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Review Article

A Comprehensive Review On: Capsule

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ABSTRACT

Capsules are a popular dosage form due to their stability, ease of administration, attractiveness, and compounding capabilities. They can be customized to meet individual patient needs and can incorporate multiple drugs. Special capsules can be prepared outside the norm of powders. Gelatine is widely used as a capsule shell material for hard and soft gelatine capsules. However, due to its animal origin and cross-linking properties, other non-animal materials like hydroxyl propyl methyl cellulose, starch, and poly vinyl alcohol copolymer are needed to meet the dietary and cultural needs of vegetarian patients and comply with regulatory requirements.

INTRODUCTION

Capsule is the most versatile of all dosage forms. Capsules are solid dosage forms in which the drug substance is enclosed in either hard [or] soft soluble containers [or] shell of a suitable form of a gelatine. The medication may be powder or a liquid or a semi solid mass.

- Capsules are usually intended to an administration orally by swallowing them whole.
- Occasionally capsules may be administered rectally [or] vaginally.
- Gelatine capsule shells may be hard [or] soft depending on their composition
- Enclosing the medication within capsule shell provides a tasteless, odourless means of administering medication.
- The solubility of gelatine at gastric Ph provides the rapid release of medication in the stomach.
- Packaged and shipped by manufacture at lower cost less breakage than liquids forms.
- The contents may be removed from the gelatine shell and employed as a premeasured medicinal powder. The capsule shell being use to contain a dose of the medicinal substance. E.g. Theo-dur sprinkle.

Advantages:

- Neat and elegance in appearance.

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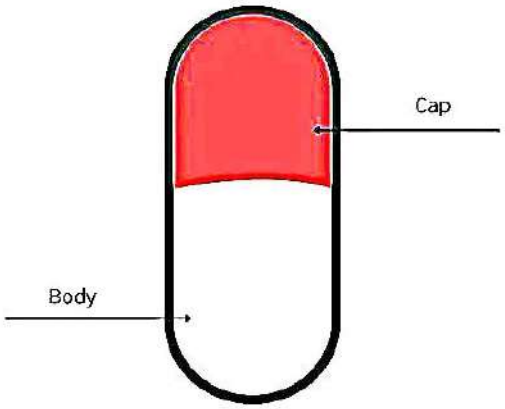

Disadvantages:

- Capsules are not suitable for liquids that dissolves gelatine, such as aqueous are hydro alcoholic solutions.
- The concentrated solutions which require previous dilution is unsuitable for capsule because if administered as such lead to irritation into stomach.
- Not useful for efflorescent or deliquescent materials. Efflorescent cause capsules to soften and deliquescent may dry the capsule shell to brittleness. Ver
- very soluble salts such as bromides, iodides should not be dispensed in capsules, as the rapid release of such materials may cause gastric irritation.

Types of capsules:

Two primary types of capsules exist:

1. Hard-shelled capsules, containing dry, powdered ingredients or miniature pellets generated through processes like extrusion or spheronization. These capsules comprise two halves: a smaller-diameter "body" filled with the medication and sealed using a larger-diameter "cap." Both classes of capsules are manufactured from aqueous solutions of gelling agents, such as animal proteins (predominantly gelatin) or plant polysaccharides or their derivatives (like carrageenans and modified starch and cellulose forms). Additional ingredients, such as plasticizers like glycerin or sorbitol, may be incorporated into the gelling agent solution to adjust the capsule's hardness

CAPSULES TYPE

Scholarly articles discuss several capsule types, including soft gelatin capsules, hard gelatin capsules, Hydroxypropylmethyl cellulose (HPMC) capsules, Polyvinyl alcohol (PVA) capsules, and starch capsules. These variations can be categorized broadly into gelatinous and non gelatinous capsules

SOFT GELATIN CAPSULES

GENERAL ASPECTS

Soft gelatin capsules were originally developed in the 19th century with the aim of masking the unpleasant taste and odor of drug substances. Since then, they have found applications in various fields, including pharmaceuticals, health and nutrition products, cosmetics, and recreational products like paintballs In the pharmaceutical sector, soft gelatin capsules are increasingly favored for strategic reasons such as line extension, technological advantages such as high content uniformity of low-dose drugs, safety considerations like reduced operator and environmental contamination with highly potent or cytotoxic compounds, and consumer preference due to ease of swallowing. Recent advancements in soft gelatin capsules have focused on developing liquid and semi-solid formulations to address specific bio performance issues. These advancements aim to enhance bioavailability and reduce plasma variability through improved solubility and absorption-enhancing techniques

