Gelatin and non-gelatin soft gel capsules: A review

Chavarría-Rojas Marianela[a,b,*], Acuña-Amador Daniel[a,b], Madrigal-Redondo German L[a,b]

[a]Escuela de Farmacia, Universidad Latina de Costa Rica, San José 11801, Costa Rica
[b]Facultad de Farmacia, Universidad de Costa Rica, San José 11801, Costa Rica

Received: May 6, 2020*; Accepted:* May 5, 2021

Review Article

ABSTRACT

Soft gelatin capsules are solid, single-dose dosage forms consisting of a shell, usually made from gelatin, that generally contain liquids. Gelatin is the most widely used film-forming agent, and it is extracted from collagen through hydrolysis. However, it is also possible to use starch and cellulose derivatives, such as hydroxypropyl methylcellulose, to form the thin ribbons required for the production of soft gel capsules. The most widely used method for making and filling soft gel capsules is using a rotary die process which is known as the first continuous manufacturing process. Due to the nature of soft gelatin capsules, the to-be-encapsulated liquid formulation must be within well-established moisture and pH limits. These liquids can be either hydrophilic or hydrophobic and can be formulated as solutions or suspensions. There are currently many soft capsules patents, some covering formulations and others covering the processes of soft capsules without incorporating gelatin. The main objective of this paper was to review both soft gelatin and non-gelatin capsules as to their general aspects, composition, manufacturing processes, and controls affecting this pharmaceutical dosage form. Additionally, some patents for soft gelatin and non-gelatin capsules are cited.

KEY WORDS: Soft-gel capsules, gelatin, starch, hydroxypropyl methylcellulose, rotary die method, excipients

INTRODUCTION

Oral pharmaceutical dosage forms are those that, after administration to the patient, achieve a systemic or local effect in the gastrointestinal tract. These can be divided into liquid or solid forms, the latter can be further divided into tablets, capsules, powders, and granules (1).

Capsules are single solid dosage forms intended to be administered orally, although they can also be administered via the rectum or the vagina. Capsules may contain one or more active pharmaceutical ingredients (APIs), as well as, excipients (substances required to formulate the API) within a small hard or soft shell, generally made of gelatin. (1-4). After administration, the gelatin dissolves in the biological fluids, and the therapeutic agents within the capsule are released (1).

Soft gelatin capsules generally contain liquids and are formed, filled, and sealed simultaneously during the same process. Hard gelatin capsules are manufactured using a cylindrical body and cap. The filling occurs after

*Corresponding address: Facultad de Farmacia, Universidad de Costa Rica, San José 11801, Costa Rica, Tel: +506 83268404, E-Mail: marianela.chavarria@ucr.ac.cr

the formation of empty capsules and usually contains powders, granules, or pellets, but may also contain semi-solids or liquids (4, 5).

Some advantages of using soft capsules are related to the API in solution or suspension in a liquid vehicle, which simplifies the filling process, allows a high reproducibility and uniformity formulation compared to tablets or hard gelatin capsules (5, 6).

Another advantage of encapsulating liquid in a soft gel capsule is the quick release of the API, which may result in achieving therapeutic blood levels faster and obtaining greater bioavailability. If the appropriate choice of vehicle is made, it is possible to improve the dispersion, dissolution, and release of the capsule contents (4-6). Drugs with poor aqueous solubility, which means drugs class II and IV based on the Biopharmaceutical Classification System (BCS) scale, could be formulated as lipid-based drug delivery systems in soft gel capsules. Such systems have demonstrated the ability to maintain the drug solubilized until absorption. Self-micro emulsifying drug delivery systems have also demonstrated improvement of intestinal permeability and bioavailability of lipophilic drugs with low bioavailability (7).

The gelatin film forming the capsule acts as a barrier to protect the API from oxidization by providing a hermetic seal, characteristic of this dosage form (4-6). The disadvantages of soft gel capsules are due to the manufacturing processes, which are slower and more expensive than for other dosage forms. Production and filling equipment is highly specialized which is why, pharmaceutical companies often contract out these services to third parties. This increases the production time, controls, complexity, and logistics. Finally, there is a possibility of incompatibilities between the formulation and some of the capsule components. These can migrate from the capsule to the contained liquid or *vice versa*, affecting the formulation composition and its stability (4, 6, 8).

Some examples of commercialized drugs formulated as soft gel capsules are shown in Table 1.

