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CAPSULES: TYPES, MANUFACTURING, FORMULATION, QUALITY CONTROL TESTS AND, PACKAGING AND STORAGE - A COMPREHENSIVE REVIEW

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ABSTRACT

Capsules are solid preparations in which drug substance(s) and/or excipients are enclosed in either a soft or hard soluble shell. The sell is normally made from gelatin or other suitable polymeric material and results in a simple, tasteless, odourless, elegant, easy-to-swallow dosage form without the need for a secondary coating step. Depending on the composition of the capsule shell, capsules may be classified as either hard or soft capsule, with soft capsules possessing a flexible, plasticized gelatin film while the hard capsule is composed of two pieces in the form of cylinders closed at one end; the shorter piece, called the 'cap' and the longer piece, called the 'body'. Capsules may be filled with a range of formulation types including dry powders, semisolids, nonaqueous liquids, and other dosage forms such as beads, mini-tablets, and even mini capsules most of which are intended for oral administration. There are also specialty applications such as capsules that can be loaded into dry-powdered inhalers, add reagents as part of a diagnostic kit, and occasionally soft-shell capsules intended for rectal or vaginal insertion as suppositories. Also, In the recent advancements, non-gelatin capsules have been discovered, which do not contain gelatin as it's shell-forming agent. Under this category of capsules are the HPMC, PVA and starch capsules. This review captures various categories of capsule types, formulation and filling of capsules, locking and sealing of capsules, and, quality control tests. The various packaging and storage method were also highlighted.

KEYWORDS: Capsules, Manufacturing, Formulation, Quality control tests, Packaging and storage.

INTRODUCTION

Drugs

A drug is any substance that causes a change in an organism's physiology or psychology when consumed. Drugs are typically distinguished from food and substances that provide nutritional support. Consumption of drugs can be via inhalation, injection, smoking, ingestion, absorption via a patch on the skin, or dissolution under the tongue.[1]

In pharmacology, a drug is a chemical substance, typically of known structure, which, when administered to a living organism, produces a biological effect. A pharmaceutical drug, also called a medication or medicine, is a chemical substance used to treat, cure, prevent, or diagnose a disease or to promote well-being. Traditionally drugs were obtained through extraction from medicinal plants, but more recently also by organic synthesis. Pharmaceutical drugs may be used for a limited duration, or on a regular basis for chronic disorders.[2]

Dosage forms

Dosage forms are pharmaceutical drug products in the form in which they are marketed for use, with a specific mixture of active ingredients and inactive components (excipients), in a particular configuration (such as a capsule shell, for example), and apportioned into a particular dose. The term dosage form can also sometimes refer only to the pharmaceutical formulation of a drug product's constituent drug substance(s) and any blends involved, without considering matters beyond (like how it is ultimately configured as a consumable product such as a capsule, patch, etc.). Depending on the method/route of administration, dosage forms come in several types. These include many kinds of liquid, solid, and semisolid dosage forms. Common dosage forms include pill, tablet, or capsule, drink or syrup, and natural or herbal form such as plant or food of sorts, among many others. Notably, the route of administration (ROA) for drug delivery is dependent on the dosage form of the substance in question. A liquid dosage form is the liquid form of a dose of a chemical compound used as a drug or medication intended for administration or consumption.[3]

Capsules

Capsules are defined as unit solid dosage form of medicaments available as small containers (shells) made up of gelatin enclosing accurately measured drug substances. The term capsule is derived from the Latin word *capsula*, meaning a small container. Capsule occupy a significant position in the drug development. They are often believed as the primary oral dosage form because of their manufacturing process compared to other dosage forms. Gelatin has the property of disintegrating when it comes in contact with water, thereby releasing the medicament completely. Instead, of gelatin, denatured gelatin, methyl cellulose and polyvinyl alcohol can also be used to make the capsule shells.[7] There are mainly two types of capsules which are:

Hard-shelled capsules, which contain dry, powdered ingredients or miniature pellets made by e.g. processes of extrusion or spheronization. These are made in two halves: a smaller-diameter "body" that is filled and then sealed using a larger-diameter "cap".

Both of these classes of capsules are made from aqueous solutions of gelling agents, such as animal protein (mainly gelatin) or plant polysaccharides or their derivatives (such as carrageenans and modified forms of starch and cellulose). Other ingredients can be added to the gelling agent solution including plasticizers such as glycerin or sorbitol to decrease the capsule's hardness.[4]

Capsule types

There exist various capsule types in scholarly articles, they are; the soft gelatin and hard gelatin capsules, Hydroxypropylmethyl cellulose (HPMC) capsules, Polyvinyl alcohol (PVA) capsules, starch capsules. These can be summarized as the gelatinous and non gelatinous capsules.[11]

Gelatin capsules

This category of capsules is basically made from gelatin; they can either be soft or hard gelatin capsules.