BASIC COMPONENT OF SOFT GELATIN CAPSULE SELL

a. Gelatin

Soft gelatin capsule shells consist of gelatin, which can be in various formulations depending on the liquid fill matrix. Most commonly, it is alkali- or base-processed (type B) and makes up 40% of the wet molten gel mass. Type A acid-processed gelatin can also be used. The properties of these

shells are controlled by the gelatin grade and plasticizer concentration.

b. Plasticising agents

Soft gelatin capsules use plasticizing agents to enhance flexibility and hygroscopicity. Glycerol is the most common plasticizer, but other materials like sorbitol, mannitol, and polypropylene glycol can be used in combination. These agents interact with gelatin chains to reduce the glass transition temperature.

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

Less commonly utilized excipients may encompass flavoring agents and sweeteners, aimed at enhancing palatability. Acid-resistant polymers are employed to confer enteric release properties, and they can also facilitate the formulation of chewable soft gelatin capsules. Additionally, a chelating agent like ethylene diamine tetraacetic acid (EDTA) may be included to prevent chemical degradation of oxidation-sensitive drugs catalyzed by free metals in gelatin, such as iron.

HARD GELATIN CAPSULES

GENERAL ASPECT

The primary material utilized in the majority of capsule products is hard gelatin capsules. Comprising two shells, namely the capsule body and a shorter cap, these capsules are designed to fit tightly over each other. The basic composition of hard gelatin capsule shells typically includes mixtures of gelatin, sugar, and water, resulting in clear, colorless, and essentially tasteless shells

Hard gelatin capsule shells are manufactured and provided empty to the pharmaceutical industry by shell suppliers, after which they are filled in a separate filling operation. During the capsule filling process, the body is filled with the drug substances, and then the shell is sealed by joining the body and the cap together

A. Gelatin

Gelatin stands as the predominant and widely recognized material utilized in the production of hard capsule shells. It represents a general designation for a blend of purified protein fractions derived from the irreversible hydrolytic extraction of collagen sourced from animals' skin, white connective tissue, and bones.

B. Plasticizer

Plasticizers are incorporated into gelatin to decrease its stiffness and enhance its flexibility. Typical examples of plasticizers include glycerine and polyhydric alcohol. Additionally, water serves as a natural plasticizer and is inherently present in gelatin.

C. Colourants

Hard gelatin capsules are often colored to improve their visual appeal and serve as a method of product identification. The colorants employed must comply with the regulatory standards of the countries where the product will be marketed.

Commonly used capsule colorants include synthetic dyes like azo dyes and xanthene dyes, as well as iron oxide pigments.

D. Opacifying agents

Opacifiers, such as titanium dioxide, might be added to transform transparent gelatin into an opaque form. Opaque capsules can serve purposes like shielding against light exposure or concealing the contents.

E. Preservatives

In the past, preservatives, commonly paraben esters, were incorporated into hard capsules during manufacturing to prevent microbiological contamination. However, manufacturers adhering to Good Manufacturing Practice (GMP) guidelines have discontinued their use. In the finished capsules, moisture levels typically range from 12% to 16% w/v. This level of moisture is tightly bound to the gelatin molecule, resulting in a water activity insufficient to support bacterial growth.

Special types of hard gelatin and soft gelatin capsules Altered Release

The release rate of capsule contents can be influenced by the drug's nature and the capsule excipients. For water-soluble drugs, hydrophilic and neutral excipients are preferred for fast release. For slow release, hydrophobic excipients reduce drug dissolution. For insoluble drugs, hydrophilic excipients provide faster release. Hydrophobic and neutral excipients slow release. Rapid capsule release can be achieved by piercing holes or adding sodium bicarbonate and citric acid to facilitate capsule opening through carbon dioxide evolution.

COATING CAPSULES

Coating capsules enhances appearance, conceals taste, and prevents medication release in the stomach. These coatings require advanced formulation skills and quality control equipment in manufacturing facilities. They can delay active drug release until it reaches a specific gastrointestinal tract area.

