CHAPTER II

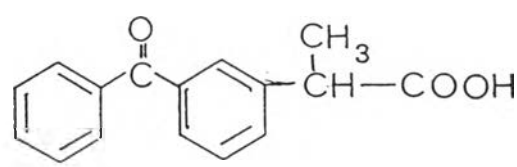
REVIEW OF LITERATURES

1. **Ketoprofen.** (Fakheddin and Dion, 1991; Reynold, 1993, and Lond, 1994)

1.1. Physicochemical Properties.

Chemical name : 2-(3-Benzoylphenyl) propionic acid, 3-benzoyl-α-methylbenzene acetic acid.

Structure :



Molecular formula : $C_{16}H_{14}O_3$

Molecular weight : 254.29

Appearance : White or almost white, odourless, crystalline powder.

Melting range : 93-96°C

Solubility : Ketoprofen is slightly soluble in water, freely soluble in ethanol, chloroform, ether and acetone, soluble in benzene.

pH : The pH of a 3.95×10^{-4} M solution in water is 6.5

pK_a : 4.45 in water.

Stability : Ketoprofen must be protected from light and moisture. It is stable at room temperature. It

has been dissolved in ethyl acetate and stored for several weeks at 4°C with no detectable decomposition. If ketoprofen is heated in an acid solution pH 1 at 98°C for 30 min. No decomposition is detected.

1.2 Pharmacological Properties (Reynold, 1993).

Ketoprofen has pharmacological actions similar to those of other NSAIDs. The drug exhibits antiinflammatory, analgesic and antipyretic activity. Ketoprofen is used to treat musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, peri-artricular disorders such as bursitis and tendinitis, mild to moderate pain such as dysmenorrhea or postoperative pain, and other painful and inflammatory conditions such as acute gout or soft-tissue disorders.

Dosage and Administration.

The usual daily dose orally is 100 to 200 mg in 2 to 4 divided doses with food, controlled formulations taken once daily may also be used. Ketoprofen may also be administered rectally as suppositories in a usual dose of 100 mg at night. The total daily dose by mouth and by rectum should not exceed 200 mg. The therapeutic range of ketoprofen is reported to be about 0.4-6.0 μg/mL.

1.3 Pharmacokinetic Properties.

Ketoprofen is well absorbed after parenteral, oral, or rectal administration. Ketoprofen is readily absorbed from the gastro-intestinal tract; peak plasma concentrations occur about 0.5 to 2 hours after dosing. It is 99% bound to plasma proteins. The elimination half-life in plasma is about 1-3 hours. Ketoprofen is metabolized mainly by conjugation with glucoronic acid, and is excreted mainly in the urine.

It is most often administered to patient orally. In the case of patients cannot take the drug orally, the administration rectally is considered as a serious alternative to the oral route and the commonly choice of rectal route medication is " Suppositories".

2. Definition of Suppositories (Lachman et al. 1986; Aulton, 1993; Ansel et al. 1995).

Suppositories are solid dosage forms intended for insertion into body orifices, which they melt, soften, or dissolve and exert, localized or systemic effects. The derivative of the word suppositories is from the Latin supponere, meaning, " to place under", as derived from sub (under) and ponere (to place). Thus suppositories are meant to be placed "under" the body, as into the rectum.

Traditionally, suppositories are chosen either for local use or for cases where alternative routes of administration are unavailable. Arguments for choosing the rectal route for drug administration include:

i The patient is not able to make use of the oral route. This may be the case when the patient has a infliction of the gastrointestinal tract, nauseous, or postoperative (when the patient may be unconscious or not able to ingest a drug orally). Furthermore several categories of patients i.g. the very young, the very old or the mentally disturbed, may more easily use the rectal than the oral route.

ii The drug under consideration is less suited for oral administration. This may be so in cases where oral intake results in gastrointestinal side effects, also the drug may be insufficiently stable at the pH of the GI tract, or susceptible to enzymatic attack in the GI tract, or during the first passage of the liver after absorption. Also drugs with an unacceptable taste can be administered rectally without this inconvenience to the patient. The formulation into suppositories of certain drugs that are candidates for abuse, as in suicide, has also been considered.

Besides these apparent advantages, the rectal route also has several drawbacks. Depending on tradition, there are strong feelings of aversion in certain countries, such as the UK and the USA, to rectal administration drugs, whereas there is complete acceptance on the continent and in Eastern Europe.

It can thus be concluded that rectal administration should certainly not be the route of first choice, but can in certain circumstances be of great advantage to the patient.

Rectal suppositories are usually 32 mm (1.5 inches) in length, are cylindrical and have one or both ends tapered. Some rectal suppositories are shaped like a bullet, a torpedo, or the little finger. The weight of rectal suppositories may vary. Adult rectal suppositories weigh about 2 grams. Rectal suppositories for use by infants and children are about half the weight and size of the adult suppositories and assume a more pencil-like shape.

The rectal route is used in many different therapies, intended either for local or for systemic effect. Local effect, the medicaments may be intended for retention within the cavity or they may be intended to be absorbed for the exertion of systemic effects. Rectal suppositories intended for localized action are most frequently employed to relieve constipation or the pain, irritation, itching, and inflammation associated with haemorrhoids or other anorectal conditions. For systemic effects, the advantages over oral therapy of the rectal route of administration for achieving systemic effects are described above.

Anatomy and Physiology of the Rectum.

Rectal dosage forms are introduced in the body through the anus and thus brought in the most caudal part of the GI tract, i.e. the rectum, anatomically the rectum is part of the colon, forming the last 150-200 mm of the GI tract.

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 with only three major folds, the rectal valves. The rectal wall is formed by an epithelium, which is one cell layer thick, and is composed of cylindrical cells and of goblet cells, which secrete mucus. A diagram of part of the rectal wall and rectum's veinous drainage is shown in Figure 1.

