates whether each agency has listed any ingredient as a carcinogen.

Component	CAS-No	IARC	NTP	ACGIH	OSHA	Mexico
Chitosan	9012-76-4	Not listed	Not listed	Not listed	Not listed	Not listed

Mutagenic Effects No information available

Reproductive Effects No information available.

Developmental Effects No information available.

Teratogenicity No information available.

STOT - single exposure None known
STOT - repeated exposure None known

Aspiration hazard No information available

Symptoms / effects,both acute and delayed No information available

Endocrine Disruptor Information No information available

Other Adverse Effects The toxicological properties have not been fully investigated.

12. Ecological information

Ecotoxicity
Do not empty into drains. .

Component	Freshwater Algae	Freshwater Fish	Microtox	Water Flea
Chitosan	Not listed	Onchorhynchus mykiss: LC50: 1.73 mg/L 96h	Not listed	EC50 = 13.69 mg/L 48h

Persistence and Degradability Insoluble in water

Bioaccumulation/ Accumulation No information available.

Mobility Is not likely mobile in the environment due its low water solubility.

13. Disposal considerations

Waste Disposal Methods Chemical waste generators must determine whether a discarded chemical is classified as a

hazardous waste. Chemical waste generators must also consult local, regional, and national hazardous waste regulations to ensure complete and accurate classification.

14. Transport information

DOT Not regulated
TDG Not regulated
IATA Not regulated
IMDG/IMO Not regulated

15. Regulatory information

All of the components in the product are on the following Inventory lists: X = listed

International Inventories

Component	TSCA	DSL	NDSL	EINECS	ELINCS	NLP	PICCS	ENCS	AICS	IECSC	KECL
Chitosan	X	X	-	-	-		X	X	X	X	X

Legend:
X - Listed
E - Indicates a substance that is the subject of a Section 5(e) Consent order under TSCA.
F - Indicates a substance that is the subject of a Section 5(f) Rule under TSCA.
N - Indicates a polymeric substance containing no free-radical initiator in its inventory name but is considered to cover the designated polymer made with any free-radical initiator regardless of the amount used.
P - Indicates a commenced PMN substance
R - Indicates a substance that is the subject of a Section 6 risk management rule under TSCA.
S - Indicates a substance that is identified in a proposed or final Significant New Use Rule
T - Indicates a substance that is the subject of a Section 4 test rule under TSCA.
XU - Indicates a substance exempt from reporting under the Inventory Update Rule, i.e. Partial Updating of the TSCA Inventory Data Base Production and Site Reports (40 CFR 710(B).
Y1 - Indicates an exempt polymer that has a number-average molecular weight of 1,000 or greater.
Y2 - Indicates an exempt polymer that is a polyester and is made only from reactants included in a specified list of low concern reactants that comprises one of the eligibility criteria for the exemption rule.

U.S. Federal Regulations

TSCA 12(b) Not applicable

SARA 313 Not applicable

SARA 311/312 Hazard Categories See section 2 for more information

CWA (Clean Water Act) Not applicable

Clean Air Act Not applicable

OSHA Occupational Safety and Health Administration
Not applicable

CERCLA Not applicable

California Proposition 65 This product does not contain any Proposition 65 chemicals

U.S. State Right-to-Know Regulations Not applicable

U.S. Department of Transportation

Reportable Quantity (RQ): N
DOT Marine Pollutant N
DOT Severe Marine Pollutant N

U.S. Department of Homeland Security

This product does not contain any DHS chemicals.

Other International Regulations

Mexico - Grade No information available

16. Other information

Prepared By
Regulatory Affairs
Thermo Fisher Scientific
Email: EMSDS.RA@thermofisher.com

Creation Date 26-Aug-2009
Revision Date 23-Jan-2018
Print Date 23-Jan-2018
Revision Summary This document has been updated to comply with the US OSHA HazCom 2012 Standard replacing the current legislation under 29 CFR 1910.1200 to align with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).