SUSTAINED RELEASE CAPSULES

The conventional dosing regimen of multiple doses throughout the day often results in fluctuations in blood concentration of the medication, alternating between excess and deficiency. To address this issue while reducing the frequency of dosing, a method involves administering a capsule containing multiple coated pellets that release the drug gradually over an extended period. Initially, the finely powdered drug is transformed into pellets by binding it to sugar granules using an adhesive. These pellets undergo treatment with protective coatings that delay drug release, with each batch receiving coatings of varying thicknesses. After thorough mixing, appropriate doses are filled into capsules. For instance, a mixture might comprise 30% uncoated pellets for immediate drug release, 30% each of coated pellets releasing at 4 hours and 8 hours, and 10% neutral pellets solely used for capsule filling. Each batch may be uniquely colored for easier identification and better control during mixing

LIQUID FILLED HARD GELATIN CAPSULES

Many New Chemical Entities (NCEs) are poorly water-soluble, making traditional methods insufficient for drug adsorption in solid oral dosage forms. To address this, dissolved systems like lipids, liquids, or semi-solids can be used to formulate new products. Two-piece hard-shell capsules are a logical approach for delivering these new liquid formulations, as they offer a more efficient and effective dosage form.

NON-GELATIN CAPSULES

Historically, gelatin has been the predominant material utilized for forming capsule shells. However, recent advancements have introduced non-gelatin capsules, which do not rely on gelatin as their shell-forming agent. Examples of such capsules include those made from HPMC, PVA, and starch.

HPMC CAPSULES

The demand from commercial and nutraceutical markets has stimulated the exploration of alternative materials for traditional gelatin capsule shells, tailored to specific requirements. Formulators seek non-cross-linking capsules that are thoroughly characterized, compatible with existing excipients and assays, and exhibit dissolution properties similar to gelatin. Marketing seeks capsules that align with dietary and cultural preferences of patients. Manufacturers aim for capsules with gelatin-like performance that can be processed using existing filling equipment. Regulatory bodies prioritize capsule polymers with established safety records and broad regulatory acceptance. Clinicians prioritize patient compliance assurance when selecting capsule materials

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

STARCH CAPSULES

The formulation of soft capsules can incorporate conventional plasticizers like glycerol and sorbitol, creating a molten mass that can be extruded and set within 20 seconds on temperature-controlled casting drums. This results in mechanically strong and elastic films. Sealing can occur at temperatures between 25°C and 80°C through a fusion process similar to soft gelatin capsules. Prototype capsules with lipophilic fill formulations display a shiny appearance and excellent stability during storage. These capsule shells lack crosslinking and demonstrate greater mechanical stability compared to soft gelatin shells. However, formulating with hydrophilic fills may pose similar challenges. The dissolution mechanism of soft capsules differs significantly from that of soft gelatin capsules. The capsule shell undergoes swelling upon contact with enzyme-free aqueous medium at 37°C, with capsule content release occurring when the shell bursts at its weakest point. In vivo conditions may trigger capsule shell dissolution by enzymatic degradation. Another International Patent Application, WO 0 137 81730, describes the formation of soft capsules using potato starch, glycerol, glidant, and disintegrant.

CAPSULE FORMULATION

Hard gelatin capsule formulation

Hard gelatin capsules are more commonly used for solid dosage forms than soft ones, with their utilization being about 10-fold higher. These capsules are fabricated and supplied empty to the pharmaceutical industry, followed by a step-by-step process requiring strict quality control.

Manufacture of Hard Gelatin Capsules

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 produced under controlled environmental conditions by immersing pairs of standardized steel pins, comprising body and cap components, into an aqueous gelatin solution maintained at approximately 50°C within a jacketed heating pan. As the molds are kept below the gelling temperature, the gelatin starts to create a thin layer or film on them. The arrangement of rows of pins is such that caps are formed on one side of the machine while bodies are concurrently formed on the opposite side.

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

After the gelatin is evenly spread across the mold, a burst of cool air is applied to solidify it. Following this, the gelatin is dried, and the pins undergo multiple drying phases to reach the desired 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

After trimming, the two halves of the capsule (the cap and body) are brought together to the pre-closed position using a pre-lock mechanism. If necessary, printing is performed at this stage before the capsules are packed into cartons for shipping.

Step 7: Printing

After that formation of the capsule shell 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.

FILLING OF HARD GELATIN CAPSULES

Hard gelatin capsule filling is a widely used process with various equipment options, including manual machines for small-scale operations, semi-automatic systems for intermediate production, and fully automatic machines for large-scale manufacturing. Hand-filling is also common in compounding pharmacies, with the main difference being the measurement of material dosage into the capsule body.

The basic steps in filling hard gelatin capsules include

- Rectification of capsules involves positioning empty gelatin capsules on a removable plate with their bodies facing downward.
- Separation of caps from bodies entails dividing the two parts of the capsule, distinguishing between the cap and the body.
- The dosing of fill material entails manually filling the capsule body with the formulation using a plastic spatula, after which any extra powder is eliminated.
- Placing the caps onto the bodies and sealing the capsule shells and
- Removing the filled capsules from the equipment.

