CHAPTER II

LITERATURE REVIEWS

Liquid Filling of Hard Gelatin Capsules

The gelatin capsule has been an established oral solid dosage form for almost 150 years. European Pharmacopoeia defines the capsule as follow " Capsule are solid preparations with hard or soft shell of various shapes and capacities, usually containing a single dose of medicaments". The hard and soft gelatin capsules are two categories available in market. The hard gelatin capsule consists of two pieces as cap and body, and traditionally has been used as a container for particulate solids that are usually in the form of powders, granules, pellets or even small tablet. For drug either dissolved or suspended in a liquid vehicle, the ordinary available oral unit dosage form was the soft gelatin capsule. However, the filling of liquid or semisolid into hard gelatin capsule was interested and developed in the past decade. This technology becomes more utilized because of various benefits. (Shah, Phuapradit and Ahmed, 1996; Walker et al., 1980)

1. It can be used for liquid or low melting point drugs that are difficult to manufacture as oral solid dosage forms due to sticky nature of such drugs in the solid state. Examples of drug are vitamin A, D and E, essential fatty acid such as fish oil, garlic oil or deliquescent drug such as nifedipine. Liquid filling process into capsule is appropriate choice for manufacturing.

2. It is appropriate for low dose active substance, which is difficult to get good uniformity and weight variation when filling as solid dosage form. Good content uniformity depended on many factors such as segregation of drug from excipient in tablet process, method of granulation, particle size of drug and granule. Cade et al. (1986) reported the value of 0.5% RSD for oily liquid filled on filling machines at speeds as greater as 30,000 capsules/hr. Walker et al.(1983) studied of triamterene as a model at a dose level of 20 μg. achieved a drug content RSD of 1.8% with a liquid-filled capsule containing PEG. In contrast, a 3.1% RSD was achieved with

powder-filled capsules. These values are equal to or better than the fill weight uniformity that can be achieved with soft gelatin capsules.

3. It can be improved drug stability since liquid base can protect active drug from direct expose to moisture and oxygen. The amount of moisture present in solid excipient could be 100-1,000 folds higher than in oily vehicle. Shah et al. (1998) studied of β-carotene, oxygen sensitive drug, by dissolving this drug in wax-base vehicles compared with PEG400. The result was shown that percent drug retained in wax base was higher than in PEG base. Bowtle et al. (1983) could prolong stability of highly hygroscopic antibiotic vancomycin hydrochloride by preparing into PEG 6000 and filled into hard gelatin capsule. This liquid filling formula can improve more than two years of expired date.

4. It can enhance bioequivalence of drug especially poor water-soluble drug. Process of matrix liquid filled preparation is the same as solid dispersion techniques, such as in PEG, which was acceptable to increase solubility. In fact, solid dispersion technique had studied and many documents were published for a long time. However, most investigations have been of limited application to manufacturing, because of problems of the wax-like sticky masses. This characteristic was not suitable to compress into tablet. The liquid filling into hard gelatin capsule may offer a simple answer to these manufacturing difficulties.

5. It can reduce many problems for manufacture of conventional solid production as followed; reducing dust generated, minimized worker exposure to drug especially the toxic drug such as hormone and cytotoxic agent, reducing cross contamination and also the air pollution from drug factory.

6. It can be prepared include fast and sustain release action depended on type of liquid vehicle. PEG and hydrophilic base can showed fast dissolution in contrast to hydrophobic base that can be prepared in sustain release. These base may blend together in order to control the suitable release that are related to HLB value. In

addition, the compoment in each formulations are simple and do not require special ingredient such as lubricant, disintegrant or binder. The manufacturing method is only simple mixing and direct filling operation.

Additionally, liquid-filled in hard gelatin capsule has several advantages over soft gelatin capsule as shown in Table 1.

Table 1 Advantages of liquid filling in hard gelatin capsules over soft gelatin capsule

Aspects	Hard Gelatin Capsule	Soft Gelatin Capsule
Formulations		
• Stability	Less sensitive to the heat	More sensitive to the heat and moisture
• Solid dispersion	Applicable	Difficult to encapsulate
• Controlled release	Applicable	Difficult to be adopted
Manufacturing process	Relatively simple 70 ^{o}C, maximum filling temperature	More complex process 35 ^{o}C , maximum filling process

1. Hard gelatin shell is stable for heat and moisture, which is suitable in hot climates but soft capsule, is more sensitive to them. If they contacted for a long time, soft capsule may become stick together due to high amount of glycerin in capsule shell. In the hard capsule shell consists of water, gelatin and little additive, whereas soft gelatin shell consist of more than 30% of glycerin that exhibited the hygroscopic property.

2. Soft gelatin capsules have more complex step in manufacturing process while hard gelatin capsules allow step-by step filling of the formulations.

3. Hard gelatin can be filled with thermostable substance at temperature up to 70 ^{o}C while soft capsule can resist thermomaterial up to 35 ^{o}C.

4. Disintegration of hard gelatin capsule is faster than soft capsule since the capsule wall being five times thinner than the walls of soft gelatin capsules (0.5-mm compare to 0.1 mm). Cade et al. (1986) compared disintegration time of soft and hard capsule and they found shorter time more than 1-2 fold of hard shell capsules.

5. Hard capsule has less product migration to the shell and less diffusion of odors than soft capsule. (Cade et al., 1986)

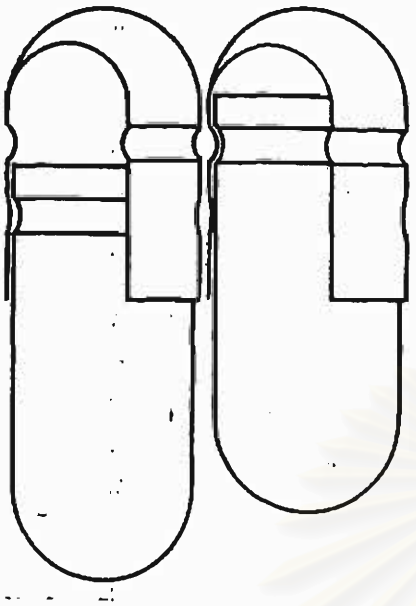
Techniques of liquid or semi-solid filling

Liquid leakage from capsule is the most important problem of filling liquid into hard gelatin capsule. In order to overcome this trouble, there are three major factors that need to be considered.

1. The empty capsule

Hard gelatin capsules are robust and show good stability on storage in a wide range of conditions. These capsules are being successfully filled and used in countries with climates ranging from cold to tropical zone, however the suitable condition for storing hard gelatin capsule is 15-20 ^{o}C and 35-65% relative humidity. The empty capsules are the relatively inert stable entity and compatible to most of material. They form a suitable delivery route for many drug formulations. Nevertheless, something that can be filled into them must not any effect the gelatin and the limitations were the nature of mobile materials. Gelatin is soluble only in strongly polar solvents, the one substance that should be avoided is water. Although, gelatin is only soluble in water at temperature above approximately 30 ^{o}C but if the temperature was below, it would absorb water, expand and the capsule can be finally distorted. The materials, which have little moisture content, are preferable and substances of an oily nature fit these criteria.

