PROTEIN-BASED FILMS and COATINGS

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CHAPTER 16

Soft Gelatin Capsules

ARISTIPPOS GENNADIOS

INTRODUCTION

SOFT gelatin capsules are one-piece, hermetically sealed soft gelatin shells containing a liquid, a suspension, or a semi-solid (Figure 16.1) (Hom and Jimerson, 1990; Wilkinson and Hom, 1990). In contrast to the rigid two-piece hard gelatin capsule shells, soft gelatin capsule shells contain large amounts of plasticizers, which make them flexible. Similar to hard gelatin capsules, they are solid dosage forms intended mainly for oral administration, although they may also be used as rectal or vaginal suppositories. In the late 1980s, a trade association comprised of soft gelatin manufacturers in the U.S. introduced the name "softgels" to further distinguish this dosage form from hard gelatin capsules.

Softgels are formed, filled, and sealed in a continuous operation, which has been most cost-effective for a few contract manufacturers (Hom and Jimerson, 1990). The list of companies operating softgel manufacturing facilities in North America in 2000 includes Banner Pharmacaps (High Point, NC), R.P. Scherer (Basking Ridge, NJ), Accucaps Limited (Windsor, Ontario, Canada), Soft Gel Technologies (Los Angeles, CA), Pharmavite (Mission Hills, CA), Nutricia Manufacturing USA (Greenville, SC), Goldcaps (Miami, FL), CapsuleWorks (Bayport, NY), Tishcon Corporation (Westbury, NY), IVC Industries (Freehold, NJ), Swiss Caps (Miami, FL), Gelcell Capsules Limited (Tecumseh, Ontario, Canada), Captek Softgel International (Cerritos, CA), and National Vitamin Company (Porterville, CA). At present, the number of in-

Figure 16.1 Softgels manufactured using the rotary die encapsulation process.

stalled softgel encapsulation lines/machines in North America is estimated at 250. This chapter discusses the advantages, limitations, uses, and manufacturing of softgels. Gelatin-enrobed and gelatin-coated tablets/caplets also are briefly discussed.

NATURE AND USES

HISTORICAL BACKGROUND

The French pharmacists Mothes and DuBlanc are credited with developing the softgel dosage form in the 1830s (Hom and Jimerson, 1990). They patented a method of preparing capsules by dipping a mercury-filled leather sac into molten gelatin. The gelatin coating was allowed to solidify, the sac was removed, and medications were added to the capsule with a pipette (Hom and Jimerson, 1990; Wilkinson and Hom, 1990). The capsule was then hand-sealed with molten gelatin. Although iron molds were later introduced, this tedious softgel preparation method had high fill variations and yield losses, and was not commercially viable.

Later, a plate method was developed that made the commercialization of softgels viable. This batch process used two sets of metallic plates with matching cavities. A gelatin sheet was cast on the surface of the lower die plate, vacuum was applied to pull the sheet into the die pockets, medication was filled into the formed pockets, a second gelatin sheet was laid on top, and the two plates were pressed together to form and separate the capsules (Hom and Jimerson, 1990). The plate method was used for many years by The Upjohn Company (Kalamazoo, MI) until it was discontinued in 1989 (Wilkinson and Hom, 1990).

In the early 1930s, Robert P. Scherer invented the continuous rotary die encapsulation process for large-scale manufacturing of softgels (Scherer, 1934). Over the years, this process has undergone various modifications and improvements in automation and has become the industry standard worldwide (Ebert, 1977). The concept of the Scherer process was the basis for two additional processes suitable for filling softgels with powders and pelleted formulations. One, the Accogel process, was developed by Lederle Laboratories in 1948, and the other, the reciprocating die process, was developed by the Norton Company in 1949 (Hom and Jimerson, 1990; Wilkinson and Hom, 1990). Today, the vast majority of encapsulating machines operating around the world are custom-manufactured based on the Scherer concept and are self-maintained by the softgel manufacturers. However, "turn-key" softgel manufacturing systems have become available in recent years, thus lowering the technological barrier for entry into the softgel business (at least for dietary supplements, such as oils and vitamin E, which require minimal fill formulation expertise).

ADVANTAGES OF SOFTGELS

The following are generally recognized as functional and commercial advantages of the softgel as a dosage form for administering pharmaceutical and dietary formulations:

(1) Softgels generally exhibit enhanced dissolution rates of encapsulated biologically active compounds because they absorb water, open at the seams, disintegrate, and rapidly release their contents (Hom and Miskel, 1970, 1971). The elevated body temperature accelerates the rapid *in vivo* release of the softgel contents because some degree of gel melting occurs.

(2) Biologically active compounds with poor water solubility can be solubilized or dispersed in oils or aqueous-miscible liquids within the softgels. Upon ingestion, the capsule shell disintegrates, and the fill formulation dissolves or emulsifies, yielding dispersions of high surface area and good bioavailability (Berry, 1983; Seager, 1985; Karunakar, 1998). The enhanced bioavailability of several pharmaceutical compounds administered within softgels compared to hard gelatin capsules and/or tablets has

been demonstrated (Mallis et al., 1975; Angelucci et al., 1976; Ghirardi et al., 1977; Lindenbaum, 1977; Lucchelli et al., 1978; Stella et al., 1978; Alvisi et al., 1979; Astorri et al., 1979; Nitsche and Mascher, 1982; Helqvist et al., 1991; Gumkowski et al., 1994). However, other studies reported no significant differences in the bioavailability of various pharmaceutical compounds administered within softgels versus hard gelatin capsules and/or tablets (Albert et al., 1974; Fuccella et al., 1977; Steinbach et al., 1980a, b; Pierce et al., 1984).

(3) The improved bioavailability of compounds delivered within softgels allows for administering lower dosages, thus resulting in reduced raw material costs (Seager, 1985).

(4) Compounds sensitive to oxidation can be protected through solubilization or dispersion in oils or aqueous-miscible liquids within the softgels (Seager, 1985). In addition, the gelatin shell is a potent oxygen barrier (Hom et al., 1975; Anonymous, 1992), as is generally the case with protein-based films (at least at low relative humidity conditions) (Gennadios et al., 1993).

(5) The softgel manufacturing process often allows for higher dosage accuracy and content uniformity than other oral dosage forms (Berry, 1982).

(6) Highly potent (e.g., cytotoxic) compounds present health and safety concerns with the resulting airborne particles during tableting. Such concerns can be alleviated by introducing the compounds into liquid formulations and encapsulating them into softgels.

(7) Although not tamper-proof, softgels are both tamper-evident and tamper-resistant. Puncturing the softgel shell, introducing a contaminant, and resealing the shell without resultant leakage or signs of alteration is a highly difficult task (Berry, 1982; Hom and Jimerson, 1990).

(8) Unpleasant tastes and odors of active compounds are masked by the capsule shell (Ebert, 1977; O'Brien, 2000).

(9) There is a high degree of flexibility in selecting softgel sizes, shapes, and colors, which, combined with capsule printing capabilities, offers wide opportunities for product identification and differentiation (Stanley, 1986; Schofield, 1999).

(10) As an oral dosage form, softgels typically rate high in consumer preference because of their elegance, ease of swallowing, and strong perceived effectiveness due to their liquid fill formulations (Berry, 1983; Schofield, 1999).

LIMITATIONS OF SOFTGELS

The following are often identified as limitations of the softgel dosage form and technology:

(1) The softgel manufacturing process is slower than tableting.
(2) Softgels require intensive inspection due to several potential defects, such as capsules that leak, have shape imperfections, or are stuck together.
(3) The lengthy drying process substantially extends the manufacturing cycle of softgels.
(4) Operation of softgel encapsulation machines requires experienced personnel.
(5) The encapsulation process is not fully automated in terms of monitoring in-process parameters, such as capsule seal strength and wet shell thickness or weight.
(6) Although the softgel encapsulation process allows for accurate dosing and thus economical use of the fill material, it results in a notable waste of shell formulations (about 30%).
(7) Due to increased labor requirements, softgels are generally produced at a higher cost than directly compressed tablets.
(8) Prior to drying, softgel shells have a high moisture content, which allows for increased interactions among shell and fill ingredients.

ENCAPSULATED MATERIALS

Pharmaceutical Compounds

Both over-the-counter (OTC) and ethical (prescription; Rx) drugs are encapsulated and marketed in softgels. It is noted that few facilities worldwide have the necessary technical expertise and regulatory approvals for manufacturing softgels containing drugs, particularly ethical drugs. The categories of OTC drugs typically available in softgels include analgesics (e.g., acetaminophen); anti-inflammatory agents (e.g., ibuprofen); antihistamines (e.g., chlorpheniramine maleate, brompheniramine maleate, doxylamine succinate, and diphenhydramine hydrochloride); stool softeners (e.g., docusate salts); decongestants (e.g., pseudoephedrine hydrochloride); antitussive agents (e.g., dextromethorphan hydrochloride); expectorants (e.g., guaifenesin); and antiflatulents (e.g., simethicone). Combinations of two or more active compounds are quite common, particularly in formulating cough and cold medications.

The ethical drugs that have been or are currently formulated within softgels cover a wide range of therapeutic indications and include nifedipine (antianginal), valproic acid (anticonvulsant), benzonatate (antitussive), isotretinoin (treatment of severe recalcitrant nodular acne), amantadine hydrochloride (antiviral and antiparkinsonian), calcitriol (hypocalcemia management), ergocalciferol (treatment of refractory rickets and hypoparathyroidism),

cephalexin (antibacterial), amoxycillin (antibacterial), etoposide (antineoplastic), cyclosporine (immunosuppressant), ritonavir (HIV protease inhibitor), ethosuximide (anticonvulsant), chloral hydrate (sedative), dronabinol (cannabinoid; complex effects on central nervous system), ethchlorvynol (hypnotic), and ranitidine hydrochloride (ulcer treatment).

Dietary Supplements

A wide array of traditional dietary supplements and compounds associated with supplement-style structure/function claims—regulated in the U.S. by the Food and Drug Administration (FDA) under the Dietary Supplement Health and Education Act of 1994 (DSHEA)—are currently available in softgels including the following:

(1) Vitamins (mainly oil-soluble such as vitamins A, D, and E), minerals (e.g., calcium as calcium carbonate and chromium as chromium picolinate), and multi-vitamin and multi-mineral combinations
(2) Antioxidants (e.g., grape skin extract, alpha-lipoic acid, rosemary extract, astaxanthin, and coenzyme Q10)
(3) Phospholipids (e.g., lecithins)
(4) Carotenoids (e.g., lycopene and lutein)
(5) Oils that are rich in essential fatty acids (e.g., flaxseed oil, borage oil, evening primrose oil, and black currant seed oil) or omega-3 fatty acids (e.g., marine oils)
(6) Herbal supplements (e.g., saw palmetto, aloe vera, panax ginseng, Siberian ginseng, St. John's wort, valerian, kava, maca, echinacea, cat's claw, dong quai, elderberry, ginkgo biloba, goldenseal, black cohosh, horsechestnut, olive leaf, and milk thistle)
(7) Enzymes (e.g., lactase)
(8) Amino acids and protein hydrolyzates

In addition to dietary supplements and herbals, which also are widely referred to as nutraceuticals, traditional food items and food processing ingredients (e.g., cooking oils, peanut butter, tallow, butter, sauces, and chocolate syrup) also have been encapsulated into softgels to form single-use, single-dosage packages (Yamada and Makino, 1986; Anonymous, 1992). However, such a use of softgels has remained a niche application with limited commercialization.

Personal Care Products

Bath oils are the most common personal care products marketed in softgels.

The functional properties of gelatin are well suited for such products (bath beads) because the plasticized gelatin shells quickly swell and then dissolve in contact with hot water, thus releasing the aromatic oils. In addition, softgels also are used as single-dose packages for higher value cosmetic formulations intended for topical use. Typically, such softgels have a "twist-off" or "break-off" feature at one end for dispensing the fill material (Spellman et al., 1991; Rinaldi et al., 1999). For example, Melnik et al. (1992) described the encapsulation of cosmetic compositions (e.g., sun screens, tanning agents, skin care, and anti-dandruff agents) using silicone polymers as carriers. Punto et al. (1996) disclosed a skin-treating formulation incorporated into softgels in the form of an emulsion comprised of a water-soluble active ingredient (e.g., ascorbic acid), polyethylene glycol, and an oil (e.g, silicone, paraffin, or vegetable oil). Lambrechts (1996) described a shampoo/conditioner formulation in a softgel that included a concentrated surfactant, a cationic conditioner, and a carrier (e.g., polyethylene glycol). Morton et al. (1997) discussed fragrance-containing softgels intended primarily for dispensing as perfume testers or samples. Lambrechts (1997) described skin conditioning compositions that were comprised of hydroxy and/or keto acids, a thixotropic agent, and an emulsifying agent (e.g., glyceryl monoesters of long-chain fatty acids) and were suitable for encapsulation into softgels. Skin lotion compositions containing vitamin E and/or vitamin A palmitate that were encapsulated into softgels were described by Fishman (1998). Softgel fill formulations intended for skin care that contained retinol-impregnated microparticles and, optionally, ascorbic acid-impregnated microparticles were described by Rinaldi et al. (1999).

