CHAPTER I

INTRODUCTION

Suppositories are solid medication for insertion into body cavities. Currently, only rectal and vaginal suppositories are in use. Besides there is urethral suppository which dose not often use in the present. They disintegrate in the body cavity either by melting or by dissolution. The term vaginal suppository is now used rather loosely and is often applied to vaginal tablets. Rectal suppositories are an infrequently used but long known form of medication which is employed for both local and systemic distribution of a drug. (4)

These suppositories gave their therapeutic action locally or systemically, either by melting at body temperature or by dissolving in the aqueous of the mucous membranes and thus allowing the release of the active ingredients. A number of other terms have been used to identify this dosage form. The term "bougie" was used as a synonym but, presently, it is more commonly used to desingnate an instrument which may be inserted through the urethra or other body passage for dilatation or exploration. Vaginal suppositories have also been known by the name "pessary". However, in the United Stated this term is usually reserved for a device which is inserted into the vagina to support the uterus. (9)

Suppositories were known to the Assyrians about 2600 B.C., to the Egyptians a thousand years later and to the ancient Greeks and Romans. While the Egyptians confined the use of suppositories to the treatment of local conditions, Hippocrates also used them to improve breathing in children and Dioscorides to produce sleep. Galen, in the second century, applied suppositories for their purgative effect only.

The vehicle was at first a shaped chip of wood or bone, which was dipped into a coating mixture of warm fat or honey and ground drug. The chips were retrieved, cleaned and used again. Other core materials, which were introduced later, were pieces of soap, raisins, ~~vegetable or cabbage introduced later, were pieces of soap, raisins~~, vegetable or cabbage stock and pieces of cloth. The suppository ranged in size from a small pellet to one weighing as much as 20 g.

The lack of dosage uniformity in such diverse forms of rectal application is probably responsible for the neglect of the suppository in subsequent century and the introduction in the 19th century of molds, first of paper, then wood and, finally, metal, the use of suppositories became more widespread.

There is no consensus about the etymologic origin of the word suppository, which is the same in Romanic and Germanic languages. However, the most likely origin is from the Latin participle 'suppositus, which means placed underneath. Until the last century, the term was supplied mostly to shaped medication inserted into any body cavity except the mouth; in the beginning of the 20th century urethral suppositories, called bougies, were not uncommon.

As a useful form for drug administration, suppositories have been more popular in Europe than in the United States. In recent years about one percent of all prescriptions in the U.S. have been for rectal suppositories; a good many suppository preparations exist that do not require a prescription. (4, 13)

Suppository Bases

The function of materials other than medication in suppositories is to present an acceptable and usable dosage form. The suppository base may be required for dilution of the drug to a nonirritating concentration. Thus, the irritant local action and the volatility of chloral hydrate are reduced to acceptable levels by incorporation into a suppository base. Other possible functions of the base are to stabilize or to control the rate of release of the drug(13)

A general classification of suppository bases is possible on the basis of their physical properites.

a. Oleaginous Bases

The oleaginous bases include cocoa butter and synthetic triglyceride mixtures.

1. Cocoa Butter (Theobroma Oil)

Cocoa butter is the most widely used suppository base; it is often used in compounding prescriptions when no base is specified

It satisfies many of the requirements for an ideal base, since it is innocuous, bland, nonreactive, and melts at body temperature. However, cocoa butter still has several disadvantages, for it can rancidify, melt in warm weather, liquify when incorporated with drugs, and with overheating, isomerizes to an undesirable lowered melting point.

Cocoa butter is primarily a triglyceried, with the predominant glyceride chains being oleopalmitostearin and oleodistearin. It is a yellowish - white, solid, brittle fat, which smells and tastes like chocolate. Its melting point lies between 30° C and 35° C (86° F to 95° F), its iodine value between 34 and 38, and its acid value not higher than 4.

Because cocoa butter can easily melt and rancidify, it must be stored in a cool, dry place, and be protected from light.

Cocoa butter exhibits marked polymorphism (the property of existing in different crystalline forms), a phenomenon probably attributable to the high proportion of unsaturated triglycerides. Each of the different form of cocoa butter has different melting points, as well as different drug release rates. When cocoa butter is heated above its melting temperature (about 36°C) and chilled to its solidification point (below 15°C), immediately after returning to room temperature this cocoa butter will have a melting point of about 24°C, approximately 12°C below its original state. A knowledge of these polymorphic states is essential for an understanding of how uniform drug release patterns can be obtained from suppository bases consisting primarily of cocoa butter.

