

Shell Formulation in Soft Gelatin Capsules: Design and Characterization

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Soft gelatin capsules (SGCs) are the most widely used pharmaceutical form after tablets. The active components, active pharmaceutical ingredients (APIs), or nutrients are dissolved, dispersed, or suspended in a liquid or semisolid fill, which is covered with a gelatin shell. Several factors can modify the properties of the gelatin shell and subsequently affect their operative handling during manufacturing process and the stability of the soft gelatin capsules. Three elements appear to be crucial: the shell formulation (type and content of the different components such as gelatins—source, extraction method—plasticizers, or additives); the manufacture and storage conditions (temperature, humidity, light) as well as the interactions between fill-shell formulas. Mechanical and thermal analysis arise as straightforward but highly useful tools to monitor the properties of the gelatin shell. This review provides an updated overview on the shell formulation and design. Additionally, it presents the uses of mechanical and thermal techniques to characterize and evaluate the impact of different parameters on the gelatin behavior over the production and stability of these pharmaceutical forms. This will help to detect changes that are yet not visible by visual inspection ensuring a suitable finished product over its shelf-life.

1. Introduction

Soft capsules are solid dosage forms comprising one or more active components, APIs, or nutrients, that can be formulated alone or with other excipients or additives in a liquid or semisolid film inside of a flexible or elastic shell (Figure 1A). Based on the polymer used to form the cover shell, softgels are classified as gelatin capsules—SGCs or “softgels”—or non-gelatin capsules, the latter based on plant-derived and/or synthetic non-gelatin alternatives.^[1]

SGCs are the second most widely used pharmaceutical form after tablets, as they offer several advantages over other solid forms.^[1–3] Depending on the route of administration chosen (oral, dermal, rectal, vaginal, or optical), they are available in a wide variety of sizes, shapes, and colors providing many attractive finished products for the consumers (Figure 1B). For human oral administration, the maximum size of

softgels shall be 20 mm oblong, 16 mm oval, and 9 mm round. In addition, due to its physical structure, they cannot be altered helping to the correct use of these medicaments and improving the patients' adherence to the treatment. Regarding oral administration, SGCs present good patients' compliance as they are easy to swallow and can mask the taste and odor of unpleasant ingredients (i.e., vitamins B, herbal extracts, etc.). Furthermore, the formulation as liquid or semi-solid fills improves the dosage unit homogeneity compared to other solid dosage forms; it also favors the absorption of poorly soluble drugs, the drug bioavailability,^[4] and the delivery of very low doses of drugs; and it decreases the plasma variability, thus faster therapeutic effects than the standard tables or hard gelatin capsules are observed and hence may be possible to reduce the dose administered.^[5] Moreover, depending on the raw materials used in the fill and/or shell formulations, softgels may be converted to delayed or controlled release systems.^[6] On the other hand, SGCs are considered one of the most stable dosage forms since the gelatin outer shell acts as a barrier exposed to external factors such as temperature or humidity, protecting the active components included in the inner fills; thus, they are especially useful for components with low melting point (i.e., vitamins A, D, and E), easily oxidized, or which undergo hydrolytic or light degradation. Finally, SGCs are considered safer dosage forms than tablets or hard capsules from the

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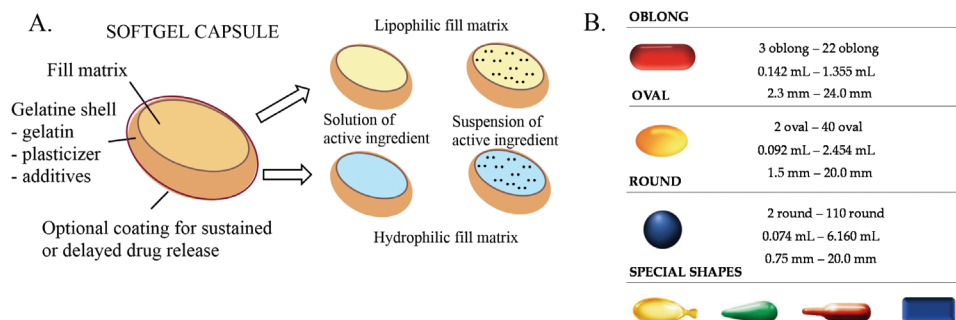


Figure 1. A) Components of softgel capsules. B) Examples of softgel shapes and sizes.

manufacture point of view, since the use of liquid or semisolid fills significantly reduces the quantity of air-borne powders, decreasing the operator exposure and environmental contamination to highly potent or cytotoxic solid compounds.

Despite the large number of above-mentioned advantages, there are many challenges to be improved in relation to the development and production of SGCs. For example, SGCs show a high production cost compared to tablets or liquids forms; there could be dietary restrictions due to the gelatin origin; and the formulation of active components as liquid fill may reduce their stability compared to the solid state. On the other hand, SGCs are very dynamic systems since (1) the gelatin is extremely water-soluble, thus SGCs show a high sensitivity to the climatic conditions, may appear sticking, fragility, and microbiological issues, and therefore reduce the shelf-life of these finished products and/or demand a special storage conditions; (2) there could be the physical migration of components between the two parts of SGCs (fill and shell) and the external environment promoting compliance and manufacturing issues; and (3) the direct contact between fill and shell parts may cause physical and chemical interactions within and between their components during manufacturing or shelf-life of the product favored by high humidity, temperature, or ultraviolet (UV) conditions,^[7] promoting stability issues such as cross-linking. Consequently, both elements of SGCs (fill and shell) affect its production and its physicochemical properties along stability, especially at long-term and extreme conditions of temperature and humidity. It is necessary to understand these properties and interactions to design and develop stable SGCs products with adequate characteristics. The focus has usually been at the fill formulation. However, the physicochemical properties of gelatin shell are critical, considering its direct effect on the product appearance, its exposure to external factors and release profile of active compounds. For instance, the uncontrolled cross-linking of the gelatin or the migration or chemical interaction of components between shell and fill affect the integrity and stability of the softgel, which is reflected, among other things, in the disintegration time and swelling behavior of the capsule. When formulating a shell material for a commercial product, knowing its future behavior becomes essential. Mechanical and thermal analysis are among the most informative tools to provide a fast and complete insight into the short- and long-term behavior of pharmaceutical products. Characterization techniques such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), dynamic mechan-

ical analysis (DMA), tensile testing, and rheology offer useful information about gelatin internal structure and the impact of multiple parameters in SGCs manufacture and storage.

This review presents a didactic overview on the information that can be obtained about the structure of the gelatin shell by its mechanical and thermal characterization. We aim to offer the reader clear indications to understand the gelatin behavior along its shelf-life and improve shell formulation during the design of a new softgel product.

2. Shell Formulations in Softgels

The shell formulation in SGCs is mainly made of gelatin, water, and non-volatile plasticizer(s). Additional ingredients as opacifiers, colorants, flavors, sweeteners, and preservatives can be included to change the gelatin shell qualities. During its development, it is necessary to look for a formula with adequate compatibility with the fill material. Additionally, the shell mass must (1) have the ability to flow at relative low temperatures (approx. 60 °C) to reach the encapsulation machine; (2) set at a fast rate into ribbons with mechanical properties sufficient to tolerate the encapsulation step; (3) maintain adequate elasticity properties after the drying process and over stability term; and (4) show appropriate swelling and dissolution behaviors over shelf-life of SGCs for human consumption.

2.1. Gelatin

In a standard softgel product, gelatin typically represents 40–45% of the shell formula.^[5] Gelatin is a natural biopolymer which consists in 84–90% of water-soluble proteins, 1–2% of mineral salts, and 8–15% of water. It is obtained by the thermal denaturation (more specifically, by partial hydrolysis) of collagen from animal skin, bones, and connective tissues, usually from pigs, cows, or fish. The gelatin production from collagen consists of seven steps: cleaning, pretreatment, extraction of gelatin, filtration, concentration or evaporation, sterilization, and drying. The second stage may be performed by different extraction method:^[8] hydrolysis without enzyme using a dilute acid (type-A gelatin) or alkali (type-B gelatin) or hydrolysis by enzymatic process (type-E gelatin). Acidic extraction is the most widely used and consists of treating the gelatin with a mild or a harsh acid, such as acetic,

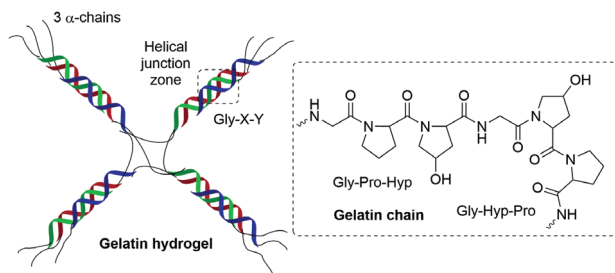


Figure 2. Typical gelatin structure and gelification process.

formic, and citric; and after this treatment, the pH is neutralized with an alkali. On the other hand, alkaline methods consist of treating the gelatin with strong alkalis, changing the pH of the precipitation, and affecting the gelatin isoelectric point; and after this treatment, the pH is neutralized with an acid. In an enzymatic extraction, enzymes such as pepsin are used to obtain the gelatin. Most of the gelatins are classified as GRAS (Generally Recognized As Safe) food ingredients and they are approved for pharmaceutical applications by the United State Pharmacopeia (USP) and European Pharmacopeia (Ph. Eur.) among others.

Gelatin is a protein soluble in water, glycerin, or propylene glycol (PG), and insoluble in alcohols and other non-polar solvents such as acetone and chloroform. In water, gelatin forms a triple helix structure which is made of three α -chains, each one with an approximate molecular size of 100 kDa and 1000 amino acids, mainly glycine (Gly), proline (Pro), and 4-hydroxyproline (Hyp)^[9] (**Figure 2**). Both amino acids are responsible for the stability of the gelatin by forming hydrogen bonds in its structure, thus these sequences determinate the strength of the seal of the softgel and functionality of the SGCs shell. On the other hand, thanks to the formation of this triple helix structure, gelatin may also form thermoreversible gels with a melting temperature (T_m) near to the body temperature. In water solution and temperatures below $\approx 35^\circ\text{C}$, gelatin chains associate and form triple helix structures, but they form spiral conformations at higher temperatures. The melting and gelling temperatures (T_{gel}) of gelatin gel depend on the amino acids sequence of the gelatin protein, and therefore the gelatin source.^[10] For example, lower T_m and T_{gel} values are observed for gelatins with lower Pro and Hyp content. In addition, several factors promote the gelification process (helix formation), such as the length of the chain (between 40 to 80 amino acids), the use of type-B gelatin, working at pH values closer to the isoelectric point (pI) of gelatin and the use of non-ionic solvents.

