June - July 2017; 6(4):2663-2677

International Journal of Research and Development in Pharmacy & Life Science
An International Open access peer reviewed journal
ISSN (P): 2393-932X, ISSN (E): 2278-0238
Journal homepage:http://ijrdpl.com

Review Article

Formulation and modifying drug release from Hard and Soft Gelatin Capsules for Oral drug delivery

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Keywords: Buccal drug delivery, folding endurance, index, *in-vitro* drug release, Permeation enhancers, swelling, Thiolated polymer

Article Information:

Received: April 15,2017;
Revised: April 30, 2017;
Accepted: May17, 2017

Available online on:
15.06.2017@http://ijrdpl.com

http://dx.doi.org/10.21276/IJRDPL.2278-0238.2017.6(4).2663-2677

ABSTRACT: Capsule is the most versatile of all dosage forms. Capsules are solid dosage forms in which one or more medicinal and inert ingredients are enclosed in a small shell or container usually made of gelatin. There are two types of capsules, "hard" and "soft". The hard capsule is also called "two pieces" as it consists of two pieces in the form of small cylinders closed at one end, the shorter piece is called the "cap" which fits over the open end of the longer piece, called the "body". The soft gelatin capsule is also called as "one piece". Capsules are available in many sizes to provide dosing flexibility. Unpleasant drug tastes and odors can be masked by the tasteless gelatin shell. The administration of liquid and solid drugs enclosed in hard gelatin capsules is one of the most frequently utilized dosage. This proves the oral bioavailability of poorly soluble compounds, delivery of low and ultra-low doses of a compound using softgel also ensures decreased plasma variability. This has led to the commercial pharmaceutical and nutraceutical industries opting for the development of alternative shell forming materials instead of the traditional capsule shell material gelatin. This review discusses establishment and the ongoing development of the manufacturing technology for liquid and semisolid capsules with focus on progress and challenges of soft and hard gelatin capsules formulation in oral administration for improved solubility and as an absorption-enhancing technique. These considerations form a basis for new applications in oral drug delivery.

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INTRODUCTION

CAPSULE FORMULATION

1. **Lubricant:** A lubricant is added to the active compound to facilitate the flow of the drug-fill into the encapsulating or tableting machinery. The use of lubricant is especially important when an automatic capsule filling machine is utilized. Magnesium stearate (frequently less than 1%) is commonly used as a lubricant in capsule and tablet making. The water-proofing property of the insoluble magnesium stearate may cause a dissolution problem in the gastrointestinal fluid.The delayed dissolution and subsequent delayed absorption may result in totally differentpharmaco-kinetic profiles than the desired.
2. **Wetting Agent**: Wetting agents are used to enhance the dissolution of solid particles. Lithium carbonate is a commonly used wetting agent. Even in the absence of water-insoluble lubricants in capsule formulation, dissolution of dry pow-ders requires displacement by liquid of air that surrounds the dry powder after the gelatin shell dissolves. Dispersion and dissolution of the capsule fill also requires penetration of liquid into the powder. Wetting agent pre-vents agglomeration of particles and accelerates the dissolution of particles by allowing water to penetrate and replace air between particles. Formulation can affect the bioavailability of a drug substance, and this is the reason why two generic capsule products of the same drug may show different bioavailability.

3. **Liquid-Fill Technology**:The liquid-fill technology developed by MW Encap, Ltd. (www.mwencap.com) also enables two-piece hard gelatin capsules to be filled with non-aqueous liquids and semi-solid substances. Liquids can be pumped directly from the container into the capsule body. The active compound can be added to a fluid thixotropic or thermosoftening carrier.

4. **Solid Dosage Forms:** Capsules design semi-solid matrix which can be heated or stirred for liquefying. The hard gelatin capsules are sealed by two gelatin bands.

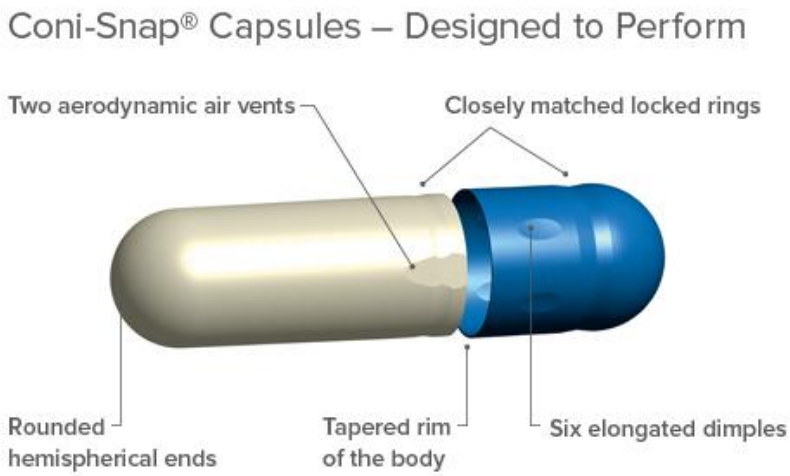


Figure 1: Coni-snap capsules

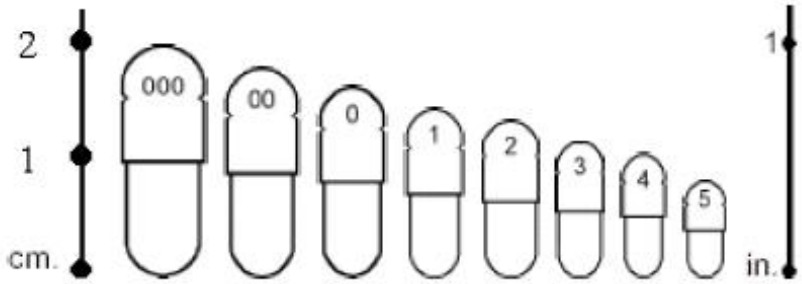


Figure 2: Relative sizes of hard gelatin capsules for human use (Torpac Inc.: Fairfield, NJ)

Table 1:Capsugel® Brand Coni-Snap® Hard Gelatin Capsule Sizes

	000	**00**	**0**	**1**	**2**	**3**	**4**	**5**
Weight (mg)	163 ± 10	118 ± 7	96 ± 6	76 ± 5	61 ± 4	48 ± 3	38 ± 3	28 ± 2
Volume (mL)	1.37	0.91	0.68	0.50	0.37	0.30	0.21	0.10
Length (mm)	26.1 ± 0.3	23.3 ± 0.3	21.7 ± 0.3	19.4 ± 0.3	18.0 ± 0.3	15.9 ± 0.3	14.3 ± 0.3	11.1 ± 0.4
Body OD (mm)*	9.55	8.18	7.34	6.63	6.07	5.57	5.05	4.68
Cap OD (mm)*	9.91	8.53	7.64	6.91	6.35	5.82	5.32	4.91
Powder Density	**Capsule Capacity (mg)**							
0.6 g/mL	822	546	408	300	222	180	126	78
0.8 g/mL	1096	728	544	400	296	240	168	104
1.0 g/mL	1370	910	680	500	370	300	210	130
1.2 g/mL	1644	1092	816	600	444	360	252	156

Figure 3: Image of Licaps®

Liquid and semi-solid filled hard gelatin capsules offer a variety of solutions for special requirements. Formulation issues such as enhanced bioavailability, sustained release or multi-release profiles can be addressed as standard. More specific customer requirements can be met by tailored solutions in formulation development, scale-up, volume production, back-up services and technology transfer.