The empty capsules for the filling of pastes and oils should be the specific type. Many companies developed special self-locking design; Eli Lilly produced the Lok-Cap® and Posilok® capsules that had the pre-lock feature to prevent the cap and the



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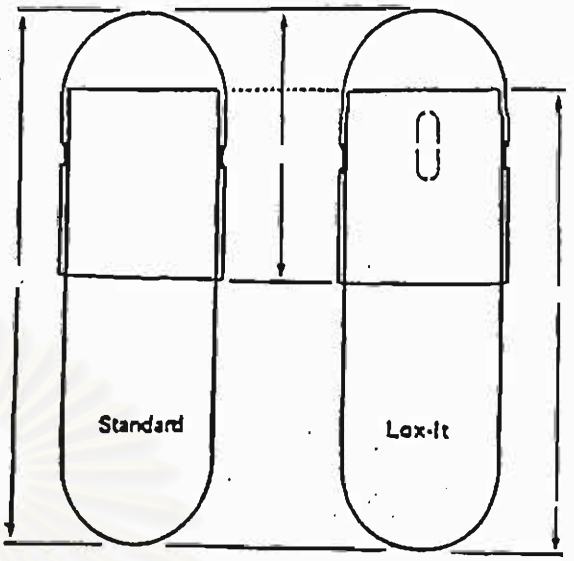

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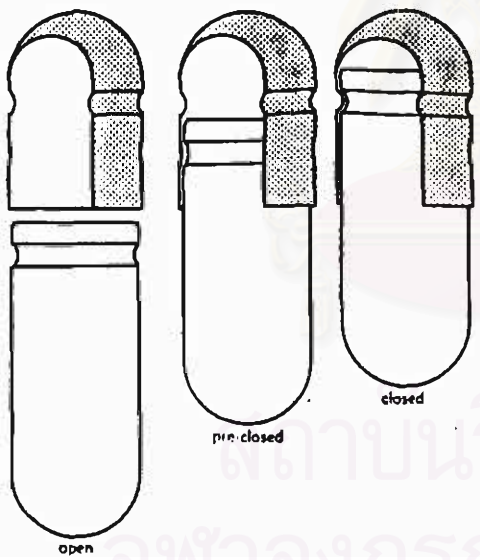

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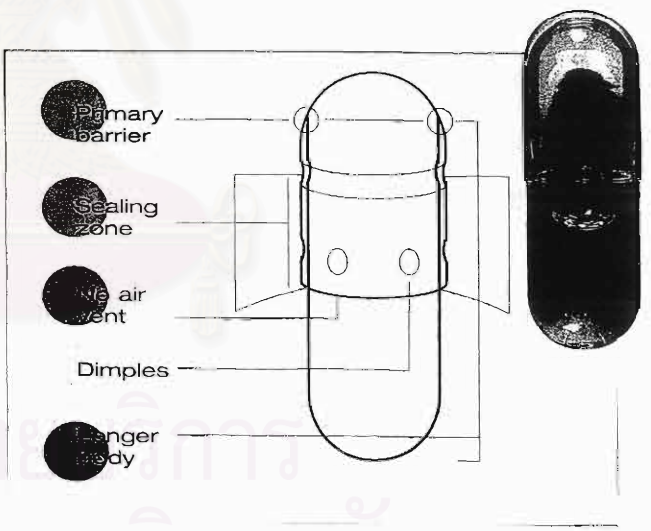


(1d)

Figure 1 Self-locking type of hard gelatin capsule

(1a) Lok-cap®

(1b) Coni-snap®

(1c) Starlock®

(1d) Licaps®

body from separation. Air was released through vents during closure with a resultant increase in the final holding force between cap and body (Figure1a). Parke Davis produce the Snap-fit® and Coni-Snap® which was claimed to reduce defects during the filling operation (Figure 1b). R.P. Scherer for the Star-lock® and Lox-It® capsules (Figure 1c). The reason for this being to the object of preventing filled capsule separation.

Parke Davis developed Licaps® that was the latest designed hard gelatin capsule for liquid filling. The feature composed of longer body design, no air vent to prevent leakage before sealing and it has six simple design maximized sealing zone (Figure1d). This type must operate with sealing equipment that will maximize efficacy to prevent liquid leakage.

Filling Capacities

The maximum limit on dosage delivery is controlled by the capacity of capsule shell that is used and on the rheological characteristics of the capsule contents at processing conditions. The capsules can be filled with liquid vehicle at different volumes as to Figure 2. The hard gelatin capsule is made in a range of eight sizes from size000, the largest, to size 5, the smallest. These sizes have been standard since the start of industrial manufacture. The most popular sizes in practice are size 0 through to size 4. The hard capsule shape has basically remained unchanged since its invention, except for the development of the self-locking capsule. When the capsule is closed together after filling, these areas form a frictional or interference lock. In practice, shells can normally be filled with liquids to approximately 90% of their body volume, although a higher filling volume can be achieved under certain conditions. Practical considerations affect dosage delivery in relation to the viscosity limits, which can be handled by the particular dosing pump used.

2. The Equipment

2.1 The capsule-filling machine

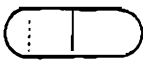
No.	Actual size	Volume in ml
5		0.13
4		0.20
3		0.27
2		0.37
1		0.48
0		0.67
00		0.95
000		1.36

Figure 2 Filling volume of liquid vehicle according to capsule size

The handling and accurate dosing of materials which process for an oily or paste-like nature has been investigated in pharmaceutical manufacturing for many years. As a result, the machinery technology for this application is well developed. A fluid pump was used instead of the powder head in the same step of filling (Figure 3). As an additional step, the capsules can be sealed if required. Sealing process can prevents leaking and ingress of oxygen and can improve stability. The process is mix/fill/seal sequence for liquids and a mix/fill sequence for semi-solids or thermosoftening products. There are five recommended requirements for liquid-filling machines.

1. They should maintain the product at a constant temperature up to 70 ^{o}C for thermosetting formula but for thixotropic technique, it is not necessary.
2. They should be stirred all time to maintain a homogenous product in the hopper.
3. They should accurately dose volumes of liquid from 0.1 to 1.0 ml
4. They should eject a filled capsule body when the cap is missing.
5. They should interrupt dosing when the capsule body is absent.