However, the uncontrolled cross-linking, which occasionally happens after exposure to high or low humidity, high temperature, UV light, metal salts, oxidizing agents, or chemical entities such as aldehydes, peroxides, epoxides, or ketones, may promote structural changes.^[2] The formation of cross-links between the amino and guanidino functionalities results in the formation of three-dimensional molecular networks of a higher molecular weight (MW) with the loss of ionizable groups (i.e., R-NH_2 and R-COOH) compared to the original molecules, reducing the solubility of the gelatin component, and forming a pellicle that affects the swelling, dissolution, and disintegration properties of

the softgel and thus the actives release. Accordingly, the selection of gelatin raw material is crucial.

To minimize this uncontrolled cross-linking problem, some strategies can be followed, as using excipients without aldehyde groups, including inhibitors of cross-linking, or using “anti-cross-linking gelatins” which are chemically modified to mask the number of available amino groups.^[2] Cross-linking can be inhibited or reduced by using different chemical compounds as amino acids (lysine, Gly), carboxylic acids (citric acid), pyridine or piperazine, among others. GELITA® RXL, RXL ADVANCED, and GELITA® RXL R² are some examples of commercial anti-cross-linking gelatins. In addition, succinic acid is often used as masking agent, as it reacts with accessible amino groups of the gelatin with one of its carboxyl groups and produces steric prevention of access of the cross-linking agent with its other carboxyl group, but these gelatins show high permeation and are still susceptible to metal salts cross-linking. However, adding these products to gelatin increases substantially its production cost.

Although strong cross-linking is usually undesired, this phenomenon can also be used for obtaining SGCs with sustained release or for reducing water vapour permeability (WVP) of gelatin film.^[11] For example, gelatin is treated with formalin, aldehyde-induced cross-linking is favored, and its solubility is reduced. GELITA® EC was the first commercially available gelatin product with enteric release; thus, capsules open in the intestine instead of the stomach, as traditional gelatin capsules do. Above-mentioned chemical modifications affect not only the properties of the finished softgel products, but also their manufacturing. In that sense, the following physicochemical aspects of gelatin raw material are considered relevant for its gelling behavior.

2.1.1. Gel, Jelly, or Bloom Strength

It is the most important physicochemical parameter of gelatin raw material. It is a measure of the gelatin stiffness and strength and reflects the average MW of their constituents. The bloom strength depends on many factors such as the source (animal, breed, age, or sex) and the extraction methods (**Table 1**). Short extractions produce high bloom gelatins while longer extractions produce low bloom gelatins with strong odor. Gelatin bloom strength appears in the range 30–300, distinguishing three “bloom” groups: low (<150), medium (150–220), and high (>220). The preferred bloom for SGCs manufacturing process is the medium range.

2.1.2. Viscosity

It is related to bloom strength, as high bloom strength gelatins show a higher proportion of cross-linked component of β and α chain and thus, high melting temperatures and higher viscosity. As bloom strength, it depends on gelatin source and extraction. For example, mammalian gelatins show higher viscosity values than marine gelatins, with values of 3.90 cP for bovine skin, 6.37–7.28 cP for pig skin and 1.87–3.63 cP for different fish gelatins.^[13] Optimal viscosity values must be in the range of 2.8–4.5 mPa s at 60°C for softgel manufacture process.

Table 1. Examples of pharmacopeial gelatin's bloom strength and viscosity.^[12]

Gelatin	Source	Bloom [g]	Viscosity at 60 °C [mPa s]
160 LB	Bovine/porcine bone	155–185	3.4–4.2
160 LH	Bovine hide	150–170	3.5–4.2
160 LB/LH	Blend of bovine/porcine bone and bovine hide	150–170	3.5–4.2
200 AB	Bovine bone	180–210	2.7–3.2
200 PS	Pig skin	190–210	2.5–3.1
160 PS/LB/LH	Blend of pig skin, bovine/porcine bone and bovine hide	145–175	2.7–3.3

AB: acid bone; LB: limed bone; LH: limed hide; PS: pig skin.

2.1.3. Molecular Weight Distribution (MWD)

In linear polymers such as gelatin, the individual polymer chains rarely have the same polymerization degree and MW, thus there is a distribution around an average value. The MWD of gelatin materials could appear between 10 and 400 kDa, although the most common distribution is in about 100, 200, and 300 kDa to α , β , and γ peptide chains, respectively. Depending on the extraction technique used, gelatins with different MWD are obtained. For example, type-A and type-B gelatin with the same bloom have different MWD, as alkali and acid pretreatment produce different collagen fragments. On the other hand, type-B gelatins show a wider relative MW while the type-E gelatins have a narrow distribution. Usually, gelatins with different extraction methods are blended to obtain a specific gelatin for a specific application. This increases the heterogeneity of the material.

2.1.4. Conductivity, pH, and pI

Gelatin is a material with low conductivity, usually lower than 1 mS cm⁻¹. The pH of gelatins is slightly acidic, usually between 4–7 (Table 2), although there are differences depending on the source. For example, the pH of gelatin from bovine skin is 4.8–5.5 and from porcine skin is 7.0–9.4.^[13] The pI of gelatin depends on the hydrolysis method used for its extraction. Type-A gelatins show a pI of around 9. However, gelatins treated with strong acid suffer some de-amination, reducing its pI. Type-B gelatins show lower pI as the alkaline pretreatment causes the deamidation of asparagine and glutamine, increasing the number of aspartic and glutamic acids. The increase in the negative net charge produces a shift in the pI. The typical pI of type-A and type-B gelatins are 7.0–9.0 and 4.6–5.2, respectively.

Table 2. Examples of commercial gelatin's pH and conductivity.

Gelatin	Source	Extraction method	Bloom [g]	pH	Conductivity [mS cm ⁻¹]
Rousselot 160 LB 8	Bovine limed bone	Alkaline	145–175	5.3–6.2	<1
Rousselot 200 AH 8	Bovine hide	Acid	175–205	5.0–6.2	<1
Rousselot 200 BH	Bovine hide	Alkaline	175–205	5.6–6.2	<1
Rousselot 200 H 6	Bovine hide	Acid	175–205	5.0–6.0	<1
Rousselot 250 PS 8	Pig skin	Acid	240–250	4.5–6.9	<0.4
Gelita 170 LB Type B NF SRM Free Bone	Bovine limed bone	Alkaline	155–185	5.3–6.0	<1

AB: acid bone; AH: acid hide; BH: bovine hide; H: hide; LB: limed bone; LH: limed hide; PS: pig skin.

2.1.5. Color

Gelatin color depends on the raw materials and extraction method. For instance, bovine and sin croaker gelatins show a whiter color, while shortfin scad gelatin shows a more yellowish appearance.^[14] Regarding the extraction method, gelatin lightness decreases, and yellowness increases when extraction temperature increases.^[15] In general, it does not affect the functional properties, but can affect the product aspect.

2.1.6. Foaming Properties

It indicates the surface activity of gelatin, which is directly related to its physicochemical and functional properties. Foaming properties are studied through parameters such as the foam expansion (FE) and the foam stability (FS) which depend on temperature extraction, among other parameters, decreasing at high temperatures.^[15] The differences in the ability to foam are caused by differences in the amount of hydrophobic amino acids in gelatin structure. A positive relationship between hydrophobic groups and surface activity was observed.^[16]

2.2. Plasticizer

Gelatin alone does not form films suitable for the manufacturing of softgels. Thus, plasticizers are added to modify properties such as flexibility, elasticity, or rigidity, and therefore, to improve the handling of the gelatin film during the manufacturing process and the stability of the final softgel product over its shelf-life. The plasticizer amount depends on the gelatin material type, capsule size, and filling type; but the use of high concentrations of subsequently mentioned ranges may promote its physical exclusion from the gelatin polymer structure.

Water is always used as plasticizer component in the shell formula (30–40% w/w in the wet shell formula to be necessary for the formation of the gelatin structure and for obtaining a gelatin mass with a suitable viscosity for its dosing) but, due to its volatile properties (4–10% w/w in final product^[2,3]), non-volatile plasticizers are also added in 15–30% w/w of shell formula and in 0.3–1.0% w/w of dry plasticizer to dry gelatin. The presence of non-volatile plasticizer is especially important during the drying step since a high-water content is migrated to the external environment modifying and stressing the gelatin shell formed.

Glycerin (85% and 98% w/w) is considered the reference plasticizer regardless of the gelatin type used since, due to its low MW and high hygroscopicity, having high plasticizer effectivity, high compatibility, and low volatility, forming stable thermoreversible gel networks. However, it is usually employed for oil-based fill formulations. Its plasticizer capacity is mainly due to direct interactions with the gelatin and slightly due to its hygroscopicity that provides an additional indirect moisturizing effect. Gelatin films made with glycerin as the plasticizer show lower moisture resistance and are more permeable to oxygen.^[1,3]

Sorbitol is mainly used for polyethyleneglycol (PEG)-based fill formulations as the migration of PEG to the shell is reduced due to its insolubility in sorbitol. It is also preferred for fill formulation with volatile components to reduce its diffusion for gelatin film. It is an indirect plasticizer, as it does not interact with gelatin but act as a moisturizing agent. Its plasticizer capacity is lower than glycerin; and may also crystallize in low-to-medium humidity conditions. Different grades of non-crystallizing sorbitol have different gelatin compatibility and plasticizer capacity. These differences are based on the number of hydrogenated oligosaccharides and sorbitol anhydrides (i.e., sorbitans). Sorbitol grades with high amounts of sorbitans, such as Sorbitol Special (SPI Pharma) and Anidrisorb or Polysorb (Roquette), show a higher plasticizer capacity, comparable to glycerins. On the other hand, the combination of sorbitols with high number of hydrogenated oligosaccharides as maltitol with glycerin increase the chewability and dissolution rate of softgels, making it a good choice for chewable products.^[1,3]

PG, low MW polyethylene(glycol)s (PEGs), xylitol, maltitol and mannitol may also be used. PG shows a higher plasticizing capacity than glycerin and sorbitol, but it can have a negative effect as it makes difficult the formation of the film. In fact, shells with PG are tackier, being necessary to use low encapsulation temperatures to form an optimal ribbon. It can also negatively affect the film formation and mechanical properties of the gelatin ribbons over stability time due to its high volatility.^[1,3] Regarding PEGs, low MW PEGs (200, 300, or 400 kDa) have a higher plasticizer capacity as they have a higher ratio of hydroxyl groups forming hydrogen bonds with gelatin chains and a higher hygroscopic grade. However, they can migrate to the exterior of the film over time leading to a phase separation (blooming or blushing phenomenon) and turning the transparent gelatin films opaque. High opacity is observed with high MW PEGs.^[17] To avoid these incompatibilities, they should be combined with glycerin or PG.^[2]

Oleic acid, triethyl citrate, acetyl triethyl citrate, tributyl citrate, and acetyl tributyl citrate may be used as plasticizers. Its use provides flexibility to gelatin films, although its plasticizing capacity and compatibility with gelatin material is worse

than the hydrophilic plasticizers, promoting the phase separation phenomenon during the drying process, which may be reduced adding an emulsifier such as lecithin. In addition, the use of hydrophobic plasticizers generally produces opaque gelatin films whose opacity is directly proportional to the plasticizer concentration.