Table 1 Commercialized drugs formulated as soft gel capsules (modified from (4,7))

DRUG	PRODUCT NAME	MANUFACTURER
Cyclosporine	Neoral®	Novartis Pharm. Corp
Dutasteride	Avodart®	GSK Canada
Calcitriol	Rocaltrol®	Roche Canada
Isotretinoin	Clarus®	Cipher Pharmaceuticals Inc.
Progesterone	Prometrium®	Merck
Valproic acid	Depakene®	Abbott Laboratories
Testosterone	Andriol®	Merck
Ritonavir	Norvir®	Abbott Laboratories
Amprenavir	Agenerase®	GlaxoSmithKline
Loratadine	Claritin®	Schering-Plough Canada Inc
Digoxin	Lanoxicap®	GlaxoSmithKline
Ibuprofen	Advil PM Liquid-Gels®	Wyeth
Naproxen sodium	Aleve®	Bayer HealthCare
Amantadine HCl	Symmetrel®	Novartis Pharmaceuticals
Isotretinoin	Accutane®	Roche Pharmaceuticals
Lopinavir, Ritonavir	Kaletra®	Abbott Laboratories
Ranitidine HCl	Zantac®	GlaxoSmithKline

SOFT GELATIN CAPSULES

Composition

The highest proportion of components in the soft capsule shells is gelatin, its origin is natural, and it is obtained from animal collagen (skin, tendons, bones, and cartilage) through acid hydrolysis and alkaline hydrolysis. This way, two types of gelatin are obtained, known as type A (acidic) and type B (alkaline) (2, 5, 9). However, the extraction of gelatin from other animal sources, mainly fish skin, has recently been investigated (Table 2). In these cases, the amino acid composition could vary without having important implications in the final product and the gelatin preparation process *per se* (10–12).

The main reason gelatin is used to produce capsules is due to its physicochemical, biological, and mechanical properties. Gelatin is non-toxic, highly soluble in bio-

Table 2 Comparison of amino acid content in gelatins obtained from fish and pork (residues/1000 total amino acid residues) (modified from (10))

AMINO ACID	COD SKIN	ALASKA POLLOCK SKIN	TILAPIA SKIN	PORK SKIN
ALA	96	108	123	112
ARG	56	51	47	49
ASX	52	51	48	46
CYS	0	0	0	0
GLX	78	74	69	72
GLY	344	358	347	330
HIS	8	8	6	4
HYL	6	6	8	6
HYP	50	55	79	91
ILE	11	11	8	10
LEU	22	20	23	24
LYS	29	26	25	27
MET	17	16	9	4
PHE	16	12	13	14
PRO	106	95	119	132
SER	64	63	35	35
THR	25	25	24	18
TRP	0	0	0	0
TYR	3	3	2	3
VAL	18	18	15	26
IMINO ACID	156	150	198	223

logical fluids, has very good rheological properties, and is an excellent film-former with a good strength-to-flexibility ratio (5, 13). However, some fill formulation components might react with the gelatin shell, such as aldehydes present in the drug. To prevent the chemical interaction seen as a shell cross-linking, it is possible to use succinylated pigskin gelatin with a Bloom value and viscosity between 190 – 210 g and 3.3 – 4.1 mPa.s. (14).

Besides aldehydes, other chemical compounds may facilitate gelatin cross-linking. Some functional groups present in drug molecules associated with cross-linking are imines, ketones, saccharides, calcium carbonate, hydrogen peroxide, sulfonic acids, carbodiimides, and benzene. Also, factors such as temperature, humidity, UV radiation and, impurities in the encapsulated fill material could increase gelatin cross-linking (7, 15). Due to the gelatin cross-linking, the drug dissolution rate may be delayed, but using enzymes like pepsin and pancreatin facilitates the rupture of cross-linked gelatin shells, increasing the drug dissolution rate. The recommended enzyme concentrations in the dissolution medium are stated in the USP General Chapter Dissolution <711>. The enzyme type and concentrations depend on pH, for example, pancreatin is used at a concentration/activity of 2000 units/1000 mL when the pH is higher than 6.8. But papain is used in a medium with a pH less than 6.8 but higher than 4. The usual concentration/activity is ≤ 550,000 units/1000 mL, and pepsin is used when the medium pH is lower than 4 at a concentration/activity of ≤ 750,000 units/1000 mL (7, 16).

Besides gelatin, other components are added to facilitate the formation of the capsule, such as plasticizers, preservatives, opacifiers, colorants and moisturizers. Plasticizing agents are added to reduce the stiffness of the film and increase its flexibility. Compared to hard gelatin capsules, soft gelatin capsules contain a higher proportion of plasticizers. This is the most important difference between soft and hard gel capsules. Glycerin, sorbitol and propylene glycol are some of the most used plasticizers, of which glycerin the most commonly used (2, 5, 6).

Anhydrous gelatin has a glass transition temperature (T_g) greater than 100°C (T_g>100°C) which is associated with the formation of an inflexible and brittle film. Plasticizing agents reduce protein-protein interactions by standing between the protein chains of gelatin thus increasing its mobility and decreasing its T_g value. Plasticizing agents facilitate moisture absorption due to their hygroscopic nature, and this also reduces interactions among adjacent polymeric chains (4, 13, 14).

Glycerin plasticization mechanism results from direct interactions with the gelatin chains, which allows the formation of a stable thermoreversible gel network.

This mechanism is known as a direct plasticization mechanism. The indirect plasticizer mechanism is related to hygroscopicity and the moisturizing effect. Sorbitol is an example of a perfect indirect plasticizer (14).

