3 SOLID DOSAGE FORMS: CAPSULES

A capsule is a shell or a container prepared from gelatin containing one or more medicinal and/or inert substances. The gelatin capsule shell may be soft or hard depending on their formulation. Capsules are intended to be swallowed whole by the patient. In instances where patients (especially children) are unable to swallow capsules, the contents of the capsule can be removed and added (*e.g.*, sprinkled) on soft food immediately before ingestion. In this case, capsules are used as a vehicle to deliver premeasured medicinal powder. Capsule dosage forms occupy more than 10% of the total dosage forms on the market (Augsburger, 1990). An example is Contac® 600 (GlaxoSmithKline) in which the active ingredients in the capsule are encapsulated in hundreds of microbeads in a sustained release form (based on the Spansule® technology).

I. HARD GELATIN CAPSULES

The majority of capsule products are made of hard gelatin capsules. Hard gelatin capsules are made of two shells: the capsule body and a shorter cap. The cap fits snugly over the open end of the capsule body. The basic hard gelatin capsule shells are made from mixtures of gelatin, sugar, and water. They are clear, colorless, and essentially tasteless.

Gelatin is a product obtained by partial hydrolysis of collagen acquired from the skin, white connective tissue, and bones of animals. Gelatin is a protein which is soluble in warm (or hot) water, but insoluble in cold water. At low temperatures, gelatin dissolved in water becomes a gel (which is insoluble in water). This property is used to prepare Jello® and other gelatin deserts. Gelatin capsules become dissolved in warm gastric fluid and release the contents.

Normally, hard gelatin capsules contain 13–16% of moisture. If additional moisture is absorbed when stored in a high relative humidity environment, hard gelatin capsule shell may lose their rigid shape and become distorted. In an opposite environment of extreme dryness, capsules may become too brittle and may crumble during handling. Since moisture can be absorbed or released by the gelatin capsules, capsules containing moisture-sensitive drugs are usually packaged in containers. Gelatin for making hard shells is of bone origin and has 220–280 g bloom strength (the weight required to depress a standard plunger 4 mm into the gel).

A. MANUFACTURING OF HARD CAPSULES

Hard gelatin capsule shells are produced by dipping of pins or pegs of the desired shape and diameter into a reservoir of the melted gelatin mixture. The pegs are made of manganese bronze. Up to 500 pegs can be affixed to each plate. As the plate is lowered to the gelatin bath, the pegs are submerged to the desired depth. The desired thickness of coating is achieved by controlling the time of coating. After the plates and pegs are lifted from the gelatin bath, the gelatin on the pegs is dried by flowing air with controlled temperature and humidity. Once dried, each capsule part is trimmed to the proper length and removed from the pegs. It is important to control the thickness of the gelatin walls, since it affects the snugness of the fit between the capsule body and cap.

1. Colored and Opaque Capsules

Colorants may be added to the gelatin solution to prepare capsule shells with a variety of colors. It is not unusual to see capsule bodies and caps having different colors. Opaque capsules are prepared by adding to the gelatin mixture an insoluble substance such as titanium dioxide. Both colored and opaque capsules make a pharmaceutical product distinctive. By combining the various capsule parts with different colors, distinctive capsules can be prepared. This is important for those who have to take more than one type of drugs in the capsule dosage form. Different drugs in different capsules may be easily distinguished by their colors of the capsules.

2. Shape of Capsules

To prepare capsules easily differentiated from those of other manufacturers, the shape of the capsule end (which is usually round) can be altered. Capsules from Eli Lilly (Pulvules®) have the body shell with a tapered end and the round shaped cap. Capsules from GlaxoSmithKline have both ends highly tapered.

To ensure reliable closing of the filled capsules, capsule shells with locking grooves (or indentations) have been prepared (Augsburger, 1990). Examples are Posilok® (Qualicaps, a division of Shionogi & Co., Ltd.), Coni-Snap® (Capsugel, a division of Pfizer, Inc.), and Uni-Lock® (Cardinal Health). The two grooves fit into each other for tight closing and prevent accidental separation (or splitting) of the capsules. Capsules from Capsugel are sold as Snap-Fit®, Coni-Snap®, and DBcaps®. Snap-Fit® has the concentric locking rings of the body and cap which prevent reopening after filling. The Coni-Snap® capsule, which is the improved form of Snap-Fit®, has the rim of the capsule body which is slightly tapered (see Figure 3.1). The slightly tapered body facilitates joining on high speed machines and prevents the problem of telescoping. Telescoping is sliding of a capsule body (or a capsule cap) over another capsule body (or a capsule cap). The tapered rim makes it more difficult to slide a capsule body over another owing to the smaller diameter. The DBcaps® capsule is different from the Coni-Snap® capsule in that the upper capsule part (cap) covers most of the lower part (body) so that only the rounded edge of the body is visible. The decrease in gripping surface makes it impossible to

