

Formulation and physical properties of soft capsules

Gabriele Reich

Introduction

Soft capsules are a single-unit solid dosage form, consisting of a liquid or semi-solid fill enveloped by a one-piece hermetically sealed elastic outer shell. They are formed, filled and sealed in one continuous operation, preferably by the rotary die process. Depending on the polymer forming the shell, they can be subdivided into two categories, namely soft gelatin capsules or 'soft-gels' and non-gelatin soft capsules. The majority of soft capsules are made from gelatin owing to its unique physical properties that make it an ideal excipient for the rotary die process. Soft capsules based on plant-derived and/or synthetic non-gelatin alternatives have, however, been patented and a few prototype products have recently entered the market. Formulation and physical properties of both soft capsule categories will be discussed.

Soft gelatin capsules

General aspects

Originally developed in the 19th century to mask unpleasant taste and odour of drug substances, soft gelatin capsules are used in many applications, for pharmaceutical and health and nutrition products, cosmetic applications and even recreational products such as paint balls.

In the pharmaceutical field soft gelatin capsules are increasingly being chosen for *strategic reasons* (line extension), *technological issues* (high content uniformity of low-dose drugs), *safety*

aspects (reduced operator and environmental contamination with highly potent or cytotoxic compounds) and *consumer preference* (easy to swallow). The most interesting advances have recently been made in the area of developing liquid and semi-solid formulations in a soft gelatin capsule to address *particular bioperformance issues*, namely increased bioavailability and decreased plasma variability by improved solubility and absorption-enhancing techniques.

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

Composition of the capsule shell

The shell of a soft gelatin capsule is composed of gelatin, a plasticizer or a combination of plasticizers and water. In addition, it may contain preservatives, colouring and opacifying agents, flavourings and sweeteners, possibly sugars to impart chewable characteristics to the shell, gastroresistant substances and in special cases even active compounds.

The water serves as a solvent to make a molten gelatin mass with a pourable viscosity at 60–70°C. The ratio by weight of water to dry gelatin (W/G) can vary from 0.7 to 1.3, depending on the viscosity of the gelatin being used. After capsule formation, most of the water is removed by drying, leading to finished capsules with a moisture content of 4–10%.

Gelatin

The gelatins used for pharmaceutical or health and nutrition soft capsule products are described by the official pharmacopoeias such as USP (United States Pharmacopoeia), PhEur (European Pharmacopoeia) etc., or approved by local authorities, with additional physicochemical specifications (Babel, 2000). The specifications and controls for gelatins are discussed in Chapter 2.

For soft capsule production, the pharmacopoeial specifications generally represent the minimum requirements. Capsule manufacturers' specifications are more detailed and stringent with respect to the performance-related physicochemical properties of the gelatins (Reich and Babel, 2001). This is due to the fact that these parameters are critical for economic soft capsule production by the rotary die process and for the quality of the final product. Gelatin types and grades that are adequate for continuous commercial soft capsule production require the ability to set at a fast rate to ribbons of defined thickness and reproducible microstructure and to produce films with a mechanical strength and elasticity sufficient to survive all the manipulations on the encapsulation machine, i.e. to allow the wet films to be easily removed from the drums, to stretch during filling, to be sealed at temperatures below the melting point of the film and to be dried quickly under ambient conditions to a specified capsule strength. Moreover, the dissolution characteristics of the resulting capsules have to fulfil the pharmacopoeial requirements.

Considering these aspects, the technologically relevant gelatin parameters are gel strength, viscosity at 60°C and 6 $\frac{2}{3}$ % w/w concentration in water, viscosity breakdown (the impact of temperature and time on the degradation of gelatin), melting point, setting point, setting time, particle size and molecular weight distribution. A perfect soft capsule gelatin should have the following specifications:

- Gel strength: 150–200 Bloom, depending on the gelatin type;
- Viscosity (60°C/6 $\frac{2}{3}$ % w/w in water): 2.8–4.5 mPa s, depending on the gelatin type;
- Well-controlled degree of viscosity breakdown;
- Well-defined particle size to allow fast dissolution and deaeration of the molten mass, even at high gelatin concentrations;
- A broad molecular weight distribution to provide a fast setting and the fusion temperature being well below the melting temperature of the plasticized wet film.

The main gelatin types and grades used for the manufacture of soft capsules are listed in Table 11.1 together with their physicochemical specifications.