Cocoa butter is thought to be capable of existing in four Crystaline states:

1. The α form, melting at 24°C, is obtained by suddly cooling melted cocoa butter to 0°C
2. The β form crystallizes out of the liquefied cocoa butter with stirring at 18-23°C. Its melting point lies between 28 and 31°C
3. The stable β form is obtained from β form melting between 34°C and 35°C
4. The γ form, melting at 18°C, is obtained by pouring a cool (20°C) cocoa butter, before it solidifies, into a container, which is cooled at deep freeze temperature.

The formation of the various forms of cocoa butter depends on the degree of heating, the cooling process, and the conditions during this process. At temperatures below 36°C, negligible amounts of the unstable form are obtained, but prolonged heat above that critical temperature.

causes the formation of the unstable crystals with resulting lowered melting points. The reconversion to the stable β form takes one to four days, depending on the storage temperature the higher the temperature, the faster the change.

The formation of the unstable forms can be avoided by various methods :

1. if the mass is not completely melted, the remaining crystals prevent the formation of the unstable form;

2. small amounts of stable crystals added to the melted cocoa butter accelerate the change from the unstable to the stable form; this process is called "seeding"

3. the solidified melt is tempered at temperatures between 28°C and 32°C for hours or days, causing a comparatively quick change from the unstable to the stable form.

All these proporties of cocoa butter may cause considerable difficulties in the manufacturing process. As a general rule, the minimal use of heating in the process to melt the fats is recommended. Prolonged heating must be avoided as much as possible. There are several additional disadvantageous characteristics inherent to cocoa butter as a suppository base. Low contractility during solidification causes the suppositories to adhere to molds and necessitates the use of mold release agents or lubricants.

The solidification point of cocoa butter lies about 12°C to 13°C below its melting poing. This property can be utilized in working with cocoa butter in suppository formulations, where the mass can be kept in a fluid state at comparatively low temperatures. Constant agitation maintains cocoa liquid at temeratures below its solidification points.

Cocoa butter does not contain emulsifiers and, therefore, does not take up large quantities of water (maximum 20 to 30 Gm. of water to 100 Gm. of cocoa butter).

The addition of emulsifiers such as Tween 61 (5 to 10%) increases the water absorption considerable. Emulsifiers also help to keep insoluble substances suspended in the fat. Suspension stability is further obtained by the addition of materials (aluminum monostearate, silica) which give melted fat thixotropic properties. There is always the possibility that the suppositories, containing these aeditives, will harden on storage. Therefore, prolonged, careful stability observations are recommended.

Such drugs as volatile oils, creosote, phenol, and chloral hydrate lower the melting point of cocoa butter to a considerable extents. To correet this condition, wax and spermaceti were commonly used. Now special bases with high melting ranges are available for this purpose.

The quality of cocoa butter varies with the origin and treatment. Thus, it is quite possible to obtain different physical characteristics with two cocoa butters from different sources, although both are within all the specifications of the U.S.P. The selection of a reliable source of supply is imperative to eliminate broad variations in color and consistency between batches.(7)

2. Synthetic Triglyceride Mixtures:-

Because of the disadvantages of cocoa butter,a number of newer materials have been developed for the preparation of suppositories. These materials generally consist of hydrogenated vegetable oils and do not have the same tendency toward polymorphism as cocoa butter. As is the case with nearly all bases, drug availability from these bases may be somewhat different from that which is normally expected from theobroma oil. These products are available in a series of synthetic mixtures which bear designations specific for each. The Wecobees (Drew chemical Co) and the Witepsole are examples. (9) Wecobees is triglycerides which derived from coconut oil, its melting point between 33-35° C. (6)

Wipepsol suppository excipients are mixture of triglycerides of natural saturated fatty acids with a chain length of C_{12}- C_{18} which contain a quantity, corresponding to the stated hydroxyl number, of partial glycerides of the same fatty acids. For the manufacture of the most variegated suppository recipes, a whole range of WITEPSOL types is available, divided into Series H, W.S and E.

b. Water-Soluble Bases

The most important water soluble bases are those containing glycerinated gelatin and the polyethlene glycol polymers.

