13

Capsules

PART ONE

Hard Capsules

VAN HOSTETLER

Mothes and Dublanc, two Frenchmen, are generally credited with the invention of the gelatin capsule. Their patents, granted in March and December of 1834, covered a method for producing single-piece, olive-shaped, gelatin capsules, which were closed after filling by a drop of concentrated warm gelatin solution. The two-piece telescoping capsule, invented by James Murdock of London (1848), was patented in England in 1865.

In addition to having the advantages of elegance, ease of use, and portability, capsules have become a popular dosage form because they provide a smooth, slippery, easily swallowed, and tasteless shell for drugs; the last advantage is particularly beneficial for drugs having an unpleasant taste or odor. They are economically produced in large quantities and in a wide range of colors, and they generally provide ready availability of the contained drug, since minimal excipient and little pressure are required to compact the material, as is necessary in tabletting.

Capsules are not usually used for the administration of extremely soluble materials such as potassium chloride, potassium bromide, or ammonium chloride since the sudden release of such compounds in the stomach could result in irritating concentrations. Capsules should not be used for highly efflorescent or deliquescent materials. Efflorescent materials may cause the capsules to soften, whereas deliquescent powders may dry the capsule shell to excessive brittleness. In some cases, this dehydration may be retarded or prevented by the use of small amounts of inert oils in the powder mixture.

Some of the material in this chapter has been retained from the previous edition, to which Mr. J. Q. Bellard contributed.

Materials

Telescoping capsules are made principally of gelatin blends and may contain small amounts of certified dyes, opaquing agents, plasticizers, and preservatives. Capsules have been made with methylcellulose, polyvinyl alcohols, and denatured gelatins to modify their solubility or produce an enteric effect. They are formed by dipping cool stainless steel mold pins into a gelatin solution, a process described in this chapter. Other methods, such as centrifugal casting, have been used, but the pin method is the only one used in large-scale commercial production.

Gelatin is a heterogeneous product derived by irreversible hydrolytic extraction of treated animal collagen, and as such, it never occurs naturally. Its physical and chemical properties are mainly functions of the parent collagen, method of extraction, pH value, thermal degradation, and electrolyte content. Common sources of collagen are animal bones, hide portions, and frozen pork skin. Bone and skin gelatins are readily available in commercial quantities in most areas of the world.

Type A gelatin is derived from an acid-treated precursor and exhibits an isoelectric point in the region of pH 9, whereas type B gelatin is from an alkali-treated precursor and has its isoelectric zone in the region of pH 4.7. Although capsules may be made from either type of gelatin, the usual practice is to use a mixture of both types as dictated by availability and cost considerations. Differences in the physical properties of finished capsules as a function of the type of gelatin used are slight.

Blends of bone and pork skin gelatins of relatively high gel strength are normally used for hard capsule production. The bone gelatin produces a tough, firm film, but tends to be hazy and brittle. The pork skin gelatin contributes plasticity and clarity to the blend, thereby reducing haze or cloudiness in the finished capsule.

An abbreviated flowchart for the manufacture of gelatin for use in capsules is presented in Figure 13-1.

Two recent developments have taken place in the gelatin supply area. First, "green" (fresh) bones are being used commercially as a source of Type B gelatin. Aside from additional pretreatment to remove residual tissues and fat, the processing coincides with that used for aged bones, and the gelatins obtained are indistinguishable from each other in practical use.

The second development is the processing of an "acid-bone" gelatin prepared from bone by techniques essentially comparable to those for Type A gelatins. The resulting gelatin shows an altered isoelectric point (pH 5.5–6.0), and generally, intermediate physical characteristics for the film. The acid extraction technique for bones is valuable to processors of gelatin because of the decreased extraction time required.

Both of the aforementioned materials are commercially available and are used in hard capsule production.

Method of Production

The three major suppliers of empty gelatin capsules are Eli Lilly and Company, Indianapolis, IN; Capsugel, Greenwood, SC; and the R. P. Scherer Corporation, Troy, MI. Several smaller volume suppliers exist throughout the world, some of which process for their own use only.

The completely automatic machine most commonly used for capsule production consists of mechanisms for automatically dipping, spinning, drying, stripping, trimming, and joining the capsules. The stainless steel mold pin (Fig. 13-2), on which the capsule is formed, controls some of the final critical dimensions of the capsule, and tolerances must be held within fractions of a thousandth of an inch.

One hundred and fifty pairs of these pins are dipped, as shown in Figure 13-2, into a gelatin sol of carefully controlled viscosity to form caps and bodies simultaneously. As shown in Figure 13-3, the pins are usually rotated to distribute the gelatin uniformly (1), during which time the gelatin may be set or gelled by a blast of cool air (2). The pins are moved through a series of controlled air drying kilns for the gradual and precisely controlled removal of water (3 to 6). The capsules are stripped from the pins by bronze jaws and trimmed to length by stationary knives (7) while the capsule halves are being spun in

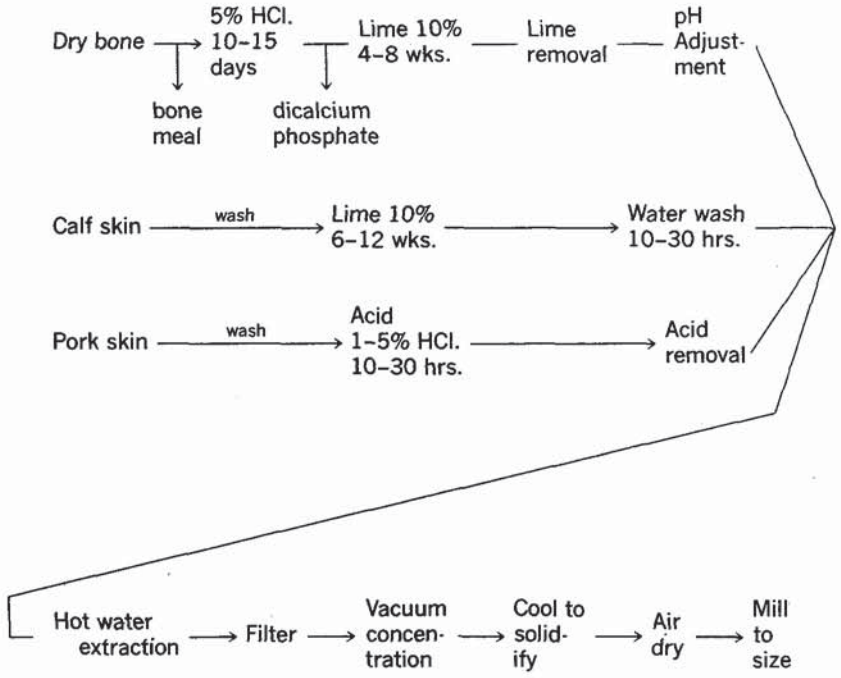


FIG. 13-1. *The process of manufacturing gelatin used in capsules.*

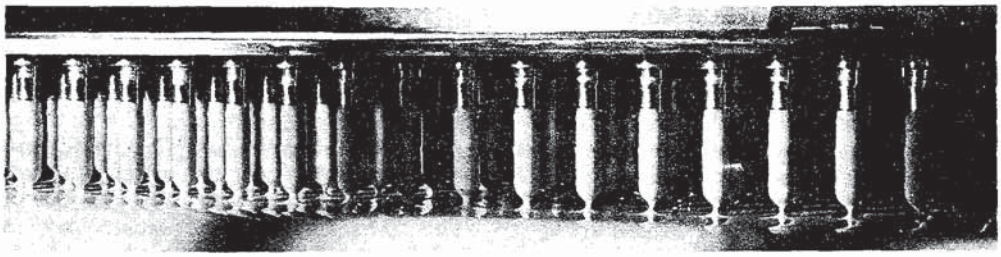


FIG. 13-2. *Mold pin dipping.*

chucks or collets. After being trimmed to exact length, the cap and body sections are joined and ejected from the machine. The entire cycle of the machine lasts approximately 45 min.

Thickness of the capsule wall is controlled by the viscosity of the gelatin solution and the speed and time of dipping. Other matters critical to the final dimensions are mold pin dimensions, precise drying, and machine control relating to cut lengths. Precise control of drying conditions is essential to the ultimate quality of the cast film.

At the least, in-process controls include periodic monitoring, and adjustment when required, of film thickness, cut lengths of both cap and body, color, and moisture content.

Recent strides have been made in several areas to provide computer control of viscosity (and consequent wall thickness) during either machine operations or gelatin solution make-up.

Inspection processes—to remove imperfect capsules—which historically have been done visually, have recently been automated following the development and patenting of a practical electronic sorting mechanism by Eli Lilly and Company. This equipment mechanically orients the capsules and transports them past a series of optical scanners, at which time those having detectable visual imperfections are automatically rejected.

Empty capsules are subject to size variation as a result of moisture content variation. This can be caused by exposure to extreme variations in absolute humidity or elevated temperature.

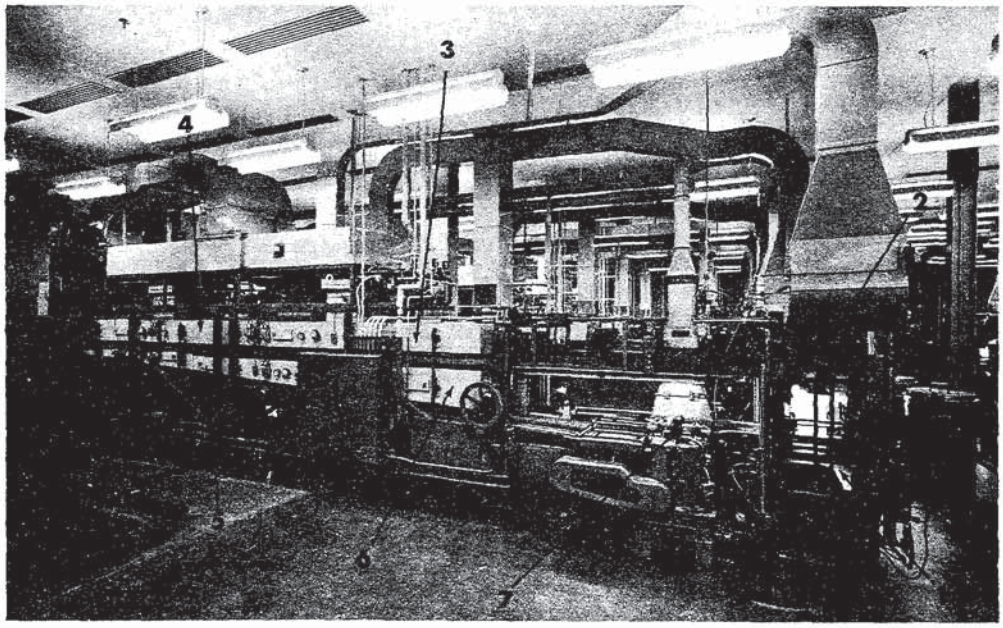


FIG. 13-3. *Hard capsule manufacturing machine. See text for explanation of labels 1 through 7.*

Unopened shipping containers are usually adequate protection against these changes, but storage in unopened containers should not be subjected to temperature conditions of over 100°F. Open storage under either high or low humidity conditions should be minimized. Empty capsules as usually received range in moisture content between 12% and 15%. Below 10% moisture content, they become brittle and may shrink to the point of not fitting into the filling equipment. Above 16% moisture content, they may cause size problems in the filling equipment, plus a loss of mechanical strength. Exposure to either heat or moisture extremes can distort empty capsules to the extent that they cannot be handled by automatic filling equipment.

Filling Equipment

At present, at least nine manufacturers of capsule filling equipment are either located in or selling their products within the United States. Most of the units manufactured outside the United States have local representatives. The nine individual companies are:

Eli Lilly and Company, Indianapolis, IN
Farmatic SNC, Bologna, Italy
Höfliger and Karg, Waiblingen, Germany
Macofar SAS, Bologna, Italy
mG2 S.p.A., Bologna, Italy
Osaka, Osaka, Japan
Parke-Davis and Company, Detroit, MI
Perry Industries, Green Bay, WI
Zanasi Nigris, S.p.A., Bologna, Italy

Each machine type is briefly discussed in the following sections, but no attempt is made to quantify or compare weight variation figures among the various types because of obvious dependence on such factors as the conditions of the equipment, formulas, methods of operation, operator competence, machine rates, and sizes of capsules. Along with suitable consideration of all other details, adequate statistical weight checks or the use of 100% check-weighing should be employed to ensure compliance with regulatory requirements.

The largest number of total machines are supplied by Lilly and Parke-Davis. Since the machines of both manufacturers have essentially the same method of operation, only one description is given.

Lilly/Parke-Davis

Each of these capsule filling machines requires an individual operator and may achieve a daily output of up to 200,000 capsules.

The Lilly machine is shown in Figure 13-4. The empty capsules are fed from the storage hopper (1) and through the rectifying unit (2), into the two-piece filling ring (3A and 3B). Rectification is based on dimensional differences between the outside diameters of the cap and body portions of the capsule. As the ring (3A and 3B) is rotated, a vacuum is applied on its underside. This vacuum seats the bodies into the lower half of the ring, while the caps are retained in the upper portion. The two pieces of the ring are separated, and the cap-containing portion is placed aside. The body-containing portion of the ring is placed on a variable speed turntable and is mechanically rotated under the powder hopper (4), which contains an auger for the forced delivery of the powder. After one (or more) complete rotations of the ring, the powder hopper (4) is removed, and the two segments of the ring (3A and 3B) are rejoined. The intact ring is positioned in front of the peg ring (5), and the closing plate (6) is pivoted to a position approximately 180 degrees from that shown in Figure 13-4. Pneumatic pressure is applied to the peg

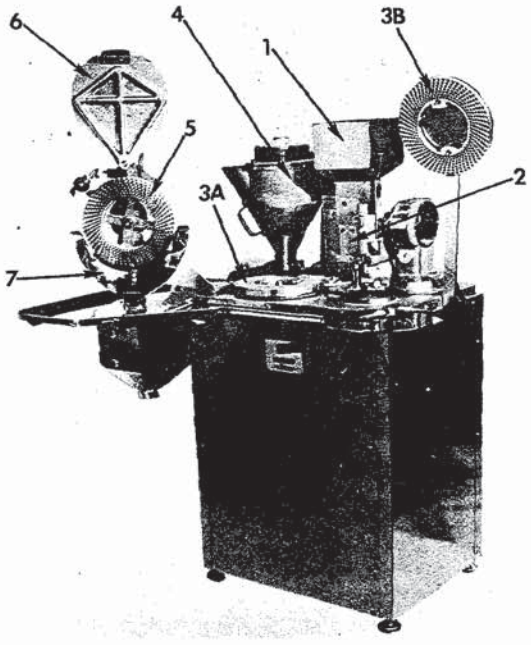


FIG. 13-4. *Lilly capsule filling machine. See text for explanation of labels 1 through 7. (Courtesy of Eli Lilly & Co., Indianapolis, IN.)*

ring (5), which forces the capsule body into the cap, and the closing plate (6) holds the caps in position. Ejection of the filled capsules from the rings cannot occur with the plate in the closing position. For ejection of the capsules, the pressure is released, the closing plate is restored to its original position, and the capsules are expelled through the upper portion of the ring. Normal closing and ejection occur with the peg ring in a vertical position, as shown in Figure 13-4, with the filled capsules being collected through a chute (7) into a collection chamber.

In this equipment, the powder is filled to the upper surface of the body-containing ring, and the fill is therefore primarily volumetric. Although changes in the total amount of powder can be caused by changes in the rotational speed of the turntable (which changes the amount of time for which each hole is under the auger), there is no way to produce a partially filled capsule consistently. Although slower speeds usually produce less weight variation, they also usually result in heavier total fill weights, which may not be economical because of the resultant decrease in productivity.

Minimum total fill weights (but usually maximum weight variation) are achieved with the highest turntable speed.

Maximum total fill weights (but generally minimum weight variation) are achieved at the lowest rotational speed.

Some of the variables that must be properly controlled in order to achieve minimum weight variation and proper uniformity of the finished capsules are given in the following list:

1. The body-containing ring (3A) must be flat across its surface to avoid creating volumetric differences from one area of the ring to another.
2. The powder hopper (4) must be properly positioned during the filling operation to avoid uneven powder distribution from the auger. The proper location includes consideration of both the centering of the auger over the ring holes and the parallelism between the lower surface of the hopper and the upper surface of the ring.
3. Extreme variations in powder level in the filling hopper (4) can cause uneven powder flow, resulting in excessive fill weight variation.
4. The individual rods in the peg ring must fit the rings being used, be of uniform length, and be perpendicular to the closing plate (6).
5. Flow properties of the powder being filled must be such that a constant amount of powder is available for delivery from the auger. Diluents and glidants should be selected with this phase of the operation in mind.

Pelletized or granular materials may be readily filled using this equipment. It is desirable to remove the auger to avoid crushing. It may also be desirable to perform the closing operations in a position other than the vertical position usually used for powder. In a vertical position, pellets or granules may escape from the body ring, and this may cause damage to the capsules.

Since filling is best accomplished without an auger in these cases, minimal change in fill weight can be achieved by alteration of rotational speed. Additional ring rotations do not increase the fill, but usually cause actual damage to the pellets or granules.

In addition to the semiautomatic machines described previously, a relatively high-speed, automatic, continuous-motion machine called the ROTOFIL is available from Eli Lilly and Company (Fig. 13-5). This machine is specifically designed to fill pellets.

The machine uses a rotary rectification system, which orients the capsules into a turret. After the capsules are seated, the blocks containing the caps are retracted, and the bodies are gravity-filled from the recirculating bed of pellets.

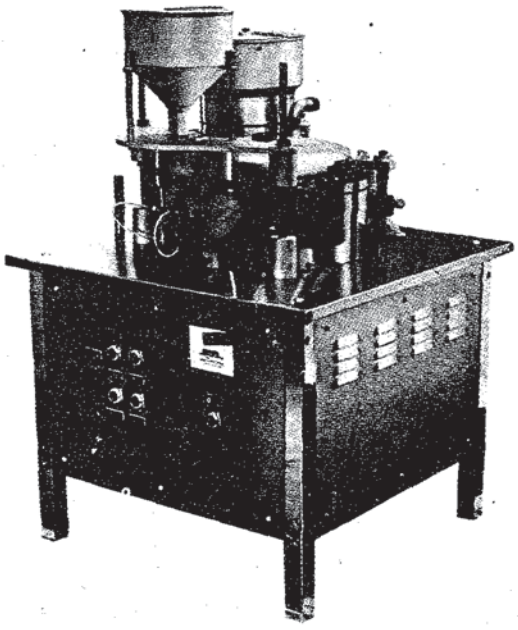


FIG. 13-5. *Lilly ROTOFIL capsule filling machine. (Courtesy of Eli Lilly & Co., Indianapolis, IN.)*

The excess pellets are rolled from the surface of the turret and are transported back to the hopper by vacuum. The cap blocks are realigned over the turret, and a simple continuous cam motion provides the closing action. Filled capsules are ejected by compressed air, and both cap and body cavities are cleaned by compressed air and vacuum prior to the next use. Fill weight may be adjusted while the machine is in operation.

The machine is rated as filling 1200 capsules per minute.

Farmatic

Farmatic offers three models of filling equipment for sale: 2000/15, 2000/30, and 2000/60, with rated outputs of up to 40,000, up to 80,000, and up to 160,000 capsules per hour, respectively. A Farmatic capsule filling machine is presented in Figure 13-6.

