CHAPTER II

REVIEW OF LITERATURE

1. Definition of suppositories (Ansel et al., 1999)

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

The rectal route is used in many different therapies, intended either for local or for systemic effect.

1.1 Local action

Once inserted, the suppository base melts, softens, or dissolves, distributing the medicaments it carries to the tissues of the region. These medicaments may be intended for retention within the cavity for localized drug effects, or they may be intended to be absorbed for the exertion of systemic effects. Rectal suppositories intended for localized action are most frequently used to relieve constipation, pain, irritation, itching and inflammation associated with hemorrhoids or other anorectal conditions. Antihemorrhoidal suppositories frequently contain a number of components, including local anesthetics, vasoconstrictors, astringents, analgesics, soothing emollients, and protective agents. A popular laxative, glycerin suppositories promote laxation by local irritation of mucous membranes, probably by the dehydrating effect of glycerin on those membranes.

1.2 Systemic action

Rectal route of administration achieves systemic effects with an advantage over oral therapy in these following aspects:

a) Drugs, these are destroyed or inactivated by pH or enzymatic activity of the stomach of intestine are not exposed to these destructive environments.
b) Drugs irritating to stomach may be given without causing such irritation.
c) Drugs destroyed by portal circulation may bypass liver after rectal absorption (drugs enter the portal circulation after oral administration and absorption).
d) This route is convenient for administration of drugs to adult or pediatric patients who are unable or unwilling to swallow medication.
e) It is an effective route in the treatment of patients with vomiting episodes.

Examples of drugs administered rectally in the form of suppositories for their systemic effects include

a) Prochlorperazine, and chlorpromazine for relief of nausea and vomiting and as a tranquilizer.
b) Oxymorphene HCl for narcotic analgesia.
c) Ergotamine tartrate, for relief of migraine syndrome.
d) Indomethacin, a non-steroidal anti inflammatory analgesic and antipyretic.
e) Ondansetron for relief of nausea and vomiting.

2. Anatomy and physiology of rectum

Rectal dosage forms are introduced in the body through anus, the most caudal part of the GI tract, the rectum. Anatomically, rectum is a part of colon, forming the last 150-200 mm of GI tract. Rectum can be subdivided into anal canal and ampulla, the latter forming approximately 80% of the organ. It is separated from the outside world through a circular muscle, the anus. Rectum can be considered as a hollow organ with a relative flat wall surface without villi. A diagram of part of the rectum's veinous drainage is shown in Figure 1. Total volume of mucous is estimated as approximately 3 mL, spread 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.

