CAPSULES PRODUCTION. MICROCAPSULES.

HARD AND SOFT GELATIN CAPSULES

Capsules are solid oral dosage forms in which the drug is enclosed within a hard or soft shell. The shell is normally made from gelatin and results in a simple, easy - to - swallow formulation with no requirement for a further coating step. They can be either hard or soft depending on the nature of the capsule shell, with soft capsules possessing a fl exible, plasticized gelatin fi lm. Hard gelatin capsules are usually rigid two - piece capsules that are manufactured in one procedure and packed in another totally separate operation, whereas the formulation of soft gelatin capsules is more complex but all steps are integrated.

There is a growing interest in using non - animal - derived products for formulation of the capsule shells to address cultural, religious, and dietary requirements. HPMC (e.g., V - caps, Quali - VC, Vegicaps) and pullulan shells (NPCaps) and starch are alternatives.

Hard - Shell Gelatin Capsules

Although the challenges of powder blending, homogeneity, and lubcricity exist for capsules as for tablets, they are generally perceived to be a more fl exible formulation as there is no requirement for the powders to form a robust compact. This means that they may also be more suitable for delivery of granular and beadlike formulations, fragile formulations that could be crushed by the normal compaction step. They are commonly employed in clinical trials due to the relative ease of blinding and are useful for taste masking.

Capsules are usually more expensive dosage forms than an equivalent tablet formulation due to the increased cost of the shells and the slower production rates. Even with modern fi lling equipment, the fi lling speeds of capsule machines are much slower than tablet presses. However, increased costs can be offset by avoiding a granulation step. Capsules, although smoother and easy to swallow, also tend to be larger than corresponding tablet formulations, potentially leading to retention in the esophagus. Humidity needs to be considered during manufacture and storage, with moisture leading to stickiness and desiccation causing brittleness. Cross – linking of gelatin in the formulation can also lead to dissolution and bioavailability concerns.

Capsule excipients are similar to those required for formulation of tablets and include diluents, binders, disintegrants, surfactants, glidants, lubricants, and dyes or

colorants. The development of a capsule formulation follows the same principles as tablet development, and consideration should be given to the same BCS issues. The powder for encapsulation can comprise simple blends of excipients or granules prepared by dry granulation or wet granulation. There is a reduced requirement for compressibility, and often the fl ow properties are not as critical as in an equivalent tablet formulation. The degree of compressibility required is the major difference, and capsules can therefore be employed when the active ingredient does not possess suitable compression characteristics.

Manufacture of Hard Gelatin Shells

Gelatin is a generic term for a mixture of purifi ed protein fractions obtained either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen. Type A normally originates from porcine skin while B is usually derived from animal bones, and they have different isoelectric points (7.0 – 9.0 and 4.8 – 5.0, respectively) [6] . The protein fractions consist almost entirely of amino acids joined together by amide linkages to form linear polymers, varying in molecular weight from 15,000 to 250,000. Gelatin can comprise a mixture of both types in order to optimize desired characteristics, with bone gelatin imparting fi rmness while porcine skin gelatin provides plasticity. Gelatin Bloom strength is measured in a Bloom gelometer, which determines the weight in grams required to depress a standard plunger in a 6.67% w/w gel under standard conditions. Bloom strength and viscosity are the major properties of interest for formulation of capsules, and Bloom strength of 215 – 280 is used in capsule manufacture.

Gelatin is commonly used in foods and has global regulatory acceptability, is a good fi lm former, is water soluble, and generally dissolves rapidly within the body without imparting any lag effect on dissolution. Gelatin capsules are strong and robust enough to withstand the mechanical stresses involved in the automated fi lling and packaging procedures.

In addition to gelatin, the shells may contain colorants, opacifi ers, and preservatives (often parabens esters). There are eight standard capsule sizes, and the largest capsule size considered suitable for oral use is size 0 (Table 5).

To manufacture the shells, pairs of molds, for the body and the cap, are dipped into an aqueous gelatin solution (25 – 30% w/w), which is maintained at about 50 ° C in a jacketed heating pan. As the pins are withdrawn, they are rotated to distribute the gelatin evenly and blasted with cool air to set the fi lm. Drying is carried out by

TABLECapsule Size and Corresponding Volume or Weight of Fill

Size	Volume (mL)	Fill weight a (g)
000	1.37	1.096
00	0.95	0.760
0	0.95	0.544
1	0.50	0.400
2	0.37	0.296
3	0.30	0.240
4	0.21	0.168
5	0.13	0.104

passing dry air over the shell as heating temperatures are limited due to the low melting point of gelatin. The two parts are removed from the pins, trimmed, and joined using a prelock mechanism. The external diameter of the body is usually wider at the open end than the internal diameter of the cap to ensure a tight fi t. They can be made self - locking by forming indentations or grooves on the inside of both parts so that when they are engaged, a positive interlock is formed (e.g., Posilok, Conicap, Loxit).

Alternatively, they may be hermetically sealed using a band of gelatin around the seam between the body and the cap (Qualicaps). This can be applied without the application of heat and provide a tamper - evident seal. LEMS (liquid encapsulation microspray sealing) used in Licaps is a more elegant seal in which sealing fl uid (water and ethanol) is sprayed onto the joint between the cap and body of the capsule. This lowers the melting point of gelatin in the wetted area. Gentle heat is then applied which fuses the cap to the body of the Licaps capsule. The moisture content of manufactured shells is 15 – 18% w/w and levels below 13% will result in problems with the capsule fi lling machinery. Therefore, capsules are stored and fi lled in areas where relative humidity is controlled to between 30 and 50%.

Hard - Gelatin Capsule Filling

The fi lling material must be compatible with the gelatin shell and, therefore, deliquescent or hygroscopic materials cannot be used. Conversely, due the moisture content in the capsule shells, they cannot be used for moisture - sensitive drugs. All ingredients need to be free of even trace amounts of formaldehyde to minimize cross - linking of gelatin.

Powders and granules are the most common fi lling materials for hard - shell

gelatin capsules, although pellets, tablets, pastes, oily liquids, and nonaqueous solutions and suspensions have been used. Filling machines are differentiated by the way they measure the dose of material and range in capacity from bench - top to high - output, industrial, fully automated machines. Those that rely on the volume of the shell are known as capsule dependent, whereas capsule - independent forms measure the quantity to be fi lled in a separate operation. The simplest dependent method of fi lling is leveling where powder is transferred directly from a hopper to the capsule

TABLE Liquid Excipients Compatible with Hard Gelatin Capsules

Peanut oil	Paraffi n oil
Hydrogenated peanut oil	Cetyl alchohol
Castor oil	Cetostearyl alcohol
Hydrogenated castor oil	Stearyl alcohol
Fractionated coconut oil	Stearic acid
Corn oil	Beeswax
Olive oil	Silica dioxide
Hydrogenated vegetable oil	Polyethylene glycols
Silicone oil	Macrogol glycerides
Soya oil	Poloxamers

body, aided by a revolving auger or vibration. Additional powder can be added to fi ll the space arising, and the fi ll weight depends on the bulk density of the powder and the degree of tamping applied.

Most automated machinery is of the independent type and compresses a controlled amount of powder using a low compression force (typically 50 – 200 N) to form a plug. Most are piston - tamp fi llers and are dosator or dosing disk machines. The powder is passed over a dosing plate containing cavities slightly smaller than the capsule diameter, and powder that falls into the holes is tamped by a pin to form a plug. This can be repeated until the cavity is full and the plugs (or slugs) are ejected into the capsule shells. The minimum force required to form a plug should be used to reduce slowing of subsequent dissolution.

In the dosator method, the plug is formed within a tube with a movable piston that controls the dosing volume and applies the force to form the plug. The dose is controlled by the dimensions of the dosator, the position of the dosator in the powder bed, and the height of the powder bed. Fundamental powder properties to ensure even fi lling are

good powder fl ow, lubricity, and compressibility. The auger or screw method, now largely surpassed, uses a revolving archimedian screw to feed powder into the capsule shell.

A liquid fi ll can be useful when manufacturing small batches if limited quantities of API are available. Liquid fi lls also offer improved content uniformity for potent, low - dose compounds and can reduce dust - related problems arising with toxic compounds. Two types of liquid can be fi lled into hard gelatin capsules: nonaqueous solutions and suspensions or formulations that become liquid on application of heat or shear stress. These require hoppers with heating or stirring systems. For those formulations that are liquid at room temperature, the capsule shells need to be sealed after fi lling to prevent leakage of the contents and sticking of the shells. It is essential to ensure the liquid is compatible with the shell (Table 6).

CAPSULES, HARD

INTRODUCTION

Hard or two-piece capsules were first produced on an industrial-scale in U.S.A. in the 19th century and are now produced throughout the world.[1] Hard capsules are welcomed by consumers because of their elegant appearance and shape, which are easy to swallow.

The majority of capsule fills are dry powder blends, which are typically simple mixtures. The processing and filling of materials involves minimum stress and is one of the reasons why products are presented in this form. The formulator is able to prepare products that have the desired release characteristics, rapid, controlled, or modified release, because of the limited number of factors involved. Hard capsules can be filled with formulation that have a wide range of physical properties from dry solids to non-aqueous solutions, thus enabling the formulator to use many different types of excipient to achieve their desired effect. Capsule products can be formulated to release their active ingredients at many sites along the gastrointestinal tract and to deliver them to the lungs.

RAW MATERIALS

Gelatin and Alternative Materials

Gelatin is a material derived from collagen, a natural protein, which occurs in the skins, bones, and connective tissues of animals.[2] It is insoluble in water and is solubilized by hydrolysis. The raw materials used for its manufacture are obtained

mainly from bovine bones or porcine skins. The reaction can be carried out at an acid pH giving a type A gelatin (primarily produced from skins) and at a basic pH giving a type B gelatin (primarily produced from bovine bones). Gelatin is an ideal material because it is edible, soluble at body temperature, forms strong thin films and undergoes a gelation process at temperatures just above ambient.[1] During the 1990s, there were concerns over the use of bovine materials owing to bovine spongiform encephalopathy, which originated in U.K. The European Commission (EC) instigated several action plans to limit the spread of the disease and to control products of bovine origin. The alkaline hydrolysis process was made the method choice for bones by the EC because of the pH levels and temperatures used in the manufacturing process. For human and veterinary pharmaceuticals, the European Medicines Evaluation Agency (www.emea.eu.int) instituted guidelines controlling the use of such materials. This led to the European Pharmacopoeia including requirements for all products that are at risk and giving rules to minimize this. All manufacturers of materials of bovine origin need to submit dossiers on their products to the European Department for the Quality of Medicines (EDQM: www.pheur.org) to obtain certificates of suitability. These certificates need to be submitted to the regulatory authorities as part of the marketing authorization for a product. In addition, the EU scientific steering committee introduced a system for risk management, which involved assessing countries in terms of their Geographical BSE Risk (GBR). There are four categories ranging form GBR I, highly unlikely, to GBR IV, confirmed at a high level. The GBR category governs the amount of precautions that have to be taken in handling bovine products.

The walls of gelatin capsules are homogenous and very robust, and can readily withstand the mechanical stresses of the filling and packaging operations. The main draw back in the use of gelatin is that it contains water, which acts as a plasticizer to the film. Their properties will change if they are not stored properly, and when water is lost, they become brittle and thus are not suitable for hygroscopic formulations. Moisturelabile substances cannot be filled into them. For certain markets, there are consumer requirements for a capsule of vegetable origin. The primary problem to overcome in finding a gelatin substitute is the need to obtain a system that gels in a similar manner to gelatin so that the same manufacturing machines and processes can be used. Since 1990, several polymers have been proposed for capsule manufacture: hypromellose, pullulan, chitosan, and pondac [copolymer of polyvinyl alcohol (PVA) and methacrylates]. Hypromellose has been the most successful one because it overcomes the problem of

brittleness when the capsules are exposed to dry conditions.[3] All the other polymers proposed suffer from this defect to some extent. Hypromellose solutions are converted into gelling system for use on standard manufacturing machines by adding a material to act as a network former, such as carrageenan or gellan gum, and a gel promoter such as potassium chloride or citric acid. Hard capsules made from hypromellose have similar but different properties from gelatin ones. Their main advantage is that their moisture content is much lower, and even if this is removed, they retain their mechanical strength.[3] Under International Conference on Harmonization (ICH)-accelerated storage conditions (40_C, 75% relative humidity (RH), for six months), they do not undergo cross-linking reactions like gelatin, and the dissolution rate of products in hypromellose capsules is unchanged.[4] Another major difference is that hypromellose capsules from different manufacturers are not interchangeable like gelatin capsules, which have the same solubility properties from all manufacturers. This is because the gelling systems used are patented, and only the ones containing carrageenan are soluble at pH < 4.0,[3] whereas, for example, those containing gellan gum are not soluble at acid pH.[5]

Gelatin capsules are also produced, which contain 5% Polyethylene glycol (PEG) 4000 as an additional plasticizer. They have improved physical characteristics over standard gelatin capsules and can loose more moisture before they become brittle. They were first developed by Shionogi Qualicaps in Japan, where they are widely used for pharmaceutical products.