The proper choice of the gelatin type and grade is related to technological issues, consumer preference and pricing. For pharmaceutical or health and nutrition products, medium bloom limed bone (LB) gelatins, or blends of limed bone and pigskin (LB/PS) or limed bone, pigskin and limed hide gelatin (LB/LH/PS) are commonly used, with a certain preference for LB gelatin in the United States and for blended gelatins in

Table 11.1 Physicochemical properties of pharmacopoeial-grade soft capsule gelatins

Gelatin	Raw material	Type	Bloom (g) (10°C; 6 $\frac{2}{3}$ % w/w)	Viscosity (mPa s) (60°C; 6 $\frac{2}{3}$ % w/w)
160 LB (= limed bone)	Bovine/porcine bone	B	155–185	3.4–4.2
160 LH (= limed hide)	Bovine hide	B	150–170	3.5–4.2
160 LB/LH	Blend of bovine/porcine bone and bovine hide	B	150–170	3.5–4.2
200 AB (= acid bone)	Bovine bone	A	180–210	2.7–3.2
200 PS (= pigskin)	Pigskin	A	190–210	2.5–3.1
160 PS/LB/LH	Blend of pigskin, bovine/porcine bone and bovine hide	A/B	145–175	2.7–3.3

Europe. Low-viscosity, high-bloom gelatins such as a 200 Bloom pigskin (PS) or acid bone (AB) gelatin are often used for the encapsulation of hygroscopic formulations and/or water-sensitive drugs, where standard gelatin formulations have to be modified to contain less water and dry faster, thus improving the product stability during capsule manufacturing. Mixtures of low (<100 Bloom) and medium Bloom (>150 Bloom) gelatins have been proposed for the formulation of chewable soft capsules (Overholt, 2001) to achieve the desired mouthfeel and solubility of the shells, a low stickiness for improved machinability and sufficient integrity for stable fill encapsulation.

In addition to the pharmacopoeial grade gelatin types listed in Table 11.1, succinylated pigskin gelatin (Bloom: 190–210 g; viscosity: 3.3–4.1 mPa s) is often used for products with reactive fill ingredients, such as aldehydes, to prevent cross-linking of the shell. Gelatins derived from poultry, fish or other sources have recently been proposed in the patent literature as alternatives to gelatin of bovine and porcine origin. Poultry and fish gelatins have recently been approved by PhEur.

From a technological point of view, poultry gelatin is a potential alternative to the conventional soft capsule gelatins derived from bovine and porcine origin, since its physico-chemical properties are comparable to those of pigskin gelatins. In practice, it has not gained high commercial interest yet because its availability is limited.

The use of cold- or warm-water fish gelatins for soft capsule production is limited by the fact that their gelling, setting and drying properties are more or less different to those of mammalian gelatins. Owing to their low degree of proline hydroxylation, cold-water fish gelatins lack the gelling and setting attributes that are required to allow their use in the conventional rotary die process. Although addition of a setting system, such as carrageenan, has been described to enable the adaptation of specific and desired gelling properties (Scott *et al.*, 1997), this approach has not yet reached commercial status. Only warm-water fish gelatins with a somewhat higher degree of proline hydroxylation, and thus an intrinsic gelling and setting ability sufficient for

conventional soft capsule production, have been used for a small number of products. Acceptable soft capsules can be produced by adjusting the formulation and process parameters, such as the production speed in accordance to the reduced setting rates, the mechanical properties and the drying characteristics of this gelatin type.

The use of plant-derived genetically engineered gelatins for soft capsule production is not practicable. This is mainly due to technological issues, supply problems, high costs and, for pharmaceutical products, the regulatory issues. Only small amounts of gelatins, with gelling and setting properties and mechanical characteristics different to mammalian gelatins, are available at a multiple of the price of conventional gelatins.

Plasticizers

The formation of a soft capsule requires the use of a non-volatile plasticizer in addition to water to guarantee the mechanical stability, i.e. the elasticity of the capsule shells during and after the drying process. The additional plasticizer has to counterbalance the stresses that are induced in the shrinking capsule shells, as the plasticizing effect of water in the shells decreases upon drying.

Practically, only a few plasticizers are in use, namely polyalcohols, which are approved by the official pharmacopoeias or by local regulatory authorities. Glycerol (85% and 98% w/w), special grades of non-crystallising aqueous sorbitol and sorbitol/sorbitan solutions and combinations of these are the most used. In addition, propylene glycol and low molecular weight polyethylene glycol (PEG 200) have been used.

The type and concentration of plasticizer(s) in the shell is related to the composition of the fill, i.e. the possible interactions with the fill, the capsule size and shape, the end use of the product and the anticipated storage conditions. The ratio by weight of dry plasticizer to dry gelatin (P/G) determines the strength of the shell and usually varies between 0.3 and 1.0. The choice of the proper shell formula with respect to the gelatin/plasticizer combination is crucial to the physical stability of the capsules, during manufacture and on storage. A rational shell design therefore requires analytical tools that allow the performance-related test parameters to be assessed.