Disclaimer
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End of SDS

ThermoFisher SCIENTIFIC

SAFETY DATA SHEET

Creation Date 22-Dec-2010 **Revision Date** 18-Jan-2018 **Revision Number** 5

1. Identification

Product Name **Tween® 20**

Cat No. : **BP337-100; BP337-500; XXBP3374LI; NC1630717**

CAS-No 9005-64-5
Synonyms Polyoxyethylene(20)sorbitan monolaurate

Recommended Use Laboratory chemicals.
Uses advised against Food, drug, pesticide or biocidal product use

Details of the supplier of the safety data sheet

Company
Fisher Scientific
One Reagent Lane
Fair Lawn, NJ 07410
Tel: (201) 796-7100

Emergency Telephone Number
CHEMTREC®, Inside the USA: 800-424-9300
CHEMTREC®, Outside the USA: 001-703-527-3887

2. Hazard(s) identification

Classification
Classification under 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200)

Not a dangerous substance or mixture according to the Globally Harmonized System (GHS)

Label Elements

Hazard Statements

Precautionary Statements
Hazards not otherwise classified (HNOC)
None identified

3. Composition/Information on Ingredients

Component	CAS-No	Weight %

Polyoxyethylene(20)sorbitan monolaurate	9005-64-5	>95

4. First-aid measures

Eye Contact Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Get medical attention.

Skin Contact Wash off immediately with plenty of water for at least 15 minutes. Get medical attention immediately if symptoms occur.

Inhalation Move to fresh air. Get medical attention immediately if symptoms occur. If not breathing, give artificial respiration.

Ingestion Do not induce vomiting. Obtain medical attention.

Most important symptoms and effects No information available.

Notes to Physician Treat symptomatically

5. Fire-fighting measures

Suitable Extinguishing Media Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

Unsuitable Extinguishing Media No information available

Flash Point > 150 °C / > 302 °F

Method - No information available

Autoignition Temperature No information available

Explosion Limits

Upper No data available

Lower No data available

Sensitivity to Mechanical Impact No information available

Sensitivity to Static Discharge No information available

Specific Hazards Arising from the Chemical
Thermal decomposition can lead to release of irritating gases and vapors.

Hazardous Combustion Products
Carbon monoxide (CO) Carbon dioxide (CO_2)

Protective Equipment and Precautions for Firefighters
As in any fire, wear self-contained breathing apparatus pressure-demand, MSHA/NIOSH (approved or equivalent) and full protective gear.

NFPA

Health	Flammability	Instability	Physical hazards
0	1	0	N/A

6. Accidental release measures

Personal Precautions Use personal protective equipment. Ensure adequate ventilation. Avoid contact with skin, eyes and clothing.

Environmental Precautions Should not be released into the environment. See Section 12 for additional ecological information.

Methods for Containment and Clean Up Soak up with inert absorbent material. Keep in suitable, closed containers for disposal.

7. Handling and storage

Handling	Wear personal protective equipment. Ensure adequate ventilation. Do not breathe vapors or spray mist. Avoid contact with skin and eyes. Do not ingest.
Storage	Keep containers tightly closed in a dry, cool and well-ventilated place. Store indoors.

8. Exposure controls / personal protection

Exposure Guidelines	This product does not contain any hazardous materials with occupational exposure limitsestablished by the region specific regulatory bodies.
Engineering Measures	None under normal use conditions.
Personal Protective Equipment	
Eye/face Protection	Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166.
Skin and body protection	Wear appropriate protective gloves and clothing to prevent skin exposure.
Respiratory Protection	No protective equipment is needed under normal use conditions.
Hygiene Measures	Handle in accordance with good industrial hygiene and safety practice.

9. Physical and chemical properties

Physical State	Very viscous Liquid
Appearance	Amber
Odor	No information available
Odor Threshold	No information available
pH	6 10% aq. solution
Melting Point/Range	No data available
Boiling Point/Range	> 100 °C / 212 °F
Flash Point	> 150 °C / > 302 °F
Evaporation Rate	No information available
Flammability (solid,gas)	Not applicable
Flammability or explosive limits	
Upper	No data available
Lower	No data available
Vapor Pressure	No information available
Vapor Density	No information available
Specific Gravity	1.100
Solubility	Soluble in water
Partition coefficient; n-octanol/water	No data available
Autoignition Temperature	No information available
Decomposition Temperature	No information available
Viscosity	400 mPa.s at 25 °C

10. Stability and reactivity

Reactive Hazard	None known, based on information available
Stability	Stable under normal conditions.
Conditions to Avoid	Incompatible products. Excess heat.
Incompatible Materials	Strong oxidizing agents

Hazardous Decomposition Products Carbon monoxide (CO), Carbon dioxide (CO_2)

Hazardous Polymerization Hazardous polymerization does not occur.