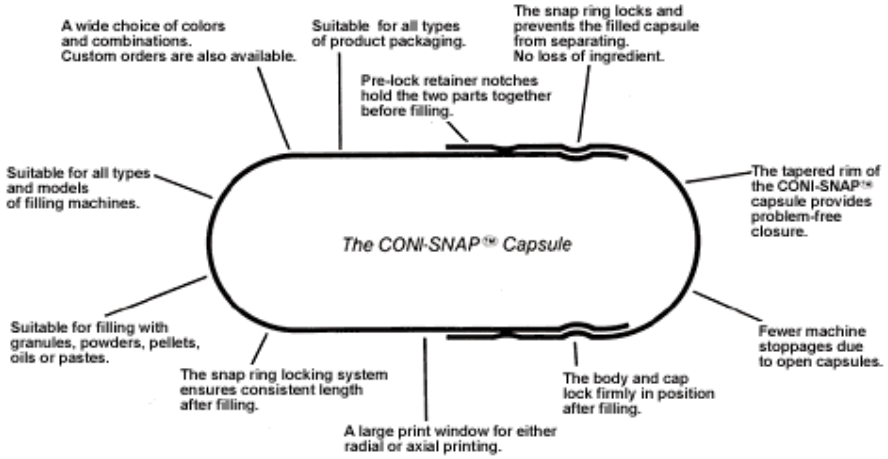

Figure 3.1 Chart indicating the characteristics of the Coni-Snap® capsule (Capsugel: Pfizer, Inc.).

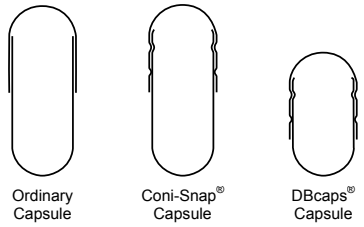

Figure 3.2 Drawings of an ordinary capsule (left), a Coni-Snap® capsule (center) and a DBcaps® capsule (right). In Coni-Snap® and DBcaps® capsules, the tapered rim of the body is designed to avoid telescoping, the grooves on cap and body lock together; the presence of indentations prevents premature opening.

hold the body and open without crushing it. Thus, the DBcaps® capsule provides increased security of the contents and the integrity of the capsule. Figure 3.2 illustrates the differences between ordinary capsules, Coni-Snap® capsules, and DBcaps® capsules.

Some capsules (Kapseal® from Pfizer, Inc., and Qualicaps® from Shionogi & Co., Ltd.) are made tamper-proof and leak proof. The joint between the two capsule parts are sealed with a gelatin or polymer band. Another approach has been developed to make capsules tamper resistant or tamper evident. The contact areas of the cap and body are wetted with a mixture of water and ethanol and then thermally bonded at 40–45 °C. Any attempt to separate a sealed capsule will destroy the capsule.

3. Capsule Size

Capsule shells are manufactured in various sizes, lengths, diameters, and capacities. For human use, capsules ranging in size from 000 (the largest) to 5 (the smallest) are commercially available. Larger capsules are used in veterinary applications. Figure 3.3 shows relative sizes and Table 3.1 lists the capacities of hard gelatin capsules for human use. Figure 3.4 shows the relative sizes of hard gelatin capsules for veterinary use.

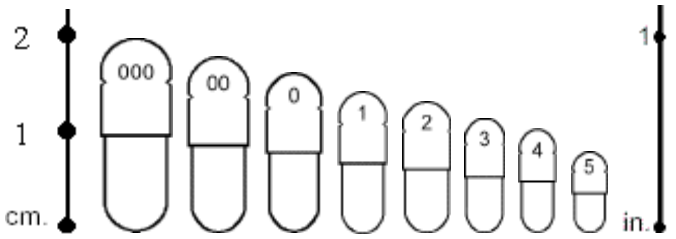

Figure 3.3 Relative sizes of hard gelatin capsules for human use (Torpac Inc.: Fairfield, NJ).