The machines feature continuous motion with dosator-type powder feeding units, and are totally enclosed for dust and noise control. Adjustable vacuum is used for separating the cap-

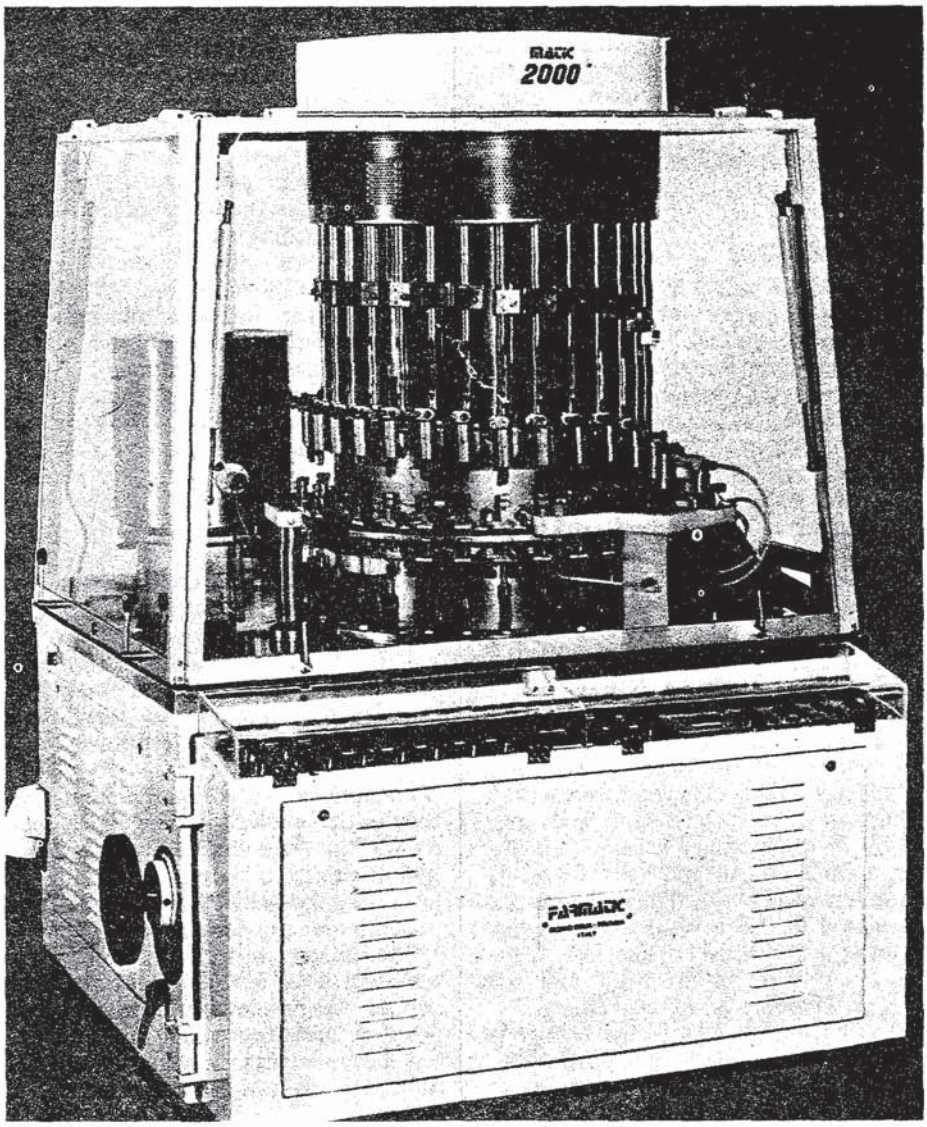


FIG. 13-6. *Farmatic Model 2000/60 capsule filling machine. (Courtesy of G.B. Gundi Bruno S.p.A., Bologna, Italy.)*

sules after rectification, and any defective or unopened capsules are automatically rejected.

Powder is moved from the product hopper by a screw conveyor to the operating tower, where its level is continuously monitored.

Dosators measure and deliver the powder as a slug to the capsules. A digital display indicates the status of the weight and compression. Adjustments are made externally.

The powder slug is ejected into the capsule body, after which the capsule is closed. In the case of a missing capsule, the slug is ejected in such a way as to avoid its being carried into the completed capsules. Following ejection, all bushings are cleaned by a combination of vacuum and air.

Various options are available, including automatic feeders for both capsules and powder, counters, and automatic sampling with feedback to the closing units to adjust incorrect weights.

Farmatic does not have U.S. representation.

Höfliger and Karg

The Höfliger and Karg (H & K) line consists basically of four machines—Models GKF-303, GKF-602, GKF-1500, and GKF-2500; the numbers represent the approximate output of filled capsules per minute. All models can be modified to accept powders, pellets, or tablets. In addition, the first three models may be equipped to handle the filling of thixotropic liquids into hard gelatin capsules, at some reduction of output.

Labels appearing in Figure 13-7, which depicts H & K Model GKF-602, signify the following: 1, empty capsule storage hopper; 2, rectifier; 3, bulk powder storage hopper; 4, capsule body transport segment; 5, closing station; and 6, filled capsules ejection station.

In Models GKF-602, GKF-1500, and GKF-2500, capsules are handled 6, 15, and 25, at one time, according to the respective model number. The empty capsule feed provides for the removal of faulty capsules, and is checked by a vacuum system, which provides a signal upon feed interruption. The rectified empty capsules are inserted into individual cap and body segments bolted to the transport wheel. The segments are then transported to the various work stations carrying the caps and bodies. Thus, only these segments, along with the rectifier and the tamps, require replacement for size change.

Removal of capsule bodies to the carrier is mechanical with a vacuum assist, to ensure gentle handling of the capsules. After separation of cap and body, the cap segment is lifted before retraction of the segment to remove the possibility of shearing off long or improperly seated bodies.

Powder is auger-fed from the supply hopper to the filling chamber, which completely surrounds the filling disc and in which the powder height is level-controlled. Tamping of powder into the holes of the filling disc is performed at five successive stations. Tamps are externally adjustable at each individual station while the machine is in operation. An additional station is available for the insertion of tablets or pellets, so that mixed fills can be achieved.

Safety features built into the system include an empty capsule feed interruption signal with automatic rejection of crushed and unjoined capsules, and automatic clearance of empty capsule feed tubes after a predetermined number of cycles. If no body is present in the body segment, the powder is discharged through the segment into a collecting container.

Closing of filled capsules is performed in two successive operations to allow for slower closing. Closing is accomplished by the use of both upper and lower closing rods.

Figure 13-8 shows Model GKF-1200/1500, and Figure 13-9 shows Model GKF-2400.

All Höfliger and Karg machines are completely automatic and require only compressed air and a power for operation.

Höfliger and Karg is represented in the United States by Robert Bosch Packaging Machinery Division, Piscataway, NJ.

Macofar

The Macofar line of capsule filling equipment consists of three models: MT-12, MT-13/1, and MT-13/2. Model MT-12 is shown in Figure 13-10. All three models are low-to-medium-capacity machines, ranging from 5,000 filled capsules per hour (MT-13/1) and 10,000 capsules per hour (MT-13/2) to over 35,000 capsules per hour (MT-12).

All units are based upon a similar method of rectification and filling. The empty capsules are rectified into bushings in a central plate. Separation of cap from body is accomplished by vacuum, and the body-carrying bushings are positioned under the dosator unit.

The dosator units pick up powder to a predetermined level from a level-controlled powder hopper. The powder is lightly tamped within the dosators, following which the units are raised, the body-carrying bushing is aligned under them, and the powder is ejected into the open bodies.

The body bushings are retracted to the central

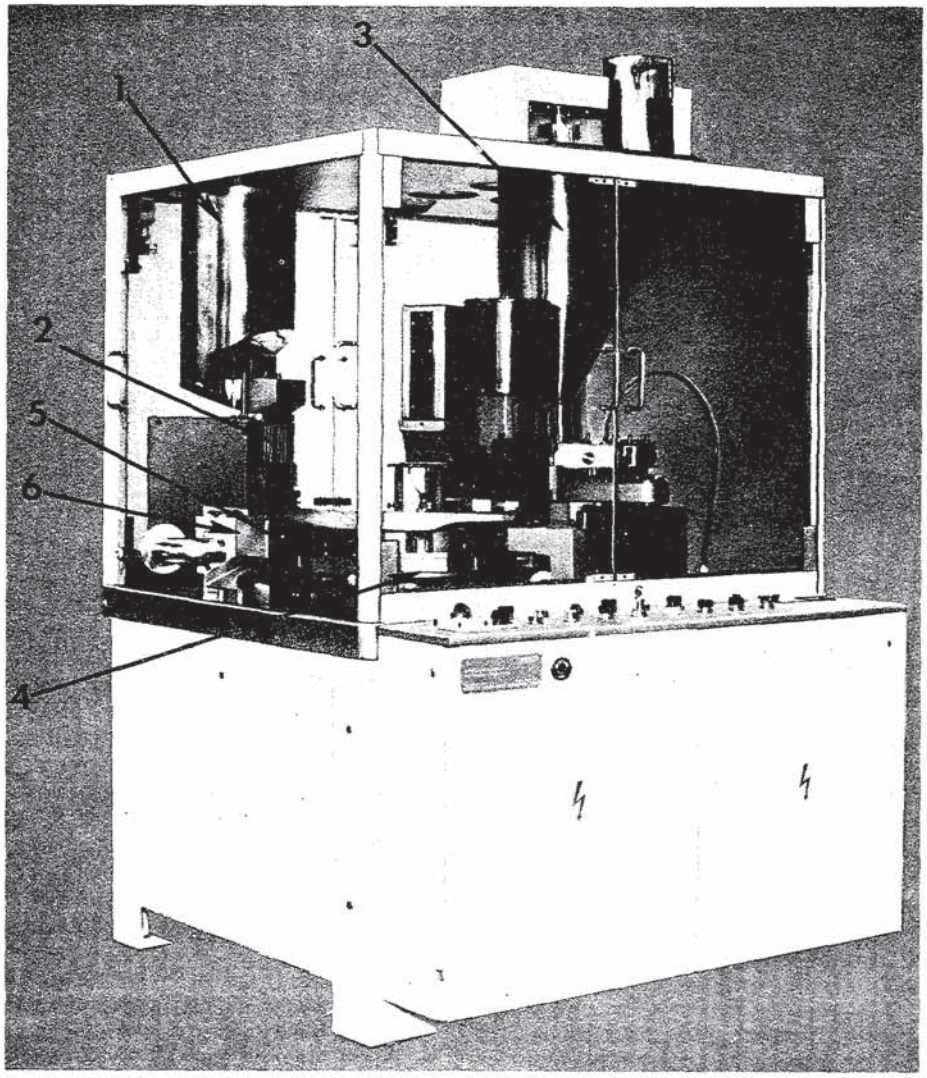


FIG. 13-7. *H & K Model 602 capsule filling machine. See text for explanation of labels 1 through 6. (Courtesy of Robert Bosch GmbH, Waiblingen, West Germany.)*

plate beneath the cap blocks, and closing of the capsule occurs. Prior to reuse, the capsule-holding bushings are cleaned of powder by means of air/vacuum.

Various filling options are available for materials other than powders.

The distributor for Macofar in the United States is Production Equipment, Inc., Rochelle Park, NJ.

mG2

Five models of continuous-motion filling machines are currently offered by mG2. Model G36/4 is rated at 150 capsules per minute, G36/2 at 300, G36 at 600, G37N at 1600, and G38 at 1000. All models utilize the same general methods for both powder and capsule handling. In the following section, Models G36, G37N, and G38 are briefly discussed.

The following identifications apply to the labels in the illustration of Model G36 (Fig. 13-11): 1, empty capsule hopper and rectifier; 2, cap holder removal station; 3, cleaning station; 4, powder dosing head; 5, bulk powder hopper; 6, cap holder replacing station; 7, capsule closing and ejection station.

In Model G36, the capsules are fed from the

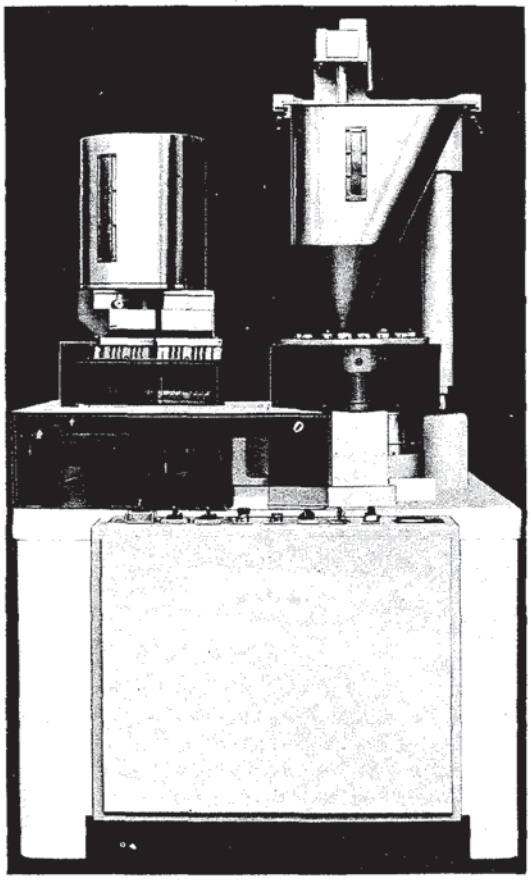


FIG. 13-8. *K & K Model 1200/1500 capsule filling machine. (Courtesy of Robert Bosch GmbH, Waiblingen, West Germany.)*

storage hopper through individual tubes and rectified (1) into individual two-piece side holders on a continuous chain. The capsules are separated within the two-piece holders by applying vacuum to the lower portion, which pulls the body into it while the cap is retained in the upper holder. As the chain and retaining blocks progress through the cycle, the cap-containing upper holder (2) is moved aside to a recess at the outer end of the conveying holder, exposing the lower holder containing the body. The powder is continuously mixed within the powder hopper (5) and is maintained at a constant level prior to discharge. The body-carrying units now are carried under a series of 12 volumetric dosing nozzles (4), each of which picks up the product from a rotating container, first compressing and then ejecting the powder into the capsule bodies. Precise weight adjustments may be made simultaneously to all dosing units while the machine is in operation. The cap container is repositioned over the body block (6), and closing is accomplished by both upper and lower closing pins (7). Ejection is accomplished by compressed air.

Each station is equipped with a safety device that automatically stops the machine in the event of an irregularity. Capsule carrying holders are cleaned by air prior to being returned to the rectifier station.

Model G37 has recently been modified (G37N) to provide several new and/or improved features: the handling of empty capsules has been improved, the powder handling system has been modified to lessen powder dusting, several noise-reduction features have been incorporated, and both cleanup and size changing have been simplified. Adjustments of weight control and powder compression can be made externally while the unit is operating.

Model G37N, shown in Figure 13-12, is a continuous-motion turret machine that provides approximately two and one-half times the filling rate of the G36. As indicated previously, it also employs a different capsule handling mechanism. It is composed of two main units. The first unit provides capsule feeding, rectifying, and opening in a manner similar to that of the G36, but with a greater number of elements. The second unit provides capsule separation, dosage, closure, and ejection. The higher output is obtained by providing 40 dosing nozzles and 40 pairs of capsule transfer holders. Dosage adjustment is the same as for Model G36, providing simultaneous control of the position of all dosing pistons.

Model G38 (Fig. 13-13) is a newly introduced machine that is slightly slower than the G37N (with 20 filling tubes versus 40), but is totally enclosed. As with the G37N, all weight adjustments can be made through external controls with the machine in operation. Several features have been added to allow machine jogging, powder-level control, and photoelectric shutoff (if more than three successive unopened capsules are encountered), as well as automatic ejection of certain other empty capsule defects.

All mG2 models either run or can be fitted with attachments to allow them to run with powders, granules, or pellets. Models G37N and G38 can be supplied with auxiliary equipment to provide for presorting of the empty capsules, automatic sampling of filled capsules, and an inspection unit, based upon weight, for filled capsules.

The representative for mG2 in the United States is Supermatic Packaging Machinery, Inc., Fairfield, NJ.

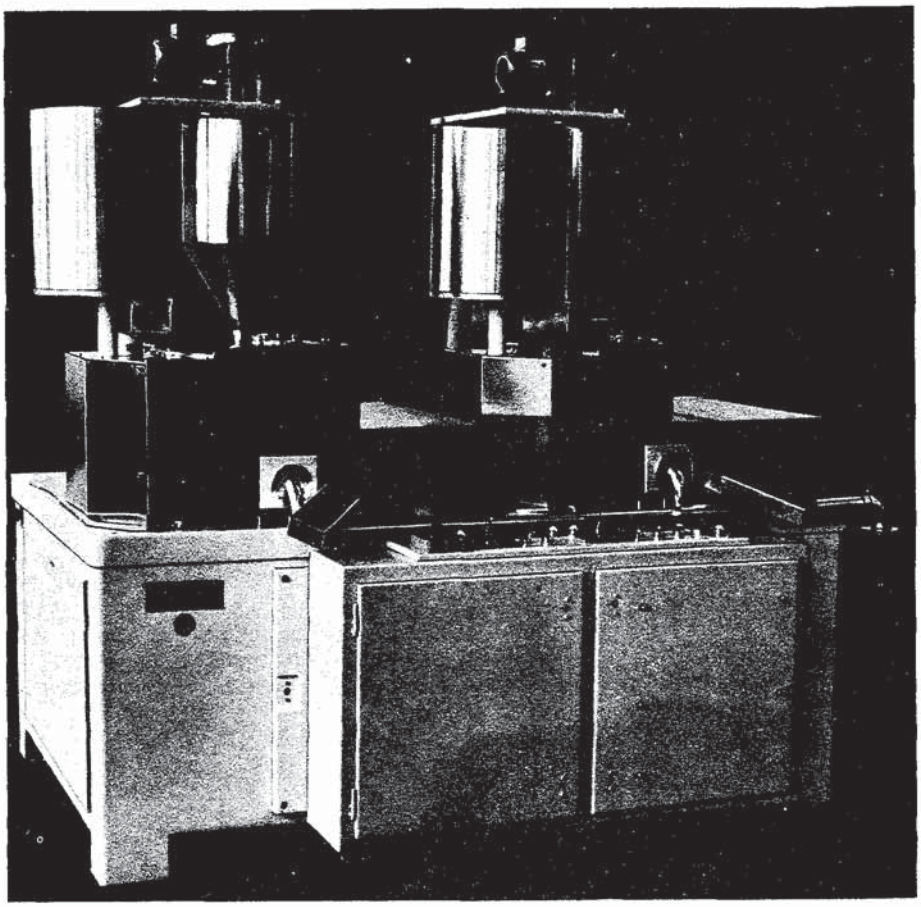


FIG. 13-9. *H & K Model 2400 capsule filling machine. (Courtesy of Robert Bosch GmbH, Waiblingen, West Germany.)*

Osaka

The Osaka filling machine is a high-capacity, continuous-motion machine recently introduced in the United States. The only model currently available is the R-180 (Fig. 13-14), which has a rated capacity of 70,000 to 165,000 capsules per hour. The unit handles either powder or granular materials.

The unit is totally enclosed, with external access to the capsule and powder hoppers.

The powder-filling principle utilized is unique in that vibration is used to move the powder from the powder hopper to powder shoes and from the powder shoes into the capsule bodies. Capsule bodies pass under the powder-filling area in two rows. Each row is fed by two vibratory units. The vibrators are externally controlled so that fill-weight adjustments can be made during machine operation. Because of this method of powder feed, correct powder formulations are essential, and limitations exist in the possible amounts with which to fill a given size capsule.

Provision is made to remove unjoined capsules during the rectification process and empty or broken capsules after filling.

The Osaka equipment can be supplemented with several pieces of auxiliary equipment, including a cleaner/polisher unit that has a rated capacity of up to 400,000 capsules per hour.

The Osaka distributor in the United States is the Sharples-Stokes Division of the Pennwalt Corporation, Warminster, PA.

