EFFECT OF VARIOUS TYPE OF GELUCIRE ON THE SUSTAINED RELEASE PERFORMANCE OF CALCIUM ALGINATE BEAD.

By

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Dedication

To my beloved father

Mr. Abdullah Al-Sheikh Wace

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List of Abbreviations

ANOVA	Analysis of variances
API	Active pharmaceutical ingredient
BP	British Pharmacopoeia
cP	Centipoise
CrDDSs	Controlled drug delivery systems
CrDDS	Controlled drug delivery system
DE	Drug entrapment
DOE	Design of experiments
DSC	Differential scanning calorimetry
EDX	Energy-dispersive X-ray spectroscopy
G unit	Guluronic acid unit
GI	Gastrointestinal
HLB	Hydrophilic lipophilic balance
HPLC	High performance liquid chromatography
ICH	International Council of Harmonization
M unit	Mannuronic acid unit
M.P	Melting point
mm	Millimeter
Nif	Nifedipine
NCE	New chemical entities
nm	Nano meter
PCM	Paracetamol
RH	Relative humidity
rpm	Rotations per minute
SD	Standard deviation
SEM	Scanning electron microscope
SITT	Small intestine transit time.
U.V	Ultra violet
USP	United State Pharmacopoeia

KESAN BERBAGAI JENIS GELUCIRE TERHADAP PRESTASI PELEPASAN MANIK KALSIUM ALGINAT

ABSTRAK

Natrium Alginat merupakan polimer asli yang banyak digunakan dalam industri farmaseutikal. Penambahbaikan terhadap sifat-sifat polimer ini penting untuk keberkesanan dan penggunaannya yang meluas dengan bahan biologi dan drug yang berbeza. Gelucire merupakan keluarga sebatian yang disediakan daripada poliethilena glikol dan minyak yang berbeza. Lipid yang terhasil mempunyai sifat pelepasan yang berbeza dan sesetengahnya digunakan sebagai agen pelepasan segera, contohnya Gelucire 44/14. Manik-manik terbentuk sebagai satu sistem baru yang menggunakan kedua-dua bahan utama ini disediakan melalui teknik "drop wise". Kajian dijalankan untuk mencirikan serta menilai manik-manik yang terhasil. Kajian tersebut termasuklah kajian pelarutan, kajian taburan saiz, kajian pengembungan, kajian mikroskopik, kajian pemerangkapan drug dan kajian kestabilan. Faktor utama yang mungkin mempengaruhi pelepasan drug dikaji menggunakan reka bentuk eksperimen Taguchi (larutan pekat kalsium klorida, larutan pekat natrium alginat, laju pengacauan, kaedah pengeringan) dan data dianalisis melalui satu program khusus (Design Expert®). Campuran kedua-dua bahan ini memberikan sifat pelepasan yang lebih baik dibandingkan dengan formula yang menggunakan hanya satu daripada bahan ini. Jenis Gelucire memainkan peranan yang penting dalam sifat pelepasaan (Gelucire 43/01 memberikan profil pelepasan yang lebih baik dibandingkan dengan Gelucire 50/13 dan Gelucire 44/14). Sifat pelepasan drug bertambah baik dan boleh kekal lebih lama dalam bentuk manik dibandingkan dengan pelepasan daripada manik kalsium alginat dan serakan pepejal Gelucire. Keadaan optimum bagi penyediaan manik adalah 10% $CaCL_2$, 2% natrium alginat, 1000 rpm dan Gelucire 43/01. Dengan menggunakan reka bentuk D optimum, nisbah drug terbaik dan nisbah Gelucire: alginat terbaik diramal melalui program (natrium alginat (larutan 2%) 90.16% : Gelucire (43/01) 7.95% : paracetamol 1.89%) dan bagi nifedipine (natrium alginat (larutan 2%) 90.14% : Gelucire (43/01) 7.90% :

nifedipine 1.96%). Keputusan yang diramal diperiksa secara praktikal dan ia memberikan profil pelepasan yang optimum dibandingkan dengan rumusan yang lain. U.S Pharmacopeia mencadangkan bahawa tidak lebih 30% daripada drug sepatutnya dilarutkan dalam satu jam pertama, di antara 30% dan 55% pada jam keempat, tidak kurang 60% pada jam kelapan dan tidak kurang 80% drug sepatutnya dilarutkan selepas 12 jam. Formula akhir terletak dalam julat ini untuk kedua-dua model drug (paracetamol and nifedipine).

EFFECT OF VARIUS TYPE OF GELUCIRE ON THE SUSTAINED RELEASE PERFORMANCE OF CALCIUM ALGINATE BEAD.