Table 3.1 Capsugel® Brand Coni-Snap® Hard Gelatin Capsule Sizes

Size	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

*Tolerances are ± 0.06Note: Sizes 000 and 5 are Snap-Fit® (Capsugel: Morris Plains, NJ)

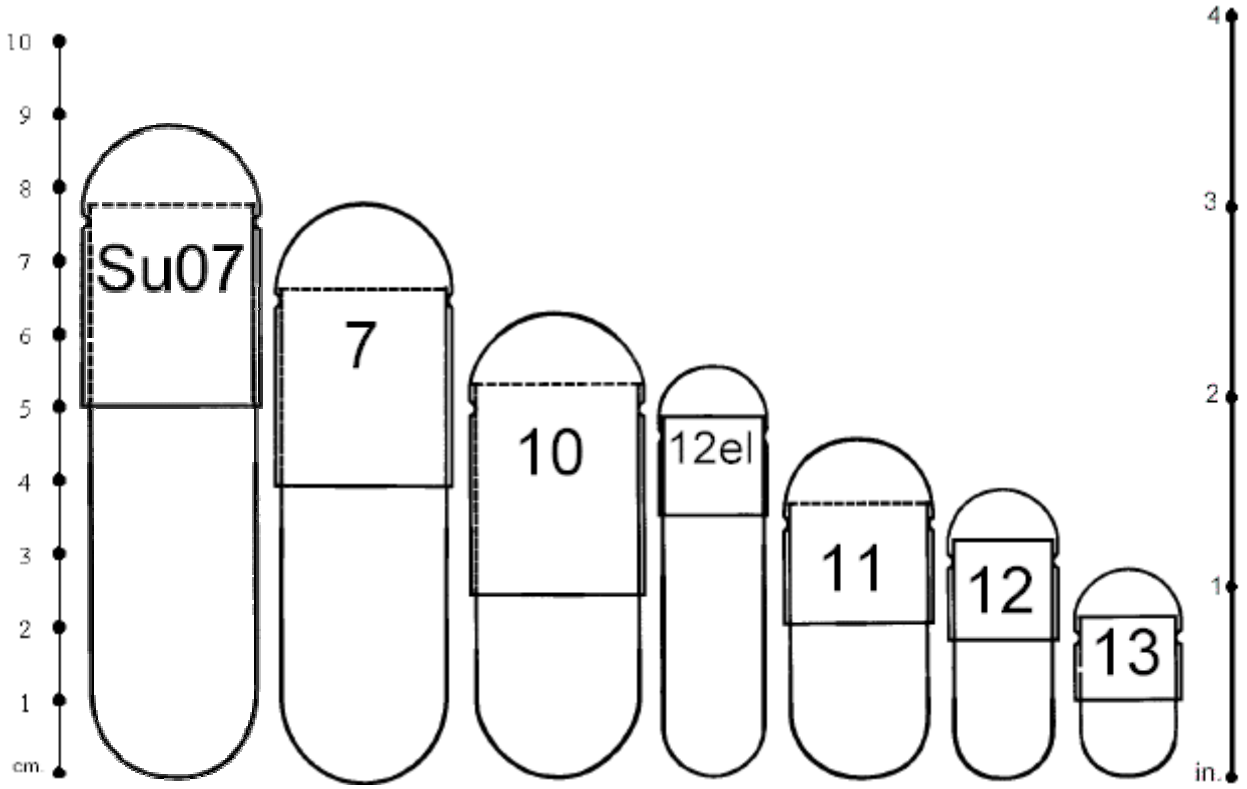

Figure 3.4 Relative sizes of hard gelatin capsules for veterinary use (Torpac Inc.: Fairfield, NJ).

B. 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 different pharmacokinetic 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 powders 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 prevents 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.

C. Liquid Filling Hard Gelatin Capsules

Licaps® (from Capsugel) is a Coni-Snap™ capsule exclusively designed to optimize liquid filling and sealing with LEMS™. Liquid excipients compatible with Licaps® are oil (corn, peanut, caster, olive, etc.), alcohol (cetyl, cetostearyl, and stearyl), stearic acid, beeswax, poly(ethylene glycol)s, and poloxamers. In the LEMS™ sealing process, approximately 50 μL of sealing fluid (50% aqueous ethanol) is sprayed during a 1-s cycle onto the joint between the cap and body to lower the melting point of gelatin in the wetted area. The presence of ethanol lowers the surface tension for easier penetration of the sealing liquid into the cap/body overlap. The temperature is then increased to 40–60 °C for one minute to complete the melting and fusion of the two gelatin layers. Upon return to room temperature, gelatin setting is complete. The maximum sealing capacity of the LEMS™ sealer is 30,000 capsules/h.