Recreational Products

Over the past 25 years, paintballs have emerged as an important application for softgels. The paintballs are softgels containing dyes in an oil (Haman and Schmoke, 1987), polyoxyethylene sorbitol monolaureate (Skogg, 1987), or polyethylene glycol (Rouffer, 1995) vehicle. They are fired from compressed air guns, including rapid firing devices, during adult war games or training and target shooting. Upon impact, the paintballs readily crush, thus "splattering" the contained dyes and marking the hit target. The paintball sport or recreational activity started in the U.S. in the 1970s and has been growing in popularity, both in the U.S. and overseas, ever since. In addition to recreational products, other niche industrial applications of softgels have been commercialized over the years. Examples include tube-shaped softgels filled with glue or technical grade grease, and round-shaped softgels filled with starter fluid for trucks.

SHAPES AND SIZES

Hard gelatin capsules are mainly produced in traditional oblong shapes and

in eight different sizes. In contrast, softgels for oral administration are manufactured in oval, oblong, and round shapes (Figure 16.2) and are able to accommodate a wide range of fill volumes. The nominal fill volume in minims is traditionally used to indicate the size of a softgel. A minim is 1/60 of a fluid dram (1 fluid dram = 1/8 fluid ounce). Thus, a 1 cm^3 volume corresponds to approximately 16.2 minims. Overall, softgels can range in size from 1 to 480 minims. For oral consumption in particular, oval-, oblong-, and round-shaped softgels typically range in size from 2 to 16, 3 to 24, and 2 to 9 minims, respectively.

Sample calculations used for determining the minimum fill volume of a softgel product based on the desired active dose and the necessary excipients were presented by Stanley (1986). Fill formulations should result in a softgel of the smallest possible size so that raw material usage, manufacturing output, and patient compliance are optimized. To some extent, the capsule shell can shrink to the volume of its contents without negatively affecting product appearance. This offers sufficient leeway for filling a capsule with a lesser than the nominal volume. According to Stanley (1970), this leeway for smaller volume filling is 10, 20, or 30% of the nominal capacity for oblong, oval, or round capsules, respectively. In contrast, overfilling is not recommended because it can affect product appearance and stress the capsule seams leading to leakage and possibly rupture. Also, overfilled products can cause problems in post-processing operations such as blister packaging.

In addition to the traditional oval, oblong, and round shapes used for human consumption, softgels also are manufactured in a wide variety of shapes for personal care products. For example, bath oil softgels often are marketed in the shapes of animals, seashells, stars, hearts, teardrops, and triangles. Bath oil softgels with a partially or fully textured outer surface also are manufactured. This surface texture can be applied on the cast, moldable gelatin ribbons

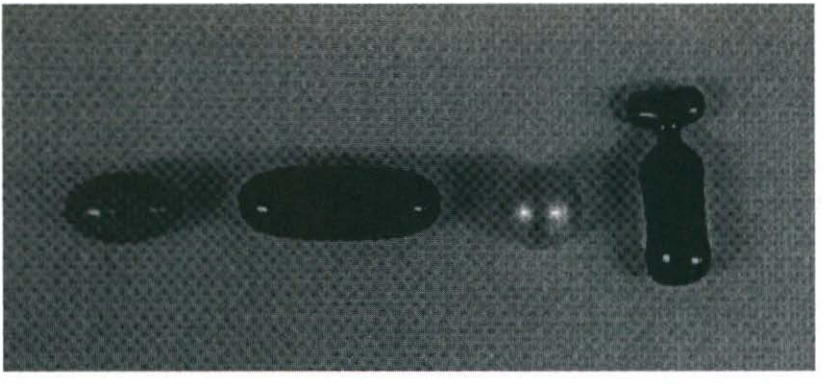

Figure 16.2 Examples of differently shaped softgels. From left to right: oval, oblong, round, and a tube with the "twist-off" feature.

through contact with a roller having a textured surface (Ratko et al., 1993). Another method for enhancing softgel appearance and differentiation was described by Schurig et al. (1997). They produced color-striped or marblelized softgels by using patterned gelatin ribbons. Stone (1998) described the manufacture of softgels having a filled and a non-filled portion with one or both portions carrying impressed graphical representations (Stone, 1998). Single-use softgels containing cosmetic formulations for topical application are marketed in the form of tubes (regular, oval, or round) with a "break-off" or "twist-off" feature (Figure 16.2). Finally, softgel suppositories are typically manufactured in bullet-like shapes.

FILL FORMULATION ASPECTS

Details on softgel fill formulations are beyond the scope of this chapter, and only a few general considerations are discussed here. A comprehensive discussion on the nature of softgel contents was presented by Stanley (1986). Furthermore, substantial information on softgel fill formulation approaches, often targeted to a specific active compound, is available in the patent literature (Grainger, 1980; Stoopak et al., 1982; Shah et al., 1984; Henmi et al., 1987; Brox, 1988a, b; Yu et al., 1991; Torosian, 1992; Makino et al., 1993; Shelley et al., 1996; Tanner and Shelley, 1996; Vàsquez, 1997; Cimiluca, 1997; Woo, 1997; Becourt et al., 1998; Cody et al., 1999; Devlin and Hoy, 1999; Goldman, 2000; Hong et al., 2000; Hoy, 2000; Lacy et al., 2000; Rouffer, 2000). Fill formulations intended specifically for chewable softgels also have been discussed in the patent literature (Steele and Montes, 1999; Lech, 2000).

Fill Materials

With the rotary die encapsulation process, the capsule contents are typically a liquid or a combination of miscible liquids; a solution of a solid(s) dissolved in a liquid(s); or a suspension of a solid(s) in a liquid(s) (Stanley, 1986). Rotary die apparatuses for encapsulating solids into softgels have been developed (Rowe, 1998) but have found limited application thus far. A large number of liquids that are either actives themselves or function as solubilization excipients for solid actives can be encapsulated. Such liquids that can be encapsulated without any limitations include water-immiscible liquids (e.g., vegetable oils, aromatic oils, aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, ethers, esters, alcohols, and organic acids) and water-miscible, non-volatile liquids (mainly limited to polyethylene glycols and non-ionic surfactants such as polysorbate 80) (Ebert, 1977; Stanley, 1986).

A few other water-miscible and relatively non-volatile liquids, such as glycerin and propylene glycol, can be included in fill formulations but only in small

amounts (not more than 5–10% of the total liquid in the fill) (Stanley, 1986). Typically, water itself cannot be present in the fill at more than 8% (Sundararajan et al., 1996). However, a method to encapsulate fills with up to a 20% water content was described by Miskel et al. (1974). They prepared fill formulations by incorporating active compounds into aqueous solutions of gelling proteins (e.g., collagen, gelatin, soy protein, egg albumin, and casein). The gelling proteins formed fluid macromolecular gel matrices, and, upon drying of the softgels, these matrices set into rigid gels that retained as much as 20% water (Miskel et al., 1974). Addition of colloidal silica into fill formulations (0.5 to 10% by weight) to immobilize water also was suggested for encapsulating fills having a high water content (Altmann, 1995).

Solid compounds that are poorly soluble in the abovementioned liquids can be encapsulated by being formulated into stable, homogeneous suspensions. To achieve good content uniformity and stability, the particle size of suspended solids typically should not exceed 80 mesh (180 μm) (Hom and Jimerson, 1990). The suspending medium (referred to as the base, carrier, or vehicle) is typically a vegetable oil (e.g., soybean oil), a combination of a vegetable oil and a surfactant, a non-ionic surfactant (e.g., polysorbate 80), or polyethylene glycol (PEG, 400 or 600 molecular weight) (Stanley, 1986). PEG having a lower molecular weight (e.g., 200) is avoided because it can easily migrate into the gelatin shell over time causing overplasticization (softening). To facilitate the complete wetting of solids by oil bases, a wetting agent (often lecithin) is added at 2–3% by weight of the oil (Stanley, 1986). Suspensions also require a suspending agent to ensure homogeneity (content uniformity) and good flow characteristics (Ebert, 1977). Typical suspending agents for oil suspensions are waxes (e.g., beeswax and paraffin wax), stearates, and cellulose ethers (Ebert, 1977; Stanley, 1986). For non-oil suspending mediums, PEGs of high molecular weight (e.g., 4000 and 6000), glycol esters, and acetylated monoglycerides are generally used as suspending agents (Ebert, 1977; Stanley, 1986).

Limitations

There are several limitations in the types of compounds that are suitable for encapsulation into softgels. Aldehydes (e.g., formaldehyde, acetaldehyde, and glutaraldehyde) can cross-link gelatin, thus slowing capsule disintegration and dissolution (Digenis et al., 1994; Hakata et al., 1994; Bottom et al., 1997). In general, the cross-linking of proteins by aldehydes is well documented (Feeney et al., 1975). Formaldehyde-induced cross-linking of gelatin mainly involves the lysine and arginine amino acids (Taylor et al., 1978; Albert et al., 1986, 1991; Gold et al., 1996). Aldehydes may be directly present as impurities in fill or shell ingredients, or they may be generated by autoxidation of lipid excipients, such as polysorbate 80 (Chafetz et al., 1984; Doelker and

Vial-Bernasconi, 1988; Singh et al., 2000). PEG can be particularly problematic because it tends to react with atmospheric oxygen to form aldehydes (Tanner and Shelley, 1996). To alleviate this problem, PEG is typically handled in an inert atmosphere, for example, under a nitrogen blanket (Tanner and Shelley, 1996). Even capsule packaging materials can function as a source of cross-linking aldehydes as was shown for furfural from the rayon fiber inserted into high-density polyethylene bottles (Schwier et al., 1993). Recently, the use of near-infrared spectrophotometry as a non-invasive and non-destructive method for assessing aldehyde-induced cross-linking in softgels was proposed (Gold et al., 1998).

Reducing carbohydrates (e.g., glucose, fructose, lactose, maltodextrin, and corn syrup solids), which often are used as drug or dietary supplement excipients, also cross-link proteins through the Maillard reaction (non-enzymatic browning) (Cheftel et al., 1985; Ames, 1998) and can affect the gelatin shell (Tanner and Shelley, 1996). However, satisfactory *in vitro* dissolution of cross-linked softgels or hard gelatin capsules may be obtained by adding proteolytic enzymes to the dissolution medium (Hom et al., 1973; Doelker and Vial-Bernasconi, 1988; Murthy et al., 1989b; Digenis et al., 1994; Gelatin Capsule Working Group, 1998).

Succinylated gelatin, which is not susceptible to aldehyde-induced cross-linking, can be used in capsule manufacturing (Kobayashi et al., 1986; Sato et al., 1986; Yamamoto et al., 1995). Acylation of proteins with succinic anhydride reduces the e-amino groups, which are the prime reactive sites for aldehydes (Cheftel et al., 1985). However, succinylated gelatin is not approved for use with ingestible softgels in the U.S. Nonetheless, personal care formulations containing high amounts of aldehydes have occasionally been encapsulated into softgels manufactured with succinylated gelatin.

Organic compounds of low molecular weight that are volatile (e.g., alcohols, ketones, acids, amines, and esters) tend to readily migrate through the capsule shell (Hom and Jimerson, 1990). Emulsions (oil-in-water or water-in-oil), although occasionally investigated as softgel fills (Bauer and Dortunc, 1984), are typically unsuitable for encapsulation because they eventually become destabilized, thus releasing water that migrates into the gelatin shell (Ebert, 1977). In general, strong acids or bases break non-covalent and covalent cross-links within the gelatin structure. Therefore, acidic liquids ($pH < 2.5$) encapsulated into softgels can hydrolyze gelatin and cause capsule leakage (Stanley, 1970). Highly alkaline liquids also can disrupt the shell structure, causing leakage. Salts of strong acids and bases (e.g., potassium, sodium, and choline chlorides) and ammonium salts (e.g., ammonium chloride) can also be destructive to the shell (Stanley, 1970; Ebert, 1977). Finally, compounds that are unstable in the presence of moisture, such as aspirin, are not suitable for encapsulation into softgels (Hom and Jimerson, 1990).

MANUFACTURING

SHELL INGREDIENTS

Gelatin

Sources

Gelatin, the product of partial hydrolysis of collagen, is the main component of the softgel shell. Its manufacture and characteristics are discussed in detail elsewhere in this book. It is estimated that about 7.6% of the total gelatin produced worldwide (19,000 out of 250,000 metric tons) in 1998 was used in softgel manufacturing (Pluvinet, 2000). In fact, the softgel business has been growing in recent years so that about 10% of the worldwide gelatin production is now allocated to softgels (Pluvinet, 2000). Both Type A and Type B gelatins (derived from acid and alkali hydrolysis of collagen, respectively), occasionally blended together by either the gelatin manufacturers or the softgel manufacturers, are used for preparing softgels. Gelatin type selection is influenced by both technical and economic considerations. Traditionally, bovine bones and skins (trimmings from the leather industry prior to tanning) have been used as collagenous raw materials for manufacturing Type A or Type B gelatin, while porcine skins have been used extensively for manufacturing Type A gelatin (Alleavitch et al., 1989; Johnston-Banks, 1990; GMIA, 1993). In recent years, porcine bones also have entered the stream of gelatin raw materials in Europe where they are either processed separately or co-processed with bovine bones to produce Type A or Type B gelatins.

