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SOFT GELATIN CAPSULE IN PHARMACEUTICAL DOSAGE FORMS: AN OVERVIEW

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ABSTRACT

Soft gelatin capsules are solid, single-dose dosage forms that typically contain liquids and have a gelatin shell. After tablets, soft gelatin capsules (SGCs) are the most used pharmacological type. In a liquid or semisolid fill that is encased in a gelatin shell, the active substances, active pharmaceutical ingredients (APIs), or nutrients are dissolved, distributed, or suspended. The goal of the current study was to evaluate the feasibility of applying a gastric-resistant coating on soft gelatin capsules using the spouted bed method. Disintegration tests, traction deformation testing, image analysis, and the assessment of the coating mass distribution and shape factor variation during the coating process were used to gauge the product quality. The tests were conducted in a spouted bed with a conical base angle of 408, and a column diameter of 200 mm. M0 ¼ 300 g had the highest coating efficiency ratings. As the Ws/Wg ratio increased, coating efficiency tended to rise as well. According to disintegration tests, a coating mass of 3.86 mg/cm2 produced the gastric-resistant effect. Throughout the coating process, the form factor increases. The initial distribution was generally maintained by the coating mass distribution of the capsule.

KEYWORDS: Soft Gelatin Capsules (SGCs); Gelatin; Soft-gel capsules; Enteric coating; Capsules; Coating efficiency;

INTRODUCTION

Pharmaceutical dosage forms that produce a local or systemic effect in the gastrointestinal tract after being administered to the patient are known as oral dosage forms. These come in liquid or solid forms, with the latter further subdivided into granules, pills, capsules, and powders.[1,2]

Although they can also be given through the vagina or the rectum, capsules are single, solid dosage forms meant to be taken orally. Within a tiny hard or soft shell, usually composed of gelatin, capsules can contain one or more active pharmaceutical ingredients (APIs) together with excipients, which are materials needed to produce the API [1]. Following administration, the therapeutic ingredients inside the capsule are released as the gelatin dissolves in the bodily fluids.[1,2]

Soft gelatin capsules are typically made, filled, and sealed all at once when containing liquids. A cylindrical body and cap are used in the production of hard gelatin capsules. Following the manufacture of empty capsules, the filling is often composed of powders, granules, or pellets, though it can also include liquids or semi-solids.[1]

Compared to tablets or hard gelatin capsules, soft capsules have the advantage of allowing for a high degree of repeatability and homogeneity in formulation, as well as simplifying the filling process due to the API being in solution or suspension in a liquid vehicle.[1,3]

Another benefit of encapsulating liquid in a soft gel capsule is that the API releases quickly, perhaps increasing bioavailability and achieving therapeutic blood levels more quickly. It is feasible to enhance the capsule contents' dispersion, disintegration, and release by selecting the right vehicle.[1,3] Lipid-based drug delivery systems in soft gel capsules could be developed for medications with poor water solubility, or medications classified as class II and IV on the Biopharmaceutical Classification System (BCS) scale. It has been shown that these systems can keep the medication soluble until it is absorbed. Additionally, intestinal permeability and bioavailability of lipophilic medicines with limited bioavailability have been shown to be improved by self-micro emulsifying drug delivery systems.[1,4]

By creating a hermetic seal, the gelatin film that forms the capsule serves as a barrier to prevent the API from oxidizing, which is a feature of this dosage form[1,3]. The longer and more costly manufacturing methods compared to other dosage forms are the main cause of soft gel capsules' drawbacks. Because production and filling equipment is so specialized, pharmaceutical businesses frequently hire outside parties to handle these tasks. Production time, controls, complexity, and logistics all go up as a result. Lastly, there is a chance that some of the capsule's ingredients and the formulation won't work together. These can change the formulation's composition and stability by migrating from the capsule to the contained liquid or the other way around.[1,3,5]

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).[1,4]

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

ADVANTAGES AND DISADVANTAGES

When compared to conventional oral solid dosage forms, SGCs have a number of benefits, and their use as a dosage form is growing for a number of reasons, including