CAPSULE MANUFACTURE

Gelatin capsules are manufactured by a dipping process.[1] The process starts by the preparation of a concentrated solution of gelatin or other suitable polymer in hot demineralized water. This solution is subjected to a low pressure to remove entrapped air bubbles. Small aliquots of this solution are (20–30 L) are taken. To this are added colorants, either solutions of soluble dyes or suspensions of pigments, preservatives, process aids, such as disodium lauryl sulfate solution, and water to adjust the viscosity. The final solution has a concentration of 25–30 wt% of gelatin. This solution is then delivered to the capsule-manufacturing machine.

The manufacturing machines are housed in rooms supplied with filtered air, conditioned to 40–45% relative humidity and 22–25_C. The most commonly used machines are approximately 12m long and 3m high and are divided down the midline into two parts that are mirror images of each other (Fig. 1). The machines are divided

lengthwise into two levels, a top and a bottom. The caps are made on the left side and the bodies on the right side of the machine. The gelatin solutions are held in temperature-controlled, jacketed hoppers

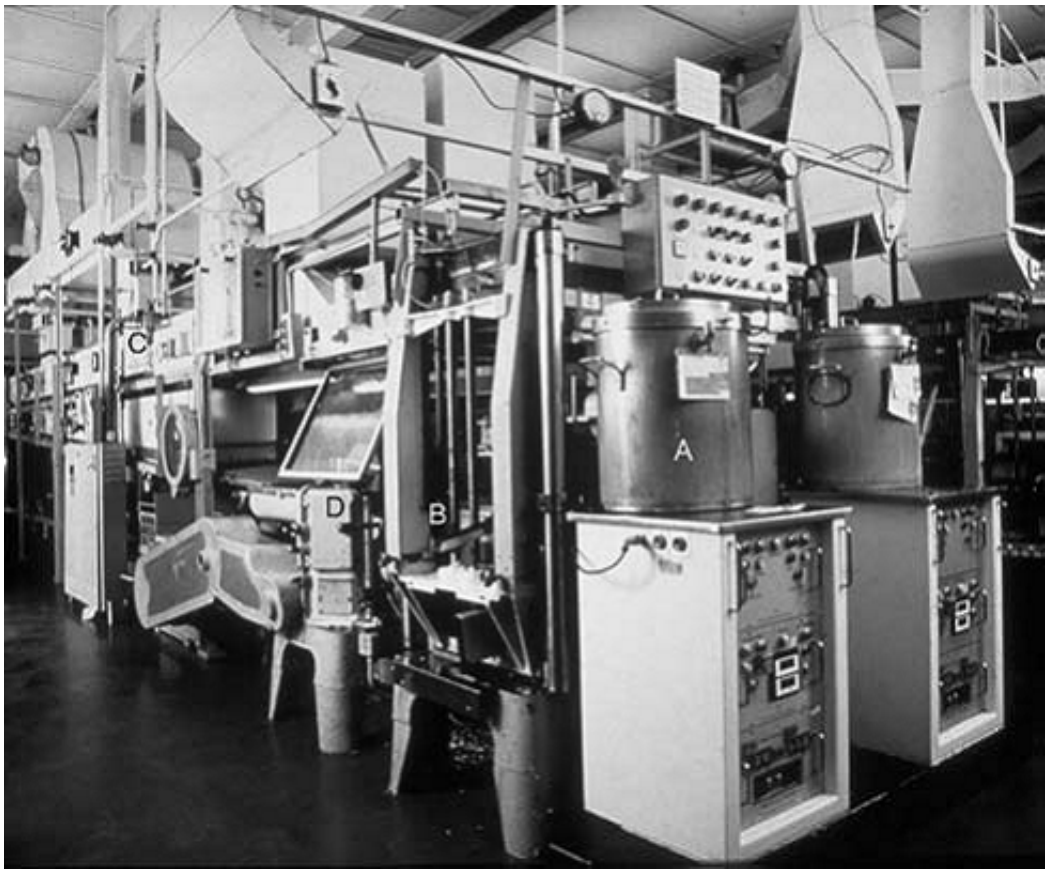

Fig. A capsule manufacturing machine: (A) gelatin solution storage tank; (B) dip pan; (C) drying kilns; and (D) Automatic section. (Reprinted with permission from Eli Lilly & Co. Ltd.)

mold pins are mounted in a row of 30 on steel bars. Sets of bars are held in a device operated by a cam, which raises and lowers them. The mold pins, which are at 22_C, are lowered into the gelatin solution, which is at 50–55_C. The gelatin immediately gels on the mold. The molds are slowly raised, and, as they do, the excess gelatin runs off (Fig. 2). The quantity picked up by the mold is proportional to the viscosity. The higher the viscosity of the gelatin solution, the more the gelatin that is picked up. Thus, the viscosity of the solution is used to control the thickness of the gelatin film. As the mold breaks the surface, a blob of gelatin forms on the end of the mold. The sets of bars are transferred from the bottom to the top level of the machine and, as they do so, the bars are rotated

Fig. Dip pan, capsule shell formation. (Reprinted with permission from Qualicaps Europe, S.A.)

to spread the film evenly over the end of the mold pin. The gelatin film is completely set by the time the molds reach the upper level of the machine. Sets of bars are grouped together and mechanically transferred through a series of drying kilns (Fig. 1C). In these, air at controlled temperature and humidity is blown over them. When the bars reach the end of the machine, they are transferred to the lower level and pushed back toward the front of the machine. When the bars emerge from the drying kilns, the moisture content of the gelatin films has been reduced from 70%, at dipping to approximately 16 wt%. The molds, which had been warmed at the start of the drying process, have returned to ambient machine room temperature before they are dipped again.

The dried gelatin films are removed from the mold pins and cut to the correct lengths, and the cap and body pieces are joined together. This is done in the automatic section of the machine (Fig. 1D). Pairs of bars, one with bodies and one with caps, are passed into the central section. Metal jaws pull the films off of the mold pins into collets, which grip them. The collets rotate against a knife, and the gelatin film is cut. The excess

is sucked away and recycled. The two pieces are transferred to a central joining block and are closed to a set length, called the unclosed joined length. The capsules are not fully closed, because the filling machines would have difficulty separating them. They are closed so that the ‘‘prelock’’ indentations on the cap are engaged by the body, which provides sufficient holding strength so that they will not separate in handling.

Hypromellose capsules are manufactured using the same conditions to similar specifications. The main difference in the process is that the speed of output is slower because their gelling system takes longer to set than gelatin solutions, which rapidly change from the sol to the gel state.

STANDARDS FOR EMPTY CAPSULES

Two sets of standards are set for empty capsules, analytical and functional.[1] Capsules, like all other pharmaceutical preparations, must comply with cGMP norms and must be made of materials that comply with pharmacopeial chemical and microbiological standards. However, these tests do not indicate whether a capsule will run well on a filling machine. Series of functional tests are applied by the manufacturers. The critical dimensions of a capsule (the lengths and diameters of the caps and bodies) are checked. It is a continuous production process, and there will be a very small proportion of visually defective capsules. Standard statistical sampling methods are used to estimate quality fromsamples. The manufacturers and users agree on acceptable quality levels (AQL). The faults are divided up into three categories depending upon the likely impact on capsule performance or the filling process. A different AQL is assigned to each category of fault.

STORAGE OF EMPTY CAPSULES

Capsules should be stored in sealed containers at uniform temperatures to maintain their properties. Empty gelatin capsules have a moisture content between 13% and 16%. The water acts as a plasticizer and is essential to maintain the flexibility and strength of the capsule. They will become brittle if the moisture content falls outside of the limits and soften if it increases above it. Empty hypromellose capsules have a moisture content of 3% to 6%. These capsules can be dried down to less than 1% moisture without losing their mechanical strength and becoming brittle.[3] The water in hard gelatin capsules is tightly bound into the polymer structure and is insufficient for active bacterial growth.[2]

The dimensions of capsules vary slightly as their moisture changes. As a general

rule, the dimensions of gelatin capsules change by 0.5% for every 1% change in moisture in the range 13.0–16.0%.[1] Hypromellose capsules contain less water than gelatin ones, and their change in dimensions with moisture content is less. Thus, higher-speed filling machine must be operated in air-conditioned areas to achieve their maximum performance. The moisture content of capsules depends upon the conditions to which they are exposed.[6] Water will be lost or gained, and the absorption/desorption isotherm follows a marked hysteresis. In practice, this means that if capsules lose excessive amounts of water, they will not fully rehydrate when exposed to standard conditions, RHs between 35% and 55%.

CAPSULE FILLING

The hard two-piece capsule can be filled with materials that have a wide range of physical properties. The types of formulations that have been filled into capsules are shown in Table . This is possible because of the

Table Formulation types for filling into hard capsules

Dry solids	Semisolids	Liquids
Powders	Thixotropic mixtures	Oily liquids
Granules	Thermosoftening mixtures	Non-aqueous solutions and suspensions
Pellets	Pastes	
Tablets		
Capsules		

way in which filling machines handle empty capsules. First, capsules are orientated so that they are all pointing in the same direction, with the body downwards. The capsules are transferred into pairs of bushes: the opening in the base of the top one only allows the passage of the body, thus retaining the cap. The body is separated from the cap by means of suction. The open end of the body is then presented to a dosing mechanism and material transferred into it. The cap is replaced on the body, and the capsule closed to the correct closed joined length to ensure that the self-locking mechanism, a series of indentations on the cap and body, is engaged correctly. This allows filled capsules to be transported and packaged on automatic equipment without them separating.

Filling machines are differentiated by the means by which they measure the dose of material. They are available with a range of outputs, from bench-scale to high-output industrial scale and from manual to fully automatic.

Powder Filling

The majority of formulations that are filled into capsules are dry powder mixtures. The methods of measuring the dose can be divided up into two groups: dependent and independent. The dependent machines use the capsule body directly to measure the dose of powder, whereas the independent machines use a separate device. The literature available on the mechanics of capsule filling is limited when compared to that available for tabletting. Part of the reason for this is that tablets, unlike capsules, are used in a wide range of industries outside the health-care sector, and thus there have been many more workers in the field.

