



A REVIEW: CAPSULE SHELL MATERIAL FROM GELATIN TO NON ANIMAL ORIGIN MATERIAL



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Abstract

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Capsule is most preferable dosage form. Till now gelatin is widely used as capsule shell material for the preparation of the Hard gelatin capsule and soft gelatin capsule , but due to its animal origin and cross linking property other suitable capsule material that meets the dietary and cultural needs of vegetarian patients and also comply with the regulatory requirement of gelatin need to be invented. Hence various non animal origin materials are synthesis such as hydroxyl propyl methyl cellulose, starch, polyvinyl alcohol copolymer, pullulan etc. and evaluate as a capsule shell material.

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INTRODUCTION

The word 'Capsule' derived from the Latin word 'capsula', which means a small box or container. The word occurs in many scientific disciplines, ranging from anatomy, as an enclosing membrane, and in botany, as a descriptive word for fruit, to astrophysics, as a space vehicle.

In pharmacy, capsule word has been used to describe a glass ampule and also as a name of protective cap over the stopper of a bottle of medicine. In more recent times, capsule has been used primarily to describe solid dosage forms, which consist of a container, filled with medicinal substance. They can be divided in main two categories, 'hard capsule' (two piece) and 'soft capsule' (one piece) according to the presence of glycerol or another plasticizer which make it soft and elastic¹.

Advantages of Capsules:

Capsules mask the taste and odor of unpleasant drugs and can be easily administered. They are attractive in appearance and shells are physiologically inert and quickly digested in the gastrointestinal tract. As compared to tablets, capsules are slippery when moist

and hence, easy to swallow with a draught of water, fewer adjuncts are required and economical. They are easy to handle and carry. The shells can be opacified (with titanium dioxide) or colored, to give protection from light.

Disadvantages of Capsules:

The drugs which are hygroscopic absorb water from the capsule shell making it fragile and hence are inappropriate for filling into capsules. The concentrated solutions which require previous dilution are unsuitable for capsules because if administered as such lead to irritation of the stomach.

Capsule manufacturing steps:

Raw Materials for Capsules

The raw materials used in the manufacture of both hard and soft gelatin capsules are similar. Both contain **gelatin, water, colorants** and optional materials such as **process aids and preservatives**.

A. GELATIN CAPSULE

Material used for the gelatin production are Bones, bovine hides and skin (Figure 1). As noted in USP-NF² gelatin is a product

obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue, and bones of animals. The hydrolysis may be catalyzed by the addition of strong acid or base. Gelatin derived from acid-catalyzed hydrolysis are referred to as Type A, and gelatin derived from the base-catalyzed hydrolysis are referred to as Type B. The main difference between gelatins derived from these two processes is that the gelatin derived from the acid-catalyzed process typically exhibits an isoelectric point (pI) of about 7-9.

Whereas the pI of gelatin obtained from the base-catalyzed process is typically 4.7–5.4. The lower pI resulting from the treatment with base is due to the hydrolysis of the amide groups of Glutamine and asparagine, creating glutamic acid and aspartic acid. Because of the manufacturing process used, gelatin molecules exhibit significant polydispersity: The molecular weight of individual molecules typically ranges from 15,000 to 250,000.

The approximate amino acid composition of gelatin(Figure2) is glycine 21%, Proline 12%, hydroxyproline 12%, glutamic acid 10%, alanine 9%, arginine 8%, aspartic acid 6%,

lysine 4%, serine 4%, leucine 3%, valine 2%, phenylalanine 2%, threonine 2%, Isoleucine 1%, hydroxylysine 1%, methionine and histidine <1% and tyrosine <0.5%. These values vary, especially the minor constituents, depending on the source of the raw material and processing technique³.

Bloom strength is a measure of the ability of a given weight of gelatin to set up in water under controlled conditions and is a function of the molecular weight of the gelatin molecules, the concentration of the gelatin in the gel, and the pH of the gel. It is a measure of the resultant gel's resistance to compression and is reported in bloom-grams or simply grams. Bloom strength increases when the gelatin concentration in the gel increases, when the average molecular weight of the gelatin increases, and when the pH of the gel approaches neutrality (from either direction). Bloom strength also can have an effect on the clarity and color of the liquid-filled capsules. Gelatin with bloom strengths ranging from 50 to 300 is available; most gelatins used in the manufacture of liquid-filled capsules have bloom strength of approximately 150–200 for soft gels and 220–280 for hard gels. Gelatin manufacturers commonly blend

different sublots of gelatin to meet bloom requirements².

A schematic presentation of the gelatin manufacturing process appears in the figure. 4.

1. Hard gelatin capsule:

The majority of capsule products is made of hard gelatin capsules. Hard gelatin capsules are made of two shells: the capsule body and a shorter cap. The cap fits tightly over the open end of the capsule body. The basic hard gelatin capsule shells are made from mixtures of gelatin, sugar, and water. They are clear, colorless, and essentially tasteless.

Two-piece capsules have been used for almost a century in the pharmaceutical field, and the gelatin has been adopted as the main material of these capsules due to its excellent characteristic as a gelatinizer. However, gelatin is one of the proteins derived from animals; therefore, it is unstable from a chemical viewpoint and has a risk of TSE.

A perfect hard gelatin capsule should have the following specifications:

- Gel strength: 200–300 Bloom, depending on the gelatin type;
- Viscosity (60°C/6–23 % w/w in water): 44–60 mPa, depending on the gelatin type;
- PH 4.5 -6.5
- Aerobic Plate Count <1000/gram

1.1 Method of production of empty hard gelatin shells:

Some of the major suppliers of empty gelatin capsules are: Eli Lilly and Company, Warner Lambert's Capsugel (formerly Park Davis) and R. P. Scherer Corporation. The metal moulds at room temperature are dipped into a hot gelatin solution, which gels to form a film. This is dried, cut to length, removed from the moulds and the two parts are joined together, these processes are carried out as a continuous process in large machines (Figure 5).