HARD STARCH CAPSULES

Hard gelatin capsules have been used most widely. Recently, however, starch capsules have been used in various controlled-release products as well as in general use as demands for non-animal based products increase. Starch capsules are more easily coated than gelatin capsules. Gelatin shells may soften and solubilize when sprayed with aqueous dispersion of coatings and can become brittle during the drying stage. The higher bulk density of the starch capsule provides for a more uniform coating bed. Starch capsules are manufactured by an injection molding process that yields exact dimensions and provides an excellent seal between "top" and "bottom." The filling and sealing process is simultaneous, resulting in a finished product that is well-sealed, secure and relatively resistant to further manipulation. Soft Gelatin Capsules.

Starch and HPMC are good are good candidates for making not only hard but also soft gelatin capsules. One of the limitations of using them is the initial high capital investment.

MICRO-FILLING SYSTEM

The new drug delivery company, called Meridica (www.meridica.com), launched a new product, Xcelodose™, in 2001. Xcelodose™ is pro-grammable equipment for the precise metering of drugs into capsules and other solid dosage form containers. Xcelodose™ may provide a solution to the problems of small manufacturing runs for clinical trials, pre-clinical trials and/or niche market drugs. It is claimed to handle drug compounds without bulking agent or excipient and can precisely fill up to 600 cap-sules/h with weights ranging from 100 µg to tens of milligrams.

Figure 4: Soft gelatin capsules

Softgel delivery system

The softgel delivery system is a unitary package, formed with gelatin outer layers, which contain between them the active ingredients in solution, suspension or paste form [4]. Hydrophobic drugs do not dissolve readily in water, gastric or intestinal fluid. When they are compounded in solid dosage forms, their dissolution rate is usually low and absorption varies resulting in poor bioavailability. Bioavailability of these drugs can be improved in the presence of fatty acids e.g. mono or di-glycerides. Fatty acids do solubilize hydrophobic drugs in the gut and enable more rapid absorption [5].The softgel delivers drugs in solution and yet offers solid dosage form. These hydrophobic drugs are dissolved in a hydrophilic solvent, which, when crushed or chewed, releases the drug immediately to produce a solution of the drug in gastric juice ready for absorption from the gastrointestinal tract into the blood stream. This results in rapid onset of desired therapeutic effects [6].

For example, Ibuprofen softgel gives rise to a shorter time to peak plasma concentration and greater peak plasma concentration compared to a marketed tablet formulation. Cyclosporine does give therapeutic blood levels which are not achievable from tablet form.

Similarly, oral hypoglycemic glipizide in softgel is also known to have better bioavailability results compared with tablet form. Softgel delivery systems can also incorporate phospholipids or polymers or natural gums to entrap the drug active in the gelatin layer with an outer coating to give desired delayed/control release effects [7].

The designs for a specific soft gelatin capsule formulation involve appropriate selection of the shell and fill composition. This is followed by optimization of the two to allow for efficient production of a chemically and physically stable product with the desired biopharmaceutical properties. The shell of a soft gelatin capsule is composed of gelatin, a plasticizer or a combination of plasticizers and water. In addition, it may contain preservatives, coloring and opacifying agents, flavorings and sweeteners, possibly sugars to impart chewable characteristics to the shell, gastro-resistant substances

and in special cases even active compounds [8]. The formulation of the fill is individually developed to fulfil the requirements for optimum therapeutic action. This entails optimizing the chemical stability of the active compound to improve bioavailability. Emphasis is also put on efficient and safe filling process in order to achieve a physically stable capsule product [6].

Figure 5:Examples of the variety of colors, shapes, and sizes available in soft gelatin capsules (Pharmagel Engineering SPA: Milan, Italy)

Gelatin soft capsules are made from gelatin and water but with the addition of a polyhydic alcohol, such as glycerol or sorbitol, to make them flexible[11]. Sorbitol is less hygroscopic than glycerol. They usually contain a preservative, such as beta-naphthol. They are available in variety of shapes and sizes as shown in figure 7.

- Spherical – 0.05 -5
- Ovoid – 0.05 - 7 ml
- Cylindrical – 0.15- 25 ml
- Tubes – 0.5 - 0 ml
- Pear shaped – 0.3 - 5ml

There are three primary types of inner fill materials:

1) **Neat Substance, especially oily liquids**eg. Cod liver oil capsules
2) **Solution Fills**: Active dissolved in a carrier

Oils such as soybean oil and Miglyol 812 (neutral oil, triglycerides of medium chain fatty acids)

Polyethylene Glycols: especially PEG 400 -600

Other solvents: Any other solvent, which doesnot degrade or solubilize the gelatin shell, i.e., dimethyl isosorbide, surfactants, diethylene glycol monoethly ether.

Optional Ingredients for solution fills:

1. Water or alcohol: up to 10% w/w (if needed for solubility).
2. Glycerin: 1 to 4% w/w (to retard the migration of the glycerin out of the shell into the fill).
3. Polyvinylpyrrolidone: Up to 10% w/w used in combination with PEG (can increase drug solubility, and also improve stability by inhibiting drug recrystallization) [12].

3)Suspension Fills: Active dispersed in a carrier.

- Suspensions can accommodate about 30% solids before viscosity and filling become a problem
- Suspensions can be heated up to 35ºC to decrease viscosity during the filling process
- Suspended solids must be smaller than 80 mesh -- mill or homogenize before filling to prevent needles from clogging during filling[13].

Base Adsorption of solids to be suspended in soft gelatin capsules – base adsorption is expressed as the number of grams of liquid base required to produce a capsulatable mixture when mixed with one gram of solid(s). The base adsorption of a solid is influenced by such factors such as the solids particle size and shape, its physical state (fibrous, amorphous, or crystalline), its density, its moisture content, and its oleophilic or hydrophilic nature [9]. In the determination of base adsorption, the solid(s) must be completely wetted by the liquid base. For glycol and nonionic type bases, the addition of a wetting agent is seldom required, but for vegetable oil bases, complete wetting of the solid(s) is not achieved without an additive.

Soy lecithin, at a concentration of 2 to 3 % by weight of the oil, serves excellently for this purpose, and being a natural product, is universally accepted for good drug use. Increasing the concentration above 3 % appears to have no added advantage. A practical procedure for determining base adsorption and for judging the adequate fluidity of a mixture is as follows:

Weigh a define amount of the solid (40g is convenient) into a 150 ml teared beaker. In a separate 150 ml beaker tared beaker, place about 100 g of the solid base. Add small increments of the liquid base to the solid, and using a spatula, stir the base into the solid after each addition until the solid is thoroughly wetted and uniformly coated with the base. This should produce a mixture that has a soft ointment like consistency. Continue to add liquid and stir until the mixture flows steadily from the spatula blade when held at a 45-degree angle above the mixture [10]. The base adsorption is obtained by means of the following formula –

Weight of the base/ Weight of the solid = Base Adsorption

The base adsorption is used to determine the “minim per gram” factor (M/g) of the solid(s). the minim per gram factor is the volume in minims that is occupied by one gram (S) of the solid

plus the weight of the liquid base (BA) required to make a capsulatable mixture. The minim per gram factor is calculated by dividing the weight of the base plus the gram of solid base (BA+ S) by the weight of the mixture (W) per cubic centimeter or 16.23 minims (V). a convenient formula is-

(BA + S) x V/ W = M/g

Thus, lower the base adsorption of the solid (s) and higher the density of the mixture, the smaller the capsule will be. This also indicates the importance of establishing specifications for the control of those physical properties of a solid mentioned previously that can affect its base adsorption. The final formulation of a suspension invariably requires a suspending agent to prevent the settling of the solids and to maintain homogeneity prior to, during, and after capsulation. The nature and the concentration of the suspending agent vary. In all instances, the suspending agent used is melted in a suitable portion of the liquid base, and the hot melt is added slowly, with stirring, into the bulk portion of the base, which has been pre-heated to 40 degrees prior to the addition of any solids. The solids are then added, one by one, with sufficient mixing between additions to ensure complete wetting. Incompatible solids are added as far apart as possible in the mixing order to prevent interaction prior to complete wetting by the base.