2.3. Additional Components

Different additives may be included in the shell formulation to modify the properties of the gelatin cover. The most common additives are colorants and opacifiers, but also other components are usually included.

2.3.1. Colorant

Certified colorants are either dyes or lakes. Dyes are water-soluble compounds while lakes are a combination of insoluble compounds (hydrous metal oxides) and dyes, offering a higher stability and oil-dispersity. Regarding its origin, colorants can be classified as natural or synthetic. Natural colorants, such as curcumin, riboflavin, annatto, vegetable carbon, or carotenes, are gaining popularity, as they are associated with being ecologically sustainable. On the contrary, synthetic colorants are facing an uncertain regulatory future as recently some of them have been banned in certain countries due to their toxic effects on humans. Examples of approved synthetic colorants are brilliant blue FCF, tartrazine, or indigotine.

Colorant is added to the shell formula (0.5–1.0% w/w) to modify the appearance of the gelatin film, which usually shows transparent and a light amber to light-yellowish color, depending on the gelatin type. The use of colorants may help to obtain homogeneous and stable gelatin shell from the point of view of color property. Thus, the selection of the colorant is critical too, as its coloring and solubility capacities define the colorant amount to be added, the color depth of the gelatin film and the grade of light diffraction. For example, opaque coloring agents such as iron oxides are usually selected for gelatin covers of unaesthetic fills and/or fills with light sensible actives. Nevertheless, colorants can also fade with time, especially natural compounds, varying the product appearance; thus, the synthetic colorants are usually chosen. Moreover, the colorants may react with the rest of shell components. Thus, the selection of non-reactive components (physical or chemical) is preferred.

2.3.2. Opacifier

It is included in the shell formula when light sensitive compounds are included in the filler, as gelatin is transparent to visible light (400–800 nm),^[18] and when the fill formulation has unaesthetic appearance, such as disperse systems that tend to phase-separate or decant. The most common opacifier, also used as a white colorant, is titanium dioxide (TiO₂, E171), inorganic compound of mineral origin that acts as an excellent light-scattering agent due to its high refractive index (2.55–2.76).^[19] Its opacifying capacity depends on (1) its particle size, where higher

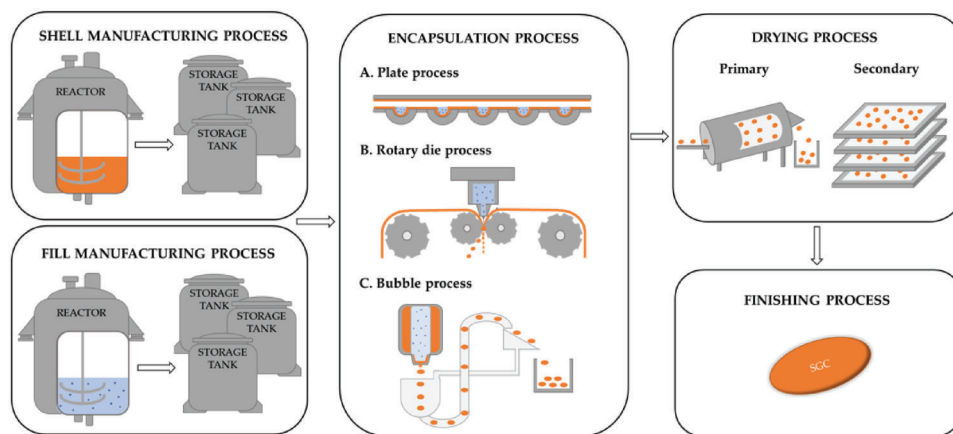


Figure 3. Manufacturing process of softgels.

effectivity in the visible range is obtained at particles >50 nm; (2) its adequate dispersion and wetting before its addition to the molten gel mass, obtaining a better effect when individual crystals or small aggregates formed by maximum two or three crystals are generated; (3) the thickness of gelatin cover, since the higher thickness, the higher opacity; and (4) the TiO_2 concentration used observing positive correlation; but this rise is stabilized in quantities more than 1%. It is usually added at 0.5–1.0% (w/w) of the total shell formulation.^[2] TiO_2 is considered an inert compound, as it is non-hygroscopic and non-reactive with gelatin and other softgel ingredients.^[20] However, it is being substituted based on the European Food Safety Authority (EFSA) indication (TiO_2 can no longer be considered as safe when used as a food additive due to many uncertainties in the toxicity studies). Starch from rice or corn may be used; however, high amounts are required to achieve opacity promoting water retention, and therefore, slow drying process, and high risk of microbiological contamination. Calcium carbonate also shows adequate whitening properties but affects the consistency and texture of final product promoting fragile gelatin films. Thus, it is usually combined with polymers such as hypromellose. Avalanche products have become the preferred alternative, wherein Avalanche is combined with starch or minerals such as calcium carbonate or zinc, to provide different opacification grade.

2.3.3. Flavor/Sweetener

They are included in the shell formula, especially for chewable softgel products, to increase palatability as they can help masking the taste and odors of drugs.^[21] Common flavors are ethyl vanillin, essential oils, and sucrose. Flavors with aldehyde groups must be avoided to decrease the risk of undesired cross-linking.

2.3.4. Preservative

They help keeping the gelatin mass and the product viable and safe for predetermined long-term storage. Common preservatives are sorbic acid, sodium benzoate, potassium sorbate, β -naphthol and methyl, ethyl, and propyl parabens in a concentration of 0.01–0.5%. Parabens are commonly used at 0.2% as they

show a high antibacterial activity and pH adaptability, usually in a combination of methyl paraben and propyl paraben 4:1.

2.3.5. Other Components

Other components can be added for special purposes, such as acid-resistant polymers to obtain softgels with enteric behavior or fumaric acid as anti-cross-linking agents to avoid dissolution problems.

3. Manufacture of Softgels

SGC was developed in the 19th century. In 1833 two French pharmacists, Dublanc and Mothes, presented the first patent application for a capsule.^[22] Nowadays, the traditional method for the manufacturing of this solid dosage form consists of five steps, **Figure 3** shell manufacturing, fill manufacturing, encapsulation process, drying, and finishing.^[2]

3.1. Shell Manufacturing Process

In general terms, gelatin powder and plasticizer(s) are added to the reactor and mixed with low agitation at 60–95 °C to melt the gelatin, depending on the gelatin shell formulation and the setting point of gelatin raw material used, which is related to its mechanical and thermal. The ratio of water to dry gelatin can vary from 0.7–1.3 w/w, depending on the viscosity of the gelatin source used. Once the gelatin is fully melted, the additional components may be directly added into the reactor or previously premixed with the plasticizer(s) in an auxiliary equipment. Normally, the opacifier is mixed in rotating drums or using drum mixers for extended periods while other ingredients, such as colorants, flavors, and preservatives, may be mixed at high speeds. Finally, the gel mixture is stirred in the reactor under vacuum condition until obtaining a homogeneous gelatin mass. High undissolved particles are removed by sieving process. Then, the gelatin shell mass may be discharged into holding tanks until being used for encapsulation process, maintaining the temperature at 57–60 °C.^[3]

The physical properties of this gelatin shell material such as viscosity, flow, and tacking qualities are critical for shell production, discharge, and encapsulation processes since the hot gel mass must be supplied to the encapsulation machine through heated transfer pipes and form a consistent gelatin ribbon, especially if plate or rotary die encapsulation processes are utilized. On the other hand, the gelatin shell mass is a “living” material whose properties vary over time and under high temperature conditions due to depolymerization process of gelatin (hydrolytic degradation), reducing the gel strength and viscosity of shell material.^[2] Thus, both variables should be carefully monitored and controlled to ensure a gelatin material with adequate properties to be encapsulated.

3.2. Fill Manufacturing Process

The fill, composed by active (API or nutrient) and non-active (excipient or additive) ingredients, could be a solution, a dispersion (liquid in a liquid), or a suspension (solid in a liquid). It is prepared in a reactor, using conventional mixer homogenizers, being the mixing conditions especially important when solid sources are used, since solid agglomerates should be broken up. After fill production, the final fill product should be stored in tanks until it is encapsulated. Vacuum or inert atmosphere may be applied during the production and/or storage stages to protect oxygen sensitive drugs.

Fill formulations must be carefully designed to optimize the stability of the active ingredient and the final product, usually related to the compatibility with the shell; to improve the bioavailability of the active; and to ensure an adequate manufacturing and filling process. Lipophilic solutions are the most frequently used formulations, which are usually made with liquid vehicles such as refined oils as soy oil or castor oil and/or medium chain triglycerides (MCT). For the lipophilic suspension, thickening or viscosifying agents such as hydrogenated oils or waxes as hydrogenated castor oil or bees wax respectively are also added. Hydrophilic formulations, mainly based on PEG, are also employed. PEG 400 and PEG 600 are the most common vehicles but compounds with similar structure such as glycerin, PG, propylene carbonate, and methoxy PEGs may be also used.^[23] To adjust the viscosity of hydrophilic fill formulas, suspending agents such as MW PEGs or cellulose polymers, among others, may be included. Surfactants (i.e., lecithin, Tween), antioxidants, and solid polymer particles mixed or as coating of the drug are usually included to improve content uniformity and/or drug stability. Recently, other agents such as self-emulsifying systems and microemulsions, composed of lipophilic solvent(s) and surfactant(s) that produce an emulsion when they contact with gastrointestinal fluids, have gained interest to increase the bioavailability of drugs.^[12]

Some components are not recommended in the fill formulation:^[24] (1) high amounts of liquids (>10% of the fill formula^[23]), such as water or low MW hydrophilic polymers such as glycerin, PG, PEG 200, or PEG 300; they tend to migrate from the inner to the gelatin cover, acting as gelatin plasticizer, and therefore, altering the shell structure; (2) volatile compounds such as ethanol, due to its rapid diffusion through the cover, almost totally disappearing at the end of drying process and carrying out other fill components; (3) aldehydes and other

carbonyl groups,^[23] as they promote the cross-linking effect, modifying the dissolution profile of the final product; and (4) fill formulas with extreme pH, as acidic and alkaline components (such as acid salts and mineral or organic acids) can promote hydrolytic degradation of gelatin, and therefore brittleness in the gelatin cover.