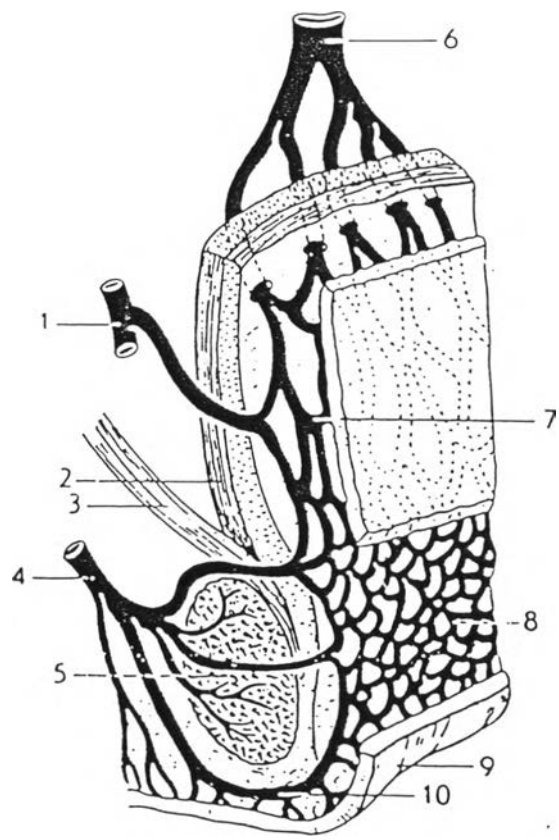


Figure 1. Veinous drainage of the human rectum: 1 middle haemorrhoidal vein; 2 tunica muscularis:stratum longitudinal; 3 m. levstor ani; 4 inferior haemorrhoidal vein; 5 m.sphincter ani externus; 6 superior haemorrhoidal vein; 7,and 8 plexus venosus rectalis (submucosus); 9 skin; 10 v.marginalis.

The suppository form of a drug could avoid the first-pass liver metabolism depending on the area at which absorption occurs in the rectum. Where drugs carried by the inferior or middle haemorrhoidal veins go directly into the circulation, thus bypassing the liver, instead of going directly to the liver before going to the general circulation. So, drugs that are extensively metabolized can avoid first-pass metabolism.

The assessment avoidance of hepatic first-pass effect of drug, in situ experiments using rectal administration of lidocaine in rabbit were studies (Kurosawa et al. 1998). The results shown that lidocaine were absorbed almost completely via the rectal route and avoidance of first-pass effect by 60%, representing twice the bioavailability via duodenal administration.

The total volume of mucus is estimated as approximately 3 mL, spreaded over a total surface area of approximately 300 cm^2. The pH of the mucous layer is reported as approximately 7.2-7.5. Furthermore there seems to be little buffer capacity.

2.1 Some factors of Drug Absorption from Rectal Suppositories.

The dose of a drug administered rectally may be greater than or less than the dose of the same drug given orally, depending upon such factors as the constitution of the patient, the physicochemical nature of the drug and its ability to transverse the physiological barriers to absorption, and the nature of the suppository vehicle and its capacity to release the drug and make it available for absorption.

The factors affecting the rectal absorption of a drug administered in the term of a suppository may be divided into two main groups:

2.1.1 Physiologic factors

The human rectum is approximately 15 to 20 cm in length. When empty of fecal material, the rectum contains only 2 to 3 mL of inert mucus fluid. In

the resting state, the rectum is nonmobile, there are no villi or microvilli on the rectal mucosa. However, there is abundant vascularization of the submucosal region of the rectum wall with blood and lymphatic vessels.

Among the physiologic factors affecting drug absorption from the rectum are the colonic contents, circulation route, the pH and lack of buffering capacity of the rectal fluids.

2.1.1.1 Colonic content.

When systemic effects are desired from the administration of a medicated suppository, greater absorption may be expected from a rectum that is void than from one that is distended with fecal matter. A drug will obviously have greater opportunity to make contact the absorbing surface of the rectum and colon in the absence of fecal matter. Therefore, when deemed desirable, an evacuant enema may be administered and allowed to act before the administration of a suppository of the drug to be absorbed. Other conditions such as diarrhea, colonic obstruction due to tumorous growths, and tissue dehydration can all influence the rate and degree of drug absorption from the rectal site.

2.1.1.2 Circulation route.

Drugs absorbed rectally, unlike those absorbed after oral administration, bypass into the general circulation, there by enabling drugs otherwise destroyed in the liver to exert systemic effects. The lower haemorroidal veins surrounding the colon receive the absorbed circulation also assisted in the absorption of rectally administered drugs.

2.1.1.3 pH and lack of buffering capacity of the rectal fluids.

Because rectal fluids are essentially neutral in pH 7-8 and have no effective buffer capacity, the form in which the drug is administered will not generally be chemically changed by the rectal environment.

2.1.2 Physicochemical factors of the drug and suppository base.

Generally the suppositories consist of the vehicle in which the drug is incorporated and in some cases additives are coformulated.

2.1.2.1 The drug.

The factor related to the drug substance which consequence for the qualities of suppositories are described as follow.

a. Lipid-water solubility

The drug solubility in vehicle is determined directly the type of product, i.g. solution suppository or suspension suppository. The drug solubility in the rectal fluid determines the maximum attainable concentration and the driving force for absorption. When a drug has a high vehicle to water partition coefficient it is likely to be in solution to an appreciable extent in the vehicle. This generally means that the tendency to leave the vehicle will be small and thus the release rate into the rectal fluid will be low. This is obviously unfavorable for rapid absorption. On the other hand certain lipid solubility is required for penetration through the rectum membranes.

b. Surface properties.

The surface properties of drug are also important, as these particles will be transferred from one phase to another. This happens first when drug is brought into contact with the vehicle and air has to be displaced from its surface. When this is not achieved particles may form agglomerates. This affects final content uniformity by an increased tendency to separate. If wetting by the vehicle has taken

place displacement by rectal fluid will be required to let the drug go into solution, which is the prerequisite for absorption. This is the underlying reason why people have tried the addition of surfactants to their formulation.

c. Particle size.

The particle size of the drug is an important parameter. To prevent undue sedimentation during or after preparation the particle size should be limited. The available literature data do not definite an exact limit, however the use of particles smaller than approximately 150 μm is an indication rather than the rule.

The smaller the particle size the less the possible mechanical irritation to the patient (esp. < 50 μm) and the higher the dissolution rate and therefore drugs with a low water solubility will be dispensed in small, preferably micronized, particles. One should be aware of the increased tendency of these particles to agglomerate due to strongly increased Van der Waals forces in that case, however. Also an unnecessary size reduction operation should be avoided when possible.

Size reduction is not a good decision for all drugs. For readily water-soluble drugs, that large particle give blood levels which are higher than or at least equivalent to small particles. This would lead to the suggestion to use particle size range 50-100 μm in that case. The lower limit of 50 μm to increase transport through the molten vehicle and the upper limit of 100 μm is a safe protection against undue sedimentation during preparation.

d. Amount of drug.

A complicating factor is the amount of drug present in a suppository. If the number of particles increases, this would also increase the rate to form agglomerates. This will very much depend on the particle size and on the presence of additives.

2.1.2.2 The suppository base.

The base must be capable of melting, softening or dissolving to release its drug components for absorption. If the base interacts with the drug inhibiting its release, drug absorption will be impaired. Also if the base is irritating to the mucus membranes of the rectum, it may initiate a colonic response and prompt a bowel movement, negating the prospect of a through drug release and absorption.