(1) Consumer Preference: SGCs dosage forms were devised to mask the unpleasant taste and odour of medications. Compared to tablets, SGCs are more comfortable to swallow when taken with water because the soft gelatin capsule is self-lubricating.[3,6,8] Because SGCs can be readily manufactured in a variety of sizes, shapes, and colours (Figure 1) and with a variety of drug delivery systems, such as chewable soft gels, they appear more enticing and pleasurable to consumers as well as soft gels that melt.[6,9]

(2) Technical Benefits: SGCs offer excellent homogeneity and dose precision as well as more stable products and uniform manufacturing standards. With more precise compounding, blending, and dispensing of liquid fill ingredients, an API can be delivered with a better degree of accuracy and improved consistency across various manufacturing batches. Because the entire encapsulation process may be carried out in an inert environment to shield medications from oxidation and degradation, SGC products often have superior stability. For medications that are susceptible to oxidative and hydrolytic breakdown, this is particularly crucial.[3,6,8]

(3) Safety Considerations: The fill material is shielded from air and environmental contaminants by the gelatin shell's tight sealing. Both visible and ultraviolet (UV) light can be blocked by the shell's formulation. Additionally, SGC formulation improves operator safety and helps prevent contamination from dust handling.[6,8]

(4) Benefits of Bioavailability: By increasing solubility and boosting absorption in the GIT, SGCs can raise the bioavailability of medications that are poorly soluble.[6,10,11] Water-insoluble medications are made into SGCs with lipophilic vehicles as part of the fill material, which significantly improves the drugs' absorption in the GIT.[6,12]

COMPOSITION

Gelatin, which is the most abundant component in soft capsule shells, is derived naturally from animal collagen (skin, tendons, bones, and cartilage) by acid and alkaline hydrolysis. In this manner, two varieties of gelatin-type A, which is acidic, and type B, which is alkaline-are produced[1,13,14]. However, recent research has looked into the extraction of gelatin from various animal sources, primarily fish skin (Table 2). In these situations, the amino acid composition may change without significantly affecting the finished product or the gelatin manufacturing procedure itself.[1,15,16]

Gelatin's mechanical, biological, and physicochemical qualities are the primary reasons it is utilized to make capsules. Gelatin has extremely strong rheological qualities, is non-toxic, highly soluble in biological fluids, and is a great film-former with a good strength-to-flexibility ratio[1,17]. Nevertheless, certain fill formulation ingredients, such the drug's aldehydes, may react with the gelatin shell. It is feasible to utilize succinylated pigskin gelatin with a Bloom value and viscosity between 190 and 210 g and 3.3 and 4.1 mPa.s. to avoid the chemical interaction that is perceived as a shell cross-linking.[1,18]

Table 2: Comparison of the amino acid content (residues/1000 total amino acid residues) of gelatins derived from pig and fish (adapted from.[1,15]

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

Gelatin cross-linking may be aided by chemical molecules other than aldehydes. Imines, ketones, saccharides, calcium carbonate, hydrogen peroxide, sulfonic acids, carbodiimides, and benzene are a few functional groups found in drug compounds linked to cross-linking. Gelatin cross-linking may also be accelerated by elements like temperature, humidity, UV light, and contaminants in the encapsulated fill material.[1,4,19] The drug dissolving rate may be slowed down by the gelatin cross-linking, but it can be accelerated by employing enzymes like pepsin and pancreatin, which help break down the cross-linked gelatin shells. The USP General Chapter dissolve specifies the appropriate enzyme concentrations in the dissolve medium. The kind and concentration of the enzymes are dependent on pH; for instance, when the pH is higher than 6.8, pancreatin is utilized at a concentration/activity of 2000 units/1000 mL. However, papain works best in a medium that has a pH of at least 4 but less than 6.8. When the medium pH is less than 4, pepsin is employed at a concentration/activity of ≤ 750,000 units/1000 mL, while the typical concentration/activity is < 550,000 units/1000 mL.[1,4]

In addition to gelatin, various ingredients like plasticizers, preservatives, opacifiers, colorants, and moisturizers are added to help the capsule form. To make the film more flexible and less rigid, plasticizing chemicals are applied. Soft gelatin capsules have a higher percentage of plasticizers than hard gelatin capsules. The primary distinction between soft and hard gel capsules is this. Among the most widely used plasticizers are sorbitol, propylene glycol, and glycerin, with glycerin being the most often used.[1,3,13]