ABSTRACT

Sodium alginate is a widely used natural polymer in the pharmaceutical industry. Improvement of the sustained release properties of this polymer is important due to its effectiveness and wide use with different biomaterials and drugs. Gelucires are a family of compounds prepared from the polyethylene glycol and different oils. These lipid excipients have different sustained release properties and some of them are used as immediate release agents e.g. Gelucire 44/14. Beads formed as a new system using these two main ingredients were prepared by the drop wise technique. Studies were carried out to characterize and evaluate the beads produced. They include the dissolution studies, size distribution studies, swelling studies, microscopic studies, drug entrapment studies and stability studies. The main factors which might affect the drug release were studied by using a Taguchi experimental design (Calcium chloride solution concentration, sodium alginate solution concentration, stirring speed, drying method) and the data was analyzed by a special program (Design Expert®). Mixing these two excipients give an improved sustained release properties compared to the formula which used only one of them. The Gelucire type plays an important role in the sustained release properties (Gelucire 43/01 give better sustained release profile compared to Gelucire 50/13 and Gelucire44/14). The drug sustained release property improved and it stayed for longer time in the beads formed compared to the release from calcium alginate beads and Gelucire solid dispersions. The optimal conditions for preparing the beads were 10% $CaCl_2$, 2% Sodium alginate, 1000 rpm, and Gelucire 43/01. By using the D optimal design the best drug ratio and the best Gelucire: alginate ratio was predicted by the program (sodium alginate (solution 2%) 90.16% : Gelucire (43/01) 7.95% : paracetamol 1.89%) and for nifedipine (sodium alginate (solution 2%) 90.14% : Gelucire (43/01) 7.90%: nifedipine 1.96%). The predicted results were examined practically and its give the optimal sustained release profile comparing to the other formulations. U.S Pharmacopeia recommend that not more than 30% of the drug should dissolved in the first hour, between 30% and 55% at hour 4, not less than 60% at hour 8 and not less than 80% of the drug should dissolved after 12 hours. The dissolution of the final formula was within the recommended range for both model drugs (paracetamol and nifedipine).

CHAPTER 1

INTRODUCTION

1.0 Introduction

The formulation of a modified release drug product containing Gelucires and alginate as excipients requires a thorough understanding of biopharmaceutics and mechanisms of controlled release process by the lipid and polymer which are being used as controlled release agents.

1.1 Biopharmaceutics

According to the Encyclopedia of Pharmaceutical Technology (Swarbrick, 2007), biopharmaceutic is defined as "the study of the interrelationship of the physicochemical properties of the drug [active pharmaceutical ingredient (API)] and the drug product (dosage form in which the drug is fabricated) based on the biological performance of the drug". Stability, solubility, pH and pKa, crystalline form (polymorph), excipient interaction and compatibility of the API are studied against their pharmacokinetics and pharmacodynamic properties. Biopharmaceutics also encompasses the effect and/or the role of different manufacturing methods and technologies on the desired or expected performance of the drug product. By using different quantitative methods and applied mathematic techniques, such as theoretical models, biopharmaceutics can evaluate the effect of the drug substance, dosage form, and routes of drug administration on the therapeutic requirements of the active pharmaceutical ingredient and the dosage form in which the drug is fabricated in. It is also the study of the effect on a certain physiological environment.

Bioavailability is defined as "a measure of the rate and extent (amount) to which the active ingredient or active moiety becomes available at the site of action" (Swarbrick, 2007). It is a measure of the drug biological performance, the rate and extent of the systemically absorbed therapeutically active drug. Biopharmaceutics is also used to logically and scientifically design drug formulations to deliver the active pharmaceutical ingredient at a specific and desired rate to certain desired target organ or system to achieve the optimum therapeutic effect with minimal adverse reactions or side effects.

Thus biopharmaceutics can be summarized to encomposed the following components:

1. The physicochemical characteristics of the active drug substance.
2. The physicochemical characteristics of the desired drug product.
3. The considerations of the anatomy and physiology of the human body.
4. The knowledge of the pharmacodynamics of the drug including the desired onset of time, duration and intensity of clinical response.
5. The knowledge of the pharmacokinetics of the drug including absorption distribution, elimination and target drug concentration.

Biopharmaceutics also involves studies of factors that influence the protection and stability of the drug within the product, the rate of drug release from the drug product, the rate of dissolution of the drug at the absorption site and the availability of the drug at its site of action

1.1.1 Biopharmaceutical considerations in drug product design

Each route of drug administration has special biopharmaceutical considerations which should be taken into account while designing the drug dosage form (Table 1.1).

An interesting example is the systemic drug absorption from an extravascular site and from oral route. This absorption is affected by:

1. The anatomic and physiologic properties of the target site.
2. The physicochemical properties of the drug and the drug product.
3. The anatomy, physiology, and the contents of the gastrointestinal tract (GIT) (Shargel and Yu, 1999).

All of these factors should be considered in the design of a drug product for oral administration. Biopharmaceutic studies usually use the *in vitro* or *in vivo* methods. *In vitro* methods are used to:

a) Understand the physico-chemical properties of the drug and drug product.

b) Evaluate the quality of the manufacturing process.

Finally, the drug must be studied *in vivo,* in humans, to evaluate different aspects of drug formulation and delivery by studying the pharmacodynamics, pharmacokinetics, therapeutics, and toxicity of the drug product.

Table 1.1 Common routes of drug administration and their advantages and disadvantages. [**Adapted from** Swarbrick (2007).]

Route		**Bioavailability**	**Advantages**	**Disadvantages**
Parenteral routes	Intravenous bolus (IV)	Complete (100%) systemic drug absorption. Rate of bioavailability considered instantaneous	Drug is given for immediate effect	Increased chance of adverse reaction. Possibility of anaphylaxis
	Intravenous infusion (IV inf)	Complete (100%) systemic drug absorption Rate of drug absorption controlled by infusion pump	Plasma drug levels more precisely Controlled. May inject large fluid volumes May use drugs with poor lipid solubility and/or irritating drugs	Requires skill in insertion of infusion set Tissue damage at the site of injection (infiltration, necrosis, or sterile abscess)
	Intramuscular injection (IM)	Rapid from aqueous solution Slow absorption from non-aqueous (oil) solutions	Easier to inject than intravenous Injection Larger volumes may be used compared to subcutaneous solution	Irritating drugs may be very painful Different rates of absorption depending upon muscle group injected and blood flow
	Subcutaneous injection (SC)	Prompt from aqueous solution. Slow absorption from repository (depot) formulations	Self-administration is allowed. Generally, used for insulin injection	Rate of drug absorption depends upon blood flow and injection volume