2.2 Classification of Suppository Bases.

There is no doubt that a suppository should either melt after insertion in the body or dissolve in (and mix with) the available volume of rectal fluid. The melting range should be small enough to give rapid solidification after preparation, thus preventing separations of suspended, especially high density, drug particles and agglomeration. When the solidification rate is high this may result in fissures, especially when rapid cooling is applied. The melting range, on the other hand, should be large enough to permit easy preparation, which may take a considerable length of time on an industrial scale.

During solidification a suppository should exhibit enough volume contraction to permit removal from the mold. A good suppository base should further be chemically and physically stable during storage as a bulk product and after preparation into a suppository. It should have no incompatibility with drug molecule and should permit on optimal release of the drug it contains.

Specifications for suppository bases usually include any number of the following: (Lachman. et al. 1986).

a. Origin and chemical composition.

The composition of the base reveals the source of origin (i.g., either entirely natural or synthetic, or modified natural products), and chemical makeup (i.g.,

compound, or a well-defined or not-too-well elucidated mixture). Physical or chemical incompatibilities of the base with the other constituents may be predicted if the exact formula composition is known: including preservative, antioxidants, and emulsifiers.

b. Melting range.

Since fats do not have sharp melting point, their melting characteristics are expressed as a range indicating the temperature at which the fate starts to melt and the temperature at which it is completely molten. The "melting range" is usually determined by the USP method, manufacturers of bases may use different methods for determining melting characteristics, such as "Wiley melting point", "capillary melting point", "softening point", and others.

c. Solidification point.

This value predicts the time required for solidifying the base when it is chilled in the mold. If the interval between the melting range and solidification point is 10°C or more, the time required for solidification may have to be shortened for a more efficient manufacing procedure by augmenting refrigeration.

d. Saponification point.

This number of milligrams of potassium hydroxide required to neutralize the free acids and saponify the esters contained in 1 g. of a fat is an indication of the type (mono-, di-, tri-) glyceride, as well as the amount of glyceride present.

e. Iodine value.

The iodine value expresses the number of grams of iodine that reacts with 100 g. of fat or other unsaturated material. The possibility of decomposition by moisture, acids, and oxygen increases with high iodine values.

f. Water number.

The amount of water, in grams, which can be incorporated in 100 g. of fat is expressed by this value. The 'water number' can be increased by addition of surface active agents and other emulsifiers.

g. Acid value.

The number of milligrams of potassium hydroxide required to neutralize the free acid in 1 g. of substance is expressed by this value. Low "acid values" or complete absent of acid are important for good suppository bases.

The ideal suppository base.

The ideal suppository base may be described as follows:

i Melts at rectal temperature 37.5 °C.
ii Completely nontoxic and nonirritating to sensitive and inflamed tissues.
iii Compatible with a broad variety of drugs.
iv No metastable forms.
v Shrinks sufficiently on cooling to release itself from the mold without
the need for mold lubricants.
vi Nonsensitizing.
vii Has wetting and emulsifying.
viii Water number is high (a high percentage of water can be incorporated in it).
ix It is stable on storage, does not change color, odor, and drug release pattern.
x Can be manufactured by molding either by hand, machine, compression, or extrusion.

If the base is fatty, it has the following additional requirements:

i acid value is below 0.2.
ii saponification value range from 200 to 245.
iii iodine value is less than 7.
iv the interval between melting range and solidification point is small.

All of these properties have not been found in any one suppository base. Often the addition of drugs changes the desirable characteristics of the base.

It is convenient to classify suppository bases according to their physical characteristics into three main categories.

2.2.1 Oleagineous suppository base or fatty suppository base or lipophilic suppository base.

2.2.2 Water soluble suppository base or water miscible suppository base.

2.2.3 Miscellaneous suppository base.

2.2.1 Oleagineous suppository base or fatty suppository base or lipophilic suppository base.

Its dominant property is water insoluble, oily. Bases are made from nature, semisynthetic or synthetic.

The examples of oleagineous suppository base are

- Theobroma oil or cocao butter.
- Stearic-oleic acid suppositories base.
- Semi-synthetic suppository bases eg. Fractional palm kernel oil BP, Dehydag, Witepsols, IV Novata, Massa Estarinum, Suppocire, Wecobee, Fattibase etc.

2.2.1.1 Theobroma oil.

Theobroma oil is defined as the fat obtained from the roasted seed of *Theobroma cocoa*. At room temperature it is a yellowish, white solid having a faint, agreeable chocolate-like odor. Chemically, it is a triglyceride (combination of glycerin and one or different fatty acids) primarily of oleopalmitostearin and oleodistearin. It is an ideal suppository base because cocoa better melts between 30 to 36 °C, melting just below body temperature and maintaining its solidity at room temperature. Specific gravity is 0.99-0.998, iodine valve is 34-38 and acid value is below 4.

However, theobroma oil has many disadvantages in application, as follow :

a. Polymorphism.

Because of its triglyceride content that is unsaturated, melting theobroma oil and allowing to solidify again obtained four different types of crystals. Temperature in melting and rate of solidification effect on type of crystal.

Gamma crystals (γ-crystals) melts 18°C, so at room temperature it forms liquid.
Alpha crystals (α-crystals) melts at 22 °C, so at room temperature it also forms liquid.
Beta-prime (β-crystals) melts at 28 °C
Stable-β crystals melts at 34.5 °C

Consequently if suppositories that have been prepared by melting cocoa butter for the base do not harden soon after molding, they will be useless to the patient and a loss of time, materials, and prestige to the pharmacist. Cocoa butter must be slowly melted to avoid the formation of the unstable crystalline form.

b. Insufficient contraction at cooling.

Because of insufficient contraction so preparation by molding must lubricate mold with suitable lubricant.

c. Low softening point.

Theobroma oil has melting range 30-36°C. It is not suitable for warm weather because it will melt easily. However, this can be solved by addition of stiffening agent e.g. white beeswax or spermaceti that have high melting point.

d. Lowering the melting point by addition drugs or substance.

Substances such as chloral hydrate, phenol, volatile oils have tendency to lower the melting point of cocoa butter when incorporates with it. So suppository appears in liquid at room temperature.

e. Oxidization.

In storage of theobroma oil, oxidization may occur because of unsaturated glyceride.

d. Poor water absorptive power.

Theobroma oil is fat and water insoluble. Addition of surfactant such as polysorbate 5-10%, cholesterol 2%, emulsifying wax not exceed 10% or wool fat 5-10% make theobroma oil mixed with water.

g. It's price is expensive.