1.2 Size and specification of hard gelatin capsule

For human use, empty capsules ranging in size from 000 the largest to 5 the smallest. Generally, hard gelatin capsule is used to

encapsulate between 65 mg to 1 gram (Figure6).

Note: refer to the [6] reference in the text.

1.3 Shape of Capsules

To prepare capsules easily differentiated from those of other manufacturers, the shape of the capsule end (which is usually round) can be altered. Capsules from Eli Lilly (Pulvules®) have the body shell with a tapered end and the round shaped cap. Capsules from GlaxoSmithKline have both ends highly tapered.

To ensure reliable closing of the filled capsules, capsule shells with locking grooves (or indentations) have been prepared. Examples are Posilok® (Qualicaps, a division of Shionogi & Co., Ltd.), Coni-Snap® (Capsugel, a division of Pfizer, Inc.), and Uni-Lock® (Cardinal Health). The two grooves fit into each other for tight closing and prevent accidental separation (or splitting) of the capsules. Capsules from Capsugel are sold as Snap-Fit®, Coni-Snap®, and DBcaps®. Snap-Fit® has the concentric locking rings on the body and cap which prevent reopening after filling. The Coni-Snap® capsule, which is the improved form of Snap-Fit®, has the rim of the capsule

body which is slightly tapered (Figure 7). The slightly tapered body facilitates joining on high speed machines and prevents the problem of telescoping. Telescoping is sliding of a capsule body (or a capsule cap) over another capsule body (or a capsule cap). The tapered rim makes it more difficult to slide a capsule body over another owing to the smaller diameter. The DBcaps® capsule is different from the Coni-Snap® capsule in that the upper capsule part (cap) covers most of the lower part (body) so that only the rounded edge of the body is visible. The decrease in gripping surface makes it impossible to Hard Gelatin Capsules hold the body and open without crushing it. Thus, the DBcaps® capsule provides increased security of the contents and the integrity of the capsule. Figure 8 illustrates the differences between ordinary capsules, Coni-Snap® capsules, and DBcaps® capsules(Figure8).

Some capsules (Kapseal® from Pfizer, Inc., and Qualicaps® from Shionogi & Co., Ltd.) are made tamper-proof and leak proof. The joint between the two capsule parts are sealed with a gelatin or polymer band. Another approach has been developed to make capsules tamper resistant or tamper

evident. The contact areas of the cap and body are wetted with a mixture of water and ethanol and then thermally bonded at 40–45 °C. Any attempt to separate a sealed capsule will destroy the capsule⁷.

1.4 Types of materials for filling into hard gelatin capsules:

Dry solids (Powders, pellets, granules or tablets), Semisolids (Suspensions or pastes), Liquids (Non-aqueous liquids).

1.5 Effect of Relative humidity and moisture content on shell property:

Gelatin is a hygroscopic material, and the relationships among relative humidity, gelatin moisture content, and hard gelatin capsule properties are shown in Figure 9⁸.

Bond and Lees⁸, Kontny and Mulski⁹ also have studied the relationship between relative humidity and brittleness of hard gelatin capsules. Because certain solvents are known hydrophilic agents, it is particularly important to monitor the mechanical properties of liquid-filled capsules stored under various conditions of temperature and relative humidity.

2. Soft gelatin capsule:

Soft gelatin (also called softgel or soft elastic) capsules consist of one-piece hermetically sealed soft shells. Soft gelatin capsules are prepared by adding a plasticizer, such as glycerin or polyhydric alcohol (*e.g.*, sorbitol), to gelatin. The plasticizer makes gelatin elastic. Soft gelatin capsules come in various shapes such as spherical, elliptical, oblong, and special tube shapes with and without twist off (Figure 11). They can contain non-aqueous liquids, suspensions, pasty materials, or dry powders. They are especially important to contain volatile drug substances or drug materials susceptible to deterioration in the presence of air.

Advantages of soft gel capsules:

Ease of use - easy to swallow, no taste, unit dose delivery, temper proof, versatile and accommodates a wide variety of compounds filled as a semisolid, liquid, gel or paste. Available in wide variety of colors, shapes and sizes. Immediate or delayed drug delivery-can be used to improve bioavailability by delivering drug in solution or other absorption enhancing media.

Disadvantages of soft gel capsules:

Requires special manufacturing equipment, stability concerns with highly water soluble compounds, and compounds susceptible to hydrolysis

A perfect soft capsule gelatin should have the following specifications¹⁰:

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

The main gelatin types and grades used for the manufacture of soft capsules are listed in Table 2 together with their physicochemical specifications. The proper

choice of the gelatin type and grade is related to technological issues, consumer preference and pricing. For pharmaceutical or health and nutrition products, medium bloom limed bone (LB) gelatins, or blends of limed bone and pigskin (LB/PS) or limed bone, pigskin and limed hide gelatin (LB/LH/PS) are commonly used, with a certain preference for LB gelatin in the United States and for blended gelatins in Europe. Low-viscosity, high-bloom gelatins such as a 200 Bloom pigskin (PS) or acid bone (AB)

Gelatin is often used for the encapsulation of hygroscopic formulations and/or water-sensitive drugs, where standard gelatin formulations have to be modified to contain less water and dry faster, thus improving the product stability during capsule manufacturing. Mixtures of low (<100 Bloom) and medium Bloom (>150 Bloom) gelatins have been proposed for the formulation of chewable soft capsules (Overholt, 2001) to achieve the desired mouthfeel and solubility of the shells, a low stickiness for improved machinability and sufficient integrity for stable fill encapsulation. In addition to the

pharmacopoeia grade gelatin types listed in Table 2¹¹.