Table 1.1 (continued) Common routes of drug administration and their advantages and disadvantages [Adapted from Swarbrick (2007)]

Route		Bioavailability	Advantages	Disadvantages
Enteral routes	Oral	Absorption may vary. Generally, slower absorption rate compared to IV bolus or IM injection.	Safest and easiest route of drug Administration. May use Immediate-release and modified-release drug products.	Some drugs may have erratic absorption, unstable in the gastrointestinal tract or metabolized by liver prior to systemic absorption
	Rectal	Absorption may vary from suppository More reliable absorption from enema (solution)	Useful when patient cannot swallow medication Used for local and systemic effects	Absorption may be erratic. Suppository may migrate to different position. Some patients feel discomfort.
Other routes	Transdermal	Slow absorption. Absorption rate may vary. Increased absorption with occlusive dressing	Transdermal delivery system (patch) is easy to use Used for lipid-soluble drugs with low dose and low molecular weight	Some irritation by patch or drug. Permeability of skin varies with condition, anatomic site, age, and gender. Type of cream or ointment base affects drug release and absorption.
	Inhalation	Rapid absorption. Total dose absorbed varies.	May be used for local or systemic effects	Particle size of drug determines anatomic placement in respiratory tract. May stimulate cough reflex. Some drug may be swallowed.

There are some major biopharmaceutical topics for research and regulatory considerations in drug development including drug dissolution, absorption, metabolism and interaction with food and other components in the GIT (Shargel and Yu, 1999 and Wise, 2000).

By choosing the suitable route of drug administration and proper design of the drug product, drug's bioavailability can be varied from rapid to slow, to obtained complete systemic drug absorption and sustained rate of absorption (Wise, 2000). Systemic drug absorption is followed by distribution and elimination processes which usually are not affected by the formulation of the drug. To get the desired release of the drug which determine the onset, intensity and duration of drug action, two important parameters should be change, i.e. the rate of drug release from the product and the rate of drug absorption (Shargel and Yu, 1999 and Wise, 2000).

1.1.2 Oral drug absorption: Physiologic considerations

Drugs may be administered by different routes (Table 1.1). All drugs are absorbed into the systemic circulation from the site of administration. The only exception to this rule is the intravenous route which is considered to have complete or 100% bioavailability since the drug is placed directly into the systemic circulation(Li and Jasti, 2004). The other routes are greatly affected by the conditions at the site of administration. The most common route of drug administration is the oral route (Table 1.1). Understanding the physiological considerations of the GI system can help us in the dosage form design. Major physiologic processes that occur in the GI system are secretion, digestion and absorption (Krowczynski, 1987 and Li and Jasti, 2004).

a) Secretion is the transport of fluid, electrolytes, peptides, and proteins into the lumen of the alimentary canal. Enzymes in saliva and pancreatic secretions are excluded because they are involved in the digestion of carbohydrates and proteins (Krowczynski, 1987). Other secretions such as mucus which protects the linings of the lumen of the GIT also are not included in the definition.

b) Digestion is defined as the breakdown of food constituents into smaller structures in preparation for absorption. The process of absorption is defined as the entry of constituents from the lumen of the gut into the body (Krowczynski, 1987).

c) Absorption may be defined in another way as the net result of both lumen-to-blood and blood-to-lumen transport movements (Wise, 2000). Most of the drugs and food constituents are absorbed in the proximal area (duodenum) of the small intestine.

When a drug is taken orally, it passes through various parts of the enteral canal including the oral cavity, esophagus, and the other parts of the GIT. Residues and undigested food exit the body through the anus. Drugs are absorbed from all parts of the alimentary canal by passive diffusion but the major sites lie in duodenum and jejunum (Wise, 2000).

The optimum site for drug absorption, after oral administration is the upper portion of the small intestine or duodenum. Due to its unique anatomy, the duodenum provides a very large surface area for the drug to diffuse passively.

The total time a drug is retained in the GIT is an important factor for biopharmaceutic studies and thus this transit of drug can be broadly divided into:

1) Total transit time, which includes gastric emptying, small intestinal transit, and colonic transit.

2) Small intestine transit time (SITT).

The total transit time ranges from 0.4 to 5 days while the small intestine transit time ranges from 3 to 4 h in most healthy subjects (Li and Jasti,2004, Swarbrick,2007). The drug absorption might be erratic or incomplete if the absorption is not completed within the small intestine transit time (SITT). This is because the small intestine is normally filled with digestive juices and liquids, which keep the lumen contents as fluid. When the lumen content reaches the colon the fluid is reabsorbed and the lumen content become semisolid or solid. This makes the drug dissolution erratic and difficult (Li and Jasti, 2004).

1.1.2.1 GI motility

GI motility causes the drug to move through the alimentary canal. If the drug is formulated as a non-biodegradable controlled-release dosage form it should get completely released into this absorption window before the movement into the large bowel. It is important because the drug might not stay at the absorption site and thus result in incomplete absorption (Swarbrick, 2007).

Some drugs are only soluble at a particular pH or they are absorbed using a specific mechanism. With such properties those drugs can only be absorbed in specific segments of the GI tract. Those particular segments are named "absorption windows". Any factors which effectively increase or decrease the Gastric emptying time and the SITT (small intestinal transit time) will affect the drug absorption from its absorption window(Swarbrick, 2007).

The transit time of the drug in the GIT depends on the Pharmacological properties of the drug, type of dosage form and various physiological factors such as the alimentary canal state that includes digestive or fed state, fasted state or inter-digestive state.