Hazardous Reactions None under normal processing.

11. Toxicological information

Acute Toxicity

Product Information
Component Information

Component	LD50 Oral	LD50 Dermal	LC50 Inhalation
Polyoxyethylene(20)sorbitan monolaurate	LD50 = 37000 mg/kg (Rat) LD50 = 36700 µL/kg (Rat)	Not listed	Not listed

Toxicologically Synergistic Products No information available

Delayed and immediate effects as well as chronic effects from short and long-term exposure

Irritation No information available

Sensitization No information available

Carcinogenicity The table below indicates whether each agency has listed any ingredient as a carcinogen.

Component	CAS-No	IARC	NTP	ACGIH	OSHA	Mexico
Polyoxyethylene(20)sorbitan monolaurate	9005-64-5	Not listed	Not listed	Not listed	Not listed	Not listed

Mutagenic Effects No information available

Reproductive Effects No information available.

Developmental Effects No information available.

Teratogenicity No information available.

STOT - single exposure None known
STOT - repeated exposure None known

Aspiration hazard No information available

Symptoms / effects,both acute and delayed No information available

Endocrine Disruptor Information No information available

Other Adverse Effects The toxicological properties have not been fully investigated.

12. Ecological information

Ecotoxicity
Do not empty into drains. .

Persistence and Degradability Soluble in water Persistence is unlikely based on information available.

Bioaccumulation/ Accumulation No information available.

Mobility Will likely be mobile in the environment due to its water solubility.

13. Disposal considerations

U.S. Department of Homeland Security	This product does not contain any DHS chemicals.

Other International Regulations

Mexico - Grade	No information available

16. Other information

Prepared By	Regulatory Affairs Thermo Fisher Scientific Email: EMSDS.RA@thermofisher.com
Creation Date	22-Dec-2010
Revision Date	18-Jan-2018
Print Date	18-Jan-2018
Revision Summary	This document has been updated to comply with the US OSHA HazCom 2012 Standard replacing the current legislation under 29 CFR 1910.1200 to align with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).

Disclaimer

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End of SDS

ThermoFisher SCIENTIFIC

SAFETY DATA SHEET

Creation Date 15-Jul-2014 **Revision Date** 17-Jan-2018 **Revision Number** 4

1. Identification

Product Name **Caffeine (USP/FCC)**

Cat No. : **O1728-500**

CAS-No 58-08-2
Synonyms 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione; Anhydrous C; Xanthrine,1,3,7-Trimethyl

Recommended Use Laboratory chemicals.
Uses advised against Not for food, drug, pesticide or biocidal product use

Details of the supplier of the safety data sheet

Company
Fisher Scientific
One Reagent Lane
Fair Lawn, NJ 07410
Tel: (201) 796-7100

Emergency Telephone Number
CHEMTREC®, Inside the USA: 800-424-9300
CHEMTREC®, Outside the USA: 001-703-527-3887

2. Hazard(s) identification

Classification
This chemical is considered hazardous by the 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200)

Acute oral toxicity	Category 3

Label Elements

Signal Word
Danger

Hazard Statements
Toxic if swallowed

Precautionary Statements
Prevention
Wash face, hands and any exposed skin thoroughly after handling
Do not eat, drink or smoke when using this product

Ingestion
IF SWALLOWED: Immediately call a POISON CENTER or doctor/physician
Rinse mouth
Storage
Store locked up
Disposal
Dispose of contents/container to an approved waste disposal plant
Hazards not otherwise classified (HNOC)
None identified

3. Composition/Information on Ingredients

Component	CAS-No	Weight %
Caffeine	58-08-2	100

4. First-aid measures

Eye Contact Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Get medical attention.

Skin Contact Wash off immediately with plenty of water for at least 15 minutes. Get medical attention if symptoms occur.

Inhalation Move to fresh air. If breathing is difficult, give oxygen. Do not use mouth-to-mouth method if victim ingested or inhaled the substance; give artificial respiration with the aid of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Obtain medical attention.

Ingestion Do not induce vomiting. Obtain medical attention.

Most important symptoms and effects No information available.