Filling of liquids/semisolid formulations into hard gelatin capsules

Drug discovery is focusing on improving drug solubility through liquid-based formulations containing lipids, solvents, or surfactants. These formulations can be filled into hard gelatin capsules as a room temperature liquid or molten semisolid. The filling depends on the formulation's viscoelastic properties and filling temperature requirements. The formulation should have a viscosity between 50 and 1000 Centipoise (cP) and not exceed 70°C. Higher viscosities may be suitable for manufacturing, but higher formulations can be suitable for manufacturing.

Liquid Excipients Compatible with Hard Gelatin Capsule Shells

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

To ensure that the caps remain attached to the bodies during packaging, transportation, and storage, manual or hand-filled capsules undergo locking and sealing processes. These procedures also help prevent the leakage of capsule contents. Various methods are employed by different manufacturers for locking and sealing the capsules, including

- 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. 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.

Vehicles used in soft gelatin capsules

Soft gelatin capsules are designed to hold various types of fill materials, including liquids, pastes, and dry substances. Examples of liquids suitable for encapsulation in soft gelatin capsules are as follows:

- 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

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

The majority of soft gelatin capsules are manufactured using the rotary die process, which was developed and refined by Robert P. Scherer in 1933. This method significantly addressed the issues associated with the plate process and resulted in soft gelatin capsules with enhanced uniformity and precision. In the rotary die process, two plasticized gelatin ribbons, prepared within the rotary-die machine, are continuously and concurrently fed with the liquid, semiliquid, or paste fill between the rollers of the rotary die mechanism. The feed material is forcibly injected between the two ribbons, causing the gelatin to expand into the left- and right-hand die pockets that determine the size and shape of the softgels as they come together. As the die rolls rotate, the matching die pockets converge, hermetically sealing and cutting out the filled capsule.

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

While the rotary die process and reciprocating die process were effective in producing soft gelatin capsules with oily liquids and pastes, Lederle Laboratories introduced the accogel process in 1949 to manufacture capsules containing powders and granules continuously. This method utilizes a measuring roll to hold the fill formulation in its cavities, positioned above a flexible gelatin ribbon. The ribbon is pulled into the capsule-shaped cavities of the capsule die roll using vacuum pressure. The fill material is then deposited into these cavities by the measuring rolls. Subsequently, the die roll meets the rotating sealing roll, which is covered with another layer of elasticized gelatin, to seal and cut the formed capsules through the pressure generated by the convergence of the two rotary rolls.

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

During the development and filling of capsules, various quality control examinations are conducted to guarantee compliance with the standards outlined in official compendiums and the conventional requirements set by industries over time. These examinations will be outlined in three phases: in-process evaluation, assessment of finished products, and testing for shelf-life

In-process quality control tests for capsule drug products 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 process of encapsulating soft gelatin capsules, the subsequent factors are typically carefully observed and regulated:

- The consistency and evenness of the gel ribbon's thickness along its entirety.
- The thickness of the seal on the softgel during the encapsulation process
- The weight of the fill material inside the capsule and its variability among individual capsules
- The weight of the capsule casing and its variability among individual capsules
- The moisture content of the capsule covering both before and after the drying process
- Visual examination, weight measurement of the fill, and uniformity of fill weight are crucial in-process assessments applied to hard gelatin capsules.

Finished product quality control tests for capsule drug products

Completed capsules undergo a series of evaluations as per compendial standards and regulatory guidelines for unit dose capsule products. These sets of assessments aid in determining the acceptability of the batch for marketing or its intended use. The finished capsules are assessed through the following tests:

Permeability and sealing

Soft gelatin capsules undergo visual inspection to ensure their physical integrity, confirming the absence of any leakage. Likewise, hard gelatin capsules are examined for any signs of physical damage such as breakage or separation of the cap and body.

Potency and impurity content

Every capsule undergoes testing to determine its drug content, assessing its potency as a percentage of the labeled claim. Furthermore, the majority of drug products are examined for related substances or impurities, all of which must meet predetermined specifications for the batch to be deemed acceptable.

Weight variation test

The consistency of dosage units can be illustrated through either assessing weight variance or content uniformity. Here's the weight variance method.

