

**DEVELOPMENT AND CHARACTERISATION OF FAST RELEASE
BIOADHESIVE SUPPOSITORY SYSTEM CONTAINING
DICLOFENAC SODIUM**

by

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LIST OF ABBREVIATIONS & SYMBOLS

ACN	=	Acetonitrile
ANOVA	=	Analysis of variance
AUC	=	Area under curve
BP	=	British Pharmacopeia
CB	=	Cocoa Butter
CBR	=	Cocoa Butter replacers
CBS	=	Cocoa Butter substitute
CE	=	ChocExa
CH ₂ Cl ₂	=	Dichloromethane
CH ₃ COONH ₄	=	Ammonium acetate
cm	=	Centimetre
cm ²	=	Centimetre square
CMC	=	Carboxymethyl cellulose
CP	=	Carbopol/Carbophil
CV	=	Coefficient of variation
Dc	=	Diclofenac
DcNa	=	Diclofenac sodium
DSC	=	Differential Scanning Calorimetry
D1	=	Conventional suppository
D2	=	Hollow suppository
D3	=	Double-layered suppository
FDA	=	Food and Drug Administration
FTIR	=	Fourier Transform Infrared
g	=	Gramme
GI	=	Gastrointestinal
GLC	=	Gas liquid chromatography
HCl	=	Hydrochloric acid
HEC	=	Hydroxyethyl cellulose
HPC	=	Hydroxypropyl cellulose
HPLC	=	High performance liquid chromatography
hr	=	Hour

HS	=	Supercocofat HS
Hysoc	=	Hysoc 36
ID	=	Internal diameter
IPA	=	Isopropyl alcohol
J	=	Joule
J/g	=	Joule per gramme
K_e	=	Coefficient of elimination
kg	=	Kilogramme
k_1	=	Initial drug release rate
L/hr	=	Litre per hour
LOD	=	Limit of detection
LOQ	=	Limit of quantification
M	=	Molarity
MA	=	Mefenamic acid
MC	=	Methyl cellulose
MeOH	=	Methanol
mEq/kg	=	Milliequivalent per kilogramme
mg	=	Milligramme
mg/L	=	Milligramme per litre
MHEC	=	Methylhydroxyethyl cellulose
min	=	Minute
mL	=	Millilitre
mm/s	=	Millimetre per second
MW	=	Molecular weight
NaCl	=	Sodium chloride
NaCMC	=	Sodium carboxymethyl cellulose
NaOH	=	Sodium hydroxide
NSAID	=	Non-steroidal anti-inflammatory drug
N'ice	=	N'ice 368
PAA	=	Polyacrylic acid
PCP	=	Polycarbophil
PEG	=	Polyethylene glycol
PGEF	=	Polyglycerol ester of fatty acid
PHPMAm	=	Poly(N-2-hydroxypropyl methacrylamide)

PVA	=	Poly(vinylalcohol)
PVP	=	Polyvinylpyrrolidone
P1	=	Physical mixture of DcNa-CP
P2	=	Coground mixture of DcNa-CP
P3	=	Granules of DcNa-CP
rpm	=	Rotation per minute
SD	=	Standard deviation
SFI	=	Solid fat index
SPSS	=	Statistical procedures for social science
SR	=	Sustained release
Super	=	Supercocofat
Soc	=	Socolate 36
TLC	=	Thin layer chromatography
T _m	=	Melting point
t _{1/2}	=	Half life
T _{50%}	=	Time to reach 50 % of drug release
USP	=	United States Pharmacopeia
UK	=	United Kingdom
US	=	United States of America
UV	=	Ultraviolet
W31	=	Witepsol W31
%	=	Percent
°C	=	Degree centigrade
°C/min	=	Degree centigrade per minute
Δ H	=	Enthalphy
μL	=	Microlitre
μg	=	Microgramme
μg/mL	=	Microgramme per millilitre
α	=	Alpha
β	=	Beta
γ	=	Gamma
>	=	Larger than
<	=	Smaller than

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PEMBANGUNAN DAN PENCIRIAN SISTEM SUPOSITORI BIOADHESIF PELEPASAN CEPAT YANG MENGANDUNGI NATRIUM DIKLOFENAK

ABSTRAK

Perpindahan dan migrasi supositori ke bahagian atas rektum merupakan suatu masalah biokeperolehan rektal yang lazim. Hanya drug yang diserap daripada supositori yang kekal di bahagian bawah rektal dapat dilindungi daripada tindakan berkesan metabolisme hati, manakala drug yang diserap daripada bahagian atas rektum pula akan mengalami metabolisme lintasan pertama. Suatu sistem supositori bioadhesif telah dibangunkan untuk mengekalkan kedudukan supositori pada bahagian bawah rektum dengan menggunakan dasar berminyak dan dasar larut-air, polimer hidrofilik Karbopol 934P (CP) dan Polivinilpirolidon K90 (PVP) serta natrium diklofenak (DcNa) sebagai drug model. Antara dasar-dasar supositori yang digunakan, ChocExa, Supercocofat HS dan Supercocofat menyerupai Cocoa Butter dengan ciri kekerasan dasar dan tempoh masa pelembutan dasar yang setara. Dasar-dasar ini juga mempunyai julat suhu peleburan, ciri bioadhesif serta profil pelepasan drug dua fasa yang hampir sama. CP merupakan polimer bioadhesif yang lebih baik daripada PVP. Kehadiran CP pada kandungan 2 % w/w mampu menyumbangkan sifat bioadhesif yang berkesan tetapi sebarang pertambahan kandungan CP boleh memanjangkan tempoh masa pelepasan DcNa dalam air suling lalu meningkatkan nilai konstan pelepasan drug awal, k_1 serta meningkatkan masa untuk mencapai 50 % pelepasan drug, $T_{50\%}$. Dengan menggunakan ChocExa dalam kehadiran 2 % w/w CP serta DcNa, tiga jenis rekabentuk supositori telah dibangunkan, iaitu supositori konvensional, supositori berliang dan supositori dwi-lapisan. Tiga sediaan DcNa-CP juga