Soft gelatin capsules

General aspects

Originally developed in the 19th century to mask unpleasant taste and odour of drug substances, soft gelatin capsules are used in many applications, for pharmaceutical, health and nutrition products, cosmetic applications and even recreational products such as paint balls.[12]

In the pharmaceutical field soft gelatin capsules are increasingly being chosen for *strategic reasons* (line extension), *technological issues* (high content uniformity of low-dose drugs), *safety aspects* (reduced operator and environmental contamination with highly potent or cytotoxic compounds) and *consumer preference* (easy to swallow). The most interesting advances have recently been made in the area of developing liquid and semi-solid formulations in a soft gelatin capsule to address *particular bio-performance issues*, namely increased bioavailability and decreased plasma variability by improved solubility and absorption-enhancing techniques.[13]

Basic components of soft gelatin capsule shell[15]

The various components of the soft gelatin capsule shell are as follows:

a. Gelatin

Similar to hard gelatin capsule shells, the basic component of soft gelatin capsule shell is gelatin. A large number of different gelatin shell formulations are available depending on the nature of the liquid fill matrix. Most commonly, the gelatin is alkali- (or base-) processed (type B) gelatin and it normally constitutes 40% of the wet molten gel mass. Type A acid-processed gelatin can also be used. The properties of gelatin shells are controlled by the choice of gelatin grade and by adjusting the concentration of plasticizer in the shell.

b. Plasticising agents

Plasticizing agents are added in a soft gelatin capsule formulation to ensure adequate flexibility. They interact with gelatin chains to reduce the glass transition temperature (Tg) of the gelatin shell and/or promotes the retention of moisture (hygroscopicity). The most common plasticizer used for soft gelatin capsules is glycerol. Sorbitol, mannitol, and polypropylene glycol can also be used in combination with glycerol.

c. Water

Water usually accounts for 30-40% of the wet gel formulation and its presence is important both during the manufacturing process (to facilitate manufacture) and in the finished product to ensure that the capsule is flexible. The desirable water content of the gelatin solution used to produce a soft gelatin capsule shell depends on the viscosity of the specific grade of gelatin used. It usually ranges between 0.7 and 1.3 parts of water to each part of dry gelatin.

d. Preservatives

Preservatives are often added to prevent the growth of bacteria and mould in the gelatin solution during storage. Examples of commonly used as preservatives include potassium sorbate, and methyl, ethyl, and propyl hydroxybenzoate.

e. Colorant and/or opacifier

A colourant (soluble dyes, or insoluble pigments or lakes) and/or opacifier (e.g., titanium dioxide) may be added to the shell for visual appeal and/or reducing the penetration of light for the encapsulation of a photosensitive drug. The colour of the capsule shell is generally chosen to be darker than that of its contents.

f. Other excipients

Other, infrequently, used excipients can include flavouring agents and sweeteners to improve palatability.

Acid-resistant polymers are used to impart enteric release characteristics. They can also be used to formulate chewable soft gelatin capsules. A chelating agent, such as ethylene diamine tetracetic acid (EDTA), can be added to prevent chemical degradation of oxidation sensitive drugs catalyzed by free metals in gelatin, such as iron.

Hard gelatin capsules

General aspect

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.[17]

Hard gelatin capsule shells are fabricated and supplied empty to the pharmaceutical industry by shell suppliers and are then filled in a separate operation. During the capsule filling unit operation, the body is filled with the drug substances and the shell is closed by bringing the body and the cap together.[18]

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 transmissible spongiform encephalopathy (TSE).

Basic component of hard gelatin capsules[19,20]

a. Gelatin

Gelatin is by far the most common and most well-known material used to produce hard capsule shells. It is a generic term for a mixture of purified protein fractions obtained from irreversible hydrolytic extraction of collagen obtained from the skin, white connective tissue, and bones of animals.

b. Plasticizer

Plasticizers are added to gelatin to reduce the rigidity of the polymer and make it more pliable. Common examples of plasticizers are glycerine and polyhydric alcohol. Water is also a good plasticizer and is naturally present in the gelatin.

c. Colourants

Most frequently, hard gelatin capsules are coloured to enhance the aesthetic properties and also to act as a means of identifying the product. Colorants used must meet the regulatory requirements of those countries where the product will be sold. Examples of commonly used capsule colourants include synthetic dyes such as azo dyes and xanthene dyes. Iron oxide pigments are also used.

d. Opacifying agents

Opacifiers (e.g., titanium dioxide) may be included to make clear gelatin opaque. Opaquse capsules may be employed to provide protection against light or to conceal the contents.

e. Preservatives

Preservatives (often parabens esters) were formerly added to hard capsules as an in-process aid in order to prevent microbiological contamination during manufacture. Manufacturers operating their plants to Good Manufacturing Practice (GMP) guidelines no longer use them. In the finished capsules, the moisture levels, 12–16% w/ v, are such that the water activity will not support bacterial growth because the moisture is too strongly bound to the gelatin molecule.