Note: Refer to ¹⁰ reference in the text.

2.1 For commercial Manufacture of Soft Gelatin Capsule

- **Plate-Process.** A warm sheet of prepared gelatin is laid over the lower plate and the liquid is poured on it. A second sheet of gelatin is carefully put in place and this is followed by the top plate of the mold. The set is placed under the press where pressure is applied to form the capsule which is washed off with a volatile solvent to remove any trace of oil from the exterior¹².
- **Rotary Die Process.** The rotary die machine is a self-contained unit capable of continuously & automatically producing finished capsules from a supply of gelatin mass and filling material which may be any liquid, semi-liquid, or paste that will not dissolve gelatin. Two continuous gelatin ribbons, which the machine forms, are brought into convergence between a pair of

revolving dies and an ejection wedge (Figure10)¹².

- **Norton Capsule Machine:** This machine produces capsule completely automatically by leading two films of gelatin between a set of vertical dies. These dies as they close, open, and close, are in effect a continual vertical plate forming rows after row of pockets across the gelatin film. These are filled with medicament and as they progress through the dies, are sealed, shaped, and cut out of the film as capsules which drop into a cooled solvent bath¹².
- **Accogel Capsule Machine.** Or Stern machine: uses a system of rotary dies but is unique in that it is the only machine that can successfully fill dry powder in a soft gelatin capsule¹².

2.2 Shape & size of capsule

Soft gelatin capsule is available in various shapes, size and color (Figure11) eg:

- Spherical – 0.05 -5 ml
- Ovoid – 0.05 - 7 ml
- Cylindrical – 0.15- 25 ml
- Tubes – 0.5 - 10 ml

- Pear shaped – 0.3 - 5ml

2.3 Types of materials for filling into soft gelatin capsules¹³:

- **Neat Substance, especially oily liquids:**
eg. Cod liver oil capsules

- **Solution Fills:**

- a. Active dissolved in a carrier:

Oils such as soybean oil and Miglyol 812 (neutral oil, triglycerides of medium chain fatty acids)

Polyethylene Glycols: especially PEG 400 - 600

Other solvents: Any other solvent, which does not degrade or solubilize the gelatin shell, i.e., dimethyl isosorbide, surfactants, diethylene glycol monoethyl ether.

- b. Optional Ingredients for solution fills:

Water or alcohol: up to 10% w/w (if needed for solubility).

Glycerin: 1 to 4% w/w (to retard the migration of the glycerin out of the shell into the fill).

Polyvinylpyrrolidone: Up to 10% w/w used in combination with PEG (can increase drug

solubility, and also improve stability by inhibiting drug crystallization).

- **Suspension Fills:** Active dispersed in a carrier.

Suspensions can accommodate about 30% solids before viscosity and filling become a problem. Suspensions can be heated up to 35°C to decrease viscosity during the filling process. Suspended solids must be smaller than 80 mesh -- mill or homogenize before filling to prevent needles from clogging during filling.

3. Special types of hard gelatin and soft gelatin capsules

3.1 Altered Release:

The rate of release of capsule contents can be varied according to the nature of the drug and the capsule excipients. If the drug is water-soluble and a fast release is desired, the excipients should be hydrophilic and neutral. If a slow release of water-soluble drug is desired, hydrophobic excipients will reduce the rate of drug dissolution. If the drug is insoluble in water, hydrophilic excipients will provide a faster release; hydrophobic and neutral excipients will slow its release. A very rapid release of

the capsule contents can be obtained by piercing holes in the capsule to allow faster penetration by fluids in the gastrointestinal tract, or by adding a small quantity of sodium bicarbonate and citric acid to assist in opening the capsule by the evolution of carbon dioxide.

About 0.1 to 1% of sodium lauryl sulfate may be added to enhance the penetration of water into the capsule and speed dissolution. If slower release of the active drug is desired, it can be mixed with various excipients, such as cellulose polymers (methylcellulose) or sodium alginate. In general, the rate of release is delayed as the proportion of polymer or alginate is increased relative to water soluble ingredients, such as lactose. It should be mentioned that it is difficult to predict the exact release profile for a drug and to obtain consistent results from batch to batch. Further, reliable, consistent blood levels and duration of action can only be proved with controlled bioequivalence studies. In addition, many medications exhibit narrow therapeutic indices as the toxic and therapeutic doses are very close. Therefore, extemporaneous attempts to

alter release rates to this extent should be avoided¹³.

3.2 Coating capsules:

Coatings have been applied extemporaneously to enhance appearance and conceal taste, as well as to prevent release of the medication in the stomach (enteric coated products). Most coatings of capsules require considerable formulation skill and quality control equipment found in manufacturing facilities. The capsules can be coated to delay the release of the active drug until it reaches a selected portion of the gastrointestinal tract. Materials found suitable include stearic acid, shellac, casein, cellulose acetate phthalate and natural and synthetic waxes; the basis of their use is their acid insolubility but alkaline solubility. Many of the newer coating materials are time: erosion-more dependent rather than acid: base-dependent, i.e. they erode over time on exposure to gastrointestinal contents rather than over a pH gradient. There are, in addition, a number of newer materials with predictable pH solubility profiles¹³.

3.2.1. Enteric-coated capsules:

Enteric-coated capsules resist disintegration in the stomach but break up in the intestine. They have largely been superseded by enteric-coated tablets. Types of coating used commercially include cellulose acetate phthalate and mixtures of waxes and fatty acids and/or their esters. Enteric coating may be given to the following categories of drugs –

- For substances that irritate the gastric mucosa or are destroyed by the gastric juice, and for medicaments, such as amoebicides and anthelmintics that are intended to act in the intestine.
- Which interfere with digestion e.g. tannins, silver nitrate and other salts of heavy metals.
- Which are required to produce delayed action of the drug.