2.2.1.2 Stearic-Oleic acid suppository base.

Combination of stearic acid and oleic acid in equal proportion, melting and allowing to solidify, suppository that melted at body temperature is

resulted. Addition of cetyl alcohol, almond oil or vegetable oil may obtain different melting point and hardness.

Examples.

R_x 1	Stearic Acid	41 g.
	Oleic Acid	49 g.
	White wax	2 g.
R_x 2	Cetyl alcohol	30 g.
	Almond oil	55 g.
	Stearic Acid	15 g.

2.2.1.3 Semi-synthetic suppository bases.

Sometimes termed *Adeps solidus*, the general composition of both types is mixed triglycerides with C_{12} – C_{18} acids. In the semi-synthetic base these acids are saturated, while cocoa butter contains amount of the unsaturated oleic acid. The melting range of the semi-synthetic bases is usually approximately 3°C and higher than that of cocoa butter.

Examples for this type of base are Suppocire® as shown in Table 1 , Suppocire® excipients are produced either from natural, predominately lauric triglycerides originating from palm tree seeds which have been purified and hydrogenated to eliminate unsaturated fatty acids by fractionation and distillation.

There are many types of Suppocire® such as.

- Suppocire®AM, it has low hydroxy valve, which is suitable for drug that chemically inert.

- Suppocire®AML, it is similar to Suppocire®AM but contained phospholipids and suitable for formulation with large amount of drug.

Table 1 Specifications of standard quality of Suppocire®

Suppocire type	Drop point °C	Acid value	Saponification value	Hydroxyl value	Iodine value	Insaponifiable matter	Alkaline impurities
AI	33/35	< 0.5	225/245	20-30	< 2	≤ 0.5%	< 10 ppm.
AIX	33/35	< 0.5	220/240	20-30	< 2	< 0.6%	< 50 ppm.
AIM	33/35	< 0.2	225/245	< 6	< 2	≤ 0.5%	< 10 ppm.
AIML	33/35	< 0.5	225/245	< 6	< 3	< 0.6%	< 50 ppm.
A	35/36.5	< 0.5	225/245	20-30	< 2	≤ 0.5%	< 10 ppm.
AM	35/36.5	< 0.2	225/245	< 6	< 2	≤ 0.5%	< 10 ppm.
AML	35/36.5	< 0.5	225/245	< 6	< 2	< 0.6%	< 50 ppm.
AS2	35/36.5	< 0.5	225/245	15-25	< 2	≤ 0.5%	< 10 ppm.
AS2X	35/36.5	< 0.5	225/245	15-25	< 2	< 0.6%	< 50 ppm.
AT	35/36.5	< 0.5	225/245	25-35	< 2	≤ 0.5%	< 10 ppm.
B	36/37.5	< 0.5	225/245	20-30	< 2	≤ 0.5%	< 10 ppm.
BM	36/37.5	< 0.2	225/245	< 6	< 2	≤ 0.5%	< 10 ppm.
BML	36/37.5	< 0.5	225/245	< 6	< 3	< 0.6%	< 50 ppm.
BS2	36/37.5	< 0.5	225/245	15-25	< 2	≤ 0.5%	< 10 ppm.
BS2X	36/37.5	< 0.5	220/240	15-25	< 3	< 0.6%	< 50 ppm.
BT	36/37.5	< 0.5	225/245	25-35	< 2	≤ 0.5%	< 10 ppm.
C	38/40	< 0.5	220/240	20-30	< 2	≤ 0.5%	< 10 ppm.
CM	38/40	< 0.2	225/245	< 6	< 2	≤ 0.5%	< 10 ppm.
CS2	38/40	< 0.5	220/240	15-25	< 2	≤ 0.5%	< 10 ppm.
CS2X	38/40	< 0.5	220/240	15-25	< 2	< 0.6%	< 50 ppm.
CT	38/40	< 0.5	220/240	25-35	< 2	≤ 0.5%	< 10 ppm.
D	42/45	< 0.5	215/235	20-30	< 2	≤ 0.5%	< 10 ppm.
DM	42/45	< 0.2	215/235	< 6	< 2	≤ 0.5%	< 10 ppm.

2.2.2 Water soluble suppository base or water miscible suppository base.

The main members of this group are bases of glycerinated gelatin and bases of polyethylene glycols.

2.2.2.1 Glycerinated gelatin suppositories.

They are prepared by dissolving granulate gelatin (20%) in glycerin (70%) and adding a solution or suspension of the medication (10%). It is most used in the preparation of vaginal suppositories. The glycerinated gelatin base is slower to soften and mix with rectal fluids than the cocoa butter does and therefore providing a more prolonged release.

Because glycerinated gelatin suppositories have a tendency to absorb moisture due to the hygroscopic nature of glycerin, so they must be protected from moisture in order for them to maintain shape and consistency. Due also to the hygroscopicity of the glycerin, the suppository may be irritating to the tissues upon insertion. The water present in the formula for the suppositories minimizes this action, however, if necessary, the suppositories may be moistened with water prior to their insertion to reduce the initial tendency of the base to draw water from the mucus membranes and irritate the tissues.

2.2.2.2 Polyethylene glycols.

Polyethylene glycols are polymers of ethylene oxide and water prepared to various chain lengths, molecular weights, and physical states. They are available in a number of molecular weight ranges, the more commonly used being polyethylene glycol 200, 400, 600, 1000, 1500, 1540, 3350, 4000, 6000 and 8000. The numerical designations refer to average molecular weights of each of the polymers. Polyethylene glycols having average molecular weights of 200, 400 and 600 are clear,

colorless liquids. Those having average molecular weights of greater than 1000 are wax - like , white solids with the hardness increasing with an increasing in the molecular weight. Various combinations of these polyethylene glycols may be combined by fusion, using two or more of the various types to achieve a suppository base of the desired consistency and characteristics.

Polyethylene glycol suppositories do not melt at body temperature but rather dissolve slowly in the body's fluids, mix with mucous secretions upon their dissolution. If the polyethylene glycol suppositories do not contain at least 20% of water to avoid the irritation of the mucous membranes after insertion, they should be dipped in water just prior to use. This procedure prevents moisture being drawn from the tissues after insertion and the "stinging" sensation.

2.2.3 Miscellaneous bases.

In the miscellaneous group of bases are included those which are mixtures of the oleagineous and water- soluble or water- miscible materials. These materials may be chemical or physical mixtures. Some are formed emulsions, generally of the w/o type, or they may be capable of dispersing in aqueous fluids. One of these substances is polyoxyl 40 stearate, a surface-active agent that is employed in a number of commercial suppository bases.