Differential scanning calorimetry (DSC) and dynamic mechanical thermal analysis (DMTA) have been reported as suitable methods to monitor phase transitions and elastic moduli indicating molecular gelatin/plasticizer interactions and their effect on shell elasticity, i.e. to evaluate plasticizer effectivity and compatibility (Reich, 1983, 1994).

An ideal plasticizer should interact with the gelatin molecules in such a way as to reduce effectively the glass transition temperature (T_g) of the gelatin shell without inhibiting the formation of crystallites that stabilise the three-dimensional gel network structure. In addition, if present in concentrations higher than saturation, it should be physically embedded in the sol phase of the gel network to avoid bleeding out (Reich, 1994).

Glycerol, the most frequently used soft gelatin capsule plasticizer, combines these advantages of a high plasticizer effectivity, a sufficient compatibility and a low volatility with the ability to interact specifically with the gelatin allowing for the formation of a stable thermoreversible gel network. Its plasticizing capability is mainly resulting from *direct* interactions with the gelatin and only slightly from its hygroscopicity allowing for an additional indirect moisturising effect (Reich, 1994).

Sorbitol, on the other hand, is an *indirect* plasticizer, mainly acting as a moisturising agent with water being the effective plasticizer. Compared to glycerol, its direct plasticizing capability is very much reduced, as indicated by a minor reduction of the gelatin glass transition temperature. Gradual differences of various grades of non-crystallising sorbitol solutions in their plasticizing capability and their compatibility with gelatin are the result of differences in the amount of by-products, namely hydrogenated oligosaccharides and sorbitol anhydrides, i.e. sorbitans (Reich, 1996). Only sorbitol grades with a high amount of sorbitans, such as Anidrisorb, can effectively replace glycerol owing to a certain direct plasticizing effect. On the other hand, hydrogenated oligosaccharides such as maltitol in combination with glycerol are very effective additives for the formulation of chewable soft gelatin capsules, since they augment the taste and chewability and assist in the rapid dissolution of the shell upon

chewing, thus improving the mouthfeel (Berry *et al.*, 1988; Montes and Steele, 1999).

Regarding plasticizing capability, propylene glycol is superior to sorbitol/sorbitan blends and even to glycerol. However, owing to its high solvent power for gelatin, it has a slightly negative effect on the formation of the gel structure that has to be compensated for by adjusting the manufacturing parameters at the encapsulation machine (Reich, 1994). Liquid polyethylene glycols can only be used in combination with glycerol or propylene glycol, since their compatibility with gelatin is limited.

Other additives

In addition to gelatin, the plasticizer(s) and water, optional components in the capsule shell are limited in their use. For economic reasons, the addition of active ingredients in the shell is usually not recommended and limited to inexpensive compounds in chewable capsules. The use of water-insoluble polymers to impart sustained-release characteristics to the capsules has failed owing to their limited compatibility with the gelatin mass (Reich, 1983). Formulations with gastroresistant enteric soluble polymers are under development.

Colouring and opacifying agents are used frequently to give the shells the desired colour and a proper finish, i.e. to allow the shell to protect the fill from light and to mask the unpleasant look of the fill. As a general rule, the colour of the capsule shell is chosen to be darker than the colour of the fill. Before a colour is chosen, mixtures should be checked to ascertain that fading or darkening of the capsule shells does not occur on storage, as a result of reactions between the colouring agent and other components of the shell or fill.

Fill compositions

Soft gelatin capsules can be used to dispense active compounds that are formulated as a liquid or semi-solid solution, suspension or micro-emulsion concentrate. The formulation of the fill is individually developed to fulfil the following requirements:

- to optimise the chemical stability of the active compound
- to improve bioavailability of the active compound
- to allow for an efficient and safe filling process
- to achieve a physically stable capsule product.

Final product stability is related to shell compatibility and will be discussed later.

For a soft gelatin capsule-filling operation, the technologically important factors to bear in mind are temperature, viscosity and surface activity of the fill material and, in the case of suspensions, the particle size of the suspended drug. Liquids or combinations of liquids for encapsulation must possess a viscosity sufficient to be precisely dosed by displacement pumps at a temperature of 35°C or below and may not show stringing to allow for a clean break from the dosing nozzle. The temperature specification is necessary owing to the sealing conditions, which are usually in the range of 37 to 40°C. Owing to certain tolerances of the encapsulation equipment, suspended solids should have a particle size below 200 µm to ensure maximum homogeneity of the suspension. Moreover, the surface-active properties of the fill, whether a solution or a suspension, may not interfere with the formation of the seals.