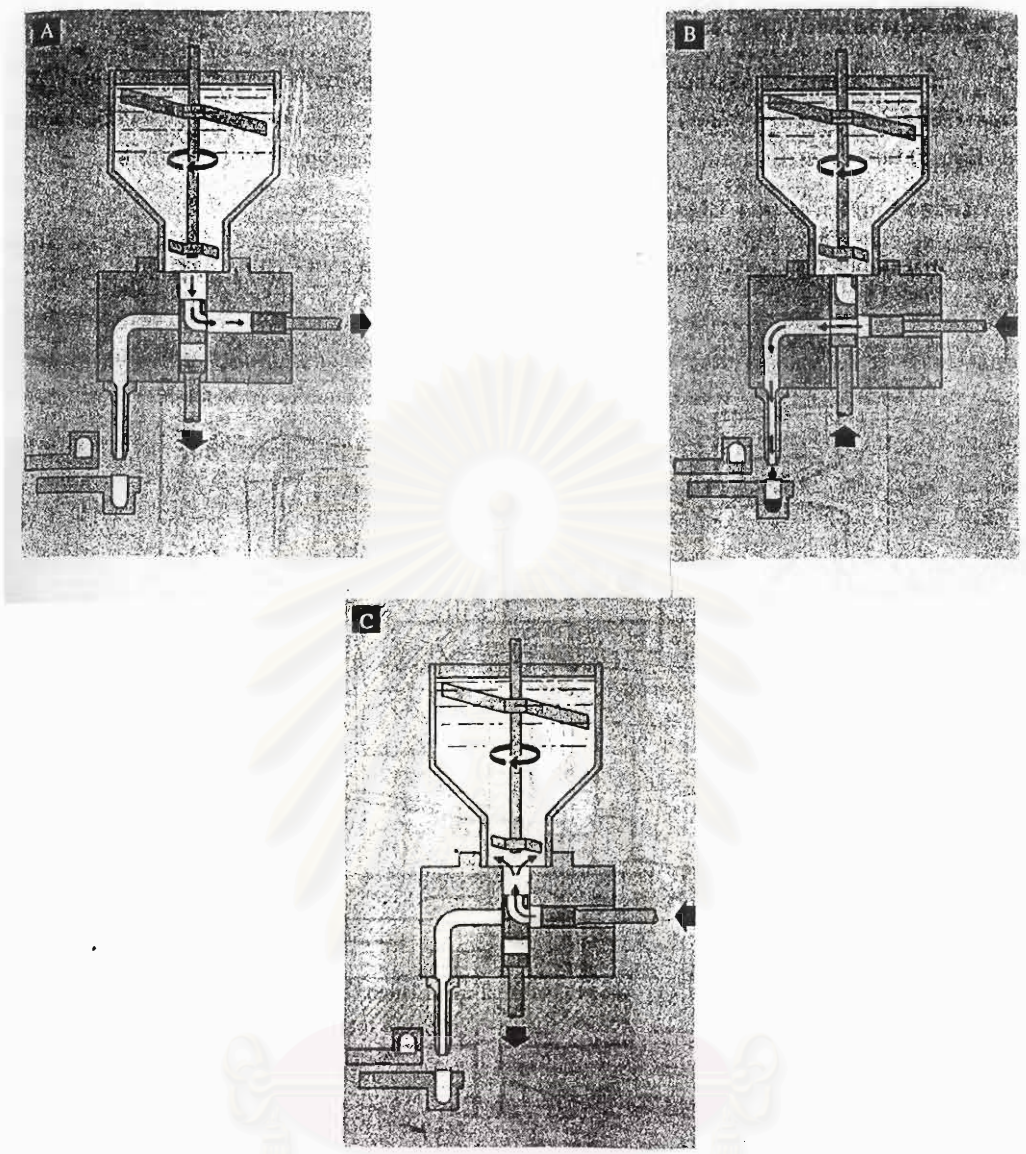


Figure 3 Principle of liquid filling operation on automatic capsule filling machine (reproduced from document of Zanasi)

(a) Pump liquid dosing

(b) Filling stage into body part

(c) The excess volume returned to liquid hopper

Zanasi, MG II, Bosch and others company can modify capsule liquid-filling machine from powder filling machine and they can develop the machine that has full capacities more than 1,000 capsules per minute. That means the liquid-filled into hard gelatin capsule can be commonly filled in process of manufacturing factory.

On the other hand, Willey, Ullay and Agharkar (1995) developed semiautomatic liquid filling machine that was used for small-scale production. This system required only minimal amount approximately 100 grams of formulation in each, provide reproducible fill weight and set up easily. The component of this equipment is illustrated in Figure 4.

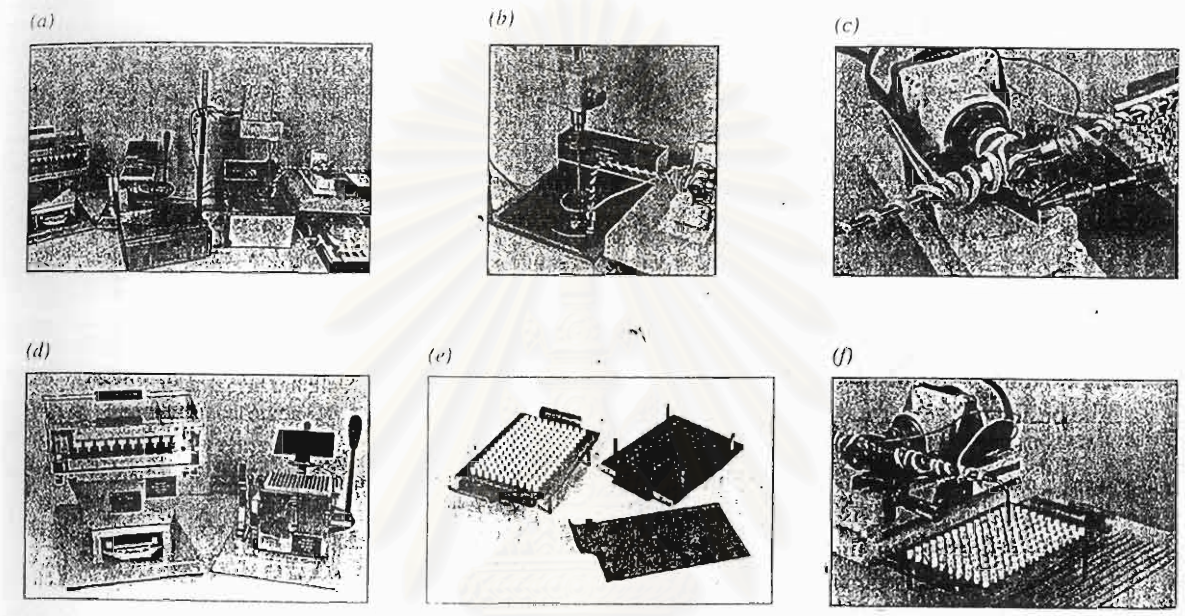


Figure 4 Components of liquid-filled hard gelatin capsule equipment(reproduced from Willey et al.,1995) : (a) overview of liquid-filling system; (b) thermostatically controlled water bath and overhead electric stirrer; (c) pump head, fill-weight adjustment control, heating coils, and thermostat sensor; (d) dry-powder encapsulation system; (e) fabricated parts for transfer of empty capsule bodies to liquid-filling tray; and (f) filling tray and indexing board