Example of suspension fills include drug suspended in the following carriers:

1. **Oily mixtures**:

a) Soybean Oil with beeswax (4-10% w/w) and lecithin (2-4% w/w). The lecithin improves material flow, and imparts some lubrication during filling. Add enough beeswax to get a good suspension, but avoid creating a non-dispersible plug.

b) **Gelified Oil** (e.g. Geloil® SC), a ready to use system composed of soybean oil, a suspending agent, and a wetting agent.

2. **Polyethylene glycol**

- PEG 800 -1000 for semi-solid fills
- PEG 10,000 -100,000 for solid fills
- • Or mixtures of the above. (Heat up to 35ºC to make fluid enough for filling) Optional Ingredients that can be added in the suspension fill
- Surfactant: sorbitan derivatives such as polysorbate 80 or lecithin.
- For hydrophobic drugs dissolved or dispersed in an oily matrix, a surfactant of HLB 10 will increase the dispersibility of the product in aqueous fluids and may improve bioavailability.

Large-scale manufacture Rotary capsule machine:This machine has two, side-by-side cylinders in each of which halfmolds are cut. These cylinders, like the rollers of a mangle, rotate in contrary direction and as they are mirror images the molds come together precisely during rotation[14]. Two ribbons of gelatin are fed between the rollers and, just before the opposing rollers meet, jets of medicament press the gelatin ribbon into the molds, filling each half. The moment of pressure follows, immediately sealing the two halves together to form a capsule. These rotary machines can produce between 25000 and 30000 capsules an hour with an accuracy of dosage of approximately ± 1 percent. An automated soft gelatin encapsulation machine is shown in figure 6.

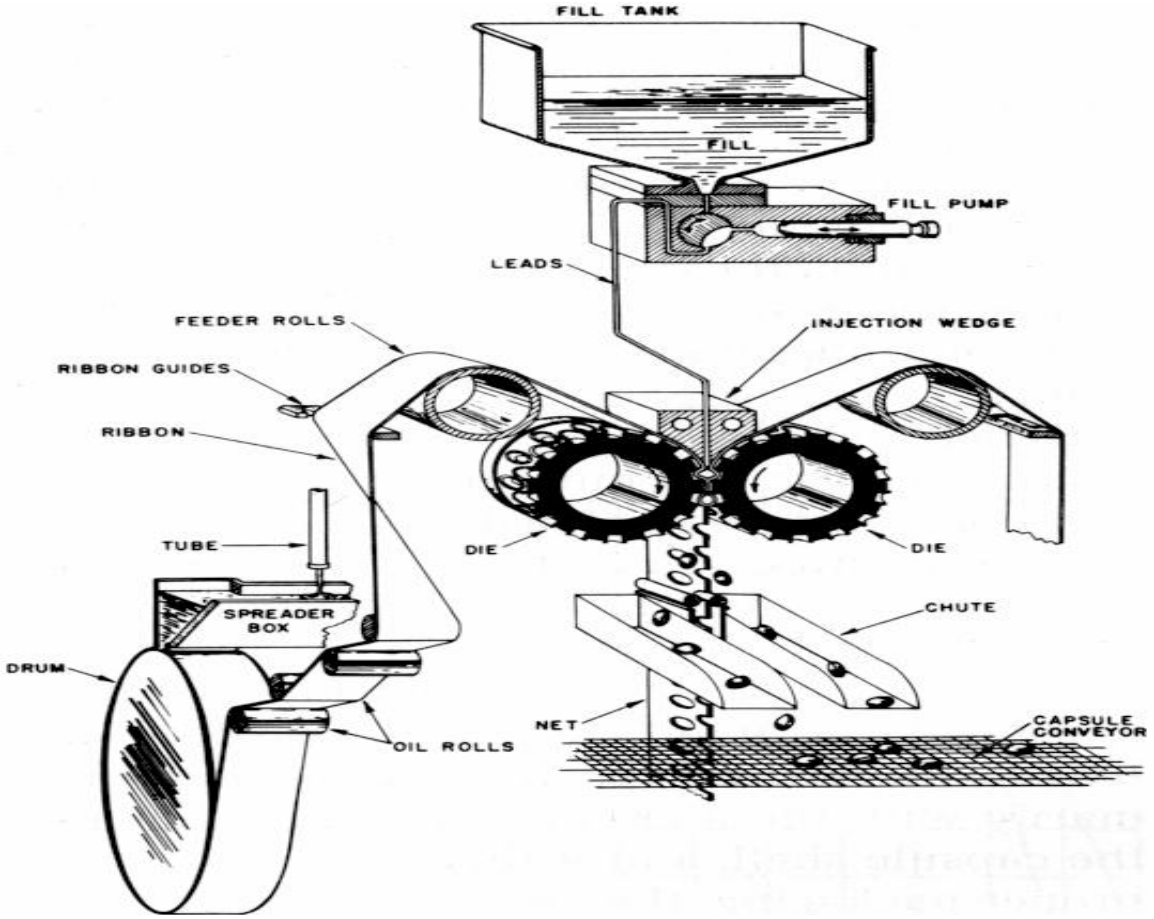


Figure 6: **Schematic drawing of a rotary-die soft gelatin capsule filler (R.P. Scherer: Detroit, MI).**

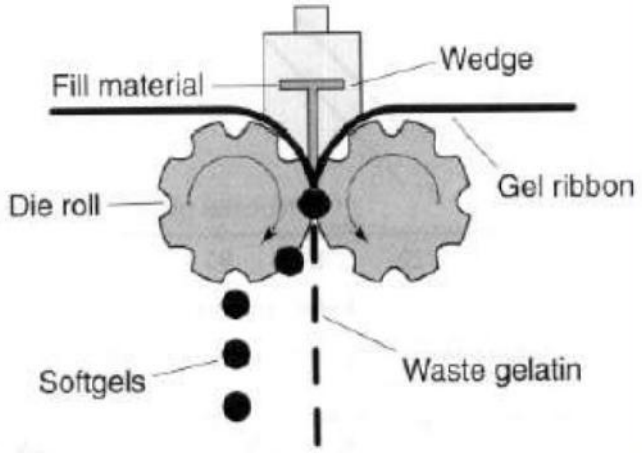


Figure 7: Mechanism of soft gel formation

Seamless gelatin capsules: Another method of making soft capsules takes advantage of the phenomenon of drop formation. The essential part of the apparatus consists of two concentric tubes. Through the inner tube flows the medicament and, through the surrounding outer tube, the gelatin solution. The medicament, therefore, issues from the tube surrounded by gelatin and forming a spherical drop [15]. This is ensured by allowing the drop to form in liquid paraffin in which the gelatin is insoluble. Regular induced pulsations cause drops of the correct size to be formed, and a temperature of 4°C ensures that the gelatin shell is rapidly congealed. The capsules are subsequently degreased and dried. Formulation of soft gelatin capsules Gelatin shell formulation: Typical soft gels are made up of gelatin, plasticizer, and materials that impart the desired appearance (colorants and/or opacifiers), and sometimes flavors.