Interestingly, soft gelatin capsule fill formulations have changed over time from basic lipophilic to hydrophilic solutions or suspensions and recently to more complex self-emulsifying systems. The reason for these developments is that new chemical entities (NCEs) present increasing biopharmaceutical formulation demands.

Basic lipophilic solutions or suspensions have been the traditional and most frequently used soft gelatin capsule fill formulations in the past. They have been applied successfully to formulate oily and lipophilic low melting point drugs such as the vitamins A, D and E, drugs with unpleasant taste and/or odour such as the vitamins of the B group or herbal extracts, drugs with critical stability, i.e. oxygen- and light-sensitive drugs and low-dose or highly potent drugs. The vehicles used for this purpose are lipophilic liquids and semi-solids, and the optional use of surfactants. The lipophilic liquids are refined speciality oils such as soya bean oil, castor oil etc. and/or medium chain triglycerides (MCT). The semi-solids, acting as viscosity

modifier for the liquid oils, are hydrogenated speciality oils or waxes, such as hydrogenated castor oil or bees wax. Surfactants such as lecithin may be present to improve the dispersion of suspended drug particles, thus improving content uniformity. Antioxidants are usually added to stabilise oxygen-sensitive drugs. Moreover, impregnation of solid polymer particles with the drug or drug coating prior to suspension in the oil formulation has been reported as a successful means to improve the content uniformity of low-dose suspended drugs and further increase chemical stability of sensitive drugs. Examples are vitamin B12 (Sanc *et al.*, 2000) and retinol (Rinaldi *et al.*, 1999).

Hydrophilic soft gelatin capsule fill formulations are based on polyethylene glycols (PEGs). Low molecular weight polyethylene glycols are usually used for liquid solutions, with PEG 400 and PEG 600 being the most frequently used. For the formulation of semi-solid solutions and suspensions, the low molecular weight polyethylene glycols (PEG 300–600) are mixed with high molecular weight solid polyethylene glycols, such as PEG 4000–10 000, to increase the viscosity.

PEG-based formulations are often chosen to address bioavailability concerns, i.e. to improve the solubility of poorly soluble drugs, or to dispense low-dose and/or high-potency drugs. Digoxin (Gardella and Kesler, 1977; Ghirardi *et al.*, 1977), nifedipin (Radivojevich *et al.*, 1983), temazepam (Brox, 1983) and ibuprofen (Gullapalli, 2001) are active compounds that have been successfully formulated as PEG solutions in soft gelatin capsules.

Complex self-emulsifying lipophilic systems and microemulsion pre-concentrates are additional approaches that have gained increasing interest as soft gelatin capsule fill formulations to increase the bioavailability and/or reduce the plasma variability of poorly soluble and/or poorly absorbed drugs (Charman *et al.*, 1992; Amemiya *et al.*, 1998, 1999). These systems are typically composed of a lipophilic solvent and surfactant(s), and optional use of co-solvent(s) and/or co-surfactant(s), and may exert solubilising and absorption-enhancing effects. On contact with aqueous gastrointestinal fluids, these formulations spontaneously produce an emulsion with an average droplet size of less than 100 nm, thus improving drug delivery.

Active compounds that have been successfully formulated as a microemulsion preconcentrate in softgels are ciclosporin and the protease inhibitor ritonavir. A patent has also been filed for ibuprofen (Rouffer, 2001). Examples of microemulsion pre-concentrate soft gelatin capsule fill formulations are given in Table 11.2, indicating the use of hydrophilic co-solvents such as ethanol and propylene glycol.

Formulation strategies

Soft gelatin capsule formulation strategies have to consider the specific shell/fill interactions that may occur during manufacture, drying and on storage and control their rate and extent to achieve a stable product.

Two major types of interactions have to be distinguished:

- Chemical reactions of fill components with the gelatin and the plasticizer
- Physical interactions, i.e. migration of fill components in or through the shell and vice versa.

Cross-linking of gelatin leading to solubility problems of the shell is a well-known problem associated with the encapsulation of drugs containing reactive groups such as the aldehyde group. It can be successfully reduced by the use of succinylated gelatin, an approach that is often

used for health and nutrition products, and in some countries even for pharmaceutical products. Esterification and transesterification of drugs with polyols present another unwanted chemical reaction that may occur. Since glycerol is more reactive than other polyols, glycerol-free shell formulations and/or the addition of polyvinyl pyrrolidone to the fill (Gullapalli, 2001) are preferred to reduce this problem.