Perry

The Model CF ACCOFIL machine offered by Perry utilizes the well-established ACCOFIL

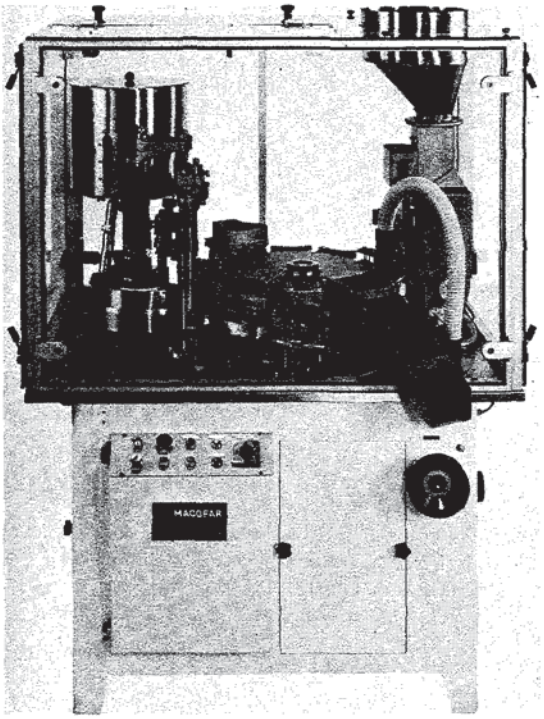


FIG. 13-10. *Macofar Model MT-12 capsule filling machine. (Courtesy of Macofar, Bologna, Italy.)*

method of powder dose control, which is unique in capsule filling (Fig. 13-15). The machine is a continuous-motion rotary machine with a rated output of up to about 60,000 capsules per hour; it fills powder mixtures only.

Capsules are rectified from 24 vertical tubes, and are cammed into a body downward position in a plate, from which they are dropped with a vacuum assist into a conveyor chain of two parts, the lower containing the bodies and the upper containing the caps. A sensor system is present, which provides for rejection of unseparated capsules and prevents ejection of powder in the absence of a capsule body. The cap-containing portion is caused to swing away from the body portion by a guide rail. Filling is accomplished while the cap links are displaced, following which the chain links are repositioned over each other.

Powder is supplied from a bulk supply hopper to a powder pan via a screw feeder. The level in the pan is controlled to a constant level. In the continuously rotating powder turret, 24 vertically operating, cam-controlled empty needles are immersed into the powder, and a vacuum is applied, sucking the powder up (in a predetermined amount) into the needle. Excess powder is doctored from the sides and tips of the needles. The vacuum is held as the needle is positioned over an empty body, at which time the vacuum is broken and a light surge of air is applied to expel the powder.

Following filling, the chain links are properly realigned, and the body is moved into the cap by the slow cam action of the 24 closing pins. Following closing, the capsule is ejected by air from the conveyor, at which time it is counted, and the count is recorded by a digital readout on the front panel. Cleaning of all bushings, as well as the powder needles, is accomplished by high-pressure air.

The Model CF ACCOFIL machine is available through Perry Industries, Inc., Green Bay, WI.

Zanasi

The line of Zanasi equipment currently available includes nine different units in four model lines. With suitable change parts, all may be capable of handling powders, pellets, or tablets. Some models may be purchased with attachments to allow the insertion of smaller capsules, and some may be capable of paste or liquid filling.

Two models, the LZ-64 (Fig. 13-16) and AZ-20 (Fig. 13-17), retain the familiar intermittent operation of past Zanasi machines. The LZ-64 is rated at about 4,000 capsules per hour, while the AZ-20 speed is variable—from approximately 9,000 to 20,000 capsules per hour.

Two newer series consist of continuous-motion machines, but retain the dosator principle. The BZ series consists of four machines: BZ-40 (30,000/hour), BZ-72 (60,000/hour), BZ-110 (110,000/hour), and BZ-150 (150,000/hour). The BZ-40 and BZ-72 can handle powders, pellets, and tablets, while the BZ-110 handles only powders and granules. The BZ-150 handles powders only. A variety of auxiliary equipment is available with the BZ series of machines, including an empty capsule presorter, a powder recovery system, a filled-capsule sampling system, and a check weighing system.

Zanasi's newest series is the Z-5000 (Fig. 13-18), consisting of the Z-5000-R1, rated at up to 70,000 capsules per hour; the Z-5000-R2, rated at up to 110,000 capsules per hour; and the Z-5000-R3, rated at up to 150,000 capsules per hour. With change parts, all are capable of filling powders, granules, and tablets. Special attention has been paid to safety devices and acoustical treatments for operator protection.

Zanasi equipment is available in the United States from Z-Packaging Systems, Monsey, NY.

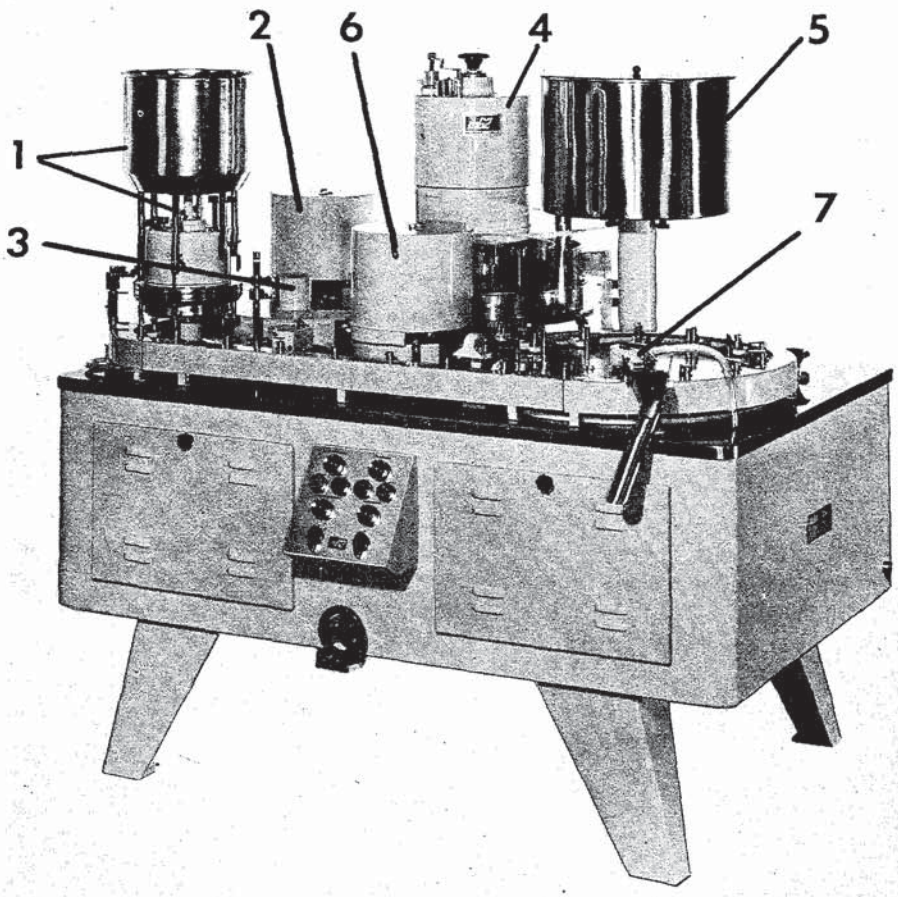


FIG. 13-11. *mG2 Model G36 capsule filling machine. See text for explanation of labels 1 through 7. (Courtesy of mG2 Macchine Automatiche, Bologna, Italy.)*

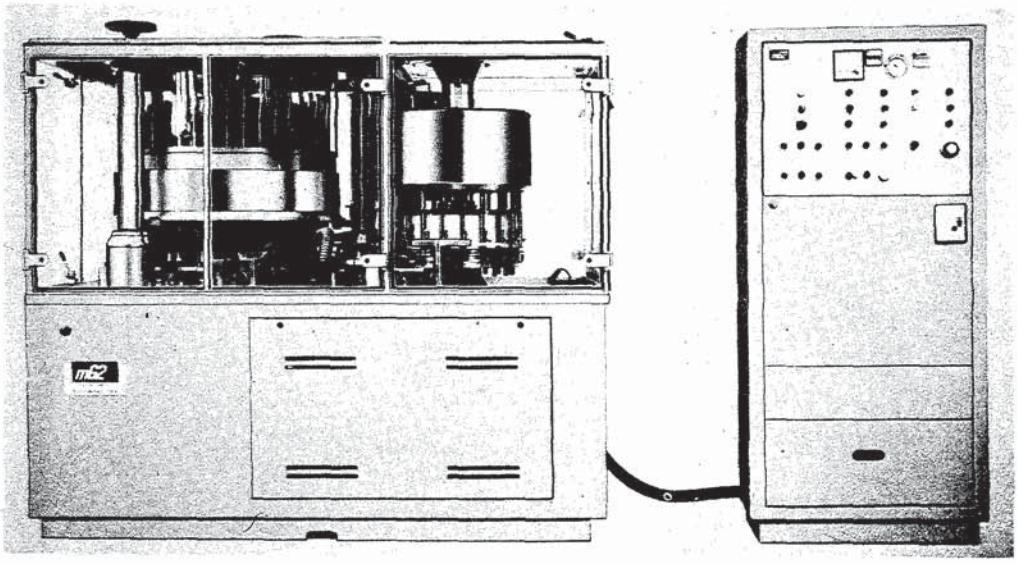


FIG. 13-12. *mG2 Model G37N capsule filling machine. (Courtesy of mG2 Macchine Automatiche, Bologna, Italy.)*

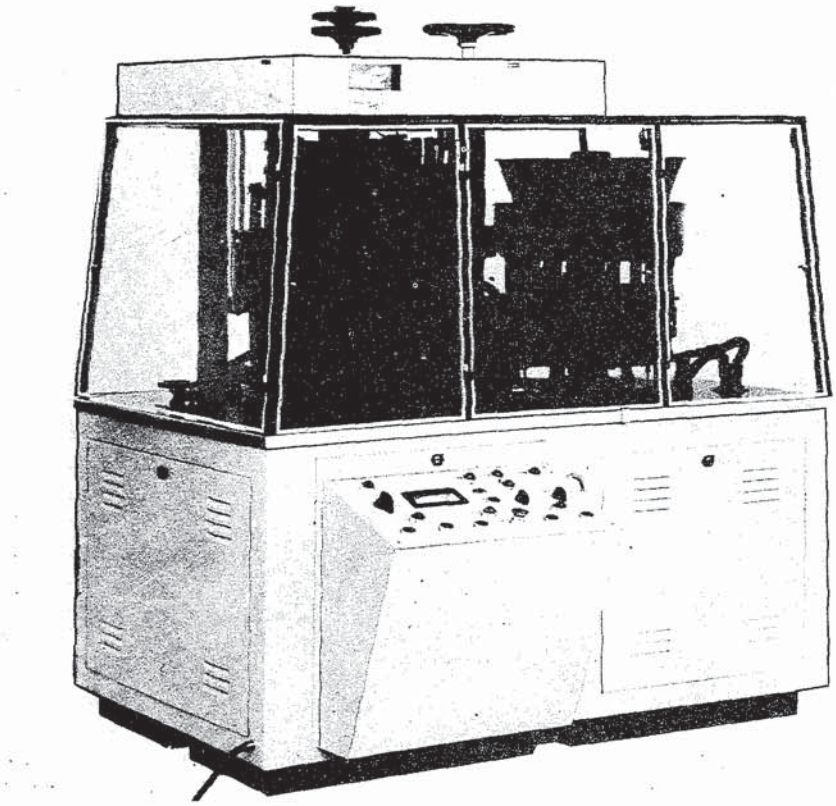


FIG. 13-13. *mG2 Model G38 capsule filling machine. (Courtesy of mG2 Macchine Automatiche, Bologna, Italy.)*

Filling Operations

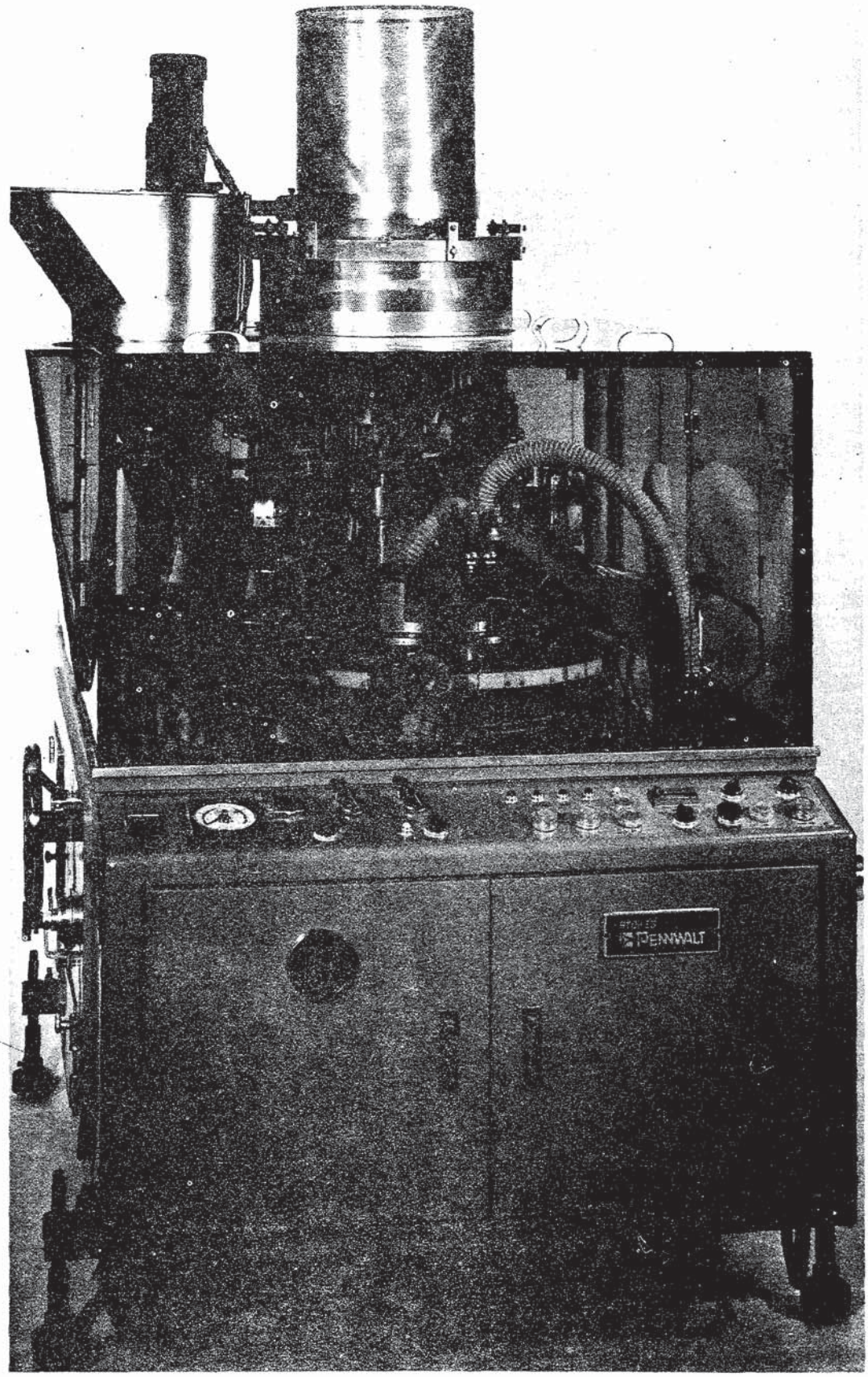
Empty Capsules

Empty capsules are sold by sizes. The ones most commonly employed for human use range from size 0, the largest, to size 5, the smallest. Size 00 capsules may occasionally be required because of the volume of material to be filled, but this size is not used commercially in large volume. Although capsules change dimensions to some extent with varied moisture content and conditions encountered before use, Table 13-1 gives an approximation of the volume that may be contained in the various sizes, along with the amounts of some powders that can be contained in these sizes. The powder weights listed are approximate and vary with the amount of pressure employed in hand filling, or with the type of equipment utilized in machine filling.

Much consideration should be given to techniques for handling and storage of empty capsules in any production facility. This is of great

TABLE 13-1. *Filling Capacity of Empty Capsules*

Capsule Size	*Approx. Volume (ml)*	*Quinine Sulfate (g)*	*Sodium Bicarbonate (g)*	*Acetylsalicylic Acid (g)*	*Bismuth Subnitrate (g)*
0	0.75	0.33	0.68	0.55	0.8
1	0.55	0.23	0.55	0.33	0.65
2	0.4	0.2	0.4	0.25	0.55
3	0.3	0.12	0.33	0.2	0.4
4	0.25	0.1	0.25	0.15	0.25
5	0.15	0.07	0.12	0.1	0.12



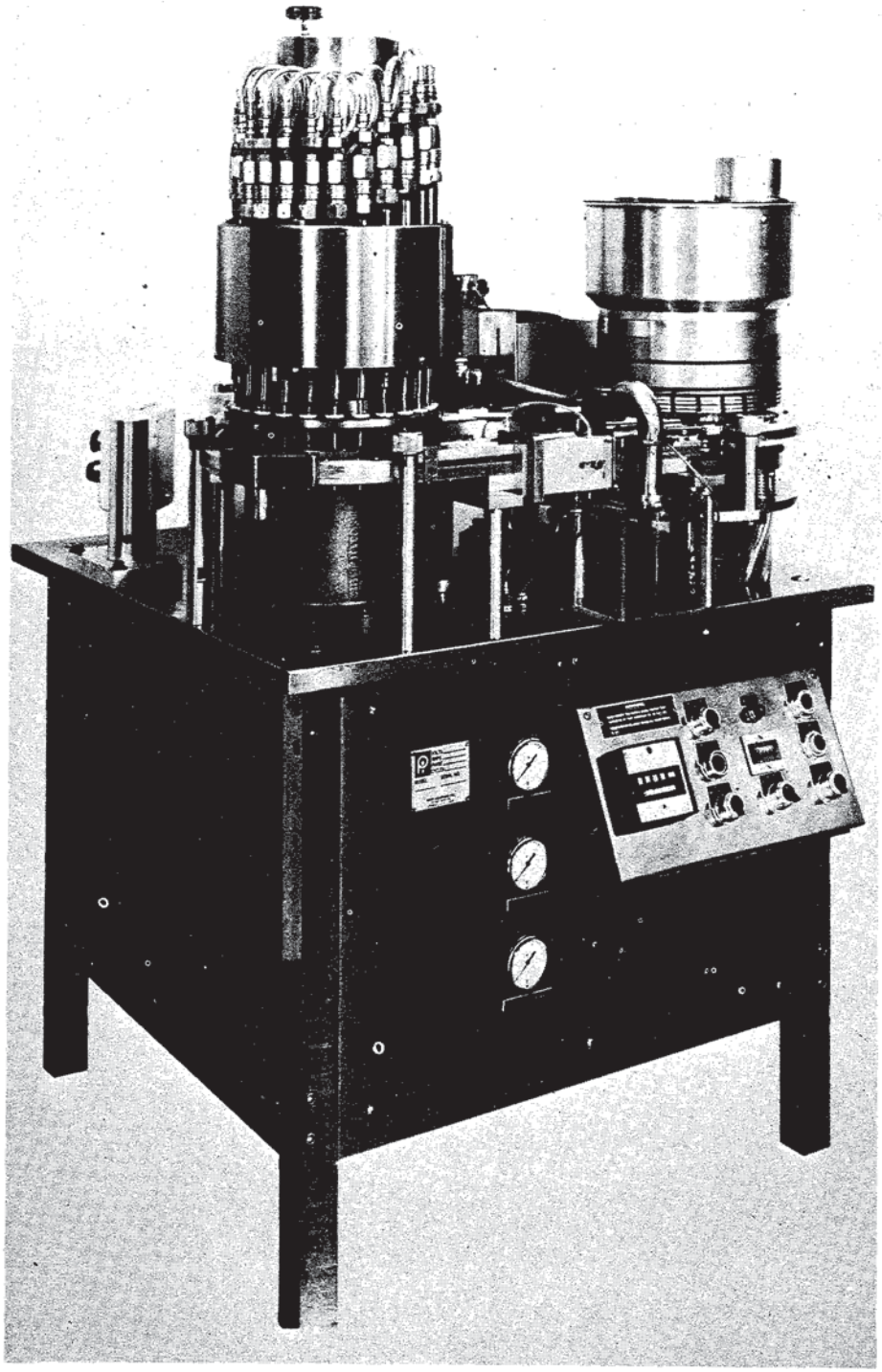


FIG. 13-15. *Perry Model CF ACCOFIL capsule filling machine. (Courtesy of Perry Industries, Green Bay, WI.)*

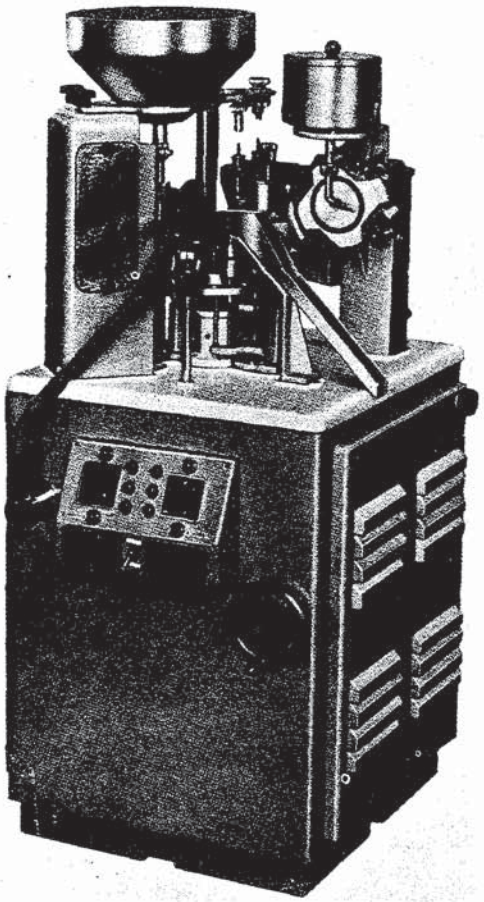


FIG. 13-16. *Zanasi Model LZ-64 capsule filling machine. (Courtesy of Zanasi, S.p.A., Bologna, Italy.)*

importance when use rates are high, as when high-speed filling equipment is used.