1. 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 to

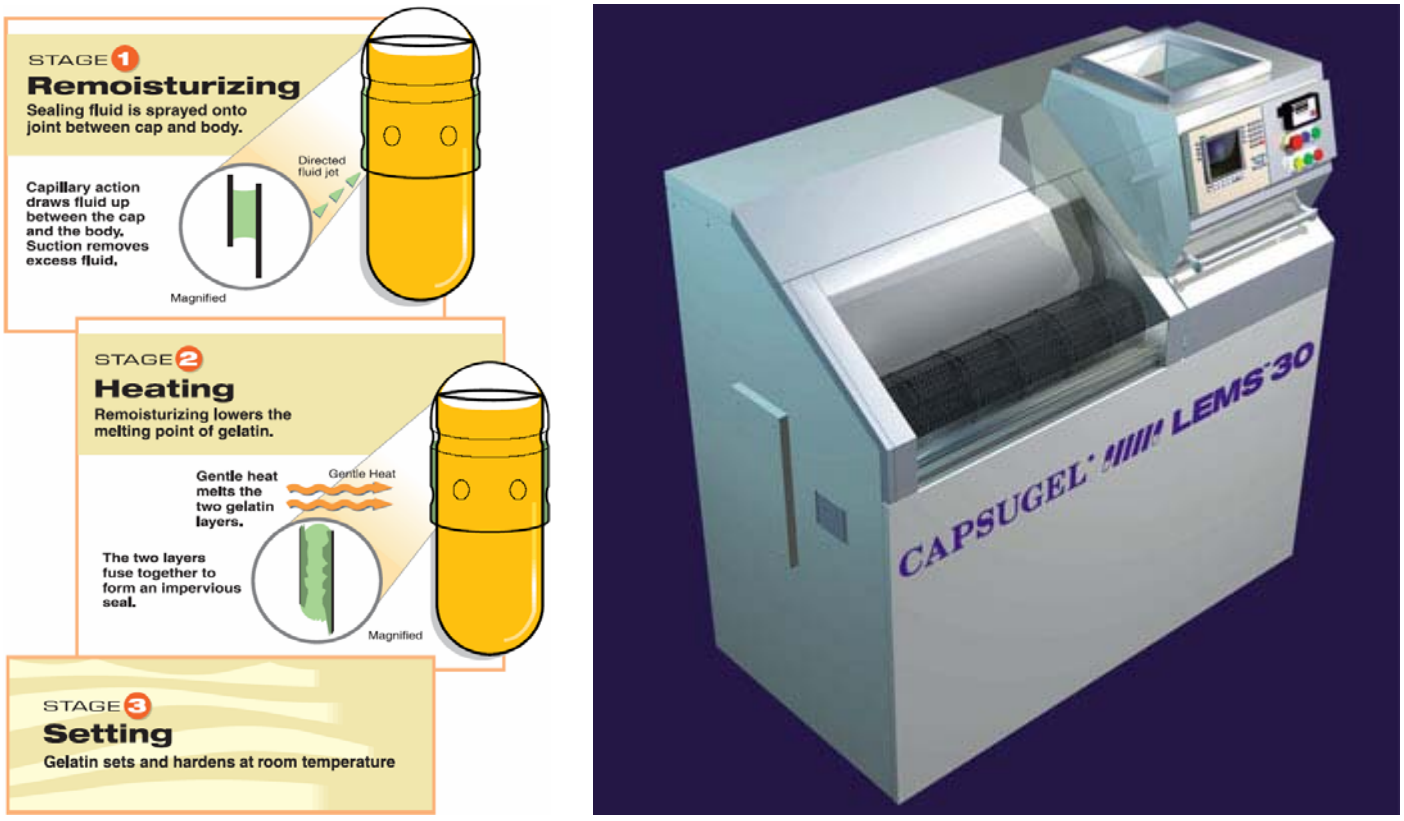

Figure 3.5 (Left) Sealing mechanism for Licaps® capsules and (right) the Capsugel LEMS™30 (Liquid Encapsulated Microspray Sealing) capsule-sealing equipment (Capsugel: Morris Plains, NJ).

design semi-solid matrix which can be heated or stirred for liquefying. The hard gelatin capsules are sealed by two gelatin bands.

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.

D. 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.

Starch and HPMC 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.

E. MICRO-FILLING SYSTEM

The new drug delivery company, called Meridica (www.meridica.com), launched a new product, Xcelodose™, in 2001. Xcelodose™ is programmable 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 capsules/h with weights ranging from 100 μg to tens of milligrams.