In the mid 1980s, fish gelatin became commercially available and has been marketed as an alternative to mammalian gelatins that present concerns for such religions as Judaism, Islam, and Hinduism. All fish are acceptable to most Islamic groups, while fish with removable scales are acceptable in Judaism with minimal restrictions (Choi and Regenstein, 2000). The skins of cod (a cold-water fish) were initially used for the commercial production of fish gelatin (Norland, 1987). However, due to its low content of hydroxyproline and proline amino acids, which contribute substantially to the gelatin gel structure through hydrogen bonding, cod skin gelatin is non-gelling at ambient temperatures (Norland, 1987; Leuenberger, 1991; Gudmundsson and Hafsteinsson, 1997; Gilsenan and Ross-Murphy, 2000) and, therefore, is not suitable for softgel manufacturing. Processes for extracting gelling gelatin having higher contents of hydroxyproline and proline amino acids from the skins of other fish species, such as tilapia (a warm-water fish), were later developed (Grossman and Bergman, 1992; Holzer, 1996). Although these gelatins have lower melting and gelling points than mammalian gelatins (Choi and Regenstein, 2000; Ross-Murphy, 2000), they are suitable for softgel manufacturing, and softgels

made of fish gelatin are commercially available. Increasing the melting and gelling temperatures of fish gelatin is feasible through the addition of salts such as magnesium sulfate (Sarabia et al., 2000). The recovery of poultry gelatin has also been investigated (Kim et al., 2000) but not commercialized yet.

Properties

The gelatin used for softgel manufacturing meets compendial requirements such as those set forth in the *United States Pharmacopeia/National Formulary (USP/NF)* or the *European Pharmacopeia (EP)*. For example, the NF monograph for gelatin (USP24/NF19, 1999) sets limits for residue on ignition (≤2.0%); sulfur dioxide (≤0.15%); arsenic (≤0.8 ppm); and heavy metals (≤0.005%). Tests for identification, odor, and water-insoluble substances, as well as microbial contamination (total bacterial count of ≤1000/g; absence of *Salmonella* species; and absence of *Escherichia coli*), also are included. Compendial requirements are general in scope and apply to gelatins used in all types of pharmaceutical dosage forms.

Several other physical and chemical properties affect the encapsulating performance of gelatin and are monitored by softgel manufacturers. Gelatin batches used for softgels, or any other application, are prepared by blending a number of individual gelatin extracts or components (often up to 35) into a final product that meets customer specifications. The component selection ("recipe") associated with this blending process can drastically affect the encapsulating performance of the gelatin batch. From a commercial standpoint, Bloom value (gel strength) and viscosity (related to average molecular weight), both determined on 6.67% w/w gelatin test solutions, are typically the two most important properties in assessing gelatin grade and quality (GMIA, 1993). Bloom strength is determined using texture analyzers, while viscosity is determined using U-tube viscometers at 60°C (GMIA, 1993). When comparing the Bloom strength and viscosity of various gelatins, it should be acknowledged that test measurements are affected by moisture content, ash content, and the pH of the gelatin (Stevens et al., 1995).

In general, acid-processed gelatins have lower viscosity values (lower molecular weight) than lime-processed gelatins of the same Bloom strength. This is related to the ability of the acid treatment to cleave the acid-labile peptide bonds, in addition to disrupting the non-covalent bonds, in collagen (Rose, 1987). Gelatins having a Bloom strength from 150 to 250 g and a viscosity from 25 to 45 mP (at 60°C) may be used in the softgel industry (Stanley, 1986). However, in the interest of consistency, the softgel manufacturers' specifications for various types of gelatins are much tighter, particularly in terms of viscosity (not more than ±3 mP). In general, gelatin solutions show Newtonian flow at most temperatures, except those just above the gel setting point where the viscosity becomes time-dependent (Johnston-Banks, 1990; Wulansari et al., 1998). The

dissolution rate of softgel capsule shells made with Type B gelatin was shown to decrease linearly with increasing gelatin Bloom values (Hom et al., 1973).

In addition to the "standard" viscosity of 6.67% (w/w) solutions, softgel manufacturers may also set specifications for the viscosity of more concentrated gelatin solutions (e.g., 12.5% w/w), because solution viscosity values are not directly proportional to gelatin concentration. Furthermore, viscosity drop (loss or breakdown) of a 12.5% (w/w) gelatin solution after 24 h at 60°C is used as a measure of the anticipated "pot-life" of a gelatin gel mass that is being heated. Usually, the greater the initial viscosity, the greater the viscosity drop in 24 h with the values for softgel grade gelatins ranging from 10 to 20%. In addition, microorganisms present in the test solutions accelerate the viscosity loss.

As mentioned, the NF monograph for gelatin sets a limit of ≤1500 ppm for sulfur dioxide (SO_2). However, SO_2 can affect the stability of several synthetic dyes used with softgels. For example, FD&C Yellow #5 and FD&C Yellow #6 dyes are susceptible to fading upon interaction with SO_2 (Downham and Collins, 2000). Therefore, stricter limits (e.g., ≤40 ppm) for the SO_2 content of gelatin are used in the softgel industry. Iron, which may be introduced into the gelatin from raw materials or process water during manufacturing, can also affect the stability of synthetic dyes and can also participate in color-generating reactions with reducing substances that may be present in the capsule fill (Wilkinson and Hom, 1990). For example, ascorbic acid in fill formulations can react with iron, causing dark "spotting" on the capsule shell. Typically, the gelatin used for softgels has an iron content of ≤15 ppm (Stanley, 1986).

Gelatin color and clarity, usually determined using spectrophotometric techniques, also are important, particularly for softgels that do not contain dyes. Generally, Type A pigskin gelatin has a lighter color and greater clarity than Type B bone or hide gelatin of the same Bloom strength. In terms of particle size, the gelatin used for softgel manufacturing ranges in mesh from 8 to 60 (2.36 mm to 0.25 mm). Fine particles in large amounts can cause dusting during handling, aggregates ("fish eyes") in the gel reactors, and even foaming during gel manufacture. Coarse particles in large amounts can reduce the hydration rate of the gelatin in the gel reactors and also can cause handling problems with reactor feeding systems. From a microbiological standpoint, gelatin, although deficient in certain essential amino acids, may support microbial growth at higher moisture contents. Therefore, in addition to the mentioned NF microbiological testing (i.e., total microbial count, *Salmonella*, and *E. coli*), softgel gelatin specifications typically require absence of *Pseudomonas aeruginosa* and *Staphylococcus aureus*, and a total mold and yeast count of ≤100 organisms/g.

The physical and chemical properties discussed above establish a basic set of quality attributes for softgel-grade gelatin. However, the overall performance of a gelatin blend during gel manufacturing, encapsulation, capsule drying, and long-term capsule storage is dictated by additional functional characteristics and can only be assessed through actual use tests. Examples of such

characteristics include the viscosity of the gel mass and the loss of viscosity with heating; the Bloom strength of the gel mass and its decrease with heating; the stickiness of the gel mass and of the capsules; the strength of the capsule seams; the capsule hardness and brittleness; the drying rate of the capsules; and the physical stability of the capsules during storage.

Plasticizers

Gelatin, plasticizer, and purified water are the main components of softgel shell formulations. In general, glycerin is widely used to plasticize various protein films and coatings (Gennadios et al., 1994). Glycerin of animal, vegetable, or synthetic origin is an effective plasticizer for softgels containing lipophilic fills. Gelatin and glycerin are highly compatible because strong intermolecular interactions are formed between the hydroxyl groups of glycerin and the hydrophilic groups of gelatin (Pouradier and Hodot, 1972). In fact, in high amounts, glycerin can be a solvent rather than a plasticizer for gelatin (Pouradier and Hodot, 1972).

However, glycerin-plasticized softgels with hydrophilic, PEG-based fill compositions become brittle over time as both glycerin and water (which itself plasticizes gelatin) migrate from the shell into the hygroscopic fill (Brox, 1988a, b; Shah et al., 1992). To prevent this embrittlement, glycerin typically is used in combination with non-crystallizing sorbitol solutions to plasticize softgels having hydrophilic fill formulations (Brox, 1988a, b). Sorbitol, being less hydrophilic, having a higher molecular weight, and being less soluble in PEG, tends to not migrate into PEG-based fills as easily as glycerin does. Non-crystallizing sorbitol solutions are mixtures of sorbitol and sorbitol anhydrides or hydrogenated oligosaccharides (Reich, 1996). They are preferred over crystalline sorbitol, which tends to re-crystallize over time, forming white spots on the surfaces of the capsules ("blooming"). In addition to using non-crystallizing sorbitol solutions, the migration of glycerin and moisture from the shell into the hydrophilic fill can be further reduced through the incorporation of glycerin or propylene glycol into the fill to bring the two phases closer to equilibrium (Brox, 1988a, b; Shah et al., 1992). Other polyhydric alcohols, such as propylene glycol (Brox, 1999), PEG 200 (Rouffer, 2000), or maltitol syrup (Borkan et al., 1990; Chiprich et al., 1997), may also be used, often in combination with glycerin, as softgel plasticizers in specialty shell formulations. Cast gelatin ribbons containing propylene glycol as a plasticizer were reported to be tackier than ribbons plasticized with glycerin or sorbitol (Brox, 1999).

The ratio (by weight) of dry plasticizer to dry gelatin is an important parameter that defines the "hardness" of the capsule shell and usually ranges from 0.4:1 to 0.8:1 (Stanley, 1986). This ratio is selected based mainly upon the fill formulation and the anticipated storage conditions of the finished product. Hy-

drophilic fills require greater plasticizer to gelatin ratios than lipophilic fills to compensate for any plasticizer migration into the fill over time. Softgels shipped to hot, humid areas require lower amounts of plasticizer than those shipped to cold, dry areas (Stanley, 1986). Capsule size may also influence the selection of the plasticizer to gelatin ratio. For the same fill composition, orally administered capsules larger than 10 minims typically have a higher content of plasticizer to increase the ease of swallowing. Low plasticizer concentrations are recommended for softgels containing oxygen-labile active compounds because the oxygen permeability of gelatin films increases with increasing amounts of glycerin (Hom et al., 1975). Finally, "overplasticization" of the capsule shell is a simple approach for preparing chewable softgels (although this is of limited effectiveness without additional shell/fill formulation adjustments).

Opacifiers

Softgel shells need to be made opaque when the encapsulated active compounds are light-sensitive. Also, opacified shells are typically used with paste fill formulations for aesthetic purposes. Titanium dioxide (TiO_2), a white pigment (insoluble in water) that has found universal regulatory approval, is the opacifier of choice for softgels. It also is used to prepare white-colored softgels, often in combination with minuscule amounts of FD&C Blue #1 dye that is used to neutralize the yellowish background color of gelatin. The natural mineral ilmenite ($FeTiO_2$) is the source of the TiO_2 used in various industrial applications. However, only synthetically produced TiO_2 can be used as a color additive for food, drug, and cosmetic applications (Francis, 1999). In addition to its opacifying and whitening ability, TiO_2 can also reduce the oxygen permeability of capsule shells, presumably by increasing the path tortuosity of diffusing oxygen molecules (Hom et al., 1975). Kellaway et al. (1978) reported that high amounts (2% w/w) of TiO_2 had negligible effects on the mechanical properties (tensile strength, elongation at break, and Young's modulus) of cast films from Type A or B gelatins. Similarly, Samura et al. (1993) determined that TiO_2 did not notably affect the tensile strength of cast softgel shell formulations. In fact, TiO_2 at high levels increased the strength of gelatin gels, presumably via strong TiO_2 particle-gelatin interactions and a degree of hydrogen bonding (Johnston-Banks, 1990). Nevertheless, TiO_2 usually is not added to softgel shell formulations in amounts greater than 1% (wet weight) (Hom et al., 1975). At greater amounts, this insoluble gel additive (filler) can negatively affect the encapsulating characteristics, particularly seam strength, of softgel shell formulations. In addition, over time, it may harm encapsulation dies and other processing equipment due to its abrasiveness.

Zinc oxide (ZnO) is another opacifying/whitening inorganic pigment. How-

ever, its hiding power is five times lower than that of TiO_2 (Marmion, 1991). ZnO is widely used in the cosmetics industry, but is not an approved color additive for dietary supplements or ingestible drugs in the U.S. However, it is occasionally added to the shells of nutritional softgels as a nutrient (elemental zinc source). Another whitener that has a weak opacifying ability is calcium carbonate ($CaCO_3$), itself a dietary supplement. It is used widely in the food industry in various roles, but is not currently listed by the FDA as an approved color additive for foods (Francis, 1999). However, it is an approved color additive for drugs in the U.S. $CaCO_3$ can be problematic as an opacifier for softgels due to its weak hiding power and low tinctorial strength (coloring power). Furthermore, dissociated divalent calcium cations in the gel can interact with negatively charged sites on the gelatin, thus causing cross-linking ("bridging" together of adjacent protein chains).

TiO_2-coated mica pigment can be added to the shells of cosmetic softgels to introduce a pearl-like appearance (Benford, 1970). Mica is a white powder obtained from the naturally occurring mineral muscovite mica, and it consists primarily of potassium aluminum silicate (Marmion, 1991). Finally, small amounts of oily substances can introduce a degree of haziness into the shell, offering an opacified appearance. For example, silicone oil has been used as an opacifier in softgels (Davies et al., 1987). In addition, large amounts of vegetable or animal oils were incorporated into shell compositions to protect capsule contents from light and to increase shell hydrophobicity and lubricity (Yamada et al., 1988).