Capsules as received from the supplier generally have moisture content between 12 and 15%, and these levels are maintained during storage in the original container. Storage under high-temperature conditions (above 100°F) must not be prolonged. Exposure to extremely high or extremely low humidity conditions for extended periods after the containers are opened causes the capsules to either gain or lose moisture. At high moisture levels, the capsules absorb moisture, and may soften and become tacky. In severe cases, the capsules may absorb sufficient moisture to cause them to deform under their own weight. At low moisture levels, they become brittle and suffer dimensional changes, which may cause handling problems in the filling equipment.

Regarding the empty capsules only, handling is ideally carried on in areas within the relative humidity range of approximately 30 to 45%, since major moisture content changes do not occur within these limits. If conditions drier than these are necessitated because of the ingredients being filled, exposures of the empty capsules prior to filling should be minimized. Strong consideration should be given to the use of air-conditioned facilities to control both temperatures and humidity when high-speed filling equipment is being operated.

Formulations

The problems encountered in handling powders during mixing and filling operations are so diverse as to preclude any but general comments. Although some problems are common to all types of filling equipment, certain machines themselves represent unique situations. Among the general problems, two major ones can be listed.

1. After the powder ingredients have been homogeneously blended by any suitable technique, the flow of the resultant mixture must be adequate to ensure delivery of sufficient powder to the capsules at the time of filling. De-mixing must not occur during the powder handling in the filling equipment itself.
2. Physical incompatibilities between active ingredients, between diluents, or between active ingredients and/or diluents and the capsule shell may create problems.

The capsule seldom contains only the active ingredient(s); most capsule formulations require the use of some diluent material. Because of the wide range of materials encapsulated, no attempt can be made to outline specific criteria for the choice of suitable diluents. The following are three major general considerations.

1. The powder mix must provide the type of flow characteristics required by the equipment. In the case of the Lilly, Parke-Davis, Höfliger and Karg, Osaka, and Perry machines, powders must be free flowing. In the case of Zanasi, Macofar, Farmatic, and mG2 equipment, the powder must have sufficient cohesiveness to retain its slug form during delivery to the capsules. For example, when one is filling with acetylsalicylic acid, an excipient such as a flowable cornstarch allows filling in the former case, whereas compactible excipients such as microcrystalline cellulose are required in the latter case. In all cases, the powder mixture must retain its homogeneous composition without de-mixing during the machine handling operations. Lubricants, such as a metallic stearate,

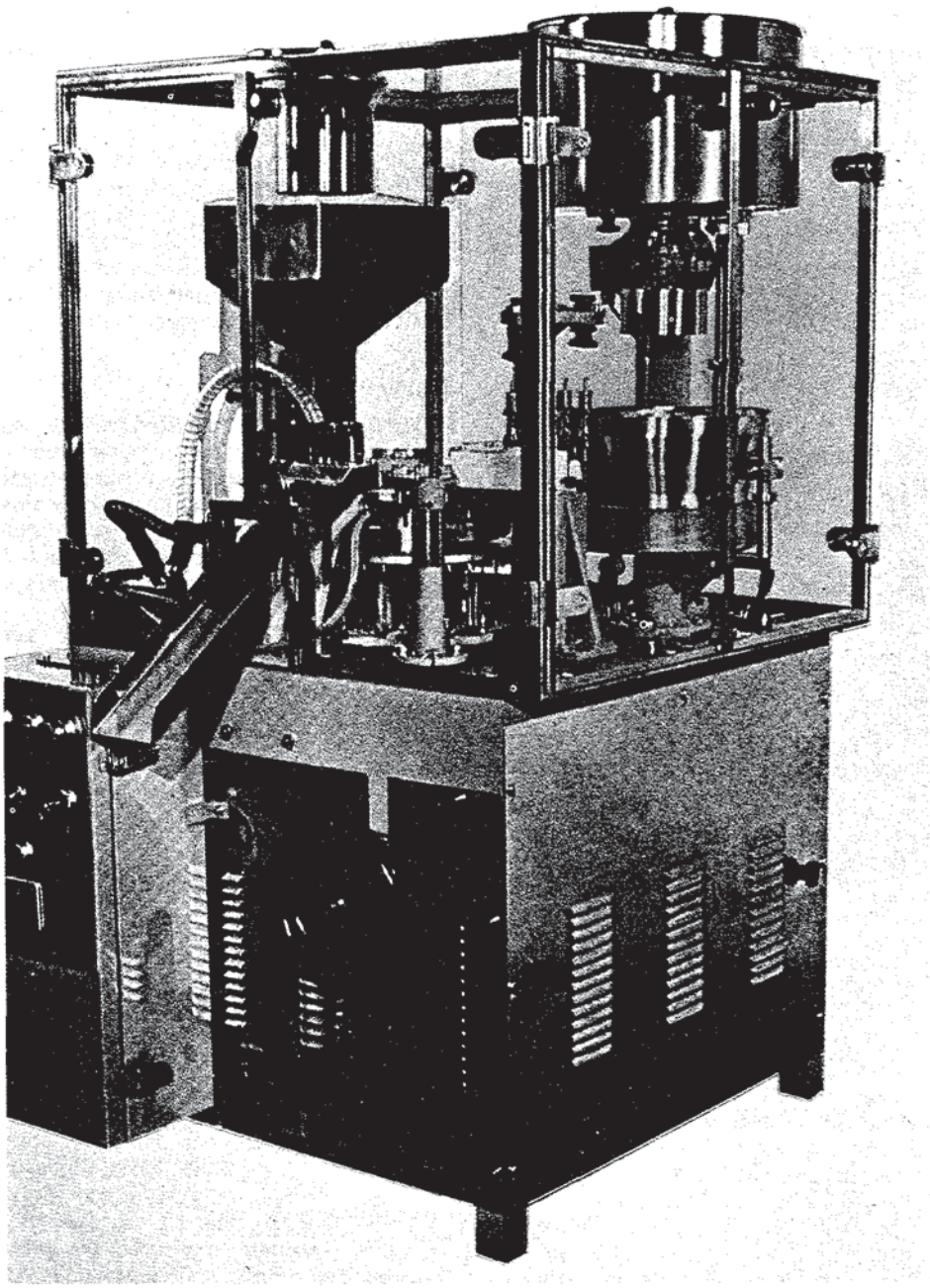


FIG. 13-17. *Zanasi Model AZ-20 capsule filling machine. (Courtesy of Zanasi, S.p.A., Bologna, Italy.)*

may be used in the former case; binders, such as mineral oil, are sometimes used in the latter. Particle sizes and powder densities of all ingredients should be matched as closely as possible to assist in the prevention of de-mixing.

2. Potential incompatibilities should be anticipated with each new mixture of materials. Reactions at elevated temperatures and humidities should be studied, for effects not only on the contained powder mixture, but also on the gelatin capsules. Studies such as these should include an evaluation in the presence of probable

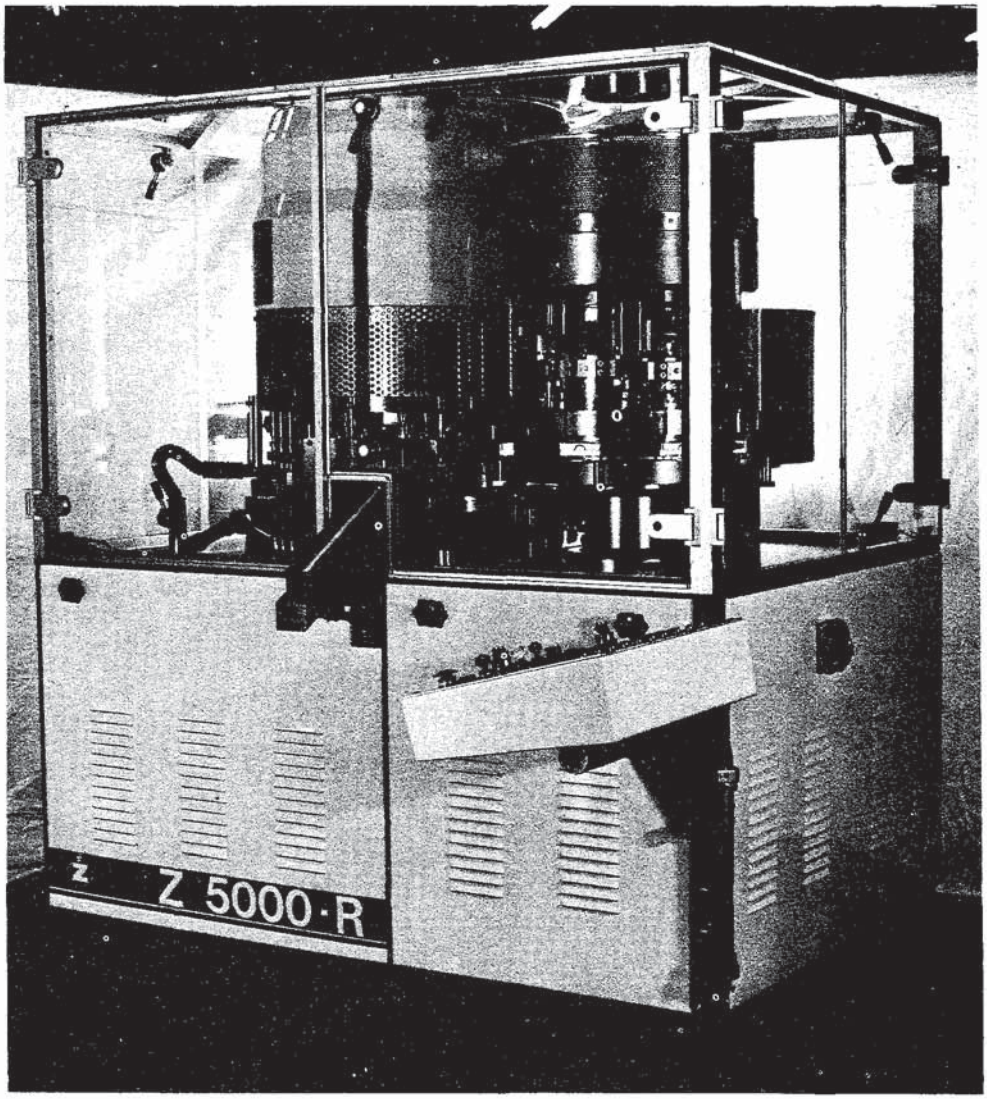


FIG. 13-18. *Zanasi Model Z-5000 capsule filling machine. (Courtesy of Zanasi, S.p.A., Bologna, Italy.)*

packaging materials. Evaluation of any test procedure should be based on sound statistical techniques.

3. The choice of excipients should be made with a view toward current Food and Drug Administration (FDA) regulations as they apply to Investigational New Drug and New Drug applications. Any applicable foreign regulations also should be considered. Some materials that may be useful as excipients are bentonite, calcium carbonate, lactose, mannitol, magnesium carbonate, magnesium oxide, silica gel, starch, talc, and tapioca powder.

If it is desirable for any reason to consider materials other than the aforementioned, first consideration should be given to materials that are given a "Generally Recognized As Safe" designation by the FDA. Obtaining approval of materials that are not in this category can be an expensive and time-consuming process, although there are occasions when it cannot be avoided.

Materials that may be considered for improvement of flow characteristics (glidants and/or lubricants, as indicated earlier) may include the following: glycol esters, silicones, silicon dioxide, metallic stearates, stearic acid, and talc.

Oils that may be considered for use in assist-

ing in the control of dusting, as well as in providing additional cohesiveness to a powder mix, could include any inert, edible, FDA-approved material.

The determination of amounts of diluents to be used is based on (1) the total amount of material that can possibly be put in the capsule in relation to the amount of active ingredients to be supplied by the capsule, and (2) the amounts of lubricant and/or oil (generally in the order of 2% or less) that can be used. Experimentation with the actual materials is the only positive way to arrive at these figures.

Serious consideration should be given to the choice of suitable control procedures for the filling operations. In addition, it may be desirable to provide 100% weight checking after filling. The control procedures must ensure that the finished, filled capsules meet the appropriate current regulatory tests, e.g., weight variation, content uniformity, solubility, and/or disintegration. Current legal requirements should be adequately explored since there are wide differences between countries. The weight variation test in USP XX has been replaced in USP XXI with the Uniformity of Dosage Units Tests However, the weight variation test, as official in USP XX, is still useful in machine set-up and evaluation.

The *weight variation* test defined by USP XX is a sequential test, in which 20 intact capsules are individually weighed and the average weight is determined. The test requirements are met if none of the individual weights are less than 90%, or more than 110%, of the average. If the original 20 do not meet these criteria, the individual *net weights* are determined. These are averaged, and differences are determined between each individual net content and the average. The test requirements are met (1) if not more than two of the individual differences are greater than 10% of the average, or (2) if in no case any difference is greater than 25%.

If more than 2 but less than 6 net weights determined by the test deviate by more than 10% but less than 25%, the net contents are determined for an additional 40 capsules, and the average is calculated for the entire 60 capsules. Sixty deviations from the new average are calculated. The requirements are met (1) if the difference does not exceed 10% of the average in more than 6 of the 60 capsules, and (2) if in no case any difference exceeds 25%.

Two new pieces of equipment determine the weight of individual capsules, providing for the automatic rejection of overfilled and underfilled capsules. These machines may be used in-line to reclaim portions of a batch as it is processed, or off-line to weigh and sort a complete batch that has been shown statistically to have unacceptable weight variation.

The ROTOWEIGH is a high-speed capsule weighing machine sold by Eli Lilly and Company (Fig. 13-19). The capsules are gravity-fed onto vacuum pins for presentation to a unique weight detection system, which measures the reflected energy (backscatter) of a low power x-ray beam directed at each capsule. This reflected energy is proportional to the weight of the filled capsule, permitting automatic rejection of any individual capsule above or below preset weights. The machine operates at 73,000 capsules per hour, and its accuracy is more than adequate to assure compliance with the USP weight requirements.

The second unit is the Vericap 1200 machine (Fig. 13-20), which is sold by Modern Controls, Inc., Elk River, MN. It operates by detecting capacitance variation as filled capsules are propelled at high speed by compressed air between two charged plates. The measured change in dielectric constant thus produced is correlated to the weight of the capsule. Capsules that are overweight or underweight are then automatically separated from the acceptable capsules. The machine operates at a rate of 73,000 capsules per hour.

A second test in USP XX that may apply to capsules is that for *content uniformity,* which is performed when specified by individual monographs. In this case, 30 capsules are selected, 10 of which are assayed by the specified procedure. The requirements are met if 9 of the 10 are within the specified potency range of 85 to 115%, and the tenth is not outside 75 to 125%.

If more than 1, but less than 3, of the first 10 capsules fall outside the 85 to 115% limits, the remaining 20 are assayed. The requirements are met if all 30 capsules are within 75 to 125% of *the specified potency range, and not less than* 27 of the 30 are within the 85 to 115% range.

Broad generalizations about stability test programs cannot be made, since the question has to be answered according to each user's criteria. The tests should be based on adequate statistical design, however, and should include evaluation of not only active ingredient stability, but also visual and mechanical aspects of the finished dosage form. These tests must include extended storage at various elevated temperatures with different humidity levels. Tests should include the filled capsules, both by themselves and in the presence of all contemplated packaging materials.

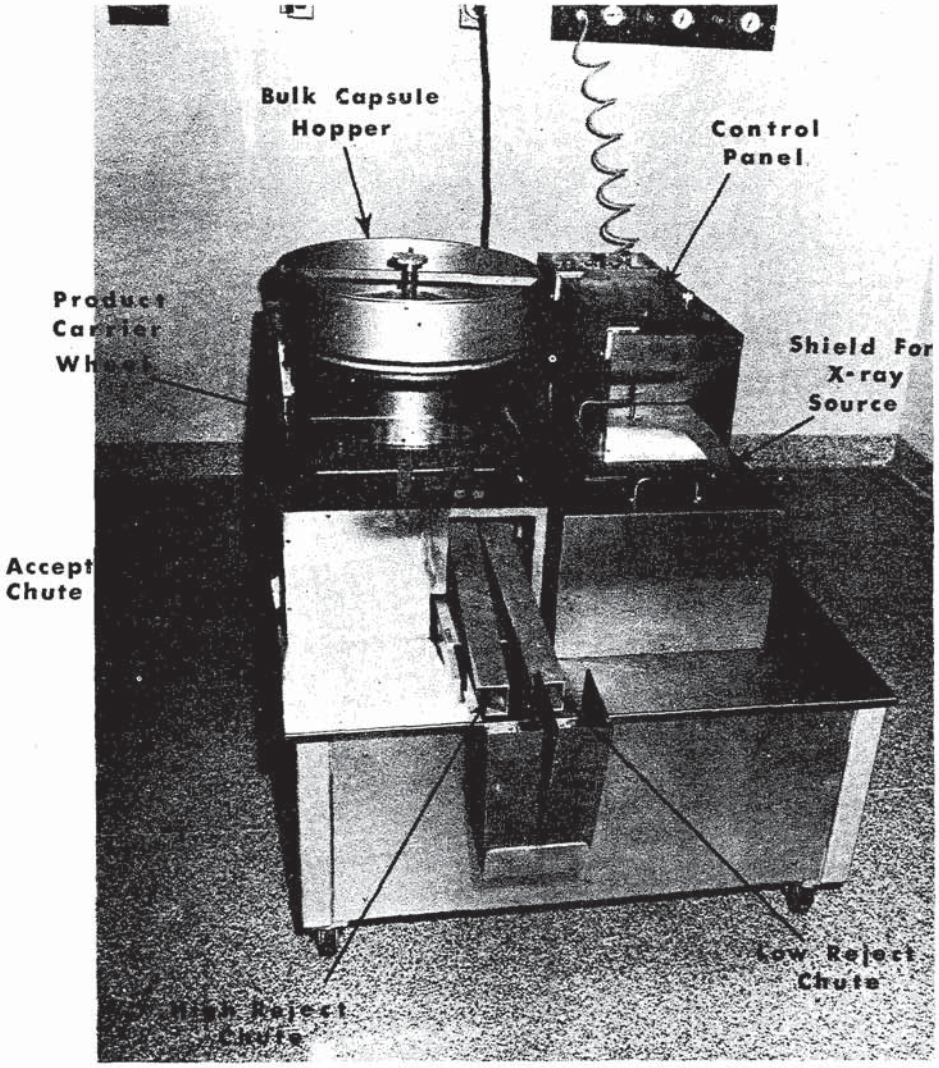


FIG. 13-19. *ROTOWEIGH capsule weighing machine. (Courtesy of Eli Lilly & Co., Indianapolis, IN.)*

Finishing

Finished capsules from all filling equipment require some sort of dusting and/or polishing operation before the remaining operations of inspection, bottling, and labeling are completed. Dusting or polishing operations vary according to the type of filling equipment used, the type of powder used for filling, and the individual desires for the finished appearance of the completed capsules. The following are the methods most commonly used, based on desired output, formulation, required final appearance, and so on.