The first industrial filling machines were of the dependent type. Powder is transferred from a hopper directly to the capsule body. The flow of the powder is aided either by a revolving auger or by a vibrating plate. The powder mass inside these capsules is a loose fill. The fill weights achievable on an auger machines are often higher than that obtained on automatic independent type machines because the body is overfilled, and thus the total internal volume of the capsule shell is used.[7] The first successful industrial filling machine, the Model No. 8, was designed by the American doyen of pharmaceutical engineering, Arthur Colton. This is a semiautomatic auger-filling machine (Fig. 3). The empty capsules are fed, aided by suction, into a pair of doughnut-shaped plates, which separates them. The upper plate containing the caps is removed and placed to one side. The lower plate containing the bodies is transferred manually to a turntable and the powder hopper pulled over the top of it. Powder is forced by the auger into the bodies as their plate

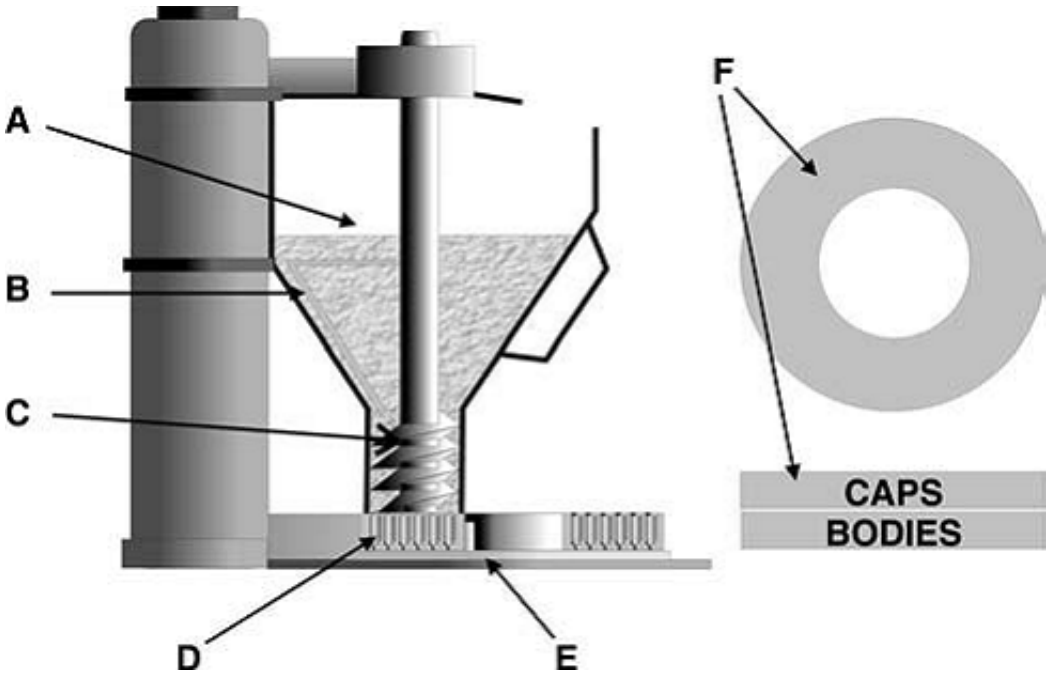

Fig. Schematic diagram of auger filling system (Model No. 8): (A) powder hopper; (B) stirrer arm; (C) auger; (D) body ring holder; (E) turntable; and (F) capsule carrying rings.

revolves under the hopper. The fill weight is controlled by the speed of rotation of the turntable and the auger. The only way on these machines to achieve good uniformity of fill weight is to completely fill the bodies. Partial filling is not an option. A fully automatic rotary auger-filling machine (LIQFILsuper JCF40/80TM, Shionogi Qualicaps) has a three-roller system for capsule orientation and continuous feeding to a revolving disk assembly where the capsules are separated, filled, and rejoined. Other automaticdependent filling does not use augers, but vibration to fluidize the powder for filling into the bodies as they pass underneath the hopper. This system works well only with dense, free-flowing material. The LIQFILsuper 40 & 80TM (Qualicaps) has overcome this problem by the use of spring-loaded fingers to further compress the powder into the capsule body after the initial fill.

Most automatic machines used in industry are of the independent type and compress the measured amount of powder to form a plug. There are two types of mechanism: the dosing tube (or dosator) and the dosing disc and tamping finger.

The dosing tube is the most widely used type. Current manufacturers are IMA (Zanazi & Farmatic) (IMA North America Inc.), MG2 (MG America Inc.), Macophar (Romaco Inc.), and Bonapace (Schaefer technologies Inc.). The plug is formed inside a

tube with a moveable piston that controls the dosing volume and applies a force to form the plug (Fig. 4). The lower output machines have an intermittent motion, whereas the higher output machines are rotary. The intermittent machines tend to apply greater stresses to the powder than the rotary machines, because there is less time in which to form the plug because a significant portion of the machine cycle is taken up in indexing the parts. Thus, formulations for these machines tend to require a higher level of lubricant. These machines are very versatile because the fill weight can be varied

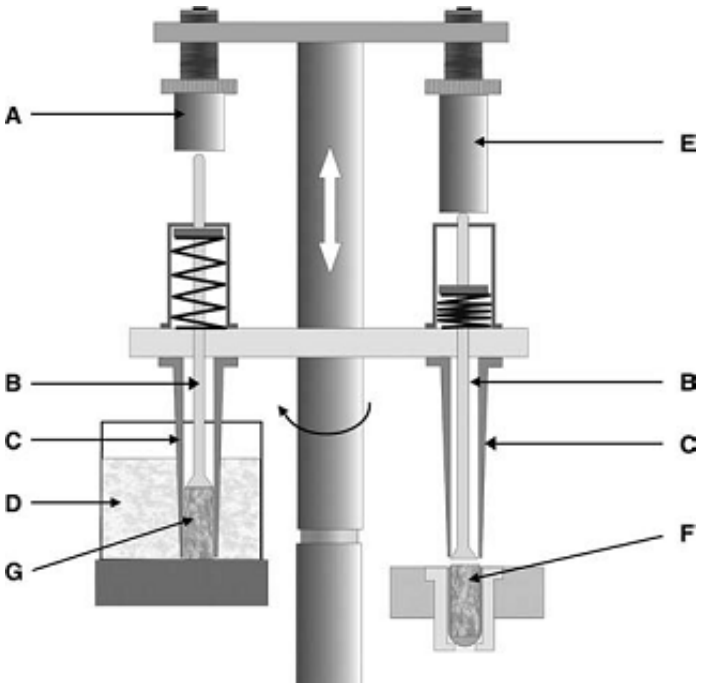

Fig. Diagram of a dosator or dosing tube system (Zanasi RM63): (A) compression force platen; (B) piston; (C) dosing tube; (D) powder hopper; (E) plug ejection platen; (F) capsule body in bush; and (G) powder plug.

over a wide range by a simple adjustment to the piston position. The rotary machines can be linked to checkweighing devices that can control the fill weight automatically, and allow them to operate unattended.

The dosing disc and tamping finger machines form a plug in a similar but different manner. They are produced by a number of companies, Bosch (Robert Bosch Corporation), A. W. Bohanan Co. and Index Manufacturing Co., Inc. The dosing disc, which forms the base of the powder hopper, has up to six sets of machined holes (Fig.). In a holder, above the powder hopper, there are sets of stainless steel-tamping fingers corresponding to the holes in the disc. These machines have an intermittent motion. After the machine has indexed and the turret is stationary, the tamping fingers are lowered into

the powder bed. The fingers are set to different levels, and they penetrate into the plate and consolidate the powder in the cavities into plugs. Thus, the plug is formed in a series of tamps and not in a single action as on the dosator machines. The dosing discs are produced in a range of thicknesses for each size of capsule. Thus selection of the correct thickness of disc is important, because if the fill weight cannot be achieved, the machine has to be dismantled to change it. The selection of the optimum disc thickness for a formulation can be made either pragmatically using a simple test rig[8] or systematically by using an Instron tester to determine plug density and strength of a formulation at known compression forces.[9] The latest developments on the Bosch series of

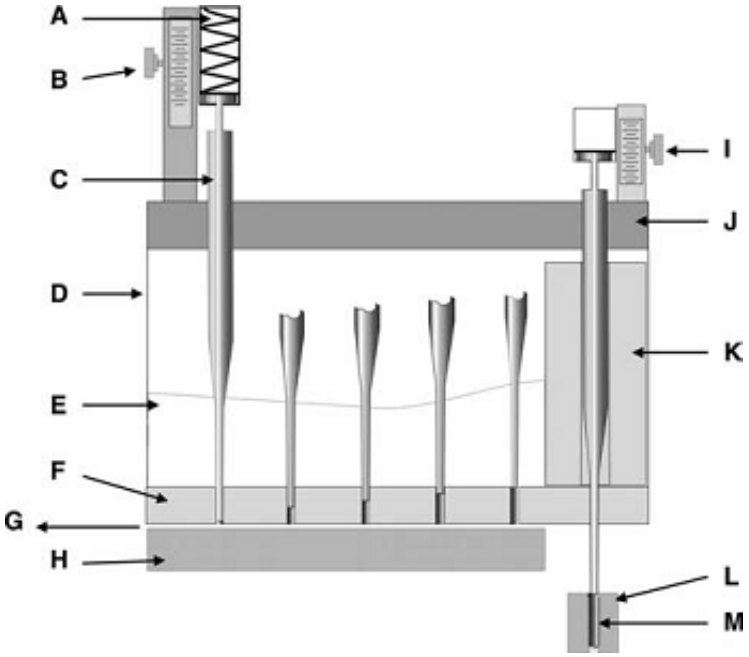

Fig. Schematic diagram of a dosing disc and tamping finger system (Bosch GKF machine): (A) over-load relief spring; (B) tamp-depth adjuster; (C) tamping finger; (D) powder hopper; (E) powder bed; (F) dosing disc; (G) suction; (H) support plate; (I) ejection adjuster; (J) guide block; (K) transfer block; (L) capsule body in bushing; and (M) powder plug.

machines are a dosing disc with an adjustable thickness, which gives a greater flexibility for altering fill weights after machine setup, and a weight-checking device that can weigh every capsule filled, as it exits the machine.

Bench-Scale Filling Machines

There are a variety of devices for the manual filling of small numbers of capsules. These typically consist of sets of plastic plates that have sets of holes drilled in them corresponding to the size of capsule that can be filled. A device made from stainless steel and other metal alloys is available from Torpac Inc., which can be autoclaved to ensure cleanliness without the risk of distortion. The capsules are fed in to the plates, either manually one at a time or in groups using a feeding device. The bodies are clamped in the lower plate and the top plate removed, which separates the caps from the body. The bodies are released so that they sit below the top of the bottom plate. Powder or pellets are filled into the capsules by spreading material over the body plate using a spatula.

A small-scale automatic machine, the In-cap_, Dott. Bonapace (Schaefer Technologies Inc.) is available. This machine measures the dose using a tamping finger and dosing disc device. The output is up to 3000 capsules per hour.

Instrumented Filling Machines

Instrumented capsule filling machines are not in widespread use unlike tabletting machines.[10] This is partly owing to the fact that less basic work has been done; there is an inherent problem in measuring the low forces (1–100 N) used in forming and ejecting plugs, and the powder bed is less controlled than in a tablet die. Most of the published studies have been made on intermittent motion dosing tube machines. Strain gauges have been applied to the piston and linear variable displacement transducers (LVDTs) to the moving parts of the system to measure the work involved in plug formation.[11] Only two groups have published work on an instrumented dosing disc and tamping finger machine.[11,12] The problem on these machines is that the plug is formed at up to five different positions, and full instrumentation would be difficult. Capsulefilling machine stimulators have been constructed to overcome some of the problems inherent in putting instrumentation on to actual machines. Rotary operation machines present the biggest problem because of the movement of the dosing parts. One solution was to use a machine turret, with a single dosator, held stationary, and to construct a rig that moved the powder hopper around the dosator, simulating machine running.[13] A conventional stimulator for an intermittent motion dosator machine has been built that, in addition to the forces of axial compression and ejection, can measure the radial compression force.[14] This has been used to study the consolidation and elastic properties of excipients. A tablet compaction simulator has been used to investigate plug formation at low forces, and the results analyzed using standard tabletting physics.[15]

Dry Solid Filling

Granules, pellets, and tablets can be filled into capsules using automatic-filling machines. Products are prepared in these forms to modify the release rates of active ingredients, separate incompatible components, or densify a product to achieve the fill weight in a specific size of capsule.

The machines that can be used to fill pellets and granules can be divided into the direct and indirect categories. In the former, the pellets and granules are fed into the body until it is completely full, e.g., Qualifill TM Pellet filler (Schaefer Technologies Inc.). Indirect machines have modified dosators that either use suction to hold the material in the tube during transfer or are filled when they pushed up through the material bed. Other indirect machines have special chambers with sliding plates to give a variable volume in which to measure the material, e.g., Bosch GKF and Qualicaps LIQFILsuper machines. Bosch has produced a pellet-filler based on their variable thickness dosing disc that uses a slide underneath it to hold the material prior to transfer. Pellets and granules, after measurement, are transferred to the capsule bodies either using gravity or assisted by air pressure, e.g., IMA Farmatic 2090 and MG2 G60. Tablets are filled into capsules by systems that can handle both single and multiple additions. They have sensing devices, either mechanical or electrical to check that the correct number of tablets has been dosed.

The physical properties of these formulations are similar. Each type must be preferably non-friable; tablets are usually film coated. Several types of tablets are filled into capsules. Generally the tablets are convex in shape and have diameters that enable them to be introduced easily into the body and with sufficient clearance so that they do not tip onto their side.[16] In U.S.A., after the ‘‘Tylenol_ incident,’’ in the 1980s, there is a need to fill large single tablets into a capsule, so that in the shell there is no room for movement. The capsule shell is either banded or shrunk onto the tablet to prevent its removal. A recent innovation is the filling of minitablets, produced on multitip tooling, to produce coated tablets with different release patterns.[17] Granules and pellets should be regular in shape so that they flow and pack well. Their size should be related to the size of the capsule. Smaller diameter pellets should be used for smaller sizes of capsules; otherwise, lower fill weights than expected will occur because of the ‘‘wall effect’’ of particle packing.