Special types of hard gelatin and soft gelatin capsules

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.[21]

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.[22]

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 mixing.[22]

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.[22]

Non-Gelatin Capsules

Traditionally, gelatin has been used almost exclusively as shell-forming material of capsules. In the recent advancements, non-gelatin capsules have been discovered, which do not contain gelatin as it's shell-forming agent. Under this category of capsules are the HPMC, PVA and starch capsules.

HPMC Capsules

The commercial and neutraceutical 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.[25]

PVA Capsules

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 shell.[26]

Starch Capsules

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 secs 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.[27]

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.[28]

Capsule formulation

Hard gelatin capsule formulation

It is estimated that the utilization of hard gelatin capsules to prepare solid dosage forms exceeds that of soft gelatin capsules by about 10-fold. Hard gelatin capsules are fabricated and supplied empty to the pharmaceutical industry by shell suppliers and are then filled in a separate operation. Manufacturing gelatin capsules involves a step by step process that requires strict quality control.

Manufacture of Hard Gelatin Capsules[10]

Hard gelatin capsules are manufactured using a dip-coating method and the various stages involved are as follows:

Step 1: Preparation of the gelatin solution (dipping solution)
A concentrated solution of gelatin is prepared by dissolving the gelatin in demineralized water which has been heated to 60–70°C in jacketed pressure vessels. This solution contains 30 – 40% w/w of gelatin and is highly viscous, which causes bubbles as a result of air entrapment. The presence of these bubbles in the final solution would yield capsules of inconsistent weight and would also become problematic during capsule filling and upon storage. To remove the air bubbles, a vacuum is applied to the solution; the duration of this process varies with batch size.

Following the above steps, colourants and pigments are added to attain the desired final capsule appearance. At this stage, other processing aids may be added, such as sodium lauryl sulfate, to reduce surface tension. The solution viscosity is measured and adjusted as needed with hot demineralized water to achieve the target specification.

Step 2: Dip-coating the gelatin solution on to metal pins (moulds)
Capsule shells are manufactured under strict climatic conditions by dipping pairs (body and cap) of standardized steel pins arranged in rows on metal bars into an aqueous gelatin solution (25 – 30% w/w) maintained at about 50 ° C in a jacketed heating pan. Because the moulds are below the gelling temperature, the gelatin begins to form a thin gelatin layer or film on the moulds.

The rows of pins are arranged so that caps are formed on one side of the machine while bodies are simultaneously formed on the opposite side of the machine.

Step 3: Rotation of the dip-coated pins
Following adsorption of the gelatin solution on to the surface of the pins, the bar containing the pins is removed and rotated several times to evenly distribute the solution around the pins, correct gelatin distribution being critical to uniform and precise capsule wall thickness and dome strength.

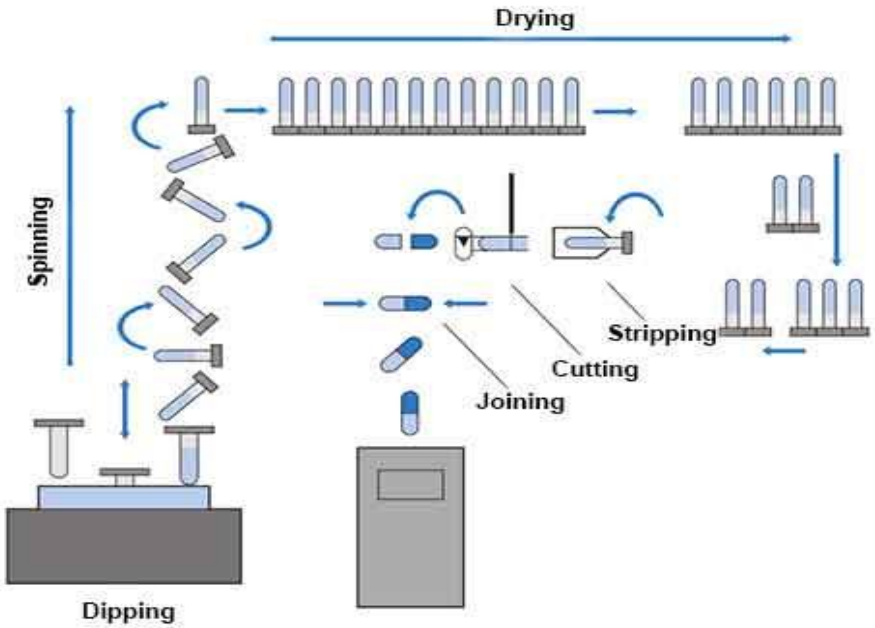
Step 4: Drying of the gelatin-coated pins
Once the gelatin is evenly distributed on the mould, a blast of cool air is used to set the gelatin on the mould. At this point, the gelatin is dried, and the pins are then passed through several drying stages to achieve the target moisture content.