2.3 Preparation of Suppositories.

Suppositories are prepared by three methods:

2.3.1 Fusion of molding from the molten mixtures method.

2.3.2 Compression.

2.3.3 Hand rolling and shaping or Cold hand shaping.

2.3.1 Fusion of molding from the molten mixtures method.

Basically, the step in molding include (a) melting of the base, (b) incorporating of any required medicaments, (c) pouring the molten mixtures into molds, (d) allowing to sodify, and (e) removing the formed suppositories from the mold. Suppositories of cocoa butter, glycerinated gelatin, polyethylene glycols, and most other suppository bases are suitable for preparation by molding.

Suppository molds.

Suppository molds are commercially available with the capability of producing individually or large numbers of suppositories of various shapes and sizes. Molds in common use are made from stainless steel, aluminum, brass, or plastic. The molds, which separate into sections, generally longitudinally, are opened before and after the preparation of a batch of suppositories, closed when the molten mixtures is poured, and opened again to remove the molded suppositories. Care must be exercised in cleaning the molds, as any scratches on the molding surfaces will take away from the desired smoothness of the resulting suppositories. Plastic molds are especially prone to scratching.

Lubrication of the mold.

Depending on the formulation, lubrication may require before the molten mixtures are poured to facilitate the clean and easy removal of the molded suppositories. Lubrication is seldom necessary when the suppository base is cocoa butter or polyethylene glycol because these materials contract sufficiently on cooling within the mold to separate from the inner surfaces and allow their easy removal. Lubrication is usually necessary when glycerinated gelatin suppositories are prepared. A thin coating of mineral oil applied with the finger to the molding surfaces usually suffices to provide the necessary lubrication.

Lubricant can be divided into two groups:

1. Oily lubricant such as mineral oil, vegetable oil e.g. arachis oil, olive oil. It is used in water soluble suppository bases.

2. Lubricant for oleagineous suppository bases e.g.

R_x	1	Soft soap	10	g
		Glycerin	10	g
		Alcohol 90%	50	mL
R_x	2	Soft soap	1	part
		Alcohol	2	parts
		Almond oil	2	parts

Besides these lubricant, silicone or sodium luaryl sulfate solution in water or propylene glycol can be used.

Calibration of the mold.

Each individual mold is capable of holding a specific volume of material in each of its openings. If the material is cocoa butter, the weight of the resulting suppositories will differ from the weight of suppositories prepared in the same mold with the mixture of polyethylene glycols as the base because of the difference of the densities of the materials. Any added medicinal agent would alter the densities of the bases, and the weights of the resulting suppositories would be different from those prepared with base material alone.

It is important that the calibration of each of suppository molds for the suppository bases in order that may prepare medicinal suppositories each having the proper quantity of the medicaments.

The first step in the calibration of a mold is to prepare molded suppositories from the base material alone. After removal from the mold, the

suppositories are weighed, and the total weight and the average weight of each suppository are records. To determine the volume of the mold, the suppositories are then carefully melted in a calibrated beaker, and the volume of the molten mixtures is determined for the total number as well as for the average of one suppository.

Determination of the amount of base required.

In determining the amount of base to be incorporated with the medicaments. It must be certain that the required amount of drug is provided in each suppository. Because the volume of the mold is known (from the determined volume of the melted suppositories formed from the base), the volume of the drug substances subtracted from the total volume of the mold will give the volume of base required. Instances in which the added amounts of medicaments are slight, they may be considered to be negligible and no deduction from the total volume of the base may be deemed necessary. However, if considerable quantities of these materials are important and should be used to calculate the amount of base actually required to completely filling the mold. The total volumes of these materials are subtracted from the volume of the mold, and the appropriate amount of base is added. Since the suppository bases are solids at room temperature, the volume of base determined may be converted to weight from the density of the material.

Another method for the determination of the amount of base in the preparation of medicated suppositories required the following steps: (a) weight the active ingredient for the preparation of a single suppository; (b) dissolve it or mix it with a portion of melted base insufficient to fill one cavity of the mold, and add the mixture to a cavity; (c) add additional melted base to the cavity to fulfil it completely; and (d) allow the suppository to congeal and harden; and (e) remove the suppository from the mold and weigh it. The weight of the active ingredients presents, subtracted from the weight of the suppository, and yields the weight of the amount of bases used. This amount of base multiplied by the number of suppositories to be prepared in the mold is the total amount of base required.

A third method involved the placing of all of the required medicaments for the preparation of the total number of suppositories in a calibrated beaker. To this is added a portion of the melted base and the drug substances is incorporated. Then sufficient additional melted base is added until the volume of mixture is reached that is required for the preparation of the necessary suppositories, based on the original calibration of the volume of the mold.

Preparing and pouring the molten mixtures.

Using the least possible heat, the weighed suppositories base material is melted, generally over a water bath, since a great deal of heat is not usually required. A porcelain casserole, which is a dish having a pouring lip and a handle, is perhaps the best utensil to use, because of convenient pouring of the molten mixtures into the cavity of the mold. Medicinal substances are usually incorporated into a portion of the melted base by mixing on a glass or porcelain tile with a spatula. After incorporation, this material is added with stirring to the remaining base, which has been allowed to cool almost to its congealing point.

It is generally best to chill the mold in the refrigerator before pouring the molten mixtures. Then, the molten mixtures are added continuously in the filling of each cavity in the mold. If any undissolved materials in the mixture are of greater density than the base so that they have a tendency to settle, constant stirring, even during pouring, is required, else the last filled cavity will contain a disproportionate share of the undissolved materials. When solidified, the excess material is even scraped off of the top of the mold with a spatula. Slightly pressure is exert with the thumb on the ends of each suppository to loosen it in the mold. Then the sections of the mold are separated, and the suppositories are dislodged with the pressure being exerted principally on their ends and only it needs on the tips.

2.3.2 Preparation by compression.

Suppositories may be prepared by forcing the mixed mass of the suppository base and the medicaments into special molds using suppository-making machines. In preparation for compression into the molds, the suppository base and the other formulative ingredients are combined by through mixing, the friction of the process causes the base to soften into a pastelike consistency. On a small scale, mortar and pestle may be used. If the mortar is heated in warm water use and then dried, the softening of the base and the mixing process is greatly facilitated. On a large scale, a similar process may be used, employing mechanically operated kneading mixers and a warmed mixing vessel.

The process of compression is especially suited for the making of suppositories containing medicinal substances that are heat labile and for suppositories containing a great deal of substances insoluble in the base. The disadvantage to the process is that the special suppository machine is required and there is some limitation as to shapes of suppositories that can be made from the available molds.