The glass transition temperature (Tg) of anhydrous gelatin is higher than 100°C (Tg >100°C), which is linked to the development of a brittle and rigid film. By separating the gelatin's protein chains, plasticizing chemicals increase the protein's mobility and lower its Tg value by reducing protein-protein interactions. Because plasticizing chemicals are hygroscopic, they make it easier for moisture to be absorbed while simultaneously decreasing contacts between neighboring polymeric chains.[1,17,18]

Direct interactions with the gelatin chains cause the glycerin plasticization mechanism, which enables the creation of a stable, thermoreversible gel network. The term "direct plasticization mechanism" refers to this process. The moisturizing impact and hygroscopicity are linked to the indirect plasticizer process. One example of an ideal indirect plasticizer is sorbitol.[1,18]

In addition to serving purely aesthetic purposes by facilitating identification, coloring compounds may also have a psychological impact that increases patient adherence to the product. Water-soluble dyes, lacquers, or inorganic pigments can be used, but only at amounts approved by the appropriate regulatory bodies.[1] When used with opacifying agents, these can increase the stability of the product. The latter prolongs the stability of photosensitive molecules by blocking light from entering the capsule. The most widely used opacifying agent is titanium dioxide, although other options include calcium carbonate and iron oxides and dioxide.[1,3,13]

If a preservative is used in the formulation, it must be introduced when the gelatin solution is being prepared in order to prevent microbial contamination. However, efforts to minimize contamination during the manufacturing process, such as heating the gelatin solutions to a temperature above 50°C, have resulted in a decrease in the addition of preservatives to soft gelatin capsule.[1,3,13]

SHELL AND FILL FORMULATION OF SGCS

The potential interaction between the fill ingredient and the gelatin shell must be taken into account while creating an SGC formulation. These interactions could occur throughout the product's production process, drying process, or shelf life. Physical interactions, such as fill material migrating into or through the shell and vice versa, or chemical reactions between the fill components and their oxidation or degradation products and the shell are examples of interaction.[6,20,21]. Numerous factors influence how much of these interactions occur. The quantity of each ingredient in the shell and fill formulation is one of these. APIs or excipients with reactive functional groups, such carbonyl, are linked to one of the most well-known issues with shell formulation, which can cause gelatin cross-linking.[6,22,23,24]

We'll talk about cross-linking in more depth later.

Temperature, viscosity, and particle size (in the case of suspension formulation) are all significant fill material aspects to take into account throughout the filling process. For displacement pumps to have precise dose and not exhibit stringing, the fill material needs to be sufficiently viscous. For optimal sealing, the temperature range is typically 37 to 40 ◦C. A vehicle for fill formulation development should fulfill the following requirements in addition to these operational ones:

(1) It should be able to fully dissolve API and stop excipients and API from precipitating during production and the duration of the shelf life.
(2) It ought to be compatible with the formulation of the gelatin shell and capable of stabilizing fill material.
(3) The developed fill formulation should maximize the API's chemical and physical stability.

It's interesting to note that the need for novel chemical entities and biopharmaceutical formulations has caused the fill content of SGCs to change from lipophilic to hydrophilic solutions/suspensions and complicated self-emulsifying systems. SGCs are often made up of lipophilic oil fillers like castor or soy bean oil, lipophilic APIs such vitamins A, D,

E, and K, and herbals that have no reaction with the shell composition[6,25,26,27]. A variety of materials that can be inserted into SGCs are depicted in Figure 1.