Besides the final pH of fill formula (optimal range 2.5–7.5^[2]), other physicochemical properties are critical for the manufacturing and filling processes, such as the viscosity and fluidity parameters. The liquids or semisolid fills must have adequate viscosity and fluidity values to ensure the homogeneity of fill formulation along the manufacturing process but also an accurate dosing of the product by displacement pumps at a temperature of approximately 35 °C or below.^[12] In addition, in the case of suspensions, the size of the solid component should be also considered; it must be under 200 μm ^[12] to ensure a good sealing of the capsules. For this, raw materials of active and non-active ingredients should be carefully selected to obtain a suitable fill formulation.

3.3. Encapsulation Process

In this step, the two materials of SGCs -fill and shell-, are joined to form the optimal soft capsule. There are different methods to form SGCs: plate process, rotary die process, and seamless process. The first two processes lead to sealed capsules while the last one is limited to form pearls, seamless and spherical soft capsules.

3.3.1. Plate Process

Softgels are formed by applying vacuum over a sheet of warm gelatin placed on a set of molds, pouring the fill on the inside, and then placing another set of molds on top to seal the capsules by pressure. Its use is limited to small scale due to the lack of dosage uniformity and high production losses (slow and manual process).

3.3.2. Rotary Die Process

It is the most common method used. Shell and fill materials are connected to the encapsulation machine through different tubes. The hot gel mass is fed by gravity to two separate metering devices, through two heated transfer pipes. Each metering device controls the flow of shell mass on to air heated rotating drums (13–14 °C), continuously forming two separate shell ribbons by casting process. The thickness of each ribbon should be frequently checked during the process since each ribbon provides one-half of the final softgel. It is controlled to ± 0.1 mm and should be measured around 0.022–0.045 in, but for most capsules it is between 0.025–0.032 in.^[3] Then, the two separated ribbons are then carried through two separate rotating rollers. For that, a small quantity of a lubricant material is required normally using lubrication oil with GRAS certification, such as MCT. These rollers rotate in opposite directions and print the shape of the mold on the shell sheets. Between the two sheets, a wedge is placed, which heats and forms the welding of the capsules.

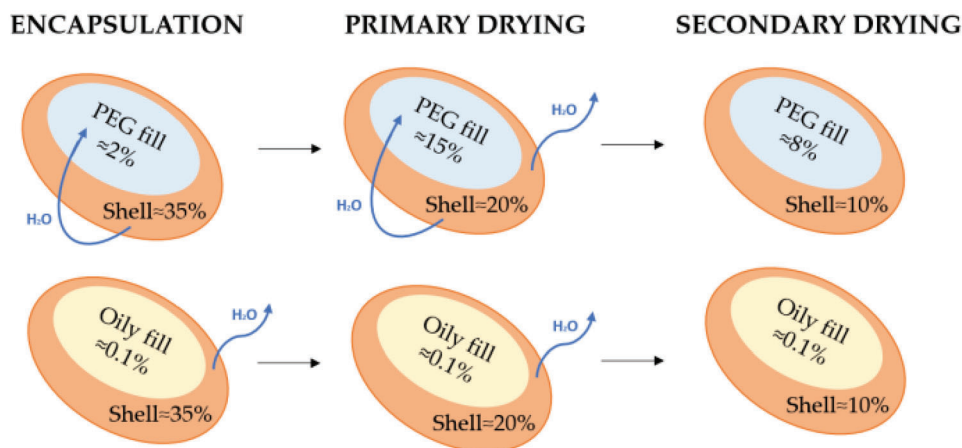


Figure 4. Drying process of softgels with PEG-based and oil-based fills.

Simultaneously, the fill is dosed in this wedge, so the injection of the fill and the forming of the capsules occur in one step. As the die rolls rotate, both gelatin ribbons are hermetically sealed (standard temperature range 37–40 °C^[12]) and cuts out the filled capsules.

3.3.3. Bubble Process

Method without dies in which softgels are formed by the phenomenon of drop formation related to the interfacial tension of liquids. The fill directly issues from the tube surrounded by shell cover, forming intermittently but steady flow seamless and spherical drops. The formed capsules are quickly removed from the nozzle and conducted to a liquid paraffin solution in which the shell mass is insoluble. The pearls are slowly frozen at 4 °C to ensure its correct formation.^[3] Finally, the capsules are degreased and automatically ejected from the system.

3.4. Drying Process

At the end of the encapsulation process, softgels are excessively soft and flexible due to the high-water content in the shell (30–40% w/w). To obtain a finished product suitable in handling and microbiological terms, most of this water should be removed until the gelatin cover reaches its equilibrium moisture content, usually 4–10% w/w.^[3]

The drying process is normally divided in two consecutive steps. The first stage—called primary, rotary, or dynamic drying process—is a low-intensity drying for 1–3 h, in which a rotary dryer continuously pumps dry air below 35 °C through a rotating drum containing the capsules. The warm temperature is recommended to keep the gel in semifluid state, ensuring appropriate sealing of capsules. In the second stage—called secondary, tray, or static drying process—the capsules are removed from the dynamic dryer to be spread over trays, which are stacked in a drying tunnel and kept at a controlled temperature (21–24 °C) and low relative humidity (20–30%). This second stage can last from hours to days, depending particularly on the nature of the fill and

shell formulations (Figure 4) but also on the ribbon thickness and size of the capsules, on the drying conditions settled, and on the number of wet capsules loaded in the dryer systems.

3.5. Finishing of the Capsules

After the drying process is complete, the resulting SGCs are sorted by appearance criteria (size and color), polished, printed if required and inspected for quality. Moreover, additional finishing operations such as coating process can be performed. Then, the capsules are conditioned for storage and distribution. For storage of SGCs, temperature between 15–30 °C and a relative humidity of not more than 50% are recommended to ensure an appropriate equilibrium moisture content between shell cover and environment, thus improving the stability of the softgel finished product.^[2]

4. Characterization of Shell Formulations of Softgels

Understanding the mechanical and thermal properties of gelatin shell material (pre- and post-encapsulation process) becomes crucial in pharmaceutical, cosmetic, and food industries. Furthermore, the mechanical properties of a polymer are strongly affected by the temperature, establishing a clear link between thermal and mechanical properties. This section presents different mechanical and thermal analyses that have been used for this purpose.

4.1. Mechanical Analysis of Gelatin Shell Materials

The mechanical properties of a material are related to the material's resistive response to an applied load and they offer information about its usefulness and expected shelf-life. These properties correlate the stresses to the strains and can only be determined experimentally. In particular, the mechanical properties of a polymer are described by three parameters: stress (σ), strain (ϵ), and rigidity or modulus (E), according to Equation (1).

$$\sigma = E \times \epsilon \quad (1)$$

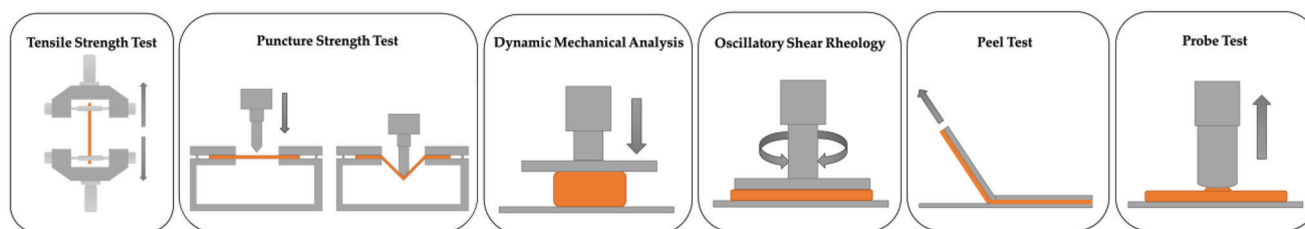


Figure 5. Schematic representation of tensile strength test, puncture strength test, dynamic mechanical analysis, oscillatory shear rheology, peel test, and probe test.

Materials can suffer different stress depending on the applied force: tensile, compressive, shear, and torsional. Strain is the materials response to this stress. Both variables are explored through stress–strain diagrams, wherein the slope of the curve in the elastic region is the modulus of elasticity or Young’s modulus.^[25] Different techniques can be used to understand the mechanical properties of materials, in particular gelatin shell materials (Figure 5).

4.1.1. Tensile Strength Test

Tensile strength test is the most popular approach for pharmaceutical films. The mechanical properties of gelatin films measured through tensile test can be expressed in different terms. The tensile strength (TS) or break stress is a measure of strength and rises with increase in MW, due to chains entanglements; with cross-linking, which restricts the motion of the chains; as well as with the crystallinity of the polymer.^[26] The elongation at break (EAB) or strain at break is a measure of ductility. Young’s modulus (modulus of elasticity, E modulus, or tensile modulus) is a measure of stiffness. Yield stress measures the stress level at which a material stops behaving elastically. Viscoelasticity represents a combined behavior of viscosity and elasticity observed in polymers at intermediate temperature and strain rate values. Finally, stress at 100% strain or yield at 100% strain related to the toughness of the gelatin material.

4.1.2. Puncture Strength Test

While tensile testing is highly informative, the studied properties do not reflect completely the behavior of a film when subjected to puncture and shear. Accordingly, other tests are required.^[27] The puncture strength (PSt) is the maximum stress required to rupture or penetrate the gelatin film.

4.1.3. Texture Profile Analysis (TPA)

Parameters such as hardness or flexibility, cohesiveness, gumminess, chewiness, and springiness can be measured by a texture analyzer.

4.1.4. DMA and Oscillatory Shear Rheology (OSR)

Both techniques may test the small-strain viscoelastic properties of shells checking its stiffness and viscoelastic damping properties under dynamic vibrational loading at different temperatures.

DMA performs oscillatory bending, compression, or tensile tests to obtain viscoelastic modulus, while OSR perform shear tests. The shear responses of the materials could be expressed as storage modulus (elastic modulus, G'), the loss modulus (viscous modulus, G''), and damping coefficient ($\tan \delta$, G''/G') as a function of temperature, frequency, or time. If $G' > G''$, the material can be regarded as mainly elastic. OSR also allows to distinguish between “strong gels”, where both moduli are nearly frequency-independent over a large frequency range, and “weak gels”, where both moduli are strongly frequency-dependent.^[28] Softgel shell formulations are considered “weak gels”.