Liquid Filling

All the major machine manufacturers have made machines that can fill capsules with liquids. There are two types of liquid fills: formulations of non-aqueous solutions and suspensions and formulations that are liquefied only for the filling process by either heat or shear stress.[18] If the formulation is mobile at ambient temperatures, then the capsules will need to be sealed after filling.

The dose of material is measured, using volumetric pumps, and thus the uniformity of fill is, in most cases, better than what be achieved normally on a powderfilling machine. Typically, coefficients of variation of fill weight less than 1.0% are routinely achievable. This value will depend upon the physical properties of the liquid, particularly its viscosity.[19] Filling machines have been made, which can handle materials with viscosities from 0.1 to 20 Pa. Liquid-filling machines operate mostly at slower speeds than the equivalent powder filling machines. This is because the liquid has to pass through a much smaller orifice than that for a powder and thus takes longer. The rates are typically 50–66% of the rated output of the same size powder-filling machine.

Capsule Fill Capacity

The fill capacity of a hard capsule is dependent upon the physical size of the capsule, the type of formulation, and the dosing mechanism on the filling device (Table 2).[7] The fill weight for powders has historically been calculated by multiplying a powder density value by the capsule volume as provided by the capsule manufacturers. This is the capsule body volume and was derived from practical experience when capsules were filled by hand in pharmacies. The relationship gives a reasonably accurate forecast for machine filling, if the volume number is multiplied by the tapped bulk density (TBD) of the powder mixture. The relationship holds because of the machine-dosing mechanisms. Dependant machines, which can fill the total internal volume of the capsule, are able only to pack the powder in to the bodies at densities less than the TBD of the fill. Independent machines, which are able to apply a higher compressive force to the powder, form plugs whose dimensions must be less than the internal diameter and length of the capsule for them to fit inside of a closed capsule (Table 2). Thus, although the density of the plug will be higher than the TBD of the fill, the machines are unable to fill the total internal capsule volume.

The same rules of packing apply to pellet and granule filling. The size of the particles is important because of the increase in voidage caused by large particles in a small diameter tube. The smaller the capsule size, the smaller the corresponding size of

the particles should be to achieve uniform fill weights. The liquid-fill capacity of capsules is restricted inorder to prevent spillage of product, the maximum fill volume should not exceed 90% of the body volume.

Capsule Sealing

Many methods have been proposed for the sealing of capsules to prevent the leakage of liquids. The method proven to be the most successful is gelatin banding.[18] Two bands of gelatin solution are applied around the center of the filled capsule, e.g., HicapsealTM 40/100 (Shionogi Qualicaps Inc.). This band is dried using air at ambient conditions to prevent moisture loss from the gelatin shells, which would make them brittle. The band can be colored, permitting a more complicated appearance for product branding. This band complies with the requirements of the Food and Drug Administration (FDA) ‘‘Tamper-Evident Packaging Requirements for Over-the-Counter Human Drug Products’’ for tamper-evident sealed capsules.[20]

Multiple Contents

Automatic-filling machines are available, which can have more than one product-dosing device. Therefore, combinations of materials can be filled into the same capsule, such as mixture of a powder and a semisolid formulation or a powder and a tablet. The same formulation rules apply as to single forms. Combinations of materials allow the formulator to achieve specific goals in terms of product stability and types of release.

FORMULATION

Powder Properties

Powder formulations for capsule filling must have good flow properties, be non-adhesive, and be cohesive enough to form plugs at low-compression forces. In addition, they must be stable and release the active ingredient in the desired manner. There is an interaction between the formulation, the filling machine, and the empty capsules, and to devise formulations logically, these need to be understood.[21]

Powder-filling properties can be assessed on the bench scale by using a variety of tests ranging from

Table Capsule fill volume data

Size	Body Volumea	Internal	Maximum Plug	Maximum Plug

	(ml)	Volumeb (ml)	Lengthc (mm)	Volumed (ml)
0E	0.78	0.87	21.9	0.68
0	0.69	0.78	19.7	0.61
1	0.50	0.56	17.7	0.44
2	0.37	0.44	16.1	0.34
3	0.30	0.32	14.3	0.26
4	0.21	0.25	13.2	0.19

simple to complex.[7] Successful correlations between powders and filling performance have been made in several papers by determining various powder property constants calculated from TBD volumetry.[22–25] For various microcrystalline celluloses, Lu¨dde–Kawakita's constant a and Hausner's ratio were shown to be good indicators of machine-filling performance.[22] Investigations on the packing properties of binary mixtures of different shaped particles have shown that Lu¨dde–Kawakita's constant a can be used as an indicator of the maximum volume reduction.[23] Microcrystalline cellulose, an angular particle, and lactose monohydrate improve packing, whereas spherical or needle-shaped particles tend to decrease the packing properties. The same methodology was used to investigate the bulk volume changes of powders after granulation or low compression.[24] This showed that capsule fill weights could be increased by high-shear granulation or by the use of machine compression, and that the outcome was directly related to the initial powder properties. The filling of capsules with powdered herbs present further challenges because of the range of tissue materials used. The flow properties of these materials are poor, and a range of powder property constants was determined to try and find a parameter that correlated with filling machine performance.[25] It was found that tamp-filling machines were able to handle a greater variety of herbs than dosator machines. The flow of powders under active conditions can be measured using specially constructed rheometers, and these data can be related to other powder properties.[26]

The flow of powders on filling machine is aided by machine design. Most machines have devices to assist flow in the form of moving mechanical parts, vibration, or suction pads. Adhesion of material to moving parts, particularly the dose-measuring

devices, is a hindrance to obtaining good fill-weight uniformity. It has been shown that the nature of the surface texture of the dosator is an important factor.[27] To reduce adhesion, the surface of the dosing parts can be coated with different metal finishes, similar to that used for tablet punches and dies.[28]

In Vitro Testing

Pharmacopeias require that hard capsules be tested in the same apparatus as tablets even though they have very different physical properties.[1] Filled capsules contain entrapped air, and most formulations will float on water. Devices are required to ensure that they sink, and these can influence the results obtained. Gelatin and hypromellose are adhesive materials and tend to block wire meshes that form part of the standard equipment. The way in which capsules disintegrate and dissolve is dependent upon several factors such as temperature and nature of the test media.[29] The literature makes reference to the hard capsule effect; however, the literature shows that the rate-controlling step is the nature of the contents and not the shell.[30]

When capsules are placed in an aqueous solution at body temperature (37_C), the walls absorb water and swell.[29] The rate of penetration is proportional to the thickness of the wall. In gelatin capsules, water droplets can be observed on the inside surface of the shell after 30–40 sec. The wall ruptures first at the shoulders of the cap and body, which is the thinnest part of the shell. The rate of gelatin solubility is dependent upon the temperature of the solution.[31] There is a significant decrease as the temperature falls below 30_C, and below about 26_C they are completely insoluble and merely swell and distort. Hypromellose capsules on the other hand have a slower but uniform solubility between 10_C and 55_C.[31] The results for both types of capsules are influenced by the nature of the test media, e.g., the ionic strength of the ions present and the pH.[29,31]

The rotating paddle method is the most frequently prescribed apparatus for measuring the dissolution rate of products in hard capsules. The test is used for manufacturing control purposes and for assessing product stability. When gelatin capsules are stored under ICH-accelerated storage conditions (45_C, 75% RH), their solubility in water decreases with time. This is owing to the formation of a ‘‘pellicle’’ that slows down release.[32] This effect is called cross-linking and can be caused either by interaction between gelatin and compounds containing reactive groups such as an aldehyde [33] or by reorientation of the gelatin molecules to a more collagen-like structure.[2] In the early 1990s, the FDA became concerned with this and initiated a test

program to measure whether this had an effect on product efficacy.[34] They filled acetominophen into capsules that had been stressed by treatment with formaldehyde at two levels and into unstressed shells. They measured the dissolution in water and in simulated gastric fluid (SGF) with and without pepsin. This produced three sets of results, those that pass in all media (unstressed shells), those that failed in water but passed in the SGF (low-stress formaldehyde), and those that failed in all media (high-stress formaldehyde). The capsules were tested in human volunteers. The pharmacokinetic parameters Cmax, Tmax, and lag times could be ranked in order and the areas under the curve (AUC) were identical. However, the products were not considered bioequivalent, because the results from the capsules that failed all the dissolution tests were outside the 80–125% confidence limits when compared to the unstressed capsules. From this study, the U. S. Pharmacopeia introduced a two-tier test for hard capsule dissolution. If the sample does not comply with the test in the required medium, then the test can be repeated by adding enzymes: in water or a solution of pH < 6.8 (add pepsin) or in a solution of pH > 6.8 (add pancreatin). A further study using gamma scintigraphy showed that there was no difference in disintegration in vivo between untreated and medium-stressed gelatin capsules.[35]

Hypromellose does not react with aldehydes or other agents that cause cross-linking of gelatin.[3,4] Hypromellose capsules start to release their contents slightly slower than gelatin ones because of the slower rate of diffusion of water through the shell walls.[31] However, once dissolution has commenced, the rates are similar and the results are comparable.[36]

In Vivo Performance

Capsule products can be formulated to deliver active ingredients to various sites along the gastrointestinal tract or to the respiratory system.[37] Buccal products can be made by filling standard capsules with semisolid matrix formulations, which give the product good sensory characteristics that allow them to be chewed or sucked and the contents retained in the mouth for absorption or action.[38] The capsule shape is a good one for swallowing, because one axis is longer than the other. This enables the tongue to line it up like a torpedo for entry into the throat. Many large tablets are made capsule shaped, the so-called ‘‘caplet,’’ to take advantage of this. The literature shows that, providing the patient takes gelatin capsules with water while upright, they do not stick in the throat any more than and, in fact, probably less than any other solid dosage form.

[39,40] Capsules can be visualized inside the patient either using radio-opaque markers and X-rays or using radioisotopes, such as technetium-99, and *g*-scintigraphy. In the stomach, they disintegrate, and the contents spread depending upon the patient's feeding state, fed or fasting.[41] Capsule products can be retained in the stomach by the use of floating formulations. These are based on the use of hydrocolloids that swell on contact with water, forming a gel that releases the active ingredients by diffusion.[42] Enteric products can be made either by coating the capsule shell with a polymer, which has the correct pH solubility characteristics, or by filling the capsule with coated particles. The challenge facing many formulators is the delivery of small peptides and proteins to the colon. This can be achieved by coating capsules with polymers that will only be broken down in the colon, e.g., mixtures of an azopolymer and a methacrylate polymer[43] or capsules coated with a mixture of ethylcellulose and amylose.[44] Delivery to the colon can also be achieved by using a fill that includes an organic acid and a combination of pH-sensitive coatings, which together deliver the active ingredients to the proximal colon.[45] Capsules can be administered rectally. They can be formulated to give either immediate or a prolonged release.[46] The administration technique is different for other solid rectal forms and they need to be coated with a glidant such as liquid paraffin.

The in vivo performance of gelatin and hypromellose capsules using gamma scintigraphy has been compared by several workers.[5,44,47,48] These have shown that hypromellose capsules with carrageenan disintegrate in the stomach in a similar manner to gelatin capsules.[44,48] Whereas the disintegration of hypromellose capsules with gellan gum is delayed.[5]

Capsules for Inhalation Products

Powders for inhalation products have been filled into capsules, which function as an inert biodegradable package, since the early 1970s.[49] The active ingredient is in a micronized state, and it is either filled directly in to the capsule or more frequently attached to a carrier particle such as lactose. Originally this delivery system was seen only as a way to treat pulmonary conditions. There has been an increased interest in this application recently, because it is seen as being useful for a wider range of therapeutic applications: systemic diseases, non-invasive delivery of peptides and proteins, vaccines, as well as lung diseases.[50] The formulations are filled on automatic machines and because the fill weight is small, i.e., less than 40 mg, microdosators are used. The product is taken using a special inhalation device, a dry powder inhaler (DPI). Powder is

usually released from the capsule shell through holes that are produced by piercing with pins or cut with blades. Thus the physical properties of the capsules especially under low humidity conditions are important. Hypromellose capsules because of their physical properties are ideally suited for this application because of their lack of brittleness when dry and their more flexible walls that are easier to penetrate.[49] The inhalers are breath actuated. When the patient inhales, there is a turbulent airflow through the device that carries the active particles directly into the lungs.