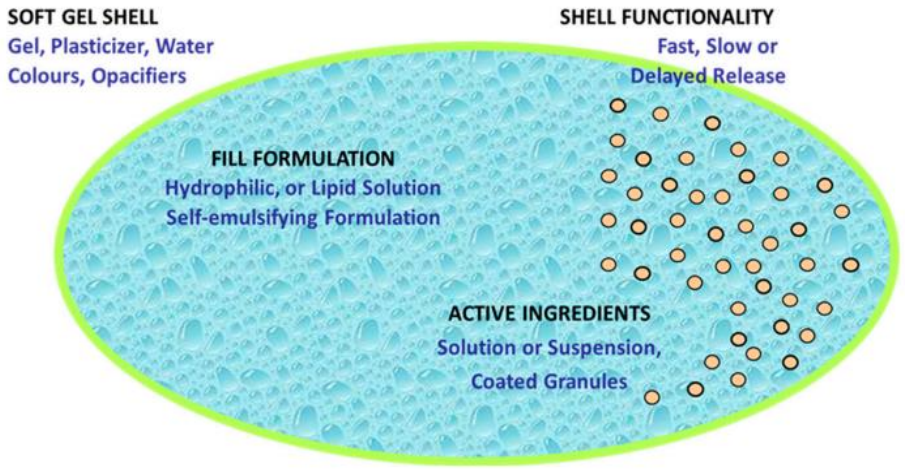

Figure 1: Schematic representation of the soft gel functional dosage form.

Polyethylene glycols (PEGs), including low molecular weight PEGs and closely related substances like methoxy PEGs, propylene carbonate, propylene glycol, glycerin, ethyl alcohol, and diethylene glycol monoethyl ether, are the foundation of hydrophilic SGC fill formulations.[6,25,28,29] Water and PEGs, particularly those with low molecular weights like 200 and 300, should not make up more than 10% of the fill content because they also function as plasticizers. PEG-based formulations are utilized to increase bioavailability, disseminate high-potency and low-dose medications, and improve solubility.

New formulation techniques known as self-emulsifying lipophilic systems include a non-ionic surfactant or surfactants, like lecithin or Tween, and most likely a co-solvent or co-solvents.[6,25,30,31] These systems are typically created to improve the bioavailability of medications that aren't very soluble. Because fill material spontaneously forms tiny droplets with an average size of less than 100 nm upon release in GI fluids, this type of formulation improves a drug's solubility and absorption.[6,32,33]

In order to prevent the precipitation of dispersed components and maintain the homogeneity of the fill formulation throughout the encapsulation process, another method in the fill formulation is the use of suspending, thickening, or viscosifying agents.[6,31] By reducing the migration of water from the shell into the fill and the diffusion of water-soluble compounds from the fill into the shell, suspending agents' high viscosity and hydrophobic qualities contribute to the stability of SGCs. Higher molecular weight PEGs like PEG 6000, cellulose polymers, and blends of mono-, di-, and tri-glycerides/mono- and di-fatty acid esters of polyethylene glycols are typically employed as suspending agents in PEG-based fill formulations. It is important to note that the pharmaceutical's and the fill materials' physical and chemical characteristics greatly influence how quickly SGCs dissolve. Figure 5 displays the solubility characteristics of SGCs for a medicine classified as a Biopharmaceutics Classification System (BCS) II that was made with varying proportions of mono- and di-glyceride mixes (MCM) and medium-chain triglycerides (MCT). The information shown in this picture supports the idea that fill properties have an impact on how well SGCs dissolve poorly soluble medications.

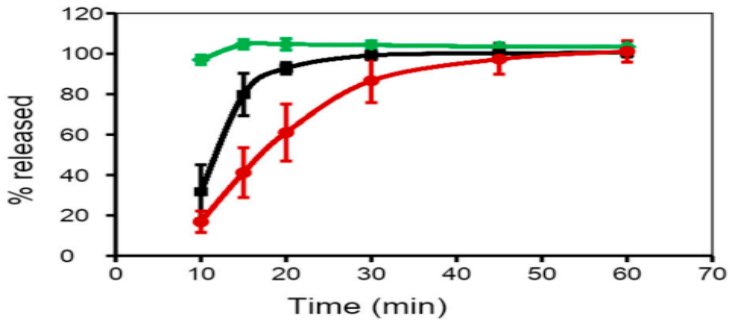

Figure 2: (■) MCM to MCT (50:50), (■)MCM to MCT (75:25), and (•)MCM to MCT (100:0) are the dissolution profiles of loratadine drug products made with varying concentrations (in percentage) of the fill materials using the USP dissolution apparatus 1 (basket) at 75 rpm in 0.1 N hydrochloric acid (HCl) in purified water. The average ± standard deviation is represented by each data point (n = 6). Reproduced from Dissolution Technologies (2006) with permission.[6,34]