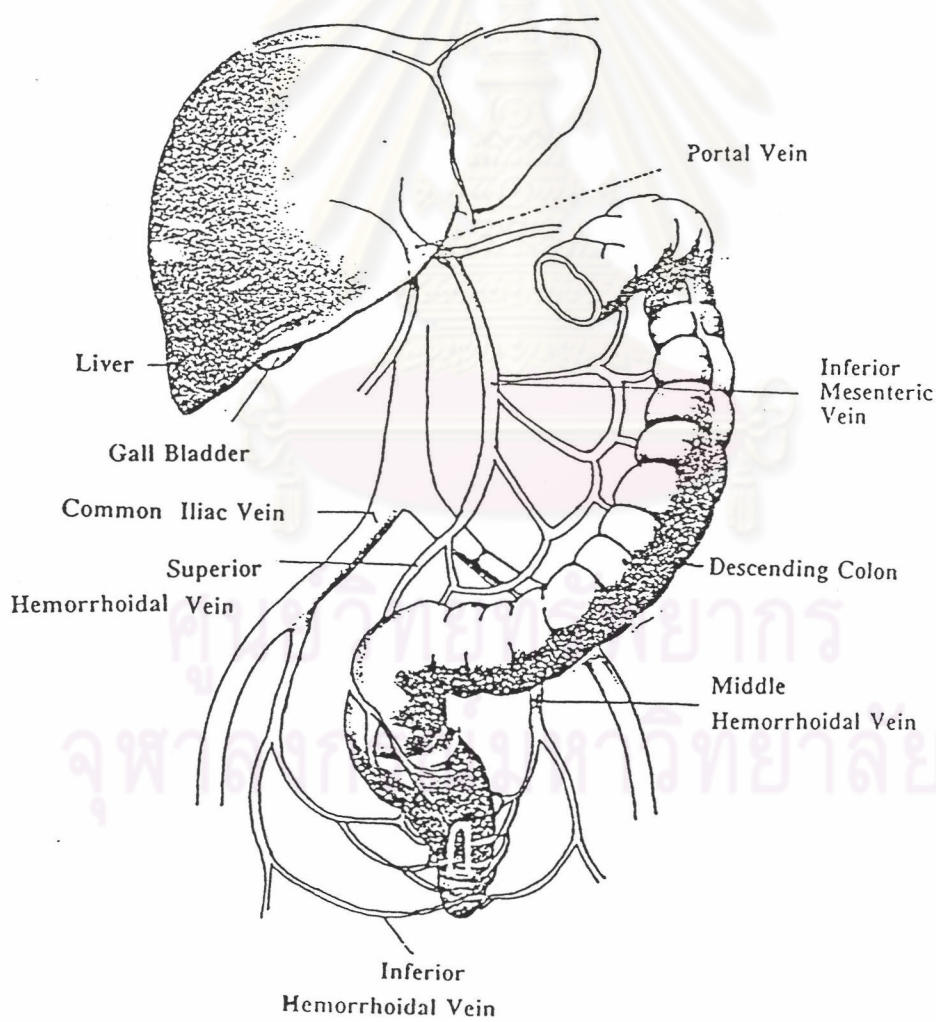


Figure 1. The veinous blood system of rectum. (Plaxco, 1984)

In rectum, the lower veinous drainage system (inferior and middle hemorrhoidal veins) is connected directly to the systemic circulation by iliac veins and vena cava. The upper veinous drainage system (superior hemorrhoidal vein) is connected to the portal system as same as the other regions of GI tract. Thus, there exists an opportunity to reduce the extent of hepatic first-pass elimination by rectal delivery, especially when drug is administered in the low region of rectum. Fifty to seventy percent of drugs absorbed rectally pass directly into systemic circulation avoid the liver and consequently the possibility of metabolism and biliary excretion by that organ (Gilbert and Christopher, 1992).

Effect of rectal administration on hepatic first-pass metabolism of drugs was demonstrated by studying systemic bioavailability of a high-clearance drug, e.g., lidocaine. Studies conducted in six healthy volunteers indicated that rectal absorption of lidocaine in aqueous solution results in a systemic bioavailability as high as 69% comparing to the 30.5% by oral administration. It is estimated that rectal administration of lidocaine has resulted in 55% of the dose bypassing the hepatic first-pass metabolism (Yie, 1992). Effect of sites of rectal infusion on the systemic bioavailability of lidocaine was also investigated. The results suggested that an infusion site located at only 2 cm from the anus produce a greater systemic bioavailability of lidocaine than the infusion site located 4 cm away. This implies that the rectal absorption via inferior rectal veins has a greater chance to bypass the hepatic first-pass metabolism.

Human rectal mucosa is composed of epithelium, lamina propria, and double-layer muscularis mucosae, The epithelial surface consists of closely packed columnar cells with some areas interrupted by crypt regions. Within the crypt regions, there are mucous - producing globlet cells. There are two routes potentially involved in drug permeation across epithelial membranes: the transcellular route and the paracellular route. In studies dealing with mechanisms of transmembrane permeation, the structure of epithelial membrane is frequently simplified to consist of a lipodal pathway and an aqueous pore pathway (Figure 2).

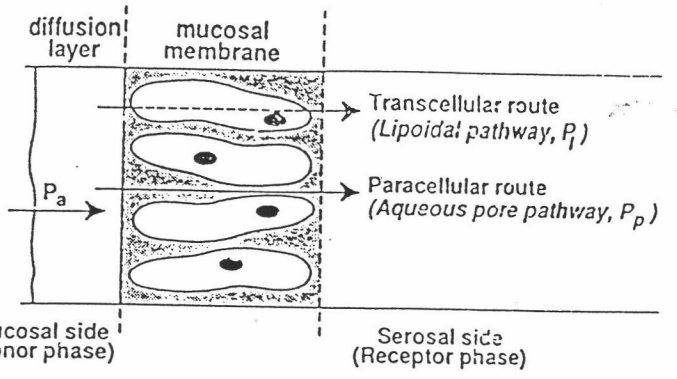


Figure 2. Diagram showing the physical model for transmembrane permeation across a mucosal membrane consisting of lipoidal and aqueous pore pathways in parallel, which is in series with an aqueous diffusion layer on the mucosal surface. *P*'s are the permeabilities across the aqueous diffusion layer P_a, the lipoidal pathway P_l, and the aqueous pore pathway P_p

3. Factors affecting drug absorption from rectal suppositories

Dose of a drug administered rectally may be greater than or less than the dose of 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 vehical and its capacity to release the drug and make it available for absorption.