1.1.2.1.1 Gastric emptying time

Since the duodenum has the greatest capacity for the absorption of drugs from the GIT, a delay in the gastric emptying time can slow the rate and possibly the extent of drug absorption from the duodenum, thereby prolonging the absorption of the drug . Factors that tend to delay gastric emptying include consumption of high fat meals, cold beverages, and anticholinergic drugs.

1.1.2.1.2 Intestinal motility

The drug must have a sufficient resident time at the site of absorption for optimum absorption. In the case of high motility in the intestinal tract, as in diarrhea, the drug has a very brief residence time and less opportunity for adequate absorption.

1.1.2.2 Blood perfusion of the GIT

Either the blood carries the absorbed drug from the absorption site to the systemic circulation directly or drugs are absorbed from the small intestine into the mesenteric vessels which flow to the hepatic-portal vein and then to the liver prior to reaching the systemic circulation, this is known as first pass effect.

The rate of systemic drug absorption from the intestinal tract will decrease if there is any decrease in mesenteric blood flow, as in the case of congestive heart failure. Microvilli in the intestinal lining possess lymphatic ducts that play a role in the absorption of the dietary lipids and possibly some lipophilic drugs. Such drugs,that are absorbed through the lymphatic vessels (passing the first pass effect), are not metabolized in the liver prior to entering blood circulation.

1.1.2.3 Effect of food and other factors on GI drug absorption

Digested foods may affect the intestinal pH and solubility of drugs. Food effects are not always predictable. Food in the GI lumen stimulates the flow of bile, that contains bile acids which act as surfactants. These acids are involved in the digestion and solubilization of fats and lipophilic drugs by increasing their solubility through micelle formation.

However the presence of food in the stomach together with some basic drugs possessing limited aqueous solubility (e.g. cinnarizine) stimulate hydrochloric acid secretion, which lowers the pH, causing rapid dissolution of the drug and better absorption. Generally, the bioavailability of drugs is better in patients in the fasted state and with a large volume of water (Swarbrick, 2007).

The drug dosage form may also be affected by food. For example, enteric-coated tablets may stay in the stomach for a longer period of time because food delays stomach emptying (Shargel and Yu, 1999). If the enteric-coated tablet does not reach the duodenum rapidly, drug release and subsequent systemic drug absorption are delayed. In contrast, enteric-coated beads or microparticles that disperse in the stomach, are less affected by food, and demonstrate more consistent drug absorption from the duodenum(Li and Jasti, 2004).

Food may also affect the integrity of the dosage form, causing an alteration in the release rate of the drug. For example, theophylline bioavailability from Theo-24® controlled-release tablets is much more rapid when given to a subject in the fed rather than fasted state(Wise, 2000).

Drugs or nutrients or both may also affect the absorption of other drugs. For example, propantheline bromide is an anticholinergic drug that slows stomach emptying and motility of the small intestine and may reduce stomach acid secretion. Grapefruit juice was found to increase the plasma level of many drugs due to inhibition of their metabolism in the liver (Swarbrick, 2007).

1.1.3 Oral drug absorption: Pharmaceutical factors affecting drug bioavailability

Different biopharmaceutical considerations in the design and manufacture stage affect the drug product to deliver the active ingredient with the desired bioavailability. These factors include: the type of drug product e.g., tablet, capsule, solid dispersion etc; the nature of the excipients in the drug product, the physicochemical properties of the drug molecule and the route of drug administration.

1.1.3.1 Dissolution

Dissolution is the process by which a chemical or drug becomes dissolved in a solvent. In human bodies, drug dissolution in an aqueous medium is an important prior condition of systemic absorption (Banakar, 1992). The rate of dissolution of the solid dosage form in the GIT often controls the rate of systemic absorption of the drug. Thus, "dissolution tests can discriminate the formulation factors that may affect drug bioavailability "(Swarbrick, 2007).

The rate of dissolution, (dC/dt) x (1/A), is the amount of drug *dC* dissolved per unit area *A* per time *dt* (e.g., g/cm^2 per min) (Swarbrick, 2007, Banakar, 1992). The Noyes–Whitney equation shows that dissolution rate is influenced by: the physicochemical characteristics of the drug, the formulation of the drug, the solvent, the temperature of the medium and the agitation strength (Banakar, 1992).

A dissolution test *in vitro* gives us information about the rate and extent of drug dissolution in an aqueous medium in the presence of the excipients contained in the drug product. Choosing unsuitable dissolution method may lead to a potential bioavailability problem. Dissolution testing conditions differ with each drug formulation depending upon agitation rates, medium (including pH) and simulating technique (basket, paddles and others)

The nature of the dissolution medium, the solubility the drug and the amount of drug in the dosage form all can affect the dissolution test (Banakar, 1992, Wise, 2000).

1.1.3.2 Physicochemical nature of the drug

1.1.3.2.1 Solubility, pH, and drug absorption

The natural pH of the GIT environment varies from acidic in the stomach to slightly alkaline in the small intestine. Drug solubility may be improved or delayed with the addition of acidic, basic, or lipid excipients. For relatively insoluble compounds the dissolution rate is often the rate-determining step in the overall absorption process. Alternatively, for soluble compounds the rate of permeation across biological membrane is the rate-determining step.

To protect the physically or chemically unstable drugs from degradation, special excipients, coating or manufacturing process may be used. Controlled release drug products are non-disintegrating dosage forms and buffering agents may be added to slow or modify the release rate of a fast-dissolving drug (Wise, 2000).