Step 5: Stripping and trimming
After the gelatin is dried, the capsule is stripped off the mould and trimmed to the proper length.

Step 6: Joining of the trimmed capsule shell
Once trimmed, the two halves (the cap and body) are joined to the pre-closed position using a pre lock mechanism. At this point, printing is done if needed before packing in cartons for shipping.

Step 7: Printing
After formation, the capsule shells can be printed to improve identification. Printing can be achieved using one or two colours, containing information such as product name or code number, manufacturer's name or logo and dosage details.

Printing reduces the risk of product confusion by the numerous handlers and users of the product including manufacturers, pharmacists, nurses, doctors, caregivers, and patients.



The sequence of two-piece hard gelatin capsule shell manufacture.

Filling of hard gelatin capsules

The filling of hard gelatin capsules is an established technology, with equipment available ranging from that for very small-scale manual filling (e.g., Feton capsule filling machine), through intermediate-scale semi-automatic filling to large-scale fully automatic filling. Hard gelatin capsules can also be hand-filled one at a time, as done in a compounding pharmacy. The difference between the many methods available is the way in which the dose of material is measured into the capsule body.[24]

The basic steps in filling hard gelatin capsules include[23]

- Rectification of capsules (placing empty gelatin capsules on the removable plate with bodies facing downward).
- Separation of caps from bodies.
- Dosing of fill material (The body is filled with the formulation manually using a plastic spatula, and the excess powder is removed).
- Replacement of caps/ closing capsule shells and
- Ejection of filled capsules

Filling of liquids/semisolid formulations into hard gelatin capsules

As drug discovery continues to yield poorly water-soluble molecules, there is an increasing need for formulation techniques that can improve drug solubility. One such approach is the use of liquid-based formulations containing lipids, solvents, or surfactants, usually in combination, to improve drug solubility and bioavailability. The final formulation may be filled through piston pump systems into hard gelatin capsules as a room temperature liquid, or as a molten semisolid.

The filling of a liquid or semi-solid formulation is dependent on the viscoelastic properties of the formulation and the need to fulfil certain characteristics at the filling temperature. As a general rule, the formulation should have a viscosity of between 50 and 1000 Centipoise (cP) (although formulations of much higher viscosity can be suitable for manufacturing) and should not exceed 70 °C.[16]

Liquid Excipients Compatible with Hard Gelatin Capsule Shells[13]

Lipophilic excipients	**Vegetable oils e.g.,** Peanut oil, Castor oil, Olive oil, Fractionated coconut oil, Corn oil, Sesame oil, Hydrogenated vegetable oil, Soybean oil
	Esters e.g., Glycerol Stearate, Glycol Stearate, Isopropyl myristate, Ethyl oleate
	Fatty Acids e.g., Stearic acid, Laurie acid, Palmitic acid, Oleic acid, Oleic acid
	Fatty Alcohols e.g., Cetyl alcohol, Stearyl alcohol
Hydrophilic excipients	PEG 3000–6000 MW
Amphiphilic excipients	Poloxamers, Lecithin, PEG esters (e.g., Gelucir 44/14; 50/13; Labrafil)
Abbreviations: PEG, polyethylene glycol; MW, molecular weight.	

Locking and sealing of hard gelatin capsules[14]

For the capsules filled by manual or hand filling machines, locking and sealing is done to prevent the detachment of caps from the bodies during packaging, carrying or storing. Locking and sealing also prevents the exudation of the capsule contents. Different manufacturers adopt different methods for locking and sealing the capsules.

- ✓ Banding method
- ✓ Moistening method
- ✓ Spot welding method
- ✓ Thermal welding method
- ✓ By using coni-snap capsules

Soft gelatin capsule formulation

Soft gelatin capsules have gained popularity in the pharmaceutical industry for human and veterinary use due to the many advantages it possesses over other commonly used solid dosage forms such as tablets, hard gelatin capsules etc. The bioavailability of hydrophobic drugs can be significantly increased when formulated into soft gelatin capsules.[9]

Many problems associated with tableting, including poor compaction and lack of content or weight uniformity, can be eliminated when a drug is incorporated into a soft gelatin capsule. Also, improved stability of drugs that are highly susceptible to oxidation can be achieved with soft gelatin capsule.[5]

Vehicles used in soft gelatin capsules[35]

Soft gelatin capsules are prepared to contain a variety of liquid, paste, and dry fills. Liquids that may be encapsulated into soft gelatin capsules include the following:

- Water-immiscible volatile and non-volatile liquids such as vegetable and aromatic oils, aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, ethers, esters, alcohols, and organic acids.
- Water-miscible non-volatile liquids, such as polyethylene glycols, and nonionic surface-active agents, such as polysorbate 80.
- Water-miscible and relatively non-volatile compounds such as propylene glycol and isopropyl

alcohol, depending on factors such as concentration used and packaging conditions.