Formulation for Release

Most products are formulated to release their contents into the stomach. The rate-controlling step for release is the nature of the contents inside the capsule. A formulator in preparing a formulation needs to take into account the physicochemical properties of the active ingredient, the nature and type of excipients required, and the filling process. [7,37]

The properties of the active drug that are most significant are its aqueous solubility and particle size. The particle size needs to be chosen carefully. Smaller particles should dissolve faster because of their greater surface area, but when filled inside a capsule they may aggregate together, and the dissolving liquid may not be able to reach the individual particles (Fig. 6)[51] Thus the available surface area of the active ingredient is more important than the actual surface area. Usually, the excipient that is the largest single quantity in the formulation is the filler (diluent), which functions both to increase the amount of fill material for potent active ingredients and to aid in the formation of the powder plug. They can also play a role in the release of the active ingredients. People were first alerted to this in the late 1960s by the diphenylhydantoin incident in Australia, which showed that fillers need to be selected with solubility properties complimentary to those of the active ingredients.[52] Poorly soluble active ingredients are best formulated with soluble excipients. The overall aim should be to make a powder mass that is as hydrophilic as possible. This can easily be done with potent active ingredients, because there is space available inside the capsule to accommodate excipients with the necessary properties, in terms of both flow and solubility. For higher-dose active ingredients, excipients must be chosen, which are active at low concentrations. Thus, disintegration and wetting agents need to be added. Excipients such as starch do not function as disintegrants in capsules like they do in tablets, because the powder fill is much more porous. Sodium Starch Glycolate and Croscarmellose are used, because of their greater

swelling and wicking capability.[53]

Certain excipients that are added to formulations to improve filling-machine performance can have an adverse effect on release,because they are hydrophobic in nature. This is true of lubricants, which are added to formulations to prevent adhesion and to improve flow. The most used excipient in capsule formulations in both U.S.A. and Europe is magnesium stearate.[53,54] This is hydrophobic, and there are many reports in the literature concerning its adverse effect on dissolution rates. However, the relationship between the concentration of magnesium stearate and release rate is not quite as simple as for tablets, in which an increase in amount brings a proportional decrease in release. The reason for this is the very different nature of tablets and capsules. A tablet is compressed using high forces to form a solid compact of relatively low porosity and must be if it is to survive subsequent handling. A hard capsule product, on the other hand, contains a powder mass of high porosity, which may or may not have been compressed in to plug, and is contained within the shell that can withstand handling. Magnesium stearate functions as a lubricant when it is dispersed on the surfaces of other particles. At this site, it also reduces the cohesion between particles, and thus as its concentration increases, the powder mass will ecome less cohesive. Several workers have shown that an increase in magnesium stearate concentration has increased dissolution rates: small particles are made less cohesive (Fig. 7),[55] and powder plugs are weakened, thus breaking apart more readily when the capsule shell has dissolved (Fig. 8).[56] If the level in the formulation is not optimized, then there is a possibility that during the filling operation, the magnesium stearate will be gradually dispersed to a greater extent, resulting in changes in dissolution or weight uniformity.[7,57]

The method to improve the release rate of poorly soluble active ingredients by dissolving or suspending them in polyethylene glycol was first suggested in 1970.[58] Since then, the filling of semisolid matrix formulations for filling into hard capsules has been developed, which enables this simple concept to be turned into a practical application.[18] This formulation technique gives a different means to control the release of active ingredients from a capsule, either improving or delaying release. The technique involves dispersing or dissolving the active ingredients in excipients that are available in a range of melting points and hydrophile–lipophile balance values.[18] It is possible to modify the release rate of an active ingredient from such a matrix capsule by simply changing the properties of the single excipient. This technique has the added advantage

that when working with potent and toxic material, it significantly reduces cross-contamination within an area.[59] The active ingredients once dispersed in a semisolid matrix are safe to handle without resorting to the use of expensive containment areas, i.e., any material that is spilt does not spread through the local environment, unlike a powdered material.

Formulation optimization and expert systems

Product formulations must meet a number of goals. They must be able to be filled by machines to give a uniform stable product. They must release the active ingredients in a manner to give the desired therapeutic effects. They must comply with the regulatory and compendial specifications. The excipients used in formulations often have properties that aid in compliance with one aspect but, at the same time, can have a negative effect on another goal. The relationship between the factors is complex. There are a variety of statistical tools that can be used to optimize formulations to achieve the best values of all the factors.[60]

Another method of obtaining the best formulation is to use a so-called expert system to devise a formulation. The computer software is based on the use of neural networks and knowledge-based systems.[61–63] They serve two functions. First, they are able to reduce development time by suggesting the probable formulations, and secondly, they act as a teaching tool to pass on the knowledge of experts in the field.

CAPSULES, SOFT

Soft gelatin capsules (Softgels) offer the possibility of delivering a liquid in a solid oral dosage form. Softgel's ability to enhance bioavailability not only makes it the preferred dosage form for new chemical entity with poor bioavailability owing to poor aqueous solubility, but also for reformulation of marketed drugs with the purpose of life cycle extension. This entry reviews the fundamental requirements and techniques in Softgel formulation, manufacturing, and product development. The review of recent advances in this dosage form, such as non-gelatin-based Softgel, modified release/controlled release Softgel, and chewable Softgel are also included.

BACKGROUND

Soft gelatin capsules (also referred to as soft elastic gelatin capsules, Liqui-Gels_, or Softgels) are a unique drug delivery system that can provide distinct advantages over

traditional dosage forms such as tablets, hard-shell capsules, and liquids. However, owing to economic, technological, and patent constraints, there are relatively few manufacturers of Softgels in the world.[1]

The major advantages of Softgels include the following:

- Improved bioavailability. More than 40% of the NCEs (new chemical entity) discovered have good membrane permeability but poor aqueous solubility (i.e., Biopharmaceutics Classification System II).[2] By formulating the NCE in solution inside a Softgel (e.g., lipid based) or in micro/nano emulsion, the solubility and hence the bioavailability of the compound may be improved.[3]
- Enhanced drug stability (protection against oxidation, photodegradation, and hydrolysis in lipophilic systems).
- Superior patient compliance/consumer preference and pharmaceutical elegance. Results of studies done through the years show that consumers expressed their preference for Softgels in terms of ease of swallowing, perceived speed of delivery, lack of unpleasant odor or taste and modern appearance.[4]
- Excellent dose uniformity.
- Better tamper evidence (tampering leads to puncturing and visible leakage).
- Safer handling of highly potent or cytotoxic drug compounds.
- Product differentiation (through selection of novel shapes, colors, and sizes).
- Excellent product life-cycle management. For example, product enhancement via faster onset of action.[5–8]

In comparison, the disadvantages of Softgels are relatively few. These include the following:

- Specialized manufacturing equipment requirements.
- Higher manufacturing cost as compared to tablets.
- Stability concerns with compounds susceptible to hydrolysis.

Softgels are formed, filled, and sealed in a single operation. Once production for a specific product begins, the manufacturing process normally continues 24 hr per day until the lot of product is completed. This results in a manufacturing environment that operates around the clock, up to seven days a week.

The standard Softgel shapes for oral pharmaceutical products are oval, oblong, and round. The size of the Softgel is represented by a numerical number, which represents its nominal capacity in minims (1 cc j 16.23 minims). For example, an 11 oblong Softgel

can be filled with 8.5–11.0 minims of fill formulation.

Softgels can be easily manufactured in any shape with a plane of symmetry and any size (to contain up to _25 ml) via appropriate die design. A recent survey has shown that smaller sized Softgels are preferred within each shape category, with oval being the most popular shape.

Fig. Examples of Softgels.

DESCRIPTION

The Softgel (Fig. 1) is a hermetically sealed, one-piece capsule shell with a liquid or semisolid fill without a bubble of air or gas (Fig. 2). The fill materials can include a wide variety of vehicles and can be either a solution or a suspension. Though the Softgels may be either clear or opaque, it is standard practice to use a clear shell (clear colored or natural amber) only when the fill is also a clear solution. In the finished product,

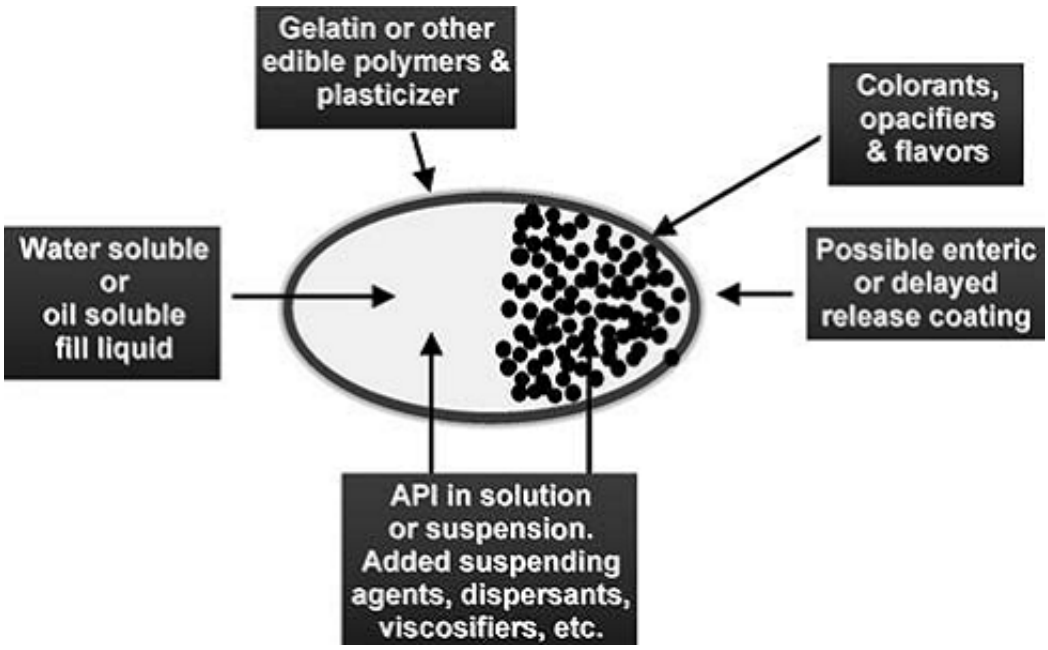

Fig. Softgel components.

the shell historically is primarily composed of gelatin, plasticizer, and water. Recently, shells composed of non-gelatin materials[9–11] (e.g., starch/carrageenan) have been developed for Softgel applications. Softgels may be coated with suitable enteric coating agents, such as cellulose acetate phthalate, to obtain enteric release of encapsulated material.[12]

Because of their special properties and advantages, Softgels are used extensively in many pharmaceutical, cosmetic, and nutritional products. The primary pharmaceutical applications include oral dosage forms, chewable Softgels, suppositories, and topical products.

VEGICAP SOFT_ CAPSULES

VegiCap Soft_ capsules are an alternative patentprotected Softgels that deliver all of the key attributes of traditional soft gelatin capsules without gelatin. They are made using a modification of the Scherer rotary die encapsulation machines.

VegiCap Soft_ capsules provide some technical benefits that gelatin-based capsules cannot provide. One of the disadvantages with gelatin capsules is the incompatibility with alkaline fill solution. VegiCap Soft_ shell is compatible with fill solution with pH value as high as 12.[13]

FORMULATION DEVELOPMENT

This section will discuss the formulation principles of Softgels, including gelatin shell and fill formulations.

Shell Formulation

Historically, Softgels have required gelatin as the polymer basis for the shell. The most frequently used gelatins are derived from bovine source. Gelatins derived from poultry, fish, or other sources have been reported in the literature as alterative for bovine and porcine gelatins. However, they have not gained high commercial interest yet because their availability is limited. In addition to the base polymer, plasticizer, water, and materials that impact the desired appearance (colorants and/or opacifiers) and, on occasion, flavors and/or preservatives are added. For starch/ carrageenan, a shell buffer (sodium phosphate dibasic) is also required. When required, enteric or delayed release coatings can also be applied to Softgel capsules. A description of the functions, types, and amounts of materials most often used in manufacturing Softgel shell formulations is detailed in the following paragraphs.

Gelatin

For gelatin-based Softgels typically 40–50% of the wet gel formulation can be either Type A (acid processed) or Type B (alkali processed) gelatin. The selection for the type of gelatin for a particular Softgel formulation is based on compatibility with the other ingredients (both active and inactive) within the Softgel and upon manufacturing experience. The physicochemical properties of gelatin are largely controlled by the source of collagen, extraction method, pH, thermal history, and electrolyte content.