The buffering agent can be defined as an agent when is solution form will maintains pH of a solution at a constant value when small amounts of acidic or basic substances are added. To function in this manner, a buffer solution will necessarily contain either a weak acid and its conjugate base, or a weak base and its conjugate acid. The added buffering agents play its role when it is released slowly rather than rapidly so that the drug does not dissolve immediately in the surrounding GI fluid (Swarbrick, 2007).

1.1.3.2.2 Stability, pH, and drug absorption

The pH-stability profile is "a plot of reaction rate constant for drug degradation versus pH" (Swarbrick, 2007) and it helps to predict if some of the drug will decompose in the GIT. For example, the stability of erythromycin is pH-dependent. In acidic medium, erythromycin decomposes rapidly, whereas at neutral or alkaline pH the drug is relatively stable. As a result, erythromycin tablets are enterically coated to protect against acidic degradation in the stomach (Krowczynski, 1987,Schreier, 2001).

Drug partition coefficients is important to predict how well it will be able to cross biological membranes. The measure of drug's partition coefficient between an oil and water phase (log P) gives a measure of the lipophilicity of the drug.

1.1.3.2.3 Particle size and drug absorption

The effective surface area of the drug is increased enormously by reducing the particle size which can lead to rapid dissolution rate of drug. Although the geometric shape of the drug particle affects the surface area, and during dissolution the surface changes constantly during dissolution, the solute particle is usually assumed to have retained its geometric shape for the purpose of dissolution calculations (Banakar, 1992, Swarbrick, 2007).

Studies of particle size and particle size distribution are important for drugs that have low water solubility. Smaller particles will have higher total effective or specific surface area which enhances contact with water penetration into the particles leading to increases in the dissolution rates(Shargel and Yu, 1999).

1.1.3.2.4 Polymorphic crystals, solvates, and drug absorption

Polymorphism refers to the arrangement of a drug in various crystal forms (polymorphs). Polymorphs have the same chemical structure but different physical properties, such as solubility, density, hardness, and compression characteristics (Schreier, 2001). Some polymorphic crystals may have much lower aqueous solubility than the amorphous forms, causing a product to be incompletely absorbed.

In general, the crystal form that has the lowest free energy is the most stable polymorph. Polymorphs that are meta-stable may convert to a more stable form over time. A change in crystal form may cause problems in manufacturing the product. For example, a change in crystal structure of the drug may cause cracking in a tablet or even prevent granules from being compressed into a tablet resulting in a need to reformulate of the product (Wise, 2000).

1.1.4 Formulation factors affecting drug dissolution

Excipients are pharmacodynamically inactive substances that are added to a formulation to provide certain functional properties to the drug and dosage form. Excipients may be added to stabilize the drug, prevent from degradation, control the rate of drug absorption from the absorption site and increase drug bioavailability, etc. Improper use of excipients may lead to altered drug bioavailability and pharmacodynamic activity. They may affect the drug dissolution rate by altering the medium in which the drug is dissolved or by drug-excipient interaction (Swarbrick, 2007) and may enhance or diminish the rate and extent of systemic drug absorption. Those which increase the aqueous solubility of the drug generally increase the rate of drug dissolution and absorption and may interact directly with the drug to form a water-soluble or water-insoluble complex (Shargel and Yu, 1999, Schreier, 2001).

Excipients may increase the retention time of the drug in the GIT and therefore increase the amount of drug absorbed. Some of them may act as carriers to increase drug diffusion across the intestinal wall. The addition of surface-active agents may increase wetting as well as solubility of drugs. In contrast, many excipients may retard drug dissolution and thus reduce drug absorption (Florence and Attwood, 2006). For example Shellac used as a tablet coating, upon aging, can slow the drug dissolution rate (Limmatvapirat *et al.*, 2004).

Surfactants affect the drug solution according to its concentration, low concentrations of surfactants lower the surface tension and increase the rate of drug dissolution, whereas higher concentrations of surfactants tend to form micelles with the drug and thus decrease the dissolution rate (Florence and Attwood, 2006).

1.2 Controlled release

Conventional solid pharmaceutical dosage forms, like tablets and other traditional pharmaceutical products are still commonly seen today in the prescription and over-the-counter drug market place. Such types of drug delivery systems often necessitate repeated and short dosage intervals to achieve and maintain the drug concentration in therapeutic index range. This yields an undesirable "seesaw" drug level in the body (for drugs with short $t_{1/2}$, t_{max} and high absorption rate) as shown by Figure 1.1, thus the release of such drugs should be modified to increase the $t_{1/2}$, t_{max}

and slow down the absorption rate. This could lead to large dosage intervals and reduction in the frequency of dosing.

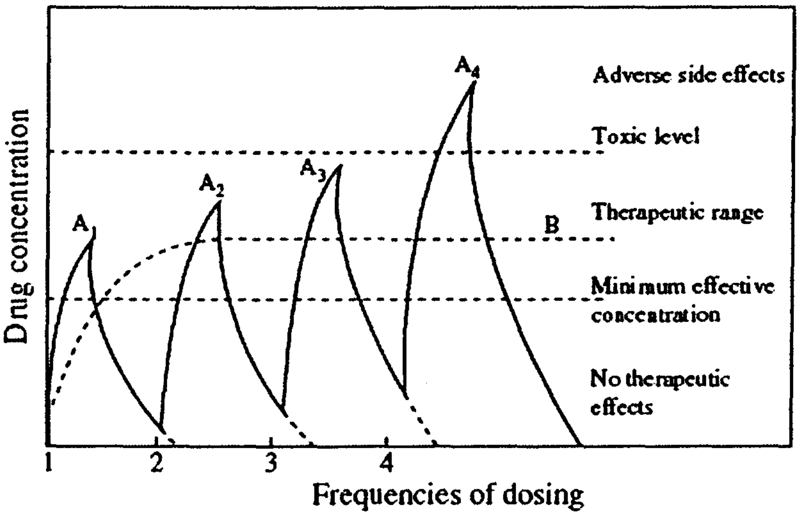


Figure 1.1 Drug concentration profiles in the systemic circulation as a result of taking a series of multiple doses of a conventional drug-delivery system(for drugs with short $t_{1/2}$, t_{max} and high absorption rate) (A1, A2, A3, A4.....) in comparison with the ideal drug concentration profile (B).
[**Adapted from** (Chien, 1992)]