Manufacture of Soft Gelatin Capsules[6]
Softgels are manufactured using the following methods

Plate process
This is the oldest commercial process used in the manufacture of soft gelatin capsules. In this process, a warmed sheet of plain or coloured plasticized gelatin is placed over a die plate having a number of depression or moulds or numerous die pockets. By applying vacuum, the sheet is drawn into these depressions or pockets to form capsule wells. The capsule wells are then filled with medication-containing liquid. A second sheet of gelatin is carefully placed on top of the filled wells followed by the top plate of the mould. Pressure is then applied to the combined plate to form, seal and cut the capsules into individual units. This method is used for small scale preparation of soft gelatin capsules and capsules formed generally, had one flat side.

The major problems with this method of manufacturing softgels were the lack of dosage uniformity, high manufacturing losses, and its labour-/cost-intensiveness. This equipment is no longer available.

Rotary Die Process
Most soft gelatin capsules are prepared by the rotary die process, a method developed and perfected in 1933 by Robert P. Scherer. This process almost eliminated all the problems associated with the plate process and produced soft gelatin capsules with improved uniformity and high standards of accuracy.

In this process, two plasticized gelatin ribbons (prepared in the rotary-die machine) are continuously and simultaneously fed with the liquid, semiliquid or paste fill between the rollers of the rotary die mechanism. The forced injection of the feed material between the two ribbons causes the gelatin to swell into the left- and right-hand die pockets which govern the size and shape of the softgels as they converge. As the die rolls rotate, the convergence of the matching dies pockets hermetically seals and cuts out the filled capsule.

Schematic drawing of a rotary-die soft gelatin capsule filler.

Reciprocating Die Process (Norton Capsule Machine)
This continuous soft gelatin capsule processing technology was developed by Norton Company in 1949. This process is similar to rotary process in that ribbons of gelatin are formed and used to encapsulate the fill, but it differs in the actual encapsulating process. The gelatin ribbons are fed between a set of vertical dies that continually open and close to form rows of pockets in the gelatin ribbons. These pockets are filled with the medication and are sealed, shaped, and cut out of the film as they progress through the machinery. As the capsules are cut from the ribbons, they fall into a cooled solvent bath that prevents the capsules from adhering to one another.

Accogel Process
Although the rotary die process and reciprocating die process were capable of producing soft gelatin capsules containing oily liquids and pastes, Lederle Laboratories in 1949 developed accogel process, a continuous process that produces soft gelatin capsules containing powders and granules.

The process involves a measuring roll that holds the fill formulation in its cavities under the vacuum and rotates directly above the elasticized sheet of the gelatin ribbon. The ribbon is drawn into the capsule cavities of the capsule die roll by vacuum. The measuring rolls empty the fill material into the capsule-shaped gelatin cavities on the die roll. The die roll then converges with the rotating sealing roll covered with another sheet of elasticized gelatin. The convergence of two rotary rolls creates pressure to seal and cut the formed capsules.

Seamless process (Bubble Method)
The seamless technique produces one-piece soft gelatin capsules without the use of dies. The process is often referred to as a bubble method that creates seamless, spherical soft gelatin capsules called pearl.

In this process, a molten gelatin stream flows though the outer nozzle of a concentric tube at a constant rate, and the medicated liquid formulation is dispensed through the inner orifice by means of a precision metering pump. The emerging stream is broken up into an intermittent but steady flow of uniform-sized by a pulsating mechanism, leading to the formation of droplets enveloped in molten gelatin. The formed capsules are quickly removed from the nozzle, slowly congealed, and automatically ejected from the system.

Quality control tests for capsules
In capsule formulation development and during filling of capsules, a number of quality control tests are performed to ensure that capsules produced meet the requirements as specified in official compendium and conventional requirements established by the industries over the years. These tests will be discussed in three stages: in-process testing, finished product testing and shelf-life testing.[8]

In-process quality control tests for capsule drug products[10]
In-process quality control tests for capsule drug products are carried out at predefined intervals during the product manufacturing, by the manufacturing personnel, and their results recorded on the batch record. Adverse findings in these tests can be used as a guide to altering the manufacturing-process parameters.

During the encapsulation of soft gelatin capsules, the following parameters are usually closely monitored and controlled:

- Gel ribbon thickness and uniformity across the ribbon
- Softgels seal thickness at the time of encapsulation
- Weight of the capsule fill and its variation from capsule-to-capsule
- Weight of the capsule shell and its variation from capsule-to-capsule
- Moisture level of the capsule shell before and after drying
- Visual inspection, fill weight, and fill-weight uniformity are the key in-process tests used for hard gelatin capsules.