The rate and extent of physical shell/fill interactions depend strongly on the qualitative and quantitative composition of both, the shell and the fill. As a general rule, the water content of the fill should not exceed a critical value of about 5%.

Fill formulations simply composed of a lipophilic drug in a lipophilic oily vehicle do not interact with the hydrophilic gelatin capsule shell at any time, i.e. either during production or on storage. The proper choice of the shell composition therefore only depends on the stability of the active ingredient, the capsule size, shape and end use and the anticipated storage conditions. For very soft capsules and those stored at ambient conditions, glycerol is the plasticizer of choice. For more rigid soft gelatin capsules and those intended to be used in hot and humid climates, glycerol/sorbitol blends are preferred. The latter is also valid for soft capsules containing oxygen-sensitive compounds in the fill (Hom *et al.*, 1975; Meinzer, 1988). In any case, the P/G ratio is adjusted to the size and intended use of the capsules. To obtain light protection, the shell

Table 11.2 Examples of microemulsion preconcentrate compositions for soft gelatin capsules

Active ingredient	Fill excipients
Ciclosporin	Ethanol Propylene glycol Mono-, di-, triglycerides from corn (maize) oil Polyoxyethylene (40) hydrogenated castor oil DL-alpha-tocopherol
Ritonavir	Ethanol Propylene glycol Polyoxyethylene (35) castor oil Polysorbate 80 Polyoxyethylene/glyceryl mono-, di-, tri-alcanoate (C8–C18) Medium chain triglycerides Citric acid

can be formulated with pigments such as titanium dioxide and/or iron oxides.

Compared to lipophilic solutions, fill compositions with hydrophilic components are more challenging to encapsulate, since they are prone to interact with the shell (Armstrong *et al.*, 1984, 1985, 1986). The most critical period for diffusional exchanges between shell and fill is the manufacturing process, since the moisture content of the initial shells before drying is around 40% and the equilibrium moisture level is only reached after several days. Thus, during manufacture and drying, hydrophilic components of the fill may migrate rapidly into the shell and vice versa, thereby changing the initial composition of both, the shell and the fill (Serajuddin *et al.*, 1986). On storage, these processes may continue until equilibrium is reached. As a result, the capsule shells can become brittle or tacky and the fill formulation may be deteriorated, either shortly after production or on storage. To guarantee the stability of the final product, the initial composition of shell and fill has to be designed in such a way as to minimise exchange processes. Several approaches to demonstrate the proof of this concept will be discussed as follows.

Hydrophilic and/or hygroscopic drug particles suspended in an oily vehicle may attract and retain water from the shell and/or migrate themselves into the shell. This can lead to stability problems such as hydrolysis or oxidation of the active ingredient, to assay failure and/or shell discoloration. To overcome these problems, the following solutions have been proposed:

- Use of high-Bloom, low-viscosity pigskin or acid bone gelatin to reduce the initial water content in the capsule shell and accelerate the drying process;
- Replacement of glycerol by glycerol/sorbitol or sorbitol/sorbitan blends to minimise diffusion of glycerol-soluble active ingredients into the shell;
- Coating of drug particles to inhibit the browning reaction between active ingredients, such as ascorbic acid and gelatin (Oppenheim and Truong, 2002).

Considerable difficulties have been encountered with the design of physically stable and

durable soft capsules containing liquid polyethylene glycols (PEG 300–600) as the fill vehicle. This is owing to the fact that polyethylene glycols have a high affinity for water, glycerol and even gelatin, i.e. they have a high tendency to attract water and glycerol from the shell and may migrate to a certain extent into the shell. As a result of these processes, capsules may become brittle shortly after production or on storage, especially when exposed to cold temperatures (Shah *et al.*, 1992). Several approaches have been reported in the patent literature to provide PEG-containing soft capsules, in which the optimum shell strength and elasticity and the desired constitution of the fill, adjusted after production, remain unchanged on storage (Brox, 1983, 1988).

EP 0 121 321 (Brox, 1983) describes the combined use of glycerol and a sorbitol/sorbitan blend, namely Anidrisorb 85/70, as shell plasticizers. At the same time the addition of minor amounts of glycerol and/or propylene glycol to the liquid PEG fill is proposed. The combination of these two strategies prevents capsule shell embrittlement, since exchange processes between shell and fill are reduced to a minimum. The tendency of PEG to migrate into the shell is significantly reduced owing to the fact that PEG is less soluble in the sorbitol/sorbitan blend than in glycerol. On the other hand, the excess of plasticizer in the fill prevents the glycerol from migrating from the shell into the fill (Shah *et al.*, 1992; Reich, 1996). US 4 744 988 (Brox, 1988), an extended version of EP 0 121 321, recommends the selection of PEG 600 with a higher molecular weight and a lower hygroscopicity compared to PEG 400 as an additional means of reducing shell/fill interactions and improving capsule shell elasticity.