USP pharmacopeia define the Extended release tablets as they are "formulated in such manner as to make the contained medicament available over an extended period of time following ingestion" and allows a twofold reduction in dosing frequency or increase in patient compliance or therapeutic performance. It is interesting to note that the USP considers that the terms repeat action, prolonged release and sustained release are interchangeable with extended release. While controlled release give us a dosage form release drug at a constant rate and provide plasma concentrations that remain invariant with time (U.S.Pharmacopoeia, 2007).

1.2.1 Advantages of controlled release systems

A number of advancements have been made recently in the development of new techniques for drug delivery. These techniques are capable of regulating the rate of drug delivery, sustaining the duration of therapeutic action, and/or targeting the drug to specific tissue (Craig, 2002)

These advancements have already resulted in the development of several novel drug delivery systems that could provide one or more of the following benefits:

a) Controlled administration of a therapeutic dose at a desirable rate of delivery

b) Maintenance of drug concentration within an optimal therapeutic range for prolonged duration of treatment

c) Maximization of efficacy-dose relationship

d) Reduction of adverse side effects

e) Minimization of the needs for frequent dose intake

f) Enhancement of patient compliance.

1.2.2 Classification of controlled release systems

According to the encyclopedia of pharmaceutical technology, controlled release systems which are based on the technical sophistication of the controlled-release drug delivery systems (CrDDSs) that have been marketed so far or that are under active development can be classified as follow:

a) Rate-preprogrammed drug delivery systems

b) Activation-modulated drug delivery systems

c) Feedback-regulated drug delivery systems

d) Site-targeting drug delivery systems

As shown in plate1.1, the scientific concepts and technical principles behind the development of this new generation of drug-delivery systems are outlined

1.2.2.1 Rate-preprogrammed drug delivery systems

"In this group of CrDDSs, the release of drug molecules from the delivery systems has been preprogrammed at a specific rate profile. This is accomplished by system design, which controls the molecular diffusion of drug molecules in and/or across the barrier medium within or surrounding the delivery system. Fick's laws of diffusion are often followed"(Swarbrick, 2007).

These CrDDSs can further be classified as follow:

1. Polymer membrane permeation-controlled drug delivery systems.
2. Polymer matrix diffusion-controlled drug delivery systems.
3. Polymer (membrane/matrix) hybrid-type drug delivery systems.
4. Micro-reservoir partition-controlled drug delivery systems.

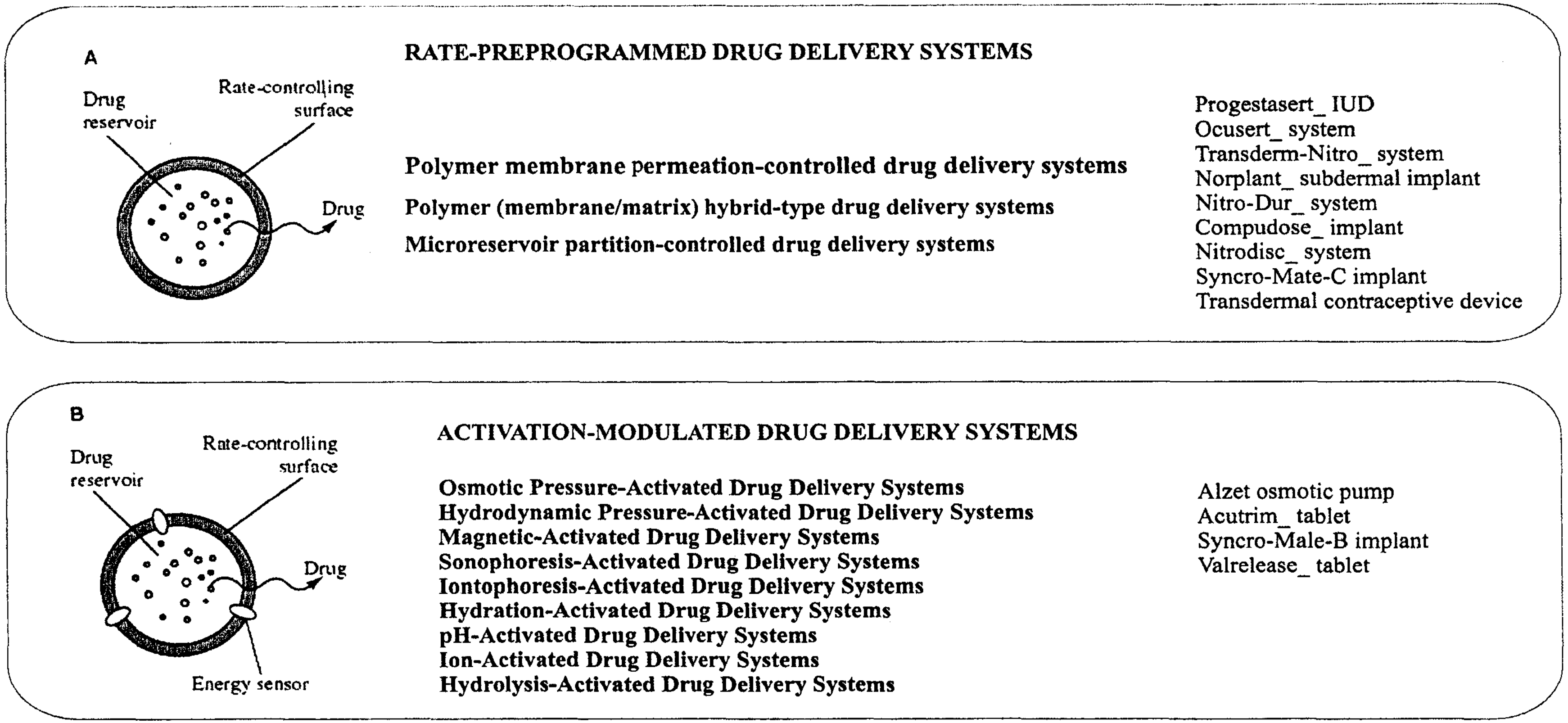
1.2.2.1.1 Polymer membrane permeation-controlled drug delivery systems