1. Glycerinated Gelatin Bases -A base comprised of 70 parts glycerin, 20 parts gelatin, and 10 parts water furnishes a useful mixture, especially for the preparation of vaginal or urethral suppositories. Suppositories made with this mixture are translucent, resilient solids that disperse or dissolve very slowly in the mucous secretions to release incorporated active ingredients (9)

2. The Polyethylene Glycols

The various polyethylene glycols polymers are marketed in the United States as Carbowax and Polyglycols and suggested for use as suppository bases. Long-chain polymers of ethylene oxide exist as liquids when their average molecular weight ranges from 200-600, and as wax-like solids with molecular weights above 1000. Their water solubility, hygroscopicity and vapor pressure decrease with increasing average molecular weights. The wide range of melting points and solubilities makes possible formulation of suppositories with various degrees of heat stability and with different dissolution rates. They do not hydrolyze or deteriorate, also they are physiologically inert, and will not support mold growth. (7)

Several combinations of polyethylene glycols have been prepared for suppository bases having different physical characteristics. Examples of these formulars can be illustrated by a few suggested in the work of Collins, Hohmann, and Zopf as follow :

Base 1

Polyethylene glycol 1000 96%

Polyethylene glycol 4000 4%

This base is low melting and may require refrigeration during the summer month. It is useful if rapid disintegration is desired.

Base 2

Polyethylene glycol 1000 75%

Polyethylene glycol 4000 25%

This base, more heat stable than Base 1, may be subjected to storage at higher temparatures than the previous one. It is useful when a slow release of active ingredients is preferred.

Bases 1 and 2, which do not contain water, are generally dipped in water before insertion,so that possible irritation to mucous membranes may be eliminated. This irritation, or "sting", is caused when the water is drawn from the mucosa. Most patients do not feel discomfort from the use of these suppositories. Cheymol, Buffet, and Lechat suggested the addition of 10% of water to facilitate solution of the suppository after insertion.

The polyethylene glycol suppositories can be prepared by both molding and cold compression method. A mixture of 6% hexanetriol-1, 2,6 with polyethylene glycol 1540, and 12% of the polyethylene oxide polymer 4000 are especially suitable bases for the cold compression technique. The drug is incorporated by dissolving or dispersing in the molten base. Special precautions are necessary in preparing a molded suppository with the polyethylene glycol bases. The mold must be dry because of the solubility of the base in water. The melted mass must be allowed to cool almost to the congealing point before-

point, or the resultant suppository will be fissured owing to the crystallization and contration of the polymer. Such suppositories may be easily fractured in packaging or handling. The polyethylene glycol base suppositories cannot be prepared suitably by hand rolling. Polyethylene glycol suppositories do not require a mold lubricant and are easier to prepare than cocoa butter suppositories.

Disintegration times of polyethylene glycol type suppository bases; measured in vitro by determining the rate of solution in water at body temparature, do not coincide with the human in vivo results, measured by x-ray study of suppositories containing barium sulfate.

See Table 1 for comparative results. Thus clinical results seem to be the best criterion for choosing the desired polyethylene glycol base, and in vitro test method should be used for controlling product uniformity of different production lots.

Reports of many workers on adverse reactions of these polymers indicated little difference in sensitivity to individual bases,but a diminished reaction with 6000 polymer. In one study the problem of safety,sensitization, and chemical inertness was attributed to impurities and not to the base itself.

TABLE 1 Comparision of In Vivo Solution Time to In Vitro Disintegration Time of Three Suppository Bases :

Base	Solution Time (min)	Disintegration Time (min)
Polyethylene glycol 1000	13	15
Cocoa butter	3	3
A Base made of :		
Polyethylene glycol 1540-94%		
Hexanetriol 1.2.6. - 6%	18	40

From Collins, A.P., Hohmann, J.R., and Zopf, L.E.; American Professional Pharmacist, 23:231,1957.

c. Hydrophilic Bases :

Cocoa butter can be modified into oil-in-water (O/W)or water-in oil (W/O) emulsion type suppository bases by the incorporation of suitable emulsifying agents. In the preparation of suppositories it is generally more desirable to form emulsions of the W/O type because those of the O/W variety are more prone to lose their water by evaporation, with the result that these preparations are relatively unstable. (9)