dinilai, iaitu campuran fizikal yang biasa, campuran berkisar dan sediaan granul basah. Supositori berliang and supositori dwi-lapisan mempunyai kadar pelepasan drug yang lebih cepat berbanding supositori konvensional. Kedua-dua jenis supositori ini memiliki nilai kekerasan dasar yang lebih rendah serta tempoh masa pelembutan yang lebih cepat. Kesemua rekabentuk supositori yang mengandungi sediaan granul DcNa-CP pula mempunyai kadar pelepasan yang lebih cepat berbanding campuran biasa dan campuran berkisar. Kedua-dua profil FTIR dan DSC menunjukkan bahawa campuran berkisar DcNa-CP mempunyai profil perantaraan campuran biasa dan sediaan granul basah. Sebelum kajian *in vivo* dijalankan, suatu kaedah isokratik HPLC-UV yang mudah, spesifik dan sensitif telah divalidasi untuk tujuan kuantifikasi kandungan DcNa dalam plasma arnab. Kajian *in vivo* ke atas enam ekor arnab ini dijalankan berdasarkan kajian saling melintang tiga arah secara rawak. Supositori konvensional yang mengandungi sediaan granul DNa-CP (B) serta supositori berliang yang mengandungi sediaan granul DcNa-CP (C) telah dibandingkan dengan supositori konvensional yang mengandungi sediaan granul DcNa sahaja (A). Kadar dan jumlah penyerapan ($AUC_{0-\infty}$) serta nilai kepekatan maksimum plasma drug (C_{max}) untuk formulasi B dan C didapati lebih tinggi secara signifikan berbanding formulasi A. Namun, nilai $AUC_{0-\infty}$ dan C_{max} antara B dan C pula tidak berbeza secara signifikan, walaupun pada dasarnya nilai $AUC_{0-\infty}$ untuk formulasi C lebih tinggi daripada B. Secara kesimpulannya, suatu sistem supositori bioadhesif yang mampu ditempatkan di bahagian bawah rektum telah berjaya dibangunkan. Formulasi bioadhesif yang baru ini telah menunjukkan peningkatan biokeperolehan, sekaligus memperlihatkan kelebihan berbanding supositori konvensional.

**DEVELOPMENT AND CHARACTERISATION OF FAST RELEASE
BIOADHESIVE SUPPOSITORY SYSTEM CONTAINING
DICLOFENAC SODIUM**

ABSTRACT

The migration of suppository towards the upper rectum has always posed a problem in rectal bioavailability. Only drug absorbed from suppositories retained at the lower rectum can bypass the strongly metabolising liver, while drug absorbed from the upper rectum will experience first-pass metabolism. A bioadhesive suppository system was developed to localise the suppository onto the lower rectum by using fatty and water-soluble bases, hydrophilic polymers of Carbopol 934P (CP) and Polyvinylpyrrolidone K90 (PVP) and diclofenac sodium (DcNa) as model drug. Of all the bases evaluated, ChocExa, Supercocofat HS and Supercocofat resembled Cocoa Butter with comparable base hardness, short softening time and similar melting range, bioadhesive properties and biphasic drug release profiles. CP was a better bioadhesive polymer than PVP. The presence of CP at 2 % w/w yield considerable bioadhesive properties, but higher amount of CP prolonged DcNa release in distilled water with higher value of initial drug release constants, k_1 and longer time to achieve 50 % of drug release ($T_{50\%}$). By employing CP at 2 % w/w in the ChocExa with DcNa, three different designs of suppositories, namely the conventional, hollow and double-layered suppositories were developed. Three different DcNa-CP mixtures were also evaluated, namely the physical mixture, co-grinding and wet granulations of DcNa-CP. The hollow and double-layered

suppositories released DcNa faster than the conventional design but with less base hardness values and shorter softening time. On the other hand, all designs of suppository containing granules of DcNa-CP were released faster than physical mixture and co-grinding of DcNa-CP. Both FTIR and DSC profiles of co-grinding preparation showed an intermediate profile of the physical mixture and granulation preparation. Prior to the *in vivo* study, a simple, specific and sensitive isocratic HPLC-UV method was validated for the quantification of DcNa in rabbit plasma. An *in vivo* study of three-way crossover design was performed on six rabbits for conventional suppository containing DcNa-CP granules (B) and hollow suppository containing DcNa-CP granules (C) in comparison to conventional suppository containing DcNa granules without CP (A). The rate and extent of absorption ($AUC_{0-\infty}$) and the maximum drug plasma concentration (C_{max}) for B and C were found to be significantly higher than A. However, the $AUC_{0-\infty}$ and C_{max} between B and C were not significantly different, although the $AUC_{0-\infty}$ for C appeared to be higher than B. In conclusion, a bioadhesive suppository system that could be retained on the lower rectum was successfully prepared. The newly developed bioadhesive formulations resulted in an improvement of bioavailability, hence offering advantages over the conventional suppository.

CHAPTER 1

INTRODUCTION

1.1 Suppositories

Suppositories are solid dosage forms that are used to administer medicine through the rectum, vagina and to a lesser extent, the urethra. The suppository is a very ancient form of medication, as is evidenced by its mention in the Hippocratic Oath (Ohmart, 1949; Plaxco *et al.*, 1967). Suppositories were used in the ear and nose, but these uses are now obsolete. The forms of suppository in use today have been developed within the past hundred years.