Finished product quality control tests for capsule drug products[12]

Finished capsules are subjected to a number of tests in accordance with compendial standards and regulatory requirements for unit dose capsule products. These batteries of tests help identify whether the batch is acceptable for marketing or its intended usage, the finished capsules are evaluated by the following tests:

Permeability and sealing

Soft gelatin capsules are tested for physical integrity (absence of leakage) by visual inspection. Similarly, hard gelatin capsules are tested for any breach of physical integrity (breakage or opened cap and body).

Potency and impurity content

All capsules are tested for drug content (potency, as a per cent of label claim). In addition, most drug products are tested for related substances or impurities. These must meet predefined specifications for a batch to be acceptable.

Weight variation test

The uniformity of dosage units may be demonstrated by determining weight variation or content uniformity. The weight variation method is as follows.

Weight variation test for hard gelatin capsules

Ten hard gelatin capsules are usually weighed individually and the contents are removed. The emptied shells are individually weighed and the net weight of the contents is calculated by subtracting the weight of the shell from the respective gross weight. The content of active ingredient in each capsule may be determined by calculation based on the per cent drug content in the formulation.

Weight variation test for soft gelatin capsules

For soft gelatin capsules, the gross weight of 10 gelatin capsules is determined individually. Then each capsule is cut open with a suitable clean, dry cutting instrument (e.g., scissors or a sharp open blade), and the contents are removed by washing with a suitable solvent (that dissolves the fill but not the shell). The solvent is allowed to evaporate at room temperature over a period of about 30 minutes, followed by weighing of the individual washed shells. The net contents are calculated by subtraction and the content of active ingredient in each of the capsules can be determined by calculation based on the per cent drug content in the formulation.

Fill-weight variation of capsules is often a function of equipment setup and filling operation. An automated capsule sizing machine and/or weight checker is frequently used to discard over- or underfilled capsules.

Uniformity of content

This test is performed only when the content is specified in the individual monographs and when capsules fail weight variation test. If the weight of capsules is completely filled no need of this test.

Unless otherwise stated in the monograph for an individual capsule, the amount of drug substance, determined by assay, is within the range of 85.0% to 115.0% of the label claim for nine (9) of ten (10) dosage units assayed, with no unit outside the range of 75.0% to 125.0% of the labelled drug content. Additional tests are prescribed when two or three dosage units are outside of the desired range but within the stated extremes.

Disintegration time test for capsules

Disintegration of hard and soft gelatin capsules is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. The compendial disintegration test for hard and soft gelatin capsules follows the same procedure and uses the same apparatus described in the article "Quality Control Tests for Tablets".

The capsules are placed in the basket-rack assembly, which is repeatedly lowered 30 times per minute into a thermostatically controlled bath of fluid at 37 ± 2 ˚C and observed over the time described in the individual monograph.

Dissolution test for capsules

Drug absorption and physiological availability depend on the drug substance being in the dissolved state at the site of drug absorption. The rate and extent of dissolution of the drug from the capsule dosage form is tested by a dissolution test. This test provides means of quality control in ensuring that, different batches of the drug product have similar drug release characteristics and also, a given batch has similar dissolution as the batch of capsules that was shown initially to be clinically effective.

Moisture content

Water content of the entire capsule or the capsule contents are determined by Karl Fisher titrimetry to enable the correlation of water content with the degradation profile or drug-release characteristics of capsules.

Moisture permeation test
The USP requires determination of the moisture-permeation characteristics of single-unit and unit dose containers to assure their suitability for packaging capsules. The degree and rate of moisture penetration is determined by packaging the dosage unit together with a colour-revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for colour change (indicating absorption of moisture) and comparing the pre-test and post-test weight of the packaged unit.

Microbial content
The capsules are tested to ensure lack of growth of bacteria and mould by microbiological tests. These tests are usually carried out by incubation of the capsule contents in a growth medium and counting the colonies formed after a predefined period of time. Selection of the growth medium and duration of the test, as well as maintenance of aseptic conditions during the testing, are critical to successful assessment of microbial contamination by this method.

Shelf-life test[14]
These tests are frequently carried out after defined periods of storage at predetermined conditions. They help to assign and verify the shelf life and usability of the drug product.

Stability testing of capsules
Stability testing of capsules is performed to determine the physicochemical stability of the drug substance in the finished drug product under specified package and recommended storage conditions intrinsic stability of the active drug molecule and the influence of environmental factors (e.g., temperature, humidity, light), on formulation components, and the container and closure system. The battery of stress-testing, long-term stability and accelerated stability tests help determine the appropriate storage conditions and the product's anticipated shelf life.

Packaging and storage of capsules
Packaging and storage of hard gelatin capsules[15]
Finished hard gelatin capsules normally contain an equilibrium moisture content of 13 to 16%. This moisture is critical to the physical properties of the shells since at lower moisture contents (<12%), shells become too brittle and may crack when exposed to the appropriate stress. At higher moisture contents (>18%) they become too soft and may lose shape. It is therefore important to avoid extremes of temperature and to maintain a relative humidity of 40 to 60% when handling and storing capsules.