2.2 The capsule-sealing equipment

A prerequisite to filling liquid into hard gelatin capsules is the ability to seal the filled capsule. 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 a wheel that revolved in a gelatin bath. A quantity of gelatin was picked up by the wheel and deposited on the junction between the body and

cap. However, the acceptable method used to hermetically seal involving spraying the filled capsule with a mixture of water and alcohol. The low surface tension of this solution allowed its rapid penetration between the body and cap. The gelatin band was then dried by passing the capsule through the drying chamber of sealing unit. In this unit, the temperature is increased to approximately 45 ^{o}C to bring about the sealing of the cap and the body (Figure 5).

The gelatin seal can be making color if required, for example, for marketing and product identification purposes. The other methods that can be used to seal capsules include an ultrasonic welding device that melts the gelatin either in a spot position or in a ring around the cap part of the capsule.

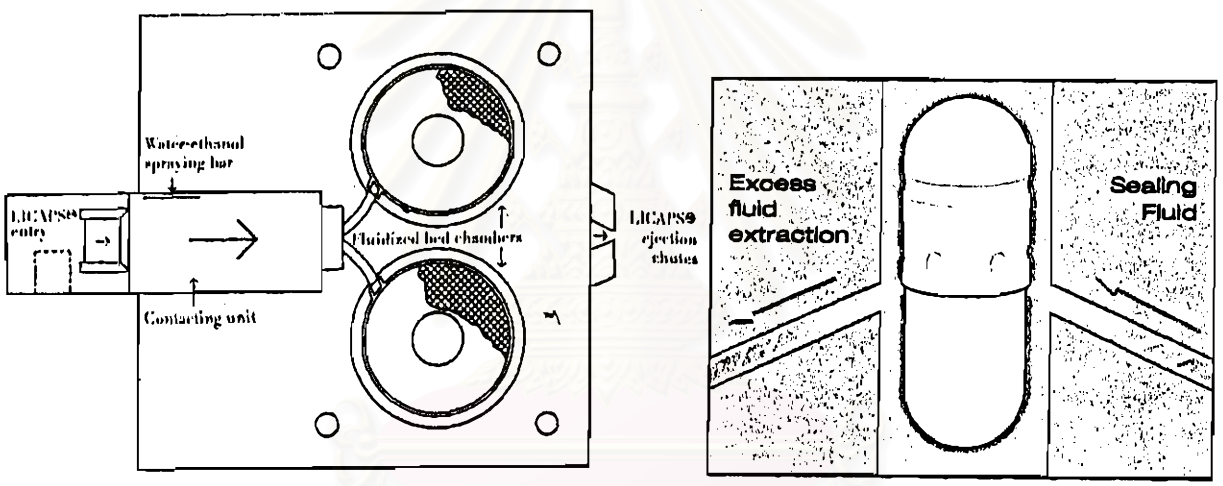


Figure 5 Process of sealing operation (reproduced from Cole,1989)

3. The formulation of the contents

There are two different ways of achieving liquid filling formulations and they are classified according to rheological properties during the filling stage.

1. Thixotropic formulations: this system produces stable and resistant matrix against leakage by gelation. The substance looks like semisolid and becomes liquid when stirring. This can, for instance, be achieved with a mixture of liquid and thickening agent like silicon dioxide.

2. Thermoplastic or thermosetting or thermosoftening formulations: this system can prevent leakage from capsule by the low melting point of material. The system were melt into liquid state when obtained heat according to their melting point and become solid again at room temperature.

The physical characteristic of the excipient for hard gelatin capsules should enable the fill material to be satisfactory. The important physical properties of the formulated mass are its viscosity, surface tension and melting point. Three parameters will indicate how well the capsule product can withstand handling and storage.

The recommended viscosity of liquid vehicle differed in many publishes, however the viscosity should be greater than 500 mPa.s at 20 $^{\circ}$C (Walker et al., 1980) or 0.01-25 Pa.s (Rowley et al., 1998) or 300-600 mPa.s (Shah et al., 1996) as measured on viscometer. Formulation viscosity above the lower limit leads to

(a) minimal losses through splashing during filling.

(b) reduce chance of leakage from two piece shell.

The upper limit of viscosity of the formulation is imposed by the limitations of the pump on currently filling machine. In addition, the high liquid viscosity affected to weight variation of filling capsule because of bridging that is displayed in Figure 6.

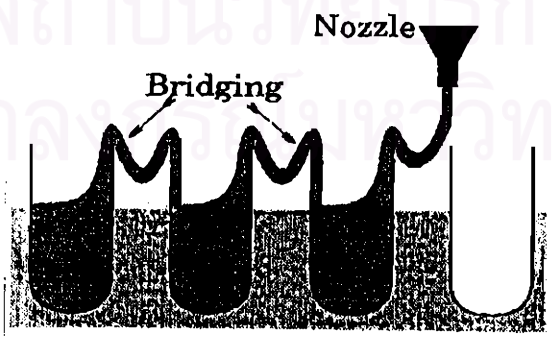


Figure 6 Bridging of liquid vehicle between capsules during filling process (reproduced from Rowley et al., 1998)

The preparation should show a thixotropic effect that mean after stirring its viscosity will be significant lower. If the thixotropic effect is low then many problems on filling occur because initial viscosity must be low for pumping liquid into hard capsule therefore it creates risk of product leakage. Thixotropic systems as shown in Figure 7, usually contain asymmetric particles that, through numerous points of contact, set up a loose three-dimensional network throughout the sample. At rest, this structure confers some degree of rigidity on the system, and it resembles a gel. As shear is applied and the flow starts, this structure begins to break down as the points of contact are disrupted and the particles become aligned. The material undergoes a gel-to-sol transformation and exhibits shear thinning. Upon removal of the stress, the structure starts to reform. This process is not instantaneous; rather, it is a progressive restoration of consistency as the asymetric particles come into contact with one another by undergoing random Brownian movement. The rheograms obtained with thixotropic materials are therefore highly dependent on the rate at which shear is increased or decreased and the length of time a sample is subjected to any one rate of shear. This characteristic usually showed the hysterisis loop.