II. SOFT GELATIN CAPSULES

Soft gelatin (also called softgel or soft elastic) capsules consist of one-piece hermetically-sealed soft shells. Soft gelatin capsules are prepared by adding a plasticizer, such as glycerin or polyhydric alcohol (*e.g.*, sorbitol), to gelatin. The plasticizer makes gelatin elastic. Soft gelatin capsules come in various shapes such as spherical, elliptical, oblong, and special tube shapes with and without twist off (see Figure 3.8). They can contain non-aqueous liquids, suspensions, pasty materials, or dry powders. They are especially important to contain volatile drug substances or drug materials susceptible to deterioration in the presence of air.

Figure 3.8 Examples of the variety of colors, shapes, and sizes available in soft gelatin capsules (Pharmagel Engineering SPA: Milan, Italy)

A. PREPARATION

There are several procedures to prepare soft gelatin capsules, such as the plate process, the rotary die process, and reciprocating die process. Most soft gelatin capsules produced in industry are prepared by the rotary-die process (see Figures 3.9 and 3.10). In this process, two continuous gelatin ribbons are brought together between twin rotating dies. At the moment that the dies form pockets of the gelatin ribbons, metered-fill material is injected between the ribbons. Then the pockets of fill-containing gelatin are sealed by pressure and heat. The capsules are subsequently severed from the ribbon. As the capsules are cut from the ribbons, they may be collected in a refrigerated tank to prevent capsules from adhering to one another and from getting dull.