1. *Pan polishing.* Because of its unique design (primarily in the area of airflow), the Accela-Cota tablet coating pan may be used to dust and polish capsules. A polyurethane or cheese cloth liner is placed in the pan, and the liner is used to trap the removed dust as well as to impart a gloss to the capsules.
2. *Cloth dusting.* In this method, the bulk-filled capsules are rubbed with a cloth that may or may not be impregnated with an inert oil. This procedure is a hand operation, but one that can handle reasonable volumes, and that results in a positive method for removal of resistant

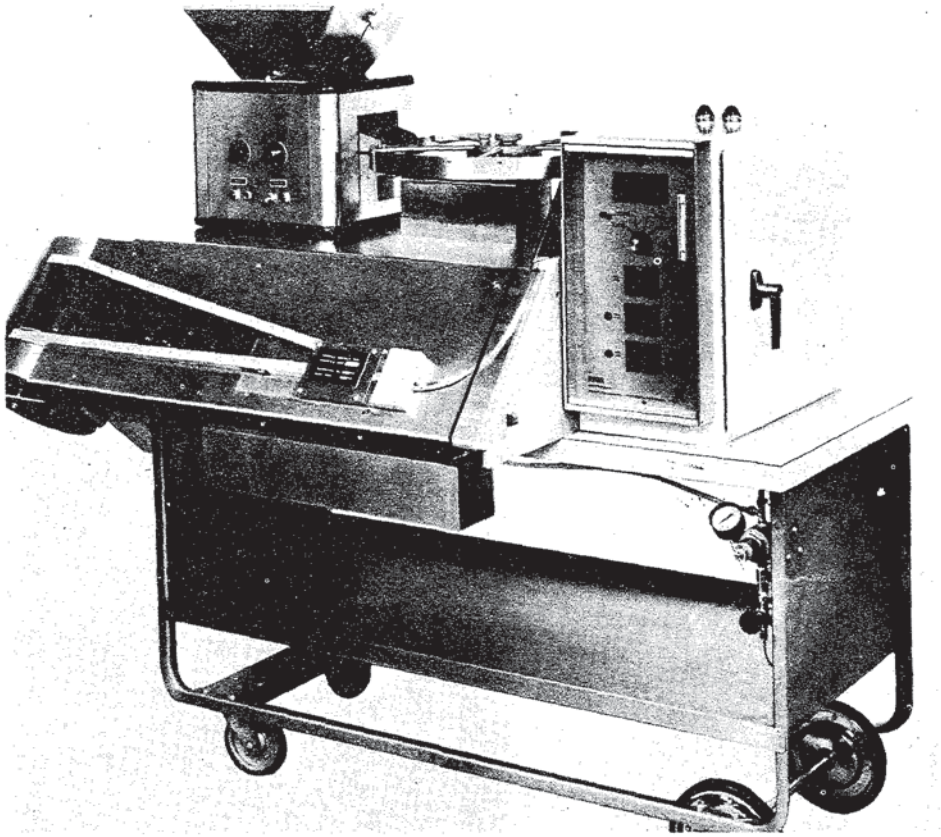


FIG. 13-20. *Vericap 1200 capsule weighing machine. (Courtesy of Modern Controls, Elk River, MN.)*

materials. In addition, it imparts a somewhat improved gloss to the capsules.

3. *Brushing.* In this procedure, capsules are fed under rotating soft brushes, which serve to remove the dust from the capsule shell. This operation must be accompanied by a vacuuming for dust removal. Some materials are extremely difficult to remove by brushing, even to the point of impregnating the brushes and causing scratches or deformation of the capsules.

Commercial capsule sort/polish equipment has become available. Some of the units, in addition to the Accela-Cota pan, are as follows.

ROTOSORT is a new filled capsule sorting machine sold by Eli Lilly and Company (Fig. 13-21). It is a mechanical sorting device that removes loose powder, unfilled joined capsules, filled or unfilled bodies, and loose caps. It can handle up to 150,000 capsules per hour, and it can run directly off a filling machine or be used separately.

The Erweka KEA dedusting and polishing machine for hard gelatin capsules is sold in the

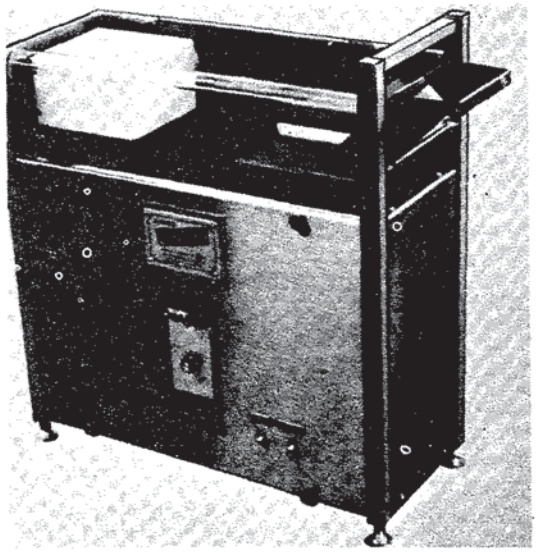


FIG. 13-21. *ROTOSORT capsule sorting machine. (Courtesy of Eli Lilly & Co., Indianapolis, IN.)*

United States by Key Industries, Englishtown, NJ (Fig. 13-22). The unit is designed to handle the output from any capsule filling machine. It moves the capsules between soft plastic tassels against a perforated plastic sleeve, under vacuum. Any residual powder is removed by the vacuum.

Seidenader Equipment, Totowa, NJ, offers two units that may be used separately or may be combined in the finishing of filled gelatin capsules. A belt is available that presents capsules for visual inspection, and it may include a vacuum system to automatically remove unfilled capsules. Cleaning and polishing machine PM60 (Fig. 13-23) may be used to polish finished capsules. It consists of two lamb's wool belts moving in opposite directions. The capsules are carried on the lower belt, and both belts are under suction.

Special Techniques

Some special techniques that may be applied to the capsules as a dosage form include the following.

1. Imprinting is a convenient method by which company and/or product identification information can be placed upon each capsule. The imprinting operation is best performed on the empty capsules, although filled capsules can be printed. The preference for imprinting empty capsules arises from the fact that the imprinting operation may occasionally damage some capsules. When filled capsules are imprinted, contamination, poor print quality, and actual damage to the imprinting equipment result. Various types and capacities of equipment are commercially available for this purpose in the United States. The three major suppliers of this equipment are Ackley Machine Corporation, Moorestown, NJ; R. W. Hartnett Company, Philadelphia, PA; and the Markem Machine Company, Keene, NH.

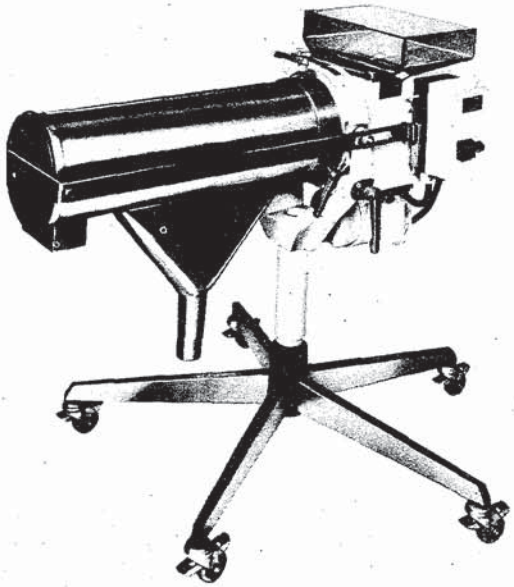


FIG. 13-22. *Erweka KEA capsule dedusting and polishing machine. (Courtesy of Erweka-Apparatebau, Heusenstamm, West Germany.)*

Hartnett offers a variety of machines with outputs as high as 500,000 capsules per hour (model B, Fig. 13-24). Also available is a unit that prints around the circumference of the capsules, as opposed to a longitudinal imprint; however, this machine operates at a slower rate. A lower-capacity unit (up to 250,000 capsules per hour) allows printing on both sides of the capsule, in different colors if desired.

Markem offers three models, which range from approximately 60,000 to 250,000 capsules per hour (Model 280A, Fig. 13-25). All three models allow for two-sided printing, but not circumferential.

Ackley offers a straight-line imprinter with an output rate of about 500,000 capsules per hour, and has recently announced a new circumferential printer rated at about the same output.

In addition, several firms, including the major empty capsule suppliers, offer custom imprinting services.

All imprinting machines operate on a rotogravure process, and a wide variety of colors of edible inks, both water- and solvent-based, are commercially available.

2. Special purpose capsules are capsules to which a special treatment has been given in an attempt to retard the solubility in some manner. This may be done in an attempt to delay absorption of the active ingredient, or to provide enteric properties. Normal solubility for gelatin capsules, either empty or filled, is not defined by the USP XX. However, the General Service Administration, in Federal Specification #U-C-115b (2/10/58), defines solubility limits for empty capsules as follows: (a) water resistance—fails to dissolve in water at 20 to 30°C in 15 min; (b) acid solubility—dissolves in less than 5 min in 0.5% aqueous HCl (w/w) at 36 to 38°C.

None of the following is used for any commercial products as far as is known and cannot be seriously recommended except for experimental purposes, because of generally unpredictable results.

a. Formalin treatment has been employed to modify the solubility of gelatin capsules. Expo-

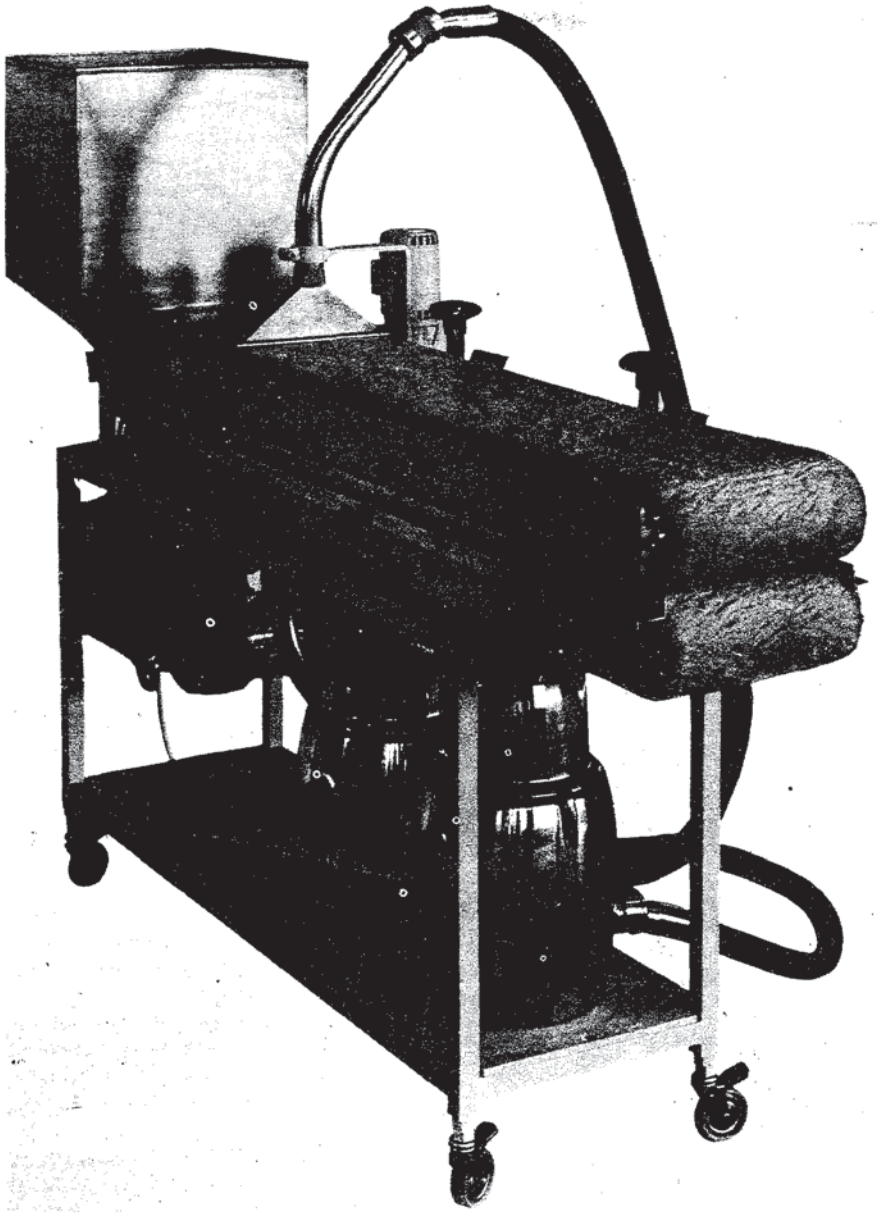


FIG. 13-23. *Seidenader Model PM60 capsule polishing machine. (Courtesy of Seidenader Maschinenbau München, West Germany.)*

sure to formalin vapors or treatment with aqueous formalin results in an unpredictable decrease in solubility of the gelatin film, owing to cross-linkage of the gelatin molecule initiated by the aldehyde. This result may also be noted if the product being filled contains aldehydic materials, or if aldehyde flavorants are added. Because of the nature of the reaction initiated in this manner, it is difficult to control the degree of insolubilization, or indeed, to prevent ultimate complete insolubility.

b. Various coatings have been used in an effort to provide similarly modified solubility characteristics. These coatings include salol, shellac, cellulose acetate phthalate, and certain resins that have usually been applied by usual pan coating techniques.

Gelatin capsules do, however, provide a con-

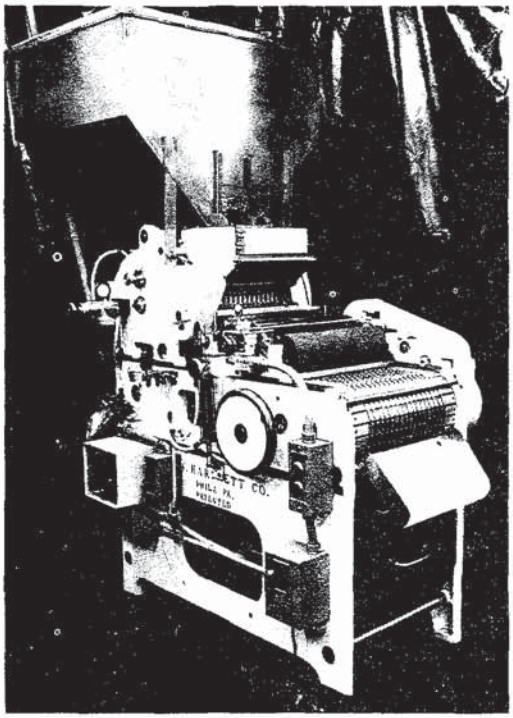


FIG. 13-24. *Hartnett Model B capsule imprinting machine. (Courtesy of R. H. Hartnett Co., Philadelphia, PA.)*

venient way to deliver pellets or granular material when delayed or prolonged release properties have been incorporated in all or portions of the material to be filled.

3. Separation of incompatible materials (a technique used for some commercial products) is carried out by the use of a two-phase fill in the capsule. One phase consists of either a soft capsule, a smaller hard capsule, a pill, or a suitably coated tablet that is filled into each capsule. Following this as a second phase, a powder fill is added in the usual manner. If this technique is used on commercial filling equipment, modifications must be made to the filling cycle of the machine. These changes would include, at minimum, the necessary changes in the machine operation to allow materials to be loaded at two points during the filling cycle. Tamp type powder filling machines require the disabling of the tamp cycle.

4. Recently, there has been a revival of interest in the filling of conventional two-piece gelatin capsules with liquids and semisolids. Hard gelatin capsules were commonly used as early as the 1890s for oils, ethereal extracts, and pill masses,[1] but the ability to fill the capsules on semiautomatic and automatic equipment is a recent development. The formulations used for filling are usually semisolids at ambient temper-

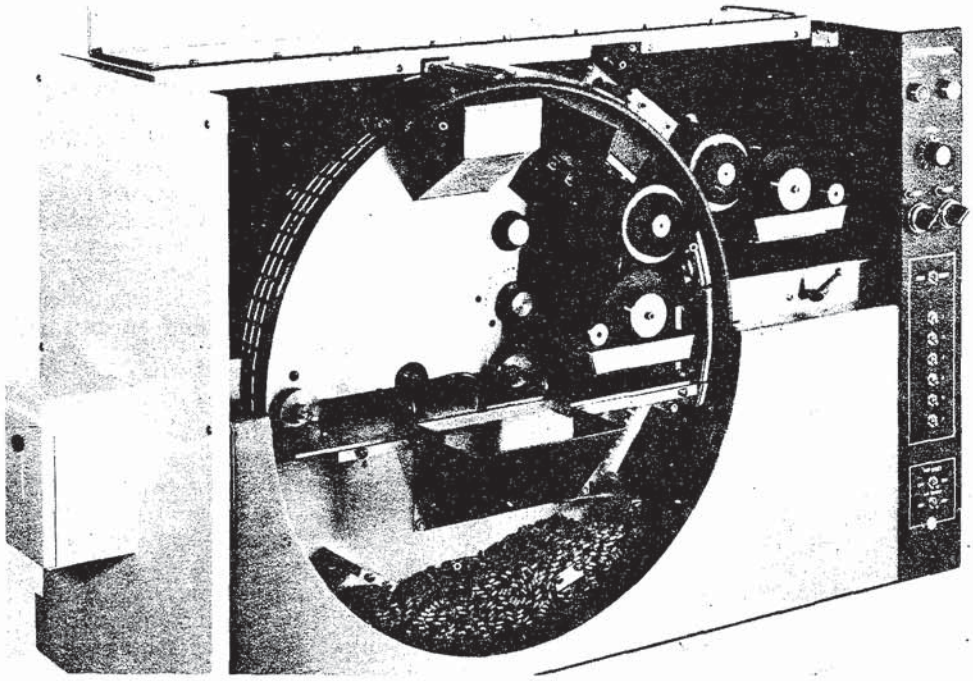


FIG. 13-25. *Markem Model 280A capsule imprinting machine. (Coursety of Markem Co., Keene, NH.)*

atures, which are melted to allow filling.[2] Or they are thixotropic formulations in which the shear developed in filling allows pumping, but whose high viscosity when shear is absent prevents leakage after filling. Quantitative assessment of the gastric emptying of hard gelatin capsules filled with thixotropic liquids can be made in terms of the lag time prior to emptying, and the slope of the first order emptying curve. Results have shown that the viscosity of the fill has no significant influence on the emptying characteristics of these dosage forms.[3] Machines for filling semisolid materials are currently available from Robert Bosch GmbH, Elanco, Harro Hofliger, and Zanasi.

5. A recent series of developments—primarily in Europe—have resulted in allowing the use of a liquid fill into two-piece hard capsules. The fills are either thermosetting (and filled warm) or thixotropic. Modified commercial equipment is available for filling.

References

1. Francois, D., and Jones, B.E.: Man. Chem. Aerosol News, 37:37, 1979.
2. Hunter, E., Fell, J.T., Sharma, H., and McNeilly, A.M.: Die Pharm. Ind., 44:90, 1982.
3. Hunter, E., Fell, J.T., Sharma, H., and McNeilly, A.M.: Die Pharm. Ind., 45:443, 1983.