Coloring agents usually have a strictly aesthetic function providing a means for identification and may provide a psychological effect to improve patient compliance of the product. It is possible to use water-soluble dyes, lacquers, or inorganic pigments, but they must be incorporated at concentrations recognized by the relevant regulatory authorities (4). These can improve product stability when combined with opacifying agents. The latter prevents light from passing through the capsule thus prolonging the stability of photosensitive molecules. Titanium dioxide is the most commonly used opacifying agent, however, calcium carbonate, iron oxides, and dioxides can also be used (2, 5 ,6).

Preserving agents are added to prevent microbial contamination, and if incorporated into the formulation, it must be included during the preparation of the gelatin solution. However, adding preservatives into soft gelatin capsules has decreased due efforts to reduce contamination during the manufacturing process, for example by heating the gelatin solutions to a temperature above 50°C (2, 5, 6).

The chemical structure of gelatin

Gelatin is obtained through collagen hydrolysis, a three-chain protein arranged into a triple helix structure, stabilized by tightly bound water molecules. The triple helix breaks during the high-temperature collagen denaturation process, resulting in different compositions and different molecular weight polypeptide mixtures (4, 12, 17).

Because of polypeptide chain interactions, a random spiral structure is formed. In aqueous solutions, the gelatin chains associate with each other and form a triple helix analogous to collagen. At high temperatures, the three-dimensional conformation of gelatin is a spiral, but as the temperature decreases, a helical structure, very similar to that of collagen, is formed. There is a reversal and partial recovery of gelatin to native collagen (4, 8, 12, 17).

Some gelatin factors affecting the formation of the helical structure are the polypeptide chains' molecular weight, gelatin type and concentration, production and temperature process conditions, drying rate, and using cosolvents. For helical structure formation, the length of the chain must be between 40 and 80 amino acid residues, type B gelatin is more similar to collagen than type A gelatin, therefore, type B gelatin forms helical structures easier (4,8).

Media characteristics also influence the gelification properties of gelatin. For example, pH values close to the isoelectric point of gelatin facilitate the formation of helical structures. Using non-ionic solvents and solutes also promotes helix formation, the greater the number of hydroxyl groups and the greater the solutes and solvents concentration are, the easier the formation of helical structures will be. But long-chain salts and alcohols decrease the gelification rate (4,8).

Gelatin properties

The gelatin used in pharmaceutical, cosmetic, and food industries consists of high purity gelatin protein. Many factors influence the gelatin properties, such as the natural source, collagen type, and gelatin extraction treatment. The main gelatin properties in pharmaceutical, cosmetic, and food industries are bloom value, viscosity, and polyelectrolyte properties (18, 19). Gelatin particle size and solubility are strictly related to the afore mentioned properties. The gelatin water absorption capacity is greater than ten times its weight. It depends on particle size, thus, particle size is, indirectly, related to gel formation (18).

The gel formation depends on the gelatin and its concentration, and is formed when the gelatin solution temperature is less than 25°C. Gel preparation requires that the solution is heated followed by the cooling process without agitation to avoid bubble formation. At higher temperatures, the mobility of the gelatin chains increase and arrange randomly, but at low temperatures, during and after the cooling process,

the gelatin chains adopt an orderly arrangement, and the mobility of the chains is reduced. The association between gelatin chains are analogous to a helicoidal collagen structure (12, 18).

Gel strength, also known as Bloom strength, is the weight required to depress the surface of the gelatin by 4 mm using a flat-bottomed cylindrical plunger with 12.7 mm diameter (12, 18). The Bloom strength value is generally between 30 and 300 Bloom. The greater the bloom value, the greater the gel strength (19). The gelatin Bloom strength must be between 155 and 210 for the soft gelatin manufacturing process (12).

The Bloom test is a standardized test and should be performed under strict conditions related to gelatin concentration and preparation. According to the specifications, the gel should be prepared at a concentration of 6.67 % (w/w) and should be maintained in a water bath at 10°C for 16 to 18 hours (12, 18).

Additionally to Bloom strength, viscosity is an important property in gel formation. It is related to a gelatin sample's average molecular weight. Viscosity is expressed in mPa.s. and is determined by the flow time measured of 100 mL of 6.67 % (w/w) gelatin solution at 60°C. Other viscosity measuring techniques allow the use of different temperatures and gelatin concentrations (12).

The molecular weight distribution and the average molecular weight of gelatin could be considered gelatin property due to gel formation. The gelatin solution viscosity is related to the molecular weight distribution and the average molecular weight, but the Bloom values are not. Gelatin is formed by three polypeptides chains, denominated α-chains, β-chains and γ-chains. It is well known that α-chains and β-chains consist of one polypeptide chain and two polypeptides chains, respectively, while γ-chain comprises three peptides chains. If gelatin contains a high proportion of α-chains, the gel strength will be high, and the viscosity will be low, but if the gelatin solution is rich in γ-chains, the gel viscosity and gelatin setting are higher (12, 19). The amounts of proline and hydroxyproline are important for the gelling effect. Both amino acids form nucleation zones, therefore, helical structure stability is proportional to their content. Hyp content has been related to collagen melting temperature, the lower the Hyp content, the lower is the melting temperature. Hyp stabilizes the triple helix through the involvement in a hydrogen-bonding structure and through inductive and stereo electronic effects (20, 21).