Sometime surface active agents (surfactants) are also used in - combination with these bases to in crease the rate of drug releasing. Because of their high wetting and detergent properties surfactants - are used so widely as emulsifier, solubilizers and formulation adjuncts. When a surfactant is dissolved in water at very low concentrations, a fraction of it will be adsorbed at the air-water interface, and the remainder will reside in the bulk in the form of monomers. As the concentration is increased,a level is reached where the interface becomes saturated with surface active agent and,usually simultaneously, the limiting solubility of monomer in the bulk is approached. At this concentration an unusual phenomenon occurs. Rather than precipitate, the monomers in the bulk tend to form colloidal aggregates termed micelles, consisting of 50 to 150 molecules or ions of surface active agent. The concentration at which aggregation occurs is called the critical micelle concentration or CMC. The molecules in the micellar unit have a definite orientation: the hydrocarbon or nonpolar portion is oriented to the center of the micelle and is shielded from the aqueous solution. In essence a micellar solution consists of many nonpolar "droplets", which can function as a discrete phase and there by interact with or "dissolve" drugs that normally would be insoluble in aqueous systems. This phenomenon is termed micellar solubilization (7)

Surfactants can exert a two-phase effect which is a function of concentration. Below the CMC, absorpion of drugs may be enhanced due to better contact of solution with the membrane; this is a "wetting"

or spreading effect resulting from a decrease in the surface tension of the solution. There may also be a direct effect of the surfactant on the permeability of the biologic membranes. Above the CMC, a portion of the drug molecules may become entrapped in micella and, as such, be unavailable for absorption.

The net effect (absorption enhancement or retardation) depends to some degree on the relative magnitude of interaction between drug and surfactant. The absorption-retarding effect usually predominated at higher surfactant concentrations because a larger fraction of the drug is bound to micelles. However, repeated or prolonged exposure to high doses of surface-active agent may lead to partial disruption of biologic membranes and there by reduce their barrier effect significantly. In this case, a high concentration of surfactant would increase absorption of the drug. (13)

The Ideal Suppository Base (7,12)

The ideal suppository base may be described as follows;

(1) melt at rectal temparature 37.5°C, but bases with higher melting points are employed for eutectic mixtures, addition of oils, balsams, and suppositories intended for use in tropical climates;

(2) completely nontoxic and nonirritating to sensitive and inflamed tissues.

(3) compatible with a broad variety of drugs.

(4) no metastable forms.

(5) shrinks sufficiently on cooling to release itself from the mold without the need for mold lubricants.

(6) nonsensitizing.

(7) has wetting and emulsifying properties.

(8) "water number" is high- a high percentage of water can be incorporated in it.

(9) it is stable on storage, does not change color, odor, and drug release pattern.

(10) can be manufactured by molding either by hand, machine, compression or extrusion.

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

(11) "acid value" is below 0.2.

(12) "Saponification value" range from 200 to 245.

(13) "iodine value" is less than 7.

(14) the interval between "melting point" and "solidification point" is small.

Factors Affecting Drug Absorption from Suppositories

Rates of absorption of active ingredients from suppositories may vary not only with different formulations, but also with identical formulations, in different patients, depending upon a number of factors which come into play.

1. Physiological Factors- When a rectal suppository is administered it is subjected to a number of environmental conditions which frequently have a profound effect upon its therapeutic efficiency. These factors are:-

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 with 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 suppository of a 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.

1.2 Circulation route Drugs absorbed rectally, unlike those absorbed after oral administration, bypass the portal circulation, thereby enabling drugs otherwise destroyed in the liver to exert systemic effects. The lower hemorrhoidal veins surrounding the

colon receive the absorbed drug and initiate its circulation throughout the body, bypassing the liver. Lymphatic circulation also assists in the absorption of rectally administered drugs:

1.3 pH and Lack of Buffering Capacity of The Rectal Fluids. Unionized drug are generally more readily absorbed from the various sites of absorption than highly ionized drugs. Since the rectal fluids are essentially neutral in pH and have no effective buffer capacity, the form in which the drug is administered will not generally be chemically changed by the rectal environment. Thus, for increased absorption, a drug may be issued by the suppository in the unionized form, or the pH of the rectal fluids may be modified easily by a formulative component of the suppository to maintain the pH at which the drug is best absorbed.