Notes to Physician Treat symptomatically

5. Fire-fighting measures

Suitable Extinguishing Media Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

Unsuitable Extinguishing Media No information available

Flash Point Not applicable
Method - No information available

Autoignition Temperature 540 °C / 1004 °F

Explosion Limits
Upper No data available
Lower No data available
Sensitivity to Mechanical Impact No information available
Sensitivity to Static Discharge No information available

Specific Hazards Arising from the Chemical
Thermal decomposition can lead to release of irritating gases and vapors. Keep product and empty container away from heat and sources of ignition.

Hazardous Combustion Products
Carbon monoxide (CO) Carbon dioxide (CO_2) Nitrogen oxides (NOx)
Protective Equipment and Precautions for Firefighters

As in any fire, wear self-contained breathing apparatus pressure-demand, MSHA/NIOSH (approved or equivalent) and full protective gear.

NFPA

Health	Flammability	Instability	Physical hazards
2	0	0	N/A

6. Accidental release measures

Personal Precautions Use personal protective equipment. Ensure adequate ventilation. Avoid dust formation. Avoid contact with skin, eyes and clothing.

Environmental Precautions Avoid release to the environment. See Section 12 for additional ecological information.

Methods for Containment and Clean Up Sweep up or vacuum up spillage and collect in suitable container for disposal. Avoid dust formation.

7. Handling and storage

Handling Wear personal protective equipment. Ensure adequate ventilation. Avoid dust formation. Avoid contact with skin, eyes and clothing. Avoid ingestion and inhalation.

Storage Keep containers tightly closed in a dry, cool and well-ventilated place.

8. Exposure controls / personal protection

Exposure Guidelines This product does not contain any hazardous materials with occupational exposure limitsestablished by the region specific regulatory bodies.

Engineering Measures Ensure adequate ventilation, especially in confined areas. Ensure that eyewash stations and safety showers are close to the workstation location.

Personal Protective Equipment

Eye/face Protection Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166.

Skin and body protection Wear appropriate protective gloves and clothing to prevent skin exposure.

Respiratory Protection Follow the OSHA respirator regulations found in 29 CFR 1910.134 or European Standard EN 149. Use a NIOSH/MSHA or European Standard EN 149 approved respirator if exposure limits are exceeded or if irritation or other symptoms are experienced.

Hygiene Measures Handle in accordance with good industrial hygiene and safety practice.

9. Physical and chemical properties

Physical State	Solid
Appearance	White
Odor	Odorless
Odor Threshold	No information available
pH	No information available
Melting Point/Range	237.8 °C / 460 °F
Boiling Point/Range	177.8 °C / 352 °F
Flash Point	Not applicable
Evaporation Rate	negligible
Flammability (solid,gas)	No information available
Flammability or explosive limits	
Upper	No data available

Lower	No data available
Vapor Pressure	negligible
Vapor Density	No information available
Specific Gravity	1.23
Solubility	Slightly soluble in water
Partition coefficient; n-octanol/water	No data available
Autoignition Temperature	540 °C / 1004 °F
Decomposition Temperature	No information available
Viscosity	No information available
Molecular Formula	C8H10N4O2
Molecular Weight	194.0956

10. Stability and reactivity

Reactive Hazard None known, based on information available

Stability Stable under normal conditions.

Conditions to Avoid Avoid dust formation. Incompatible products. Excess heat.

Incompatible Materials Strong oxidizing agents

Hazardous Decomposition Products Carbon monoxide (CO), Carbon dioxide (CO_2), Nitrogen oxides (NOx)

Hazardous Polymerization Hazardous polymerization does not occur.

Hazardous Reactions None under normal processing.

11. Toxicological information

Acute Toxicity

Component Information

Component	LD50 Oral	LD50 Dermal	LC50 Inhalation
Caffeine	LD50 = 192 mg/kg (Rat)	Not listed	Not listed

Toxicologically Synergistic Products No information available

Delayed and immediate effects as well as chronic effects from short and long-term exposure

Irritation No information available

Sensitization No information available

Carcinogenicity The table below indicates whether each agency has listed any ingredient as a carcinogen.

Component	CAS-No	IARC	NTP	ACGIH	OSHA	Mexico
Caffeine	58-08-2	Not listed	Not listed	Not listed	Not listed	Not listed

Mutagenic Effects No information available

Reproductive Effects No information available.

Developmental Effects No information available.

Teratogenicity No information available.