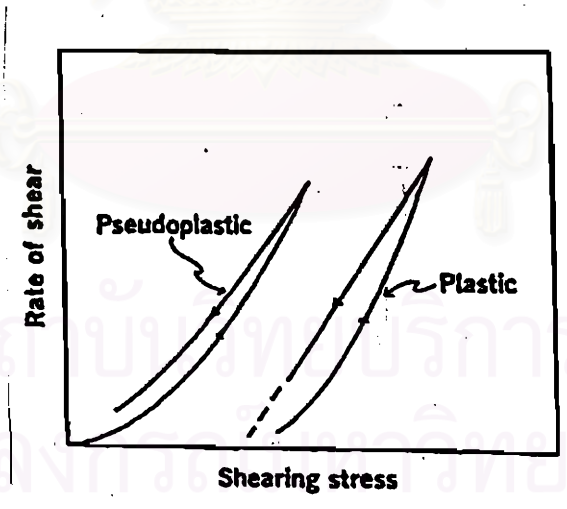


Figure 7 Thixotropic effect exhibited by a suitable mass (measured using viscometer)

The surface tension has an important effect to indicate of the likelihood of product leakage between the cap and body overlap. The higher of surface tension, this value is better. In practical terms it should be greater than 20 dynes/m^2 and preferably

Table 2 Examples of oily vehicles and thickening agents that used for capsules filling.

Oils	Thickening agents
Natural	Natural
- Vegetable Oil - Safflower Oil	- Veegum - Bee wax
- Mineral Oil - Soybean Oil	- Bentonite - Hard paraffin
- Corn Oil - Castor Oil	- Canuba Wax - White Petrolatum
- Olive Oil - Arachis Oil	- Theobroma Oil - Lecithin
Semi-synthetic	Synthetic
- Hydrogenated castor Oil (Cutina)	- Colloidal Silicon Dioxide
- Fractional Coconut Oil (Neobee)	- Magnesium sterate
Synthetic	- Polyethylene Glycol (PEG) high MW
- Isopropyl myristate (IPM)	- Cetyl Alcohol, Stearyl Alcohol
- Isopropyl Palmitate (IPP)	- Stearic acid
	- Poloxamer

greater than 30 dynes/m^2. The melting points or in most cases the temperature is which the viscosity falls below requirement should be greater than the storage temperature.

Excipient Selection

The selection of base is clearly important as this may affect the filling process, drug release and stability of product. The potential wide range of applicability of liquid-filled hard gelatin capsule formulations requires a range of compatible excipients, suitable for thixotropic or thermosoftening material. As generally known, highly hygroscopic excipients, such as glycerin, propylene glycol and low MW of polyethylene glycols should be avoided since they are likely to break the capsule shell.

The formulation was prepared by adding any substance to give higher viscosity (It may be called thickener) that shown in Table 2. Most of these substances are used for thermosoftening formulation and it is summarized in Figure 8. An approach to selecting carriers, according to the drug substance and the desired release profile of formulation was concluded in the diagram.

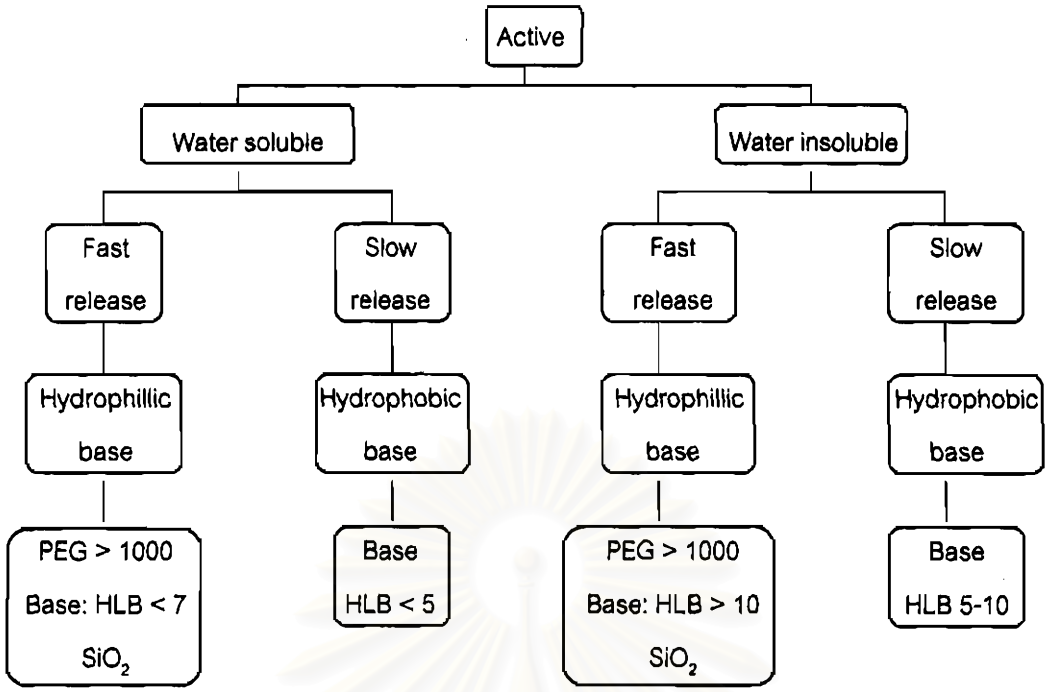


Figure 8 Selection of bases for thermosoftening formulations (reproduced from Bowtle,1999)

Stability of drug substances during processing

The thermal stability of the drug substance is a major property, to which consideration must be given, in early selection of the formulation route. Although of minor significance for the short preparation times of bench scale processing, any thermal instability of the active may preclude long processing periods at elevated temperatures. It is therefore extremely important to perform a thermal stability test of the formulation during realistic processing time periods. A solution to this problem for particular compounds might be a thixotropic formulation or preparing and maintains the melt under nitrogen or reduced temperature exposure.

The filling of molten or thixotropic liquids into hard gelatin capsules may be used to overcome a number of problems, which are frequently associates with the development, and produce of conventional pharmaceutical capsules. The formulations are simple and use a small number of standard excipients, which are able to provide the

combined functions of diluent, disintegrant and lubricant. As a result, the numbers of unit operations required are less than the conventional solid dose forms.

Coating of Gelatin Capsule

Conventional capsules are regarded as a convenient drug delivery system because they provide a smooth, slippery, easily swallowed and tasteless container for drugs. Nevertheless, many researchers studied in coating of capsule in order to expand the use of capsule in drug delivery systems i.e., enteric, colonic coating. This operation, although fundamentally performed in the same way as that for film-coated tablets, involves some problems due to the smooth, non-porous and non-absorptive nature of capsule shell material. It is difficult for anything to anchor in the surface of them. As a result of the poor adhesion of the film and the difference in elasticity between film and capsule, there is the risk that the film will burst (also known as eggshell effect) when moisture causes the capsule to swell or mechanical stress is applied to the capsule.