Soft gelatin formulations

Soft gelatin capsule formulation involves liquid technology rather than solid technology, despite classified as a solid pharmaceutical form. A formulation is considered successful if it achieves high stability over time, high therapeutic effectiveness, and if its manufacture is efficient. All the above should also be contained in a capsule with the smallest possible size. The encapsulated formulations can be non-aqueous suspensions, solutions, or microemulsions without water. The most used vehicles can be classified as water-miscible or water-immiscible liquids for example vegetable oils, medium-chain triglycerides, mineral oil, and low molecular weight polyethylene glycols. When the formulation is a suspension, it must include a suspension stabilizing agent, such as beeswax, paraffin, or high molecular weight polyethylene glycols (2, 6 ,22). Self-emulsifying drug delivery systems are also a formulation alternative to increase the absorption and bioavailability of poorly soluble drugs. These systems contain non-ionic surfactants, cosolvents, and the API. After administration, the shell capsule releases the fill material in the gastrointestinal fluids, which allows the spontaneous formation of small droplets and facilitates the enhancement of drug dissolution and absorption (7).

Generally, the vehicles should have good rheological properties at a temperature below 35°C, the water content should be less than 5% by weight, and the acidity should not be too high to reduce the risk of gelatin shell hydrolysis (4, 6).

During formulation, it is important to consider the possible physical or chemical interactions that might affect soft gel capsules' characteristics and performance,

and those interactions are defined by the qualitative and quantitative shell and fill composition. The water-soluble components' migration or diffusion from the fill to the shell or *vice versa* is an example of physical interaction. Lipophilic drugs and vehicles are not linked to interactions between fill and shell, but hydrophilic agents in filling formulation might interact and affect the soft capsule shell characteristics. The components migration during the manufacturing process and storage is a major problem because it represents a change in the initial capsule composition that might cause brittle or tacky soft capsules. There are many approaches to prevent this problem, for example, reduce the initial shell water content facilitating the drying process, or look for the replacement of components that might migrate or facilitate the migration process, such as glycerin (4, 14).

Drug esterification or transesterification are examples of chemical interactions. Plasticizers polyols, such as glycerin, are capsule shell components that might react with some drug molecules. An alternative to minimize those reactions would be to use polyols substitutions or polyvinylpyrrolidone in the formulation (14).

Soft gelatin manufacturing

There are several methods for manufacturing soft gelatin capsules, such as plate, rotary die, reciprocating die and Accogel processes, as well as, the bubble method. Some processes are rarely used, but specifically, the Accogel process is not used much these days. The rotary die process, also known as the roller method, is the most commonly used process and was the first continuous method employed (2, 6).

The apparatus used in the rotary die method consists of two rollers with cavities on their external surface that rotate in opposite directions, forming the capsule. A laminated plasticized gelatin ribbon flows over each roller, the filler formulation is injected, and the capsule is sealed. The newly formed capsules are cut off for release and expulsion in the bottom of the apparatus. The sealing and cutting are attributed to the rollers' mechanical pressure and heating (2, 5).

The two gelatin ribbons that form the capsule should be lubricated to prevent scratches or apparatus adherence. The rollers have opposing cavities that shape the soft gelatin capsule so that it is possible to contain the formulation to be encapsulated at the injection time. Compared to hard gelatin capsules, where the filling, closing, and sealing process occurs sequentially, the production of soft gelatin capsules by the rotary die method involves a simultaneous filling and sealing process (4, 8).

The recently expelled soft capsules have high flexibility due to excess moisture. They undergo a drying process that comprises two stages. In the first stage, low intensity and short duration, the capsules are placed in rotary perforated-wall drums, and a hot air stream is blown through the perforations at a temperature below 35°C. The hot air breaches the capsule and facilitates its drying from the inside towards its surface through a moisture dragging mechanism. The air temperature allows the film to be kept in a semi-fluid state that enables the capsule sealing (4).

Before the drying process, the newly filled capsules are rinsed to remove the lubricating agent added during the encapsulation process. Occasionally, highly absorbent cloth towels are placed in the perforated-wall drums to assist these agents' removal. Once the soft capsules complete the first stage of the drying process, their moisture is expected to decrease significantly due to water migration to its surface from inside. At the end of this stage, the residual moisture value rarely exceeds 20% by weight (4).

The second stage requires more time and high intensity than the previous stage. It consists of placing the capsules in trays and exposing them to a drying process under regulated temperature and humidity conditions, 21-24°C and 20-30%, respectively. The duration of this step can vary from a few hours to several days, depending on the formulation characteristics, the shell, the quantity and type of plasticizer, the thickness of the film, and the capsule size. At the end of this step, the residual humidity must be below 8% by weight (4, 8).

Following the drying stage, the capsules are classified, cleaned, polished, and subjected to quality verification tests. Then they are placed in the primary packaging, usually plastic containers or blisters. The recommended storage conditions are a temperature 15-30°C and less than 50% relative humidity (4).