Colorants

The psychological effects of color upon consumers of oral dosage forms have long been recognized (Woznicki and Schoneker, 1991). Therefore, the color of softgels is quite important from both a marketing and product identification/differentiation standpoint. Oil fills (e.g., vitamin E, marine oils, and lecithin) are often encapsulated into softgels that do not have dyes or pigments within the shell. Such transparent softgels have light yellow to light brown colors imparted to them by the combination of the oil color and the inherent amber color of gelatin (which varies slightly by gelatin type, grade, and manufacturer). It is possible to completely "neutralize" the inherent color of gelatin, thus obtaining clear, colorless softgels, by combining various dyes and pigments in appropriate amounts (Tanner and Orange, 1997). In addition, Ext. D&C Violet #2 (Alizarin Violet), which is approved in the U.S. only for externally applied drug and cosmetic products, may be used to "neutralize" the inherent yellowish color of gelatin. Softgels containing suspensions (pastes) and hydrophilic fills are typically colored. Because two gelatin ribbons are fed into the encapsulation machine to form softgels, each ribbon may have a different

color, thus resulting in bi-colored (two-toned) softgels. Generally, the shell color should not be lighter in hue than the encapsulated fill (Stanley, 1986). Also, darker colors are more appropriate for large, orally administered softgels (e.g., greater than 14 oblong) because they do not accentuate the capsule size (Stanley, 1986).

The selection of colorants for softgels containing pharmaceuticals or dietary supplements requires careful consideration of the regulatory approvals and restrictions for the various colorants that apply to the targeted markets (Jones, 1993). Both chemically synthesized colorants and colorants derived from plant, animal, or mineral sources are used to color softgels. The latter are often referred to in the food and dietary supplement industries as natural colorants, although the term "natural colorant" is not appropriate from a regulatory standpoint in the U.S. unless the colorant is natural to that food (Boyd, 1998). In the U.S., the approved colorants for food, pharmaceutical, and cosmetic uses are listed in Title 21 of the Code of Federal Regulations (CFR), Parts 73 and 74. The CFR specifies two groups: colorants that are certified to comply with the established purity specifications of the FDA and color additives that are exempt from certification (Francis, 1999). In the U.S., the Nutritional Labeling and Education Act of 1990 mandates that certified color additives are specifically declared with their individual names on product labels (Francis, 1999). However, exempt colorants can still be declared generically as "artificial color" or with any other specific or generic name for the colorant (Francis, 1999). In the European Union (EU), 43 colorants (17 synthetic and 26 either naturally derived, synthesized to match naturally occurring counterparts, or inorganic pigments found in nature) are approved as food additives with each one assigned an "E number" (Downham and Collins, 2000).

Synthetic Colorants

In the U.S., seven synthetic FD&C ("food, drug, and cosmetic") dyes are certified without restrictions for use in coloring foods and, therefore, dietary supplements (Francis, 1999). These are FD&C Blue #1 (Brilliant Blue), FD&C Blue #2 (Indigo Carmine or Indigotine), FD&C Green #3 (Fast Green FCF), FD&C Yellow #5 (Tartrazine), FD&C Yellow #6 (Sunset Yellow FCF), FD&C Red #3 (Erythrosine), and FD&C Red #40 (Allura Red AC). Due to their water-soluble nature, these FD&C dyes can be readily incorporated into a gel mass and, thus, be used to color softgels. However, FD&C Blue #2 has poor heat, light, and oxidative stability (Kuramoto et al., 1958; Kellaway et al., 1978; Downham and Collins, 2000) and, therefore, is typically avoided in the softgel industry. In addition, FD&C Blue #1 has only a fair light stability (Downham and Collins, 2000) and, therefore, may be problematic in softgels.

In addition to the seven FD&C dyes, several other dyes designated as D&C ("drug and cosmetic;" considered safe in drugs and cosmetics when in contact

with mucous membranes or when ingested) are available (Marmion, 1991) and may be used with pharmaceutical softgels. Among them, D&C Yellow #10 (Quinoline Yellow WS), D&C Red #27 (Tetrabromotetrachlorofluorescein), D&C #28 (Phloxine B), and D&C Red #33 (Acid Fuchsine) are the ones most commonly used with softgels. Synthetic dyes are available both in powder and granular form. However, powder forms, although less expensive than granular forms, can cause dusting (Dziezak, 1987). For this reason, and also for avoiding "fish eyes" upon incorporation into the gel masses, granular dyes are preferably used in the softgel industry. Although incorporating synthetic dyes (and other colorants) directly into shell formulations prior to capsule manufacturing is the norm in the softgel industry, surface dyeing of finished softgels using solutions of various water-soluble dyes in aqueous isopropyl alcohol has been studied (Smith, 1974).

The FD&C and D&C dyes commonly used with softgels can be broadly assigned to one of six chemical classifications based on their chemical structure (Marmion, 1991). These are azo dyes (i.e., FD&C Yellow #5, FD&C Yellow #6, FD&C Red #40, and D&C Red #33), indigoids (i.e., FD&C Blue #2), xanthenes (i.e., FD&C Red #3 and D&C Red #28), quinolines (i.e., D&C Yellow #10), triphenylmethanes (i.e., FD&C Blue #1 and FD&C Green #3), and fluorans (i.e., D&C Red #27). Over the years, some of these dyes, particularly azo dyes, have faced consumer distrust due to their perceived association with largely unsubstantiated health concerns, such as hyperactivity and food intolerances (Downham and Collins, 2000). In particular, FD&C Yellow #5 was suspected of causing allergic-type reactions, including asthmatic symptoms, especially in individuals allergic to aspirin (Rumore et al., 1992). As a result, several companies marketing pharmaceutical or nutraceutical compounds in softgels presently avoid the use of azo dyes in shell formulations.

Besides the water-soluble FD&C and D&C dyes, their corresponding water-insoluble lakes (still provisionally listed by the FDA with the exception of FD&C Red #40 lake, which has full approval and FD&C Red #3 lake, which is not permitted due to concerns over its iodine content) are occasionally used to color softgels (or gelatin-enrobed or gelatin-coated tablets/caplets). Lakes are the aluminum salts of water-soluble dyes that usually are adsorbed onto an alumina substrate (other substrates, such as clay, TiO_2, and $CaCO_3$, also are approved for D&C lakes) and impart color by dispersion (Francis, 1999). The dye content of lakes usually ranges from 10 to 40% (Marmion, 1991). Lakes have excellent light and heat stability (Francis, 1999). The main use of lakes in the softgel industry is with bi-colored capsules where they minimize color "bleeding" at the seams and color transfer marks between capsule halves. In addition to color, lakes also introduce a high degree of opacity to the softgel shells.

Association of synthetic dyes and lakes with gelatin through ionic bonding and also hydrogen and hydrophobic interactions has been documented (Sheppard et al., 1942; Cooper et al., 1973; Gautam and Schott, 1994). Factors

that affect these dye-gelatin interactions include pH, temperature, and gelatin type (A or B). At the typical pH (around 5) of softgel gel mass preparations, the synthetic dyes, due to their anionic nature, will electrostatically associate to a greater extent with the positively charged Type A gelatin than the slightly negatively charged Type B gelatin (Cooper et al., 1973; Kellaway et al., 1978). However, because they are present in small amounts, synthetic dyes and lakes are not considered to appreciably affect the disintegration and dissolution characteristics of softgels. Nevertheless, Cooper et al. (1973) reported that FD&C Red #3 dye notably reduced the disintegration rate of type A gelatin. UV or visible irradiation under high relative humidity (RH) conditions notably reduced the disintegration and *in vitro* dissolution rates of hard gelatin capsules colored with various dyes such as FD&C Red #3 and FD&C Yellow #5 (Murthy et al., 1989a). Another study showed that FD&C Red #3, FD&C Blue #1, and FD&C Blue #2 at 0.1 or 1% (w/w) had minimal effects on the tensile strength and Young's modulus of cast gelatin (Type A or B) films, but they reduced film contraction at a constant strain (Kellaway et al., 1978).

Synthetic iron oxides also find use as softgel colorants. Yellow, red, and black iron oxides, typically produced from ferrous sulfate, are available commercially (Marmion, 1991). They are water insoluble (Francis, 1999), thus coloring gelatin gel masses by dispersion and also introducing a degree of opacity. Their stability to heat, light, pH, and oxidation is excellent (Downham and Collins, 2000). In the EU, synthetic iron oxides are approved color additives for both foods and pharmaceuticals, and are used to color softgels containing nutraceutical or pharmaceutical products. In the U.S., synthetic iron oxides are permitted colorants for ingestible drugs, but not for foods/dietary supplements. When used with softgels, synthetic iron oxides do not offer colors as vibrant and glossy as those obtained with synthetic dyes. However, the synthetic iron oxides are used often with pharmaceutical softgels because of their wide regulatory approval worldwide as colorants for drug products (Jones, 1993).

Natural Colorants

The list of color additives exempt from certification in the U.S. includes 26 colorants, but some of them are only approved for use with animal feed (Francis, 1999). Five of these 26 colorants (i.e., caramel, annatto extract, cochineal extract, turmeric, and turmeric oleoresin) are commonly used, often in combinations of two or more, to color softgels containing nutraceutical compounds. Three of them (caramel, annatto extract, and cochineal extract) also are permitted for use with pharmaceuticals in the U.S. However, their use in pharmaceutical softgels has been scarce, if at all.

Caramel is a brown colorant manufactured by the controlled heat treatment of food-grade carbohydrates, typically corn syrup solids (Kamuf et al., 2000).

Sulfite and/or ammonia compounds may be used as catalysts in the caramelization process (Downham and Collins, 2000). Due to its high tinctorial strength, good solubility in gelatin gel masses, good stability, and low cost, caramel is widely used to impart brown colorations to nutritional softgels.

Annatto is a yellow carotenoid obtained from the seeds of the plant *Bixa orellana* (Francis, 2000a). The main pigments in annatto extract are the water-insoluble bixin and the water-soluble norbixin (Boyd, 1999). Bixin, the monomethyl ester of a dicarboxylic carotenoid, is the naturally occurring pigment form, while norbixin is the saponified form (Francis, 2000a). Aqueous preparations of norbixin at various concentrations are often added to the hydrophilic softgel shell to obtain orange/yellowish colorations. Oil-based bixin preparations also are used in softgels with the oil introducing a degree of haziness to the shells. Some fading upon exposure to light may occur with annatto-colored softgels. From a regulatory standpoint, there are no restrictions on the use of annatto as a color additive in the U.S. However, since 1994, the EU has significantly restricted the use of annatto colorant by categorizing it as a "color only permitted for certain uses" (Boyd, 1999). Saffron is another approved yellow color additive in the U.S. (no longer listed in the EU). Its carotenoid pigments (crocetin, crocin, and zeaxanthin) are chemically similar to those of annatto (Francis, 2000a). However, although suitable for coloring softgels, it is rarely used in the softgel industry due to its prohibitively high cost.

Cochineal extract is the red, concentrated solution obtained after removing the ethanol from aqueous ethanol extracts of the dried bodies of the female insect *Dactylopius coccus* Costa (Francis, 1999). The main pigment in a cochineal extract is carminic acid, a hydroxyanthraquinone linked to a glysosyl group (Schul, 2000). Carmine is the lake of carminic acid (typically about 50%) (Marmion, 1991). The water-insoluble carmine pigment can be converted to a water-soluble dye by treatment with alkali (Schul, 2000). Cochineal extract, the carmine lake, and water-soluble carmine (often called carmine hydrosoluble) are stable to light and heat, resistant to oxidation, and not affected by sulfur dioxide (Francis, 1999). They function well as colorants for softgels where they impart pink/red/purplish colorations. However, their use is self-limiting due to cost considerations.

Turmeric is a yellow colorant prepared from the dried roots of *Curcuma longa*, a tuberous rhizome (Pszczola, 1998). It owes its yellow color to three structurally related pigments (i.e., curcumin, demethoxy curcumin, and bis-demethoxy curcumin) (Chaterjee et al., 1998). Turmeric oleoresin is prepared by extracting turmeric powder with one or more organic solvents (Marmion, 1991). Both turmeric powder (ground rhizomes) and turmeric oleoresin (typically sold as a dispersion in propylene glycol or glycerin) are used as softgel colorants. Due to its water-insoluble nature (Francis, 1999), turmeric also introduces an opacifying effect to softgel shells, thus offering a degree of light protection to the capsule contents. Softgel shells colored with pure

curcumin (0.02 to 0.04% w/w) effectively increased the half-life of encapsulated photolabile test compounds (i.e., nifedipine, chloramphenicol, furosemide, or clonazepam) compared to non-colored softgel shells following irradiation with light of 240–600 nm (Tønnesen and Karlsen, 1987). The main drawback of turmeric as a colorant is its high susceptibility to light degradation (Boyd, 1998).

Sodium copper chlorophyllin is a green colorant obtained from chlorophyll by replacing the methyl and phytyl ester groups with sodium and replacing the magnesium with copper (Marmion, 1991). Commercial sources of sodium copper chlorophyllin include alfalfa, mulberry tree leaves, and nettle. It finds wide use in the EU, Japan, and other parts of the world as a "natural," green colorant in various applications, including softgels. Sodium copper chlorophyllin is susceptible to thermal degradation during heating (Milosevic et al., 2000). Although it may degrade to some extent during the heating of a gel mass in softgel manufacture, it yields quite stable color shades in stored softgels. In the U.S., sodium copper chlorophyllin is sold in powder and liquid forms as a dietary supplement. However, its use as a color additive is only permitted for dentifrices provided that it is derived from alfalfa (Francis, 1999).