STOT - single exposure None known

STOT - repeated exposure None known

Aspiration hazard No information available

Symptoms / effects,both acute and delayed No information available

Endocrine Disruptor Information No information available

Other Adverse Effects The toxicological properties have not been fully investigated.

12. Ecological information

Ecotoxicity
Do not empty into drains.

Component	Freshwater Algae	Freshwater Fish	Microtox	Water Flea
Caffeine	Not listed	LC50: = 151 mg/L, 96h flow-through (Pimephales promelas)	Not listed	EC50: = 182.12 mg/L, 4h (Daphnia species)

Persistence and Degradability No information available

Bioaccumulation/ Accumulation No information available.

Mobility .

Component	log Pow
Caffeine	-0.07

13. Disposal considerations

Waste Disposal Methods Chemical waste generators must determine whether a discarded chemical is classified as a hazardous waste. Chemical waste generators must also consult local, regional, and national hazardous waste regulations to ensure complete and accurate classification.

14. Transport information

DOT
- **UN-No** UN1544
- **Proper Shipping Name** ALKALOIDS, SOLID, N.O.S.
- **Proper technical name** (CAFFEINE)
- **Hazard Class** 6.1
- **Packing Group** III

TDG
- **UN-No** UN1544
- **Proper Shipping Name** ALKALOIDS, SOLID, N.O.S.
- **Hazard Class** 6.1
- **Packing Group** III

IATA
- **UN-No** UN1544
- **Proper Shipping Name** ALKALOIDS, SOLID, N.O.S.
- **Hazard Class** 6.1
- **Packing Group** III

IMDG/IMO
- **UN-No** UN1544
- **Proper Shipping Name** ALKALOIDS, SOLID, N.O.S.
- **Hazard Class** 6.1
- **Packing Group** III

15. Regulatory information

All of the components in the product are on the following Inventory lists: Australia X = listed China Canada Europe TSCA Korea Philippines Japan

International Inventories

Component	TSCA	DSL	NDSL	EINECS	ELINCS	NLP	PICCS	ENCS	AICS	IECSC	KECL
Caffeine	X	X	-	200-362-1	-		X	X	X	X	X

Legend:
X - Listed
E - Indicates a substance that is the subject of a Section 5(e) Consent order under TSCA.
F - Indicates a substance that is the subject of a Section 5(f) Rule under TSCA.
N - Indicates a polymeric substance containing no free-radical initiator in its inventory name but is considered to cover the designated polymer made with any free-radical initiator regardless of the amount used.
P - Indicates a commenced PMN substance
R - Indicates a substance that is the subject of a Section 6 risk management rule under TSCA.
S - Indicates a substance that is identified in a proposed or final Significant New Use Rule
T - Indicates a substance that is the subject of a Section 4 test rule under TSCA.
XU - Indicates a substance exempt from reporting under the Inventory Update Rule, i.e. Partial Updating of the TSCA Inventory Data Base Production and Site Reports (40 CFR 710(B).
Y1 - Indicates an exempt polymer that has a number-average molecular weight of 1,000 or greater.
Y2 - Indicates an exempt polymer that is a polyester and is made only from reactants included in a specified list of low concern reactants that comprises one of the eligibility criteria for the exemption rule.

U.S. Federal Regulations

TSCA 12(b) Not applicable

SARA 313 Not applicable

SARA 311/312 Hazard Categories See section 2 for more information

CWA (Clean Water Act) Not applicable

Clean Air Act Not applicable

OSHA Occupational Safety and Health Administration
Not applicable

CERCLA Not applicable

California Proposition 65 This product does not contain any Proposition 65 chemicals

U.S. State Right-to-Know Regulations Not applicable

U.S. Department of Transportation

Reportable Quantity (RQ): N
DOT Marine Pollutant N
DOT Severe Marine Pollutant N

U.S. Department of Homeland Security
This product does not contain any DHS chemicals.

Other International Regulations

Mexico - Grade No information available

16. Other information

Prepared By Regulatory Affairs
Thermo Fisher Scientific
Email: EMSDS.RA@thermofisher.com

Creation Date 15-Jul-2014
Revision Date 17-Jan-2018
Print Date 17-Jan-2018

Revision Summary	This document has been updated to comply with the US OSHA HazCom 2012 Standard replacing the current legislation under 29 CFR 1910.1200 to align with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS). SDS sections updated. 2.

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End of SDS

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