In preparing suppositories with the compression machine, the suppository mass is placed into a cylinder which is then closed, and pressure is applied from one end, mechanically, or by turning a wheel, and the mass is forced out of the other end into the suppository mold or die. When die is filled with the mass, a movable end plate at the back of the die is removed and when additional pressure is applied to the mass in the cylinder, the formed suppositories are ejected. The end place is returned, and the process is repeated until all of the suppository mass has been used. Various sizes and shapes of die are available. It is possible to prepare suppositories of uniform circumference by extrusion through a perforated place and by cutting the extruded mass to the desired length.

2.3.3 Preparation by hand rolling and shaping

With the ready availability of suppository molds of accommodating shapes and sizes, there is little requirement for shape suppositories by hand. Hand rolling and shaping is a historic part of the art of the pharmacist.

2.4 Suppository quality control.

Subsequent to suppository development, the finished product must undergo a number of simple tests in order to ascertain quality. List of properties that should be controlled is below:

2.4.1 Physical appearance.
2.4.2 Uniformity of weight.
2.4.3 Uniformity of content.
2.4.4 Disintegration
2.4.5 Melting range.
2.4.6 Liquefaction time.
2.4.7 Mechanical strength.
2.4.8 Dissolution study,
2.4.9 In vivo study.
2.4.10 Stability study.

2.4.1 Physical appearance.

Surface appearance and color can be verified visually to evaluate:

- Absence of fissuring.
- Absence of pitting.
- Absence of fat blooming.
- Absence of exudate.
- Absence of migration of active ingredients.

Taking longitudinal section to verify the homogeneousness of the distribution of the active ingredient can complete the test.

2.4.2 Uniformity of weight.

In preparation of suppositories, the weight of each suppository least difference in order to confirm the quality of suppositories. The difference must be available in acceptable range. The requirements for uniformity of weight are given in the British Pharmacopoeia, The United States Pharmacopoeia and The European Pharmacopoeia.

2.4.3 Uniformity of content.

Amount of active ingredient in each suppository may differ depended on many factors such as the volume of each mold, the error in preparation, unequal in weight of prepared suppositories. Therefore it is necessary to determine content of active ingredient. The requirement for uniformity of content appeared in the similar Pharmacopoeias to uniformity of weight.

2.4.4 Disintegration.

The test for disintegration of molded suppositories determined whether suppositories disintegrate or soften within 30 minutes for fat based and not more than 60 minutes for water soluble suppositories.

The apparatus for the disintegration of suppositories according to BP 1993 was shown in Figure 2.

2.4.5 Melting point.

The melting range is a decisive factor in the release rate of the active ingredients and must be checked periodically using a non-destructive method (U-tube) on the suppository just as it is. No method that leads to melting before measuring should be used because this would change the suppository constituents into metastable state. The finished suppository melting point should generally not be higher than 37°C.

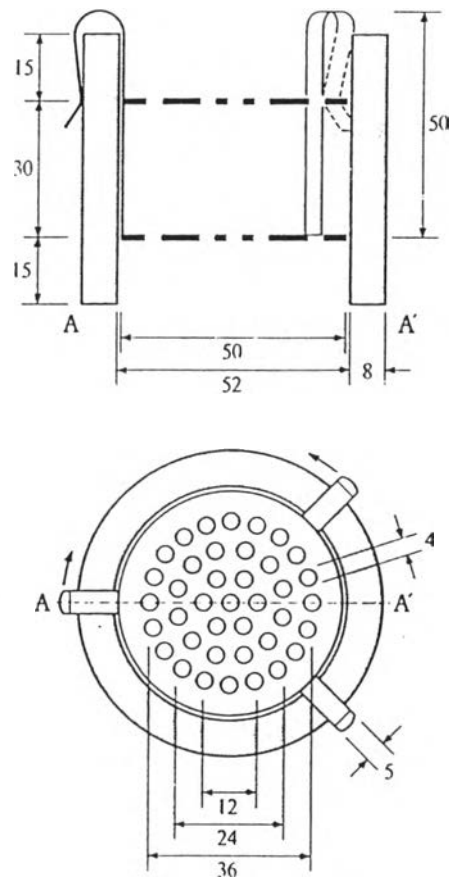


Figure 2. The apparatus for the disintegration of suppositories.

2.4.6 Liquefaction time.

This important element indicates the physical behavior of a suppository subjected to its maximum working temperature (37 °C). Krowczynski's method is well suited to this type of study, which is complementary to, and directly related to, the melting point.

It measures the time necessary for a suppository to liquefy under pressure similar to those found in the rectum (e.g., 30 grams.) in the presence of water at body temperature. A rule of thumb is that the liquefaction time should be no longer than 30 minutes.

2.4.7 Mechanical strength.

This is the determination of the mechanical force necessary to break a suppository, and it indicates whether a suppository is brittle or elastic. The ERWEKA method is suitable for this test, and it measures the mass (in kg.) which a selected suppository can bear without breaking. For satisfactory results, the mechanical strength should in no case be less than 1.8 to 2.0 kg.

2.4.8 Dissolution study (Banakar, 1991).

Testing for the rate of in vitro release of drug substances from suppositories has always posed a difficult problem, owing to melting, deformation, and dispersion in the dissolution medium.

Suppository Dissolution Methods.

The continued interest in suppositories and suppository bases has led to recognition that a dissolution test would be helping during the initial phase of dosage form design.

General techniques have been employed in the past for the study of in vitro drug release rates from suppositories. These methods can be classified into five different types:

2.4.8.1 Beaker method.

This type consists of simple placement of the suppository in a flask or a beaker and allows settling.

2.4.8.2 Basket method

This type utilizes an existing tablet dissolution apparatus that provides a wire mesh basket for holding the suppository.

2.4.8.3 Membrane diffusion method.

This type involves a flow system in which the sample is placed on cotton or wire screen. In one of the more recent ones the system entails use of a release chamber where the suppository is surrounded by glass beads or placed on a screen. The principal advantage claimed for the beaded system is that it maintains constant interfacial area while allowing direct contact between the dosage from and the dissolution medium, whereas the screen system does not.

2.4.8.4 Dialysis method.

This type employs dialysis tubing as a natural membrane. This apparatus has been one of the few designed where the suppository is in an upright position.

2.4.8.5. Continuous-flow method.

This type involves a flow system in which the sample is placed on cotton or a wire screen. In one of the more recent ones the system entails use of a release chamber where the suppository is surrounded by glass beads or placed on a screen. The principal advantage claimed for the beaded system is that its maintains constant interfacial area while allowing direct contact between the dosage form and the dissolution medium, whereas the screen does not.