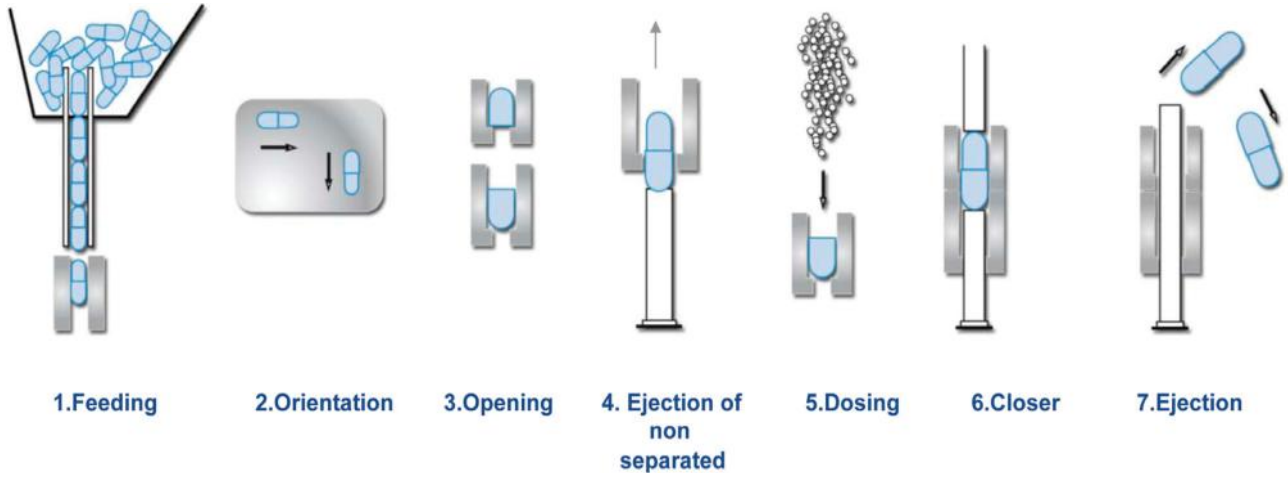


Figure 7: Capsule filling process

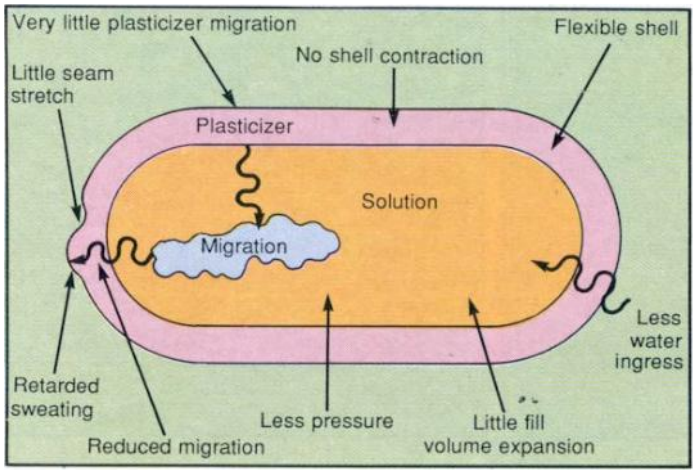


Figure 8:

Plasticizers: These are used to make the softgel shell elastic and pliable. They usually account for 20-30%. The most common plasticizers used in softgels is glycerol, although sorbitol and propylene glycol are used frequently often in combination with glycerol. The amount and choice of the plasticizer contribute to the hardness of the final product and may even affect its dissolution or disintegration characteristics, as well as its physical and chemical stability.

Plasticizers are selected based on their compatibility with the fill formulation, ease of processing, and the desired properties of the final soft gel, including hardness, appearance, handling characteristics and physical stability. One of the most important aspect of softgel formulation is to ensure that there is minimum interaction or migration between the liquid fill matrix and the soft gel shell. The choice of plasticizer type and concentration is important in ensuring optimum compatibility of the shell with the liquid fill matrix [16].

Water: The other essential component of the soft gel shell is water. Water usually accounts for 30-40 % of the wet gel formulation and its presence is important to ensure proper processing during gel preparation and softgel encapsulation. Following encapsulation, excess water is removed from the softgels through controlled drying. In dry gels the equilibrium water content is typically in the range 5-8% w/w, which represents the proportion of water that is bound to the gelatin in the soft gel shell. This level of water is important for good physical stability, because in harsh storage conditions softgels will become either too soft and fuse together, or too hard and embrittled.

Colorants/opacifiers: Colorants (soluble dyes, or insoluble pigments or lakes) and opacifiers are typically used in the wet gel formulation.

Colorants can be either synthetic or natural, and are used to impart the desired shell color for product identification. An opacifier, usually titanium dioxide may be added to produce an opaque shell when the fill formulation is a suspension, or to prevent photo degradation of light-sensitive fill ingredients. Titanium dioxide can either be used alone to produce a white opaque shell or in combination with pigments to produce a colored opaque shell.

Quality control of capsules Whether capsules are produced on a small scale or large scale all of them are required to pass not only the disintegration test, weight variation test and percentage of medicament test but a visual inspection must be made as they roll off the capsule machine onto a conveyor belt regarding uniformity in shape, size, color and filling. As the capsules moves in front of the inspectors the visibly defective or suspected of being less than the perfect are picked out. The hard and soft gelatin capsules should be subjected to following tests for their standardization[17].

1. Shape and size
2. Color
3. Thickness of capsule shell
4. Leaking test for semi-solid and liquid ingredients from soft capsules
5. Disintegration tests
6. Weight variation test [20]
7. Percentage of medicament test in official books the following quality control tests are recommended for capsules [18]

Disintegration test: For performing disintegration test on capsules the tablet disintegration test apparatus is used but the guiding disc may not be used except that the capsules float on top of the water. One capsule is placed in each tube which are then suspended in the beakers to move up and down for 30 minutes, unless otherwise stated in the monograph. The capsules pass the test if no residue of drug or other than fragments of shell remains on No. 10 mesh screen of the tubes.

Weight variation test: 20 capsules are taken at random and weighed. Their average weight is calculated, then each capsule is weighed individually and their weight noted. The capsule passes the test if the weight of individual capsule falls within 90-110% of the average weight. If this requirement is not met, then the weight of the contents for each individual capsule is determined and compared with the average weight of the contents. The contents from the shells can be removed just by emptying or with the help of small brush. From soft gelatin capsules the contents are removed by squeezing the shells which has been carefully cut. The remainder contents are removed by washing with a suitable solvent. After drying the shells, they are weighed and the content weights of the individual capsules are calculated. The requirements are met if;

(1) not more than 2 of the differences are greater than 10 % of the average net content and;
(2) in no case the difference is greater than 25 %. Content uniformity test

This test is applicable to all capsules which are meant for oral administration. For this test, a sample of the contents is assayed as described in individual monographs and the values calculated which must comply with the prescribed standards [18].