In addition, during coating, especially with aqueous spray formulations, the gelatin shell can become softened and sticky due to water solubilization and capsule shell can become brittle due to water evaporation when drying. Further problems arise when the coating is unevenly distributed on the capsule. This strongly reduces the gloss and clarity of transparent capsule coatings (Bauer et al., 1998)

However, the applying of adhesive layers such as two-layer coatings with subcoats of PVP, HPMC or Eudragit and increasing the plasticizer content can be reduce problem of adhesion of film coatings on capsules and avoid the eggshell effect. Another possibility of eliminating these problems is the use of coating emulsions with little solvent, which produce optically appealing and clear-transparent coatings. The gelatin capsules do not become brittle in the process and retain less than 0.1% solvent on film. Highly suitable formulations for partially aqueous processes are water/alcohol mixtures of isopropyl alcohol, ethylene glycol monoethylether and water.

Types of coated capsule

1. Enteric coats

The enteric films are usually designed to prevent disintegration in stomach but allow rapid dissolution in the intestinal tract, which has higher pH. Nowadays, enteric coatings are in particular used to

1. Protect active substances that can be destroyed by the gastric juice.
2. Improve tolerability of medicaments irritating the stomach by releasing them in the small intestine instead.
3. Make active substances available after a time delay (sustain release).
4. Provide targeted release and concentration in the small intestine.

If capsules are coated, it is usually intended to achieve gastric resistance. A dosage form is classified as enteric-coated type. Firstly, hard gelatin capsules were made insoluble in gastric juice by crosslinking the gelatin macromolecules with aldehydes. Thus, the dissolution of the capsule wall is delayed and can give enteric effect and formaldehyde treated capsules called "Formagules" (Jones, 1970). However, the hardening process with formaldehyde proceeds upon storage and the solubility will decrease further at a rate and safety of remained formaldehyde in capsule shell was considered. Because of the consequent uncertainly regarding the release of drug, this system has been abandoned. After that the combination of cellucephate and gelatin is developed to produce enteric effect but hydrolysis of cellacephate to phthalic acid and acetic acid can be occurred, then it affected to capsule brittleness and dissolving of capsule. Enteric coating capsule procedures is now used as an alternative choice.

Many materials, both natural and synthetic, have been used for the production of an enteric film on a capsule. The materials mean benzoin, salol, shellac in castor oil, n-butyl stearate/canuba wax mixture, cellulose acetate phthalate and other cellulose derivative, polyvinyl acetate resin include polyacrylate group such as methacrylic acid and methyl methacrylate (Eudragit®L), Dimethylaminoethyl methacrylates and neutral methacrylic acid esters (Eudragit ®E). These were used to coat hard gelatin capsule with many processes to get an enteric effect.

2. Protecting coats

One of the disadvantages of capsule is adhesion when the gelatin surface becomes sticky by partial hydration to mucous membrane. An investigation indicated that improving the non-adherence to the esophagus of soft and hard gelatin capsules and reducing tackiness by coating the capsules with suitable material. An additional interest for coating is the inherent sensitivity of capsules to heat and moisture, properties due to the chemical physical nature of gelatin. Under unfavorable storage conditions, capsules may stick to each other or melt. Suitable packaging can reduce the injurious effect of moisture, but heat sensibility remains a severe problem, especially in tropical countries. Moreover, Coated capsule is considered to enhance their stability against heat and moisture. Treatment of soft gelatin capsules with powdery canuba wax in a coating pan, so that the wax forms a uniform layer over the capsule surface, effectively stabilizes the water content of the shell: thus also preventing the shell from dehydrating.

An anionic methracrylate derivative, acting as an enteric coat in the form of a sufficiently thick layer is also suited to protect soft gelatin capsules against heat and mechanical strain if applied as a thin layer. The thin coating layer does not act as an enteric or disintegration delaying coat since the capsules disintegrate in vitro in gastric juice within 20-30 minutes. Even at elevated temperatures up to 55°C, no softening, no melting or tackiness of the capsules has been noticed. On the other hand, other film forming agents, such as ethylcellulose, CAP or polyvinylpyrrolidone, do not protect the capsules against the injurious effect of heat.

Ridgway et al. (1984) reported the method to reduce sticky together of soft gelatin capsule by coating with mixed copolymer of methracrylic acid and methyl methracrylate (Eudragit®L). These polymers were dissolved in isopropyl alcohol or methanol and blended with dibutyl phthalate or castor oil. The conventional pan-coater was used to coat soft capsule to get the desire effect. It was found that 3-5 mg/cm^2 of polymer coating is enough to reduce sticking problem of soft gelatin capsule.

Polyacrylate groups (Eugragit®) are appropraite for protective coating. Many types of Eugragit® polymer including Eugragit® L 100, Eugragit® L 30D-55 and Eugragit® L 100-55 are developed to exhibited the excellent of moisture protection. They were compared to HPMC group as displayed in Figure 9.

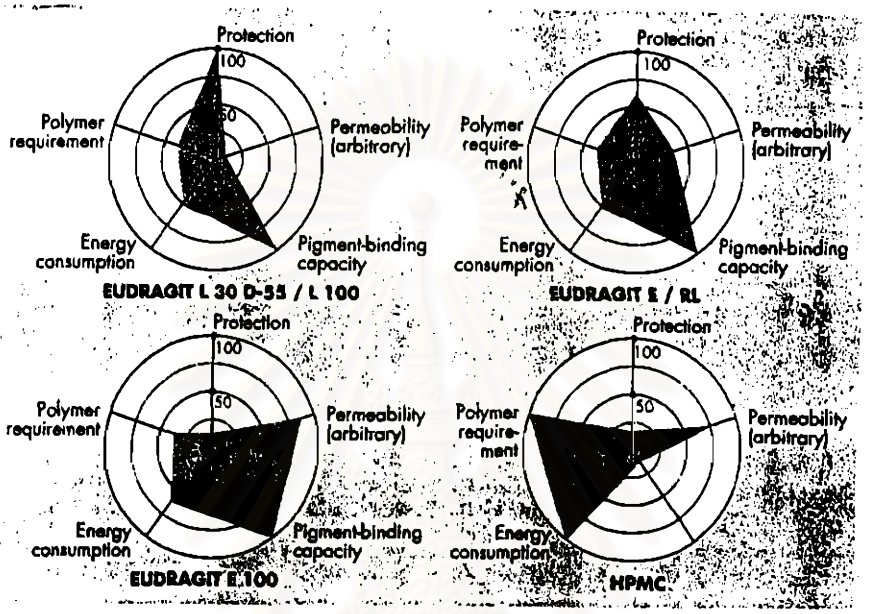


Figure 9 The properties of each type of Eudragit® compared to HPMC (reproduced from Rohm's document)

3. Gliding coats

The latest development in hard gelatin capsules concerns firstly the use of liquid and paste-fillings, and secondly the rectal or vaginal application of hard gelatin capsules. Because the amount of water present in these body cavities is negligibly small, the introduction of hard gelatin capsules is almost impossible. Similarly, soft gelatin capsules for rectal and vaginal application glide poorly without special treatment. The problem cannot be solved satisfactory by dipping the capsules into water or by lubricating them with a cream or oil just before application. Hence, the only solution for a capsule formulation suitable for introduction into body cavities is an effective gliding coat (Hannular and Speiser, 1988).