4.1.5. Viscosity Test

Viscosity is related to shear stress and shear strain, without reference to modulus.^[19] The values are related to the MWD and the average MW. Gelatins comprising a high ratio of α -chains exhibit high gel strength and low viscosity, compared to those with high ratio of γ -chains. On the contrary, viscoelasticity is related to all three parameters σ , ϵ , and E , with E being of primary importance.^[19]

4.1.6. Peel Test and Probe Test

The adhesive properties are usually studied through peel test and probe test approaches.

4.1.7. Hardness Test

The hardness is determined by measuring the depth of indenter penetration or by measuring the size of the impression left by the indenter.^[29]

4.1.8. WVP Test

The WVP can be calculated using different methods. For instance, by measuring the weight gain of films after putting them in contact with distilled water at 30 °C.^[30]

4.2. Thermal Analysis of Gelatin Shell Materials

The thermal properties of gelatins are as equally important as mechanical properties as gelatins are very sensitive to changes

in temperature. Relevant properties include the glass transition temperature (T_g) and the T_m . The T_g value depends on the polymer structure. Polymers with high MW and/or a high degree of cross-linking exhibit lower chain mobility and a higher T_g . Polymers with inflexible side groups that decrease the chains mobility or polar groups that increase the molecular interactions, show a higher T_g too.^[31] Polymers with a higher MW or with stronger interactions between chains also show a higher T_m . It can be used to estimate the crystallinity degree of a material by normalizing its enthalpy to a 100% crystallin sample of the same material.^[16]

It is important to note that the T_g and T_m values obtained depend on several factors, such as the analytic method. For example, at higher heating rates, the amorphous phase of the polymer is increased, making the change in the glass transition enthalpy bigger and the melting peak wider. The pan used for the analysis must be selected according to the type of sample analyzed, as great weight loss due to the evaporation of volatile compounds can lead to misleading results and to the appearance of chimera peaks.^[32] While DSC is the golden analytic tool, TGA, DMA, or OSR can provide complementary information.

4.2.1. DSC

DSC is useful to monitor the stability of softgels, to study the thermal history of gelatin and to detect changes that are yet not visible by visual inspection. The calorimeter measures the heat flux (mJ s^{-1}) between the sample and an inert reference, i.e., the thermal transitions. The enthalpy (ΔH) of a thermal transition is calculated by integrating the area under the peak (Equation 2):

$$\Delta H = c_p \times \Delta T \rightarrow \frac{dH}{dt} = c_p \times \frac{dT}{dt} + \text{thermal events} \quad (2)$$

being ΔH the enthalpy (J), c_p the specific heat capacity of the material ($\text{J g}^{-1} \text{ } ^\circ\text{C}^{-1}$), ΔT the variation of temperature ($^\circ\text{C}$), $\frac{dH}{dt}$ the heat flux (J min^{-1}) and $\frac{dT}{dt}$ the heating rate ($^\circ\text{C min}^{-1}$). Thermal transitions can be endothermic ($\Delta H > 0$), such as glass transition, melting and evaporating; or exothermic ($\Delta H < 0$), such as crystallization and decomposition.^[33]

In gelatins, typical thermal events observed by DSC are a second order glass transition, attributed to the mobility of the amorphous phases, followed by a first order melting, attributed to the melting of the crystalline phases. Other transitions are thermal unfolding and decomposition at high temperatures (Figure 6). For example, a 10% solution of gelatin presents a melting point in the range 21–34 $^\circ\text{C}$, while the gelation point is approximately 5 $^\circ\text{C}$ below the melting point. High-bloom gelatins exhibit T_g and T_m values above 170 $^\circ\text{C}$. These events have been explained by the isomerization of the peptide bonds that change from the *trans* configuration (low energy) to the *cis* configuration (high energy). It is known as isomerization peak (T_i).^[32] Other authors explain T_m as the protein unfolding temperature of gelatin and T_i as the fusion temperature of the solids.^[34]

4.2.2. TGA

TGA events are divided into weight loss events (decomposition, evaporation, and desorption); and weight gain events (oxidation

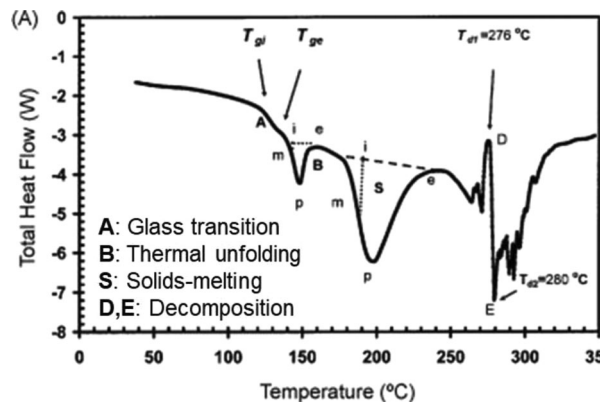


Figure 6. Example of a gelatin DSC thermogram, depicting typical thermal events: Glass transition, thermal unfolding, solids-melting, and decomposition. Reproduced with permission.^[34] Copyright 2010, Elsevier.

and absorption or adsorption). Neelan et al. characterized different gelatin-based films by TGA.^[35] Three main events were identified for the TGA profiles of gelatin: at temperatures below 150 $^\circ\text{C}$ low MW compounds such as water decompose first, at temperatures between 150–250 $^\circ\text{C}$, higher MW molecules such as additives decompose. Finally, at 250–500 $^\circ\text{C}$ thermal decomposition occurs.

4.2.3. DMA

Besides giving very useful mechanical information, DMA is one of the most sensitive tools to determine the T_g . The common experiment to determine T_g via DMA is to ramp the temperature of a specimen while applying a small-amplitude linear oscillation to measure the tensile response of the material, that could be expressed as storage modulus (elastic modulus, E'), loss modulus (viscous modulus, E''), and damping coefficient ($\tan \delta$, E''/E'). DMA was selected by Sobral et al. to analyze the thermomechanical properties of gelatin/poly vinyl alcohol (PVA) blends.^[36] While DSC showed a single T_g in the range 43–49 $^\circ\text{C}$, DMA spectra distinguished two T_g values on the $\tan \delta$ curves at higher PVA concentrations, indicating phase separation.

4.2.4. OSR

In addition to give information about mechanical properties, it is one of the most sensitive tools to determine the T_{gel} , defined as the point where $G' = G''$ in a frequency inside the linear viscoelastic region. The T_{gel} marks the transition of an amorphous material from liquid to solid due to gelation, which is caused by the growth of connected structure in the material, a structure that correlates molecular or supramolecular motion over large distances. Before reaching the T_{gel} , the material can flow and relax while, beyond T_{gel} , stress and/or strain invariants need to exceed a yield value to allow flow. A polymer at its T_{gel} is called a critical gel and it is in a critical state.^[37] A critical gel presents universal rheological properties that are in-between liquid and solid, including temperature shift factors. It can be related to shell mechanical properties, as a critical gel presents extreme fragility and

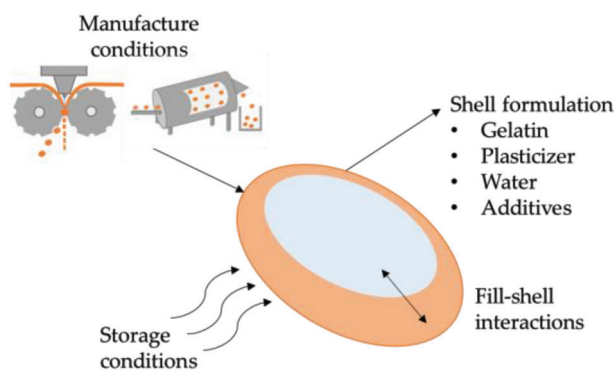


Figure 7. Main parameters affecting the mechanical and thermal properties of softgels.

ductility when it is exposed to large strain. It also presents high adhesion strength (tackiness) as it is starting to gain the cohesive strength of the solid while maintaining the wetting properties of the liquid (low MW polymer). Zhou et al. studied the effect of acidulants addition on the T_{gel} , observing lower values with higher acid concentrations.^[38]

5. Impact of Different Variables on the Properties of Gelatin Shells of Softgels

The mechanical and thermal properties of gelatin depend on four main parameters (Figure 7): (1) the intrinsic properties of gelatin, such as the source (species, breed, age, sex...) and the extraction method used to isolate gelatin from collagen; (2) the shell formulation, including gelatin content, water content, plasticizer content or any other additives; (3) the manufacture and storage conditions; and (4) the fill-shell interactions.

5.1. Shell Composition: Gelatin

Mainly, the intrinsic properties of gelatin, such as the source (species, breed, age, sex...) and the extraction method used to obtain it directly affect the mechanical and thermal properties of gelatin shells of softgels. In addition, the chemical treatment performed to obtain chemically modified gelatins may also affect but this variable is not further discussed in this review since information about these changes is not available.

5.1.1. Gelatin Source

The source produces a clear impact on the mechanical and thermal properties of gelatin films. In relation to mechanical properties, Suderman et al. characterized gelatins ribbons of different gelatin origins by their puncture properties among other techniques.^[30] A higher composition of Pro and Hyp amino acids promotes a harder material. Avena-Bustillos et al. studied the puncture deformation of gelatins of different animals and manufacturers by applying 100 N to the gelatin films and recording the maximum force and maximum puncture deformation.^[39] Mammalian gelatins and warm-water fish gelatins showed a higher

puncture deformation than cold-water fish gelatins. This is due to the differences in the amino acid composition of the gelatin films and their helical content. A higher proportion of Pro and Hyp increase the amount of hydrogen bonds in the coil-helix, increasing the mechanical and thermal stability of the gelatin.^[40] In addition, the mechanical properties of beef, pork, and fish gelatins at different concentrations were studied by Hanani et al.^[41] Tensile and puncture strengths of the films increased when an 8% of gelatin component was used compared to 4% and 6%; however, at the same concentration, pork gelatin showed higher values than beef and fish films, forming a more consistent gelatin ribbon. On the other hand, the gelatin source affects the thermal properties of gelatin ribbons too^[41] (Table 3).^[13] However, marine and poultry gelatins show a higher imino acid composition and thus higher T_m , TS, and EAB values. Moreover, differences between the T_g values of the same gelatin source are explained by the animal age and sex, or even seasonal reasons.^[42] Summer gelatin from silver carp showed higher viscosity, emulsion stability, T_m and lower concentration for gelling, compared to winter gelatin.^[43]

5.1.2. Extraction Method

The extraction method affects the properties of the gelatin films, which indirectly impacts on the dissolution grade in aqueous solution among other things. In general terms, gelatins show similar behavior in aqueous solutions at $pH \geq 3$ regardless of pH environment, precipitating in strong acid and alkali pH; however, type-B gelatin dissolves better than type-A in aqueous solution at a specific pH. Casanova et al. analyzed by DSC saithe skin gelatin extracted with two different acids, chlorohydric acid and citric acid, and observed differences of more than 10 °C in their T_g values.^[44] Al-Saidi et al. extracted shaari fish skin gelatin with different concentrations of acetic acid (0.01 N, 0.1 N, and 1.0 N) and temperatures (50–80 °C), concluding that T_g values were lower at higher extraction temperatures, being the change more noticeable at an acid concentration of 0.01 N.^[45] In addition, Jridi et al. evaluated the impact of enzymatic extraction method on the thermal properties of gelatin fill using different concentrations of pepsin to obtain cuttlefish gelatin.^[46] Gelatins treated with a higher concentration of pepsin showed a higher content in peptides with a low MW and a lower interaction between the triple helixes. This resulted in lower T_g and lower thermal stability ΔH_g than gelatins treated with a low pepsin concentration. Moreover, enzymatic pretreatments can affect the MWD of the peptides forming the gelatin, thus reducing the denaturalization temperature.^[47] In that sense, non-enzymatic method may also affect the denaturalization of gelatin by hydrolytic degradation, which is indirectly related to its mechanical properties since the higher hydrolysis, the lower gel strength and viscosity. Type-A gelatins are more easily degraded under alkaline conditions whereas type-B gelatins are more prone to acid degradation.