Generally, rectal suppositories are cylindrical, cone-shaped with a rounded apex or bullet-shaped. Such shapes have the advantage that when the widest part has been inserted the anal sphincter muscle presses the suppository forward into the rectum (Carter, 1975). In this way, the possibility of backward sliding is eliminated (Merkus, 1980). The shape and size of a suppository should assist easy insertion into the intended body orifice without causing undue distension, and once inserted, it must be retained for an appropriate period of time (Ansel, 1981). The rectal suppositories usually weigh about 2 g and are about 1 to 1.5 inches long. Infant and pediatric rectal suppositories weigh about half that of adult suppositories.

Once inserted, the suppository base melts, softens or dissolves, distributing the medicaments it carries to the tissues of the region (Ansel, 1981). These medicaments may be intended for retention within the cavity for localised drug

effects, or to be absorbed for the exertion of systemic effects (Coben and Liebermann, 1986; Allen, 1995).

Local applications, generally delivered within half an hour and last at least 4 hours are frequently employed for laxative effects to relieve constipation or to counter pain, irritation, itching, infections and inflammation associated with hemorrhoids or other anorectal conditions. Drugs intended for local action are generally nonabsorbable, such as drugs for hemorrhoids, local anesthetics and antiseptics. The bases used for these drugs are slow in melting and slow in drug release, contrasted with suppository bases intended for systemic drugs. For systemic effects, the mucous membranes of the rectum permit the absorption of many soluble drugs, including antinauseants, antiasthmatics, antihistamines, antispasmodics, antibiotics, analgesics, tranquilizers and hormones (Carter, 1975; Ansel, 1981; Coben and Liebermann, 1986; Blaey and Tukker, 1988).

1.2 Advantages of rectal administration

The administration of drugs by routes other than orally has to be considered in several circumstances and for varying reasons. Arguments for choosing the rectal route for drug administration have, for decades, been presented by many workers (Carter, 1975; Moolenaar and Schoonen, 1980; Young *et al.*, 1987; Blaey and Tukker, 1988; Choi *et al.*, 1998a; Ryu *et al.*, 1999; Uzunkaya and Bergisadi, 2003; Takatori *et al.*, 2004):

1. The patient is unable to make use of the oral route. This may be the case when the patient has an inflection of the gastrointestinal (GI) tract, is

nauseous, or is postoperative (the patient may be unconscious or not able to ingest a drug orally), or when the patient is unable to swallow (jaw fractures, throat injury or advance diseases). Several categories of patients, namely infants, the very old or mentally disturbed may more easily use the rectal than the oral route.

2. The drug under consideration is less suited for oral administration. This may be so in cases where oral intake results in gastric irritation or other GI side effects. Furthermore, drugs that can be easily destroyed or inactivated by the pH or enzymatic activity of the stomach or intestines need not be exposed to the destructive environments.
3. The avoidance of the first pass hepatic elimination or metabolism. Drugs that are destroyed by portal circulation may bypass the liver through rectal absorption.
4. Drugs with an unacceptable taste can be administered rectally without causing any inconvenience to the patients.
5. The formulations into suppositories of certain drugs that are candidates for abuse (as in suicide) have also been considered.

Apart from these apparent advantages, the rectal route also has several drawbacks. Depending on tradition, there are strong feelings of aversion in certain countries, such as in UK and USA to rectal administration of drugs, whereas there is complete acceptance in Eastern Europe. More rational points in this respect are slow and sometimes erratic and incomplete absorption that has been reported and the considerable inter and intrasubject variation. Also, the development of proctitis (inflammation of the rectum) has been reported

(Blaey and Tukker, 1988). There are also problems with the large scale production of suppositories and a suitable shelf life achievement (the latter demanding stringent storage conditions).

Thus, it can be concluded that rectal administration might not be the route of first choice, but in certain circumstances it can be of great advantage to the patients.

1.3 Anatomy and physiology of rectum

Rectal dosage forms are introduced in the body through the anus and are thus brought into contact to the most caudal part of the GI tract, namely the rectum. Anatomically, the rectum is part of the colon, forming the last 150-200 mm of the GI tract (Blaey and Tukker, 1988). Taking this into account a very limited absorption surface emerges.

Under normal circumstances, the rectum does not have any active motility (Moolenaar and Schoonen, 1980) and filling provokes a defecation reflex which is under voluntary control. Usually the rectum is empty, containing only 2-3 mL of inert mucus fluid (pH 7-8) which has no enzymatic activity or buffer capacity. The mucus spreads over a total surface area of about 300 cm² and approximately 100 µm thick over the organ (Blaey and Tukker, 1988).

The rectum can be subdivided into the anal canal and the ampulla, the latter forming approximately 80 % of the organ. It is separated from the outside world through a circular muscle, the anus. The rectum can be considered as a hollow

organ with a relatively flat wall surface, without villi and microvilli, and with only three major folds known as the rectal valves. The rectal wall is formed by an epithelium, which is one cell layer thick, and is composed of cylindrical cells and goblet cells which secrete mucus.

1.4 Rectal absorption

Insertion of a suppository into the rectum results in a chain of effects leading to the bioavailability of the drug. The sequence of events leading to drug absorption from the anorectal area can be represented as follows:

Drug in vehicle → Drug in colon fluids → Absorption through the rectal mucosa

To be available for absorption, drugs must be released from the suppository and distributed by the surrounding fluids to sites of absorption. Depending on the character of its vehicle a suppository will either dissolve in the rectal fluid (water-soluble bases) or melt on the mucous layer (fatty bases).