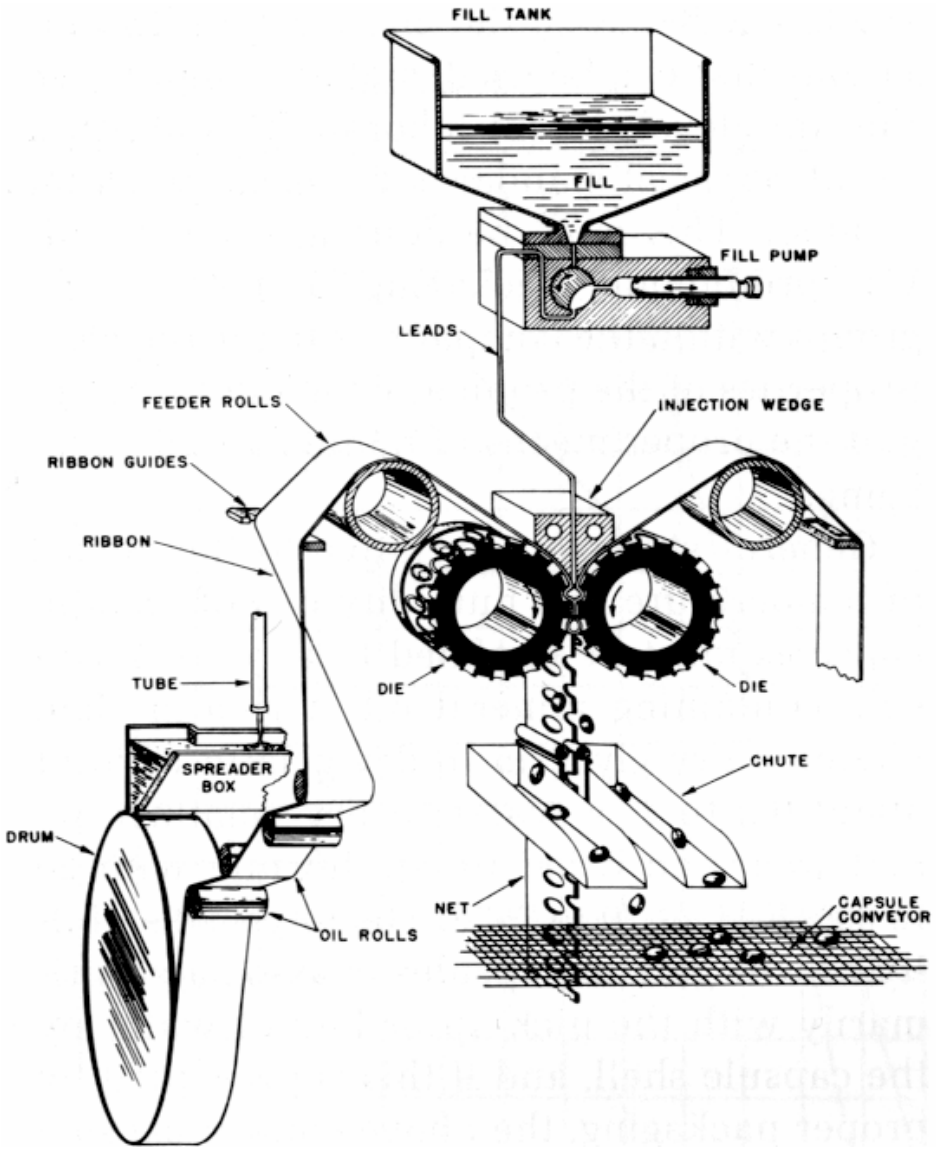

Figure 3.8 Schematic drawing of a rotary-die soft gelatin capsule filler (R.P. Scherer: Detroit, MI).

Figure 3.9 A rotary-die soft gelatin capsule filler (Pharmagel Engineering SPA: Milan, Italy)

Soft gelatin capsules contain more moisture than the hard capsules. Since gelatin is subject to microbic decomposition when it becomes moist, soft gelatin capsules may be prepared with preservatives to prevent the

growth of fungi. Gelatin used for making soft capsules is usually of bone and skin origin and has 150–175 g bloom strength.

1. Excipients of Softgels

a. Gelatin
b. Softener (plasticizer): sorbitol, xylose, maltitol, glycerin, PEG, water)
c. Preservatives (methyl paraben, propyl paraben, butylated hydroxyaniline, EDTA, sodium benzoate)
d. Dyes, pigments,
e. Solvent
   Polar: glycerin, PEG, PEG 400, PEG 3350, ethanol, PPG, water
   Nonpolar: beeswax, coconut oil, triglycerin, corn oil, mineral oil, soybean oil, D,L-α-tocopherol
f. pH-adjusting additive
g. flavor and fragrance
h. Pigment: titanium oxide, ferric oxide
i. Anticaking agent: Silicone dioxide
j. Humectant: polyol

2. Important Factors in Soft Gelatin Capsule Decision

a. Solubility
b. Permeability
c. Organic solubility
   Common organic solvents: DMSO
   Acceptable softgel excipients: fatty liquids, PEGs, propylene glycol, surfactants
d. Drug-excipient compatibility
   Chemical stability
   Physical stability: Drug migration into shell, gelatin disintegration, recrystallization of gelatin
e. Polymorphism

3. Advantages of Soft Gelatin Capsules

a. Ease of swallowing
b. Dosage accuracy/uniformity: Precise fill volume of liquid fill unit delivers a greater degree of accuracy and consistency from capsule-to-capsule and lot-to-lot.
c. Consistent manufacturing requirements: More accurate compounding, blending, and dispensing of liquid fill facilitates manufacturing. Liquid blends are more homogeneous.
d. Increase in bioavailability: Absorption and bioavailability can be enhanced by formulating compounds in solution including solubilizers and absorption enhancers, if necessary. Water-insoluble drugs may be formulated in a softgel. Clinical studies have shown enhanced absorption and bioavailability with softgel forms. Examples are temazepam (Salonen *et al*., 1986) and ibuprofen (Saano *et al*., 1991).

e. Enhanced stability and security: The tight hermetical sealing protects fill from air and environmental contamination. Gelatin shell can be formulated to block out ultraviolet light. Streamlined, one-piece design is tamper-evident.
f. Pliable shell: soft gel shell allows for custom shapes and sizes appropriate for oral, topical, chewable and suppository delivery.
g. Portability: Encapsulated liquid dosage formulations become highly portable for consumers/patients

B. APPLICATION

Soft gelatin capsules can be used to encapsulate a variety of liquids, such as oils, hydrocarbons, organic acids, polyethylene glycols, and nonionic surfactants. Some liquids can migrate through the capsule shell, and those liquids can not be encapsulated into the soft gelatin capsules. These include water and low molecular weight water-soluble organic compounds. Soft gelatin capsules can also be used to encapsulate dry fills, such as powders, granules, and pelletized materials. Table 3.2 shows some examples of commercial products which are prepared in soft gelatin capsules.