Several coating methods may be used are Beaker-flask coating, Dipping, Spraying¹³.

3.2.2. Sustained release capsules:

The traditional method of taking a dose three or four times a day leads to periods of excess and deficiency in blood concentration of the medicament. One way of correcting this and, at the same time,

reducing the number of doses per day, is to administer a capsule containing numerous coated pellets that release the drug successively over a long period.

The finely powdered drug is first converted into pellets, usually by attaching it to sugar granules with an adhesive. The pellets are then treated with protective coatings that delay release of the drug, each batch receiving a different thickness. The batches are mixed thoroughly and suitable doses are filled into capsules. For example, a mixture might contain 30 percent of uncoated pellets, for immediate release of drug, 30 percent each of coated pellets that release at 4 hours and 8 hours, and 10 percent of neutral pellets, used solely to fill the capsule. Each batch may be colored differently to simplify identification and facilitate control of mixing¹³.

3.3 Liquid filled hard gelatin capsules

It is generally accepted that many of today's NCE's (New Chemical Entities) are poorly water soluble and the classical methods, such as reduction in particle size are no longer adequate to achieve satisfactory drug adsorption from a solid oral dosage form. One of the most promising strategies

to deliver these insoluble compounds is using dissolved systems like using lipids, liquids or semi-solids to formulate new products. Two piece hard shell capsules are one of the most logical approaches when choosing the best dosage form to deliver these new liquid formulations.

The new technology of packaging liquids in hard gelatin capsules is considered a major breakthrough. It can make a significant contribution to the development of efficacious pharmaceutical products by providing the flexibility to rapidly develop and test in-house formulations when only small quantities of drug substance is available. The process can be scaled-up and also kept in-house similar to the operations of tableting or powder/pellet filling of hard gelatin capsules¹³.

Alternative material for Gelatin capsules

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

production especially in the rotary die process. Despite these great advantages, gelatin has several drawbacks that limit its use for soft capsules:

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

- For low-price health and nutrition products, pricing of commercially available gelatin might be an additional problem.

Common causes of cross-linking include:

- Aldehydes present in active pharmaceutical ingredients (APIs), excipients, packaging materials, or degradants formed in situ during storage
- High humidity
- Indirect catalysis in cross-linking reactions
- Decomposition of a stabilizer in corn starch (hexamethylenetetramine), which forms ammonia and formaldehyde, which in turn promote cross-linking reactions
- Rayon coils that contain an aldehydic functional group¹⁴
- Polyethylene glycols that may auto-oxidize to form aldehydes
- UV light, especially in the presence of high heat and humidity^[15,16]

- Heat, which can catalyze aldehyde formation.

To address these concerns, there has been a great interest in the soft capsule industry in looking for gelatin substitutes. Indeed, several concepts based on synthetic polymers and/or plant-derived hydrocolloids have been described in the patent literature. However, only few have gained commercial interest. This is due to the fact that a change in the capsule shell polymer material requires more than just overcoming the aforementioned shortcomings of gelatin. It requires both legal approval and machinability, i.e. either to mimic most of the physicochemical gelatin characteristics that are important for rotary die soft capsule production with some adjustments of the production equipment for the new material characteristics or to use completely redesigned machinery¹⁰.

B. HPMC CAPSULE

The commercial and nutraceutical markets have driven the development of alternative forming materials for traditional capsule shell material gelatin according to need. Formulator requires a non-cross-linking

capsule that is well characterized, compatible with current excipients and assays, and has a gelatin-like dissolution. Marketing prefers a capsule that meets the dietary and cultural needs of patients. Manufacturing needs a capsule with gelatin-like performance that can run on existing filling equipment. Regulatory wants a capsule polymer that has a proven safety record and wide regulatory acceptance. Clinicians need to be certain that patient compliance is assured.

Develop alternative should provide improvement in the shell property, physical strength, protection from moisture protection from microbial contamination protection from light and oxygen; improve compatibility of fill material with capsule shell.

Several materials have been examined as a substitute for the gelatin in two-piece hard capsules. Hydroxypropylmethyl cellulose (HPMC) has become a successful alternative material for two-piece capsules and is actually on the market in the world. Hydroxypropyl methylcellulose (HPMC), now commonly known as hypermellose, is produced by synthetic modification of the

naturally occurring polymer cellulose and is considered safe for normal consumption in humans¹⁷.

HPMC is white to slightly off white powder or granules, hygroscopic after drying, practically insoluble in hot water, in acetone, in dehydrated ethanol and in chloroform, but dissolves in cold water giving a colloidal solution owing to the reversible thermal gelation property. HPMC is available in different substitute type with limits on methoxy and hydroxypropoxy groups. These groups influence many of the HPMC properties such as gelation temperature, viscosity, flexibility and hydration¹⁸. HPMC capsules may offer attractive alternative to gelatin capsules because of gelatin and drug incompatibilities and the strict regulations regarding the use of animal derived gelatin requiring the absence of bovine spongiform encephalopathy(BSE)/ transmissible spongiform encephalopathy(TSE) have encouraged the search for gelatin replacement. Religious culture and personal issues may affect patient preference towards the medications presented in capsule dosage form. HPMC capsule are well suited for moisture sensitive drugs, no risk

of capsule cross-linking, excellent for modified release coatings, flexibility under extreme storage conditions and machinability.

HPMC is also being adopted as a film coating or a sustained-release tablet material in the pharmaceutical field. HPMC capsules have been developed for both pharmaceutical products and dietary supplements. QUALI-V, developed by Shionogi Qualicaps, is the first HPMC capsule developed for eventual use in pharmaceutical products. QUALI-V has been submitted to the FDA and its DMF number is 12900¹⁹.