Plasticizers

Plasticizers are used to make the Softgel shell elastic and pliable. The ratio of plasticizer to shell polymer determines the hardness of the shell, assuming there is no effect from the fill. Plasticizers generally account for 20–30% of the wet gel formulation and are commonly glycerin, sorbitol, or propylene glycol, either individually or in combination. Several proprietary blends of sugar mixtures with sorbitol anhydrides can also be used and are available from excipient suppliers.[14,15] The amount and choice of the plasticizer help to determine the hardness of the final product, and may also affect the dissolution or disintegration of the Softgel, as well as its physical and chemical stability. Plasticizers are selected on the basis of their compatibility with the fill formulation, processing (drying) time, and desired properties of the final Softgels, including hardness,

appearance, handling characteristics, stability, and even the geographical location in which the product will be sold.

Water

Water usually accounts for 30–50% of the wet gel formulation and is critical to ensure proper processing during gel preparation and Softgel encapsulation. Following encapsulation, excess water is removed from the Softgels through controlled drying, leaving the equilibrium water content typically at less than 10%.

Colorants/opacifiers

Colorants and opacifiers are typically used at low concentrations in the wet gel formulation. A wide range of colorants such as FD&C and D&C water-soluble dyes, certified lakes, pigments, and vegetable colors have been incorporated into Softgel shells alone or in combination to produce the desired color, tint, or hue for product identification. A general rule in color selection is that the color of the capsule shell should be similar to or darker than the fill material to reduce the contrast with the seams.

An opacifier is sometimes added to the Softgel shell to obtain an opaque shell for suspension fills or to protect light sensitive fill ingredients. Titanium dioxide is the most commonly used opacifier. Flavors such as ethyl vanillin and essential oils are sometimes included in the Softgel shell to impart desirable odors or flavors or to offset odoriferous materials that may be contained within the Softgel itself.

Fill Formulation

Softgels can be used to dispense active compounds that are formulated as a liquid or semisolid solution, suspension or microemulsion preconcentrate.

The large groups of liquids that can be encapsulated into Softgels fall into one of two categories: watermiscible liquids and water-immiscible liquids.[16]

Water-miscible liquids include polyethylene glycols (PEG) and non-ionic surfactants, such as the polysorbates. Low molecular weight grades of PEG (e.g., PEG 400) are used most commonly as they remain liquid at ambient temperatures. Small amounts (up to 5–10%) of other water-miscible liquids, such as propylene glycol, ethanol, and glycerin, can also be used.

Water-immiscible liquids include vegetable and aromatic oils, aliphatic, aromatic

and chlorinated hydrocarbons, ethers, esters, high molecular weight organic acids, and some alcohols.

Liquids that are likely to cause problems following encapsulation are low molecular weight water-soluble and volatile organic compounds, such as some alcohols, acids, ketones, and esters; water (above 5%); emulsions (whether oil in water or water in oil); liquids with extremes of pH; and aldehydes.

Drugs that are not sufficiently soluble in a solvent or combination of solvents can be formulated into suspensions and encapsulated. Suspension formulae present different challenges to solutions. Drug solubility in the excipients should be kept to a minimum to reduce the chance of particle size or polymorphic changes during the shelf life. In addition, drug particle size needs to be controlled to (i) provide better process reproducibility and (ii) for poorly water-soluble drugs, to reduce the negative effect upon bioavailability.

The particle size of insoluble drugs should be 180 *m*m or finer for suspension homogeneity and capsulation equipment requirements. Examples of suspending agents for water immiscible vehicles include paraffin wax, beeswax, and hydrogenated vegetable oil, and for water miscible vehicles include solid glycol esters (such as higher molecular weight PEG). Surfactants, such as polysorbates, are often added to the dispersion to promote wetting of the ingredients and/or dispersion of the fill in vivo. In general, many different materials may be encapsulated; however, limitations exist for some compounds owing to high solubility in water and/or inherent chemical reactivity and the resultant effect on the shell. These compounds include strong acids and alkalis and their salts, as well as ammonium salts. Some compounds, such as aldehydes, can react with gelatin, causing cross-linking and resulting in a product that lacks bioavailability. Some surfactants interfere with the gelatin sealing process, leading to leaking capsules. In addition, any substance (such as aspirin) that is unstable in the presence of moisture may also exhibit unacceptable chemical stability in Softgels.

PRODUCT DEVELOPMENT

This section will describe the typical stepwise process by which Softgels may be developed. The steps generally include fill formulation development, shell compatibility, prototype development (lab scale encapsulation), experimental batch manufacture (process development), clinical supply and conclude with a product performance review

of the manufacturing process and specialized formulation approaches to enhance pharmacokinetic performance.

Fill Formulation Development

The Softgel process relies on the use of a positive displacement pump for fill dosing. These pumps are capable of dosing a reasonably wide range of viscosities (up to 10,000 cps or more), though there are several other factors, which may affect the dosing of a particular formulation, most notably the rheological properties. The fill liquid is typically either a solution of drug or a suspension (rather than both in the same capsule), and is generally designed to fit in the smallest possible Softgel with acceptable chemical and physical stability, therapeutic effectiveness, and production efficiency. Solutions are generally the first choice, as they may help reduce the negative effect of drug particle dissolution upon bioavailability. For solution formulae, the challenge is generally to develop a solution that is robust enough to remain in solution throughout manufacturing and shelf life, whilst concentrated enough to produce a Softgel size capable of satisfying requirements for patient compliance and economics. It is very important to note that, when formulating the fill material for Softgel encapsulation, appropriate consideration is given to the shell development at the same time. It is commonly and erroneously assumed by those not skilled in the art of Softgel manufacture, that the shell is inert and undergoes no changes itself nor imparts any changes on the encapsulated material.

The first step in developing a solution containing Softgel is to determine the solubility of the drug in a range of pharmaceutically acceptable solvents. After the solubility is determined, the solvents are selected on the basis of their regulatory acceptability and known compatibility with Softgel dosage forms. The types of excipient typically include the following:

- Hydrophilic solvents
- Lipophilic materials
- Hydrophilic surfactants
- Lipophilic surfactant
- Cosolvents

Solvents that provide adequate solubility of the drug can be selected, though it may be necessary to combine them to achieve the desired in vitro or in vivo characteristics and to ensure good physical stability. It is particularly important, for solutions of poorly

water-soluble drugs, to ensure that the fill solution is robust enough to withstand the inevitable dynamic changes that take place within the first 72 hr after encapsulation. This is because of the migration of components (water, plasticizers, drugs, etc.) within the Softgel both during and following encapsulation, which do not occur to the same extent in other ‘‘dry’’ dosage forms. Therefore it is important to conduct moisture, plasticizer challenge studies and temperature cycling studies to ensure that a robust fill formulation is achieved.

For Softgels containing suspension fills, the solubility of the drug in a range of pharmaceutically acceptable solvents is also determined and excipients in which the drug shows little or no solubility are then selected. These formulations generally require viscosity enhancers to provide adequate suspending characteristics for the drug during processing. This is vital in maintaining drug homogeneity during manufacture. The type and level of viscosity enhancer is optimized to provide the best manufacturability. Ideally, the fill material is designed to set slightly after encapsulation, such that the effects of long-term migration caused by gravity are reduced. Suspension formulae should be developed around a drug with controlled particle size, to enable proper process development. For Softgel suspension formulae, dissolution method development is a key activity, which requires expert attention to help ensure that proper interpretation is made.

Shell Compatibility

Shell compatibility testing between the fill and shell formulation is an important part of the development process. A variety of problems may result if the fill is not well matched to the proper shell formulation. These may be observed either immediately after encapsulation or after prolonged storage as described earlier. Traditionally, shell compatibility is performed using fill material and swatches or samples of gel ribbons. One of the challenges for Softgel development is to decide whether it is even feasible to determine shell compatibility without ever making Softgels. For this reason, it is preferred to perform an encapsulation trial as soon as possible. To make this easier and more economic, this work may be performed using lab scale equipment.

Prototype Development

(Lab Scale Encapsulation)

Traditionally, one of the features of Softgel manufacture has been that all the manufacturing encapsulation equipments were designed for commercial production.

Whilst this helped reduce the occurrence of scale-up issues, the minimum batch size for such machines was about 2.5–5 L, depending upon the expected yield and capsule quality. This is a large figure for certain NCEs where drug availability is a restricting factor. Recently, lab scale equipment has become available at Cardinal Health that uses as little as 100 ml of fill liquid to produce capsules (Fig. 3). It is now possible to produce first time Softgels in a laboratory setting, using the same encapsulation principle as full-scale encapsulation equipment, and to produce prototypes to help evaluate whether the Softgel dosage form is viable for a particular drug. This equipment makes the use of air-filled capsules to perform compatibility studies obsolete, as the latter, being a dry process, is never able to truly represent the wet capsule process.

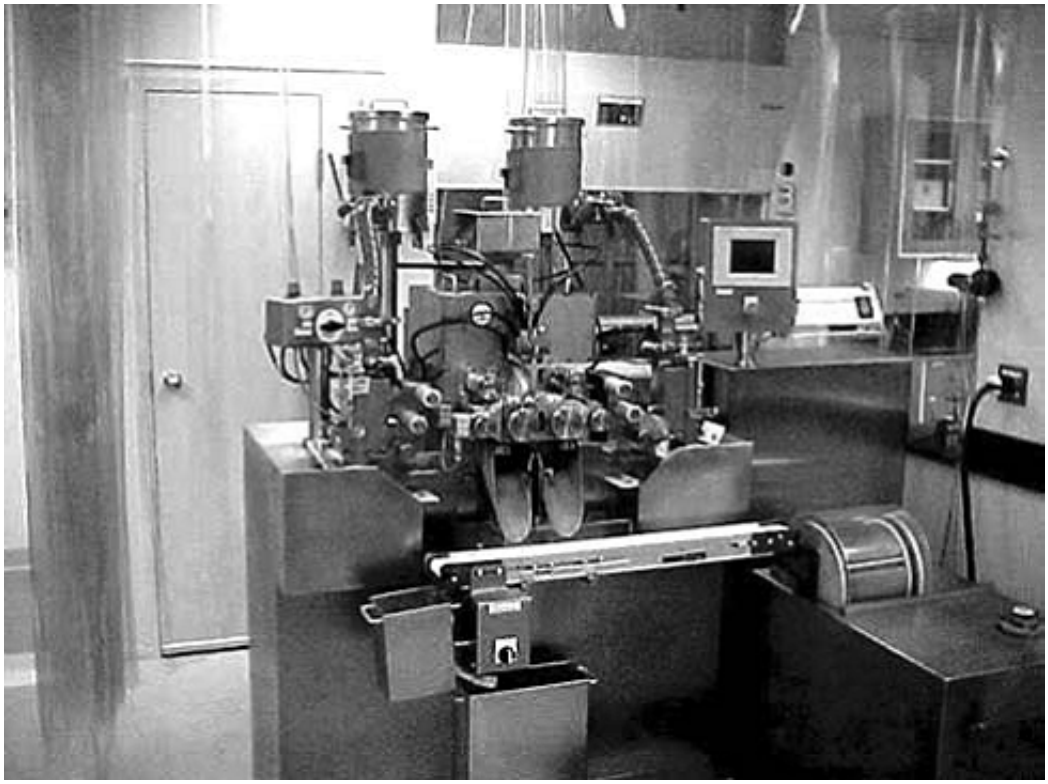

Fig. Lab-scale Softgel encapsulation machine.

Process Development

Having identified potential fill and shell formulations at the laboratory scale, a suitable manufacturing process that will enable successful preparation of the trial batch materials required for regulatory and clinical studies must be developed. Such process development includes selection of equipment and investigating critical processing parameters, such as the order of addition, temperature, mixing condition, and speed. The

information obtained from these development batches will provide valuable information for later process ranging and validation studies. For example, the fill moisture and hardness of the capsules during the drying stages will be monitored to optimize the drying process and resulting product stability. Fig. 4 shows the drying profile of a Softgel product. Note that the reduction in fill moisture is accompanied by an increase in capsule hardness. As more process development studies are completed, the in-process test data will be reviewed to help develop preliminary specifications intended to control product quality. For example, statistical analysis of in-process fill weight data may be performed to show that the process is capable of meeting the proposed in-process specification.

Clinical Supply

Manufacture of clinical batches will be performed according to the need for clinical studies (whether Phase I, II, or III). Process development studies should be carefully coordinated to ensure that the process is robust at the time of the registration batch manufacture.

Product Performance Review/Preparation for Process Validation

At the end of the product development phase and prior to process validation, a product review should be performed to ensure that the development is complete, and that the various processes for manufacture are capable of passing process validation. At this point, any gaps in the development process may be further studied and attended to, prior to performing process validation (e.g., logo printing process development), preferably at full scale. It is advisable to manufacture two or more process challenge batches to show that the product is acceptable at the upper and lower process ranges. This helps to ensure that validation will be successful.