Soft gel capsules characterization

Soft gelatin capsules characteristics and performance are determined using some of the following tests:

- Differential scanning calorimetry allows thermal behavior determination. Glass transition temperature, melting temperature, and melting enthalpy are parameters used to evaluate different agents, manufacturing process and storage, on soft gel capsules' characteristics and performance (14, 17).
- Critical swelling ratio is used to study the equilibrium between the shell moisture and the fill material water content (17).
- Gel strength is determined by the Bloom test, explained previously (12, 19).
- Near-infrared spectroscopy is used for component identification and to determine molecular interactions between different functional groups that contribute to gelatin film formation and study the effect of agents that affect the gelatin cross-linking (14, 23).
- Dynamic vapor sorption technique measures the water absorption of gelatin sheets and desorption properties to investigate the moisture content effect in shell mechanical properties (23). Capsules' hardness or strength measurement is performed using a durometer, known as the hardness test. Hardness values above or below the manufacturer specified values indicate capsules' low flexibility or high softening (14, 17).
- Rupture test is performed in capsules containing semi-solid or liquid formulations. The test is described in the USP General Chapter Dissolution <711>, using apparatus 2 at a rotation of 50 RPM in 500 mL for 15 minutes. As a disintegration test alternative, the rupture test meets the requirements when the tested soft gelatin capsules are rupture in not more than 15 minutes. If 1 or 2 capsules rupture in more than 15 minutes and less than 30 minutes, 12 additional units must be tested. Only 2 units of 18 units tested are ruptured in more than 15 minutes but less than 30 minutes (7, 16).

NON-GELATIN CAPSULES

Gelatin has traditionally been the main film-forming agent for the production of soft gelatin capsules. However, there are other options, such as hydroxypropyl methylcellulose (HPMC) and starch (8, 14).

Hydroxypropyl methylcellulose

Hydroxypropyl methylcellulose (HPMC) is a cellulose ether polymer in which the hydroxyl groups are substituted. It is a hydrophilic, biodegradable and biocompatible polymer with many applications in the pharmaceutical, cosmetic, textile, and agricultural industries. It is soluble in polar solvents, both aqueous and non-aqueous, providing a formulation benefit since the solvent choice is flexible. The HPMC ribbons formed in an aqueous solution are highly flexible, transparent, and glossy; they are also tasteless and odorless (24).

There are cases where HPMC capsules have been developed combined with a secondary gelling agent, such as kappa-carrageenan. These may delay the *in vitro* and *in vivo* capsules dissolution process since it depends on the pH and the composition of the dissolution media. If using a secondary gelling agent is avoided, the dissolution process will be independent of the media's composition and the pH (8).

HPMC ribbons and capsules are less hygroscopic and have lower moisture content than gelatin capsules. Therefore, moisture transfer from the ribbon to the formulation decreases, which improves the physical and chemical stability of products with high hydrolysis susceptibility or precipitation induced by water excess susceptibility. The interaction and migration of polar and hygroscopic components of the formulation towards the gelatin shell cause instability for soft gelatin capsules; using HPMC reduces the possibility

of this phenomenon occurring (8).

Starch

Starch and its derivatives have been proposed as alternatives to gelatin to produce soft capsules (24, 25). Starch is one of the most broadly available biopolymers, it is also biodegradable, inexpensive, and can be extracted from various plant sources, such as corn, rice, cassava, potato, and others. It is formed of amylose and amylopectin, two polysaccharides formed of glucose monomers (24).

For the thin ribbons formulation, it is possible only to use starch or mix it with other gelling agents, *iota-carrageenan,* for example (24, 25). In contrast to soft gelatin capsules that require formulations within a specific pH range, capsules made from starch are compatible with alkaline formulations and those that contain strong acids or alkalis or salts (8, 14).

Starch has a thermoplastic behavior when plasticizing agents are added providing increased film flexibility but they do not provide efficient barrierd against humidity or oxygen (24).

Soft capsule products and formulations examples

It is possible to find quite a few products formulated in soft gelatin capsules. Many of these patents look for new gelatin substitutes for soft capsule formulation sand production. A few examples are shown in Table 3.

An important amount of information is also available to formulate different products of soft-gel capsules or, for non-gel capsules. Some of these products are detailed in Table 4.

Gastro-resistant and chewable soft gelatin capsules

Modified drug release systems are very common in solid oral dosage forms, including soft-gel capsules. These may be formulated using gastro-resistant systems with three main objectives: protect the API from acidic degradation, minimize adverse effects associated with gastric mucosa irritation and allow drug delivery directly in intestines, not the stomach (8, 46).