Capsule stability: Unprotected soft capsules (i.e., capsules that can breathe) rapidly reach equilibrium with the atmospheric conditions under which they are stored. This inherent characteristic warrants a brief discussion of the effects of temperature and humidity on these products, and points to the necessity of proper storage and packaging conditions and to the necessity of choosing an appropriate retail package. The variety of materials capsulated, which may influence the gelatin shell, together with the many gelatin formulations that can be used, makes it imperative that physical standards are established for each product. General statements relative to the effects of temperature and humidity on soft gelatin capsules must be confined to a control capsule that contains mineral oil, with a gelatin shell having a dry glycerin to dry gelatin ratio of about 0.5 to 1 and a water to dry gelatin ratio of 1 to 1, and that is dried to equilibrium with 20 to 30 % RH at 21 to 24°C, the physical stability of soft gelatin capsules is associated primarily with the pick-up or loss of water by the capsule shell.

If these are prevented by proper packaging, the above control capsule should have satisfactory physical stability at temperature ranging from just above freezing to as high as 60°C, for the unprotected control capsule, low humidities (less than 20 % RH), low temperature (less than 2°C) and high temperatures (greater than 38°C) or combinations of these conditions have only transient effects. The capsule returns to normal when returned to optimum storage conditions. As the humidity is 21 increased, within a reasonable temperature range, the shell of the unprotected control capsule should pick up moisture in proportion to its glycerin and gelatin content. The total moisture content of the capsule shell, at equilibrium with any given relative humidity within a reasonable temperature range, should closely approximate the sum of the moisture content of the glycerin and the gelatin when held separately at the stated conditions.

Special types of hard gelatin and soft gelatin capsules:

Modifications throughAltered Release: The rate of release of capsule contents can be varied according to the nature of the drug and the capsule excipients. If the drug is water-soluble and a fast release is desired, the excipients should be hydrophilic and neutral. If a slow release of water-soluble drug is desired, hydrophobic excipients will reduce the rate of drug dissolution. If the drug is insoluble in water, hydrophilic excipients will provide a faster release; hydrophobic and neutral excipients will slow its release. A very rapid release of the capsule contents can be obtained by piercing holes in the capsule to allow faster penetration by fluids in the gastrointestinal tract, or by adding a small quantity of sodium bicarbonate and citric acid to assist in opening the capsule by the evolution of carbon dioxide. About 0.1 to 1% of sodium lauryl sulfate may be added to enhance the penetration of water into the capsule and speed dissolution.

If slower release of the active drug is desired, it can be mixed with various excipients, such as cellulose polymers (methylcellulose) or sodium alginate. In general, the rate of release is delayed as the proportion of polymer or alginate is increased relative to water soluble ingredients, such as lactose. It should be mentioned that it is difficult to predict the exact release profile for a drug and to obtain consistent results from batch to batch. Further, reliable, consistent blood levels and duration of action can only be proved with controlled bioequivalence studies. In addition, many medications exhibit narrow therapeutic indices as the toxic and therapeutic doses are very close. Therefore, extemporaneous attempts to alter release rates to this extent should be avoided.

Modification for control release of drug:

Coating capsules: Coatings have been applied extemporaneously to enhance appearance and conceal taste, as well as to prevent release of the medication in the stomach (enteric coated products). Most coating of capsules requires considerable formulation skill and quality control equipment found in manufacturing facilities. Capsules can be coated to delay the release of the active drug until it reaches a selected portion of the gastrointestinal tract. Materials found suitable include stearic acid, shellac, casein, cellulose acetate phthalate and natural and synthetic waxes; the basis of their use is their acid insolubility but alkaline solubility. Many of the newer coating materials are time:erosion-dependent rather than acid:base-dependent, i.e. they erode over time on exposure to gastrointestinal contents rather than over a pH gradient. There are, in addition, several newer materials with predictable pH solubility profiles [10].

Enteric-coated capsules: Enteric-coated capsules resist disintegration in the stomach but break up in the intestine. They have largely been superseded by enteric-coated tablets. Types of coating used commercially include cellulose acetate phthalate and mixtures of waxes and fatty acids and/or their esters. Enteric coating may be given to following categories of drugs –

- For substances that irritate the gastric mucosa or are destroyed by the gastric juice, and for medicaments, such as amoebicides and anthelmintics that are intended to act in the intestine.
- Which interfere with digestion e.g. tannins, silver nitrate and other salts of heavy metals [11].
- Which are required to produce delayed action of the drug. In general, the application of a coating requires skill and additional equipment. A general coating can be applied but should probably only be used in medications that would not be of a critical nature. In many cases, experience must be developed for specific formulations depending upon the requests of the physicians and the needs of the individual patients. Several coating methods may be used and are described as follows:

1. **Beaker-flask coating** - Place a very small quantity of the coating material in the flask and gently heat until it has melted. Add a few capsules, remove from the heat and rotate the flask to start application of the coating. Periodically add a few more drops of melted coating material with continued rotation.
   The addition of very small quantities is all that is required to keep the capsules from sticking together and clumping [18].
2. **Dipping** - Heat the coating material in a beaker at the lowest feasible temperature. Individual capsules can be dipped using tweezers, allowing the coating to cool and repeating the process until a sufficient layer has been developed.
3. **Spraying** - An alcoholic or ethereal solution of the coating material is prepared and placed in a small sprayer (a model airplane paint sprayer works well). The capsules are placed on a screen in a well-ventilated area. The solution of coating material is applied in very thin coats with sufficient time allowed for drying between coats (A hair dryer may be used cautiously for this step). The process is repeated until a sufficient layer has been developed [17].

ADVANCES AND CHALLENGES IN SOFTGEL CAPSULES DEVELOPMENT:

Advances in development of softgels as a dosage form:

Soft gelatin capsules have received enormous consumer acceptance due to their numerous advantages over other traditional dosage forms such as tablets and even hard capsules[31]. It has become not uncommon for pharmaceutical companies to reformulate marked solid dosage form in the form of soft gelatin capsules in order improve consumer acceptability owing to dissolution in the gastrointestinal tract of drugs formulated as soft gelatin capsules [32].

Advancement of softgel capsules are traced back to Fuccella*et al* study which showed that, softgel capsules of temazepam ensured a more rapid and complete absorption of the drug and seemed to be an appropriate pharmaceutical form for treatment of sleep disturbances [33]. This observation led to the development of the soft gel capsules and assessment of bioavailability of the formulation, plasma levels of temazepam determined in healthy volunteers [34]. Formulation of a hydrophobic amine antimalarial with oleic acid in softgel capsules has been reported as an advancement which resulted in the enhancement of bioavailability [35].