5.1.3. Gelatin Bloom

The gelatin bloom affects to the mechanical and thermal properties of gelatin films but also impacts the shell manufacturing

Table 3. Main thermal and mechanical properties of gelatin shells of different gelatin origins.

Gelatin source		T_g [°C]	T_m [°C]	TS [MPa]	EAB [%]
Bovine	Bovine skin	30.0, ^[18] 47.2 ^[20]	60.42–82.20	0.70–51.68	0.78–30.83
	Bovine lime	37.5 ^[20]			
	Yak skin	120.5 ^[20]			
Porcine	Pig skin	29.0, ^[18] 36.3, ^[20] 50.0 ^[21]	66.80–87.70	2.40–63.25	4.40–90.55
Marine	Tuna skin (fish)	–24.0 ^[18]	53.14–124.45	0.98–33.66	2.96–76.73
	Nile tilapia scales (fish)	65.9–75.0 ^[19]			
	Saithe skin (fish)	69.3–77.1 ^[17]			
	Sponge collagen	70.0 ^[20]			
Poultry	Chicken tendon	23.5–37.9 ^[20]	49.51–134.22	34.20–44.86	3.87–561.00
	Chicken skin	51.1 ^[21]			

process. Gelatin raw materials with high bloom have higher T_m and T_{gel} and require shorter time for gelation. Anhydrous gelatin forms inflexible and brittle films, with $T_g > 100$ °C; that is the reason why the addition of plasticizers in the shell formulation is required to obtain manageable gelatin films. Applied to softgels, gelatin ribbons which have the same composition but include gelatins with a higher bloom and with a higher content in the Hyp and Proamino acids show higher T_g values^[34] and are prone to more efficient gelification as less links are needed to obtain greater lengths of gelatin chains.^[35] Thus, in general, films formed with high bloom gelatins are stronger and more physically stable. However, gelatins with higher blooms show a higher risk of unwanted cross-linking, higher dissolution time and higher cost of raw material.^[48] Accordingly, its use is usually limited to specific products where is necessary to improve its physical stability or large size softgels which require strong gelatin film structure during their production.

5.1.4. MWD

MWD is difficultly correlated with the mechanical properties of the gelatin ribbons due to its heterogeneity, but it may help to predict the functional performance during the SGCs production as well as along its shelf-life.^[23] For example, high or wider relative MW forms more rigid gelatin structures,^[49] lead to higher viscosity materials favoring encapsulation issues, and shows high risk of cross-linking phenomenon, prolonging the dissolution times and, therefore reducing shelf-life of final product.^[50] By contrast, low MW accelerates depolymerization reactions,^[51] promotes shortened holding time and poor seals; but it may extend the shelf-life of softgel.

5.1.5. Gelatin Concentration

Gelatin concentration affects the mechanical properties, as hardness and adhesiveness increase when the concentration increases.^[41] Lizhe et al. studied the mechanical properties of different films, with 4% and 8% of gelatin. They reported TS, PSt, and EAB values of 5.69 MPa, 0.12 N, and 45.26% for 4% films and 6.60 MPa, 0.30 N, and 89.69% for 8% films, confirming the clear influence of gelatin concentration.^[52] In addition,

Table 4. Effect of different plasticizers on the thermal and mechanical properties of films.

Plasticizer	Effect on thermal properties	Effect on mechanical properties
Glycerin	↓ T_m with ↑ amounts ^[45,46]	↑ EAB and ↓ PSt, TS and E modulus with ↑ amounts ^[46]
Sorbitol	↑ T_m and T_g with ↑ amounts ^[44]	↓ PSt with ↑ amounts ^[44]
PG	↑ T_m ^[43] and ≈ T_g ^[46] with ↑ amounts	≈ PSt with ↑ amounts ^[46]
DTG	↓ T_g with ↑ amounts ^[46]	≈ PSt with ↑ amounts ^[46]
ETG	↓ T_g with ↑ amounts ^[46]	≈ PSt and ↑ TS with ↑ amounts ^[46]

high gelatin concentration increases foaming and reduces emulsifying activity.^[15]

5.2. Shell Composition: Non-Gelatin Components

5.2.1. Plasticizer

Plasticizer is used to modify the mechanical and thermal properties of polymers or proteins. They increase the free volume between gelatin chains and subsequently their relative movement, making the films more ductile and flexible, increasing its EAB, water retention, and WV permeability for water vapor, oxygen, and volatile solute components; and decreasing the melt viscosity, TS, E, and T_g of the product. Higher water contents reduce the cross-linking in the gelatin films and the hydrogen bonds formed to stabilize the structure, leading to lower T_g and T_m values.^[34,53] However, higher amounts of non-volatile plasticizers in the shell formula have been related to a higher degree of cross-linking in the presence of aldehyde groups.^[54]

Depending on its volatility and hydrophilia, its effect is different on the thermal and mechanical properties of films (Table 4); however, its concentration is important too. Nazzal et al.^[53] studied the effect of the concentration of PG in softgel shells, observing that higher T_m values were obtained with a higher PG concentration. A similar effect was observed using sorbitol, which increased the T_g and T_m values, and decreased the PSt.^[55] However, at high concentrations of sorbitol, the glass transition event was broader due to a phase separation between the polymer and the plasticizer. On the contrary, Maria et al. observed a decrease

in T_g values when using higher glycerol concentrations.^[56] A comparative study was performed to evaluate the effect of different plasticizers (glycerol, PG, diethylene glycol (DTG) and ethylene glycol (ETG)) at five concentrations.^[57] The higher plasticizing effect and efficiency was observed with DTG and ETG on the thermal properties, as the lowest T_g was obtained with low amounts. Higher amounts of plasticizer produce a decrease of the T_g for glycerol, DTG, and ETG, but no change in T_g is observed with PG. It is worth highlighting that the mechanical properties of the gelatin films were also altered through the change in T_g . From the four plasticizers studied, glycerol showed the highest plasticizer effect on the mechanical properties producing the lowest values of puncture force, obtaining lower values with higher amounts of glycerol. Moreover, gelatin films plasticized with glycerol show a higher EAB and films plasticized with ETG show a higher TS. Same results were obtained by Sobral et al., obtaining lower TS and E modulus and higher EAB with higher glycerol content.^[58] Another study was performed to evaluate the effect of oligosaccharides, organic acids, mannitol, sorbitol, PEGs of different MWs, among others, on gelatin films regarding its mechanical properties.^[17] Of all the molecules studied, only malic acid, PEG 300, sorbitol, ETG, DTG, triethylene glycol (TTG), ethanolamine, diethanolamine, and triethanolamine showed suitable plasticizer properties. From these, films plasticized with ETG, DTG, and TTG showed the highest water vapor transmission values while sorbitol and malic acid showed the lowest ones. On the other hand, the effect of hydrophobic plasticizers derived from citric acid on functional properties of gelatin films was tested, observing that the increase in the plasticizer concentration (acetyltributyl citrate and tributyl citrate) reduced the TS values by 57%, not detecting a relation with EAB in the quantities tested.^[59]

The type and concentration of plasticizer not only affect the properties of gelatin shell at time zero, but also influence its properties over shelf-life. Glycerin has a higher plasticizer capacity producing a higher reduction of T_g of gelatin film but tend to pick up quicker and higher water amount than other polyol plasticizers such as sorbitol, maltitol, or xylitol, due to its extreme hygroscopic nature, promoting sticking issues. In addition, it shows a higher permeability for oxygen and volatile ingredients.^[60] The higher glycerin amount, higher diffusion in the softgel shells.^[61,62] On the other hand, sorbitol may crystallize under low or medium relative humidity storage conditions promoting blooming or blushing issues and also modifying the mechanical properties of the film which tends to be more fragile.^[63] To avoid these undesirable effects, the combination of both plasticizers or the use of partially dehydrated sorbitol is recommended. Mannitol has also crystallization issues.^[17]

5.2.2. Additives

The addition of colorants and opacifiers on the gelatin mass modifies their appearance but also affects its mechanical and thermal properties. For instance, TiO_2 reduces the T_g , TS, and EAB of gelatin films, proportionally to its concentration.^[64] Other colorants based on metal oxides, such as iron oxide, can be linked to a decrease of the storage and loss moduli, and thus, a decrease of the mechanical strength.^[34] Some soluble colorants, such as

FD&C Red # 3 and # 4, promote ionic, hydrogen, and van der Waals interactions with ionizable gelatin groups and thus the cross-linking phenomenon. Murthy et al. observed that FD&C Red # 3 extends the dissolution profile of softgels stored under high humidity and light.^[65] Cotes et al. studied the effect of the colorant FD&C Red # 40 on the cross-linking of two types of gelatin, NF type-B 150 bloom and RXL type-B 130 bloom, observing that the rate of cross-linking, and thus, the thermal stability, was higher as the colorant concentration increased in both types of gelatin.^[66] In general terms, anionic dyes are more reactive with a cationic type-A gelatin than with an anionic type-B gelatin promoting high resistant structures, and therefore potentially affecting the disintegration profile of the final product.^[67]

On the other hand, the use of preservatives and antioxidants also affect the mechanical and thermal properties of gelatin film. Villasante et al. studied the effect of preservers extracted from pecan walnut on neutral gelatin.^[68] It resulted in a greater thermal stability as more energy is needed to break the internal structure. At higher concentrations, two melting points were detected, suggesting a crystal formation that was not present in the control samples. Wang et al.^[69] studied the effect of adding three different natural antioxidants (sodium ascorbate, d-sodium erythorbate, and tea polyphenols) to type-A bovine hide gelatin-calcium carbonate films. All antioxidants increased the TS and EAB. However, these values did not increase when increased four times the antioxidant amount. Tea polyphenols showed the biggest increase, showing TS and EAB values of 37.10 MPa and 27.22% respectively, when used at a concentration of 0.1%. On the other hand, films without antioxidant showed TS and EAB values of 28.47 MPa and 10.02%, respectively. In addition, the use of blueberry juice as additive in gelatin gels to increase the nutritional and antioxidant properties was explored.^[70] The study found the optimal ratio when the mixture exhibited a soft texture, requiring less energy to swallow, and could be easily chewed, since it had a weaker structure. This information is crucial in the development of softgels with good patient compliance.