The design, formulation, and manufacturing of gastro-resistant soft gelatin capsules is a challenge, as the drug release control can be achieved only by modifying the capsule shell. There are two general technological alternatives to formulate a capsule shell resistant to stomach pH, that is, capsule coating and incorporating gastro-resistant polymers in the shell materials. However, the last alternative means an important change in shell formulation and composition, which may prejudice the gelatin films' physicochemical properties. Enteric coatings used in soft gelatin capsules must not affect the performance characteristics or physicochemical

Table 3 Gelatin substitutes for soft capsules

PATENT NUMBER	NAME	PUBLICATION DATE	REFERENCE
US5342626A	Composition and process for gelatin-free soft capsules	1994	(26)
CA2341024C	Non-gelatin substitutes for oral delivery capsules, their composition and process of manufacture	2000	(27)
US6193999B1	Gum acacia substituted soft gelatin capsules	2001	(28)
WO01/3677 A1	Film forming compositions comprising modified starches and iota-carrageenan and methods for manufacturing soft capsules using same	2001	(29)
US6375981B1	Modified starch as a replacement for gelatin in soft gel films and capsules	2002	(30)
AU2003237365B2	Non-gelatin capsule shell formulation comprising iota-carrageenan and kappa-carrageenan	2003	(31)
US 20050014852A1	Homogeneous, thermoreversible gel film containing kappa-2 carrageenan and soft capsules made therefrom	2005	(32)
US009339474B2	Soft capsule based on starch and a method and device for the production thereof	2016	(33)

Table 4 Soft-gel and non-gel capsules products

PATENT	NAME	PUBLICATION DATE	REFERENCE
US 20060292217A1	Nutritional supplement and soft gelatin capsule delivery system	2006	(34)
US 007723390B2	Pharmaceutical Formulation for Thyroid Hormones	2010	(35)
WO 2009/069139Al	Dosage form providing an ibuprofen-containing liquid fill	2009	(36)
CA 2816538	Probiotic soft gel composition	2017	(37)
US 20040213857A1	Multi-vitamin and mineral supplement for pregnant women	2004	(38)
US 4002718	Gelatin-encapsulated digoxin solutions and method of preparing the same	1977	(39)
US006759395 B2	Soft-gelatin capsule comprising s-adenosylmethionine and a method for producing the same	2004	(40)
US008642030B2	Compositions containing coenzyme Q-10 and Dihydrolipoic acid	2014	(41)
US008309107B2	Stable solutions of orlistat for pharmaceutical dosage forms	2012	(42)
US008287904B2	Stable soft capsule dosage form for acetylsalicylic acid	2012	(43)
US005173304A	Agents for the treatment of severe pain and preparation of said agents	1992	(44)
US007446101B1	Bioavailable carotenoid-cyclodextrin formulations for soft-gels and other encapsulation systems	2008	(45)

properties of the pharmaceutical dosage form (46).

Patents related to enteric coating formulations of soft-gel capsules are listed in Table 5.

CONCLUSION

This article provides an overview of soft gelatin and non-gelatin capsules. The manufacturing process for these dosage forms is complex, and many critical parameters can affect the final product quality. There are different alternatives for the non-gelatin capsules formulation, such as starch and HPMC. The patents reviewed in this work confirm that many pharmaceutical formulations are administered in soft gelatin and non-gelatin capsules. It is also possible to highlight the recent research oriented to the gelatin-free soft capsules design and development.

Table 5 Inventions related to gastro-resistant soft gelatin capsules

PATENT	NAME	PUBLICATION DATE	REFERENCE
US 2011/0002986A1	Stable Shellac enteric coating formulation for nutraceutical and pharmaceutical dosage forms	2011	(47)
US 20170367985A1	Enteric film coating compositions, method of coating, and coated forms	2017	(48)
WO2001024780A2	An improve pharmaceutical composition and process for its preparation	2001	(49)
WO2004030658A1	Enteric composition for the manufacture of soft capsule wall	2004	(50)
WO 2014/140991	Enteric coating for soft capsule	2014	(51)
WO 2015/200149 A1	All natural enteric soft capsules comprising active ingredients	2015	(52)
CA2625554A1	Enteric soft capsule comprising valproic acid	2006	(53)
US009820947B2	Method of manufacturing enteric seamless soft capsule	2017	(54)
US 2007/0196463 A1	Enteric soft gelatin capsule containing esomeprazole and method of preparation	2007	(55)

AUTHOR'S CONTRIBUTION

The data acquisition was generated by Marianela Chavarría-Rojas. The critical content review was carried out by Marianela Chavarría-Rojas, Daniel Acuña-Amador and Dr. German Madrigal-Redondo.

FINANCIAL SUPPORT

This project received no financial support.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

REFERENCES

1 Villiers M. Oral Conventional Solid Dosage Forms: Powders and Granules, Tablets, Lozenges, and Capsules. In: Ghosh TK, Jasti BR, editors. Theory and Practice of Contemporary Pharmaceutics. New York: CRC Press; 2005. p. 273–326.

2 Lozano M del C, Córdoba D, Córdoba M. Manual de Tecnología Farmacéutica. Barcelona: Elsevier; 2012.

3 Deepak G, Kamal K, Ajay B, Kumar Mahesh K. Soft Gelatin Capsules:development, applications and recent patents. Int Res J Invent Pharm Sci. 2014;2(3):163–73.