Microemulsion pre-concentrates, comprising hydrophilic co-solvents such as propylene glycol and/or ethanol, in addition to oil(s) and surfactant(s), are another type of fill composition with challenging demands on the soft gelatin formulation concept. The hydrophilic co-solvents are prone to migrate into the shell, with propylene glycol softening the shell and ethanol volatilising through the shell, thereby upsetting the fill formulation in such a way as to change its solubilising and/or emulsifying properties.

The problems associated with *propylene glycol* may be solved by adjusting the shell formulation

in such a way as to reduce the tendency of propylene glycol to migrate, during production and on storage, by using it as a plasticizer component in the shell and adjusting the manufacturing conditions at the drums to reduce tackiness of the ribbons (Brox *et al.*, 1993; Woo, 1997). An additional benefit of this approach is, that the amount of water required for dissolving and melting the gelatin may be reduced owing to the lower viscosity of propylene glycol compared to glycerol and sorbitol solutions, thus reducing the overall water exchange between shell and fill.

The problems associated with the use of a volatile solvent such as *ethanol* are more difficult to solve. To prevent volatilisation of ethanol, the finished capsules have to be enclosed in a solvent-tight packaging material such as an aluminium blister. Moreover, replacement of glycerol by higher polyols such as xylitol, sorbitol, sorbitol/sorbitan blends and/or hydrogenated starch hydrolysates has been reported as an effective means of reducing the rate and extent of ethanol diffusion into the shell (Reich, 1996; Moreton and Armstrong, 1998). In certain cases, however, both approaches may not be sufficient to prevent fill deterioration, since ethanol diffusion cannot be fully prevented. Thus, for a microemulsion pre-concentrate formulation that is very sensitive to the co-solvent concentration, the only way to overcome the problem at present, is the use of a co-solvent other than ethanol, that is not volatile and does not show any diffusion into the capsule shell. For ciclosporin microemulsion pre-concentrate soft capsules, such approaches have been filed in two patents, namely a European Patent Application (Woo, 1995) describing the use of dimethylisosorbide and a US Patent Application (Shin *et al.*, 2000) that describes the use of a microemulsion pre-concentrate containing a lipophilic instead of a hydrophilic co-solvent.

Post-treatments and coatings

Soft gelatin capsules may be post-treated after production or coated to improve product stability, to modify the dissolution rate and to enable enteric capsules to be produced. Several patents have been filed describing the use of protective coatings to overcome the stability problems of soft

capsules arising from the hygroscopic nature and heat sensitivity of the soft capsule shell. However, most of these attempts have failed in practice, since coating of soft capsules is not an easy task. The low surface roughness of soft capsule shells and the intrinsic insolubility of the shell components in organic solvents means that coatings applied as an organic solution usually do not adhere properly to the capsules, resulting in onion-like coatings of layers peeling off immediately after drying or on storage. Aqueous coatings, on the other hand, may result in capsule swelling, softening and/or sticking together, since water is acting as a plasticizer for the gelatin capsule shells. To balance the two extremes, emulsion-based formulations or solutions in a mixture of water and alcohol have been recommended (Osterwald *et al.*, 1982). The technological approach of choice for soft capsules to be coated is using the fluidised-bed air-suspension technique.

Capsules with modified dissolution characteristics, such as gastroresistant enteric soft gelatin capsules, have been described in the scientific and patent literature and can be achieved by adding gastroresistant, enteric-soluble polymers to the gelatin mass prior to capsule formation, or by aldehyde post-treatment or enteric coating of the dried capsules. All three attempts have their specific difficulties. For soft gelatin capsules produced by the rotary die process, the last two approaches are in practical use.

Aldehyde post-treatment of soft gelatin capsules has been known for many years as a popular means to reduce their dissolution rate, i.e. the capsules take a long time to dissolve and have left the stomach before this occurs. Formaldehyde has been described to cross-link effectively soft capsules to render them gastroresistant. Since safety questions have been raised about the presence of trace amounts of formaldehyde in foods and pharmaceuticals, the use of aldehydes without health concerns such as aldoses have been claimed in a patent (Fischer, 1986) and are actually used. The major disadvantage of any aldehyde treatment of soft gelatin capsules is that cross-linking can continue on storage. Alternatively, soft gelatin capsules may be coated with a gastroresistant, enteric-soluble polymer. Owing to the aforementioned difficulties associated with organic and aqueous soft capsule coating, a

protective subcoat is usually applied as an alcoholic solution prior to the application of the gastroresistant, enteric polymer layer (Virgilio and Matthews, 1989).