Independent of the vehicle type, drugs that are dissolved in the suppository diffuse out towards the rectal membranes. On the other hand, the suspended drugs first leave the vehicle (if it is water immiscible) under the influence of gravity or motility movements, and then start to dissolve in the rectal fluid. The dissolved drug molecules diffuse through the mucous layer into the epithelium forming the rectal wall to be absorbed by the tissues and eventually transported into the general circulation (Chicco *et al.*, 1999). The process of absorption is through passive diffusion throughout the whole GI tract for nearly all drugs.

Blood supply, especially venous drainage, is important for the understanding of drug absorption. There is abundant vascularisation of the submucosal region of the rectum wall with blood and lymphatic vessels. A diagram of part of the rectal wall and the rectum venous drainage is shown in Figure 1.1.

As can be seen from the figure, there are three separate veins. Depending on the height at which absorption occurs in the rectum, the drug passes into the inferior, middle or superior haemorrhoidal veins. Inferior vein is nearest to the anus. The inferior and middle haemorrhoidal veins drain directly into the general circulation (via the inferior vena cava) and bypass the liver, while the superior haemorrhoidal vein drains into the hepatic portal vein which flows to liver. There are extensive anastomoses between the lower and upper hemorrhoidal veins (Ryu *et al.*, 1999). The lymphatic circulation also helps in absorbing a rectally administered drug and in diverting the absorbed drug from the liver. This means that drug molecules can enter the general circulation directly or by passing the strongly metabolising liver. In the latter, only a proportion of the drug molecules (if they are of the high clearance type) enters the general circulation intact. Thus the bioavailability may be less than 100 %.

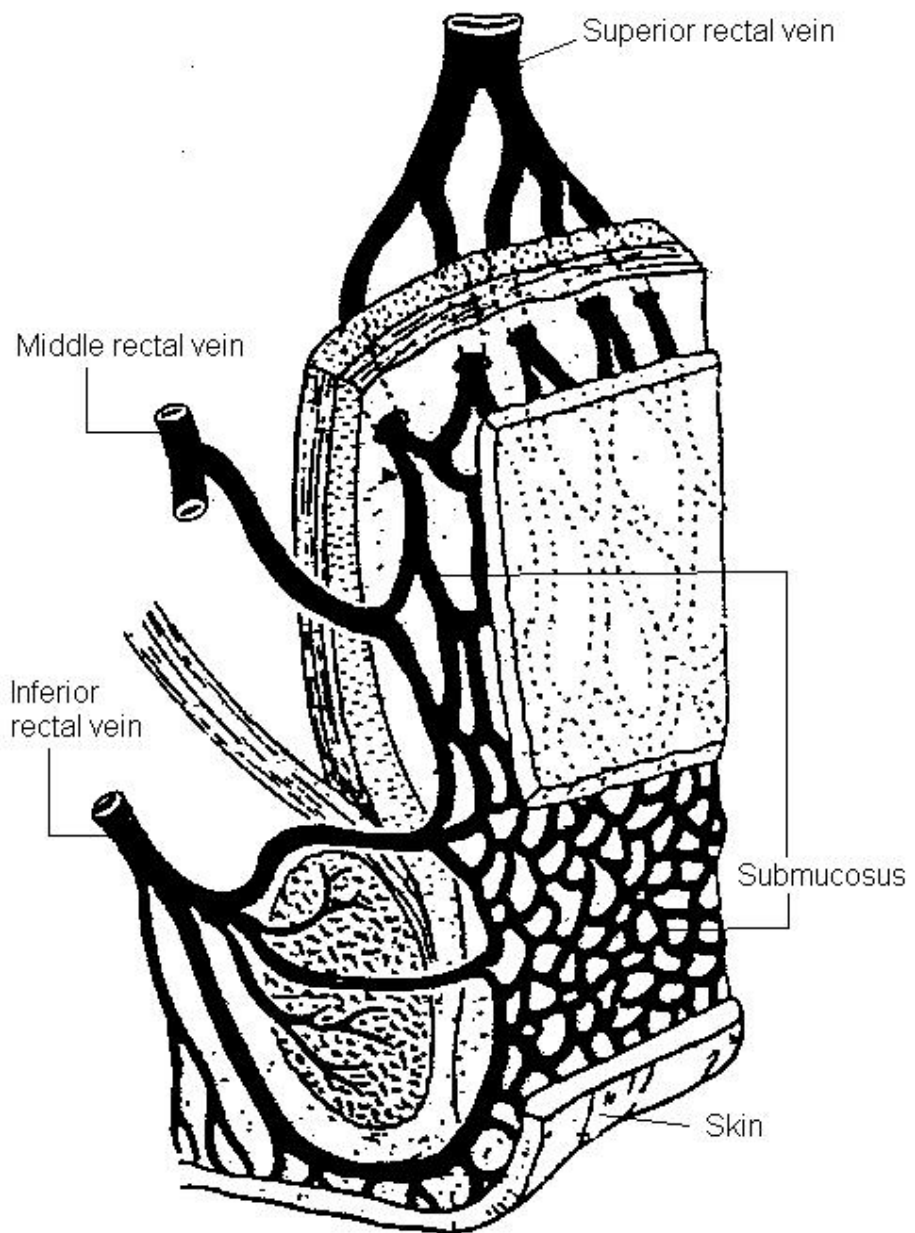


Figure 1.1: Venous drainage of human rectum (Blaey and Tukker, 1988).