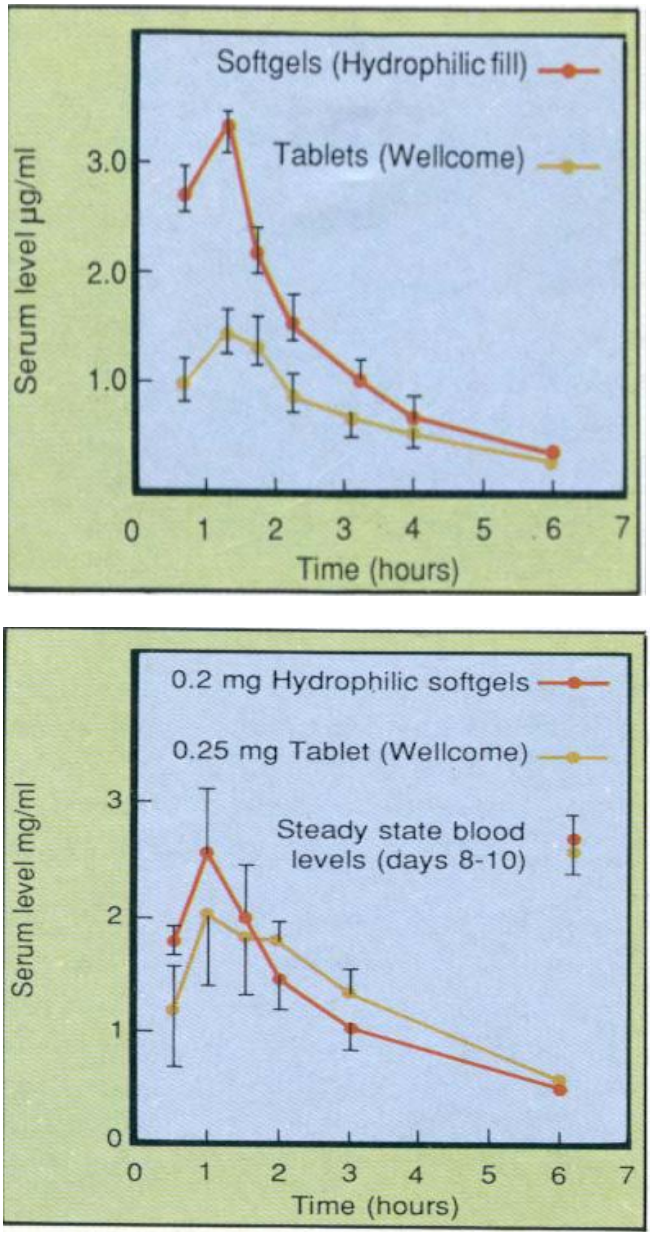
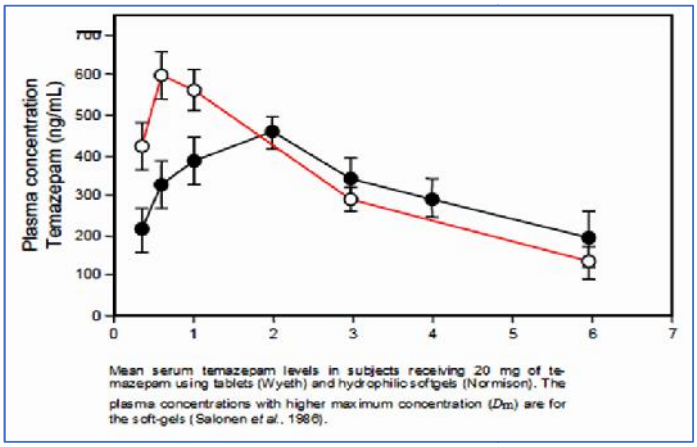


Figure 9:(Above) Plasma concentrations of digoxin (mean values and standard errors)after oral intake (six subjects in a cross-over study) of 0.4 mg digoxin as two tablets(Wellcome) and two softgel products with a hydrophilic fill. (Right) Mean digoxin serumlevels (and standard errors) of eight subjects receiving 0.25 mg digoxin tablets (Well-come) and 0.2 mg digoxin in hydrophilic softgels. Repeated dosage showed that

different dose levels gave the same steady-state blood levels (Patel, Morton, & Seager, 1989).



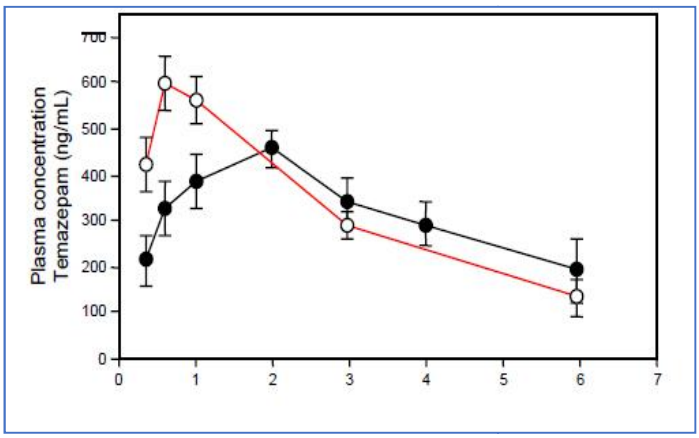


Figure 10: Mean serum Temezepam in subjects receiving 20 mg of temezepam using tablets (Wyeth) and hydrophilic softgels normison the plasma concentration with higher maximum concentration $D_{(m)}$ are for the soft gels(salonen*et al*. 1986)

Several advances have been made in the development of softgel capsules including;

1. Ensuring of suitable physical features. The soft gelatin capsule has been developed to have a tidy and beautiful appearance compared to tablet pills. These features have been reported to ensure faster

The capsule has been made into instant-effective, slow-releasing, enteric coated or gastro coated soft gelatin capsule.

2. Achievement has been reported in formulation of medicines with dosage form of higher oil concentration that cannot be easily made into tablets or pills and small dosage principle agent that is not water-soluble and hard to be ingested in the digestive [37, 38].

3. Soft capsules technology has facilitated light-sensitive and unstable drugs to be filled into opaque lightproof opageopa capsule to improve the stability and prevent the drug from been affected by moisture, oxygen and light in the air.

Advances have enabled soft gelatin capsules to be used to make nutriceuticals, cosmetics and paintball for simulated shooting [36].

MODIFYING HARD CAPSULES MANUFACTURE FOR DELAYED RELEASE:

Gelatin:

Gelatin is by far the most common and well-known material used to produce two-piece hard capsules. Its origin has already been described in this article. Gelatin has a long history of safety and outstanding performance characteristics making it an excellent polymer for producing capsules. It is nontoxic, widely used in foods, acceptable for use worldwide, and recognized in all pharmaceutical pharmacopeia.