Gelatin, plasticizer(s), water, and other small additions such flavorings, colorants, opacifiers, sweeteners, and possibly sugar, as well as preservatives and, in rare instances, active substances, make up the shell formulation for SGCs.[6,25] A liquefied gelatin formulation with a pourable viscosity at 60 to 70 °C is made using water as a solvent. Pigments like titanium dioxide and iron oxides can be included in the shell formulation to provide protection for light-sensitive chemicals or to create a more aesthetically pleasing appearance for consumers.[6,35]

A plasticizer must be used to give soft gelatin capsule shells their flexibility.[6,36,37] By counteracting the stresses brought on by the capsule shell's shrinkage, the plasticizer gives the shell mechanical stability both during and after drying. The glass transition temperature of the gelatin blend should be lowered by a plasticizer. The kind and concentration of plasticizer, like other shell components, is determined by the size and shape of the capsule, the fill material formulation, and the conditions of usage and storage. Potential interactions between the plasticizer and the fill material should be anticipated in order to prevent difficulties with the product, including dissolution and cross-linking.[6,38] Between 15% and 30% w/w of a shell formulation's total wet mass is made up of plasticizers during encapsulation.[6,25] The properties of the finished medicinal product are influenced by the kind and concentration of plasticizers used, and a broad variety of plasticizers are available for use in the formulation of SGC shells. The most common plasticizers for SGCs are sorbitol, glycerol, and sorbitol/sorbitan solutions.[6,8,39] A stable, thermally reversible gelatin is formed by glycerol, a very effective plasticizer with low volatility.[6,8] Soft capsules are primarily stored under ambient conditions using this method. Combinations of glycerol and sorbitol work well for more stiff capsules that are utilized in warm, humid conditions as well as capsules that include fill material that is sensitive to oxygen. Sorbitol functions as a moisturizing agent and an indirect plasticizer, as opposed to glycerol, which is a direct plasticizer. Furthermore, low molecular weight polyethylene glycol, such PEG 200, and propylene glycol are commonly employed as plasticizers. Compared to glycerol and sorbitol, propylene glycol is better at plasticizing, but it also dissolves gelatin, which limits its use.[6,8,39] The gelatin shell's composition and the state of age will determine how quickly SGCs burst or disintegrate.

The formulation of SGCs may provide difficulties depending on the composition of the fill and shell. Fill compositions including hydrophilic components, for instance, can occasionally be more difficult since they may diffuse to the shell throughout the product's manufacture, drying, and shelf life.[6,8,21,25,37,40,41] The composition of shell and fill materials

should be designed to limit migration in order to address migration difficulties and product stability. This problem has been addressed in a number of ways, such as (1) employing higher-Bloom strength to lower the initial water content in the capsule shell, (2) using blends of glycerol and sorbitol or sorbitol and sorbitan as plasticizers rather than glycerol alone, and (3) coating drug particles to stop formulations from discoloring because of the browning reaction between the active ingredients.[6,8] For instance, material migration has been documented in microemulsion fill formulations containing surfactants and hydrophilic co-solvents such ethanol and propylene glycol.[6,20,42] The softening and volatilizing qualities of propylene glycol and ethanol, respectively, can help material migrate from fill to shell or vice versa.[6,43] Propylene glycol can be utilized as a plasticizer component in the shell to address problems produced by it. Because propylene glycol has a lower viscosity than glycerol, this approach has the advantage of using less water in the formulation. Ethanol volatilization can be avoided by (1) employing solvent-tight packaging materials, like an aluminum blister, and (2) substituting higher polyols, like sorbitol or xylitol, for glycerol. Sometimes the only solution to this problem is to substitute ethanol with a different co-solvent, like dimethyl isosorbide, that does not exhibit any diffusion into the shel.[6,43]

MANUFACTURE OF SGCS

This section provides a quick summary of the industrial SGC filling process before going into shell and fill formulation of SGCs. These actions are crucial because they have the potential to affect how SGCs dissolve. For further information about how SGCs are made, readers should consult Gullapalli[6,25]. The following are the primary steps in the SGC production process:

(1) Depending on the gel formulation, raw ingredients like raw gelatin, plasticizers, and purified water are combined under vacuum at a temperature of roughly 70 °C (Figure 3C,D). Filtration is used to remove any gel that hasn't dissolved.