The bulk of the moisture in capsule shells is physically bound, and it can readily transfer between the shell and its contents, depending on their relative hygroscopicity. The removal of moisture from the shell could be sufficient to cause splitting or cracking, as has been reported for the deliquescent materials potassium acetate and sodium cromoglycate. Conditions that favour the transfer of moisture to powder contents may lead to caking and retarded disintegration or other stability problems. It may be useful to first equilibrate the shell and its contents to the same relative humidity within the acceptable range before filling.

Another problem that has received substantial attention in recent years is the loss of water solubility of shells, apparently because of sufficient exposure to high humidity and temperature or to exposure to trace aldehydes. Such capsules develop a "skin" or pellicle, during dissolution testing, exhibit retarded dissolution, and may fail to meet the USP drug dissolution specifications. This decrease in solubility of gelatin capsules is presumed to be the result of gelatin cross-linking caused by impurities such as formaldehyde.

Hard gelatin capsules can be individually protected by enclosure in strip or blister packs. In the former, the units are hermetically sealed in strips of aluminium foil or plastic film. In the latter one of the films enclosing the units is formed into blisters. An ideal foil or film for these packs should be:

- Heat stable
- Impermeable to moisture, water vapour, air, and odours
- Strong enough for machine handling
- Reasonably easy for patients to tear and open

Packaging and storage of soft gelatin capsules[14]
Soft gelatin capsules generally contain the medicament dissolved or dispersed in oils or hydrophilic liquids (i.e., fill liquid). The inherent flexibility of the soft gelatin capsule is due to the presence of plasticizers and residual moisture in the capsule shell. Thus, the soft gelatin capsule is a more dynamic system than conventional tablets. The atmospheric moisture may permeate into the capsule shell or into the fill liquid. The drug or fill liquid may migrate into the capsule shell, while the plasticizer or residual water in the gelatin shell can potentially migrate into the fill. Volatile components in soft gelatin capsules may escape into the atmosphere. It is these characteristics that must be considered when designing a shelf life stability program for soft gelatin capsules.

In most instances, the recommended storage conditions are stated on the label in which case it is imperative to maintain stability. Normally, the recommended storage conditions for empty capsule shells are 15 to 25°C and a relative humidity of between 35% and 65%. This condition is designed to minimize moisture absorption or loss, and the resultant changes in physical dimensions, during the encapsulation operation. While there is no strict guidance for stability testing of soft gelatin capsules, there are a couple of guidelines available that will help evaluate the storage conditions and length of study required for specific formulations of soft gelatin capsules.

The guidelines indicate that testing of soft gelatin capsules should be evaluated in terms of appearance (including brittleness), color, and odor of content, assay, degradation products, dissolution, microbial content, pH, leakage, and pellicle formation. Also, fill medium should be examined for precipitation and cloudiness. In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test the thermal stability, and if applicable, its sensitivity to moisture or potential for solvent loss. If it is determined that a particular product is heat sensitive, then these drug products should be stored under an alternative lower temperature condition which will eventually become the designated long-term storage temperature. For example, a 30°C storage condition versus a 40°C condition may be justified.

Future perspective

In recent years, the interest in using hard gelatin capsules in developing and manufacturing medicines has increased considerably. This is most probably due to rapid advances in capsule dosage form. The choice available in terms of capsule type, the range of sizes, the capsule's attractive appearance and printing directly onto the capsule, ensure better patient compliance, product recognition and product differentiation. The demand for plant-based capsules will grow as customers look for performance, quality and lifestyle fit. The unique features of non-animal capsules offer distinct advantages in manufacturing ease, marketing, global certification, dissolution profiles, delivery of specific ingredients and more. For multiple-units, hard and soft gelatin capsules are the ideal solution. The latest developments in the field of formulation in hard gelatin capsules (HGC) offer new opportunities for filling liquid and semi-solid formulations in them, as a rapid and easy sealing technology is now available and the capital outlay is reasonable. Formulation in liquid dosage form incorporated in HGC enhances the bioavailability of several slightly soluble drug actives. Also controlled release characteristics can be developed using semisolid formulation. The combination of liquid-filled formulations with coatings that will reliably deliver the capsule contents to the colon (for example, Encap's ENCODE colonic coating technology) where there is minimal water for dissolution of conventional powder filled capsules or tablets could be a major advance for the delivery of many drugs including proteins and peptides – a growing area of interest to the pharmaceutical industry. With appropriate process controls, careful machine set-up and trained operators, leak-free liquid filled HGC products can be manufactured. It is likely that there will be further developments in the area of sealing technology. Mapping of drugs is particularly valuable for modified release development and for compounds in which local enteric delivery is central to the product target profile. The electronic and magnetic capsule drug delivery enables the conventional capsule for novel therapies, diagnosis, localized drug delivery, modified release and the next move for monitoring drug absorption in developmental stage (i.e. clinical evaluation).