It was once believed that medicaments from suppositories were largely transported by the inferior and middle haemorrhoidal veins and therefore rectal administration of a drug provided a means of avoiding degradation of the drug by liver and damage of the liver by drug. Indeed, the liver modifies many drugs chemically and thereby often reduces their systemic effectiveness.

However, it appears that suppositories have the tendency to migrate to the upper rectum after administration (Yahagi *et al.*, 1999). In such cases, only drug released from suppositories and absorbed at the lower rectum could avoid first-pass effect and retain their therapeutic values (Coben and Liebermann, 1986; Chicco *et al.*, 1999). Hence, keeping the drug in lower part of the rectum is strongly advisable, specifically if the suppository is retained in the bottom one-third of the rectal vault (Hosny *et al.*, 1995; Hosny *et al.*, 1996a).

1.5 Factors influencing rectal absorption

The rate-limiting steps in suppository drug absorption are the partitioning of the dissolved drug from the melted base (Coben and Liebermann, 1986) and diffusion of the drug to the site on the rectal mucosa where absorption occurs (Moolenaar and Schoonen, 1980). The factors influencing rectal drug absorption are as follows:

1. Quantity of fluid available

Partitioning between base and rectal fluid is affected by the varied volume of water in the rectum. This volume is very small and varies among individuals at different time (Blaey and Tukker, 1988). Only under non-physiological

circumstances is this volume enlarged, such as through osmotic attraction by water-soluble vehicles or diarrhoea.

2. Properties of the rectal mucous

Properties of rectal fluid, such as composition, viscosity and surface tension are unknown. The mucous blanket acts as a mechanical barrier for free passage of drug through the pore space for absorption (Coben and Liebermann, 1986).

3. Rectal pH

The pH of the rectal mucosa plays a significant rate-controlling role in drug absorption (Ansel, 1981). The principal method of drug absorption is diffusion through lipid regions of cell membranes and therefore unionised drugs (which are more soluble in lipids than the ionised forms) are absorbed more readily. The completely ionised drugs and unionised substances which are lipid-insoluble are also poorly absorbed. The state of ionisation of drug depends on the environmental pH. Rectal fluids are essentially neutral in pH and have virtually no buffer capacity. As a consequence, the dissolving drugs may influence the pH existing in the anorectal area. The weaker acids and bases are more readily absorbed than the stronger, highly ionised ones (Coben and Liebermann, 1986). It seems that the anorectal and colonic mucosa are selectively permeable to the uncharged drug molecule.

4. Contents of rectum

The rectum is usually empty except when fecal matter arrives from higher part of the colon temporarily. This material is either expelled or transported back into colon, depending on the voluntary control exhibited by the anus sphincter. A drug has greater opportunity to make contact with the absorbing rectal surface in the absence of fecal matter. Other conditions such as diarrhoea, colonic obstruction and tissue dehydration can influence the rate and degree of drug absorption from the rectal site (Ansel, 1981).

5. Motility of the rectal wall

The rectal wall may exert a pressure on a suppository present in the lumen by two distinct mechanisms (Ansel, 1981). The abdominal organs that simply press on to the rectum, especially when the body is upright may stimulate spreading and promote absorption. The second source of pressure is the motility of the rectal wall muscles originated from the normally occurring colonic motor complexes. These are waves of contractions running over the wall of the colon in caudal direction and are associated with the presence of food residues in the colon.

6. Partition coefficient of drug

Drug solubility in rectal fluid determines the maximum attainable concentration and thus the driving force for absorption. When a drug has high vehicle to water partition coefficient, the tendency to leave the vehicle is small and thus the release rate into the rectal fluid is low. This is unfavourable for rapid absorption. On the other hand, a certain lipid solubility

is required for penetration through the rectal membrane. The optimal balance between these two requirements is usually found using the rules listed in Table 1.1 (Blaey and Tukker, 1988).

Table 1.1: Drug solubility and suppository formulation.

Drug solubility		Choice of base
Fat	Water	
Low	High	Fatty base (Rule 1)
High	Low	Aqueous base (Rule 2)
Low	Low	Indeterminate

Assuming that the release from the dosage form is considered as the rate-limiting step, the tendency to remain in the base should be lowered as much as possible (Rules 1 and 2). When the solubility in fat and water are both low no definite rule can be given.

7. Drug particle size

The absorption of a drug in suspension is limited by its dissolution rate. Therefore, when a drug is formulated in the suppository as suspension in the undissolved state, it is advantageous to use fine powder to increase surface area and enhance dissolution (Blaey and Tukker, 1988). This is particularly relevant to rectal dosage forms because the rectum lacks the large surface area and considerable movement of contents that aid absorption in the gut.

8. Nature of base

If the suppository base interacts with the drug inhibiting its release, drug absorption will be impaired or even prevented. Also, if the base is irritating to the mucous membranes of the rectum, it may initiate a colonic response and prompt a bowel movement, negating the prospect of a thorough drug release and absorption (Ansel, 1981).

9. Presence of additives in base

Emulsifying agents such as wax, wool fat, wool alcohols and polysorbates may be included in suppository bases to facilitate incorporation of aqueous solutions or polar liquids, but they should be used with caution as their effects on release and absorption are unpredictable. The inclusion of a powerful surface-active agent may greatly increase absorption of a drug but with subsequent toxic effects.

1.6 Suppository bases

Suppository bases play an important role in the release of the medication they hold and therefore in the availability and absorption of drug for systemic or localised effects (Ibrahim *et al.*, 1990). Generally, suppository bases fall into two categories; fatty bases that melt at body temperature and water-soluble or water-miscible bases that dissolve or disperse in rectal secretions.