(2) Under the proper vacuum and nitrogen blanket conditions, all of the components needed for a particular formulation are introduced and combined. Samples are taken from various parts of the vessel during the mixing process to control viscosity and guarantee mixture uniformity. A drug product's commercial stage determines the size of the vessel; for instance, gelatin melting tanks might be small (e.g., 100 L) or large (e.g., 1200 L), and gelatin service tanks can be 50 L (lab scale) or 300 L (large scale).[6] In order to reduce the particle size to less than 180 µm for the encapsulation process, these tanks are linked to a mill.

(3) The receiver containers hold the mixture (Figure 3F,G).

(4) The soft gelatin encapsulation process will begin once the gel and fill material are prepared (Figure 3H). Through heated tubing and a nitrogen environment, the gel and fill material are connected to the encapsulating machine. SGCs go through a tumbler for the first drying step after encapsulation. Depending on the composition and size of the capsule, they are then kept in a drying tunnel for a few days to continue drying. At the conclusion of this procedure, the moisture content and hardness of the capsules are measured after the majority of the moisture has been eliminated.

(5) Capsules are sorted and graded once they reach the appropriate amount of dryness (Figure 3I,J); grading is particularly crucial and significant for blister formation.

(6) The capsules are polished for a predetermined amount of time using a cloth soaked in isopropanol, and again for the same amount of time using a dry cloth. Capsules are finally printed and packaged (Figure 3).

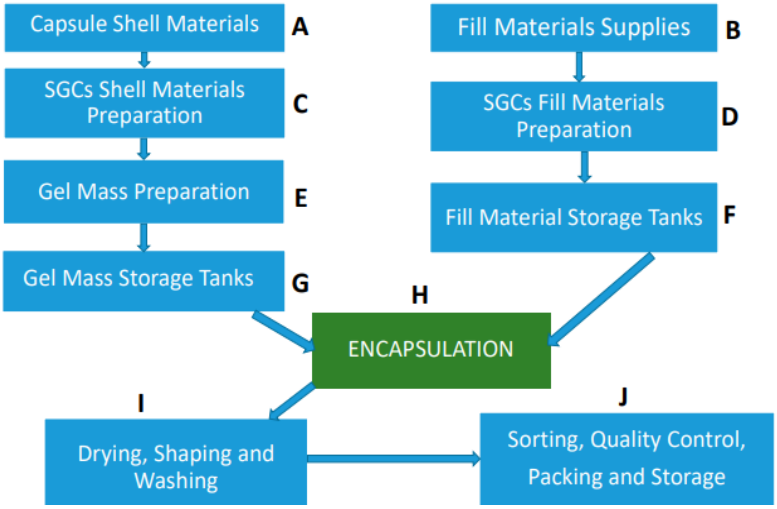

Figure 3: Schematic representation of (A–J) different steps in the manufacturing of SGCs.

SOFT GEL CAPSULES CHARACTERIZATION:

Some of the tests listed below are used to assess the performance and features of soft gelatin capsules:

- Thermal behavior can be determined using differential scanning calorimetry. Parameters such as glass transition temperature, melting temperature, and melting enthalpy are used to assess the effects of various agents, manufacturing procedures, and storage conditions on the properties and functionality of soft gel capsules.[1,18,44]
- The balance between the water content of the fill material and the shell moisture is studied using the critical swelling ratio.[1,44]
- The Bloom test, previously described is used to measure gel strength.[1,16]
- Near-infrared spectroscopy is used to identify components, identify molecular interactions between various functional groups that contribute to the creation of gelatin films, and investigate the impact of substances that alter the crosslinking of gelatin.[1,18,45]
- To examine the impact of moisture content on shell mechanical properties, the dynamic vapor sorption technique analyzes the water absorption of gelatin sheets and desorption properties[1,45] The hardness test, which uses a durometer, is used to determine the firmness or hardness of capsules. Low flexibility or high softening of capsules is indicated by hardness values that are more or lower than those stated by the manufacture.[1,18,44]
- The rupture test is carried out in capsules that contain liquid or semi-solid formulations. The test, which uses apparatus 2 rotating at 50 RPM in 500 mL for 15 minutes, is explained in the USP General Chapter Dissolution. When the examined soft gelatin capsules burst within 15 minutes, the rupture test, which is an alternative to the disintegration test, satisfies the requirements. Twelve more units need to be tested if one or two capsules burst in more than fifteen minutes but less than thirty. Out of the eighteen units examined, only two rupture in more than fifteen minutes but less than thirty.[1,4]