Non-gelatin soft capsules

Traditionally, gelatin has been used almost exclusively as shell-forming material of soft capsules. This is due to its legal status and its unique physicochemical properties, namely its oxygen impermeability and the combination of film-forming capability and thermoreversible sol/gel formation, that favour its use for the industrial soft capsule production especially in the rotary die process.

Despite these great advantages, which have been described in detail in the section above on 'Soft gelatin capsules', gelatin has several drawbacks that limit its use for soft capsules:

- The animal source of gelatin can be a problem for certain consumers such as vegetarians or vegans and religious or ethnic groups (Jews, Muslims, Hindus, etc.) who observe dietary laws that forbid the use of certain animal products.
- Since unmodified gelatin is prone to cross-linking when in contact with aldehydes, solubility problems might be expected with certain fill formulations.
- Transparent low-colour capsules are difficult to produce owing to the effect of the intrinsic Maillard reaction on gelatin colour.
- The temperature and moisture sensitivity of gelatin-based soft capsules is an issue that complicates the use of soft gelatin capsules in very hot and humid regions and requires special packaging and storage conditions to ensure product stability.
- For low-price health and nutrition products, pricing of commercially available gelatin might be an additional problem.

To address these concerns, there has been a great interest in the soft capsule industry in looking for gelatin substitutes. Indeed, several concepts based on synthetic polymers and/or plant-derived hydrocolloids have been described

in the patent literature. However, only few have gained commercial interest. This is due to the fact that a change in the capsule shell polymer material requires more than just overcoming the aforementioned shortcomings of gelatin. It requires both legal approval and machinability, i.e. either to mimic most of the physicochemical gelatin characteristics that are important for rotary die soft capsule production with some adjustments of the production equipment for the new material characteristics or to use a completely redesigned machinery.

To date, three non-gelatin soft capsule concepts with different process adjustments have reached prototype status: two are based on plant-derived hydrocolloids (Draper *et al.*, 1999; Menard *et al.*, 1999), the third is based on a synthetic polymer (Brown, 1996).

WO 0 103 677 (Draper *et al.*, 1999) describes the use of a combination of iota carrageenan (12–24% w/w of dry shell) and modified starch, namely hydroxypropyl starch (30–60% w/w of dry shell), as a gelatin substitute. Both components are accepted as food additives with E numbers, thus allowing their use in health and nutrition products. Hydroxypropyl starch is also approved as a pharmaceutical excipient. The combination of the two hydrocolloids leads to a synergistic interaction that produces a gel network, which is suitable for soft capsule production using the rotary die process. It can be formulated with conventional plasticizers such as glycerol, sorbitol, etc. (10–60% w/w of dry shell) and water to form a molten mass that can be extruded to set within less than 20 s producing mechanically strong, elastic films on temperature-controlled casting drums. Sealing may be performed at temperatures between 25 and 80°C, by a fusion process comparable to the one observed with soft gelatin capsules. After drying, mechanically strong and highly elastic products can be achieved.

Prototype capsules with lipophilic fill formulations are shiny with a high appearance stability on storage. The capsule shells do not show cross-linking and exhibit a greater mechanical stability than soft gelatin shells when exposed to elevated humidity and temperature, i.e. even under hot and humid storage conditions they may not become sticky. Formulation approaches with

hydrophilic fills are expected to be as challenging as for soft gelatin capsules. Oxygen permeability is comparable to gelatin-based shells. The dissolution mechanism is completely different to the one of a soft gelatin capsule. On contact with an enzyme-free aqueous medium at 37°C, the capsule shell only swells, at a rate and to an extent depending on the type and concentration of electrolytes present. The capsule content may be released when the shell bursts at its point of lowest resistance, i.e. at the seams. Under *in vivo* conditions, capsule shell dissolution may be induced by enzymatic degradation.

WO 0 137 817 (Menard *et al.*, 1999) describes the formation of soft capsules from a potato starch (45–80% w/w), with a specific molecular weight distribution and amylopectin content, together with a conventional plasticizer such as glycerol (>12% w/w), a glidant and a disintegrant. Soft capsule production may be performed with a rotary die machine with nearly water-free formulations that are processed by hot melt extrusion. A narrow production window and the use of a high molecular weight amorphous starch with a high amylopectin content (>50% w/w) are necessary for the formation of acceptable capsules.