Gliding properties of capsules have been improved by coating capsules with materials, which later, in contact with water, spontaneously form an emulsion on the surface of the capsule. As coating agents, fats, waxes, polyethylene glycols or resins are used in combination with emulsifiers and dissolved in suitable solvents. The moistened capsule can be introduced e.g. into rectum without difficulty. It has, however, been observed that these coats felt greasy when handled. More pleasant touch was claimed for a coating mixture, which swelled to form a hydrogel on contact with water. Organic and inorganic gel forming polymers, such as methylcellulose and acrylic acid polymers in organic solution have been used as gliding, i.e. non-adhering, hydrophillic and hydrogelling agents.

Both of these systems, however, possess several disadvantages. Before application, the capsule must be dipped into water. An optimum gliding coat should, however, allow immediate insertion. Furthermore, modern application technologies such as spraying techniques were not suitable for many of the traditional coating formulation also required organic solvents, which should nowadays be avoided for several reasons.

An easily applied and effective gliding coat for hard gelatin capsules has recently been developed on the basis of polyethylene glycol in combination with suitable subcoats. Bilayer techniques, which have already been shown to be effective for enteric capsule coatings, in combination with an anionic methacylate derivative (Eudragit®L) or with a cationic polyacrylate derivative (Eudragit®E) as a sublayer, gave unsatisfactory results. With the former subcoat material, the capsules entirely loose their elasticity, while the latter causes cracking of the final PEG coating. A three-layer coat eventually showed the desired effect. In this system, the cationic polyacrylate serves as an isolating sublayer. It could be shown that the capsule shell did not become brittle. The anioinic polyacrylates, which has formerly proven to be a good sublayer for gliding coats, is selected as a second layer. Finally, the capsules are coated with a gliding layer of PEG. This three-layer structure can improved the smoothness and gliding effect by reducing the adherence and exhibiting fast disintegration time of coated capsule. The gliding property was preliminarily assessed by finger test and finally evaluated by acceptance of

volunteers. The result showed that the coated capsules were easily applied and well acceptation (Hannular et al., 1986).

4. Colonic coats

Because of higher pH of large intestine, few of digestive enzyme and longer transit time of bolus, the delivery of drugs to colon has implications in a number of therapeutic areas. These included the colonic disease treatment and many drug delivery especially peptide and protein. There are many strategies to administer drug and act in colon; polymeric coating is one the simplest method.

Vilivalam et al. (1998) developed colonic dosage form using 5-ASA as a model drug. Starch capsules were coated by methacrylic copolymer in isopropanol-water mixture until weight gain of 8.5 mg/capsule. The dissolution profile of coated starch capsules showed that capsules remain intact in 0.1 M HCl and release the drug at pH 6.8 by three hours. For a targeted drug delivery, the result shown such a delay release in vitro correlates well to in vivo delivery in the colonic region.

Dew et al. (1989) studied colonic drug delivery in vivo, using both radiology and serum levels of sulphapyridine after ingestion. The result shown that 120 microns in thickness of, acrylic based coating of Eudragit®S, capsules give remained intact after oral ingestion until they reached the right side of colon when they broke releasing their contents. The coating of Eudragit®S broke down above pH 7.0 and in the human intestine, the pH did not become elevated above 7 until the distal ileum and colon was reached.

Processes for coating hard gelatin capsule

In order to overcome the objective of coating, the amount of coating substance was considered. Surface area of capsule was shown in Table 3. Many methods of coating gelatin capsule were studied and mentioned in the literature over the last few years, these processes can be classified into two groups.

Table 3 Surface area of hard gelatin capsule

Capsule size	Surface area(cm^2)
0	5.07
1	4.06
2	3.43
3	2.81
4	2.31
5	1.77

1. Small Scale Production

1.1 Dipping processes

This is the simplest method that used occasionally on a small scale or in the formulations made up by pharmacists. Each capsule is dipped into the film solution. The process is repeated until layer has the desired thickness. However, this technique usually gets non-homogeneous film and it is not suitable for industrial manufacturing. (Stoklosa M.J. and Ohmart, 1993)

Figure 10 Apparatus for coating hard gelatin capsule(reproduced from Remon, 1982)

1.2 Developed apparatus

This method is study by Jean pal remon(1982), they developed small scale apparatus for enteric coating of hard gelatin capsules. This equipment was designed to avoid time consuming manipulation and can produce good quality and reproducible film. The apparatus consists of a roller with a support; the capsule is hold on the wheel and rotate pass coating solution and then to be dried. This process is repeated until get the desire thickness (Figure 10).

2. Large scale production

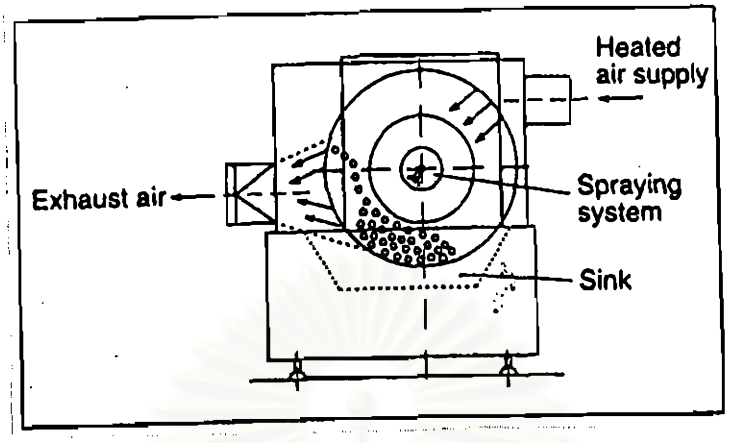
2.1 Pan coating

Conventional pan coating methods are also used for coating capsules. For this purpose, coating solutions are applied to the capsule by pouring or spraying the material onto the rotating capsule bed. The use of an atomizer system produces a faster and more even distribution of the solution. However, a conventional coating pan has an inherent disadvantage due to the low bulk density of powder filled capsules, which do not flow as well as tablets, thus causing difficulties in applying a thoroughly uniform coat.