The factors affecting rectal absorption of a drug may be divided into two main groups:

3.1 Physiologic factors

Human rectum is approximately 15 to 20 cm in length. As empty of fecal material, rectum contains only 2 to 3 mL of inert mucous fluid. In resting state, rectum is nonmobile, there are no villi or microvilli on the rectal mucosa. Howerver, there is abundant vascularization of the submucosal region of the rectum wall with blood and lymphatic vessels.

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

3.1.1 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 wiil 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.

3.1.2 Circulation route

Drugs absorbed rectally, unlike those absorbed after oral administration, bypass the portal circulation during their pass 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 drug and initiate its circulation throughout the body, by passing the liver.

3.1.3 pH and lack of buffering capacity of the rectal fluids

Because rectal fluids are essentially neutral in pH 7.2 - 7.5 and have no effective buffer capacity, the form in which the drug is administered will not generally be chemically changed by the rectal environment.

3.2 Physicochemical factors of the drug and suppository base

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

3.2.1 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 lipid-water partition coefficient of a drug is an important consideration in the selection of suppository base and in anticipating drug release from the 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 extend approaching its saturation. Water soluble base, which dissolve in anorectal fluids, release for absorption both water soluble and oil soluble drug.

b. Surface properties

The surface properties of drug are also important, as these particles will be transferred from one phase to another. 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 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. However, one should be aware of the increased tendency of these particles to agglomerate due to strongly increased Van der Waals forces in that cast. 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.

3.2.2 The suppository base

The base must be capable of melting, softening or dissolving to release its drug component 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 mucous membranes of the rectum, it may irritate a colonic response and prompt a bowel movement, negating the prospect of a through drug release and absorption.

4. Gelatin capsules

The gelatin capsule has been established dosage form for almost 150 years. The hard and soft gelatin capsules are two categories in current commercial pharmaceutical usage. The hard gelatin capsules consist of two pieces as cap and body, and these hard gelatin capsule are use to contain substances being drug and drug mixtures in the solid form (powder, granules, microcapsules, pellet etc.). However, soft gelatin capsules include plasticizers such as glycerin, gum arabic, sorbitol, sucrose, polyols and consist of only one piece and there are used to contain drug and drug mixture in the liquid and semi solid form (oil, emulsion, suspension, ointment, solution, paste, etc.). But, some of essential disadvantages exist at the production of soft gelatin capsules containing flowable and semi solid substances.

- A specialized group is necessary for formulations and filling processes of drug, according to the specific technological method and know-how.
- They require significantly more gelatin for encapsulation of a given dose of drug than hard gelatin capsules.
- The outer diameters of soft gelatin capsules exhibit more deviations than hard gelatin capsules.

5. Hard Gelatin Capsule sizes and types

There are eight sizes of hard gelatin capsules commercially available:

Capsule size	000	00	0	1	2	3	4	5
Volume in mL.	1.37	0.95	0.68	0.50	0.37	0.3	0.21	0.13

The main suppliers of capsules are the Elanco Qualicaps division of Eli Lilly & Co., the Capsulegel Division of Parke, Davis & Co. Ltd, and R.P. Schere Ltd. The sizes and specifications adopted by the three manufacturers are very similar, which allows any of their sizes to be used on standard automatic filling machines. Each manufacturer

produces a range of standard capsules which are designed so that the body and the cap do not separate before the filling operation takes place. They each also make a range of capsules which are locked after filling to ensure that the contents do not leak during packaging and distribution. The self- locking capsule was developed by many companies, Eli Lilly produce the Lock-Cap and Posilock capsules, Parke, Davis the Snap-Fit and Coni-Snap capsules, and R.P. Schere the Star-Lock and Lox-It capsules. These are described and illustrate below (Ridway, 1987).