4 Gullapalli R. Soft Gelatin Capsules. J Pharm Sci. 2010;99(10):798–809.

5 Aulton M, Taylor K. Aulton´s Pharmaceutics. The design and manufacture of medicines [Internet]. 4th editio. Churchill Livingstone. Elservier; 2013. Available from: http://ir.obihiro.ac.jp/dspace/handle/10322/3933

6 Augsburger L. Hard and soft shell capsules. In: Modern Pharmaceutics. 4th editio. Maryland; 2002. p. 512–75.

7 Damian F, Harati M, Schwartzenhauer J, Van Cauwenberghe O, Wettig SD. Challenges of dissolution methods development for soft gelatin capsules. Pharmaceutics. 2021;13(2):1–30.

8 Gullapalli RP, Mazzitelli CL. Gelatin and Non-Gelatin Capsule Dosage Forms [Internet]. Vol. 106, Journal of Pharmaceutical Sciences. Elsevier Inc.; 2017. 1453–1465 p. Available from: http://dx.doi.org/10.1016/j.xphs.2017.02.006

9 Yap BK, Gam LH. Differentiation of bovine from porcine gelatin capsules using gel electrophoresis method. Food Chem [Internet]. 2019;274(March 2018):16–9. Available from: https://doi.org/10.1016/j.foodchem.2018.08.111

10 Karim AA, Bhat R. Fish gelatin: properties, challenges, and prospects as an alternative to mammalian gelatins. Food Hydrocoll [Internet]. 2009;23(3):563–76. Available from: http://dx.doi.org/10.1016/j.foodhyd.2008.07.002

11 Boran G, Regenstein JM. Fish gelatin [Internet]. 1st ed. Vol. 60, Advances in Food and Nutrition Research. Elsevier Inc.; 2010. 119–143 p. Available from: http://dx.doi.org/10.1016/S1043-4526(10)60005-8

12 Haug IJ, Draget KI. Gelatin. Handbook of Food Proteins. 2011. 92–115 p.

13 He H, Ye J, Zhang X, Huang Y, Li X, Xiao M. κ-Carrageenan/locust bean gum as hard capsule gelling agents. Carbohydr Polym [Internet]. 2017;175:417–24. Available from: http://dx.doi.org/10.1016/j.carbpol.2017.07.049

14 Reich G. Formulation and physical properties of soft capsules. Pharmaceutical Capsules. 2004. 201–212 p.

15 Singh S, Rao K., Venugopal K, Manikandan R. Alteration in dissolution characteristics of gelatin-containing formulations: A review of the problem, test methods, and solutions. Pharm Technol. 2002;26:36–58.

16 <711> Disolution. The United States Pharmacopoeia and National Formulary (USP 42, NF-37). Rockville: The United States Pharmacopoeia Convention; 2019.

17 Nazzal S, Wang Y. Characterization of soft gelatin capsules by thermal analysis. Int J Pharm. 2001;230(1–2):35–45.

18 Harris P, Normand V, Norton IT. Gelatin. In: Encyclopedia of Food Sciences and Nutrition. Second Edi. Academic Press; 2003. p. 2865–71.

19 Hanani ZAN. Gelatin. Encycl Food Heal. 2016;191–5.

20 Gomez-Guillen MC, Gimenez B, Lopez-Caballero ME, Montero MP. Functional and bioactive properties of collagen and gelatin from alternative sources: A review. Food Hydrocoll [Internet]. 2011;25(8):1813–27. Available from: http://dx.doi.org/10.1016/j.foodhyd.2011.02.007

21 de Wolf FA. Collagen and gelatin. In: Progress in Biotechnology. Elsevier Science; 2003. p. 133–218.

22 Brox W, Zande H y, Meinzer A. Fabricación de cápsulas de gelatina blanda [Internet]. 2001. p. 16. Available from: http://www.espatentes.com/pdf/2152281_t3.pdf

23 Shimokawa Y, Hayakawa E, Takahashi K, Okai K, Hattori Y, Otsuka M. Pharmaceutical formulation analysis of gelatin-based soft capsule film sheets using near-infrared spectroscopy. J Drug Deliv Sci Technol [Internet]. 2018;48(September):174–82. Available from: https://doi.org/10.1016/j.jddst.2018.09.012

24 Deshmukh K, Basheer Ahamed M, Deshmukh RR, Khadheer Pasha SK, Bhagat PR, Chidambaram K. Biopolymer Composites With High Dielectric Performance : Interface Engineering [Internet]. Biopolymer Composites in Electronics. Elsevier Inc.; 2017. 27–128 p. Available from: http://dx.doi.org/10.1016/B978-0-12-809261-3/00003-6

25 Oishi S, Kimura S ichiro, Noguchi S, Kondo M, Kondo Y, Shimokawa Y, et al. New scale-down methodology from commercial to lab scale to optimize plant-derived soft gel capsule formulations on a commercial scale. Int J Pharm [Internet]. 2018;535(1–2):371–8. Available from: https://doi.org/10.1016/j.ijpharm.2017.11.029

26 Winston PE, Miskiel FJ, Valli RC. Composition and process for gelatin-free soft capsules. Estados Unidos; US005342626A, 1994. p. 1–5.

27 Gennadios A. Non-gelatin substitutes for oral delivery capsues, their composition and process of manufacture. Canada; CA2341024C, 2000. p. 22.