5.3. Manufacturing and Storage Conditions

5.3.1. Manufacture Conditions

Gelatin shell mass is a “living” material whose mechanical properties vary over time and under high temperature conditions. Thus, both variables should be carefully monitored and controlled during (1) the manufacturing and storing of gelatin mass to ensure adequate properties for encapsulation and (2) the drying process of SGCs. It is worth highlighting the important shift in hardness and adhesiveness when temperature decreased from 40 °C to 30 °C. For example, for 30% gelatin gels, hardness was more than 65 times greater at 30 °C than at 40 °C (164.20×10^{-2} N versus 2.52×10^{-2} N), while adhesiveness was nine times higher (-107.15×10^{-2} N·s versus -12.11×10^{-2} N·s).^[71] During gelatin gel formation, Gly, Pro, and Hyp form regions where water is trapped. At higher temperatures, gelatin molecules appear as random coils, which begin to form triple helical junction zones as the gel cools down. However, cohesiveness and springiness did not show a relation either with temperature nor with concentration for most cases. Ling studied the degradation of the shell mass af-

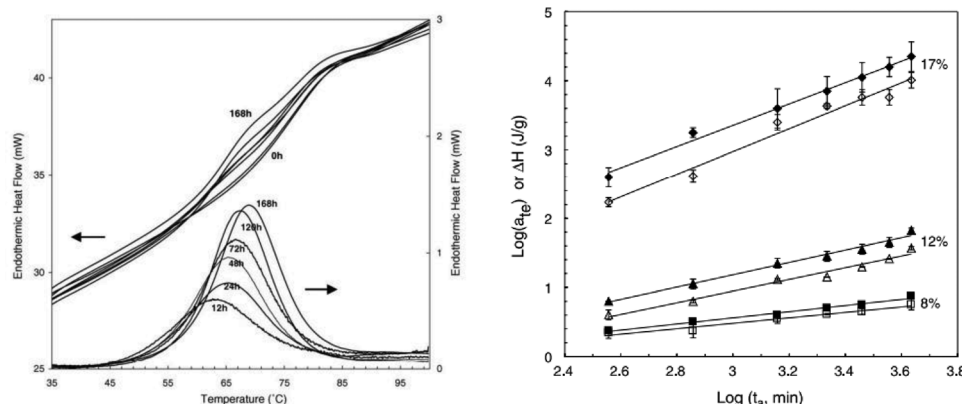


Figure 8. A) DSC thermograms acquired by heating the partially crystalline gelatin after different ageing times. Reproduced with permission.^[74] Copyright 2005, Elsevier. B) Comparison of mechanical (filled symbols) and enthalpy (open symbols) relaxations for gelatin films with 8%, 12%, and 17% water. Reproduced with permission.^[75] Copyright 2006, Elsevier.

ter storing it at high temperatures.^[51] Over time, gelatin mass increased its rigidity. Moreover, the thermal degradation of gelatin was higher with higher storage temperatures. Regarding drying step, Aguirre-Álvarez et al. studied the effect of three drying conditions (20 °C, 40 °C, and 60 °C) on pig gelatin films of different blooms.^[72] Young's Modulus was not affected, but films dried under high temperatures showed higher brittleness, lower degree of crystallinity, and worse fracture properties (TS and EAB). These results are due to differences in the gelatin structure once dried. As drying temperatures of 40 °C and 60 °C are close to T_m of gelatin mass, the structure of the films is disordered and characterized by entangled and closely packed chains. On the contrary, films dried at 20 °C show junction zones and helical order conformations. In addition, drying conditions and time are related to the final water content in the gelatin cover, which directly affect its hardness and adhesion mechanical properties. The final moisture level must be optimized to prevent a high adhesiveness of the capsules, as moisture levels $\geq 11\%$ significantly increase the risk.

5.3.2. Storage Conditions

Storage conditions (temperature, humidity and light) can affect the softgel stability. As above mentioned, the water content on gelatin cover of SGCS has a direct impact on the hardness and adhesion mechanical properties, observing that high temperature and humidity storage conditions can lead to increase of adhesiveness.^[5] When the gelatin at temperatures below its T_g change the rigidity and the C_p of the material, unstable amorphous polymer is formed. This phenomenon is known as enthalpy relaxation. The magnitude of the enthalpy relaxation depends on various factors, such as rate of cooling/heating, aging conditions, or time. Materials that are cooled down slowly below their T_g show lower excess enthalpies and are closer to thermodynamic equilibrium, as the polymer chains have had time to find energetically favorable conformations.^[73] By contrast, high temperatures during storage significantly increase the risk of cross-linking.^[2] Badii et al. studied the enthalpy relaxation event of gelatin in a partially crystalline state (raw material) and

in amorphous state (obtained after rapid cooling of the melted state) in different aging conditions and times.^[74] Enthalpy relaxation peaks become more pronounced with increasing aging time, temperature, and humidity (Figure 8a). Moreover, E modulus increased with increasing the aging time along with enthalpy relaxation^[75] (Figure 8b). Díaz-Calderón et al. confirmed these results with films plasticized with glycerol and sorbitol and stored for several days below their T_g .^[76] The presence of these plasticizers reduced the enthalpy relaxation event compared to raw material gelatin, proportionally to the polyol amount. Nazaal et al.^[53] studied the effect of storing the softgels in three different conditions of temperature and relative humidity (RH): 37 °C/75% RH, 37 °C/33% RH, and 4 °C/75% RH, for 1 week. At 37 °C, two endothermal peaks were obtained (melting events), observing a lower T_m for the 75% humidity due to a higher moisture uptake by the softgels. At 4 °C, only one endothermal peak was obtained, and the T_m was smaller than in the condition 37 °C/75%. Chuaynukul et al.^[77] stored gelatin at 25 °C/60% RH for 2 days and dried it with phosphorous oxide for 2 weeks. DSC results showed that the T_g peak overlapped with a relaxation peak associated with the destruction of residual crystalline structures in the amorphous phase. Dried gelatin showed a bigger T_m than moist gelatin due to the plasticizer effect of water. This demonstrates that the water content in the capsule affects the thermal properties, the mechanical strength, and even the shelf-life. Moreover, a high humidity during storage may increase gelatin cross-linking, which could affect its dissolution and drug release.^[2]

5.4. Fill-Shell Interactions

5.4.1. Diffusion of Components

During the production (encapsulation and drying steps) and storage of SGCS, water-soluble components may diffuse from the fill to the shell or vice versa, changing its initial composition. For instance, Nazzal et al. studied the effect of water and PEG contents in the shell formulation of softgels, observing a big loss of hardness after 1 day in contact with a fill formulation.^[53] This event can induce the formation of a three-dimensional network in the

gelatin that affects its strength. For example, ethanol from the fill can diffuse through the gelatin destabilizing the triple helix structure and reducing the T_g and T_m ; thus a maximum of 30% of ethanol is recommended.^[53] Polyols such as sorbitol or lycasin reduce the diffusion coefficient of ethanol in softgels compared to glycerol.^[62] PEG-based hydrophilic fills can diffuse into the shell too having the same effect as plasticizers in its mechanical and thermal stability.^[2]

5.4.2. Chemical Interactions

Chemical reactions may also occur between the shell components, such as esterification with polyol plasticizers. Gelatin cross-linking is induced by aldehydes in the fill, which led to a higher thermal stability with an increased T_g due to a less binding of water than normal gelatin.^[78] However, non-cross-linked gels exhibit an extremely weak mechanical strength.^[34] Gelatin, as a denatured product of collagen, contains many ions such as Ca^{2+} , Cu^{2+} , Fe^{2+} , and Zn^{2+} , which form ionic bonds with the carboxylic acid groups on gelatin and interfere in the network formation. Rheological measurements confirmed this behavior. The average G' and G'' increased 2.1 ± 0.65 fold and 18 ± 2.0 fold for unpurified gelatin, while 16 ± 4.4 fold and 100 ± 14 fold after purification.^[79] Both G' and G'' of cross-linked gelatin samples gradually decreased when soaked in phosphate buffer saline at 37 °C, indicating a decrease in mechanical strength. However, uncontrolled cross-linking is not desirable for a softgel product as it affects its physical properties such as dissolution or disintegration time.

6. Future Trends on Softgels Research

The emergence of high amount of proof about the impact of environmental factors on human health, especially since the 1970s,^[80] has evidenced the need for restoring our responsibility wanes toward our environment and future generations. There has been growing concern in the last decades about sustainable and healthy consumption, determining consumer choices, savings, and investments. Currently, the consumers are looking for natural and environmentally friendly products and is growing a global social movement for sustainability and zero waste.^[81]

In relation to the first point, there is a growing demand for natural-claimed products. In fact, the market for natural products showed an annual growth of about 7.2% in recent years only in Europe, and the “naturalness” has become the top claim for beauty and personal care products. In the world of the “capsule”, different types of gelling agents may be used to form the shell cover, dividing them by their origin in two groups, synthetic or natural. Despite the appearance of new alternatives on the market in the last years, gelatin is still the most preferred gelling agent. One of the main reasons is its natural origin which makes it classified as “food”, while some of the new alternatives such as hydroxypropyl methylcellulose (HPMC) and modified starch, are considered as additive food (also known as E-numbers). In those cases, both compounds are plant-derived, but they are processed by synthetic chemicals. For example, the HPMC production requires to treat cellulose with reagents such as methyl chloride

and propylene oxide. By contrast, although gelatin is derived from natural resources and shows pure and high quality protein, it is obtained through partial hydrolysis of collagen contained in animal skins and bones. Therefore, it is necessary to attend the increasing demands of natural animal-free products promoted by religious reasons and/or emerging lifestyles such as vegetarianism or veganism. The non-gelatin polymers most studied include starch, carrageenan, HPMC, chitosan, pullulans, pectins, behenates, among others, and their possible combinations.^[82] Accordingly, many commercial products are being launched, as LYCAGEL® from Roquette which is a softgel shell formulation based on pea-starch, carrageenan, sorbitol, and salt; Vegicaps® from Catalent and chewable VegaGels® from AENOVA with algae-based omega-3.