The ideal suppository base (Carter, 1975; Coben and Liebermann, 1986) should melt at body temperature or dissolve and disperse in body fluids, release any medicament readily, able to keep its shape while being handled, completely

non-toxic and non-irritant to sensitive and inflamed tissues, non-sensitising, has no metastable forms and stable on storage, such as does not change colour, odour or drug release pattern. It should have wetting and emulsifying properties, stable if heated above its melting point and shrinks sufficiently on cooling to release itself from the mould without the need for mould lubricants. The base should also possess a high 'water number', namely a high percentage of water that can be incorporated in it. Last but not least, the suppository base should be esthetically acceptable and mouldable by hand, machine, extrusion or cold compression.

A suppository base containing all these properties is not yet found (Carter, 1975). Indeed, some of the properties are mutually exclusive and not ideal in all situations. Often, the addition of drugs changes the desirable characteristics of the base.

1.6.1 Fatty bases

1.6.1 (a) Theobroma Oil (Cocoa Butter)

Cocoa Butter USP (CB) is defined as the fat obtained from the roasted seed of theobroma cocoa. This oleaginous base is a classic suppository vehicle, having been used for over 200 years. It is yellowish-white solid, brittle fat with a chocolate-like odour that melts to form non-viscous, bland oil and has an emollient or soothing action.

CB has several disadvantages. It can become rancid due to oxidation of the unsaturated glycerides, melt in warm weather and liquefy when incorporated

with certain drugs. CB does not contain emulsifiers and therefore does not take up large quantities of water. As CB can easily melt and become rancid, it must be stored in cool, dry place and be protected from light.

CB exhibits marked polymorphism (the ability to exist in different crystalline forms, namely α , β , β' and γ with melting points of 22, 34, 28 and 18 °C respectively), a phenomenon probably attributed to the high proportion of unsaturated triglycerides. The most stable β form is preferable for suppositories. The formation of the various crystalline forms depends on the conditions and degree of heating and cooling. Prolonged heating above 36 °C causes the formation of the unstable crystal with lower melting points. The conversion to the stable β form takes 1 to 14 days, depending on the storage temperature – the higher the temperature, the faster the change. As a general rule, minimal use of heating in the process of melting the fat is recommended.

1.6.1 (b) Cocoa Butter Substitutes (CBS) or Cocoa Butter replacers (CBR)

CBS or CBR are terms used for the almost exclusively semi- or fully synthetic fatty vehicles in use nowadays. The disadvantages inherent to CB have prompted a search for more superior substitutes. The satisfactory bases maintain the many desirable properties of CB, and attempts are made to eliminate the objectionable properties.

The general composition of CBS is derived from hydrogenated cottonseed oil, palm oil, palm kernel oil and coconut oil, with self-emulsifying and suspending

agents (Allen, 1995). Hydrogenated palm kernel oil was recommended as a suppository base as early as 1939 by Caldwell (Carter, 1975).

Palm kernel oil is produced from the center kernel of the *Elaeis guineensis* palm. By optimising the fractionation and hydrogenation conditions, several grades of palm mid-fractions with different solid fat content and melting characteristics can be produced (Malaysian Palm Oil, 1995). Palm oil and palm kernel oil are consumed worldwide as cooking oil, in margarines and shortening, and as ingredient in fat blends and a vast array of food products.

Most manufacturers market a series of CBS grades with slightly different melting point ranges and degree of hardness. CBS is generally stable with a low irritation profile, need no special storage condition, uniform in composition, and has bland taste with controlled melting range. Their solidifying points are unaffected by overheating.

CBS bases also have good resistance against oxidation due to their reduced unsaturated fatty acids. Their acid value is low (almost < 0.5 compared to > 4 for CB) that accounts for the slower ageing of suppositories in semi-synthetic vehicles. CBS also exhibits excellent mould release characteristics and do not require mould lubrication. The emulsifying and water-absorbing capacities of CBS are good as they usually contain a proportion of partial glycerides, such as glyceryl monostearate which are water/oil emulsifying agents. CBS is opaque-white, almost odourless and has very attractive, clean, polished appearance.

The difference between melting and setting points in CBS is small; generally only 1.5 to 2 °C. Hence, they set quickly. The risk of sedimentation is low, and they are easier to administer. When the setting point of base is well below the melting point, the suppositories soften quickly when handled and become too slippery to administer.

However, precaution should be taken not to cool CBS too quickly lest they become brittle. They are also more fluid than CB when melted and at this stage sedimentation is greater. Thickeners, such as magnesium stearate, bentonite and colloidal silicon dioxide, may be added to counter such problems.

1.6.1 (c) Witepsol

Witepsol comes in different grades, all nearly white and almost odorless. These bases solidify rapidly in the mould, and lubrication is not necessary as the suppositories contract nicely. Witepsol will absorb limited quantities of water since these bases contain emulsifiers.

1.6.2 Water soluble bases

1.6.2 (a) Polyethylene glycol (PEG)

PEG (also known as macrogol) is widely used as a water soluble suppository base. They are mixtures of PEGs of different molecular weights (MWs). The more commonly used being PEG 200, 400, 600, 1000, 1500, 1540, 3350, 4000 and 6000. The numerical designation refers to the average MW of each polymer.

The PEG bases generally have a melting point above 42 °C. Hence, cold storage is not required, they are satisfactory for use in hot climates, and administration is easy because they are not slippery to handle. Their physical properties can be varied by suitable mixture of high and low MW polymers. High MW polymers give hard products that disintegrate and release drug slowly. Softer and less brittle suppositories that liberate drug more quickly are obtained by mixing high with either medium or low MW polymers.