An official dissolution method is not as yet available to test for drug release of rectal dosage systems in vitro. However, it is apparent from the literature that many research groups have been examining different techniques such as Muranishi method (Ermis and Tarimci, 1995) diagram of the apparatus shown in Figure 3.

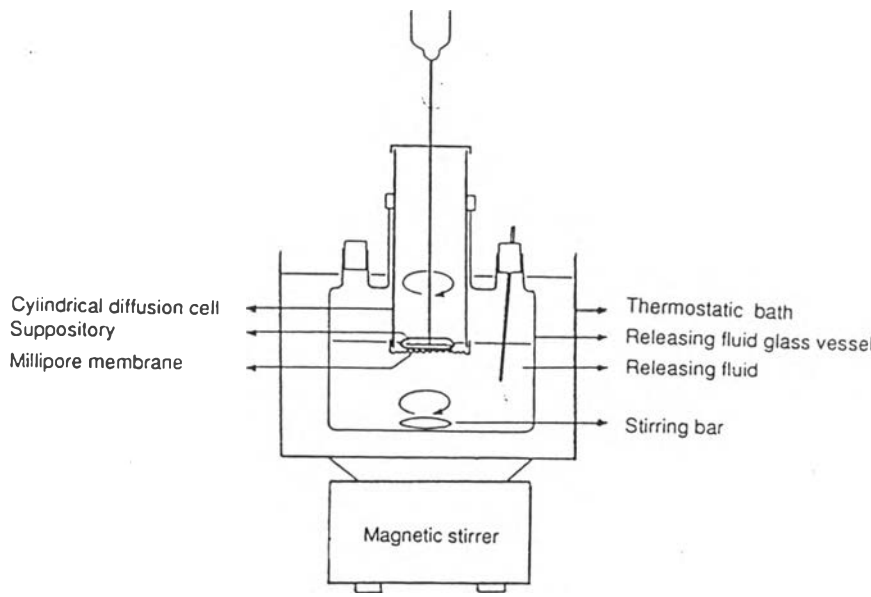


Figure 3. Cross-sectional diagram of the *in vitro* release and diffusion rate apparatus.

The other modified apparatus was the modified dialysis membrane method (Yamazaki, 1992) shown in Figure 4.

2.4.9 *In Vivo* study (Liversidge and Grant, 1983).

Ideally, the human volunteer is the best choice, although some workers have used humans in tests of the bioavailability of certain drugs from suppositories (Nishihata et al. 1988; Moolenaar et al. 1995; Lindmark et al. 1997). Human studies were impractical in the present work, because of legal, ethical and economic considerations.

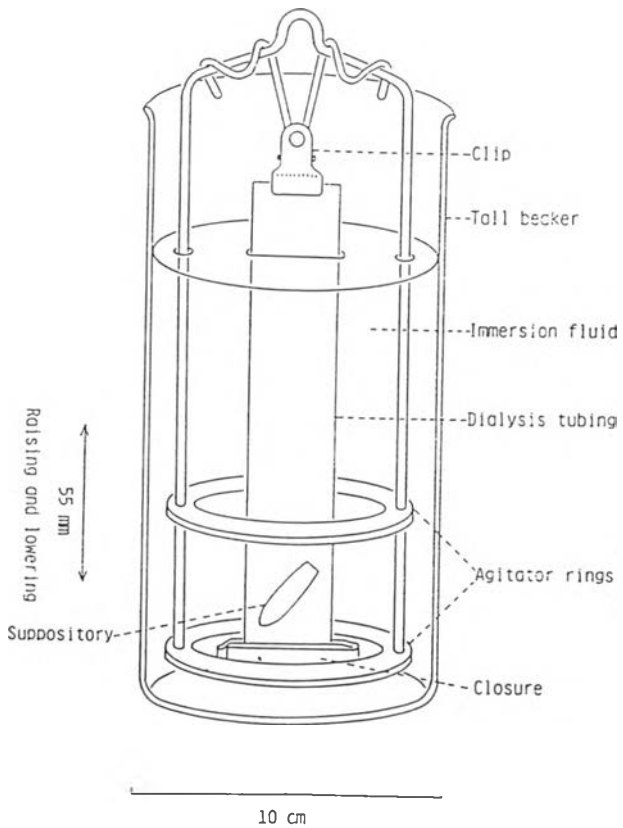


Figure 4. Diagram of the apparatus used in the modified dialysis membrane method.

The results obtained in animal studies may not be applicable to humans on account of differences in the relative concentrations of the drug in the various tissues and the physiology of the rectum. The differences in rectal physiology will generally pronounced effect on the bioavailability of a drug for the following reasons.

a. The amount of liquid present in the rectum, will vary from species to species and hence the amount of drug in solution and available for absorption will also vary.

b. The pressure and peristaltic movement in the rectum, which together control spreading, will vary from species to species.

c. The anatomy of the rectum will vary, so that absorption through the membrane and transport away from the membrane will vary and may affect the first-pass metabolism, which is frequently encountered in the administration of suppositories.

d. The liquefaction time of the suppository will differ on account of differences in suppository size required for different species.

e. The temperature and temperature gradient of the rectum may vary between different animal species and man.

f. Most animals are anaesthetized prior to insertion of a suppository. The administered anaesthetic then reduces body temperature, blood flow to the rectum and peristaltic movement, which may give a reduced absorption.

However, even with these constraints, *in vivo* data obtained using animals can be valuable because it can lead to more refined human studies.

The animal used in rectal work highlights 5 species, namely, dog, mice, guinea pig, rabbit and rat.

2.4.9.1 Dog.

The dog is the preferred animal model because its rectum is similar to that of man. Suppositories of normal commercial size can be applied to dogs, so that spreading and liquefaction time should be similar to those in human. The disadvantages of the dog are high maintenance expenses and certain legal restrictions.

2.4.9.2 Mice.

The mice are very inexpensive, but their small size gives rise to the following disadvantages:

a. The small suppository used in mice has a liquefaction time quite different from the used for humans.

b. The amount of blood available for assay (up to 1 ml) is very much smaller than from man.

2.4.9.3 Guinea pig.

The guinea pig is relatively inexpensive and is large enough to enable suitable quantities of blood to be taken for assay, but has the disadvantages:

a. The guinea pig has no tail and very loose coat, making handling of the animal and insertion of the suppository very difficult.

2.4.9.4 Rabbit.

The rabbit has the advantage of requiring a suppository of a more representative size and the capacity for providing plenty of blood for assay. The disadvantages of rabbits are that they are relatively expensive and difficult to handle.