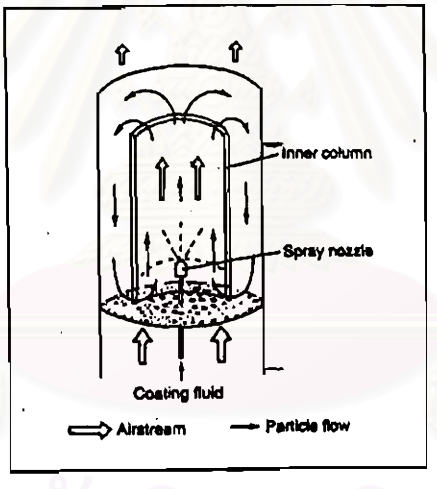
A perforated pan coating has proved to be suitable for the production of transparent and shiny coats on hard gelatin capsules. In this closed system, there are hollow perforated ribs inside the drum through that dry air passes and fluidize the capsule bed. The spraying nozzles for coating solution or suspension are positioned inside the drum.

2.2 Fluid bed spray coating

Method of fluid bed coating seems to be the best choice for capsule coating. In a fluid bed, capsules are suspended in a stream of warm air. The coat is sprayed from an enclosed atomizer. Even distribution of the coat is achieved and thin coats can be applied homogeneously. Movement of the material can be controlled more accurately by use of guide column (Wurster inserts). The capsules are propelled upwards in an almost laminar flow through the central guide tube by a powerful air flow, sprayed with the coating formulation and simultaneously dried by the stream of air. On discharge from



(11a)



(11b)

Figure 11 Coating equipment of hard gelatin capsule

(11a) Perforated pan coater

(11b) Fluidized bed coater

the tube, the capsule flows freely downwards under gravity and passes back into circulation. The time needed for fluid bed coating is extremely short when compared to pan coating, The procedure need to be repeated several times in order to obtain a

perfect coating due to the shape of capsules. Although the airflow in the fluidized bed is controlled so that more air enters the center of the chamber, it is sometimes necessary to use special modifications in order to improve the capacity of airflow (Hannula et al, 1986).

2.3 Combination process

In the drum process the material is mainly moved by rotation of the container and in the fluidized air bed process it is moved by the stream of air. Combination of both principles yields new possibilities of handling the material and optimizing the stream of air as a mean of drying. In this combined process the stream of drying air does not have to move the material on its own and consequently less air is needed. The interaction of centrifugal force, stream of air and gravitation causes circular movement of the material.

A report by Osterwald et al. (1982) on the coating gelatin capsules compared the Driacoater, Wurster-WSG and Rotor-WSG with respect to HPMCP-55 film coatings. It was found on the basis of the process parameters that the fluidized bed coater permitted a large batch volume but needed more energy because of the large amount of inlet and exhaust air. There was, however, a comparative saving in energy due to the rotor technology with optimizes the air input. Application of HP-55 emulsion in classic fluidized air bed processing in the WSG produced relatively rough coating since drying occurred very quickly in the strong flow of air, moreover the spraying losses were higher than when other machine were used. The rotor model produced a comparatively faster film coating: capsules quickly became gastric juice resistant and had glossy, transparent coats. Other examples of more recent combined process are the Roto-Processor (Niro, Switzerland), the Ultracoater(Niro, Switzerland) and the CF-Granulator(Freund Industrial, Japan). However, practical trials are needed in each individual case to determine the best coating equipment and best film coating formulation.

Stability of coated hard gelatin capsule

Regardless of which enteric-coated dosage form is used, instability does occur when films are applied. Investigations involving many preparations, predominantly

tablets, revealed a number of stability problems depending on duration of storage, temperature coated active substances and other factors.

Particularly in the case of hard gelatin capsules stability problems are encountered above all in enteric coats applied in the form of aqueous dispersion systems. Murthy et al. (1986) studied of comparative evaluation of enteric polymer in hard gelatin capsules coatings. The styrene maleic acid copolymers, cellulose acetated phthalate (CAP), cellulose acetate succinate, polyvinyl acetate phthalate (PVAP) and polyacrylates methacrylates (Eudragit®L) was investigated. The result showed that slower release after three months storage at room temperature occurred due to reaction of the gelatin coat with Cellulose acetate phthalate (CAP) or with its hydrolysis products: phthalic acid and acetic acid which make the gelatin insoluble.

Good stability was reported for Eudragit®L-30D. Film characteristics and release performance remain constant, even after somewhat more stringent storage conditions. Enteric film formers with an ester structure are liable to hydrolyse under the influence of moisture. In case of cellulose derivatives, hydroxypropyl methylcellulose acetate succinate (HPMCAS) is considered more stable than hydroxypropyl methylcellulose acetate phthalate (HPMCP) and this, in turn, more stable than cellulose acetate trimellitate (CAT) and CAP.

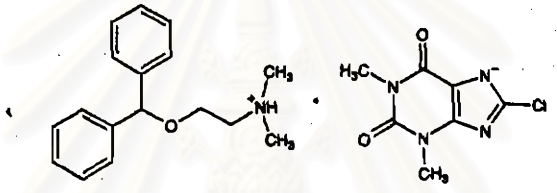
Stability study compared organically applied films of polymethacrylic acid-methylmethacrylate(Eudragit®L100), polyvinyl acetate phthalate and cellulose acetate phthalate with films obtained from aqueous dispersion of these polymers. Aqueous dispersions of polyacrylate groups (Eudragit®) were nonetheless somewhat superior to organic polyarylate solutions whereas CAP (Aquateric®) only matched up to organic CAP systems when an overcoat was used. Coated capsule with CAP (Coateric®) displayed signs of instability in the form of lost gastric-juice resistance. PVAP organic system coats needed a protective coating to prevent adhesion of the product.

Dimenhydrinate

Dimenhydrinate is an antihistamine, containing not less than 53 percent and not more than 55 percent of diphenhydramine ($C_{17}H_{21}NO$) and not less than 44 percent and not more than 46.5 percent of 8-chlorotheophylline ($C_7H_7ClN_4O_2$), both calculated with reference of the dried substance.

Physicochemical Properties

Synonym	:	Anatin, Choranantine, Diphenhydramine theoclate
Empirical formula	:	$C_{17}H_{21}NO.C_7H_7ClN_4O_2$
Molecular weight	:	470
Structural Formula	:	



Description	:	A white crystalline powder or colorless crystal
Solubility	:	1 in 95 of water,1 in 2 in ethanol and 1 in 2 in chloroform , Sparingly soluble in ether
Melting range	:	102-107 ^{o}C
Commercial Dosage Form	:	Tablets, Injections, Syrups, Suppositories
Infrared Spectrum	:	Principal peak at wave number 1640, 1685, 1118, 755, 712, 1255 (KBr disk)
Ultraviolet Spectrum	:	Aqueous acid – 270 nm, Aqueous alkaline – 278 nm