PEG bases do not melt but gradually dissolve and disperse in the body, freeing medication slowly and providing longer action than fatty bases. PEG suppositories have smooth appearance, absorb water and do not leak from the anus as do many fatty suppositories. They also absorb water and have excellent solvent properties. Unlike glycerol-gelatin bases, PEGs do not stick to the mould since they contract significantly on cooling and moreover no lubricant is required.

However, PEG suppositories are hygroscopic and therefore attract water, resulting in painful sensation for patients. They may produce slight dehydration of the rectal mucosa as they take up water to dissolve. Furthermore, a considerable number of incompatibilities with various drugs, such as phenols and sulphonamides have also been reported (Allen, 1995). The solubilising character of this base (low dielectric constant) can result in the retention of the drug in the liquefied base with reduction in therapeutic activity. PEG suppositories sometimes fracture and exhibited crystal growth on storage, particularly if they contain water. One cause is the high solubility of PEGs which

can lead to a supersaturation in water and subsequent crystallisation which makes the mass granular and brittle.

In practice, PEGs have been found to be valuable for drugs which are practically insoluble in water (diazepam, indomethacin) and where solubility can be improved by the presence of water soluble vehicles (Moolenaar and Schoonen, 1980).

1.6.2 (b) Glycerinated gelatin base

Glycerinated gelatin suppositories which are composed of glycerin (70 %), gelatin (20 %), and water (10 %), should be packaged in air tight containers since they are hygroscopic. They are not recommended as rectal suppository base because they may exert an osmotic effect and a defecation reflex. A glycerin base is composed of glycerin (87 %), sodium stearate (8 %) and water (5 %). These bases have occasionally been used for the preparation of pessaries.

The most commonly used suppository bases are listed in Table 1.2.

Table 1.2: Suppository bases

Base	Composition	Melting Range (°C)	References
CB	Mixed triglycerides of oleic, palmitic and stearic acids	34.0-36.0	Vidras <i>et al.</i> , 1982; Zuber <i>et al.</i> , 1988; Ibrahim <i>et al.</i> , 1990; Hosny <i>et al.</i> , 1996a; Webster <i>et al.</i> , 1998; Babar <i>et al.</i> , 1999; Nair and Bhargava, 1999.
Suppocire AIML		33.0-35.0	Pryce-Jones <i>et al.</i> , 1992; Zuber <i>et al.</i> , 1988
AM		35.0-36.5	Zuber <i>et al.</i> , 1988
AP	Eutectic mixtures of mono-, di- and triglycerides derived from natural vegetable oils	33.0-35.0	Reid <i>et al.</i> , 1987; Young <i>et al.</i> , 1987; De Muynck <i>et al.</i> , 1994; Nair and Bhargava, 1999; Victoria and David, 2003.
AS ₂		35.0-36.0	Zuber <i>et al.</i> , 1988; Margarit <i>et al.</i> , 1991
BX2X		36.0-37.5	Ceschel <i>et al.</i> , 2001
OSIX		33.0-35.0	Reid <i>et al.</i> , 1987
Novata BD	Mixtures of mono-, di- and triglycerides of saturated fatty acids	33.5-35.5	Asikoglu <i>et al.</i> , 1995; Webster <i>et al.</i> , 1998
299		33.5-35.5	Webster <i>et al.</i> , 1998
Witepsol H12	Lauric triglycerides mainly containing C ₁₂ and C ₁₄ saturated vegetable fatty acids with varied portions of the corresponding partial glycerides	32.3-33.5	Reid <i>et al.</i> , 1987; Young <i>et al.</i> , 1987; Pryce-Jones <i>et al.</i> , 1992; Gjellan <i>et al.</i> , 1994a; Realdon <i>et al.</i> , 1997;
H15		33.5-35.5	Nishihata <i>et al.</i> , 1985; Fontan <i>et al.</i> , 1992; Hosny <i>et al.</i> , 1996b; Iwata <i>et al.</i> , 1997; Yahagi <i>et al.</i> , 2000; Hanaee <i>et al.</i> , 2004; Takatori <i>et al.</i> , 2004

“Table 1.2....continued”

Base	Composition	Melting Range (°C)	References
H19		34.8-36.0	Reid <i>et al.</i> , 1987; Victoria and David, 2003
W35		33.5-35.5	Webster <i>et al.</i> , 1998; Chicco <i>et al.</i> , 1999
W45		33.5-35.5	Hosny <i>et al.</i> , 1996a; Nair and Bhargava, 1999
E75		37.0-39.0	Ibrahim <i>et al.</i> , 1990
E85		42.0-44.0	Saito <i>et al.</i> , 1994a,b
S55		33.5-35.5	Pryce-Jones <i>et al.</i> , 1992; Realdon <i>et al.</i> , 1997
Massa Estarinum B	Mixtures of mono-, di- and triglycerides of saturated fatty acids	33.5-35.5	Ermis and Tarimci, 1995
PEG 400	Linear polymers of ethylene oxide	4.0-8.0	Archondikis and Papaioannou, 1989; Oribe <i>et al.</i> , 1995; Tarimci and Ermis, 1997
600		20.0-25.0	Nair and Bhargava, 1999
1000		38.0-41.0	Vídras <i>et al.</i> , 1982; Babar <i>et al.</i> , 1999; Onyeji <i>et al.</i> , 1999
1450		42.0-47.0	Lee and Wang, 1999; Główka, 2000
4000		40.0-48.0	Kuroda <i>et al.</i> , 1983, Ibrahim <i>et al.</i> , 1990, Oribe <i>et al.</i> , 1995; Hosny <i>et al.</i> , 1996a, Onyeji <i>et al.</i> , 1999

1.7 Bioadhesives

Generally, bioadhesive is defined as synthetic or natural substance that is capable of adhering or interacting with biological materials and able to be retained on the biological surface and retard natural clearance processes for an extended period of time (Hassan and Gallo, 1990; Mortazavi, 1995; Prudat-Christiaens *et al.*, 1996; Lee *et al.*, 2000; Singla *et al.*, 2000). Specifically, mucoadhesives are polymers which interact primarily with the mucus layer covering the mucosal epithelial surface and mucin molecules that constitute a major part of mucus (Smart, 1991; Ahuja *et al.*, 1997).