From the regulatory point of view, starch-based soft capsules are a low-price alternative to soft gelatin capsules, appropriate for pharmaceutical and health and nutrition products. Moisture sensitivity and fill compatibility of the capsule shells are comparable to soft gelatin capsules, with the exception that cross-linking is not a problem. Oxygen permeability is expected to be a little higher compared to soft gelatin capsules (Reich, unpublished results). Shell dissolution requires enzymatic degradation by amylases; on contact with amylase-free aqueous media at 37°C, the capsules release their content only by swelling-induced disintegration. The addition of calcium carbonate is one option to enhance capsule disintegration further.

The visual appearance, the seam quality, and the long-term stability of the finished product of the prototype starch capsules cannot compete with soft gelatin capsules. This is due to the structural rearrangements within the capsule shells associated with the tendency of starch to retrograde on storage, in some instances leading to a

subsequent plasticizer syneresis (Reich, unpublished results).

WO 9 755 37 (Brown, 1996) describes the preferable use of polyvinyl alcohol (PVA) and optional use of some other materials, all being film-forming polymers that lack the gelling properties that are necessary for soft capsule production using the conventional rotary die process. The invention therefore provides the use of preformed rolls of nearly water-free plasticized films that may be fed to a rotary die encapsulation unit for soft capsule production. To render the film material more flexible and to assist seam formation at temperatures depending on the film composition, the films are partially spray-solvated prior to encapsulation.

PVA films according to this invention may be composed of 70–75% w/w PVA, 10–15% w/w glycerol and 5–10% w/w starch, with a sealing temperature of 140–180°C, depending on the degree of solvation. PVA as an optional gelatin substitute has the advantage of being less hygroscopic, thus leading to soft capsule shells that are less sensitive to moisture than soft gelatin capsule shells. Moreover, the capsules are readily water soluble with no cross-linking tendency. However, prototype capsules lack the shiny and smooth surface appearance and the seam quality of conventional soft gelatin capsules. In addition, the regulatory issues and the formulation of hydrophilic fills are problems that have to be solved.

To summarise, it may be concluded that none of the gelatin-free soft capsule concepts is fully developed yet. Nevertheless, soft capsules based on plant-derived or synthetic polymers are an interesting line extension to soft gelatin capsules with the potential to gain a market share for certain niche products.

Analytical approaches for soft capsule testing

Finished soft capsule products, either gelatin- or non-gelatin-based, are routinely specified by strength values, drug content, dissolution properties and in some cases by their water content. Moreover, they are checked for long-term stability under ICH (International Conference on

Harmonisation) conditions. The official tests for soft capsules are discussed in Chapter 13.

Drug content is determined by either HPLC (high performance liquid chromatography) or any other appropriate QC (quality control) method. Dissolution properties are checked according to the pharmacopoeial requirements, with a two-tier test being approved for products with reduced solubility. Water content may be assessed by Karl Fischer titration.

Strength measurements ('hardness' measurements) are performed using a commercially available tester (Barreiss Hardness Tester) in which the capsules are compressed to a certain extent between a measuring detector and a slowly moving plate. The counter force exerted by the capsules is displayed in newtons. Under these test conditions, an optimum strength range is specified by the manufacturer for each product. Strength values above or below this specified range are indicative of insufficient flexibility or softening, respectively.

Recently, the use of conventional or modulated DSC has been proposed as an additional analytical tool to determine performance-related microstructural features of soft capsule shells, such as the glass transition temperature (T_g), the melting temperature (T_m) and the melting enthalpy (H_m) (Reich, 1994, 1995, 1996; Nazzari and Wang, 2001). T_g , T_m and H_m are important parameters for monitoring process- and storage-induced structural changes within a capsule shell and have been successfully applied to the design and optimisation of soft capsules, i.e. to evaluate plasticizer effectivity and compatibility, and shell/ fill interactions.

Near infrared (NIR) spectroscopy is another modern analytical technique with great potential for soft capsule specification and efficient stability testing (Reich, 2000). NIR is a fast and non-invasive spectroscopic method that allows for simultaneous evaluation of soft capsule identity, drug and water content (Buice *et al.*, 1995) and in some cases film coat thickness of the finished product directly after production. In addition, storage-induced chemical and physical changes in both the shell and the fill can be assessed, thus allowing for an early and non-destructive detection of stability problems such as moisture changes and shell/fill interactions leading to

cross-linking, softening or hardening of the capsule shell (Gold *et al.*, 1997; Reich, 2000).

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