MATERIALS AND METHODS

1. Materials

Capsules and coating composition

Lecithin oil-containing soft gelatin capsules, generously provided by RP-Scherer of Brazil Inc., served as a platform for the application of the coating. Gelatin accounted for 60.57% of the capsule shell's weight, followed by glycerin (28.0%), water (11.18%), and preservatives (0.25%). There were two sizes utilized, 5 and 10, both of which had an

oval shape. The capsules' primary physical attributes are shown in Table 3, where mpo stands for mean mass, dpv for mean diameter, ρp for density, Se for specific surface, and ⌀ for shape factor. Oliveira has explained the process employed in these determinations.[46,47]

Twenty percent triethyl-citrate (related to the concentration of the polymer, as plastifying ingredient), 0.25% carboxymethyl cellulose, 4.85% talc, 15.0% Eudragit L-30-D-55 (a gastric-resistant polymer – dry basis), and distilled water made up the coating formulation. The physical characteristics of this mixture are displayed in Table 4, where the density, viscosity, and solid content are denoted by the letters rf, mf, and Cs, respectively.

Spouted bed

A 400 mm cylindrical column with an internal diameter of 200 mm is attached to conical bases with an input orifice diameter of 52 mm and an included angle of 408 or 608 as part of the apparatus. Stainless steel is used to make every component. An acquisition board (PCL-711B; Advantech) installed in a personal computer running the LABTECH software was connected to a temperature reading board (PCLD 789D; Advantech) and two pressure transducers (Model XL dp, Dresser Industries Inc.) as part of a data acquisition system used to monitor the experiments. The experimental rig's schematic diagram is shown in Fig. 1.

TABLE 3: MAIN PHYSICAL CHARACTERISTICS OF THE CAPSULES

Size	$m_{po\ (mg)}$	d_{pv} (mm)	ρp (g/ml)	S_e (cm^2/g)	⌀
5	389	8.87	1.07	6.62	0.96
10	664	10.55	1.08	5.44	0.97

TABLE 4: PHYSICAL PROPERTIES OF THE COATING SUSPENSION USED.

$\rho_{t\ (g/ml)}$	μ_f (mPa)	C_s (g/g)
1.04	4.4	0.23

2. EXPERIMENTAL METHODS

1. fluid-dynamic characterization of the equipment

A fluid-dynamic characterization of the spouted bed was performed to ascertain the global parameters of the spouted bed, including the minimum spouting flow rate, Qms, the pressure drop of stable spouting, DPs, and the maximum pressure drop, DPm. Measurements of pressure decreases in the soft gelatin capsule bed as a function of the injected gas flow rate were used for this characterization.[46,48]

2. Coating Operation

A load of soft gelatin capsules was placed onto the bed to begin the coating process. Air was injected at the bed's base to encourage the spouting of this load. The air was heated to the appropriate temperature as soon as spouting was established. Following thermal equilibrium, the atomizing air and coating suspension were fed at a predetermined flow rate and room temperature. Every fifteen minutes, samples of the coated product were taken out using a little ladle that was inserted into the spout zone. After being weighed, the samples were kept for use in later studies. Throughout every experimental run, the spouting gas's input temperature was kept at 55 8C. Forty-five minutes was the entire coating time. The following formula was used to estimate the experimental data of the coating efficiency, h.[46,49,50]

$$\eta = \frac{n_0 \cdot (m_p - m_{p0})}{W_s \cdot C_s \cdot \theta} \qquad (1)$$

In Eq. (1), n0 is the initial number of the soft gelatin capsules in the bed, mp0 is the initial mean mass of the capsules, mp is the mean capsule mass as a function of processing time, u, and Ws and Cs are, the mass feed flow rate and the solid content of the coating formulation, respectively.

3. Gas temperature and humidity and variation of the capsules temperature during the coating process

A digital thermohygrometer (Traceable Digital Hygrometer/Thermometer/- Dew Point instrument, Control Co., USA) was used to measure the outlet gas temperature and humidity at the start of the process and during the coating operation. In several tests, the temperature of the capsule was recorded while the coating process was underway. At five-minute intervals throughout the coating process, capsule samples were taken out of the spouted bed and promptly placed in an insulated bottle fitted with three thermocouples that were linked to the data collection device. The temperature of the capsule was recorded for one minute, and the mean value of this measurement was used to determine the temperature of the capsule.