Several other "natural" colorants, such as anthocyanins, betalains, β-carotene, riboflavin, and paprika oleoresin, are approved for use with foods/dietary supplements in the US and other countries. Commercial sources of anthocyanin pigments include grape skins, elderberries, chokeberries, black carrots, and red cabbage (Boyd, 2000; Downham and Collins, 2000). These pigments are presently receiving attention due to the health-related benefits ascribed to them (Boyd, 2000; Espín et al., 2000). However, anthocyanins have not typically been used for coloring softgels because of their pH sensitivity (lower color intensity at pH > 4) and susceptibility to degradation by light, heat, and oxygen (Francis, 2000b). Recently, commercialized acylated anthocyanins, such as those extracted from black carrots and red cabbage, were reported to have enhanced heat and light stability (Downham and Collins, 2000). Betalains, which are commercially extracted from beet roots, are largely unsuitable for coloring softgels because they have poor light and heat stability (Francis, 2000b). β-Carotene and riboflavin are susceptible to light degradation (Marmion, 1991) and are used sparingly with softgels. Paprika oleoresin is produced by extracting dehydrated ground paprika with organic solvents (Locey and Guzinski, 2000). The pigments in paprika oleoresin are a mixture of carotenes and xanthophylls (Locey and Guzinski, 2000). Paprika oleoresin also is prone to degradation (Jarén-Galán et al., 1999) and is largely unsuitable for the softgel manufacturing process. Lycopene, the principle carotenoid pigment (red/orange) in tomato, is a listed color additive in the EU (Downham and Collins, 2000). However, it is not currently approved as a color additive in the U.S., although efforts are under way to obtain its approval (Boyd, 2000). The use of lycopene as a colorant for softgels in Europe has been hindered by its high cost and poor sta-

bility, as it tends to isomerize and degrade over time (Anguelova and Warthesen, 2000).

Arguably, softgels colored with "natural" colorants are more susceptible to variability in color shades from lot to lot compared to softgels colored with synthetic colorants. To improve lot to lot color consistency, commercial preparations of "natural" colorants often are "standardized" with excipients. Such excipients may include reducing sugars (e.g., maltodextrin and corn syrup solids); however, they can cross-link gelatin, and, therefore, their presence should be monitored when coloring softgels. The demand for "natural" colorants in the dietary supplement industry is quite strong and is expected to keep growing. This demand is generated by the increasing consumer pressure for "all-natural" products. In addition, several of the "natural" colorants are perceived to be functional ingredients themselves because they possess antioxidant and/or antimicrobial properties (Boyd, 2000). Undoubtedly, the stability concerns associated with various "natural" colorants present technical challenges regarding their use with softgels. Microencapsulation is currently receiving attention in the color industry as an approach for improving colorant stability (Downham and Collins, 2000).

Miscellaneous Shell Additives

Several minor additives may occasionally be added to softgel shell compositions. In the past, preservatives often were incorporated into the gelatin shell, particularly with pharmaceutical products. However, at present, the use of preservatives with softgels is uncommon. The large amount of humectants, such as glycerin and/or sorbitol, present in the softgels suppresses water activity (Hom and Jimerson, 1990). Due to the low water activity of dried, properly stored softgels, molds and yeasts had been the main concern in terms of microbial growth rather than bacteria. For this reason, the preferred preservatives for softgels were the alkyl esters of *p*-hydroxybenzoic acid (methyl, ethyl, propyl, butyl, or heptyl), which are known as parabens. Parabens, which are widely used antimicrobial agents in foods, pharmaceuticals, and cosmetics, have little effect on flavor, effectively inhibit molds and yeasts, and are relatively ineffective against bacteria, especially gram-negative bacteria (Lindsay, 1985). Two or more parabens often are used in combination because together they exhibit enhanced antimicrobial activity (Thompson et al., 1993). Typically, a mixture of methyl paraben and propyl paraben at a ratio of 4:1 w/w was added at 0.2% by weight of the wet gel mass (Stanley, 1986). Thompson et al. (1993) reported that parabens can interact with glycerin or sorbitol forming substances that could present problems with the assay validations of pharmaceutical formulations. Sorbates (Heizi et al., 1979) or propionates (Wittwer and Mayer, 1986) also were suggested as shell-added preservatives (Heizi et al., 1979).

Flavorings, such as ethyl vanillin and essential oils, can be used to mask the

unpleasant odors and tastes of fill formulations (Stanley, 1986). Multivitamin/multimineral compositions are examples of softgels that often contain shell flavorings. However, aldehydes present in flavorings can be a concern because, as mentioned earlier, they cross-link gelatin. The use of flavorings is becoming less and less common. Buffering salts and acids (e.g., citric acid, tartaric acid, fumaric acid, and malic acid) have been used to adjust the pH of the gel mass (Mima et al., 1969; Henmi et al., 1987). Fumaric acid, in particular, incorporated at up to 1% (w/w) in a wet gel mass can prevent gelatin cross-linking by aldehydes (Stanley, 1986). Addition of fumaric acid or other acids at amounts greater than 1% is not recommended because the acids increase the viscosity degradation rate of gel mass preparations (Johnston-Banks, 1990), most likely due to acid hydrolysis of the protein chains. In general, the rate of viscosity loss of gelatin preparations is affected by the type of acid in the order (from least to most degradation) of citric, malic, tartaric, adipic, and fumaric acid (Johnston-Banks, 1990). In addition, Hom et al. (1973) reported that incorporating organic acids (e.g., fumaric, tartaric, or maleic acid) notably increased the dissolution rate of a typical softgel shell formulation. Besides fumaric acid, hydrolyzates of gelatin or other proteins as well as amino acids can be added to soft or hard gelatin capsules to "scavenge" aldehydes (or other reactive agents), thus preventing gelatin cross-linking (Tatematsu et al., 1991; Cade and Madit, 1997). Naturally, added hydrolyzates, which lack gelling strength, have a weakening effect on gelatin gels (Surówka, 1997).

Antifoaming agents are used in the shell compositions of paintballs, which are typically manufactured with Type A pigskin gelatin (150 to 220 Bloom), to prevent excessive foaming during gel manufacturing. In contrast, the manufacture of softgels using foamed gelatin ribbons that were prepared by microdispersing a gas into the gel mass was described (Wittwer and Mayer, 1986). The purpose was to introduce opacity, to accelerate shell disintegration, and to reduce manufacturing costs through lower gel consumption and faster capsule drying (Wittwer and Mayer, 1986).

In theory, incorporation of active compounds into capsule shells is feasible. However, this is not economical because a substantial proportion of the gelatin ribbons used in softgel manufacturing ends up as waste (Stanley, 1986). During the storage of softgels, migration of active compounds, particularly water-soluble compounds, from the fill into the shell can occur. For this reason, when the softgels are intended for oral use, the entire capsule needs to be assayed for the active compounds rather than just the fill (Stanley, 1970).

GEL MASS MANUFACTURING

As previously mentioned, gelatin, plasticizer, and purified water are the main ingredients of the softgel shell. Typical gel formulations contain 40 to

50% gelatin, 20 to 30% plasticizer, and 30 to 40% purified water (w/w) (Hom and Jimerson, 1990) with most of the water subsequently lost during capsule drying. The ingredients are combined to form a molten gel mass using either a cold melt or a hot melt process.

The cold melt process involves mixing gelatin, plasticizer, and chilled water and then transferring the resulting light, "fluffy" mixture to a jacket-heated tank (melter) (Wilkinson and Hom, 1990). Alternatively, mixing and melting can be successively accomplished within a single jacket-heated, batch reactor equipped with a blade agitator (Figure 16.3). Typically, gelatin is first added to the slightly chilled plasticizer (14 to 18°C) followed by mixing for 10 to 30 min, a step referred to as "creaming." The purpose of creaming is to "wet" the gelatin particles and facilitate their subsequent hydration without clumping. Chilled (7 to 12°C), purified water is then dispensed, and the mass is mixed without heating for another 15 to 30 min, a step referred to as "fluffing." Water may be added to the creamed mass in one (total quantity) or more cycles (equal or unequal partial quantities). The fluffed mixture is melted ("cooked") under a vacuum of 15 to 30 in. Hg (50.8 to 101.6 kPa) to a homogeneous, deaerated gel mass. Vacuum application may be continuous or intermittent during the melting process. The cooking temperature can range from 57 to 95°C, depending on the type of melter/reactor, and the process lasts 1.5 to 3 h. Shell additives, such as colorants/opacifiers, preservatives, and flavorings, can be added to the mass at any point during the gel manufacturing process, or they may be incorporated into the finished gel mass using a high-torque mixer. Colorants/opacifiers, in particular, often are added during the creaming stage.

The hot melt process involves adding the gelatin, under mild agitation, to a preheated (60 to 80°C) mixture of plasticizer and water and stirring the blend until complete melting is achieved. Compared to the cold melt method, the hot melt method is faster but is often more susceptible to foaming and dusting. When the gel mass is intended for manufacturing non-ingestible capsules, such as paintballs, antifoaming agents often are added to the gel formulation.

Once the gel masses are prepared, they are transferred to preheated, temperature-controlled, jacketed holding tanks (receivers) where they are kept ("aged") at 50 to 60°C until encapsulation. Often, the gel mass is filtered prior to being transferred to the receivers so that any undissolved gelatin aggregates or impurities initially present in the raw materials are removed. In addition, a visual comparison of the gel mass with a color standard (e.g., gel swatch or finished capsule) commonly is made in the case of colored gels. Gel aging can last from two to 72 hours or ever longer depending on the gel formula. Besides serving logistical needs, the aging of the gel mass for certain time periods is often needed to "break down" the gel to a desired viscosity. The functional life of the molten gel mass in the receivers can be extended by cooling it to ambient temperature, thus gelling it, a process referred to as "caking." They are then remelted (reheated to 50 to 60°C) and used. In general, the time-temperature

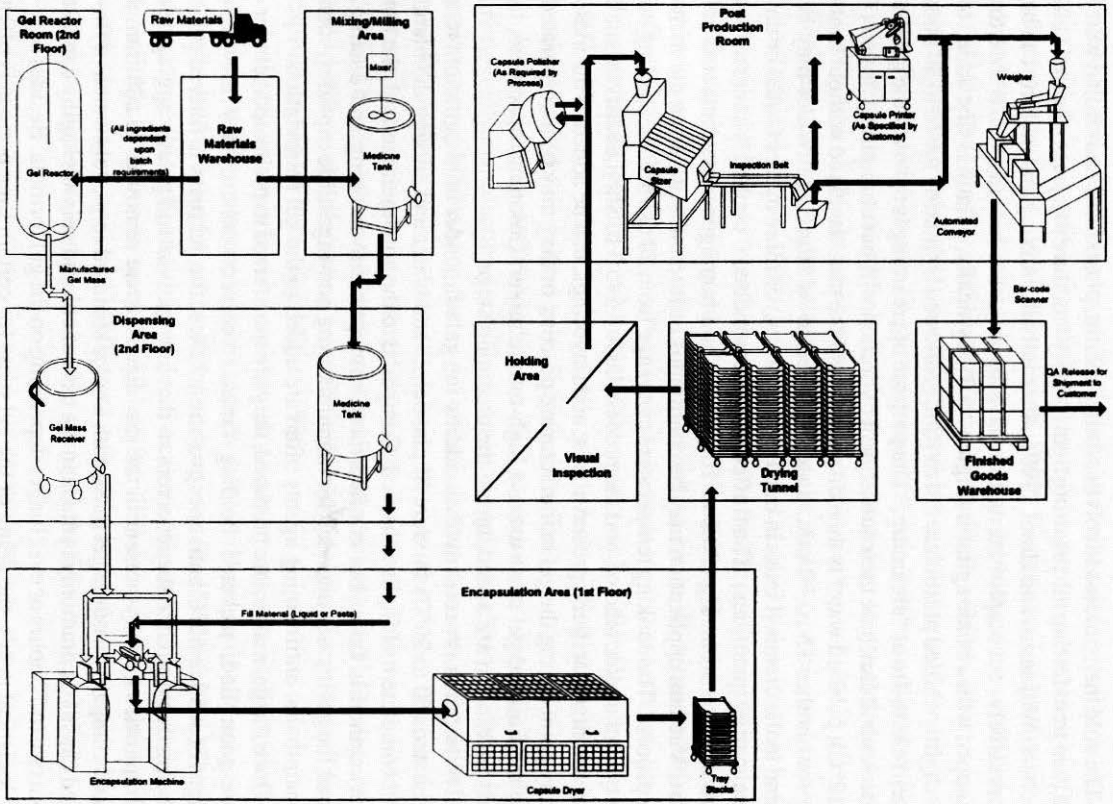

Figure 16.3 Process flow diagram for softgel manufacturing (courtesy of Banner Pharmacaps Inc., High Point, NC).

history of gelatin gels affects their thermal stability, melting characteristics, and tensile properties (Castello and Goyan, 1964; Michon et al., 1997). Gelatin gels conditioned (matured) at higher temperatures can have higher melting points than gels of the same solution prepared by rapid chilling at a lower temperature (Te Nijenhuis, 1981; Michon et al., 1997; Choi and Regenstein, 2000). Aging "caked" (4°C), dilute (1.5 or 2.0% w/w) Type A or Type B gelatin gels for up to 90 h did not markedly affect the viscoelastic properties of the gels (Robinson et al., 1975). However, a decrease in gel structure was evident, and this was attributed to hydrolysis of amide links (Robinson et al., 1975).