PART TWO

Soft Gelatin Capsules

J. P. STANLEY

Many pharmaceutical companies have the equipment and facilities for the development and production of tablets, liquids, and hard-shell capsule products, but they usually depend upon custom manufacturers for the development and production of soft gelatin capsules. The custom manufacturers are specialists in this field, owing primarily to economic, patent, and technologic factors. Although few become directly involved in the manufacture of soft capsules, pharmaceutical chemists must be prepared to investigate this dosage form and to participate in its development, either in their own laboratories or in cooperation with the technical personnel of a custom manufacturer.

Owing to their special properties and advantages, soft gelatin capsules are used in a wide variety of industries, but they are used most widely in the pharmaceutical industry. Billions of capsules are made each year in various sizes and shapes (Fig. 13-26), and in a variety of colors and color combinations. Their pharmaceutical applications are:

1. As an oral dosage form of ethical or proprietary products for human or veterinary use.
2. As a suppository dosage form for rectal use,[1] or for vaginal use. Rectal dosage forms are becoming more acceptable for pediatric and geriatric use. Vaginal use is confined to applications that require the medication to be inserted at bedtime. Because of the action of the sphincter muscle, rectal use is not similarly limited.
3. As a specialty package in tube form, for human and veterinary single dose application of topical, ophthalmic, and otic preparations, and rectal ointments.

In the cosmetic industry, these capsules may be used as a specialty package for breath fresheners, perfumes, bath oils, suntan oils, and various skin creams.

Methods of Manufacture

Soft gelatin capsules have been available since the middle of the nineteenth century. Originally, they were made one at a time; leather molds—and later, iron molds—were used for shaping the capsule. The capsules were filled by medicine dropper and sealed by hand with a "glob" of molten gelatin. Since those early days, many methods of capsulation have been proposed and patented, but this discussion is confined to equipment of commercial significance in present use.

As technology advanced, the individual iron molds gave way to multiple molding units, and these eventually led to sets of plates containing die pockets. The *plate process* is the oldest commercial method of manufacture, but today this equipment can no longer be purchased, and consequently, only a few companies still use this process. The plate process—a batch process that requires two or three operators for each machine—has given way to the more modern continuous processes, which require considerably less manpower for operation.

The continuous processes became a commercial reality in 1933, when the late R. P. Scherer

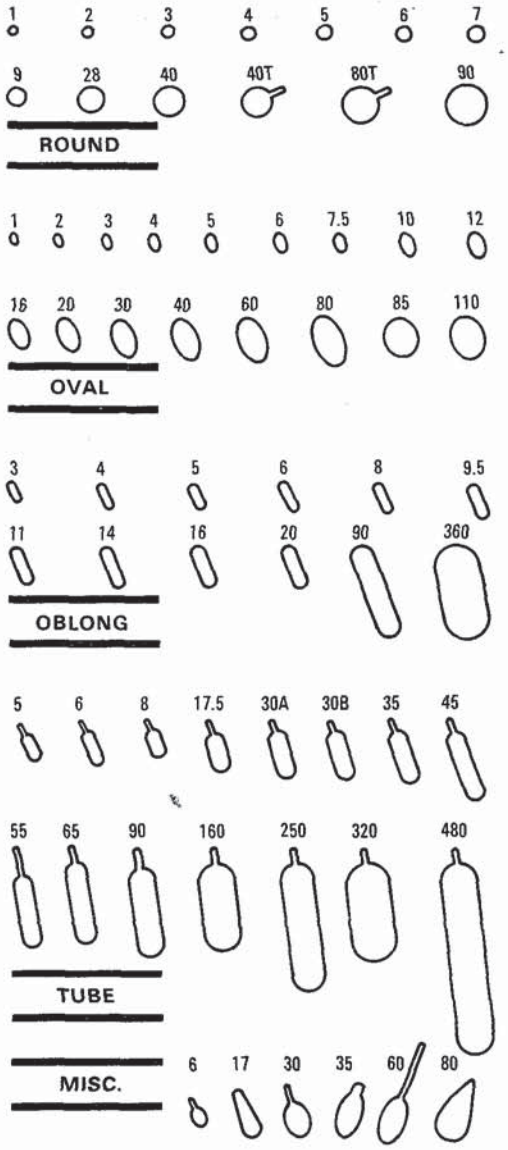


FIG. 13-26. *Sizes and shapes of soft gelatin capsules (1 cc = 16.23 m). Numbers represent the nominal capacity in minims. (Courtesy of R.P. Scherer Corporation, Troy, MI.)*

invented the *rotary die process*. Prior to this invention, soft gelatin capsules were not looked on favorably by the pharmaceutical industry, owing to the relatively large amount of the capsulated material (15 to 20%) lost during manufacture, and to the variation in the net content of the capsule (possibly 20 to 40%). The rotary die process reduced manufacturing losses to a negligible figure and content variation to less than ±3%. The Scherer machine cannot be purchased or leased, but the Scherer organization provides plant and laboratory facilities for the manufacture of this dosage form in the United States and nine foreign locations.

The early success of the rotary die process led others to develop continuous methods of soft gelatin capsule manufacture. One such method, known as the *reciprocating die process*, was announced in 1949 and was developed by the Norton Company, Worchester, MA. Another continuous process, also announced in 1949, was developed by the Lederle Laboratories Division of the American Cyanamid Company and has been used solely in the manufacture of that company's products. This equipment, known as the *Accogel machine*, is unique in that it is the only equipment that accurately fills powdered dry solids into soft gelatin capsules.

A discussion of the comparative advantages and disadvantages of the foregoing four processes—plate, rotary die, reciprocating die, and Accogel machine—is beyond the scope of this chapter and would have little instructive value, since the pharmaceutical chemist seldom has the opportunity to choose between the four types of equipment. One must consider, however, that for maximum production efficiency, the continuous processes demand almost 24 hours per day, 5 (preferably 7) days per week, of continuous operation. Thus, medicament formulations must be so designed as to maintain their desired physical characteristics during this period of operation as well as during periods of weekend shutdowns, should they occur. The production capacity of each of these machines is determined by (1) die size, which determines the number of die pockets on the standard-sized die plate, rotary die, or reciprocating die; (2) the speed of the machine (of the operators for the plate process); and (3) the physical characteristics of the material to be capsulated. Formulations are designed to achieve maximum production capacity consistent with maximum physical and ingredient stability and therapeutic efficacy

All of the aforementioned equipment is limited to the production of gelatin capsules. Other films and film-forming polymers have not as yet been successfully adapted for use on these machines. An interesting review of the patent literature, covering capsule technology, has been published.[2]

The Nature of the Capsule Shell

The capsule shell is basically composed of gelatin, a plasticizer, and water; it may contain additional ingredients such as preservatives, color-

ing and opacifying agents, flavorings, sugars, acids, and medicaments to achieve desired effects.

Gelatin's chemical, physical, and physiological properties make it an ideal substance for the capsulation of pharmaceutical products.[3-6] The *gelatin* is USP grade with additional specifications required by the capsule manufacturer. The additional specifications concern the Bloom strength, viscosity, and iron content of the gelatins used.

The *Bloom* or *gel strength* of gelatin is a measure of the cohesive strength of the cross-linking that occurs between gelatin molecules and is proportional to the molecular weight of the gelatin. Bloom is determined by measuring the weight in grams required to move a plastic plunger that is 0.5 inches in diameter 4 mm into a 6⅔% gelatin gel that has been held at 10°C for 17 hours. Bloom may vary with the requirements of the individual custom manufacturer but ranges from 150 to 250 g. In general, with all other factors being equal, the higher the Bloom strength of the gelatin used, the more physically stable is the resulting capsule shell. The cost of gelatin is directly proportional to its Bloom or gel strength and thus is an important factor in the cost of soft capsules. Consequently, the higher Bloom gelatins are only used when necessary to improve the physical stability of a product or for large capsules (over 50 minims), which require greater structural strength during manufacture.

Viscosity of gelatin, determined on a 6⅔% concentration of gelatin in water at 60°C, is a measure of the molecular chain length and determines the manufacturing characteristics of the gelatin film. The desired film characteristics are usually based on standard gelatin formulations, which allow production at a set sealing temperature and definite drying conditions, and produce a firm, nontacky, nonbrittle, pharmaceutically elegant product. The viscosity for gelatin can range from 25 to 45 millipoise, but the individual manufacturer sets a narrow range, e.g., 38 ± 2 millipoise, for a particular type of gelatin, to make use of a standard formulation and thus conform to standard production conditions.

Low-viscosity (25 to 32 millipoise), high-Bloom (180 to 250 g) gelatins are used in conjunction with the capsulation of hygroscopic vehicles or solids, and standard gelatin formulas can be modified so as to require up to 50% less water for satisfactory operation on the capsulation machine. These modified formulas afford less opportunity for the hygroscopic fill materials to attract water from the shell and thereby improve the ingredient and physical stability of the product.[7]

Iron is always present in the raw gelatin, and its concentration usually depends on the iron content of the large quantities of water used in its manufacture. Gelatins used in the manufacture of soft gelatin capsules should not contain more than 15 ppm of this element, because of its effect on Food, Drug, and Cosmetic (FD&C) certified dyes and its possible color reactions with organic compounds.

The *plasticizers* used with gelatin in soft capsule manufacture are relatively few. Glycerin USP, Sorbitol USP, Pharmaceutical Grade Sorbitol Special, and combinations of these are the most prevalent. The ratio by weight of dry plasticizer to dry gelatin determines the "hardness" of the gelatin shell, assuming that there is no effect from the capsulated material. (Some examples of glycerin/gelatin ratios are shown in Table 13-2 along with their typical usage.) The ratio by weight of water to dry gelatin can vary from 0.7 to 1.3 (water) to 1.0 (dry gelatin) depending on the viscosity of the gelatin being used. For most formulations, however, it is approximately 1 to 1. Since only water is lost during the capsule drying process, the percentage of plasticizer and gelatin in the shell is increased, but the important plasticizer to gelatin ratio remains unchanged.

In general, the additional *components* of the gelatin mass are limited in their use by (1) the

TABLE 13-2. *Typical Shell "Hardness" Ratios and Their Uses*

Hardness	*Ratio Dry Glycerin/ Dry Gelatin*	*Usage*
Hard	0.4/1	Oral, oil-based, or shell-softening products and those destined primarily for hot, humid areas.
Medium	0.6/1	Oral, tube, vaginal oil-based, water-miscible-based, or shell-hardening products and those destined primarily for temperate areas.
Soft	0.8/1	Tube, vaginal, water-miscible-based or shell-hardening products and those destined primarily for cold, dry areas.

amounts required to produce the desired effect; (2) their effect on capsule manufacture; and (3) economic factors. Examples of ingredients falling into the first two categories are shown in Table 13-3.

The addition of *medicaments* to the gelatin mass usually is not recommended, for economic reasons, since only 50% of the gelatin mass is incorporated into the capsules. This results in a 50% loss of the added medicament. However, certain highly active, relatively inexpensive compounds such as benzocaine (3 mg/capsule shell) in chewable cough capsules may be used successfully.

Additional comments relative to the *color* of the gelatin shell are in order, since color is such an important aspect of all products. This is particularly true of soft gelatin capsules, in which the color of the capsule can be definitely affected by the color or type of material capsulated. As a general policy, the color of the capsule shell should never be lighter in hue than the capsulated material.

More specifically, darker colors are more appropriate for large-size (14 to 20 minim oblong) oral products, since they will not accentuate the size. Also, before a color is chosen, mixtures should be checked in the laboratory by addition of water to ascertain if reactions take place to cause the mixture to darken, as in the case of ascorbic acid and iron salts in vitamin and mineral formulations, or as in the case of reactions between iron and compounds of a phenolic nature. Since iron is present in gelatin, dark spots may occur in the shell owing to the migration of water-soluble iron-sensitive ingredients from the fill material into the shell. As a rule, clear colors usually are employed with clear type fill materials, and opaque colors are used with suspensions, but the reverse of this rule can be chosen to achieve a particular appearance or for ingredient stability purposes. For special effects or identification purposes, two colors, both opaque or one opaque and one clear, may be chosen since the manufacturing process involves two gelatin films.

TABLE 13-3. *Additional Components of the Gelatin Mass*

Ingredient	*Concentration*	*Purpose*
Category I		
Methylparaben, 4 parts; Propylparaben, 1 part	0.2%	Preservative
FD&C and D&C water-soluble dyes, certified lakes, pigments, and vegetable colors, alone or in combination	q.s.	Colorants
Titanium dioxide	0.2 to 1.2%	Opacifier
Ethyl vanillin	0.1%	Flavoring for odor and taste
Essential oils	to 2%	Flavoring for odor and taste
Category II		
Sugar (sucrose)	to 5%	To produce chewable shell and taste
Fumaric acid	to 1%	Aids solubility; reduces aldehydic tanning of gelatin

A publication by Hom and co-workers describes a gelatin disk method for the determination of the effects of agitation, temperature, dissolution medium, and shell composition on the dissolution rate of soft gelatin capsules.[8] This information should be helpful in the formulation of gelatin capsules for various purposes.

From the foregoing discussion on the gelatin shell, one may conclude that the pharmaceutical chemist must rely heavily on the experience of the custom capsule manufacturer. However, in order to choose the proper gelatin, gelatin formula, and color, the custom manufacturer must rely on the technical and product information designed and developed by the pharmaceutical chemist. With such mutual cooperation and free exchange of information, new products or dosage forms can be efficiently developed.

The Nature of the Capsule Content

Soft gelatin capsules can be used to dispense a variety of liquids and solids. Requirements and specifications of these materials vary, depending on the equipment of the manufacturer, but there are basic precepts that may be used as a guide for the formulation and production of commercially and therapeutically acceptable capsules, regardless of method of capsulation. The formulation of the capsule content for each product is individually developed to fulfill the specifications and end-use requirements of the product.

Except for the Accogel process, which is primarily concerned with the capsulation of dry

powders, the content of a soft gelatin capsule is a liquid, or a combination of miscible liquids, a solution of a solid(s) in a liquid(s), or a suspension of a solid(s) in a liquid(s). All such materials for capsulation are formulated to produce the smallest possible capsule consistent with maximum ingredient and physical stability, therapeutic effectiveness, and production efficiency. Once the smallest capsule size is determined, personnel in the sales or marketing departments usually choose the color, shape, and ultimate size of the retail product, unless there is a technical or production reason for the development chemist to specify a particular size, shape, and color. The maximum capsule size and shape for convenient oral use in humans is the 20 minim oblong, the 16 minim oval, or the 9 minim round as shown in Figure 13-26.

Liquids are an essential part of the capsule content. Only those liquids that are both water-miscible and volatile cannot be included as major constituents of the capsule content since they can migrate into the hydrophilic gelatin shell and volatilize from its surface. Water, ethyl alcohol, and, of course, emulsions fall into this category. Similarly, gelatin plasticizers such as glycerin and propylene glycol cannot be major constituents of the capsule content, owing to their softening effect on the gelatin shell, which thereby makes the capsule more susceptible to the effects of heat and humidity. As minor constituents (up to about 5% of the capsule content), water and alcohol can be used as cosolvents to aid in the preparation of solutions for capsulation. Also, up to 10% glycerin and/or propylene glycol can be used as cosolvents with polyethylene glycol or other liquids that have a shell-hardening effect when capsulated alone.

There are a large number of liquids that do not fall into the foregoing category and thus can function as active ingredients, solvents, or vehicles for suspension-type formulations. These liquids include aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, and high-molecular-weight alcohols, esters, and organic acids. Many of these are used in veterinary, cosmetic, and industrial products. For human use, however, the pharmaceutical chemist is often limited in his selection or use of a particular liquid because of government regulations, product performance specifications, ingredient incompatibilities, and liquid-solid adsorption characteristics. The most widely used liquids for human use are oily active ingredients (clofibrate), vegetable oils (soybean oil), mineral oil, nonionic surface active agents (polysorbate 80), and polyethylene glycols (400 and 600), either alone or in combination. Such active ingredient oils as fish oil may also function as a solvent, or as the suspending medium for one or more additional active ingredients, as in vitamin capsules.

All liquids, solutions, and suspensions for capsulation should be homogeneous and air-free (vide infra), and preferably should flow by gravity at room temperature, but not at a temperature exceeding 35°C at the point of capsulation, since the sealing temperature of the gelatin films is usually in the range of 37 to 40°C. In general, liquids ranging in *viscosity* from ethyl ether (0.222 cp at 25°C)[9] to heavy adhesive mixtures (exceeding 3000 cp at 25°C) may be encapsulated, but there are some exceptions since the property of viscosity alone is not the sole criterion. Liquids that exhibit the rheologic property of tack or tackiness, such as glycerin (954 cp at 25°C),[9] are exceptions, since such liquids can eventually cause the binding of slide valves and pumps in the capsule filling mechanism. Also, preparations for encapsulation should have a pH between 2.5 and 7.5, since preparations that are more acidic can cause hydrolysis and leakage of the gelatin shell, and preparations that are more alkaline can tan the gelatin and thus affect the solubility of the shell.

The capsulation of water-immiscible liquids is the simplest form of soft gelatin capsulation and usually requires little or no formulation. The minimum size capsule depends on the dosage desired, the minimum fill volume being calculated from the specific gravity of the liquid. A die size and shape may then be chosen from those shown in Figure 13-26. The nearest die size above the calculated fill volume may be used, or any larger die may be chosen if the active ingredient is to be diluted for some reason. For example, a 25,000-unit vitamin A capsule using vitamin A palmitate (1,000,000 units A/g) as a source for the vitamin A would have a minimum fill volume of about 0.45 minims, and thus could be diluted to any size capsule desired. On the other hand, the same potency capsule using fish oil (50,000 units A/g) as a source for the vitamin A would have a minimum fill volume of about 8.8 minims.

The minimum fill volume for water-miscible, nonvolatile liquids, such as polysorbate 80, is determined in the same manner. Because of their hygroscopic nature, however, they cause water to migrate from the gelatin shell into the fill material. This migration is rapid and could amount to 20% of the weight of the miscible liquid. During the drying period of the capsule, most of this water returns to and passes through the gelatin shell, but up to 7.5% of the original water can remain in the fill material, depending

on the hydrophilic properties of the liquid. Thus, *for liquids of this type, a safety factor must be* used in establishing the minimum fill volume and in choosing the die.*

Although oily liquids do not retain moisture, water does pass from the shell of the capsule into the fill material and out again during the *manufacture and drying of these capsules. This* is important for the formulator to remember, since such water transfer can and does have a bearing on formulations in which oily liquids are used as solvents or as vehicles for suspensions. If such suspensions contain hydrophilic solids, water may be retained up to 3% by weight of the hydrophilic material.

Combinations of miscible liquids often are used to produce desired physiological results such as increased or more rapid absorption of active ingredient (vitamin A and polysorbate 80); or to produce desired physiochemical results, such as improved flow properties (dilution or partial substitution with a thinner liquid), or improved solubility (steroid with oil and benzyl alcohol).

Except for when the Accogel process is used, solids are filled into soft gelatin capsules, in the form of either a solution or a suspension. The preparation of a suitable solution of a solid medicament should be the first goal of the pharmaceutical chemist. Usually, a solution is more easily capsulated and exhibits better uniformity, stability, and biopharmaceutical properties than does a suspension. For oral products, the medicament must have sufficient solubility in the solvent system so that the necessary dose is contained in a maximum fill volume of 16 to 20 minims (1 to 1.25 cc).

Solids that are not sufficiently soluble in liquids or in combinations of liquids are capsulated as suspensions. Most organic and inorganic solids or compounds may be capsulated. Such materials should be 80 mesh or finer in particle size, owing to certain close tolerances of the capsulation equipment and for maximum homogeneity of the suspension. Many compounds cannot be capsulated, owing to their solubility in water and thus their ability to affect the gelatin shell, unless they are minor constituents of a formula or are combined with a type of carrier (liquid or solid) that reduces their effect on the shell. Examples of such solids are strong acids (citric), strong alkalies (sodium salts of weak acids), salts of strong acids and bases (sodium chloride, choline chloride), and ammonium salts. Also, any substance that is unstable in the presence of moisture (e.g., aspirin) would not exhibit satisfactory chemical stability in soft gelatin capsules.