The Snap-Fit principle is show in Figure 3a. A development of this design is the Coni-Snap (Figure 3b) which is claimed to reduce defects during the filling operation. Standard and Lox-It are illustrated in Figure 3c, the manufacturer recommended storage at 24 ^{o}C and about 50% relative humidity. A Posilock capsule is illustrated in Figure 3d. The pre-lock feature is designed to prevent the cap and body from separating during transit from the manufacturer to the purchaser. Air is released through vents during closure with a resultant increase in the final holding force between the cap and the body.

6. Liquid Filling of Hard Gelatin Capsules

There are several advantages of liquid filled capsules over conventional capsule formulations and some of the more common benefits are mentioned here.

The filling of liquids into capsules presents no dust hazard and the possibility of cross contamination via airborne particles is also eliminated. It is possible to obtain much better capsule weight uniformity by liquid filling than with powder filled capsules. The base can provide protection against moisture and oxygen by totally surrounding the drug particles thus improving the formulation of very hygroscopic drug and extending their shelf life, e.g. vancomycin (Hawley, et al.,1992). It should be possible to produce fast release preparations of poorly water soluble hydrophobic drugs by dispersing micronised drug particle in a very soluble base, alternatively a very soluble drug may be formulated with a suitable base to give controlled release characteristics.