"In this type of CrDDSs, a drug formulation is either totally or partially encapsulated in a drug reservoir compartment whose drug-releasing surface is covered by a rate-controlling polymeric membrane"(Swarbrick, 2007).

The drug reservoir can be:

1. Drug solid particles.
2. Dispersion of drug solid particles.
3. Concentrated drug solution in a liquid.
4. Solid-type dispersing medium.

The polymeric membrane can be fabricated from different types of materials for example; homogeneous or heterogeneous polymeric material, non-porous, microporous or semi-permeable membrane.



RATE-PREPROGRAMMED DRUG DELIVERY SYSTEMS

Polymer membrane permeation-controlled drug delivery systems
Polymer (membrane/matrix) hybrid-type drug delivery systems
Microreservoir partition-controlled drug delivery systems

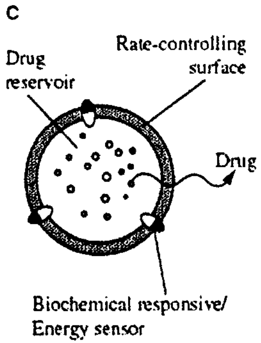
Progestasert_ IUD
Ocusert_ system
Transderm-Nitro_ system
Norplant_ subdermal implant
Nitro-Dur_ system
Compudose_ implant
Nitrodisc_ system
Syncro-Mate-C implant
Transdermal contraceptive device

ACTIVATION-MODULATED DRUG DELIVERY SYSTEMS

Osmotic Pressure-Activated Drug Delivery Systems
Hydrodynamic Pressure-Activated Drug Delivery Systems
Magnetic-Activated Drug Delivery Systems
Sonophoresis-Activated Drug Delivery Systems
Iontophoresis-Activated Drug Delivery Systems
Hydration-Activated Drug Delivery Systems
pH-Activated Drug Delivery Systems
Ion-Activated Drug Delivery Systems
Hydrolysis-Activated Drug Delivery Systems

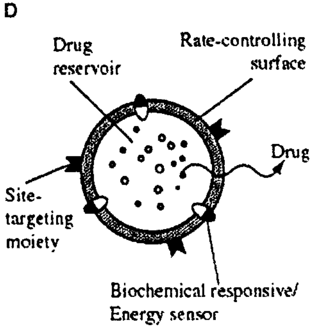
Alzet osmotic pump
Acutrim_ tablet
Syncro-Male-B implant
Valrelease_ tablet

Plate 1.1 Classification of controlled release drug delivery systems. [**Adapted from** (Swarbrick, 2007 and Wise, 2000)] with modifications.


C
Drug reservoir
Rate-controlling surface
Drug
Biochemical responsive/ Energy sensor

FEEDBACK-REGULATED DRUG DELIVERY SYSTEMS

Bioerosion-Regulated Drug Delivery Systems
Bioresponsive Drug Delivery Systems
Self-Regulating Drug Delivery Systems


D
Drug reservoir
Rate-controlling surface
Drug
Site-targeting moiety
Biochemical responsive/ Energy sensor

SITE-TARGETING DRUG DELIVERY SYSTEMS

Plate 1.1 (continued) Classification of controlled release drug delivery systems. [**Adapted from** (Swarbrick, 2007 and Wise, 2000)] with modification.

The encapsulation of drug into the reservoir compartment can be done by different techniques for example; molding, capsulation or micro-encapsulation to form different shapes and sizes of drug delivery systems, (Figure 1.2).

Different factors control the release of drug molecules from this type of CrDDS. These include partition coefficient, diffusivity of drug molecule, rate-controlling membrane and thickness of the membrane.