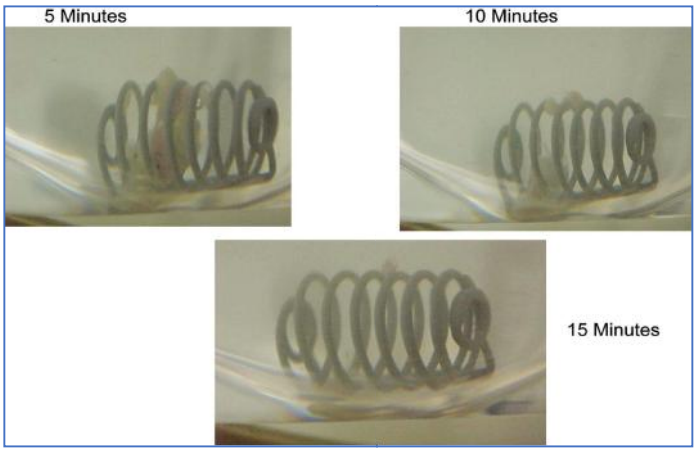


Figure 11: **Passing capsules**

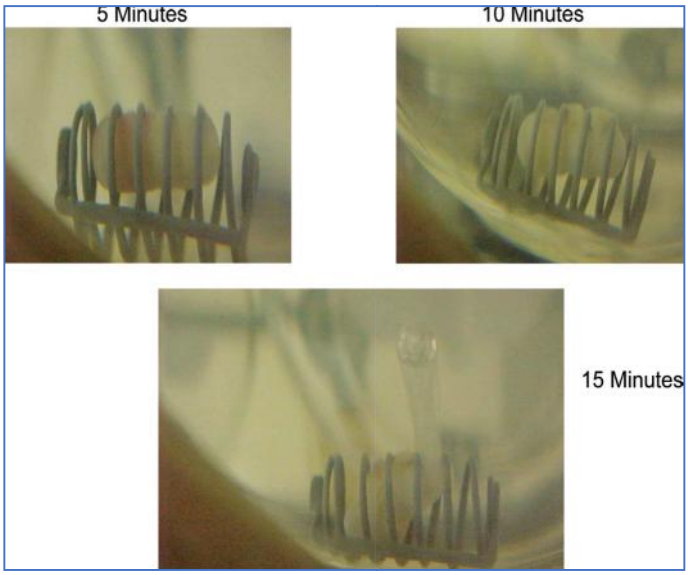


Figure 12:Cross linked capsules shell delays dissolution (Dannismurachanian 2010)

Hypromellose :

In recent years gelatin alternatives have been investigated for reasons of stability and also because of objections to animal-derived materials. Hypromellose has been extensively and successfully developed into two-piece capsules for use in the pharmaceutical and nutritional industries and is available from numerous suppliers. Hypromellose is a plant-derived material and, therefore, answers the need for certain religious, cultural, and dietary restrictions.

Important benefits of hypromellose include a moisture content of approximately 4%-6% making it an excellent container for moisture-sensitive drugs. Hypromellose capsules are also less prone to brittleness. Additionally, hypromellose does not bind to itself; therefore, dissolution delays due to crosslinking are not an issue. However, capsules made with hypromellose have a higher oxygen transmission rate than those made from gelatin, which may be a consideration for oxygen-sensitive compounds.

Hypromellose capsules are manufactured by a dipping and curing process somewhat similar to that of gelatin capsules. Though numerous manufacturers now produce such capsules, it is important to be aware that unlike gelatin capsules, there may be important differences in the composition of hypromellose capsules. Depending on the capsule manufacturing process, a gelling agent may be necessary. These gelling agents vary by supplier. For example, some capsules may be produced using gellan gum while others are produced with various types of carrageenan. Each of these gelling agents imparts different performance characteristics to the capsules.

For certain manufacturing processes a gelling agent may not be required and these are reported to have dissolution benefits over those made with gelling agents. It is important to be aware of the complete composition of the hypromellose capsules being used when developing a new product.

MODIFICATIONS AND ADVANCES IN SOFT CAPSULE SHELL

Different types of capsule constitutive materials are usually selected for different products. Apart from the traditional gelatin, in recent years new materials have been explored and their application in the development of capsules is progressing rapidly[5].

Traditionally used gelatin materials:

Due to their availability, animal skins and bones have been used extensive as a source of raw material for the formulation of the shell of gelatin capsules. Their excellent film-forming ability and mechanical stability properties of gelatin result in the desired physical properties. Furthermore, they can be re-cycled and retain their good performance[6]. The gelatin made from the traditional material like animal skin, bone, tendon and collagen have been noted to meet the necessary pharmaceutical requirements as being quickly hydrolysed by gastrointestinal enzymes. In addition, they contain a variety of nutritious amino acids. The purified products obtained therefore are easily swallowed and rapidly absorbed[5].

Development of news materials or excipients:

In the recent past a number of new sources of raw materials for the gelatin capsule shell have been reported. This range from natural resources like fish to polymers, the fish gelatin has been obtained from fish skin products and formulated as natural hollow capsules of fish oil, spirulina and cellulose[9]. Natural herbal capsules have been reported as concentrated herbal capsules of gold *Lippo* plant capsules. The polymer material Hydroxyl Propyl Methyl Cellulose (HPMC) have also been explored, the odorless, milky, fibrous or granular powder, from lint or wood pulp, dissolves completely in cold water but is almost insoluble in ethanol and other organic solvents. FDA has highlighted it as a non-active component that can be used for ophthalmic preparations, oral capsules and suspensions[5]. The gelatin made of hypromellose and pullulan displays chemical stability, friability, low moisture content and oxygen absorption rate [20].

Progress in soft capsules liquid:

The formulations of capsule fill have been developed to fulfilling specifications and end-use requirements of the product. Capsulation of liquids that are immiscible with water and non- volatile, such as vegetable oils and vitamin E, have been easily made requiring little or no formulation. However, solids which are not sufficiently soluble in liquids are reported to be capsulated as suspensions having a particle size of 80 mesh or finer [21].

A large group of dietary products are reported to have been commonly capsulated in suspensions form. The two-suspension formulation gel production equipment widely utilized domestically is the Chatsworth Machine and the GIC Engineering. Basically, all these machines produce soft gels in a similar manner, they have rotating dies and an independent wedge with a pump that control the fill [7].

Filling of soft gel capsules with liquid and semi-solid materials has been successful carried out with selected "fillings" that do not dissolve the gelatin [21].

Donato and group (2008) showed that the following types of compounds may not be suitable candidates for soft gel encapsulation [22]:

- Liquids that can easily migrate through the gelatin shell, such as water hygroscopic and volatile compounds. Water soluble compounds that may affect the gelatin shell unless they are minor constituents of a formula or combined with a carrier that reduces their effect on the shell.

    1. Aldehydes, which can harden the shell and hence affect its dissolution property.

    2. Acidic or alkaline solutions should be avoided, unless they are adjusted to become neutral; acids and alkalis can cause hydrolysis and leakage of the gelatin shell.

Advantages:

Modifications improves bioavailability of drugs:

Increased the rate of absorption of drugs:

Major modifications have been made in the formulation of softgels to address particular drug absorption issues. One of the best advances is the delivery of the drug into the gastrointestinal tract in the form which it can be rapidly absorbed. This has been achieved by using a drug solution matrix in a softgel formulation whereby absorption is significantly faster than from other solid oral dosage forms, such as compressed tablets. While absorption of a poorly soluble drug from a tablet formulation is rate-limited by the need for disintegration into granules before drug dissolution into gastrointestinal fluid, the solution-softgel approach, the shell ruptures within minutes to release the drug solution; it is usually the rate of absorption[8].