Soft gelatin capsules are available in many sizes to provide dosing flexibility. Unpleasant drug tastes and odors can be masked by the tasteless gelatin shell. They are suitable for encapsulation of lipid solutions, fish oil, suspensions, or paste-like formulations, making them a useful option when formulating poorly water-soluble drugs. This will inherently lead to better absorption of the active ingredient as compared with delivery in a tablet or as a powder. Development of soft gelatin capsule (soft gel) dosage form is of growing interest for the oral delivery of poorly water soluble compounds (BCS class II or class IV). There are establishments and an on-going development of the manufacturing technology for liquid fill capsules with focus on progress and challenges of soft gelatin capsules formulation in oral administration for improved solubility and as an absorption-enhancing technique. These considerations form a basis for new applications in oral drug delivery.

Capsule manufacturers will continue to improve the materials, processes, and related technologies to this versatile dosage form.

CONCLUSION

From the above premises, capsules are solid preparations in which drug substance(s) and/or excipients are enclosed in either a soft or hard soluble shell. The shell is normally made from gelatin or other suitable polymeric material and results in a simple, tasteless, odourless, elegant, easy-to-swallow dosage form without the need for a secondary coating step.

Depending on the composition of the capsule shell, capsules may be classified as either hard or soft capsule, with soft capsules possessing a flexible, plasticized gelatin film. The shells may be composed of two pieces in the form of cylinders closed at one end; the shorter piece, called the 'cap' and the longer piece, called the 'body', or they may be composed of a single piece. The two-piece capsules and one-piece capsules are commonly referred to as hard-shell capsules and soft-shell capsules respectively.

Capsules may be filled with a range of formulation types including dry powders, semisolids, nonaqueous liquids, and other dosage forms such as beads, mini-tablets, and even mini capsules most of which are intended for oral administration. There are also specialty applications such as capsules that can be loaded into dry-powdered inhalers, add reagents as part of a diagnostic kit, and occasionally soft-shell capsules intended for rectal or vaginal insertion as suppositories.

Also, In the recent advancements, non-gelatin capsules have been discovered, which do not contain gelatin as it's shell-forming agent. Under this category of capsules are the HPMC, PVA and starch capsules.

Regardless of the type of capsule, the basic components of these capsules include but not limited to; gelatin, plasticizer, colourants, opacifying agents, preservatives, water, thickening agents, flavouring agents, sweetening agents, etc.

Hard gelatin capsules are manufactured using a dip-coating method which involves the preparation of the gelatin solution (dipping solution), dip-coating the gelatin solution on to metal pins (moulds), rotation of the dip-coated pins, drying of the gelatin-coated pins, stripping and trimming, joining of the trimmed capsule shell and printing. Also, the basic steps in filling hard gelatin capsules include; rectification of capsules, separation of caps from bodies, dosing of fill material replacement of caps/ closing capsule shells and, ejection of filled capsules, which is then followed by locking and sealing, polishing and brushing among others. On the other hand, softgels are manufactured using the following methods; plate process, rotary die process, reciprocating die process, accogel process and, seamless process. The soft gelatin manufacturing and filling occurs simultaneously.

The quality control process s involves the in-process testing, finished product testing and shelf-life testing. The in-process quality control tests for soft gelatin capsule drug products are carried out at predefined intervals during the product manufacturing which involves; gel ribbon thickness and uniformity across the ribbon, softgels seal thickness at the time of encapsulation, weight of the capsule fill and its variation from capsule-to-capsule, weight of the capsule shell and its variation from capsule-to-capsule and, moisture level of the capsule shell before and after drying. Visual inspection, fill weight, and fill-weight uniformity are the key in-process tests used for hard gelatin capsules. Also, the finished product quality control tests for capsule drug products include; permeability and sealing, potency and impurity content, weight variation test, weight variation test for hard gelatin capsules, weight variation test for soft gelatin capsules, uniformity of content, disintegration time test for capsules, dissolution test for capsules, moisture content, moisture permeation test and, microbial content. While the shelf-life test involves the stability testing of capsules.

The main aim of packaging of filled capsules is to prevent contamination and moisture gain or loss during long term storage. They are plastic blister packed or aluminium foil strip packed or packaged in glass or other materials which are designed in such a way that they prevent exposure of capsules to excessive humidity. On the other hand, the storage which can be for a very long time period requires proper maintenance of temperature and humidity.

Recommendation

It is recommended that going by available research articles, research should be focused on non-gelatinous capsules, improvement of gelatinous capsules, and, also presentation of capsule shells that will suit various norms, cultures and, religions of various societies to mention but few.

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