The rotary die encapsulation process inherently generates a notable amount of gel mass waste in the form of unused gel ribbons remaining after the formed capsules are cut out by the dies. Due to its appearance, this unused portion of the ribbon is referred to as "netting." Additional, smaller amounts of gel mass waste are generated through leftover gel (overage) at the completion of an encapsulating run and through unused gel ribbons cast during the start-up of the encapsulation machines. The percentage of unused gel mass typically varies between 15 and 30%. This excess gel mass is for the most part discarded. However, it can be recovered and reused, a practice that is driven by economic factors and is mainly limited to non-colored, low-value, non-pharmaceutical products such as nutritional oils. In this case, the reused gel mass is combined with a new ("virgin") gel mass and may account for up to 50% of the total mass.

In the past, the reprocessing of netting involved chopping and washing with naphtha to remove the lubricant oil applied to the ribbon during the encapsulation process (Wilkinson and Hom, 1990). This residual oil needs to be removed because it causes gel "cloudiness." The oil-free, chopped netting was then remelted and added to a new gel mass or was "caked" until needed (Wilkinson and Hom, 1990). Recently, as softgel manufacturers have been reducing their use of organic solvents, different approaches have been implemented for removing residual oil (and fill material) from the netting. The simplest approach is decanting, which involves remelting the netting (no chopping necessary), possibly with added purified water, in heated gel receivers. A phase separation occurs in the molten mass with a thin, oil-rich phase forming at the top. The clean gel (lower aqueous phase) is then recovered from the bottom of the tank.

Although effective, the decanting method for netting recovery is time- and energy-consuming, because the remelted mass is kept heated for several hours to ensure a thorough oil-gel phase separation. Hot filtering and subsequent vacuum distillation of the recovered gel has been suggested to enhance purification (Schmidt et al., 1994). Furthermore, diafiltration, a filtration technique that uses ultrafiltration membranes and washing, may be employed to remove plasticizers and other water-soluble components from the recovered gel, thus yielding a recyclable gelatin solution (Schmidt, 1999). Alternatively, a gel netting recovery device was recently described that removed lubricant oil by feeding cut, rod-like gel pieces between adjacent, rotating belts of differing speeds

(Ohzeki and Ishikawa, 2000). The lubricant adhered to the belts and was removed from the belt surface by blades (Ohzeki and Ishikawa, 2000).

ENCAPSULATION

The principles of the rotary die encapsulation process have been described (Stanley, 1986; Hom and Jimerson, 1990; Wilkinson and Hom, 1990; Stringer, 1994). A schematic diagram of the process is presented in Figure 16.4. The gel mass is fed either by gravity (Figure 16.3) or by positive displacement pumping to two heated (48 to 65°C) metering devices (spreader boxes), usually made of brass. The dynamic viscosity of the gel mass as it is fed to the encapsulation machine typically ranges from 5000 to 20,000 cP, depending on temperature, gel formulation, and raw gelatin viscosity. However, a range of 8000 to 12,000 cP often is preferred. The spreader boxes control the flow of gel through adjustable openings onto cooled, rotating casting drums (Figure 16.4). The temperature on the surface of the casting drums, which is controlled by either cool air or water, is maintained at 20 to 30°C.

Ribbons are formed as the cast gel masses set (sol-gel transformation) on contact with the cool drum surface. Controlled (±10%) wet ribbon thickness can vary between 0.50 and 1.14 mm. However, a range of 0.63 to 0.81 mm is more representative (Stanley, 1986). Besides gel mass temperature, gelatin concentration in the gel mass, and drum surface temperature, the blending profile (molecular weight distribution) of the gelatin greatly influences the setting

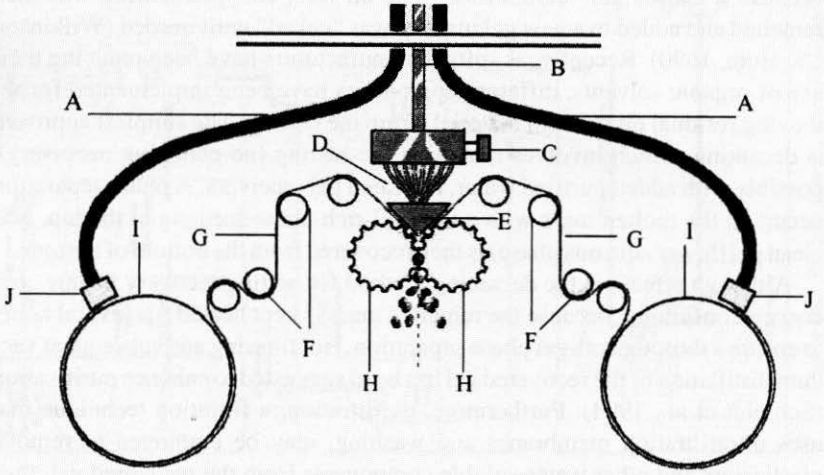

Figure 16.4 Schematic diagram for the rotary die process of softgel manufacturing (courtesy of Banner Pharmacaps Inc., High Point, NC). A = gel hoses; B = medicine (fill) hose; C = (medicine) fill pump; D = leads; E = injection wedge; F = guide rolls; G = gel ribbons; H = reciprocating dies; I = gel casting drums; and J = spreader boxes (gel metering devices).

rate of the cast gel mass. Generally, the setting rate of gelatin solutions at a given cooling temperature is reduced by high molecular weight components (Johnston-Banks, 1990; Kobayashi et al., 1992).

The formed ribbons are fed through a series of guide rolls and between the injection wedge and the counter-rotating, cylindrical capsule-forming dies (Figure 16.4). A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their handling by the rollers. In addition, the lubricant prevents sticking among freshly formed capsules and also seals the ribbons along the injection wedge, thus preventing air from entering the capsules as they are formed (Stroud et al., 1998). The oil may be applied by passing the ribbons through an oil bath or, to better control the amount of applied lubricant, by having the ribbons directly contact application rolls. Mineral oil or medium chain triglycerides are the most commonly used lubricants, although other oils, such as soybean oil, may be used. Eliminating lubricant application has been proposed (Makino, 1996).

Fill formulations, often referred to as medicines, are held in stainless-steel, jacketed tanks (receivers) and are fed to the encapsulation machine by gravity (Figure 16.3). Fill preparation may involve simple blending or, in the case of suspensions, successive mixing, milling or homogenizing, and deaeration steps (Stanley, 1986). Nitrogen blanketing of the medicine tank head space often is practiced with fills susceptible to oxidation. The fill material is precisely metered by a positive displacement pump through a series of leads and the injection wedge, and is pumped between the gelatin ribbons, which are passing through the cylindrical dies (Hom and Jimerson, 1990). Brass, aluminum, or stainless-steel may be used to manufacture the dies, which are typically six or 10 inches (15.2 to 25.4 cm) long. The maximum fill formulation viscosity that can be handled by the process is around 20,000 cP. However, materials that are highly tacky may be unsuitable for processing through the pump filling mechanism even if their viscosities are low (Stanley, 1986). Small orifices at the bottom of the wedge are lined up with the die pockets (Hom and Jimerson, 1990). The leading edge of the capsule is already sealed when the pumped fill material forces the ribbons into the die pockets where the capsules are then filled and shaped, their trailing edge sealed, and the filled softgels cut from the gelatin ribbon. Capsule sealing is achieved by the combination of heat from the wedge (33 to 43°C) and mechanical pressure (0.3 to 0.6 MPa) on the die rolls.

Ribbon thickness, seam thickness, and fill weights are the most commonly monitored process parameters during the encapsulation operation and often are included in process validation programs (Berry, 1984). The seam strength of the finished softgels may also be assessed by determining their bursting strength. A device for measuring the bursting strength of softgels was described by Trenktrog et al. (1998). Alternatively, a compression test with a texture analyzer may be used. The theoretical output of an encapsulation machine depends on capsule size, die width, and the rotating speed of the casting drums/dies,

which typically varies between 3 and 5 rpm. Usual production rates range from 30,000 to 120,000 capsules per hour. Environmental conditions in the encapsulation areas are usually controlled within 18 to 22°C and 20 to 40% RH. For manufacturing pharmaceutical products, the encapsulation lines are usually segregated from each other into individual suites.

In the past, the formed capsules were typically conveyed through a washing unit of naphtha or another organic solvent to remove residual lubricant and traces of fill material from the capsule surfaces (Stanley, 1986). Recently, as softgel manufacturers have focused on reducing their use of organic solvents, the capsule washing step has been viewed as not essential and often is skipped. Limiting lubricant application to a minimum helps negate the need for the washing step (Stroud et al., 1998). Subsequently, the capsules are transferred pneumatically or by a conveyor belt to a stainless-steel tumbler (dryer) consisting of successive rotating baskets (hollow drums) with perforated walls (Figure 16.3). The air coming in contact with the capsules in the tumbler typically is at the same temperature as the encapsulating room (18 to 22°C). Alternatively, heated (30 to 35°C) air may be pumped through the rotating baskets. Absorbent towels often are added to the tumblers to remove oil residues from the capsule surfaces. Immediately cooling the formed capsules to 2 to 7°C with low RH (20%) air prior to transferring them into the tumbler was suggested in a patent disclosure (Herman, 1992). The purpose was to prevent deformation of the warm capsules and to facilitate moisture removal from the capsule surfaces (Herman, 1992). However, the potentially negative influences of rapid cooling upon the shell structure should be considered. The tumbling action, which may last from 45 to 90 min, removes a large amount of moisture from the capsules. Alternatively, an infrared dryer may be used, which removes 60 to 70% of the total moisture eventually lost (Stanley, 1986).

DRYING AND FINISHING

After the capsules are "dumped" from the tumbler into a stainless-steel container ("back bin"), they are manually "scooped" and spread onto shallow fiberglass trays. The trays are then stacked and kept under controlled environmental conditions (18 to 24°C and 20 to 30% RH), often in drying tunnels with forced air circulation, to complete the drying process. Drying may last anywhere from 0.5 to 15 days depending on several factors such as environmental conditions, shell composition, shell thickness, fill formulation, number of capsules on the drying trays, and amount of residual oil on the capsule surfaces. The "dry" softgels have a final moisture content of 5 to 10%. Naturally, softgels with hydrophilic fills (e.g., PEG-based) require longer drying times. Determination of moisture content (usually by Karl Fischer titration) or hardness are the most commonly used criteria for releasing softgels from the drying room.

It is possible to remove additional moisture from the dry capsules through

heating at higher temperatures (e.g., 40°C), but such practice is not considered practical or necessary (Stanley, 1986). Also, a "stress-relieving" step where dry softgels are tempered at 32 to 43°C and 35 to 60% RH to remove dimples and other physical defects from the capsule shells has been suggested (Steele and Dietel, 1993). However, gelatin insolubility due to dehydrothermal cross-linking induced by heat treatments at elevated temperatures (55 to 105°C), especially at a reduced pressure, is well documented (Yannas and Tobolsky, 1967; Marks et al., 1968; Welz and Ofner, 1992; Vassileva et al., 1999). Therefore, subjecting dry softgels to elevated temperatures, even as low as 40°C, should be viewed cautiously as it may negatively affect shell solubility characteristics. In general, both the drying conditions and the drying rate of softgels are critical parameters. Accelerated ("aggressive") drying, although economically appealing (faster throughput), can result in brittle capsules (Reich, 1995). On the other hand, incomplete drying results in soft, tacky capsules.

Dry softgels typically are polished in revolving pans using absorbent towels carrying trace amounts of lecithin, isopropyl alcohol, or naphtha. Lecithin is not used for this purpose if the softgels are to be subsequently printed because it interferes with the printing inks. This polishing removes oil residues and other impurities from the capsule surfaces and maximizes the shiny, glossy appearance of the softgels. The polished softgels are passed through a mechanical sizer/sorter that removes any undersized/oversized capsules. From the sizer, the softgels are deposited onto a conveyor belt where they are visually inspected to detect and manually remove any defective capsules. Alternatively, the visual inspection may be accomplished prior to sizing while the capsules are still spread one layer thick on the shallow drying trays. Finally, the softgels are automatically filled by an electronic counter into bulk shipping cartons lined with polyethylene bags (moisture barrier) that are then labeled, sealed, palletized, and shipped. Subsequent retail packaging into plastic bottles, glass bottles, or blisters is accomplished with the same packaging equipment used for other solid dosage forms.

PRINTING

Pharmaceutical (and occasionally nutritional) softgels are printed (parallel or perpendicular to the long axis) for product identification. Both contact printing (i.e., rotogravure) and non-contact printing (i.e., ink jet or laser) may be used for this purpose. Rotogravure using Ackley, Hartnett, and Markem machines is the most common printing method for softgels and offers good quality printing. On-line printing of the cast gelatin ribbons prior to softgel formation using ink rollers also is feasible. The basic ingredients of ink formulations are pigments that impart color and opacity; resins that bind pigments and facilitate adherence onto printable surfaces; solvents that alter the physical characteris-

tics of the inks and control the drying rate; and special additives such as wetting agents, defoamers, and pH adjusters (Lykens, 1979). Similar to the selection of colorants, printing ink ingredients must be carefully monitored for regulatory compliance in the intended product markets.