Lanoxicaps® deserves a special attention (Grainger, 1980). Lanoxicaps® is a new form of digoxin in a soft elastic gelatin (SEG) capsule formulated by R.P. Scherer Company. Hydrophobic drugs, such a digoxin, do not dissolve readily in water or gastric juice, and thus, their bioavailability is low owing to the slow dissolution. The SEG capsule dosage form contains a solution of digoxin in a hydrophilic solvent composed of poly(ethylene glycol) 400, 8% ethyl alcohol, propylene glycol, and water. The capsule shell includes gelatin, glycerin, sorbitol, methylparaben (added as a preservative), and water. Sorbitol or sorbitol and sorbitan mixtures are used in combination with glycerin as plasticizers to avoid the problem of sweating. Sweating occurs as a result of migration of water vapors from the environment through the shell to become dissolved in the fill (see Figure 3.11). The shell contacts owing to the loss of glycerin and the fill volume expands to generate high internal pressure. In some cases, fill liquid can be forced to migrate through the shell and deposit a liquid on the product surface (*i.e.*, the capsules sweat) (Patel, Morton, & Seager, 1989).

When ingested, the softgel shell becomes ruptured to rapidly release digoxin in the gastric juice. Since digoxin is in a solution state, the released digoxin is quickly absorbed to give good bioavailability. Figure 3.12 shows higher blood level of digoxin with hydrophilic soft gel formu-

Table 3.2 Examples of commercial products prepared in soft gelatin capsules

Ethchlorvynol (Placidyl®, Abbott)	Vitamin E (Aces®, J.R. Carlson Lab.)
Demeclocycline HCl (Declomycin®, Lederle)	Neoral® capsule
Chlortrianisene (TACE®, Marion Merrell Dow)	Zantac® Geldose capsule
Digoxin (Lanoxicaps®, Burroughs Wellcome)	Procardia® capsule (PEG based)
Docusate calcium (Surfak®, Upjohn)	Advil® liquicapsule

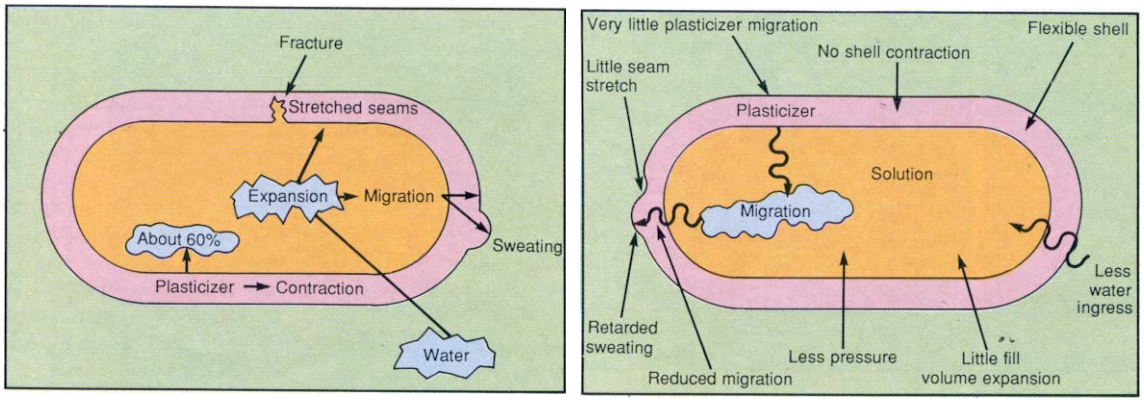

Figure 3.11 Illustration demonstrating the retardation in sweating of the active through the walls of a capsule shell (Patel, Morton, & Seager, 1989)

lation (Patel, Morton, & Seager, 1989). The increase in the maximum concentration (D_m) occurs at the same time (t_m). This means that the drug concentration in the stomach is increased. Since lower dose of digoxin can be given to produce the same steady state blood levels, it may decrease the unwanted side effects as well as the raw material costs. The bioavailability of cyclosporin was also known to be increased by delivering in a softgel formulation (Neoral® capsule)

For some drugs such as temazepam, the more rapid absorption may change the therapeutic value of the drug. As shown in Figure 3.13, earlier t_m and higher D_m indicates that the absorption rate constant (k_a) increased. The improved bioavailability of temazepam from softgels changed the therapeutic effect from a transquilizer to a hypnotic with no hangover (Patel, Morton, & Seager, 1989).