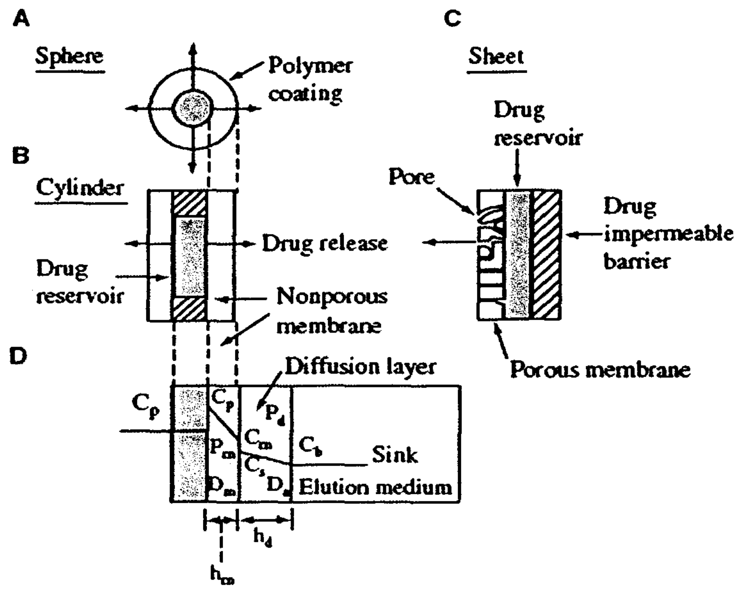

A
Sphere
Polymer coating
B
Cylinder
Drug reservoir
Drug release
Nonporous membrane
C
Sheet
Drug reservoir
Pore
Drug impermeable barrier
Porous membrane
D
Diffusion layer
C_p
C_p
P_d
P_m
C_m
C_b
Sink
C_s
D_m
D_d
Elution medium
h_m
h_d

Figure 1.2 Release of drug from various shapes of polymer membrane permeation-controlled drug-delivery systems: (A) sphere-type, (B) cylinder-type, and (C) sheet-type. In (D), the drug concentration gradients across the rate-controlling polymeric membrane and hydrodynamic diffusion layer exist in series. Both the polymer membrane, which is either porous or non-porous, and the diffusion layer have a controlled thickness (hm and hd, respectively).

[**Adapted from** (Swarbrick, 2007)]

1.2.2.1.2 Polymer matrix diffusion-controlled drug delivery systems

"In this type of CrDDSs, the drug reservoir is produced from the homogeneous dispersion of drug particles in either a lipophilic or a hydrophilic polymer matrix"(Swarbrick, 2007).

The drug dispersion in the polymer matrix is accomplished by either blending a dose of finely ground drug particles with a viscous liquid (or a semisolid) polymer, followed by a crosslinking of polymer chains, such as; sodium alginate and the calcium chloride solution or mixing solid drugs with a molten polymer at an elevated temperature for example; Gelucires.

The resultant drug-polymer dispersion is then molded or extruded to form drug delivery devices of various shapes and sizes designed for a specific application (Figure.1.3). Another way to achieve this dispersion is by dissolving the drug and the polymer in a common solvent, followed by solvent evaporation, at an elevated temperature and/or under a vacuum, in a mold.

Factors that control the release of drug molecules from this type of CrDDSs are the loading level, polymer solubility of the drug, and the diffusivity of the drug in the polymer matrix. Several CrDDSs of this type have been successfully marketed for therapeutic uses.

1.2.2.1.3 Polymer (membrane/matrix) hybrid-type drug delivery systems

"This type of CrDDSs, is developed with the objective of combining the constant drug release kinetics of polymer membrane permeation-controlled drug delivery systems with the mechanical superiority of polymer matrix diffusion-controlled drug delivery systems" (Swarbrick, 2007).

1.2.2.1.4 Micro-reservoir partition-controlled drug delivery systems

"In this type of CrDDSs, the drug reservoir is a suspension of drug solid particles in an aqueous solution of a water-miscible polymer, like polyethylene glycols" (Swarbrick, 2007). Different shapes and sizes of drug-delivery devices can be prepared from this micro-reservoir-type CrDDS by molding or extrusion techniques (Chien, 1992).

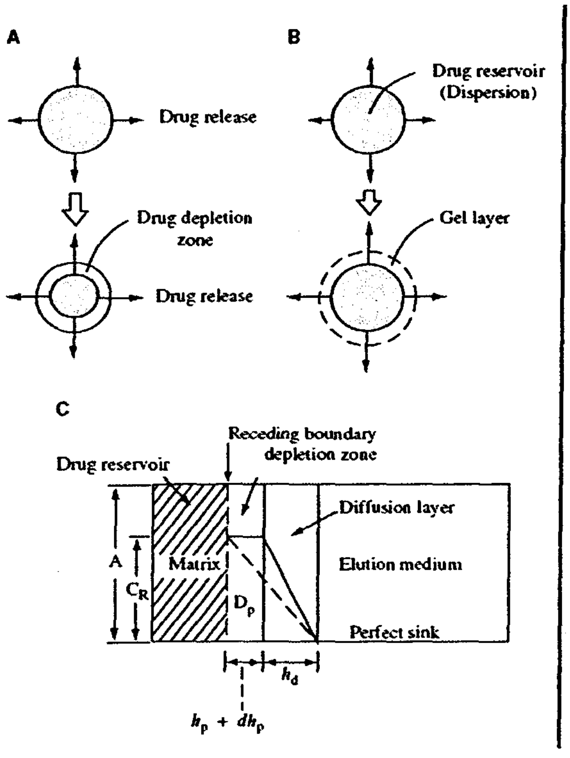

A
B
Drug release
Drug reservoir (Dispersion)
Drug depletion zone
Gel layer
Drug release
C
Receding boundary depletion zone
Drug reservoir
Diffusion layer
Elution medium
Perfect sink
Matrix
A
C_R
D_p
h_d
$h_p + dh_p$

Figure 1.3 Release of drug from the polymer matrix diffusion controlled drug delivery systems with drug reservoir exists as a homogeneous dispersion in (A) lipophilic, non-swellable polymer matrix, with a growing thickness of drug depletion zone, or (B) a hydrophilic, swellable polymer matrix, with a growing thickness of drug-depleted gel layer. In (C), the drug concentration gradients across the time-dependent drug depletion zone, with a growing thickness (hp dhp), and the hydrodynamic diffusion layer, with a controlled thickness (hd), are shown in series.
[Adapted from (Swarbrick, 2007)]