The capsulation of *suspensions* is the basis for the existence of a large group of products. Again, the design of suspension type formulations and the choice of the suspending medium are directed toward producing the smallest size capsule having the characteristics previously described, i.e., maximum production capacity consistent with maximum physical and ingredient stability and therapeutic efficacy.

The formulation of suspensions for capsulation follows the basic concepts of suspension technology. Formulation techniques, however, can vary depending on the drug substance, the desired flow characteristics, the physical or ingredient stability problems, or the biopharmaceutical properties desired. In most instances, these techniques must be developed through the ingenuity of the formulating chemist; however, in the formulation of suspensions for soft gelatin encapsulation, certain basic information must be developed to determine minimum capsule size.

One laboratory tool for this purpose is known as the "base adsorption" of the solid(s) to be suspended. Base adsorption is expressed as the number of grams of liquid base required to produce a capsulatable mixture when mixed with one gram of solid(s). The base adsorption of a solid is influenced by such factors as the solid's particle size and shape, its physical state (fibrous, amorphous, or crystalline), its density, its moisture content, and its oleophilic or hydrophilic nature.

In the determination of base adsorption, the solid(s) must be completely wetted by the liquid base. For glycol and nonionic type bases, the addition of a *wetting agent* is seldom required, but for vegetable oil bases, complete wetting of the solid(s) is not achieved without an additive. Soy lecithin, at a concentration of 2 to 3% by weight of the oil, serves excellently for this purpose, and being a natural product, is universally accepted for food and drug use. Increasing the concentration above 3% appears to have no added advantage.

A practical procedure for determining base adsorption and for judging the adequate fluidity of a mixture is as follows. Weigh a definite amount (40 g is convenient) of the solid into a

* For example, a capsule to contain 500 mg of Polysorbate 80 would have a calculated $\left(\frac{0.5\text{g} \times 16.23 \text{ minim}}{1.08\text{g}}\right)$ fill volume of about 7.5 minims. Assuming, however, that there is 5% residual water in the dry capsule, the final fill volume would be about 8 minims $\left(\frac{.525\text{g} \times 16.23 \text{ minim}}{1.08\text{g}}\right)$.

150-ml tared beaker. In a separate 150-ml tared beaker, place about 100 g of the liquid base. Add small increments of the base to the solid, and using a spatula, stir the base into the solid after each addition until the solid is thoroughly wetted and uniformly coated with the base. This should produce a mixture that has a soft ointment-like consistency. Continue to add liquid and stir until the mixture flows steadily from the spatula blade when held at a 45-degree angle above the mixture. The flow is even and continuous, and not in "globs." Attention also should be given to the nature of the "cut-off" quality of the mixture. As the mixture tends to stop flowing, proper cut-off is exhibited when the stream contracts rapidly upward toward the spatula blade rather than "stringing out" in intermediate flow.

At the conclusion of the foregoing test, the base adsorption is obtained by means of the following formula:

$$\frac{\text{Weight of Base}}{\text{Weight of Solid}} = \text{Base Adsorption}$$

The base adsorption mixture is milled or homogenized, and deaerated (a desiccator under vacuum is suitable), and the specific gravity is taken. The specific gravity is the weight of mixture (W) per cubic centimeter or per 16.23 minims (V). As in the case of liquids and solutions, the specific gravity may be used to determine the die size required for a given quantity of the particular mixture.

The base adsorption is used to determine the "minim per gram" factor (M/g) of the solid(s). The minim per gram factor is the volume in minims that is occupied by one gram (S) of the solid plus the weight of liquid base (BA) required to make a capsulatable mixture. The minim per gram factor is calculated by dividing the weight of base plus the gram of solid (BA + S) by the weight of mixture (W) per cubic centimeter or 16.23 minims (V). A convenient formula is:

$$\frac{(\text{BA} + \text{S}) \times \text{V}}{\text{W}} = \text{M/g}$$

Thus, the lower the base adsorption of the solid(s) and the higher the density of the mixture, the smaller the capsule will be. This also indicates the importance of establishing specifications for the control of those physical properties of a solid mentioned previously that can affect its base adsorption.

The BA and M/g data need not be obtained on any material that is to be capsulated alone at concentrations of 50 mg or less, since the smallest capsules can accommodate such quantities. If such material is to be used in combination, however, the data become necessary to allow for its inclusion in the formulation. The convenience of using M/g factors is particularly evident in the vitamin field, where there may be many ingredients and numerous combinations. Since the minim per gram factors are additive, they can be used for a more rapid calculation of capsule size than can be given by the preparation of the many possible mixtures in the laboratory. See Table 13-4 for BA and M/g data on some typical solids.

The final formulation of a suspension invariably requires a *suspending agent* to prevent the settling of the solids and to maintain homogeneity prior to, during, and after capsulation. The nature and concentration of the suspending agent vary, depending on the job to be done. Also, a rather delicate balance must be achieved between the requirement for a stable suspension and the requirement for the mixture to have the proper flow characteristics. There is evidence, too, that the proper suspending agent coats the suspended solids, imparting a certain lubricity to them and thereby aiding capsulation. Also, the coating can prevent contact with possible incompatible components in the mixture. Of the examples shown in Table 13-5, the most widely used suspending agent for oily bases is wax mixture, and in nonoily bases, the polyethylene glycols 4000 and 6000.

In all instances, the suspending agent used is melted in a suitable portion of the liquid base, and the hot melt is added slowly, with stirring, into the bulk portion of the base, which has been preheated to 40°C prior to the addition of any solids. The solids are then added, one by one, with sufficient mixing between additions to ensure complete wetting. Incompatible solids are added as far apart as possible in the mixing order to prevent interaction prior to complete wetting by the base.

Additional aids to formulation involve the physical and ingredient stability of the capsules. There should be little concern with oxidation or the effects of light as a cause of ingredient instability, since the gelatin shell is an excellent oxygen barrier and may be opacified.[10,11]

Most ingredient stability problems are associated with the available moisture from the gelatin shell, which when absorbed into the capsule content, can cause areas of high concentration of water-soluble solids, leading to ionization and interaction of the solids. Such problems may be alleviated or eliminated by employing a less soluble salt (procaine penicillin instead of potas-

TABLE 13-4. *BA and M/g Factors of Some Typical Solids*

Ingredient	*Base**	*BA*	*M/g*
Acetaminophen	Veg. oil	0.76	25.97
Acetaminophen	PEG 400	0.75	23.07
Ascorbic acid	Veg. oil	0.60	20.60
Ascorbic acid	Polysorbate 80	1.10	26.92
$Al(OH)_3$—$MgCO_3$ (FMA 11)	Veg. oil	1.90	41.30
$Al(OH)_3$—$MgCO_3$ (FMA 11)	PEG 400	2.44	42.10
Danthron	Veg. oil	1.30	33.75
Danthron	Glyceryl monooleate	1.39	33.94
Danthron	Polysorbate 80	1.38	31.28
Danthron	PEG 400	1.60	33.62
Danthron	Triacetin	1.83	36.02
Ephedrine SO_4	Veg. oil	1.30	36.80
Ferrous SO_4 exsiccated	Veg. oil	0.30	10.60
Ferrous SO_4 exsiccated	Polysorbate 80	0.47	12.90
Guaifenesin	Veg. oil	1.28	34.68
Lactose	Veg. oil	0.75	23.87
Desiccated liver	Veg. oil	0.80	25.70
Mephenesin	Veg. oil	2.50	57.38
Mephenesin	PEG 400	2.13	44.77
Meprobamate	Veg. oil	1.59	42.55
Meprobamate	PEG 400	1.30	32.52
Niacinamide	Veg. oil	0.80	25.63
Neomycin sulfate	Veg. oil	0.60	20.66
Phenobarbital	Veg. oil	1.20	33.60
Procaine penicillin G	Veg. oil	0.91	28.63
Sodium ascorbate	Veg. oil	0.76	22.40
Salicylamide	Veg. oil	0.80	25.80
Sulfathiazole	Veg. oil	0.43	17.90
Sulfanilamide	Veg. oil	1.03	28.55
Tetracycline (amphoteric)	Veg. oil	0.61	21.63

*Vegetable oil bases contain 3% soy lecithin.

sium), employing coatings (gelatin-coated B_{12}), adjusting pH with appropriate small quantities of citric, lactic, or tartaric acids or with less restrictive quantities of sodium ascorbate or magnesium oxide, or salting-out with appropriate small quantities of sodium chloride or sodium acetate.

Usually, the *physical stability* of a product is associated primarily with the type of gelatin and gelatin formulation used but can be aided by proper fill formulation. If a particular solid may have a deleterious action on the gelatin shell, the form of the solid that is least water-soluble and the most oleophilic would be the form of

TABLE 13-5. *Typical Suspending Agents*

Type	*Concentration of Oily Base (%)*	*Type*	*Concentration of Nonoily Base (%)*
White wax, NF	5	Polyethylene glycol 4000 and 6000	1–15
Paraffin wax, NF	5	Solid nonionics	10
Animal stearates	1–6	Solid glycol esters	10
Wax mixture*	10 and 30	Acetylated monoglycerides	5
Aluminum monosterate, NF†	3–5		
Ethocel (100 cps)†	5–10		

*1 part hydrogenated soybean oil; 1 part yellow wax, NF; 4 parts vegetable shortening (melting point 33 to 38°C); used at 10% on the adsorption oil and at 30% on any filler oil required.

†Used with volatile organic liquids such as butyl chloride; toluene; tetrachlorethylene; benzene.

choice for an oil-based suspension. An example would be the use of calcium salicylate rather than the sodium or magnesium salts. Also, the type of liquid base used can have an effect on physical stability. For example, the proteolytic effect of chloral hydrate on the gelatin shell is greatly reduced when a polyethylene glycol base is used in place of an oily base.

With the proper selection of materials and formulation techniques, the pharmaceutical chemist can prepare solutions or suspensions for comparisons of stability and dissolution rate with formulations of other solid dosage forms. By accurately filling two-piece gelatin capsules with such formulations, comparative absorption, urinary excretion, and metabolic studies can be made prior to the actual preparation of the soft gelatin capsule dosage form. Today the product development laboratory must evaluate all potential formulations for a new drug substance or for product improvement.

Capsule Manufacture, Processing, and Control

Although this aspect of soft gelatin capsules is the primary responsibility of the custom manufacturer, the pharmaceutical chemist should have an understanding of the materials and equipment involved in the capsule's manufacture, processing, and quality control. The several methods of capsulation referred to in the early part of this chapter, although differing somewhat in mechanical principles, do require the use of similar materials, processing steps, and equipment, and the use of equivalent control procedures.

Except for the gelatin preparation department, the manufacturing areas of a typical plant are air-conditioned to assure the proper conditioning of the gelatin films, the proper drying of the capsules, and the consistent low moisture content of raw materials and mixtures. The temperature is usually in the range of 20 to 22°C, and the humidity is controlled to a maximum of 40% in the operating areas and a range of 20 to 30% in the drying areas.

In the *gelatin preparation* department of a typical manufacturer, the gelatin is weighed on printomatic scales and mixed with the accurately metered (printomatic) and chilled (7°C) liquid constituents in suitable equipment, such as a Pony Mixer. The resultant fluffy mass is transferred to melting tanks and melted under vacuum (29.5″ Hg) at 93°C. The mixing process requires about 25 min for 270 kg of mass, and the melting procedure requires about 3 hours. A sample of the resulting fluid mass is visually compared with a color standard, and additional colorants are blended into the mass if adjustments are required. The mass is then maintained at a temperature of 57 to 60°C before and during the capsulation process.

The *materials preparation* department will have a weigh-off and mixing area containing the necessary equipment and facilities for the preparation of the variety of mixtures that may be capsulated. Typical equipment would include printomatic scales for exacting measurements and control records; stainless-steel jacketed tanks for handling from 10- to 450-gallon batches of mix; and mixers, such as the Cowles, for the initial blending of solids with the liquid base. After the initial blending is completed, the mixture is put through a *milling* or *homogenizing* process, using equipment such as the homoloid mill, stone mill, hopper mill, or the Urschel Comitrol. The purpose of the milling operation is not to reduce particle size, but to break up agglomerates of solids and to make certain that all solids are "wet" with the liquid carrier, so as to achieve a smooth and homogenous mixture.

Following the milling operation, all mixtures are subjected to *deaeration*, and particularly so if the capsulation machine is equipped with a positive displacement pump. Deaeration is necessary to achieve uniform capsule fill weights; it also protects against loss of potency through oxidation prior to and during capsulation. When small amounts of volatile ingredients are included in a formulation, they are carefully added and blended into the bulk mixture after deaeration. Most liquids and suspensions may be deaerated by means of equipment designed to expose thin layers of the material continuously to a vacuum (29.5″ Hg) and at the same time transfer the material from the mixing tank to the container that will be used at the capsulation machine. Suspensions or liquid mixtures containing volatile liquids or liquid surface active agents as chief constituents of the formula may be deaerated by subjection to temperatures up to 60°C for the period required to achieve the results desired. After deaeration, the mixture is ready to be capsulated.

At this point, samples of the mixture are often sent to the quality control laboratory for various tests, such as ingredient assays and specific gravity, and tests for homogeneity of suspension, moisture content, or air entrapment. This in-process quality control step may or may not be routine, depending on the product or anticipated problems, but should always occur with new products until the process is validated.

Owing to space limitations, a detailed description of each capsulation process is not possible. A schematic drawing of the rotary die process is presented, however, to acquaint the pharmaceutical chemist with the fundamental aspects of capsulation (Fig. 13-27). The gelatin mass is fed by gravity to a metering device (spreader box), which controls the flow of the mass onto air-cooled (13 to 14°C) rotating drums. Gelatin ribbons of controlled (±10%) thickness are formed. The wet shell thickness may vary from 0.022 to 0.045 inch, but for most capsules, it is between 0.025 and 0.032 inch. Thicker shells are used on products requiring greater structural strength. Product cost is directly proportional to shell thickness. The ribbons are fed through a mineral oil lubricating bath, over guide rolls, and then down between the wedge and the die rolls.

The material to be capsulated flows by gravity into a positive displacement pump. The pump accurately meters the material through the leads and wedge and into the gelatin ribbons between the die rolls. The bottom of the wedge contains small orifices lined up with the die pockets of the die rolls. The capsule is about half sealed when the pressure of the pumped material forces the gelatin into the die pockets, where the capsules are simultaneously filled, shaped, hermetically sealed, and cut from the gelatin ribbon. The sealing of the capsule is achieved by mechanical pressure on the die rolls and the heating (37 to 40°C) of the ribbons by the wedge.

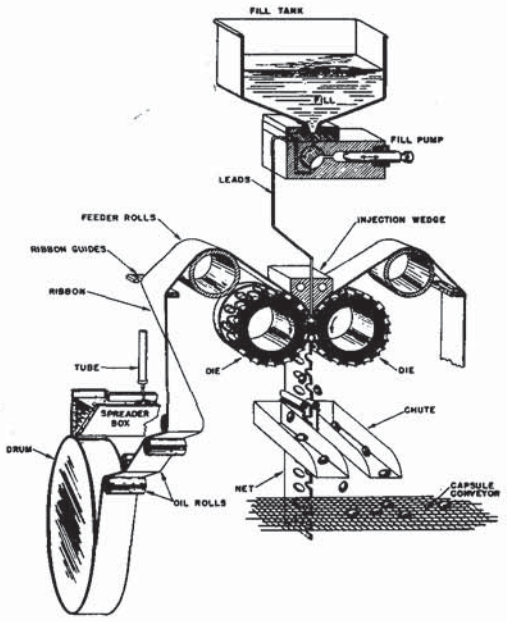


FIG. 13-27. *Schematic drawing of rotary die process. (Courtesy of R.P. Scherer Corporation, Troy, MI.)*

During manufacture, capsule samples are taken periodically for seal thickness and fill weight checks. The seals are measured under a microscope, and changes in ribbon thickness, heat, or die pressure are made if necessary. Acceptable seal thickness is one half to two thirds of the ribbon thickness. Fill weight checks are made by weighing the whole fresh capsule, slitting it open, and expressing the contents. The shell is then washed in a suitable solvent (petroleum ether), and the empty shell is reweighed. If necessary, adjustments in the pump stroke can be made to obtain the proper fill weight.

Immediately after manufacture, the capsules are automatically conveyed through a naphtha wash unit to remove the mineral oil lubricant. The washed capsules may be automatically subjected to a preliminary infrared drying step, which removes 60 to 70% of the water that is to be lost, or may be manually spread directly on trays. Capsules from the infrared dryer are also spread on trays, and all capsules are allowed to come to equilibrium with forced air conditions of 20 to 30% relative humidity at 21 to 24°C.

Capsules at equilibrium with 20 to 30% RH at 21 to 24°C are considered "dry," and the shell of such a capsule contains 6 to 10% water, depending on the gelatin formula used. The moisture content of the shell is determined by the toluene distillation method, collecting the distillate over a period of one hour. Additional water may be removed from "dry" capsules by further heating, e.g., at 40°C, but such a manufacturing step has not been found to be practical or necessary.

After drying, the capsules are transferred to the inspection department and held until released by the quality control department. The *inspection and quality control* steps in the processing of capsules are much the same as with other dosage forms and must conform to good manufacturing practice. Control tests specifically applicable to the quality of soft gelatin capsules may involve seal thickness determinations, total or shell moisture tests, capsule fragility or rupture tests, and the determination of freezing and high temperature effects.

Also, capsules may be sent after drying to a finishing department for heat branding or ink printing for purposes of identification.

Final physical control processing and packaging may be accomplished by the following in-line continuous operations.

1. A capsule diameter sorter allows to pass to the next unit any capsule within ±0.020 inch of the theoretic diameter of the particular capsule being tested. Overfills, underfills, and "foreign"

capsules are discarded. The unit is fed from a hopper, and the capsules are passed through a final naphtha washing unit just prior to the sorter. The unit employs a syntron vibrator, which is a series of divergent wire lanes, and can be used for capsule diameters ranging from 0.200 to 0.500 inch.

2. A capsule color sorter is the next unit in line. The capsules are fed to it automatically from the diameter sorter by a pneumatic conveyor. In this unit, any capsule whose color does not conform to the reference color standard for that particular product is discarded, while satisfactory capsules pass immediately to an electronic counting and packaging unit.

3. The electronic counting unit can count as many as 8,000 capsules per minute (depending upon size) directly into the bulk shipping carton. A printout of the content of each carton and a printout of the number of cartons are automatically produced and made a part of the production record. Following this step, the cartons are labeled, sealed, and palletized and are then ready for shipment.

Capsule Physical Stability and Packaging

Unprotected soft gelatin capsules (i.e., capsules that can breathe) rapidly reach equilibrium with the atmospheric conditions under which they are stored. This inherent characteristic warrants a brief discussion of the effects of temperature and humidity on these products, and points to the necessity of proper storage and packaging conditions and to the necessity of choosing an appropriate retail package. The variety of materials capsulated, which may have an effect on the gelatin shell, together with the many gelatin formulations that can be used, makes it imperative that physical standards are established for each product.

General statements relative to the effects of temperature and humidity on soft gelatin capsules must be confined to a control capsule that contains mineral oil, with a gelatin shell having a dry glycerin to dry gelatin ratio of about 0.5 to 1 and a water to dry gelatin ratio of 1 to 1, and that is dried to equilibrium with 20 to 30% RH at 21 to 24°C. The physical stability of soft gelatin capsules is associated primarily with the pick-up or loss of water by the capsule shell. If these are prevented by proper packaging, the above control capsule should have satisfactory physical stability at temperatures ranging from just above freezing to as high as 60°C.

For the unprotected control capsule, low humidities (<20% RH), low temperatures (<2°C) and high temperatures (>38°C) or combinations of these conditions have only transient effects. The capsule returns to normal when returned to optimum storage conditions. The transient effects are primarily brittleness and greater susceptibility to shock, requiring greater care in handling or a return to proper storage conditions prior to further handling.