2.4.9.5 Rat.

The rat has the advantage of cheapness, of being large enough to provide sufficient blood for assay and of ease of handling but the rat is the unrepresentative size of the suppository used.

2.4.10 Stability studies (Lieberman and Anschel, 1986)

Suppositories should be protected from heat, preferably by storing in the refrigerator. The suppository, including active ingredients and the base, must be chemically and physically stable at refrigerator temperatures as well as at room temperature storage conditions for at lease two years. Storage stability studies are normally conducted at 4°C and at room temperature (25 ±3 °C).

Cocao butter suppositories in storage sometimes "bloom". i.g., form a white powdery deposit on the surface. This is unsightly and usually can be avoided if the suppositories are wrapped in foil and stored at uniform cool or refrigerator temperatures.

Fat base suppositories have been shown to harden for a period of the time after manufacture. The upward shift in melting range is due to slow crystallization to the more stable polymorphic forms of the base. Depending on the initial melting range and the formula of the suppository, this phenomenon may affect the melting of the suppository and subsequent drug absorption rates.

The softening time test and differential scanning calorimetry can be used as stability indicating test methods to predict problems of this sort. Storage immediately after manufacture at an elevated temperature below the melting range speed up the aging process. Since the hardening phenomenon is a finite process. This tempering approach can minimize further changes in melting range, which may be worth the addition to manufacturing cycle time.

Stability studies of suppositories intended for tropical climates must be conducted in the final package at temperatures at which the suppositories will eventually be kept. High-melting bases, water-soluble bases, and special polyethylene shell packages must be considered. Labeling should emphasize storage in a cool place. Efforts should be made in formulating suppositories for the tropics to maintain the physical and chemical stability of these suppositories in their final package, even when are stored at temperatures as high as 50°C.

Storage studies also should include anticipated problems resulting from shipment. To test the effects of handling the product in the field, suppositories often are shipped by the desired transport facilities to several areas in the country, and tested physically, and occasionally, chemically, for stability. Cool conditions for shipment often are required.

2.5. Packaging and Storage.

Glycerin suppositories and glycerinated gelatin suppositories are generally packaged in tightly close glass containers to prevent a moisture change in the content of the suppositories. Suppositories prepared from a cocoa butter base are usually individually wrapped or otherwise separated in compartmentalized boxes to prevent contact and adhesion. Suppositories containing light-sensitive drugs are generally individually wrapped in an opaque material such as a metallic foil. In fact, most commercially available suppositories are individually wrapped in either foil or a plastic material. Some are packages in a continuous strip with suppositories being separated by tearing alone perforations placed between suppositories.

Since suppositories are adversely affected by heat, it is necessary to keep them in a cool place. Suppositories having cocoa butter as the base must be stored below 30 °F, preferably in the refrigerator. Glycerinated gelatin suppositories are best stored at temperatures below 35 °F. Suppositories made from a base of polyethylene glycol may be stored at usual room temperatures without the requirement of refrigeration.

Suppositories stored in the environments of high humidity may absorb moisture and tend to become spongy, whereas suppositories stored in placed of extreme dryness may loss moisture and become brittle.

Besides the conventional form, prolonged release suppositories can be prepared in order to achieve prolonged action medication clinically, alleviation of pain during sleep being often helpful in reducing anxiety.

In this study, the poorly water soluble carriers were Eudragit S-100 and hydroxypropyl methylcellulose phthalate (HP55), their properties were described as follow.

3. Eudragit S-100 (Wade and Weller, 1994).

Eudragit S-100 are polymethacrylates that as a fully polymerized copolymer of methacrylic acid and an acrylic or methacrylic ester. They are divided in three types, type A (Eudragit L), type B (Eudragit S) and type C (Eudragit L30 D-55) defined which vary in their methacrylic acid and solution viscosity.

For Eudragit S-100 is an anionic copolymerization product of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1:2. It is readily soluble in neutral to weak alkaline conditions (pH 6-7). It does appear in white free flowing powders with at least 95% of dry polymers.

Eudragit S-100 is soluble in acetone, ethanol, methanol, propan-2-ol and 1N NaOH but insoluble in dichloromethane, ethyl acetate, petroleum ether and water.

The application of Eudragit S-100 recommended for enteric coating and the polymethacrylate copolymers are widely use as film coating materials in oral pharmaceutical formulations. A daily intake of 2 mg/kg body-weight of Eudragit (equivalent to approximately 150 mg for a average adult) may be regarded as essentially safe in humans.

The Eudragit as used in preparation of sustained release suppositories such as indomethacin suppositories prepared with Eudragit L-100 and polyethylene glycol 2000 solid matrix (Ohnishi, 1988), the *in vitro* studied showed that the rate of indomethacin release decreased with increase of the Eudragit L-100 content. Because these matrix suppositories was attributed to the development of a network structure of Eudragit L-100. Rectal administrations in rabbit resulted in good characteristics for sustained release.

4. Hydroxypropyl methylcellulose phthalate (HPMCP).

Hydroxypropyl methylcellulose phthalate is a cellulose in which some of the hydroxyl groups are replaced with methyl ethers, 2-hydroxypropyl ethers or phthalyl esters. It is widely used in oral pharmaceutical formulations as an enteric coating material for tablets or granules and can be use alone or in combination with other soluble or insoluble binders in preparation of granules with sustained drug release properties. The release rate is pH dependent.various grade of hydroxypropyl methylcellulose phthalate are available with differing degree of substitution and physical property see in Table 2.

Table 2 Classification of hydroxypropyl methylcellulose phthalate

Property	Grade of HPMCP		
	HP-50	HP-55	HP-55S
Substitution type	220824	200731	200731
Hydroxypropyl content	6-10%	5-9%	5-9%
Methoxy content	20-24%	18-22%	18-22%
Phthalyl content	21-27%	27-35%	27-35%
Molecular weight	84000	78000	132000

The number following "HP" in each grade designation refers to the pH value (x10) at which the polymer dissolves in aqueous buffer solutions.

HP55 was used in prepared ketoprofen sustained release suppositories (Ermis, 1995), with polyethylene glycol as water soluble carriers. HP55 was added to the bases in two different ratios. The *in vitro* release showed that increasing the ketoprofen/HP55 ratio from 1:2 to 1: 3 yielded slower release and hence considerably sustained the duration of complete drug release.

The basket method was used in drug released studied. It was showed that ketoprofen/HP55 ratio 1:3 resulted in complete drug release within 3.5 hours while

1:2 only 1.5 hours was required. With this results were the guideline in developing ketoprofen using HP55 as poorly water soluble by solid matrix technique.