Traditionally, the softgel industry has been using ink formulations that combine organic solvents (e.g., SDA 3A alcohol, SD-45 alcohol, and N-butyl alcohol); shellac as a resin; and synthetic iron oxides, titanium dioxide, and/or lakes as pigments. However, water-based ink formulations, although generally more expensive than solvent-based formulations, have recently been gaining popularity as softgel manufacturers are undertaking efforts to reduce solvent use for environmental reasons. Water-based ink formulations use purified water with small amounts of isopropyl alcohol and/or methanol as the solvent system; hydroxypropyl methylcellulose (HPMC) as the resin; and synthetic dyes, synthetic iron oxides, and/or titanium dioxide as pigments. The removal of the oil residue from the softgel surface is particularly critical to good quality printing when using water-based inks. Solvent-based inks dry onto the softgels as the solvent evaporates, while water-based inks dry by adsoprtion onto the hydrophilic softgel surfaces (Spicer, 2000). Compared to solvent-based inks, water-based inks have a wider regulatory acceptance and are easier to clean up, but they offer a slightly less sharp image, dry slower, and are more expensive (Spicer, 2000).

Ink-jet printing of softgels results in images of lower aesthetic quality than contact printing. In addition, only dyes, not iron oxides or lakes, can be used with jet printing, which presents stability concerns due to the light sensitivity of dyes (Spicer, 2000). Laser printing involves directing a high-intensity light beam onto the product to burn away a surface layer, thus imparting the printed image. As an obvious advantage, laser printing does not require pigments or solvents. However, it offers no color choices, is expensive, and the printed image tends to lose its sharpness over time.

STORAGE

Because softgel shells are hydrophilic, the environmental conditions during storage of bulk or retail packaged softgels can affect product quality. For optimum physical and chemical stability, softgels should be stored in the temperature range of 15 to 30°C and at RH less than 50% (Murthy and Ghebre-Sellassie, 1993). Packaging materials, such as high-density polyethylene (HDPE) liners in bulk cartons or retail HDPE bottles, protect softgels from moisture, but they are not an absolute moisture barrier. Therefore, upon prolonged exposure to elevated RH, packaged softgels can pick up moisture. The absorbed moisture softens, tackifies, and bloats the capsules (Stanley, 1986). Sticking ("bricking") of capsules within the package can occur in such cases. In addition to the adverse physical effects, absorbed moisture can also negatively

affect the chemical stability of hydrophilic fills as moisture migrates from the shell into the fill. For example, increased water content can reduce the solubility of poorly water-soluble drugs in PEG or other fill excipients, thereby causing drug crystallization (Serajuddin et al., 1986). Drug hydrolysis is another possible negative effect of absorbed moisture (Yoshioka et al., 1992). The disintegration characteristics of the capsule shells may also be affected by increased water content. However, Armstrong et al. (1983) reported that oil-filled softgels that absorbed moisture through exposure to elevated RH did not have significantly ($P > 0.01$) lower disintegration times.

Increased storage temperatures, especially combined with increased RH (as is the case during stressed stability testing at 40°C and 75% RH), can have even more drastic effects on softgels. Capsule shell softening can occur, possibly causing the softgels to stick to each other or to even fuse together. Hakata et al. (1981, 1983) reported that softgels stored at 40 and 50°C had increased disintegration times. This was attributed to structural changes within the shell and, in particular, to denaturation of the collagen-like triple helix structure assumed by the gelatin in the dry shells (Hakata et al., 1981, 1983). The increase in disintegration time due to the storage of softgels at 40°C was prevented by the presence of desiccating agents (Hakata et al., 1992).

Light is another environmental parameter that can cause physical changes to softgels, such as color fading or discoloration. This is particularly a concern with bath beads and other personal care softgel products that often are marketed in transparent retail packages. In contrast, pharmaceutical and nutritional softgels are generally marketed in light-resistant packages. A study by Hakata and Sato (1992) showed that exposure to fluorescent light did not affect the disintegration times of softgels. In a recent study, exposure to UV and visible illumination at 40°C and 75% RH for 8 days considerably retarded the dissolution rate of nimesulide softgels (Singh et al., 2000).

SOFTGELS WITH MODIFIED RELEASE CHARACTERISTICS

DELAYED RELEASE

Orally administered softgels are intended to provide immediate release of their encapsulated contents upon exposure of the gelatin shell to the acidic environment and gastric enzymes in the stomach. Over the years, there has been an interest in developing softgels with modified release characteristics, such as delayed (sustained or continual) release or enteric release. A few fill formulation approaches to achieving a delayed release of active compounds from softgels have been proposed (Cohen et al., 1987, 1989; Hom and Ebert, 1989; Hom and Jimerson, 1990). The concept involves the use of insoluble natural or synthetic polymers (e.g., chicle, polyvinyl acetate, ethylcellulose, and calcium alginate) to prepare liquid to semi-solid cohesive matrices or microcapsules

containing the active compounds that are subsequently filled into softgels. The cohesive matrices or microcapsules allow for a delayed release of the actives by diffusion once the gelatin shell disintegrates. An Abbreviated New Drug Application (ANDA) for such a sustained release softgel (300 mg theophylline) was approved in the U.S. by the FDA (Stringer, 1994).

Imparting delayed release characteristics to gelatin microcapsules or films by cross-linking the gelatin with aldehydes or reducing carbohydrates has been investigated (Po and Mhando, 1984; Bower et al., 1992; Akin and Hasirci, 1995; Cortesi et al., 1999). This approach also is applicable to softgels (Rolle, 1972; Hakata et al., 1994). In fact, softgels cross-linked with aldehydes or reducing sugars have found limited commercialization for products such as garlic oil (which causes reflux when released rapidly in the stomach). However, residual aldehydes are a cause for concern due to their toxicity. Other chemical cross-linkers may also be effective in imparting delayed release properties to softgels. For example, cross-linking of hard gelatin capsules by terephtaloyle chloride allowed for the *in vitro* sustained release of the asthma medication theophylline (Guyot et al., 1996). Recently, cast gelatin films were enzymatically cross-linked by microbial Ca^{2+}-independent transglutaminase (Lim et al., 1999). This enzyme, which catalyzes the formation of ε-(γ-glutamyl)lysine cross-links in proteins (Nielsen, 1995), may offer the potential for preparing softgels with delayed release characteristics. Thiolated gelatin that has been cross-linked by disulfide bonds also holds a potential to create a delayed release system (Johnson, 1965; Barron and Tsuk, 1967; Okamoto et al., 1973). However, thiolated gelatin is not acceptable for edible applications. Finally, cross-linking gelatin using aluminum cations to prepare gelatin capsules with modified release characteristics was suggested (Shank, 1985). Overall, commercialization of delayed release softgels has been limited, mainly due to the difficulties in precisely controlling the release rate of active compounds.

ENTERIC RELEASE

Softgels having enteric release properties may be desirable for certain active compounds that degrade in the stomach (e.g., biologically active proteins and peptides); have the intestinal tract as their intended site of action; or cause gastric irritation or nausea. In general, solid pharmaceutical dosage forms can be coated with enteric polymers, which are resistant to the acidic stomach environment but disintegrate in the neutral or slightly alkaline intestinal environment. Enteric polymers include cellulose derivatives, such as hydroxypropyl methylcellulose phthalate and cellulose acetate phthalate (Sakellariou and Rowe, 1995); polyacrylates (Lehmann, 1989); and shellac (Specht et al., 1999). For example, application of enteric polymers onto hard gelatin capsules by pan or fluidized-bed coating, typically in combination with an aqueous subcoat (e.g., hydroxypropyl methylcellulose, or polyvinylpyrrolidone) to improve ad-

hesion of the enteric coatings, has been discussed (Funakoshi et al., 1982; Tsuji, 1987; Murthy et al., 1988; Nielsen et al., 1999). However, applying enteric coatings to softgels, as a unit operation, is even more challenging due to their inherent flexibility and their potential susceptibility to mechanical deformation and sticking during the coating process (Felton et al., 1995).

A few studies or patent disclosures focused on the enteric-coating of softgels with acrylates (Leiberich and Gabler, 1976; Davies et al., 1987; Pagay and Stetsko, 1994; Felton et al., 1995, 1996) or polyvinyl acetate phthalate (Matthews and Virgilio, 1989) have demonstrated the viability of the concept, although several parameters need to be controlled to obtain a successfully coated softgel. For example, adhesion of an enteric acrylate polymer onto the gelatin shell depended upon both the plasticizer incorporated into the coating formulation and the fill formulation of the softgel (Felton et al., 1996). Consideration should also be given to the aesthetic appearance of the coated softgels. Despite the ongoing interest in developing softgels with enteric properties, commercialization has been limited, if any. Besides the technical challenges, coating softgels with enteric polymers is a post-processing step that adds to the cost of the product. As an alternate approach to coating, enteric polymers may be directly incorporated into the gelatin-based film formulation prior to softgel manufacturing. For example, the preparation of enteric softgels by combining alginates with gelatin in the shell formulation was described in a Japanese patent (Takashi and Tetsuo, 1999). Incorporation of most enteric polymers into the gelatin shell is limited mainly by their likely incompatibility with gelatin.

SOFTGELS WITH GELATIN EXTENDERS OR SUBSTITUTES

GELATIN EXTENDERS

Bicomponent gels comprised of gelatin and other biopolymers, such as maltodextrin (Alevisopoulos and Kasapis, 1999), starch (Ring and Stainsby, 1982; Khomutov et al., 1995), carrageenan (Michon et al., 1995; Kasapis et al., 1999), locust bean gum (Alves et al., 2000), pectin (Al-Ruqaie et al., 1997), microcrystalline cellulose (Kasapis, 1999), gellan gum (Chilvers and Morris, 1987), and whey proteins (Walkenström and Hermansson, 1997), have been studied. They can be mixed gels (independent polymer networks) or complex gels (coupled polymer networks) (Zasypkin et al., 1997). There has been interest in incorporating natural or synthetic polymers into softgel shell formulations to impart certain attributes (e.g., chewability), partially replace gelatin with a cheaper polymer, or substitute part of the gelatin with a smaller amount of a stronger gelling polymer. Enhancing the strength of the gelatin compositions used for capsule manufacturing through the addition of dialdehyde starch (0.5–5.0% w/w of gelatin) was disclosed in a patent by Helmstetter (1977). Dialdehyde starch, a polymeric aldehyde prepared by reacting starch with peri-

odic acid (Pfeifer et al., 1960), can cross-link proteins (Gennadios et al., 1998; Rhim et al., 1998) similar to the actions of low molecular weight aldehydes. However, it is not approved for edible applications in the U.S.

Fischer et al. (1989) described softgels containing shell additives (at least 1% w/w), such as starches, starch derivatives, microcrystalline cellulose, and cellulose derivatives. In their pure states, these additives are capable of absorbing at least 10% (w/w) of their own weight in water. Such softgels were considered suitable for encapsulating fills containing water-miscible components of low volatility (e.g., glycerin and propylene glycol) at levels greater than the typical 10% (w/w of fill) limit. Softgels that had textured (frosted or satin) finishes and were resistant to sticking and to shape changes were described by Stroud (1996). These attributes were imparted to the capsules by partially substituting gelatin with starch of high amylose content (50–90%) so that the starch accounted for 3–60% of the dry shell weight. In addition, the textured surface allowed for better adhesion of subsequently applied enteric coatings (Stroud, 1996).

Shell formulations that combined chemically modified gelatin, starch derivatives, and propylene glycol (plasticizer) with the intent to minimize gelatin-drug interactions over the capsule shelf life were described in a Japanese patent (Yamada and Makino, 1985). High amylose starch or starch derivatives were incorporated into the shells (at 5–20% of dry weight) of softgels having "break-off" features that were intended for delivering medicaments to an external body surface (Schurig et al., 1996). Such capsules had a drier feel, which enhanced their gripping and handling characteristics. Softgel shell formulations containing a non-hygroscopic plasticizer (e.g., maltitol, maltitol syrup, or hydrogenated starch hydrolyzate) and an elasticity-reducing extender (8–30% w/w of dry shell) selected from a large group of natural or synthetic polymers, such as modified starches and cellulosics, were described by Chiprich et al. (1997). Such softgels had an increased brittleness and could be broken with manual pressure to deliver their contents. Partial replacement of gelatin with gum acacia in softgel shell formulations also was proposed recently (Gennadios, 2001a).

The incorporation of potato starch acetate into capsule shells at 3–12% of the gel mass weight was suggested for preparing chewable softgels (Hutchison et al., 1998). The starch acetate allowed greater amounts of plasticizer to be used, thus improving chewability. Furthermore, the starch acetate formed a gel that lacked substantial cross-bonding within the gelatin matrix. Upon chewing, the starch acetate and the gelatin swelled at different rates and became readily separable (Hutchison et al., 1998). Another approach to preparing chewable softgels involved the incorporation of insoluble masticatory substances (at 1 to 75% by wet weight), natural (e.g., chicle and natural rubber) or synthetic (e.g., petroleum wax), into the gel mass compositions (Ebert et al., 1984).