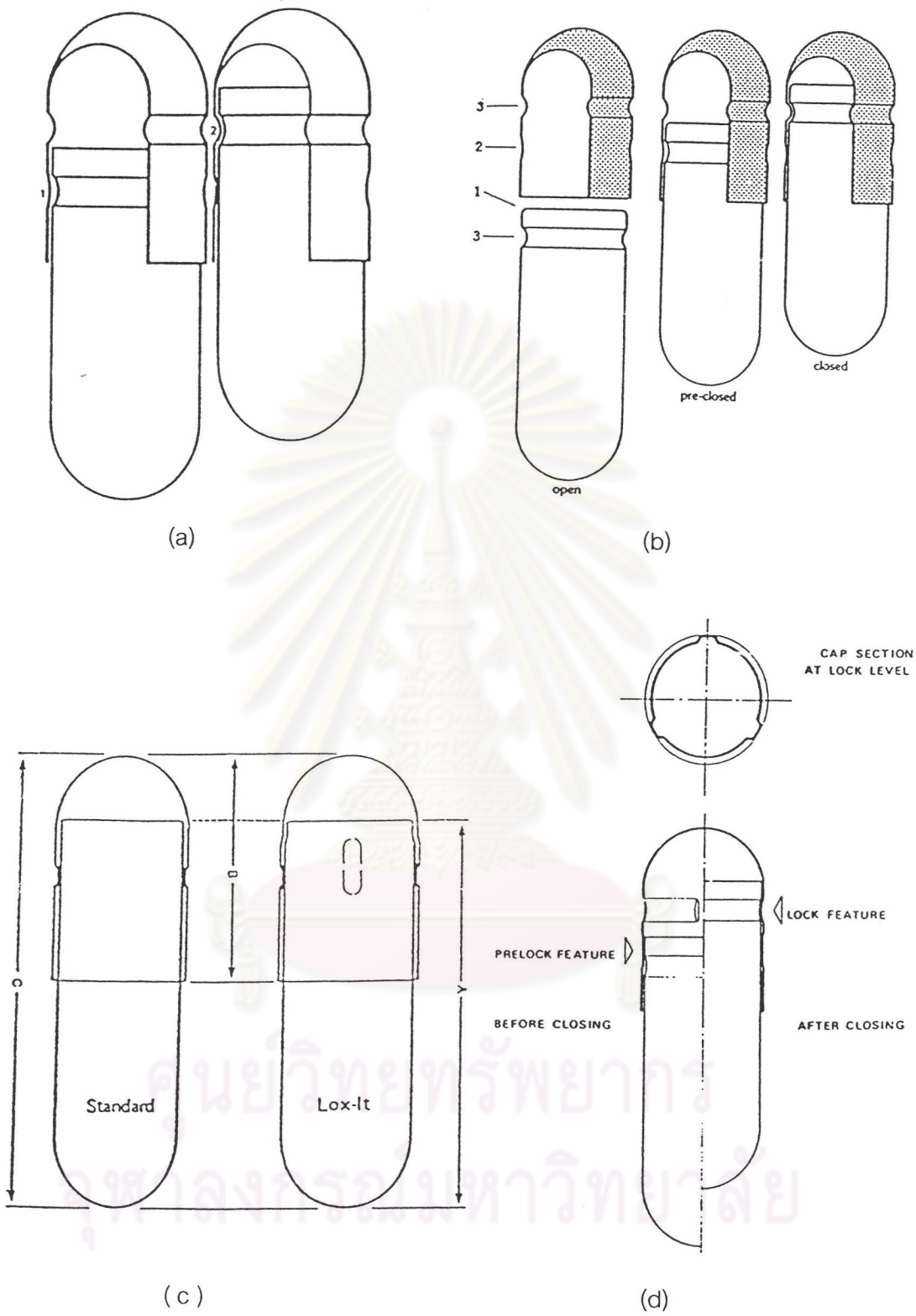


Figure 3. Self-locking type of hard gelatin capsule

(a) The Snap-fit capsule (b) The Coni-snap capsule

(c) Standard (or Star-Lock) and Lox-It capsules (d) The Posilock capsule

7. Sealing Process

To sealing the hard gelatin capsule after filling with a liquid or paste thereby eliminating the risk of leakage during storage at elevated temperatures.

7.1 Principle of sealing

The sealing process developed by Capsugel has been protected by corresponding patent rights and operates by contracting the capsule with water containing selected water-miscible organic compounds. A water-ethanol mixture is used, thereby eliminating any problems concerning the legal and toxicological status of additives. The low surface tension and the resulting high capillary forces of this liquid allow its rapid penetration between the capsule body and cap. The area over which sealing takes place is shown in Figure 4. By the application of moderate heat the body and cap are melted together, thereby creating a sealing unit.

7.2 Sealing method

The filled capsules are transferred directly from the filling machine into the contacting unit of the sealing machine, shown diagramatically in Figure 5. The contacted capsules are transported into one of the fluidized bed chambers where the excess liquid from the surface of the capsules is removed at room temperature. After this phase, the temperature is increased to approximately 45 ^{o}C to bring about the sealing of the cap and body. The two chambers operate in opposite cycle with one drying while the other is sealing. As soon as the sealing phase is completed, the capsules are discharged and cycle repeats itself. The total processing time is 6-7 minutes.

However, the most common method of sealing hard capsule, gelatin ban was applied to the junction between the body and cap of the capsule. The process basically involved passing the capsule over the wheel that revolved in a gelatin bath. A quantity of gelatin was picked up by wheel and deposited on the junction between the body and cap.

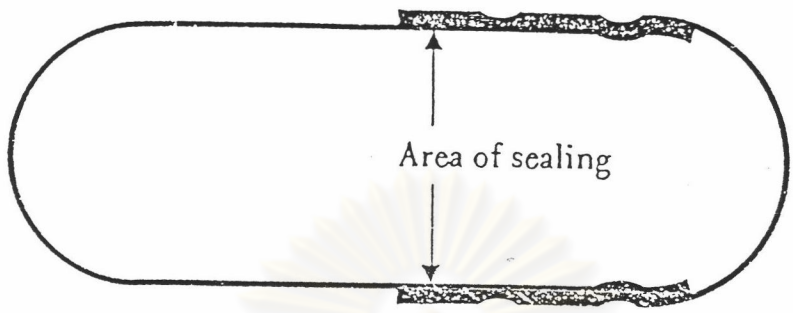


Figure 4. The area of sealing of liquid filled hard gelatin capsule.