2. Physicochemical Factors of the Drug and Suppository Base

Physicochemical factors include such properties as the relative solubility of the drug in lipid and in water and the particle size of a dispersed drug. Physicochemical factors of the base include its ability to melt, soften, or dissolve at body temperature, its ability to release the drug substance, and its hydrophilic or hydrophobic character

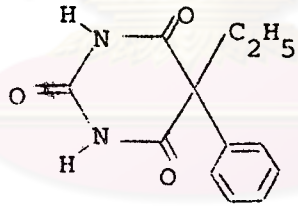
2.1 Lipid-Water Solubility. The lipid-water partition coefficient of a drug is an important consideration in the selection of suppository base and in anticipating drug release from that base. A lipophilic drug that is distributed in a fatty suppository base in low concentration has less of a tendency to escape to the surrounding aqueous fluids than would a hydrophilic substance present in a fatty base to an extent approaching its saturation. Water-soluble bases-for example, polyethylene glycols-which dissolve in the anorectal fluids, release for absorption both water-soluble and oil-soluble drugs. Naturally, the more drug a base contains, the more drug will likely be released for potential absorption. However, if the concentration of a drug in the intestinal lumen is above a particular amount, which varies with the drug, the rate of absorption is not changed by a further increase in the concentration of the drug. So, drug concentration in a suppository may mean

more drug liberated for absorption, but it does not necessarily mean that more drug will actually be absorbed.

2.2 Particle Size. For drugs present in the suppository in the undissolve state, the size of the particle will influence the amount released and dissolved for absorption. As indicated many times previously, the smaller the particle size, the more readily the dissolution of the particle and the greater the chance for rapid absorption.

2.3 Nature of the Base. As indicated earlier, 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 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 thorough drug release and absorption. (1)

Phenobarbital (Phenobarbitone) is 5-ethyl-5-phenyl-barbituric acid.



It is a white cryatalline powder, odourless; taste slightly bitter, and soluble at 20°C in 1000 parts of water; also soluble in alcohol (95%), solvent either, chloroform, and in solutions of alkali hydroxides and carbonates. (2)

Phenobarbital is classified into a long-acting barbiturate. It is used for hypnotic, sedative and anticonvulsant. The sedative dose is 15 to 30 mg, repeated two to four times daily. The average hypnotic dose for adults is 100 mg. The daily intake should not exceed 600 mg. The drug is supplied as a powder, as an elixir containin-g 4 mg/ml, and as tablets containing 15, 30, 60, and 100 mg. Phenobarbital Sodium, U.S.P., is available for parenteral use in ampuls containing 60, 125, 200, and 300 mg of sterile powder, and in ampuls or vials containing solution of 25, 50, 60, 125 or 150 mg/ml. (3,5)

Toxicity; The adverse effects of phenobarbital have been reviewed by Browning and Maynert (Symposium, 1972 a). Sedation, the most frequent undesired effect of phenobarbital, is apparent to some extent in all patients upon initiation of therapy, but tolerance develops during chronic medication. Nystagmus and ataxia occur at excessive dosage. Phenobarbital sometimes produces irritability and hyperactivity in children and confusion in the elderly.

Scarlatiniformor morbilliform rash, possibly with other manifestations of drug allergy, occurs in 1 to 2% of patients. Fatal exfoliative dermatitis is rare. Hypoprothrombinemia with hemorrhage has been observed in the newborn of mothers who have received phenobarbital during pregnancy; vitamin K is effective for treatment or prophylaxis. Megaloblastic anemia that responds to folate and osteomalacia that responds to high doses of vitamin D occur during chronic phenobarbital therapy of epilepsy, as they do during phenytoin medication.

Statement of the Problems

In spite of the widespread utilization of barbiturates, dosage forms were usually be made in tablet and parenteral, not in suppository. Sometimes these dosage forms might not be appropriated for using with mentally disturbed patients, or whooping cough children. In the case of mentally disturbed patients, or whooping cough children who refused to take drugs, suppository might be more appropriated. Besides these conditions, suppositories had been found important application in administering drug to infants or small children, to severely debilitated patients, to those who cannot take medication orally, e.g comatos or nauseated individuals, and to those for whom the parenteral route might be unsuitable. (9)

Therefore it is the purpose of this study to investigate the best suppository base, which would result in highly effective releasing rate of phenobarbital. The study was initiated to measure the concentration of phenobarbital and compare the releasing rate of drugs with different kind of suppository bases, i.e. PEG bases, Witepsol E 85, Witepsol S 55 and cocoa butter plus 10% white beeswax. The effect of surfactant on the releasing rate of phenobarbital from suppository bases was also study.