HPMC capsules have a lower moisture content specification compared to gelatin capsules. Shionogi Qualicaps Quali-V capsules contain 4-6% and Capsugel Vcaps contain 5-7%. HPMC films have less permeable to water vapor and moisture played a different role to that in gelatin films. It does not act as a plasticizer, which means that if the capsules lose their moisture for whatever reason, e.g. exposure to low humidities or are filled with hygroscopic formulations, they do not become brittle²⁰. Dried gelatin and HPMC

capsules down to below their standard moisture content and subjected them to a brittleness test that involved dropping a 50 g weight on to them from height of 10 cm. The results showed that gelatin capsules below about 11% moisture content become very brittle even when dried down to below 1%²¹.

The first vegetable capsules with the trademark Vegicaps made of HPMC were produced in 1989 by G.S. Technologies Inc.(now R.P. Scherer Technologies ownership). The production of HPMC capsules is by thermal gelation and a gelling system used to lower thermal gelation temperature of HPMC²². The production technique remains similar to that of hard gelatin capsules and involves the use of pins dipping into HPMC solution, although the machinery may require some modification such as the use of heated pins. The HPMC capsules patented are not all the same and differ mainly in whether a gelling system is used and in the type of gelling system. Information regarding the empty HPMC capsules and their manufacturer is listed in table 5.

C. PVA CAPSULE

International Patent Application WO 9 755 37²³ describes the preferable use of polyvinyl alcohol (PVA) and optional use of some other materials, all being film-forming polymers that lack the gelling properties that are necessary for soft capsule production using the conventional rotary die process. The invention therefore provides the use of preformed rolls of nearly water-free plasticized films that may be fed to a rotary die encapsulation unit for soft capsule production. To render the film material more flexible and to assist the seam formation at temperatures depending on the film composition, the films are partially spray solvated prior to encapsulation. PVA films according to this invention may be composed of 70–75% w/w PVA, 10–15% w/w glycerol and 5–10% w/w starch, with a sealing temperature of 140–180°C, depending on the degree of solvation. PVA as an optional gelatin substitute has the advantage of being less hygroscopic, thus leading to soft capsule shells that are less sensitive to moisture than soft gelatin capsule shells. Moreover, the capsules are readily water soluble with no cross-linking tendency. However, prototype capsules lack the shiny and

smooth surface appearance and the seam quality of conventional soft gelatin capsules. In addition, the regulatory issues and the formulation of hydrophilic fills are problems that have to be solved. To summarize, it may be concluded that none of the gelatin-free soft capsule concepts are fully developed yet. Nevertheless, soft capsules based on plant-derived or synthetic polymers are an interesting line extension to soft gelatin capsules with the potential to gain a market share for certain niche products.

Polyvinyl alcohol (PVA) copolymer capsules is a form of nongelatin capsule under development. PVA, acrylic acid (AA) and methyl methacrylate (MMA) are used as raw materials. As previously reported, these capsules have advantages, such as low gas permeability, and can be particularly suitable for encapsulation of hydrophilic solvents, such as polyethylene glycol (PEG) 400, and surfactants^[24,25,26,27,28] Using such capsules facilitates the formulation of insoluble drugs and is expected to enhance bioavailability.

PVA copolymer capsules were prepared by the dipping and forming method.

Carrageenan (0.05-0.5%) was added as a gelling agent and potassium chloride (0.05-0.5%) was added as a gelling promoter. This method requires no additional investment for capsule manufacturers because conventional gelatin capsule manufacturing machines can be used. Prototype PVA copolymer capsules were coloured, showed a good gloss and were not different from conventional capsules.

The PVA copolymer capsules displayed the lowest level of electrification, as well as a negative charge. The attenuation of the surface potential charge of the capsules was affected by the functional groups of the raw materials and their polymeric structure. The PVA copolymer capsules are not easily electrified and show easy attenuation of any electricity that is generated.

In contrast with gelatin and HPMC capsules, it has been proven that PVA copolymer capsules are compatible with PEG 400, Tween 80 and LABRASOL^[24,25,26].

Comparison of capsule characteristic

Comparison with conventional capsules. Current commercially available hard capsules are made of gelatin or HPMC. Table 6 lists the advantages and

disadvantages of PVA copolymer capsules compared with these capsules. PVA copolymer capsules have similar advantages to HPMC capsules because both have been developed to overcome the drawbacks of gelatin capsules. The advantages of PVA copolymer capsules include no animal-derived material, a low water content, no Maillard reaction and a low electrostatic propensity. Additionally, PVA copolymer capsules demonstrate the unique properties of having very low oxygen permeability and the ability to contain macrogol 400²⁹.

D. STARCH CAPSULE

It can be formulated with conventional plasticizers such as glycerol, sorbitol, etc. (10–60% w/w of dry shell) and water to form a molten mass that can be extruded to set within less than 20 s producing mechanically strong, elastic films on temperature-controlled casting drums. Sealing may be performed at temperatures between 25 and 80°C, by a fusion process comparable to the one observed with soft gelatin capsules. After drying, mechanically strong and highly elastic products can be achieved.

Prototype capsules with lipophilic fill formulations are shiny with high appearance stability on storage. The capsule shells do not show crosslinking and exhibit a greater mechanical stability than soft gelatin shells when exposed to elevated humidity and temperature, i.e. even under hot and humid storage conditions they may not become sticky. Formulation approaches with hydrophilic fills are expected to be as challenging as for soft gelatin capsules. Oxygen permeability is comparable to gelatin-based shells. The dissolution mechanism is completely different to the one of a soft gelatin capsule. On contact with an enzyme-free aqueous medium at 37°C, the capsule shell only swells, at a rate and to an extent depending on the type and concentration of electrolytes present. The capsule content may be released when the shell bursts at its point of lowest resistance, i.e. at the seams. Under *in vivo* conditions, capsule shell dissolution may be induced by enzymatic degradation. International Patent Application WO 0 137 817³⁰ describes the formation of soft capsules from a potato starch (45–80% w/w), with a specific molecular weight distribution and amylopectin content, together with a

conventional plasticizer such as glycerol (12% w/w), a glidant and a disintegrant.