METHOD OF MANUFACTURE

As early as the 1830s, Softgels were used as a method of drug delivery. Early manufacturing included both a hand-dipping method and a plate-press method. The hand-dipping method created individual empty Softgel shell that was subsequently filled with a syringe or a dropper. The plate-press method was a batch process that involved pressing two sheets of wet gelatin together between two molds. The molds provided depressions in the gelatin sheet into which active fill was then placed. A second gelatin sheet was laid over the first and both were pressed together with fill material sandwiched in between. The pressure of the plate dies sealed the top and bottom sheets of gelatin together and cut

out the individual Softgels for subsequent drying. Today, almost every Softgel on the market is made using the rotary die process patented by Scherer in 1933.[17] The equipment and manufacturing process has improved dramatically over the years, but the underlying manufacturing principle remains essentially unchanged. Two independent processes take place, often simultaneously, yielding two different materials, the gel mass and the fill material. Both are united in the encapsulation process that produces wet Softgels.

The wet gel mass is manufactured by mixing together and melting, under vacuum, the gelatin shell ingredients (gelatin, plasticizer, water, colorants and sometimes opacifiers, flavors, and preservatives). At the encapsulation machine (Fig. 5), molten gel mass flows through heated transfer tubes and is cast onto

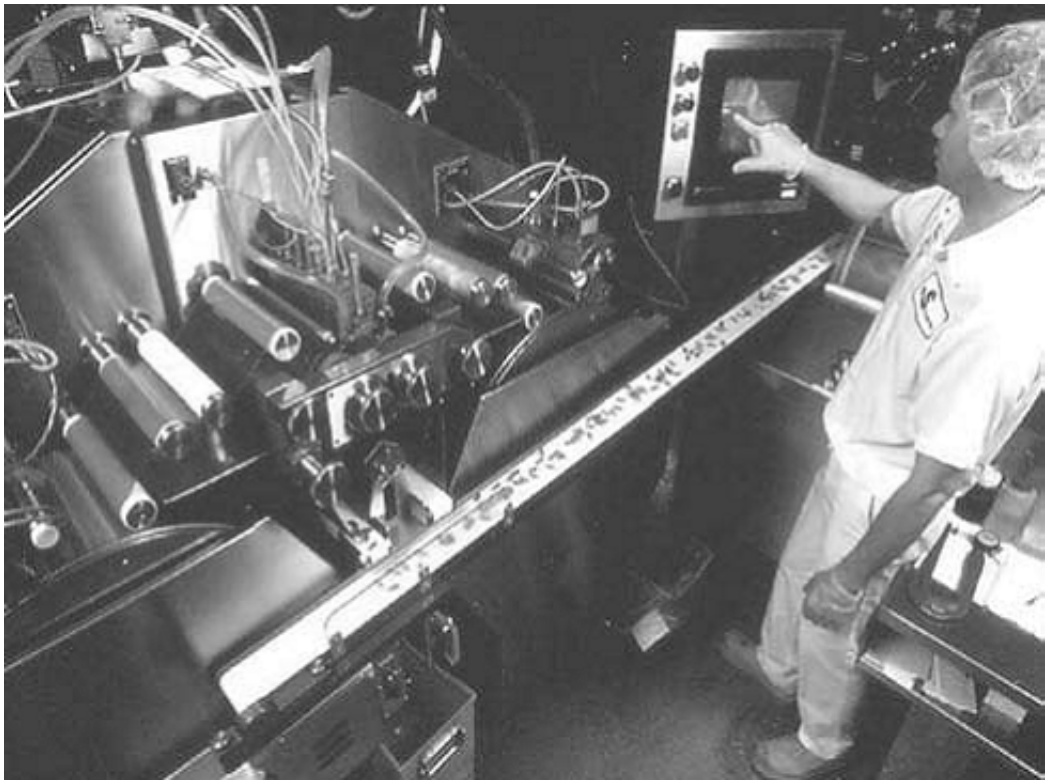

Fig. Encapsulation equipment.

chilled drums, forming two separate ribbons, each approximately 6 in. wide. The thickness of the ribbons (usually 0.02–0.04 in.) is carefully controlled and checked periodically throughout manufacture. The gel ribbons traverse through rollers that provide proper alignment of the ribbons and apply lubricant to both surfaces of the ribbons. Each gel ribbon forms one half of the Softgel. Two-toned Softgels are made using two different colored gel ribbons. Active fill materials are manufactured in a

process separate from the gel mass manufacture. The viscosity of all fills and the particle size of suspended materials are important parameters established during development and controlled throughout manufacture.

Softgels are formed during the encapsulation part of the process, using the two gel ribbons and the fill material. Lubricated gel ribbons are fed between a pair of counter rotating dies, the surface of which contains matching pockets of appropriate size and shape that serve as molds for forming the Softgels. The die pockets also seal both sides of the Softgel and cut the formed Softgel away from the residual gel ribbon. Fig. 6 shows Softgels immediately following encapsulation as they are being separated from the ribbons. The Softgels are then conveyed to a tumble dryer to initiate drying.

Situated between the ribbons and rotating dies is the wedge as shown in Figs. 7 and 8. The wedge serves three separate functions during the encapsulation process. First, it heats the gel ribbons close to the gel–sol transition temperature to ensure that melting (welding) of the two gel ribbons occurs when the ribbons are pressed together between the dies. Second, the wedge is part of the system that distributes the fill material from a positive displacement pump to each of the die pockets. Finally, the wedge, in conjunction with the lubricant, provides a sealing surface against the ribbons to eliminate air and allows a seal to be formed

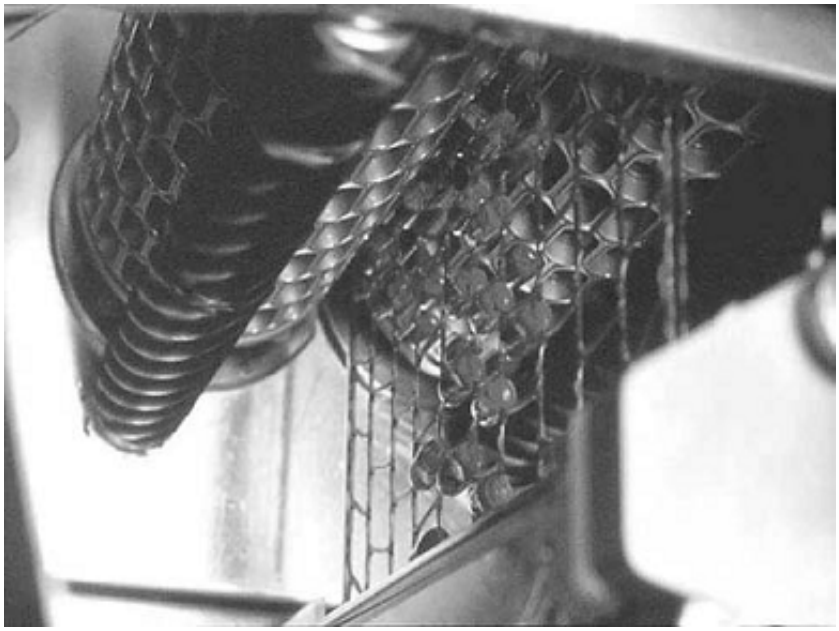

Fig. Newly formed Softgels.

between the shell and fill material without the introduction of air into the product. To properly manufacture the gel mass and form the gel ribbons, the gel mass formulation contains excess water. Following encapsulation, Softgels must be dried to obtain a final product that will be durable enough to withstand subsequent processing, packaging, and shipping, and possess good long-term physical stability. Drying occurs in two stages. Initial drying takes place in a rotating basket dryer that tumbles the Softgels in temperature and humidity controlled air. This removes approximately half of the excess water and is intended to remove sufficient water such that the capsules are firm enough to withstand tray drying without undergoing substantial deformation of the shape owing to gravity. The balance of the excess water is removed during the secondary drying stage, when the Softgels are spread in a single layer on shallow trays. The trays are designed and stacked to allow air to pass through the rack and around the Softgels (Fig.). Secondary drying proceeds under controlled conditions of temperature

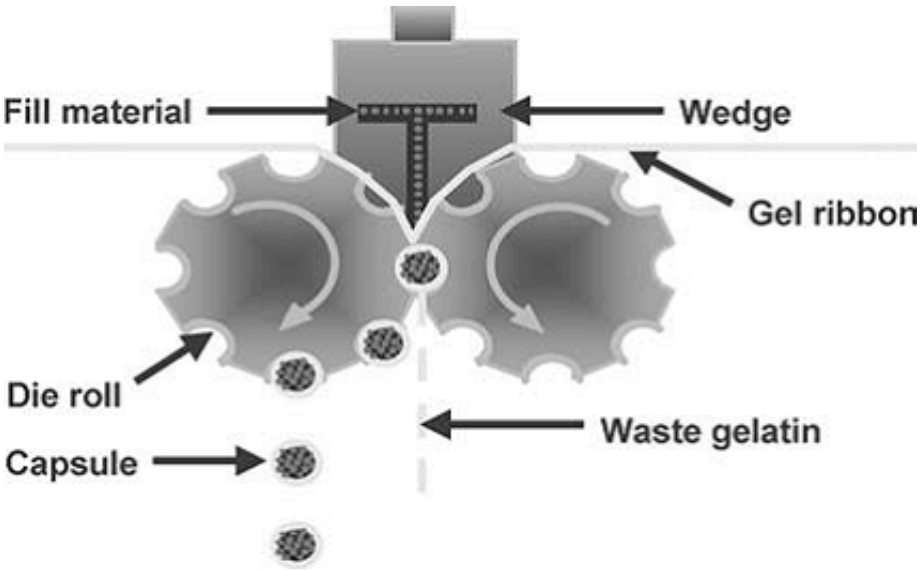

Fig. Softgel encapsulation process.

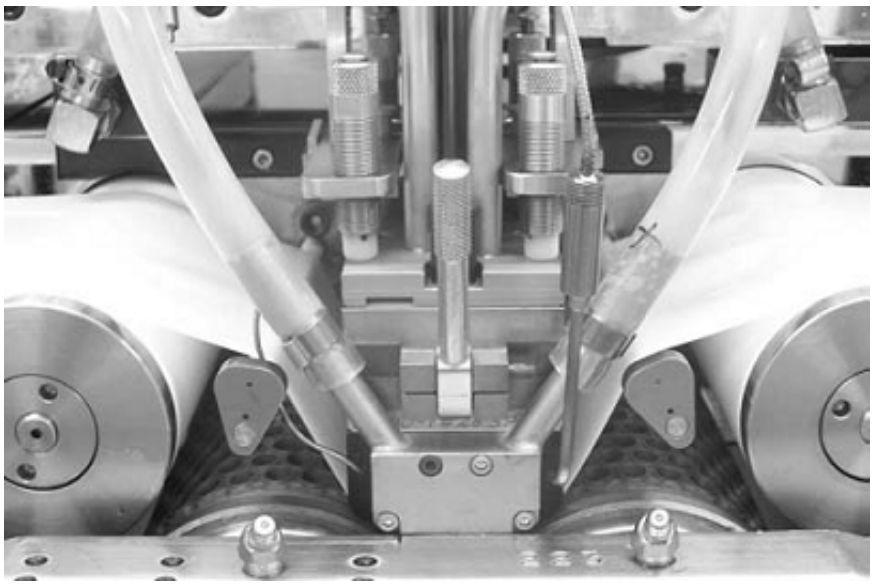

Fig. Close-up of die-wedge equipment.

and humidity until the appropriate level of capsule hardness and/or fill moisture is achieved.

Complete drying can take from three days to three weeks depending on shell and fill formulations and the size of the Softgel.

Once the Softgels have reached the desired drying end point, they are placed into bulk holding containers to prevent further drying.At this point, several additional operations may be performed, including washing, off line printing, inspecting, and packaging.

THERAPEUTIC PERFORMANCE

The pharmacokinetic performance of drugs can be enhanced by Softgel dosage form, the exact formulation

Fig. Tray drying of Softgels in controlled drying tunnels.

of which depends on the desired pharmacokinetic improvement. The two most common requirements are faster and more complete absorption. In both cases, the ideal situation is for the drug to be dosed in solution and formulated to remain in solution after dispersion in gastrointestinal media, possibly as a nanoemulsion. Formulation of nanoemulsion preconcentrates for Softgel encapsulation requires the drug to be in solution in a mixture of oils, surfactants, cosurfactants, and possibly cosolvents.