Besides incorporating gelatin extenders into the capsule shell, applying

coatings onto softgels has been proposed. For example, a carnauba wax coating was used to improve shell strength and moisture resistance of softgels (Mizuno and Kayano, 1982). The use of chocolate coatings to improve palatability was discussed in a Japanese patent (Takemori et al., 1985). Coatings based on polysaccharides (e.g., gum arabic, pectin, and agar), possibly containing water-soluble nutrients (e.g., vitamin C), were applied onto softgels to improve taste, flavor, and stability (Ozawa et al., 1984). In a different type of invention, Sundararajan et al. (1996) prepared bilayer (or multilayer) softgels having one (or more) barrier layer(s) between the gelatin shell and the fill. The barrier layer prevented the migration of hydrophilic or hydrophobic ingredients from the fill into the shell, thus allowing for encapsulation of fill formulations having higher than typical contents of water and other low molecular weight substances (e.g., propylene glycol and ethanol). The barrier layer was a mixture of a polymer (e.g., ethylene acrylic acid co-polymer) and a microcrystalline wax. The capsules were manufactured using rotary die encapsulation machines that were modified so that the two capsule shell layers were formed simultaneously by co-extrusion on the casting drums using double-exit sheet dies (Sundararajan et al., 1996).

GELATIN SUBSTITUTES

Due to its animal origin, gelatin is associated with religious and dietary concerns in certain segments of consumer populations. Over the years, such concerns have sustained interest in identifying viable, non-animal alternatives for gelatin in various edible and pharmaceutical applications, including hard and soft gelatin capsules. Injection-molded hard capsules made of potato starch (Kenyon et al., 1994) were commercialized in the early 1990s, but are not currently marketed. Also, the manufacture of gelatin-free hard capsules based on cellulose ethers has been discussed in patent disclosures over the years (Eli Lilly & Company, 1950; Sarkar, 1977; Chiba et al., 1990; Grosswald et al., 1998). In recent years, cellulose ether-based hard capsules have been commercialized but remain a niche product in terms of market share.

The rotary die process for manufacturing softgels was developed to match the properties of gelatin, particularly its thermoreversibility. Adapting the same process to polysaccharides that form thermoreversible gels, such as gellan gum and carrageenan (Winston et al., 1994; Viaud, 1999; Gennadios, 2001b) has been attempted. Gellan gum is an extracellular, linear, anionic polysaccharide produced by the bacterium *Pseudomonas elodea* (Chilvers and Morris, 1987). Winston et al. (1994) used blends of gellan gum, κ-carrageenan, and mannan gums (e.g., locust bean gum) to prepare the gel mass for softgel manufacturing. The mannan gums were added to increase gel elasticity. The main limitation in processing such gels with the rotary die process is their notably higher melting/setting temperatures compared to gelatin gels. At similar

concentrations, κ-carrageenan gels have lower melting/setting temperatures than gellan gum gels (Nishinari et al., 1996). Recently, the formation of softgels from gel formulations based on either ι-carrageenan (Viaud, 1999) or κ-carrageenan (Gennadios, 2001b) was discussed.

In the late 1980s, soft capsules made of glycerin-plasticized mixtures of sodium alginate and agar were commercialized for the encapsulation of dietary supplements. These spherical-shaped, seamless capsules were manufactured using the Globex process, which also is suitable for making gelatin capsules (Rakucewicz, 1988). With this process, two-layer droplets are ejected from a double orifice type nozzle. The inner layer is comprised of a lipophilic fill formulation, while the outer layer is a liquid shell formulation. The droplets are dropped into a liquid bath that hardens (solidifies) the outer layer (shell) forming the seamless capsules (Suzuki et al., 1995, 1999). For gelatin capsules, solidification is accomplished with a cooling bath (typically paraffin oil), whereas for sodium alginate-based capsules, solidification is accomplished with an aqueous solution of a calcium salt (Suzuki et al., 1995). Encapsulation of hydrophilic fills into seamless gelatin, alginate, or agar capsules also is possible with this manufacturing approach by ejecting three-layer droplets from concentrically arranged nozzles (Kikuchi and Kamaguchi, 1994). The innermost layer is a solution of the hydrophilic active substance, the outermost layer is the film-forming solution, and the middle layer is a viscous liquid scarcely miscible in water (Kikuchi and Kamaguchi, 1994). In general, the seamless capsules discussed above are limited in terms of their size and shape and have remained a niche product.

An experimental technique for preparing soft capsule-like dosage forms from gliadin, the prolamin (alcohol-soluble) fraction of wheat proteins, was described by Stella et al. (1995). They prepared masses consisting of 18 to 36% (w/w) gliadin, 9 to 18% (w/w) plasticizer (sorbitol/glycerin, 2:1 w/w), and 46 to 73% (w/w) aqueous ethanol (50% v/v). The masses were cast and dried into films that were molded on stainless-steel mold pins, filled with the active compounds, and heat-sealed at 37°C and 70% RH. These gliadin-based, soft capsule-like systems showed promise for the controlled release of paracetamol (Stella et al., 1995).

Recently, gelatin-free soft capsules made of polyvinyl alcohol (PVAL), a non-ingestible material, were developed, and bath oils encapsulated into such capsules have become commercially available (Anonymous, 1998). These capsules are formed by feeding preformed, dry PVAL films to a rotary die-like encapsulation machine (Brown, 1997). Instead of heat-sealing the two halves of the capsule, the capsule seal is formed by applying a solvent to the surface of at least one of the films prior to encapsulation (Brown, 1997). Besides PVAL, this method may be used with other natural or synthetic polymers, such as alginate, HPMC, and polyethylene oxide (Brown, 1997). In addition, the formation of gelatin-free soft capsules from multilayer films comprised of a sealing layer, a

barrier layer, and a binding layer between the sealing and the barrier layers was recently described by Brown et al. (2000). Preferably, the internal sealing layer is HPMC while the outer barrier layer is sodium alginate. The binding layer between the HPMC and the sodium alginate layers is propylene glycol alginate. Preformed, dried films are used for this process, and sealing is preferably accomplished by radio frequency signals (Brown et al., 2000).

Softgels made of potato starch were commercially launched in July 2000 (VegaGelsJ, Swiss Caps, Kirchberg, Switzerland). Such capsules are formed from extruded starch-based ribbons (Anonymous, 2000). Because the extruded ribbons have a low moisture content, the capsule drying step is not necessary with this process (Anonymous, 2000). Manufacturing of flexible capsules using modified starches also was described in a recent European patent application (Laba et al., 2000). Finally, soft capsule shell compositions comprised of modified starch (preferably hydroxypropylated acid modified corn starch) and ι-carrageenan were described by Tanner et al. (2001) in a recent international patent application. They suggested a weight ratio of modified starch to ι-carrageenan in the range of 1.5:1 to 4:1.

CAPLETS/TABLETS ENROBED/COATED WITH GELATIN

Technologies have been developed for enrobing or coating solid cores (caplets or tablets) with gelatin. Such technologies may differ, more or less, from the softgel technology, but are briefly discussed here due to their relevance. Gelatin-coated caplets or tablets are typically referred to as gelcaps or geltabs, respectively. Within the past decade in the U.S., these solid oral dosage forms have captured a sizable share of the OTC drug market, and their use is expanding within the prescription drug and dietary supplement fields as well (largely driven by line extension opportunities). The main advantages of applying an outer gelatin layer onto caplets or tablets include, similar to softgels, ease of swallowing, taste and odor masking, protection from oxidation and light, color differentiation, printability, resistance to tampering, and increased core durability. The effect of the added gelatin layer upon the dissolution of the active is minimal due to the rapid solubilization of gelatin upon ingestion.

In the early 1990s, Banner Pharmacaps Inc. (High Point, NC) developed and commercialized a method for enrobing solid cores with gelatin using modified rotary die softgel encapsulation equipment (Figure 16.5). The cores were aligned through a feeding mechanism and dispensed between two cast gelatin ribbons, which were supported on a pair of rotary dies (Sadek and Dietel, 1992, 1995). The gelatin films deformed around the cores and were heat-sealed together before the dies cut the enrobed cores from the ribbons. Both monocolored and bicolored enrobed cores can be manufactured by using gelatin ribbons of the same or differing color, respectively. Similar to softgels, the

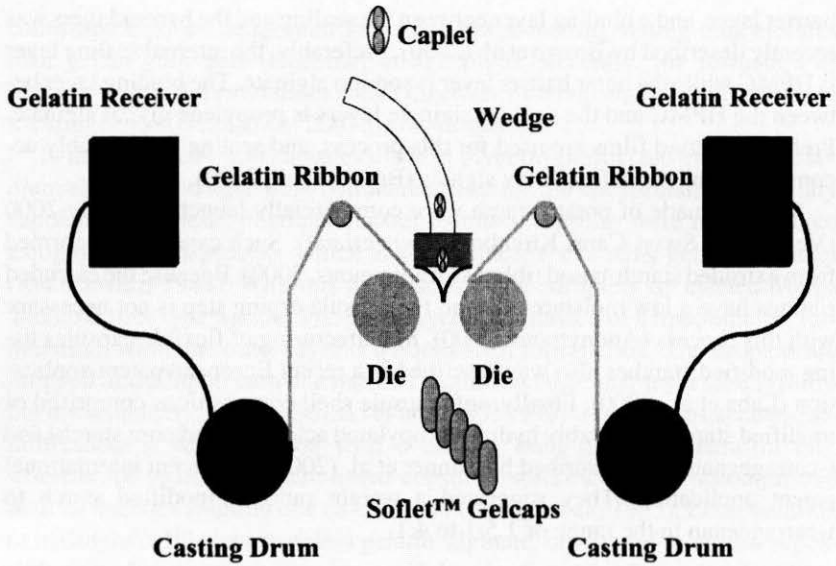

Figure 16.5 Schematic diagram of the process used by Banner Pharmacaps (High Point, NC) to enrobe caplets and tablets with gelatin (Soflet™ gelcaps or geltabs, respectively) (courtesy of Banner Pharmacaps Inc., High Point, NC).

enrobed cores, referred to as Soflet™ gelcaps or Soflet™ geltabs, require drying (to a gelatin shell moisture content of 5 to 8%) prior to inspection, polishing, printing, and packaging. Cores used in this process are typically subcoated with a water-soluble polymer, such as HPMC or hydroxypropyl ethylcellulose, to give a weight gain of around 1%. The subcoat, which typically is clear (non-pigmented), prevents dusting and improves adhesion of the gelatin outer layer. The gelatin layer applied onto the cores is thinner (by 30 to 50%) than the gelatin shell of softgels and contains a lesser amount of plasticizer. For example, the wet gel formulation may contain 45% (w/w) gelatin and 9% (w/w) plasticizer (Sadek and Dietel, 1992, 1995).

McNeil-PPC (Skillman, NJ) developed and commercialized a dipping process for coating caplets with gelatin (Berta, 1989a, b). This method involved the application of a gelatin coating onto one end of the caplet followed by application of a second gelatin coating onto the other end. The second coating was thicker than the first and could be applied using a gelatin bath having a higher viscosity than the bath used for the first coating. Because the second coating partially overlapped the first coating, which had a different color, the interlocking halves of a hard gelatin capsule were simulated (Berta, 1989a, b). The smoothness and uniformity of the outer gelatin coating was improved by using caplets that were subcoated with a mixture of a water-soluble polymer, such as HPMC, and a hydrophobic plasticizer, such as castor oil (Batista and Markley,

1994; Parekh et al., 1998). This dipping process also was applied to tablets after the appropriate equipment modifications were made (Berta, 1993, 1995, 1997).

Gelatin solutions also can be sprayed onto solid cores using various coating pan systems. For example, Becker (1992) spray-coated tablets and caplets (subcoated with HPMC or methylcellulose) with solutions of hydrolyzed (Bloom strength below 80 g) gelatin. The thin (25 to 100 μm) gelatin coatings reduced the coefficient of friction of the cores, thus increasing their ease of swallowing. Gelatin coating compositions having improved drying characteristics and a reduced stickiness were discussed by Daher et al. (2000). Gelatin (preferably from fish) having a Bloom strength up to 200 g was combined with a surfactant (e.g., sodium stearoyl lactylate, calcium stearoyl lactylate, or glyceryl monostearate), a drying agent (e.g., sodium sulfate), and optionally a plasticizer (preferably propylene glycol monostearate). The surfactant was incorporated to reduce stickiness, while the drying agent accelerated the drying of the gelatin coating (Daher et al., 2000). These coating compositions could be applied to both subcoated and uncoated ("raw") solid cores (1 to 5% weight gain) (Daher et al., 2000).

Another approach to covering caplets with gelatin is by encapsulation into hard gelatin capsules. Barshay and Mayer (1990) described a method for adhesively bonding a caplet to the inner end surfaces of a hard gelatin capsule using an edible, water-based or organic solvent-based adhesive. An automatic device for filling caplets into hard gelatin capsules was designed by Boyd et al. (1992). In recent years, Warner-Lambert (Morris Plains, NJ) has developed and commercialized an improved process for encapsulating caplets that involves treating the two halves of the hard gelatin capsule with cold shrinking (Amey et al., 2000).

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