Soft capsule production may be performed with a rotary die machine with nearly water-free formulations that are processed by hot melt extrusion. A narrow production window and the use of a high molecular weight amorphous starch with high amylopectin content (50% w/w) are necessary for the formation of acceptable capsules. From the regulatory point of view, starch-based soft capsules are a low-price alternative to soft gelatin capsules, appropriate for pharmaceutical and health and nutrition products. Moisture sensitivity and fill compatibility of the capsule shells are comparable to soft gelatin capsules, with the exception that cross-linking is not a problem. Oxygen permeability is expected to be a little higher compared to soft gelatin capsules³¹.

Shell dissolution requires enzymatic degradation by amylases; on contact with amylase-free aqueous media at 37°C, the capsules release their content only by swelling induced disintegration. The addition of calcium carbonate is one option to enhance capsule disintegration further.

The visual appearance, the seam quality, and the long-term stability of the finished product of the prototype starch capsules cannot compete with soft gelatin capsules. This is due to the structural rearrangements within the capsule shells associated with the tendency of starch to retrograde on storage, in some instances leading to a subsequent plasticizer syneresis³¹.

Manufactured by the process of injection moulding, starch capsules have been shown to be a very useful alternative delivery system for orally administered compounds. Made from potato starch and represent a direct alternative to hard gelatin capsules. It Offers advantages like: pH independent dissolution, suitable for enteric coating, tamper evident, produced from non-animal derived ingredients. Different size capsules are manufactured (number 0, 1, 2, 3, 4). Officially recognized in USP 23 and NF 18

TARGIT technology (West Pharmaceutical Services) is designed for site-specific delivery of drugs in the gastrointestinal (GI) tract and, in particular, targeted release into the colonic region. A key area of application is the delivery of therapeutic agents for local treatment of lower GI

diseases. The technology is based on the application of pH-sensitive coatings onto injection-moulded starch capsules³².

1. Pullulan Capsule

Pullulan is a natural water-soluble high molecular polysaccharide produced from starch or saccharide by microbial fermentation. It has numerous uses as additives in the food, pharmaceutical and consumer goods industries. It is also the source of dissolvable fiber. Pullulan capsule is another kind of vegetable capsule. The advantages of pullulan capsule are as follows:

- Low oxygen transmission, is about one eighth of the gelatin capsules and one three hundred of the HPMC capsules. So pullulan capsules provide enhanced protection of capsule ingredients and extend shelf life.
- It has the crystal-clear transparency as the animal origin capsule.
- No animal protein and fat, no microbial breeding stable in quality.

- Free from animal products, no potential hazard of mad cow disease, mouth and foot disease etc.
- Natural vegetable origin, suitable for all people with different religions and vegetarians

2. NPCaps Pullulan Capsules

NPCaps® a non-animal capsules are made from pullulan, a vegetable-derived, water-soluble polysaccharide produced through a

fermentation process. Because pullulan capsules are highly impermeable to oxygen transmission, NPCaps capsules are recommended for encapsulating oxidation-sensitive ingredients to provide enhanced protection. Pullulan is highly stable and well-characterized, and has achieved broad regulatory acceptance around the world with its proven safety record³³.

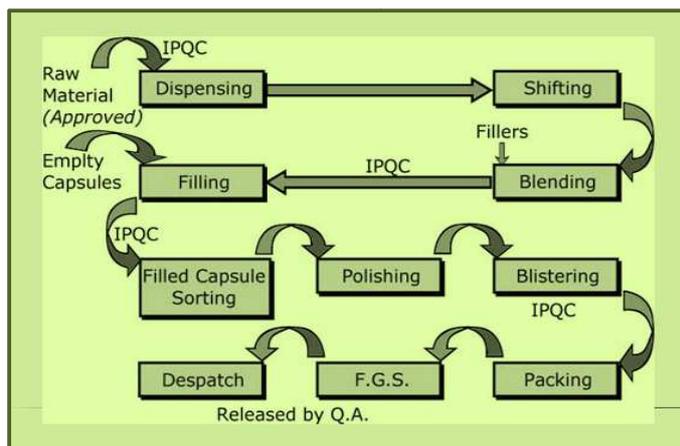


Figure 1: Flow chart for Capsule manufacturing steps.

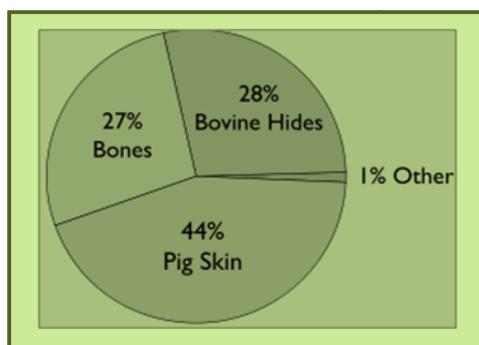


Figure 2: Amino acid composition of gelatin[4].

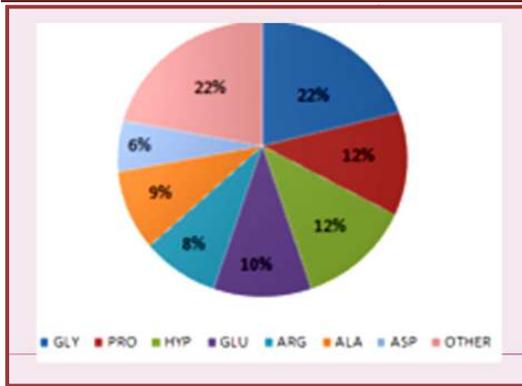


Figure 3: Material used in gelatin production [4].