Modification of drug delivery increase bioavailability:

This has been exploited in the recent past as a valuable attribute for therapeutic reasons, such as the treatment of migraine or acute pain. In a recent clinical trial, the dietary supplement glucosol in a soft gel capsule showed a 30% decrease in blood glucose levels compared to a 20% drop seen with dry-powder filled two-piece hard gelatin capsule formulation, suggesting that soft gel formulation made of glucosol improved its bioavailability[23]. This is further illustrated by Lissy*et al* (2010） in the pharmacokinetic comparison of an oral diclofenac potassium liquid-filled soft gelatin capsule (DPSGC) with a diclofenac potassium tablet, study which showed that, DPSGC, 25mg and 50mg were more rapidly and consistently absorbed than diclofenac potassium 50-mg comparator tablets. The C (max) of DPSGC 25mg was equivalent to the 50-mg diclofenac potassium comparator tablet[24,25].

Increased bioavailability of drugs:

As well as increasing the rate of absorption, softgels have also been reported to improve the extent of absorption. This can be particularly effective for hydrophobic drugs with a relatively high molecular weight. An example of such a product is the protease inhibitor saquinavir, which has been formulated as a solution-softgel product. The solution-softgel formulation provided around three times the bioavailability of saquinavir as measured by the area under the plasma-time curve (AUC), compared to a hard-shell capsule formulation [25]. The bioavailability of digoxin was reported to have increased significantly when formulated and administered as a liquid in a soft capsule and that dose adjustment were necessary when patients were switched from tablets to liquid-filled capsules [26].

Decreased variability of plasmatic drugs:

High variability in drug plasma levels is a common characteristic of drugs with low bioavailability. By dosing drug optimally in solution, the plasma level variability of such drugs has been significantly reduced. The cyclic polypeptide drug cyclosporine (SandimmunNeoral®) was successfully improved by this approach by using a microemulsion preconcentrate in a softgel [27].

Patient compliance and consumer preference:

A number of self-medicating consumer preference studies have been carried out in an attempt to gauge the relative perception of softgels compared to hard shell capsules and tablets. The results showed consistently that softgels were perceived to be appealing dosage forms to most consumers, and outperformed all other dosage forms in answering patient needs. Consumers expressed their preference for softgels in terms of ease of swallowing, absence of taste and convenience. One further aspect of improved compliance is that if, by using a drug solution in a softgel delivery system, its bioavailability is enhanced, it may be possible to reduce the dose administered in order to achieve therapeutic effectiveness. In this way, it may also be possible to reduce the capsule size, which will further improve patient compliance [28].

Safety for potent and cytotoxic drug:

The mixing, granulation and compression/filling processes used in preparing tablets and hard-shell capsules has been noted to generate a significant quantity of air-borne powders. By preparing a solution or suspension of drug, where the active component is essentially protected from the environment by the liquid, such safety concerns and associated toxicities have been significantly reduced [29].

Dose uniformity of low-dose drugs:

Liquid dosing has been realized to avoid the difficulties of poor powder flow and hence content uniformity. This is an important benefit for formulations containing drug doses in the microgram region. Attempts to produce adequate mixtures of small quantities of a low-dose drug in larger quantities of powdered excipients for tabletting or hard-shell filling are often unsatisfactory.

In contrast, improved homogeneity has been achieved by dissolving the drug in a liquid and then encapsulating the liquid matrix in a softgel [30].

Product stability

Preparations of liquid-filled softgel have proven beneficial to oxidative or hydrolytic degradable drugs. The liquid is prepared and encapsulated under a protective nitrogen atmosphere and the subsequently dried shell has very low oxygen permeability. By formulating in a lipophilic vehicle and packaging in well-designed blister packs using materials of low moisture transmission, the drug is protected from moisture. Unlike for formulation in solution, where the drug may be more reactive than in the dry state and hence potentially less stable[31].

Disadvantages:

High Cost of production:

Production costs are usually high compared to the other ordinary tablets. This has been accounted for by elaborate machinery involved in production of softgels which also gives rise to high maintenance costs. These costs usually do increase the price the consumer pays. This has been proven by comparison of health

The effective dissolution of gelatin in the body has been attributed to it's extremely water solubility. On the other hand,in regard to shelf stability it has been realized that this is a drawback given soft gelatin capsules are very sensitive to heat and humidity. In hot or humid climates, soft gel caps may stick together or even break open and this decreases their life expectancy [8].

Dietary restrictions:

Gelatin is traditionally made from the bones and skins of pigs and cows. Many groups, however, have dietary proscriptions that prevent them from consuming animal products found in soft gelatin capsules. Soft gel caps violate the religious dietary restrictions of observant Jews, Muslims, Buddhists and Hindus. Because soft capsules are made from animal parts, many vegetarians also opt not to use them. Due to this there is an emergence of animal-free substitute gelatin capsules made from seaweed extract or other sources, but they are generally more expensive and harder to find [9].

Some recent updates in Capsule technology

A) New products by Capsugel:

1. **Capsugel has introduced Oceancaps capsules, these capsules** made from all natural fish gelatin derived from farm-raised fish, they have the same characteristics as traditional gelatin capsules, including appearance, machinability, mechanical properties, hygroscopic and oxygen properties, chemical stability, and versatility. Plus, they are odorless and tasteless [13]
2. **Licaps**new 000 size capsules are ideal for maximizing liquid dosage with a fill capacity of 1000mg to 1400mg depending on the density of the liquid fill material. This two-piece capsules has been specially designed to be sealed for secure containment of liquids and semi-solids without banding. Available in both gelatin and HPMC (Hydroxypropyl Methylcellulose) capsules they are available in a variety of colors to meet your specific needs[13,14].

B) New products by Banner Pharmacaps Inc.
Banner Pharmcaps has developed an Enteric Softgel called Entericare, with enteric properties built into the shell matrix of the capsules for delivering very potent (small quantities) as well as drugs that require larger quantities and provide sustained delivery for more than an 8- to 12-hour period[14].

C) New product by Shionogi Qualicaps
QUALI-V, developed by Shionogi Qualicaps, is the first HPMC capsule developed for eventual

D) SMART PILLS CAPSULE: Some people suffering from inflammatory bowel syndrome or Crohn's disease – they need drugs thattarget the large intestine directly. smart pill capsule ismanufacture which release the drug at the particular site of the intestine by the magnet implanted to the intestine which triggers capsule lid when it reaches and drug will get released.(Babak Ziaie)

CONCLUSION

Interesting Modifications and advances have recently been made in the area of developing liquid and semi-solid formulation in a gelatin capsule to address particular bioperformance issues, namely an increase of bioavailability and decrease of plasma variability by improving solubility and absorption-enhancing techniques.

By observing release kinetics of drug, different polymers were used for the control delivery of the drug, this could be studied for the further research subject.

By comparing the soft gelatin and hard gelatin capsules softgel capsules shows more bioavailability than that of hard gelatin capsules. Although the softgel capsules have many advantages, they also face stability problem, mainly for the soft capsules stored for longer than six months. After this time, their soluble products decreased, and the remnants cannot be re-dissolved and/or reabsorbed into the gastro-intestinal tract. These problems could be investigated as a research subject.

The proper designs for a specific gelatin capsules formulation requires the appropriate selection of shell and fill composition and the optimization of the two to allow for the efficient production of a chemically and physically stable product with the desired biopharmaceutical properties.

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How to cite this article

Prasad VD. Formulation and modifying drug release from Hard and Soft Gelatin Capsules for Oral drug delivery.*Int. J. Res. Dev. Pharm. L. Sci. 2017; 6(4)*: 2663-2677.doi: 10.13040/IJRDPL.2278-0238.6(4).2663-2677.