Regarding environmental and sustainable education, the so-called “three Rs” rule synthesizes the guidelines to care for our environment: (1) reduce; (2) reuse; and (3) recycle.

Reduce: It is related to the reduction of the consumption of resources to the minimum necessary and the waste. As previously mentioned, SGCs are formed by fill mass, wherein is usually included the active ingredients, covered by a gelatin shell. This outer material acts as a barrier for the active compounds to external factors such as temperature or humidity. In fact, this good protective attribute of the gelatin films has been studied to be used as a biodegradable and sustainable food packaging, since gelatin is an environmentally friendly substitute for traditional plastic packaging. Lan et al. demonstrated that gelatin-based composition films can effectively inhibit the growth and reproduction of microorganisms and lipid oxidation in food.^[83] The design of a gelatin shell cover with high protective properties may help to reduce the extra-amounts of actives (stability overdose) that are usually added to ensure or increase the SGC shelf-life. On the other hand, during the softgel manufacturing, the gelatin material waste in rotary die process can reach 50% of the total gelatin mass used, depending on the encapsulation process and nature of the product being encapsulated, what is a serious waste of raw materials.^[84] For this reason, in recent years, the research in softgel technology has focused in reducing the discarded gelatin. For instance, companies are working on lean manufacturing by optimizing production machinery to obtain zero gelatin waste processes, such as with new mold designs from Jangli Machinery CO that reduce the space between capsules and allow a 5–10% reduction in gelatin waste.

Reuse: It means using the resource again and again for the same or different purpose without altering the form of the product. Gelatin mass scraps may become an environmental concern due to their strong swelling ability properties in contact with water and high nitrogen and carbon content, that can cause a high oxygen demand when they reach the wastewater treatment plants.^[84] However, as gelatin mass used in encapsulation process contains other residues such as lubrication oils, it is not possible to reuse it without processing for the same purpose.

Recycle: It refers to turn waste into a resource for a new life. The main waste of SGC production is related to the gelatin material which is not as simple to recycle as it may seem since it contains other components apart from raw gelatin. To recover the gelatin, lubricating oils and additives must be removed. Particularly important is the removal of the active ingredients from the

Table 5. Variables that affect the thermal and mechanical properties of gelatin shell and the possible risk along long-term soft gelatin capsules (SGCs) stability.

Variable		Effect on gelatin shell stability	Risk along long-term SGC stability
Shell composition:	+ Source (↑ Pro/Hyp content)	Positive	No risk identified
Gelatin	+ Extraction method (harsher conditions)	Negative	↑ Dissolution issues
	Type-A & type-B	Negative	↑ Cross-linking and dissolution issues
	Type-E	Positive	↑ Cross-linking issues and dissolution issues
	+ Bloom	Positive	↑ Cross-linking issues and dissolution issues
	+ MWD	Positive	↑ Sticking and fragility issues
	+ Gelatin content		
Shell composition:	+ Higher plasticizer content	Positive	↑ Fragility issues
Non-gelatin	Group I (i.e., PG, sorbitol)	Negative	↑ Sticking issues
components	Group II (i.e., glycerol, DTG, ETG)	Negative	↑ Sticking and fragility issues
	+ Presence of additives	Positive	↑ Cross-linking and dissolution issues
	Group I (i.e., metal oxides)		
	Group II (i.e., FD&C Red # 40, saccharides)		
Manufacture & storage	+ Manufacture conditions	Negative	↑ Sticking and fragility issues
	↑Time (shell production, shell storage)	Negative	↑ Fragility issues
	↑Temperature (shell production, encapsulation)	Negative	↑ Fragility issues
	↑Temperature (drying)	Positive	↑ Cross-linking and dissolution issues
	+ Storage conditions	Negative	↑ Cross-linking, dissolution, sticking issues
	↑Temperature		
	↑RH		
Fill-shell interactions	+ Diffusion of components (water, PEG, ethanol)	Negative	↑ Sticking and fragility issues
		Positive	↑ Cross-linking and dissolution issues
	+ Chemical reactions		

gel-mass-containing waste material to avoid cross-contamination if the gelatin is later used for encapsulating a different product. Several patents are published with the objective of recycling both gelatin wastes in softgel manufacturing, whose treatment should be differed based on composition variations in gelatin mass (without lubricating components) and gelatin film (with lubricating components). For instance, the patent WO2016010207A1 describes a process to eliminate additives such as colorants from gelatin mass to obtain raw gelatin reusable for softgel production. The process consists of mixing the gelatin mass with a solvent to later separate the different layers that form in the dissolution and then separate the colorants from the gelatin mass by an ion separation step. The resultant gelatin is later concentrated for easy storage. Patent WO2017083254A1 describes a process for recovering gelatin mass by separating it from the oils used as lubricants in the encapsulation process. This is achieved by melting the mass to obtain an oil phase and a non-oil phase mass to later mix the non-oil phase mass with fresh encapsulating material. Moreover, as gelatin is a versatile material, it can be recycled for other uses too. Kandil et al. developed a vehicle for the herbicide 2,4-dichlorophenoxy acetic acid based on gelatin waste from softgel production blended with synthetic materials such as polyvinyl alcohol and other natural wastes such as sawdust and sugar cane.^[85] As a result, films with controlled-release properties of the herbicide were obtained.

In conclusion, SGCs are a popular and versatile pharmaceutical form with almost two centuries of history, that opens a wide range of possible innovation routes and thus, constitutes a promising technology for future developments aligned with the global compromises with the health and environment.

7. Conclusions

Softgels are an oral dosage form that offers several advantages over other solid forms, such as a good patient compliance, higher dosage unit homogeneity, or higher absorption of poor soluble drugs, among others. They consist of a fill formulation with the active component(s) embedded by a gelatin shell. Both elements impact the production of the final product and on its physicochemical properties along stability. Although the focus for the SGC design is usually at the fill formulation, understanding the gelatin cover properties and their changes during long-term stability is crucial for an optimal softgel product development.

As this review summarizes, several techniques can be useful for the gelatin shell characterization, especially those capable of measuring the mechanical properties (i.e., TS, PSt, shear properties, texture profile, viscoelasticity, adhesive properties, hardness, and WVP) or the thermal properties (i.e., T_g , T_m , and T_{gel}). A better understating of shell material behavior is obtained by a complementary use of these techniques, as a change in its mechanical or thermal stability may have a positive or negative effect on the stability of the SGC. Four main variables may affect the shell properties of the gelatin film and final product of SGC (Table 5): (1) the intrinsic properties of gelatin, (2) the shell composition, (3) manufacture and storage conditions; and (4) the fill-shell interactions.

Regarding the shell formula, gelatin is the main component, and its intrinsic properties greatly affect the final product stability. A higher imino acid content, bloom, MWD and gelatin content impact positively on the mechanical and thermal stability of gelatin film. However, this increment may negatively affect

the long-term stability of the SGC, as unwanted cross-linking problems or physical problems such as too high adhesiveness or hardness may arise. Non-gelatin compounds are decisive too for the SGC stability, especially plasticizers. Two groups of non-volatile plasticizers have been identified, one formed by sorbitol or PG, that increases the stability of the material but can derive in fragility problems; and the other formed by glycerol, DTG or ETG that reduce the stability as they increase the water uptake in the final product. Thus, a combination of both groups may be optimal. On the other hand, manufacture and storage conditions are determinant for SGC stability. Higher manufacturing and drying temperature show a negatively effect on gelatin film stability, leading to products with possible rigidity and brittleness problems. By contrast, higher temperature during storage increases mechanical and thermal stability of gelatin film but negatively impacts the final product stability as it significantly increases the risk of unwanted cross-linking, same as high humidity conditions. Last, fill-shell interactions must be considered for an optimal softgel design, as migration of components from fill to shell or vice versa and/or chemical interaction between components of both areas affect the gelatin film stability and can produce physical problems in the final product.

Moreover, softgel shell formulation research is pursuing the current consumption trends by following the “three Rs” rule, working in the optimization of softgel manufacturing process to reduce gelatin waste and in the development of new gelatin mass recycling processes to reuse the gelatin waste for another products. In addition, as gelatin has an animal origin, plant-based alternative materials such as starch or carrageenan are being investigated to adapt softgel products to vegan and vegetarian diets.

Overall, softgel shell cover is a complex material that determines the long-term SGC stability and thus, must be considered along with fill formulation for a softgel development. Through mechanical and thermal characterization, shell formulation can be improved to predict the behavior of SGCs during their shelf-life.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

S.G.-G. and M.A.C.G. worked on conceptualization. A.N.M. investigated the work. A.N.M. and S.G.-G. prepared the original draft. S.G.G. and M.A.C.G. reviewed and edited the work. S.G.-G., M.A.C.G., and F.J.d.l.M. supervised the work. S.G.-G. and M.A.C.G. worked on funding acquisition. All authors have read and agreed to the published version of the manuscript.

Keywords

active pharmaceutical ingredients, capsules, DSC, gelatin, mechanical properties, softgels, thermal properties

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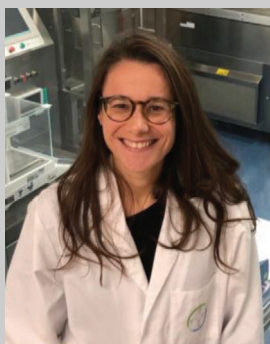
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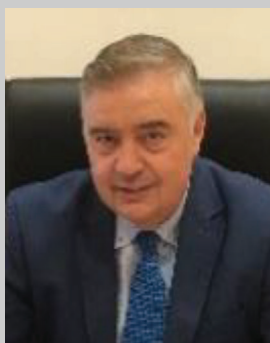
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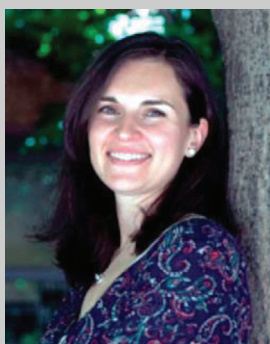
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