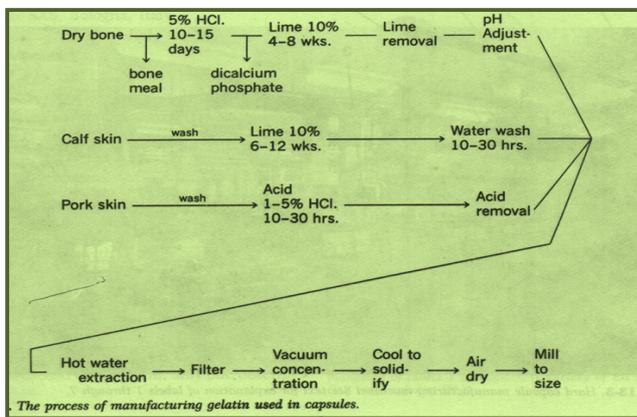


Figure 4: Manufacturing process of gelatin.

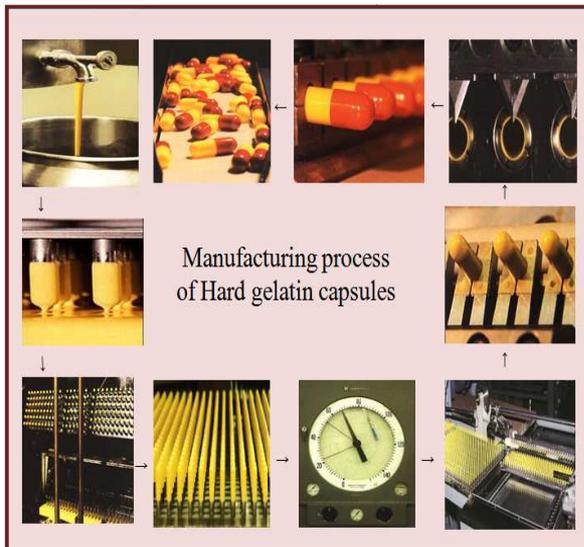


Figure 5: Manufacturing process of hard gelatin capsule[5].

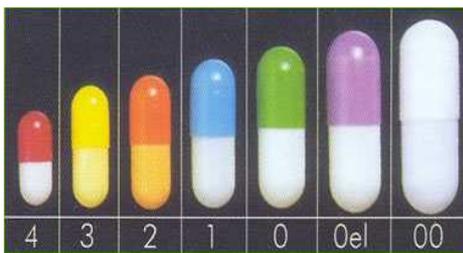


Figure 6: Size of capsule

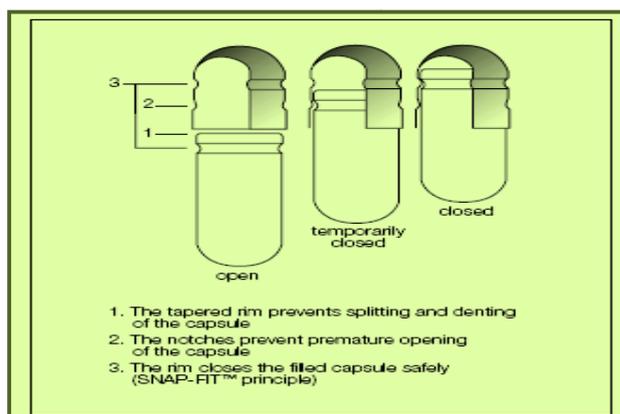


Figure 7: Recent hard gelatin capsule with features (notches or dimples) for pre-closing; closing features (e.g. SNAP-FIT™) and tapered rim (e.g. CONI-SNAP™).

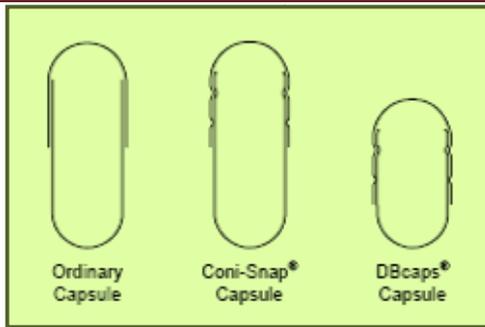


Figure 8: Drawings of an ordinary capsule (left), a Coni-Snap® capsule (center) and a DBcaps® capsule (right). In Coni-Snap® and DBcaps® capsules, the tapered rim of the body is designed to avoid telescoping, the grooves on cap and body lock together; the presence of indentations prevents premature opening.

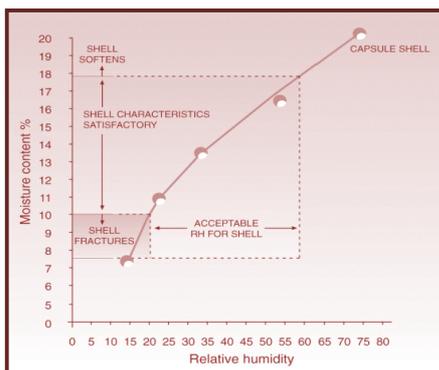


Figure 9 : Relative Humidity (RH), Gelatin Moisture Content, and Hard Gelatin Capsule Properties.