The goal of the development of bioadhesive is to mimic or improve biological adhesives (Ahuja *et al.*, 1997). The majority of bioadhesive polymers studied for drug delivery adhere to epithelial tissues and perhaps to the mucus coat present on the surface of these tissues. Mucus-coated tissue is found in most nonparenteral routes of administration (Mortazavi *et al.*, 1993). Target sites for bioadhesive drug delivery include the eye (Saettone *et al.*, 1999), buccal (Wong *et al.*, 1999a), peroral, nasal (Nagai and Machida, 1985), vaginal (Ceshel *et al.*, 2001), GI tract (Ch'ng *et al.*, 1985), rectal (Hosny *et al.*, 1995; Hosny *et al.*, 1996a) and cervical (Nagai and Machida, 1985).

Bioadhesive force in the rectal delivery system denotes the force and strength with which suppositories bind to rectal lining at 36.5 °C (Choi *et al.*, 1998a,b; Kim *et al.*, 1998; Choi *et al.*, 1999). Rectal mucous lining consists of oligosaccharide chains with sialic acid. Hence, polymers with macromolecules hydrocolloids containing numerous hydrogen bond forming groups can bind

strongly to oligosaccharide chains, resulting in strong bioadhesive force (Kim *et al.*, 1998).

1.8 Advantages of rectal bioadhesion

1. Increasing the residence time of dosage form

Localising suppository in the rectum may help to prevent it from moving upwards, reaching the end of colon, which is the pathway for first-pass effect. In other words, it is an attempt to restrict drug absorption from suppositories at the lower rectum. Drug absorbed in this region enter directly into the systemic circulation resulting in increased systemic availability and improvement in the therapeutic efficacy due to avoidance of first-pass elimination (Yahagi *et al.*, 2000).

2. Higher drug concentration in a local area

Retaining the suppository may also provide intimate contact of dosage form with the absorbing tissue for an extended period of time (Ahuja *et al.*, 1997). This may produce a steep concentration gradient in the local area and hence, higher drug flux through the absorbing tissue favoring drug absorption (Hosny *et al.*, 1995; Hosny and Al-Angary, 1995). Furthermore, the intimate contact has been proven to increase the permeability of the epithelial tissues towards high molecular weight drugs such as peptides and proteins (Hosny *et al.*, 1996a).

1.9 Bioadhesive polymers

Most bioadhesives are based on polymers that differ in the degree of erodibility, swelling and sensitivity to the biological environment. They are generally hydrophilic macromolecules or hydrocolloids that contain anionic charges and strong hydrogen bond forming groups (hydroxyl, oxide and carboxyl groups) with high molecular weight, sufficient chain flexibility and surface energy properties favoring spreading onto mucus (Lehr *et al.*, 1992).

The ideal bioadhesives would be site-specific, durable when required, biodegradable when necessary, non-irritant to the mucous membrane, non-toxic and non-absorbable from the GI tract (Ceshel *et al.*, 2001), preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces, adhere quickly to moist tissue (Smart, 1991; Mortazavi *et al.*, 1993; Singla *et al.*, 2000), allow easy incorporation of the drug and offer no hindrance to its release, be cost productive and should not decompose on storage or during the shelf-life of the dosage form.

The water-soluble polymers are typically linear or random hydrophilic polymers (e.g. polyacrylic acid, PAA). The water-insoluble types are commonly called hydrogels (Rao and Devi, 1988). They are swellable network formed by covalent or ionic bonds via a cross-linking agent (e.g. polycarbophil, PCP). The swellable polymers have the ability to release entrapped drugs in aqueous medium and the release of such drug can be regulated by the control of swelling and degree of cross-linking (Bravo *et al.*, 2002).

In the case of water-soluble polymers, the duration of residence time on tissue surfaces is based on dissolution rate of the polymer. In contrast, cross-linked polymers, given their lack of solubility in common solvents, have a residence time based on the rate of mucus/tissue turnover.

Most of the current synthetic bioadhesive polymers are either PAA or cellulose derivatives. Examples of PAA-based polymers are Carbopol (CP), polycarbophil (PCP), polyacrylate, poly(isohexylcyanoacrylate) and poly(isobutylcyanoacrylate).

Cellulose ethers are becoming popular as matrices since they are easy to prepare, can accommodate a large percentage of drug and the release is less influenced by the processing variables (Rao and Devi, 1988). Chemically, cellulosic polymers share a common cellulosic backbone, but they have different substituent groups, which may be ionic or non-ionic.

These linear polymers are produced by partial or total etherification of the 3 hydroxyl groups present on the anhydroglucose repeat unit of the cellulose chain. Following the addition to an aqueous phase, the cellulose derivatives undergo swelling prior to dissolution (Jones *et al.*, 1997). Cellulosic polymers include carboxymethyl cellulose (CMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), methyl cellulose (MC) and methylhydroxyethyl cellulose (MHEC).

In addition, poly(N-2-hydroxypropyl methacrylamide) (PHPMAm), polyvinylpyrrolidone (PVP) and poly(vinylalcohol) (PVA) can also be included as