Rate of Absorption

Noteworthy advances recently have been made in the development of Softgel formulations to address particular performance issues in vivo. These include presentation of the drug to the gastrointestinal tract in a solution from which the drug can be absorbed significantly faster than that from a solid oral dosage form, which may be rate limited by the need for disintegration followed by drug dissolution. With the solution-Softgel approach, the shell ruptures within minutes to release the drug solution, usually in a hydrophilic or highly dispersing vehicle that aids the rate of absorption. This can be a valuable attribute for treatments such as migraine or acute pain, or where there is a limited absorption window in the gastrointestinal tract. Fig. 10 compares the absorption rates between a solution Softgel formulation and a tablet of ibuprofen.[18] The data are based on a pharmacokinetic comparison of 400 mg ibuprofen in 12 human volunteers.

Increased Bioavailability

In addition to increasing the rate of absorption, Softgels may also improve the extent of absorption. This can be particularly effective for large hydrophobic drugs.

The protease inhibitor saquinavir was relaunched in a patented solution–Softgel formulation, providing approximately three times the bioavailability as the original hard-shell formulation.[19]

In some cases, drugs may be solubilized in vehicles capable of spontaneously producing a microemulsion or nanoemulsion on contact with gastrointestinal fluids. This particular vehicle consists of oils and surfactants in appropriate proportions which, on contact with aqueous fluids, produce an emulsion preferably with an average droplet size less than 100 nm. The solubility of the drug should be maintained as long as possible, delivering solubilized drug directly to the enterocyte membrane. Fig. 11 depicts the enhancement in plasma levels achieved in 12 human volunteers when a nanoemulsion Softgel was used to dose a hydrophobic drug as compared to a capsule containing a

suspension of micronized drug particles.[19] It may even be possible to utilize the body's own systems for oil digestion to produce micelles containing solubilized drug.

Decreased Plasma Variability

High variability in drug plasma levels is a common characteristic of drugs with limited bioavailability. By dosing the drug optimally in solution, the variability of such drug plasma levels can often be reduced. Cyclosporin benefits from such an approach.[20] Fig. 12 depicts the administration of a 10 mg/kg dose of Cyclosporin A (Sandimmune_) Softgel solution formulation in eight human volunteers.[21] Fig. 13 depicts the administration of a 10 mg/kg dose of Cyclosporin A (Neoral_) microemulsion preconcentrate Softgel formulation in eight fasting human volunteers.[21]

PRODUCT QUALITY CONSIDERATIONS

Ingredient Specifications

Numerous specifications and control measures are employed to determine final product quality, the first of which is ensuring adequate quality of excipients and active ingredients. Excipient testing ensures compliance with compendial specifications, as well as specifications determined during development of the fill material and/ or shell formulation. Among these are limiting values for trace impurities, especially peroxides, aldehydes, some metals, and ionic salts.

Presence of these impurities can result in gelatin cross-linking and possible dissolution problems or in undesired changes in the product appearance over time.

As gelatin is the key ingredient for the shell and is present in larger quantities than other excipients, it is important to ensure that the gelatin meets not only current United States Pharmacopeia (USP) specifications, but the additional controls of particle size, viscosity, and bloom strength, all of which are significant for manufacturing process as well as final product stability. Other specifications, such as the quantity of certain ionic materials, are necessary to ensure stable product appearance during storage. Furthermore, it is essential to specify or limit other gelatin properties, such as color or even the source of the gelatin (bovine, porcine, bone, hide), depending on the formulation and intended market of the final product.

In-Process Testing

Several tests are conducted on a regular basis throughout the encapsulation portion of the Softgel manufacturing process. These include weight determinations for both the fill material and the shell, and measurements of the thickness of the seals of the Softgels themselves. Fill moisture and/or hardness measurements are performed during the drying process, the results of which are used to determine the drying end point for each lot. Specifications for fill weight, shell weight, seam thickness, and drying end points are based on the Softgel size, amount and type of fill, and the results obtained during previous process development studies.

Final Product Testing

Once the Softgels have completed all required processing steps, the lot is inspected and sampled for the final product-release test. Tests required for final product release are dependent on regulatory requirements for the product and usually include microbiological testing, assay and identity of actives, physical appearance, fill weight, dissolution or disintegration, and dosage uniformity.

RECENT ADVANCES IN NEW TECHNOLOGY

Softgel as a dosage form has been around for a long time and remained largely unchanged. Recent advances in the development of Softgel formulations and manufacturing have been mainly on the shell development. These include the development of starch-based capsules that can be made without gelatin[9,10] and enteric features of the dosage form from inside the shell.[22] Softgel technologies that provide controlled release and modified release profiles have also been reported in the literature. [22–24]

There has been great interest in the Softgel industry to look for gelatin substitutes. As a matter of fact, several concepts based on synthetic polymers[11] and/or plant-derived hydrocolloids[9,10] have been described in the literature. However, only few have gained commercial interest and commercial success. This is because of the fact that capsule shell polymer needs to match certain mechanical properties to be able to form capsules on Softgel encapsulation machine (a rotary die process). To date, only couple of non-gelatin capsules (e.g., VegiCap Soft_) with different process adjustments have reached the commercial stage. Vegi- Cap Soft, developed by Cardinal Health, utilized the combination of iota carrageenan and modified starch, as a gelatin substitute. The combination of the two hydrocolloids leads to a synergistic interaction that produces a

gel network, which is suitable for Softgel production using rotary die process. Certain modifications are required to the gel manufacturing operation, but the encapsulation and following operations may proceed relatively unchanged. These capsules do not show cross-linking and exhibit greater mechanical stability when exposed to elevated humidity and temperature. They do not become sticky even under hot and humid conditions. VegiSoft Capsules have been used in the nutritional market (with lipophilic formulation) for several years, showing that the process is robust. Recent research has shown that these capsules may be used to encapsulate hydrophilic fill formulations and fill materials that would not be possible using gelatin, for example, fill formulations with high pH.[13]

Gelatin capsule cross-linking is a well-known phenomenon that results in reduced dissolution of capsule products with time. A few approaches have been reported in the literature to reduce or prevent the cross linking by incorporating certain ingredients (e.g., citric acid, an amine agent, or a sulfite agent) either in the fill formulation[25] or in the shell formulation.[26–29]

TRENDS IN PATENT ACTIVITY

A review of the World wide patent activities from 1985 to 2004 reveals some interesting trends within the Softgel technology arena. From 1985 to 1995, there were 22 issued patents containing ‘‘soft gelatin capsule’’ in title or abstract. The number increased to 63 for the next nine years from 1996 to 2004. While this number does not necessarily include all the patents citing soft gelatin capsule in the specific claims or examples of specific dosage forms, the significant increase in the number of patents involving Softgels may suggest a broader understanding of the benefits of this technology both in clinical performance and patient and consumer appeal.

Looking more closely at U.S. patent activities, there were 45 U.S. patents issued in 1990 where the soft gelatin capsule was a specific claim. In year 2000, there were approximately 300 patents with Softgels as a specific claim. This sixfold increase in the number of patents specifically involving Softgel formulations may reflect greater and more widespread expertise with regard to Softgel formulation processes. It may also be an indication of the greater proportion of ‘‘difficult to formulate’’ drugs currently coming out of basic research centers, that is, low aqueous solubility and/ or poor or variable gastrointestinal absorption. A listing of the more significant patents, sorted into groups relating to either formulations,[30–39] manufacturing technology[24,40–49] or Softgel design innovations,[50–62] has been included in the reference section.

Examination of the patent activity of the top 20 pharmaceutical companies, or their predecessor companies, in the year 2000 vs. 1990 suggests an industry sector shift in the use of soft gelatin capsules. In 1990, the top 20 pharmaceutical firms obtained 85% of patents. This decreased to 57% in year 2000. As overall pharmaceutical application of Softgel technology has increased, a reasonable inference would be that the comparatively young and smaller biopharmaceutical industry sector is coming of age as compounds begin to move from basic research to development and commercialization.

Over the 1990 and 2000 periods, 95% of patents granted for pharmaceutical Softgel products relate to drugs or fill formulations and not to specific claims or improvements regarding shell formulations or manufacturing processes. On the surface, this would appear to indicate a mature technology, but as patents are public domain, and process patents are difficult to enforce, it is more likely that industry leaders are reluctant to pursue patents, except in unusual circumstances. In this process critical industry, it is more reasonable to expect that companies prefer to maintain technological advances as internal in-house matters for competitive reasons.

Despite the specialized manufacturing process, Softgels provide a versatile and efficient drug delivery system with distinct advantages over conventional dosage forms, including improved bioavailability, shorter development times, superior patient preference, and enhanced dose uniformity. The inherent nature of the Softgel offers a wide variety of usage and fill options. In any Softgel product development effort, formulation of the fill and gelatin shell should be considered concurrently to optimize product quality and performance.

Soft - Gelatin Capsules

Soft gelatin capsules are hermetically sealed one - piece capsules containing a liquid or a semisolid fi ll. Like liquid - fi lled hard capsules, although the drug is presented in a liquid formulation, it is enclosed within a solid, thus combining the attributes of both. Soft gelatin capsules (softgels) offer a number of advantages including improved bioavailability, as the drug is presented in a solubilized form, and enhanced drug stability. Consumer preference regarding ease of swallowing, convenience, and taste can improve compliance, and they offer opportunities for product differentiation via color, shape, and size and product line extension. The softgels can be enteric coated for delayed release. They are popular for pharmaceuticals, cosmetics, and nutritional

products, but highly water - soluble drugs and aldehydes are not suitable for encapsulation in softgels. Formulations are tamper evident and can be used for highly potent or toxic drugs. However, they do require specialist manufacture and incur high production costs.

Manufacture of Soft Gelatin Capsules

The shell is primarily composed of gelatin, plasticizer, and water (30 – 40% wet gel), and the fi ll can be a solution or suspension, liquid, or semisolid. The size of a softgel represents its nominal capacity in minims, for example, a 30 oval softgel can accommodate 30 minims (or 1.848 cm 3). Glycerol is the major plasticizer used, although sorbitol and propylene glycol can also be used. Other excipients are dyes, pigments, preservatives, and fl avors. Up to 5% sugar can be added to give a chewable quality. Most softgels are manufactured by the process developed by Scherer [11] . The glycerol – gelatin solution is heated and pumped onto two chilled drums to form two separate ribbons (usually 0.02 – 0.04 in. thick) which form each half of the softgel. The ribbons are lubricated and fed into the fi lling machine, forcing the gelatin to adopt the contours of the die. The fi ll is manufactured in a separate process and pumped in, and the softgels are sealed by the application of heat and pressure. Once cut from the ribbon, they are tumble - dried and conditioned at 20% relative humidity.

Fill solvents are selected based on a balance between adequate solubility of the drug and physical stability. Water - miscible solvents such as low - molecular – weight PEGs, polysorbates, and small amounts of propylene glycol, ethanol, and glycerin can be used. Water - immiscible solvents include vegetable and aromatic oils, aliphatic, aromatic, and chlorinated hydrocarbons, ethers, esters, and some alcohols. Emulsions, liquids with extremes of pH (□□2.5 and □□7.5), and volatile components can cause problems with stability, and drugs that do not have adequate stability in the solvents can be formulated as suspensions. In these instances, the particle size needs to be carefully controlled and surfactants can be added to promote wetting.

Vegicaps soft capsules from Cardinal Health are an alternative to traditional softgels, containing carageenan and hydroxyproyl starch. As with traditional soft gelatin capsules, the most important packaging and storage criterion is for adequate protection against extremes of relative humidity. The extent of protection required also depends on the fi ll formulation and on the anticipated storage conditions.

Dissolution Testing of Capsules

In general, capsule dosage forms tend to fl oat during dissolution testing with the

paddle method. In such cases, it is recommended that a few turns of a wire helix around the capsule be used [12] . Inclusion of enzymes in the dissolution media must be considered on case - by - case basis. A Gelatin Capsule Working Group (including participants from the FDA, industry, and the USP) was formed to assess the noncompliance of certain gelatin capsule products with the required dissolution specifi cations and the potential implications on bioavailability [13] . The working group recommended the addition of a second tier to the standard USP and new drug and abbreviated new drug applications (NDA/ANDA) dissolution tests: the incorporation of enzyme (pepsin with simulated gastric fl uid and pancreatin with simulated intestinal fl uid) into the dissolution medium. If the drug product fails the fi rst tier but passes the second tier, the product ’ s performance is acceptable. The two – tier dissolution test is appropriate for all gelatin capsule and gelatin - coated tablets and the phenomenon may have little signifi cance in vivo.