As the humidity is increased, within a reasonable temperature range, the shell of the unprotected control capsule should pick up moisture in proportion to its glycerin and gelatin content in accordance with the curves shown in Figure 13-28. The total moisture content of the capsule shell, at equilibrium with any given relative humidity within a reasonable temperature range, should closely approximate the sum of the moisture content of the glycerin and the gelatin when held separately at the stated conditions. For example, the shell of the described control capsule contains 400 mg of dry gelatin and 200 mg of dry glycerin per gram. At equilibrium with 30% RH at room temperature (21 to 24°C), the curves show that the gelatin should retain about 12% (48 mg) of water, and the glycerin 7% (14 mg) of water. Thus, the "dry" shell

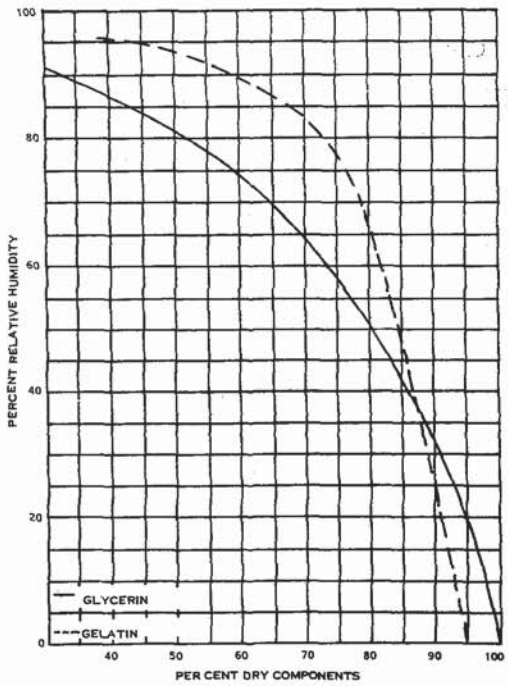


FIG. 13-28. *Equilibrium content by weight of dry glycerin (20 to 100°C) and dry gelatin (25°C) at various relative humidities.*[12,13]

would contain about 9.4% water (62 mg H_2O/662 mg of shell).

If the conditions are changed to 60% RH (21 to 24°C), the moisture content should be approximately 17.4%. In actual practice, however, such calculated moistures are considered maximum, since moisture assays (toluene distillation method) of the shells of oil-filled capsules give results somewhat lower than the theoretical values. The deviation most likely is due to an interaction between the plasticizer and gelatin, partially satisfying their respective water-binding capacities and thereby causing a lower moisture content than would be theoretically expected. Nevertheless, the curves serve to illustrate the hygroscopic nature of capsule shells, the relative effect of changes in the glycerin to gelatin ratio on the hygroscopicity of the shell, and the potential effects of humidity on the chemical and physical stability of the product.

High humidities (>60% RH at 21 to 24°C) produce more lasting effects on the capsule shell, since as moisture is absorbed, the capsules become softer, tackier, and bloated. The capsules do not leak unless the increased moisture has allowed a deleterious ingredient in the capsule content to attack the gelatin. On return to optimum storage conditions, the capsules are dull in appearance and most likely inseparably stuck together. An increase in temperature (>24°C), together with humidity (>45%), results in more rapid and pronounced effects and may even cause the unprotected capsules to melt and fuse together. Capsules containing water-soluble or miscible liquid bases may be affected to a greater extent than oil-based capsules, owing to the residual moisture in the capsule content and to the dynamic relationship existing between capsule shell and capsule fill during the drying process.

The capsule manufacturer routinely conducts *accelerated physical stability tests* on all new capsule products as an integral part of the product development program. The following tests have proved adequate for determining the effect of the capsule content on the gelatin shell. The tests are strictly relevant to the integrity of the gelatin shell and should not be construed as stability tests for the active ingredients in the capsule content. The results of such tests are used as a guide for the reformulation of the capsule content or the capsule shell, or for the selection of the proper retail package. The test conditions are (1) 80% RH at room temperature in an open container; (2) 40°C in an open container; (3) 40°C in a closed container (glass bottle with tight screw-cap). The capsules at these stations are observed periodically for 2 weeks. Both gross and subtle effects of the storage conditions on the capsule shell are noted and recorded. The control capsule should not be affected except at the 80% RH station, where the capsule would react as described under the effects of high humidity.

In the case of a newly developed product, the gross effects such as disintegration, leakers, unusual brittleness or softening, apparent color fading, or discoloration are obvious. The more subtle changes may be the loss of a volatile ingredient as detected by slight capsule indentation, or the slight darkening or widening of the capsule seams, or slight changes in color hue. Capsules often show a "soft spot" at the site at which they lie next to the tray or against another capsule. This spot is the result of slower drying and is of no consequence in the control capsule, since such areas firm up and are not flaws in the capsule shell. On the other hand, if such areas do not become firm, usually because of action by the capsule content, then physical stability problems can be anticipated during the shelf-life of the product. Such defects must be corrected before the product can be considered for production. Correction of such defects depends upon identifying their cause. Most defects can be corrected by appropriate changes in gelatin or fill material formulations, but in some cases, different colorants, machine speeds, and machine dies may have to be used. The experience and mature judgment of the custom manufacturer is invaluable in the solution of such problems.

Chemists conducting the physical stability tests in their own laboratories should keep two important points in mind: (1) Prior to testing, the capsules should be equilibrated to known atmospheric conditions, preferably 20 to 30% RH at 21 to 24°C. (2) Evaluation of the results of the previously described heat tests should be made only after the capsules have returned to equilibrium with room temperature.

After the capsules have passed the shell integrity tests, additional physical studies should be conducted using the various types of retail packages being considered for the product. These latter tests should be designed to determine the shelf-life of the product and may conform to most of the standard testing procedures employed by a company for its other solid dosage forms. Exceptions may involve those tests conducted at temperatures exceeding 45°C for time periods exceeding a month.

The soft gelatin capsule manufacturer takes great care in the production of capsules to meet the specifications of the product set forth by the customer. When *bulk shipments* of capsules are made by the manufacturer, they are temporarily

protected from normal changes in humidity by a suitable moisture barrier such as a 0.003-inch polyethylene bag within a standard fiber board carton. Since such packaging is not a permanent moisture barrier, the capsules should be retail packaged as soon as possible after receipt. If immediate packaging is not practical, the bulk capsules in their original unopened cartons should be stored in an air-conditioned area in which the humidity does not exceed 45% RH at 21 to 24°C. The retail packaging of these capsules should be done under similar conditions, for the maximum physical and chemical stability of the product.

Soft gelatin capsules may be *retail packaged* using any modern packaging equipment, including the electronic type. Capsules may be packaged in glass or plastic containers or may be strip-packaged, so long as such packaging involves tight closures and plastics having a low moisture vapor transfer rate. Suppliers of rigid plastics and plastic films can be of immeasurable service in suggesting the proper types of packaging for testing. Since strip packaging usually is done by specialists in this field, their advice should be solicited, and test strips should be made and tested for adequacy.

Pharmaceutical Aspects

The pharmaceutical chemist should be cognizant of the inherent properties of soft gelatin capsules. Essentially, these capsules are solid dosage forms containing liquid medication and therefore offer certain advantages:

1. They permit liquid medications to become easily portable.

2. Accuracy and uniformity of dosage, capsule to capsule and lot to lot, are predominant advantages. These capsules easily pass the appropriate compendial tests and surpass other solid dosage forms in this respect, because liquid formulations can be more accurately and precisely compounded, blended, homogenized, and measured or dispensed than can dry solid formulations.

3. The pharmaceutical availability of drugs formulated for this dosage form, as measured by disintegration time,[14] or by dissolution rate,[15,16] often shows an advantage over other solid dosage formulations.

In the dissolution rate studies of twenty drugs, presented previously, which included a wide variety of chemical types and pharmacologic classes, the authors showed that in the majority of cases, the drugs were more rapidly and completely available from the soft gelatin capsule than from the commercial tablets or capsules. For these studies, the NF XII (second supplement, 1967) rotating-bottle method was used.

A rationale for using a rotating-bottle method for dissolution studies on soft gelatin capsules is expressed, and examples are given by Withey and Mainville.[17] Their dissolution studies on thirteen brands of commercial chloramphenicol capsules, using their modified USP apparatus, showed the soft gelatin capsule brand to release only 22.3 to 24.8% of its chloramphenicol content in 30 min, while hard-shell capsule brands B_2 and D released 100.7% and 87.2% respectively. Upon change to a rotating-bottle method, the 30-min recoveries were 100% from the soft gelatin capsule brand, 82% from brand B_2, and 70% from brand D. None of these studies have been correlated with bioavailability data, and thus, the significance of the difference in results between the two dissolution methods is not clear. The difference could be attributed to greater agitation by the bottle method and less opportunity for the capsule to adhere to the sides or bottom of the apparatus. The effect of several variables on capsule dissolution is discussed by Hom and associates,[8] who indicate that the degree of agitation, the pH of the dissolution medium, and the presence or absence of pepsin in the medium are important to the dissolution of soft gelatin capsules.

4. The physiologic availability of drugs is often improved since these capsules contain the drug in liquid form, i.e., as a liquid drug substance, drug in solution, or drug in suspension. Nelson, in his review,[18] points out that the availability of a drug for absorption, from various types of oral formulations, usually decreases in the following order: solution, suspension, powder-filled capsule, compressed tablet, coated tablet. A study by Wagner and co-workers seems to confirm both Nelson's observation and the effective absorption from soft gelatin capsules.[19] Their study involved the effect of dosage form on the serum levels of indoxole (solubility in water 0.1 μg/ml) and showed the serum level decreased in the following order: emulsion $\simeq$ soft gelatin capsule (drug in polysorbate 80 solution), aqueous suspension, powder-filled capsule.

Maconachie, in his review article on soft gelatin capsules,[20] gives some specific examples of how this dosage form can improve drug absorption. His examples involve acetaminophen,[1] chlormethiazole,[21] and temazepam.[22] The 4-hour urinary recovery of acetaminophen from three soft gelatin rectal suppository formulations (oil base and water-miscible type base) was found to be five to eight times greater than from the traditional fatty type suppository formula-

tion. The switch from a tablet to a soft gelatin capsule form not only improved the stability of chlormethiazole by protecting the drug from oxidation, but increased its bioavailability as evidenced by comparative blood levels and by earlier onset of a minor side effect (nose tingling). Major side effects of the tablet dosage form were also eliminated or ameliorated. The capsule formulation allowed the use of the liquid drug substance (chlormethiazole base) rather than the solid derivatives used in the tablet formulations. A temazepam soft gelatin formulation, when compared with hard gelatin capsule formulations of temazepam, nitrazepam, amobarbital sodium, and a placebo, gave superior bioavailability as indicated by "onset of sleep." Furthermore, this was achieved at a lower dosage (20 mg per soft capsules versus 30 mg per hard capsule).

In an article on soft gelatin capsules,[23] Ebert discusses and reports on the bioavailability and content uniformity of digoxin solutions in soft gelatin capsules. The capsulated solutions were 0.05 mg, 0.10 mg and 0.20 mg of digoxin dissolved in a base consisting of polyethylene glycol 400, USP (89.4% w/w); alcohol, USP (6.5% w/w); propylene glycol, USP (3.4% w/w); and purified water, USP (0.6% w/w). These capsules were tested by various investigators for bioavailability in comparison with brand name tablets, digoxin solution, and digoxin elixir.[24-31] In all studies, the bioavailability of the soft gelatin capsule formulation was found to be superior to the commercially available tablets. The most surprising finding of all these studies, according to Ebert, was that the capsulated solution exhibited a more rapid and complete absorption than did the same solution not encapsulated. The commercially available tablets contain 20% more drug than the capsulated solutions. Thus, the capsule dosage form allows for a significant reduction in dose for this relatively toxic drug.

Another comparative bioavailability study of digoxin soft gelatin capsules and tablets was reported by Astorri and co-workers.[32] They found that in heart patients using digoxin, the absorption of digoxin from the capsulated solution was 36% higher than from the tablet, while in healthy volunteers absorption from the capsule was 20% higher than from the tablets.

The bioavailability of theophylline from soft gelatin capsules in comparison to a commercially available liquid aminophylline preparation and to a nonalcoholic aminophylline solution was studied by Ebert,[33] and by Lesko and coworkers.[34] Both studies found that the two dosage forms were bioequivalent as measured by the area under the plasma-level-time curves. This is an example of the capsule providing a convenient portable dosage form for a liquid medication. The capsule also effectively masked the bitter taste of theophylline.

Papaverine hydrochloride bioavailability from soft gelatin capsules was studied by Arnold et al.[35] These authors found that the peak blood level and area under the blood-level-time curve from soft gelatin capsules were equal to those obtained from an elixir and superior to those from a sustained release hard-shell capsule formulation. Healthy volunteers were used in this study. Lee et al. found not only high blood levels of papaverine 120 min after a 150-mg dose in soft gelatin capsules, but a higher degree of vasodilation after four doses (150 mg × 4) of the soft capsule dosage form when compared with equivalent doses from a sustained-release dosage form.[36] Patients with severe arteriosclerosis obliterans were used in the study. Both studies conclude that the soft gelatin capsule dosage form shows significant advantage over the sustained release tablet form of the drug.

The bioavailability of diazepam (structurally similar to that of temazepam, mentioned previously) was studied by Yamahira et al.[37] They compared diazepam, capsulated in soft gelatin using a medium-chain triglyceride base, with a tablet dosage form. They report that when these dosage forms were repeatedly orally administered to an individual subject, the capsule dosage form showed a tendency toward faster drug absorption and superior reproducibility of the plasma-level-time curve than the tablet dosage form. This suggests that capsule dosage forms have a more uniform drug absorption rate than tablets. The authors suggest that diazepam, though it is a weak base, was emptied from the stomach while mostly retained in the lipid, and this was affected by the movement of the triglyceride in the gastrointestinal tract.

5. The pharmaceutical chemist should certainly consider the bioavailability potential of soft gelatin formulations. The biopharmaceutical characteristics of such formulations can be altered or adjusted more easily than those of other solid dosage forms. Through the selection and use of liquids and combinations of liquids that range from water-immiscible through emulsifiable to completely water-miscible, and by altering the type or quantity of thickening or suspending agents, capsule formulations allow the formulating chemist more flexibility in the design of a dosage form to fit the biopharmaceutical specifications of a particular therapeutic agent.

6. Orally administered drugs, particularly if used chronically, can be irritating to the stom-

ach. The dosage form of such drugs can affect gastric tolerance, as indicated by the studies of Caldwell et al.[38] These authors compared the degree of irritation or ulcerogenic potential of soft gelatin capsule formulations of dexamethasone with a tablet formulation of the drug. Several liquid formulations and tablet formulations were administered to rats, and both ulcerogenic potential and bioavailability were determined. The authors concluded that the liquid or capsule formulations had a reduced ulcerogenic potential when compared to the tablet formulation, and that this effect is apparently not a reflection of reduced bioavailability.

References

1. Widmann, A.: Drugs Made in Germany, *3*:167, 1960.
2. Gutches, M.: Capsule Technology and Microencapsulation. Noyes Data Corp., Park Ridge, NJ, 1972.
3. Idson, B., and Braswell, E.: Advances in Food Research. Vol. VII. Academic Press, New York, 1957, p. 235.
4. Gelatin. Gelatin Manufacturer's Institute of America, New York, 1962.
5. Traub, W., and Piez, K.: Advances in Protein Chemistry. Chemistry and Structure of Collagen. Vol. 25. Academic Press, New York, 1971.
6. Ramachandvan, G. N.: Treatise on Collagen. Chemistry of Collagen. Vol. 1. Academic Press, New York, 1967.
7. Stanley, J. P., and Bradley, C. W.: U.S. Patent 2,870,062, January 20, 1959.
8. Hom, F. S., Veresh, S. A., and Miskel, J. J.: J. Pharm. Sci., 62:1001, 1973.
9. Handbook of Chemistry and Physics. 44th Ed. Chemical Rubber Publishing Co., Cleveland, OH, 1963.
10. Lieberman, E. R., Gilbert, S. G., and Srinvasa, V.: Trans. N.Y. Acad. Sci., *34*:694, 1972.
11. Hom. F. A., Veresh, S. A., and Ebert, W. R.: J. Pharm. Sci., *64*:851, 1975.
12. Miner, C. A., and Dalton, N. N.: Glycerol. ACS Monograph Series No. 117. Reinhold, New York, 1953, p. 269.
13. Bull, H. B.: J. Am. Chem. Soc., *66*:1949, 1944.
14. Eckert, V. T., Widmann, A., and Seidel, R.: Arz. neim-Forsch, *19*:821, 1969.
15. Hom, F. S., and Miskel, J. J.: J. Pharm. Sci., *59*:827, 1970.
16. Hom, F. S., and Miskel, J. J.: Lex Et. Scienta, 8:18, 1971.
17. Withey, R. J., and Mainville, C. A.: J. Pharm. Sci., *58*:1120, 1969.
18. Nelson, E.: Clin. Pharmacol. Ther., *3*:673, 1962.
19. Wagner, J. G., Gerard, E. S., and Kaiser, D. G.: 7:610, 1966.
20. Maconachie, S.: Mfg. Chemist and Aerosol News, Aug. 1977, p. 35.
21. Frisch, E. P., and Ortengren, B.: Acta Psych. Scand., 42(Suppl.):35, 1969.
22. Hindmarch, I.: Arzneimittel-Forsch., *25*:1836, 1975.
23. Ebert, W. R.: Pharm. Tech., *1*:44, 1977.
24. Binnion, P. F., and Klopp, R. W.: Lancet, *1*:1422, 1975.
25. Mallis, G. I., Schmidt, D. H., and Lindenbaum, J.: Clin. Pharmacol. Ther., *18*:761, 1975.
26. Marcus, F. I., Dickerson, J., Pippin, S., et al.: Clin. Pharmacol. Ther., *20*:253, 1976.
27. Binnion, P. F.: J. Clin. Pharmacol., *16*:461, 1976.
28. Johnson, B. J., Bye, C., Jones, G., and Sabey, G. A.: Clin. Pharmacol. Ther., *19*:746, 1976.
29. Ghirardi, P., Catenazzo, G., Mantero, O., et al.: J. Pharm. Sci., *66*:267, 1977.
30. Lindenbaum, J.: Clin. Pharmacol. Ther., *21*:278, 1977.
31. Johnson, B. F., Smith, G., and French. J.: Br. J. Clin. Pharmacol., *4*:209, 1977.
32. Astorri, E., Bianchi, G., La Canna, G., et al.: J. Pharm. Sci., *68*:104, 1979.
33. Ebert, W. R.: Pharm. Tech., *3*:61, 1979.
34. Lesko, L. J., Canada, A. T., Eastwood, G., et al.: J. Pharm. Sci., *68*:1392, 1979.
35. Arnold, J. D., Baldridge, J., Riley, B., and Brody, G.: J. Clin. Pharmacol., *15*:230, 1977.
36. Lee, B. Y., Sakamoto, H., Trainor, F., et al.: J. Clin. Pharmacol., *16*:32, 1978.
37. Yamahira, Y., Noguchi, T., Takenaka, H., and Maeda, T.: Chem. Pharm. Bull., *27*:1190, 1979.
38. Caldwell, L., Cargill, R., Ebert, W. R., and Windheuser, J. J.: Pharm. Tech., *3*:52, 1979.

PART THREE

Microencapsulation

J. A. BAKAN

Microencapsulation is a rapidly expanding technology. As a process, it is a means of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. For the purpose of this chapter, microencapsulation is arbitrarily differentiated from macrocoating techniques in that the former involves the coating of particles ranging dimensionally from several tenths of a micron to 5000 microns in size.

As the technology has developed, it has become apparent that the concept offers the industrial pharmacist a new working tool. Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection, and of controlling the release characteristics or availability of coated materials. Several of these properties can be attained by macropackaging techniques; however, the uniqueness of