4. Disintegration tests

To confirm the product's gastric-resistant qualities, disintegration tests were conducted. The capsules were submerged in 0.1 M HCl at 37-8C in a disintegration apparatus, and the apparatus was operated for 60 minutes. By the end of the test, the capsules were expected to remain intact and not become tumid if they were gastric-resistant. After that, the capsules were taken out and submerged in buffer that had a pH of 6.8, which is the enteric pH, at 37-8C. The capsules ought to dissolve entirely in less than forty-five minutes under these circumstances.[46] Tests were conducted on a number of capsules that represented various coating times and, thus, coating thickness

5. capsule's mass, diameter and shape factor distributions during the coating operation

The following measurements were made of the mass, diameter, and shape factor distributions during the coating operation. At regular intervals, 50 capsules were taken out of the bed as representative samples. The coated and uncoated capsules were weighed separately and measured in two distinctive dimensions (larger and smaller axis) using a micrometer. The frequency distributions of the capsules' mass, diameter, and form factor may be computed using this data.

The following formulas were used to determine the capsules' diameter and shape factor.

$$d_{pv} = \left(\frac{6 \cdot V_p}{\pi}\right) \qquad (2)$$

and

$$\phi = \left(\frac{\pi \cdot d_{pv}^2}{S_p}\right) = \left(\frac{\text{Surface area of the equivalent sphere}}{\text{Surface area of the capsules}}\right) \qquad (3)$$

Vp and Sp, the volume and surface area of the capsule, are used in Eqs. (2) and (3) as the volume and area of a prolate spheroid with the same characteristic axis as the capsules, respectively.

6. Mechanical resistance of the coating

Using a Universal machine (Instron 5500 R), traction versus deformation tests were performed up till the coating fractured in order to assess the mechanical resistance of the coating. Until the capsules split apart, the experiments went on. 50 kgf of cell load was employed. Verifying the change in the mechanical resistance and physical properties of the capsules following coating application was the aim of this investigation. First, a needle attached to a syringe was used to remove the lecithin oil that was inside the coated and uncoated capsules. The empty capsules were then sliced through the center, where the two shells converged. The sliced capsules' two extremities were secured to the Instron machine's claws. The analyses were carried out in triplicate, and the displacement velocity was 0.5 mm/min.

7. Photomicrographs obtained by scanning electronic microscopy (sem)

SEM was used to obtain photomicrographs for the purpose of analyzing the quality of the coated surfaces. First, the previously mentioned method was used to extract the lecithin oil from the capsules. The capsule was then divided into tiny pieces, each measuring around 0.5 cm. This process was used to prevent the microscope from being harmed while the measurements were being taken. These tiny components were placed on a metal support, coated with metallic gold, and then placed under a Zeiss DSM 960 scanning electronic microscope to produce photomicrographs of the outermost layer of the coated and untreated soft gelatin capsules.

9. Variables and operational conditions

The factors that were examined included the included angle of the conical base, g, the initial bed mass, M0, the ratio of the mass feed flow rate of the coating suspension to the mass feed flow rate of spouting gas, Ws / Wg, and the ratio of the feed flow rate of spouting gas to the feed flow rate at minimum spouting, Q/Qms. The variables and operating conditions are displayed in Table 5. A pressure of 1.5 kgf/cm and an atomization air flow rate of 15.0 l/min were maintained.[46]

Table 5: Operating conditions and variables utilized,

Variable	Range	Unit
W_s/W_g	0.0006-0.0022	-
Q/Q_{jm}	1.6-2.6	-
γ	40-60	Degrees
M_0	150-300	g
C_s	0.23	g/g

CONCLUSION

An overview of soft gelatin capsules is given in this article. These dosage forms have a complicated production process, and a number of important factors can impact the quality of the finished product. The disintegration time in relation to the surface and the mass of the coating that is attached section of Mr. Ac's soft gelatin capsule. Throughout the coating process, the form factor increases. The initial distribution was generally maintained by the coating mass distribution of the capsule. The spouted bed is a quick and effective way to coat soft gelatin capsules with enteric coating

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