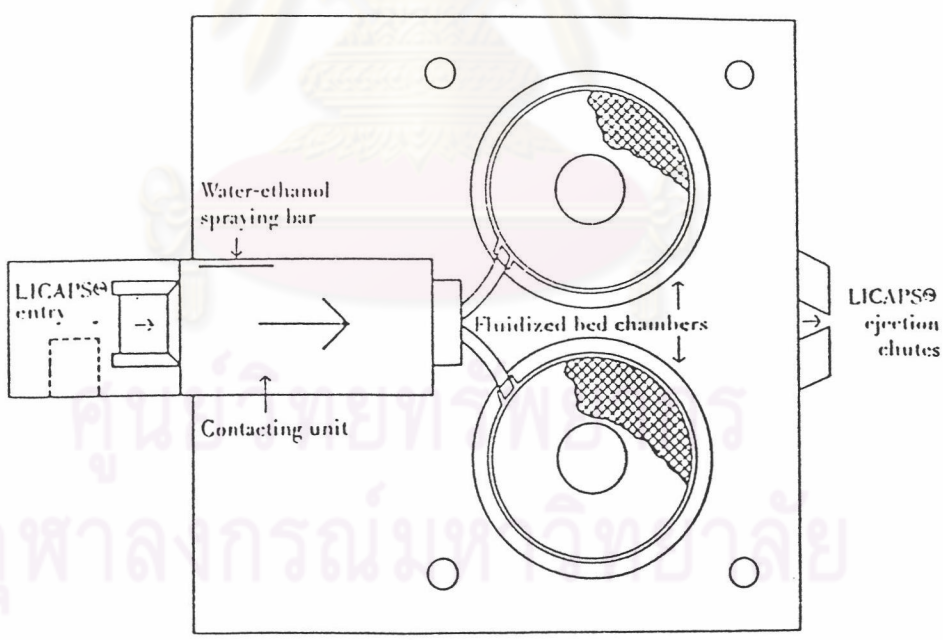


Figure 5. Process of sealing operation

The advantages of sealed hard gelatin capsule are described below.

- good protection against oxidation
- very effective barrier properties against bad smelling products
- sealed hard gelatin capsules do not stick together
- reduced risk of microbial contamination due to the absence of hygroscopic plasticizer
- same blistering equipment for liquid and powder filled capsules.

8. The formulation of the content

Empty capsules are relatively robust. If they are stored in sealed containers, they will last almost indefinitely. The most important factor to control during storage and transport of empty capsules is exposure to localized heat sources or to sudden temperature changes. The heating or cooling will cause the migration of moisture within the container and may lead to distortion of the capsules. For good stability, the moisture content of capsules should be maintained between 13% and 16%. The moisture content changes when capsules are exposed to different relative humidity. At relative humidity below 30%, capsule lose moisture and can become brittle; at relative humidity above 50%, they gain moisture and can soften (Jones, 1985). Capsule shell brittleness problems also can be reduced by overcoating of the hard gelatin capsule or incorporation of an adequate amount of water, which is a simple and effective means to minimize the moisture transfer and capsule brittleness (Chang et al., 1998).

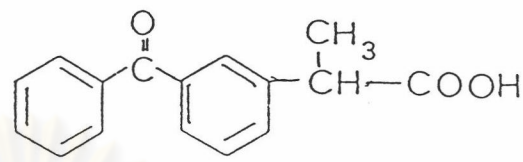
Gelatin remains the most suitable material for capsule manufacture but has limitation when used for liquid fill formulation systems which promote excessive migration of moisture. This, in turn, which will affect the integrity of the gelatin shell. Many different types of material can be filled into gelatin capsule. As generally known, highly hygroscopic excipients, such as glycerin, sorbitol, propylene glycol and polyethylene glycol of molecular weight below approximately 1000 should be avoided as they are not compatible with the capsule shell.

9. Ketoprofen

9.1 Physicochemical properties

Chemical name : 2 - (3 - Benzoyl phenyl) propionic acid, 3-benzoyl - ∝ -methylbenzene acetic acid.

Structure :



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

Molecular weight : 254.29

Appearance : A slightly coloured, odourless, tasteless powder with an irritant dust.

Melting range : 93-95 c^{o}

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 x 10^{-4} M solution in water is 6.5

pKa : 4.45 in water

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

9.2 Pharmacological properties (Reynold, 1993)

Ketoprofen has pharmacological actions similar to those of other NSAIDs. It exhibits antiinflammatory, analgesic and antipyretic activity. Ketoprofen is used to treat musculoskeletal and joint disorder 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 disorder.

Dosage and administration; The usual daily oral dose is 50 to 100 mg twice daily 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 therapeutic range of ketoprofen is reported to be about 0.4 – 6.0 μg/mL.

9.3 Pharmacokinetic properties

Ketoprofen is well absorbed after parenteral, oral or rectal administration. Ketoprofen is readily absorbed from the GI tract; peak plasma concentrations occur about 0.5 to 2 hours. It is 99% bound to plasma proteins. The elimination half-life in plasma is about 2 - 4 hours. Ketoprofen is metabolized mainly by conjugation with glucoronic acid, and is excreted mainly in urine.