28 Gennadios A. Gum acacia substituted soft gelatin capsules. Estados Unidos; US006193999B1, 2001. p. 1–6.

29 Tanner K, Getz J, Burnett S, Youngblood E, Draper P. Film forming compositions modified starches and iota-carrageenan and methos for manufacturing soft capsules using same. WO01/3677 A1, 2001. p. 52.

30 Gilleland GM, Turner JL, Patton PA, Harrison MD. Modified starch as a replacement for gelatin in soft gel films and capsules. Estados Unidos; US006375981B1, 2002. p. 9.

31 Archibald DA, Gennadios A, Fonkwe LG. Non-gelatin capsule shell formulation comprising iota-carrageenan and kappa-carrageenan. Australia; AU2003237365B2, 2003. p. 31.

32 Sewall C, Riley P, Blakemore T. Homogeneous, thermoreversible gel film containing kappa-2 carrageenan and soft capsules made therefrom. US 20050014852A1, 2005. p. 15.

33 Muller R, Innerebner F. Soft capsule based on starch and a method and device for the production thereof. Biotechnology Progress. US009339474B2, 2016. p. 6.

34 Schmidt R, Clark M, Salinas F, Madsen D, Chan J. Nutrition supplement and soft gelatin capsule dellivery system. Estados Unidos; US 20060292217A1, 2006. p. 7.

35 Garavani A, Marchiorri M, Di Martino A, Echanagorria A. Pharmaceutical Formulation for Thyroid Hormones. Estados Unidos; US 007723390B2, 2012. p. 9.

36 Sharna S, Prasad M, Narayana V, Rajan A, Sharma M, Singh S, et al. Dosage form providing an ibuprofen-containing liquid fill. India; WO 2009/069139 Al, 2009.

37 Xie X, Ko J. Probiotic soft gel composition. Canada; CA 2816538, 2017. p. 17.

38 Soldati F, Ambrosetti-Guidici L. Multi-vitamin and mineral supplement for pregnant women. Estados Unidos; US 2004O213857A1, 2004. p. 7.

39 Gardella L, Kesler H. Gelatin-encapsulated digoxin solutions and method of preparing the same. Estados Unidos; US 4002718, 1977. p. 7.

40 Bhaktavatsala C, Kumar P, Ravishankar H. Soft-gelatin capsule comprising s-adenosylmethionine and a method for producing the same. India; US006759395 B2, 2004. p. 9.

41 Shi J, Zhao C, Pan W, Feng Y. Compositions containing coenzyme Q-10 and Dihydrolipoic acid. China; US008642030B2, 2014. p. 12.

42 Liu Z, Toops D, Fatmi A. Stable solutions of orlistat for pharmaceutical dosage forms. Systems and methods for robotic gutter cleaning along an axis of rotation. Estados Unidos; US008309107B2, 2012. p. 16.

43 Borkan L. Stable soft capsule dosage form for acetylsalicylic acid. Estados Unidos; US008287904B2, 2012. p. 5.

44 Lohner M, Posselt K, Vogtle-Junkert U, Wagener H. Agents for the treatment of severe pain and preparation of said agents. Estados Unidos; US005173304A, 1992. p. 14.

45 Madhavi D, Kagan D. Bioavailable carotenoid-cyclodextrin formulations for soft-gels and other encapsulation systems. Estados Unidos; US007446101B1, 2008. p. 11.

46 Maciejewski B, Arumughan V, Larsson A, Sznitowska M. Prototype gastro-resistant soft gelatin films and capsules-imaging and performance in vitro. Materials (Basel). 2020;13(7).

47 Durig T, Zong Y. Stable Shellac enteric coating formulation for nutraceutical and pharmaceutical dosage forms. United States; US 2011/0002986A1, 2011. p. 8.

48 Yang H, Ma H, Sestrick M. Enteric film coating compositions, method of coating, and coated forms. United States; US 20170367985A1, 2017. p. 9.

49 Venkateswara Rao P, Khadgapathi P. An improve pharmaceutical composition and process for its preparation. United States; WO2001024780A2, 2001. p. 21.

50 Hassan E, Fatmi A, Chidambaram N. Enteric composition for the manufacture of soft capsule wall. United States; WO2004030658A1, 2004. p. 26.

51 Vertommen J, Martina MS. Enteric coating for soft capsule. United States; WO 2014/140991 A1, 2014. p. 24.

52 Hu Y, Piest M, Fang Q, van Duijnhoven H. All natural enteric soft capsules comprising active ingredients. United States; WO 2015/200149 A1, 2015. p. 97.

53 Chidambaram N, Fatmi A. Enteric soft capsule comprising valproic acid. Canada; CA2625554A1, 2006. p. 26.

54 Masuda K, Nishimura N, Hayano A, Shimokawa Y, Kato K. Method of manufacturing enteric seamless soft capsule. United States; US009820947B2, 2017. p. 5.

55 Podili K, Chowdary V. Enteric soft gelatin capsule containing esomeprazole and method of preparation. India; US 2007/0196463 A1, 2007. p. 9.