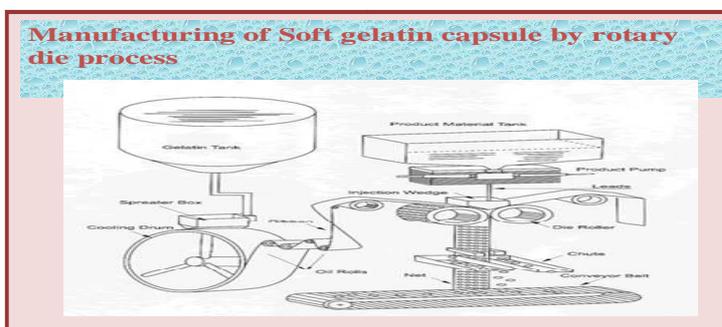


Figure10: Rotary die process. [13]

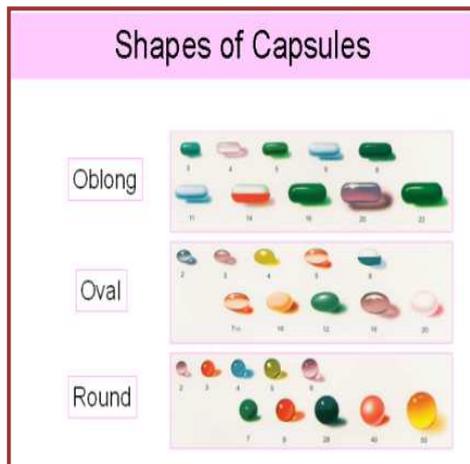


Figure 11 : Variety of colors, shapes, and sizes available in soft gelatin capsule

Table 1:

Capsule fill weight (mg) based on size and density⁶.

Powder Density (gm/ml)	Capsule volume (ml)									
	0.95	0.78	0.68	0.54	0.5	0.37	0.3	0.25	0.21	0.13
Capsule size	00	Del	0	1el	1	2	3	4el	4	5
0.3	285	234	204	162	150	111	90	75	63	39
0.4	380	312	272	216	200	148	120	100	84	52
0.5	475	390	340	270	250	185	150	125	105	65
0.6	570	468	408	324	300	222	180	150	126	78
0.7	665	546	476	378	350	259	210	175	147	91
0.8	760	624	544	432	400	296	240	200	168	104
0.9	855	702	612	486	450	333	270	225	189	117
1.0	950	780	680	540	500	370	300	250	210	143
1.1	1045	858	748	594	550	407	330	275	231	143
1.2	1140	936	816	648	600	444	360	300	252	156
1.3	1235	1014	884	702	650	481	390	325	273	169
1.4	1330	1092	952	756	700	518	420	350	294	182
1.5	1425	1170	1020	810	750	555	450	375	315	195

Table 2:

Physicochemical properties of pharmacopoeial-grade soft capsule gelatins¹¹.

Gelatin	Raw material	Type	Bloom(g) (10oC;6 2/3%w/w)	Viscosity(mPas) (60oC;62/3%w/w)
160 LB (= limed bone)	Bovine/porcine bone	B	155-185	3.4-4.2
160 LH (= limed hide)	Bovine hide	B	150-170	3.5-4.2
160 LB/LH	Blend of bovine/porcine bone and bovine hide	B	150-170	3.5-4.2
200 AB (= acid bone)	Bovine bone	A	180-210	2.7-3.2
200 PS (= pigskin)	pigskin	A	190-210	2.5-3.1
160 PS/LB/LH	Blend of pigskin, bovine/porcine bone bovine hide	A/B	145-175	2.7-3.3

Table 3:

Example of commercial products prepared in soft gelatin capsules⁷

Ethchlorvynol (Placidyl [®] , Abbott)
Demeclocycline HCl (Declomycin [®] , Lederle)
Chlortrianisene (TACE [®] , Marion Merrell Dow)
Digoxin (Lanoxicaps [®] , Burroughs Wellcome)
Docusate calcium (Surfak [®] , Upjohn)
Vitamin E (Aces [®] , J.R. Carlson Lab.)
Neoral [®] capsule
Zantac [®] Geldose capsule
Procardia [®] capsule (PEG based)
Advil [®] liquicapule

Table 4

Comparison of hard and soft gelatin capsules.

Aspect	Hard gelatin capsule	Soft gelatin capsule
In house development and manufacture	Yes	Difficult
Ability to manufacture small batches	Yes	No
Scale up	Simple and in-house	Requires large quantities of drug substance and must be outsourced
Temperature of fill	Max.-70°C	Max.-35°C
Plasticizer in shell	No	Yes
Risk of drug migration	Low	High for drugs soluble in plasticizer
Permeability of shell to oxygen	Low	High due to plasticizer varies with moisture content
Sensitivity to heat and humidity	Low	High due to plasticizer
Limitation on excipients for formulation	High concentrations of hygroscopic excipients such as glycerol must be avoided	Hygroscopic excipients can be tolerated due to presence of plasticizer in shell
Capsule dimensions	Constant	May vary

Table 5:

Information on the empty HPMC capsules and their manufacturers

Capsule Shell Name	Brands	Manufacturer	Registered Year in USA	Gelling Aid
Quali-V		Shionogi Qualicaps	July,2002	Carrageenam
Vcaps Plus		Capsugel (Adivision of Pfizer	-	None
Vcaps		Capsugel (Adivision of Pfizer	April,2003	Gellan gum
VegiCaps		G.S. Technologies Inc.(now R.P. Scherer Technologies ownership)	May,1989	None
Embo Caps-Vg		Suheung Capsules Co.,Ltd.	-	Pectin and glycerin
Capstech's Capsules	HPMC	Baotou Capstech Co., Ltd.	-	None
Natural Plant Capsule		Zhejiang LinFeng Capsules Co. Ltd.	-	Carrageenam

Table 6:

Comparison of capsule characteristic.

Property	Gelatin	HPMC	PVA copolymer
Water content	4-6%	13-15%	2-5%
Gloss	Yes	Yes	Low
Water vapour permeability	Low	Low	Low
Oxygen permeability	Vary low	Low	High
Maillard reaction with filled substance	No	Yes	No
Light degradation	No	Yes	No
Protease degradation	No	Yes	No
Static electricity	Weak	Strong	Weak
Solubility in water at room temperature	Soluble	Insoluble	Soluble
Filling of macrogol 400	Possible	Impossible	Impossible
Filling of tween 80	Possible	Impossible	Impossible

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