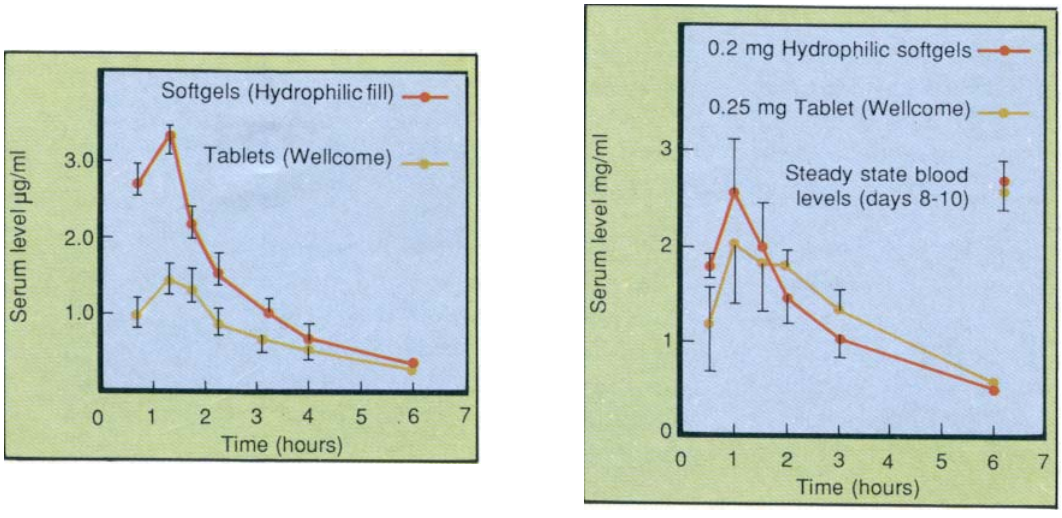

Figure 3.12 (Left) Plasma concentrations of digoxin (mean values and standard errors) after oral intake (six subjects in a cross-over study) of 0.4 mg digoxin as two tablets (Wellcome) and two softgel products with a hydrophilic fill. (Right) Mean digoxin serum levels (and standard errors) of eight subjects receiving 0.25 mg digoxin tablets (Wellcome) 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).

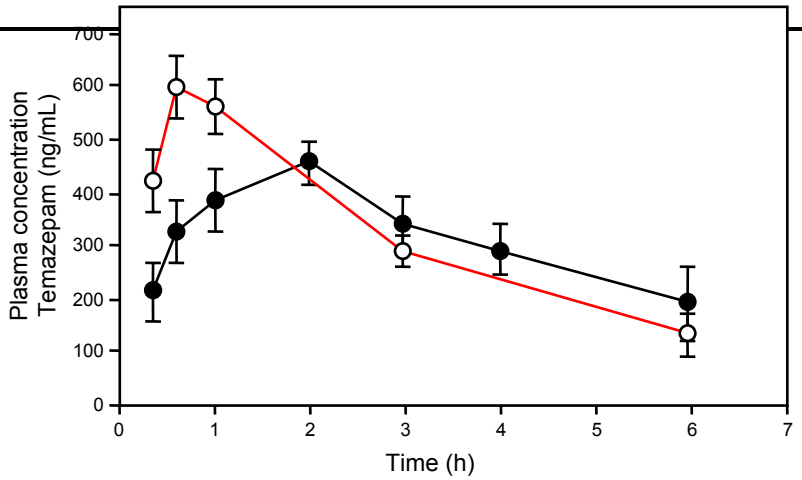

Figure 3.13 Mean serum temazepam levels in subjects receiving 20 mg of temazepam using tablets (Wyeth) and hydrophilic softgels (Normison). The plasma concentrations with higher maximum concentration (D_m) are for the softgels (Salonen *et al*., 1986).

R.P. Scherer developed a number of softgel technologies for better formulation of various drugs. Enhanced solubility system™ is designed to produce highly concentrated and readily biovailable solutions in a hydrophilic vehicle, such as PEG. Solubility is enhanced by producing a concentrated solution for both the free drug and its salt through the principle of partial neutralization. Polysol™ technology uses special plasticizers in gelatin shell formulations to prevent or minimize migration of shell components into the hydrophilic liquid fill, which results in softgels that lose their flexibility, become brittle, and are prone to fracture damage during transportation and handling. Cosol™ system uses ethanol in combination with certain partial glyceride esters of fatty acids. The unique combination allows use of ethanol as a solvent by retarding its migration from the fill through the shell. Thus, the Cosol™ system allows a higher concentration of drug in a small volume while enhancing bioavailability.

III. SOFLET™ GELCAPS

Soflet™ gelcaps (Banner Pharmacaps) are caplets in soft gelatin capsule. The advantages of Soflet™ gelcaps are listed below.

1. Protection of patients from potent compounds.
2. Added layer of protection for teratogens
3. Elimination of friability and dusting
4. Pharmaceutically elegant, and easy to swallow.
5. Product identification: gelatin shell can be produced in any color or combination of two colors for unique product identification.
6. Increased stability and integrity: hermetically sealed to protect tablet core from air and environmental contaminants.

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