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

The assessment of disintegration for both hard and soft gelatin capsules aims to ensure that the drug substance is readily available for dissolution and absorption within the gastrointestinal tract. The standardized disintegration test outlined in compendial guidelines for both types of capsules involves utilizing the same apparatus and procedure detailed in the document titled "Quality Control Tests for Tablets." Capsules are positioned within a basket-rack assembly and immersed in a temperature-controlled fluid bath set at 37 ± 2 ˚C. The assembly undergoes repeated lowering movements at a rate of 30 times per minute, and the disintegration process is observed over a duration specified in the relevant 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

The Karl Fischer titration method is employed to ascertain the water content of either the complete capsule or its contents. This analysis aids in establishing a relationship between water content and the degradation pattern or drug release properties of the capsules.

Moisture permeation test

The USP mandates assessing the moisture permeation properties of individual and unit dose containers to ensure they are appropriate for encapsulation packaging. This involves placing the dosage unit with a color-indicating desiccant pellet, subjecting the packaged unit to controlled humidity levels for a specific duration, monitoring the desiccant pellet for color alteration (signifying moisture absorption), and comparing the weight of the packaged unit before and after the test.

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 contamination by this method.

shelf-life test

Often, these tests are conducted following specific periods of storage under predetermined conditions. They assist in determining and confirming the shelf life and suitability of the drug product for use.

Stability testing of capsules

Stability testing of capsules is conducted to assess the physical and chemical stability of the drug substance within the final product under specified packaging and recommended storage conditions. This involves examining the inherent stability of the active drug molecule and how environmental factors such as temperature, humidity, and light affect formulation components, as well as the container and closure system. By employing a series of stress tests, long-term stability assessments, and accelerated stability tests, appropriate storage conditions and the expected shelf life of the product can be determined.

PACKAGING AND STORAGE OF CAPSULES

Packaging and storage of hard gelatin capsules

Hard gelatin capsules have a moisture content of 13-16%, which is crucial for their physical integrity. Moisture levels below 12% can cause brittle shells, while levels above 18% can cause soft shells. To maintain their shape, capsules should be handled and stored at a relative humidity of 40-60%. Most moisture in capsule shells is physically bound and can transfer between the shell and its contents. Removing moisture can cause splitting or cracking, while environments conducive to moisture transfer can cause clumping and stability issues. It's recommended to equalize humidity levels before filling. Another issue is the reduction in water solubility of capsule shells due to prolonged exposure to high humidity and temperature, or trace amounts of aldehydes. This can lead to a "skin" or pellicle, delayed dissolution during testing, and not meeting the US Pharmacopeia's drug dissolution criteria. This decline is believed to be caused by gelatin cross-linking induced by impurities like 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:

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

packaging and storage of soft gelatin capsules

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

The use of hard gelatin capsules for medicine development and production has seen a significant increase in recent years due to advancements in capsule dosage forms. The diverse options available in capsule types, sizes, appearance, and direct printing contribute to improved patient compliance, product recognition, and differentiation. Plant-based capsules are also in high demand due to their performance, quality, and alignment with lifestyle choices. Non-animal capsules offer advantages in manufacturing, marketing, global certification, dissolution profiles, and targeted delivery of specific ingredients. Both hard and soft gelatin capsules are ideal for multiple-unit formulations. Recent developments in hard gelatin capsule formulation have opened up new possibilities for filling them with liquid and semi-solid formulations, facilitated by rapid and convenient sealing technologies. Combining liquid-filled formulations with coatings designed to reliably deliver the capsule contents to the colon represents a significant advancement in drug delivery, particularly for drugs like proteins and peptides. Electronic and magnetic capsule drug delivery systems enable conventional capsules to be utilized for innovative therapies, diagnosis, localized drug delivery, modified release formulations, and monitoring drug absorption during clinical evaluation stages. Soft gelatin capsules come in various sizes and mask unpleasant drug tastes and odors due to their tasteless gelatin shell. They are well-suited for encapsulating poorly water-soluble drugs, enhancing absorption compared to tablet or powder delivery. Continuous progress in manufacturing technology for liquid-filled capsules focuses on advancing soft gelatin capsule formulations for oral administration to improve solubility and enhance absorption. Capsule manufacturers will continue to enhance materials, processes, and associated technologies for this adaptable dosage form.

CONCLUSION

Capsules are solid formulations enclosed within a soluble shell, either hard or soft. These shells are typically made of gelatin or similar polymeric materials, providing a tasteless, odorless, and easily ingestible dosage form. Capsules can be filled with various formulations, including dry powders, semisolids, nonaqueous liquids, and other dosage forms like beads, mini-tablets, and mini capsules. Recent advancements have

introduced non-gelatin capsules that use alternative shell-forming agents, such as HPMC, PVA, and starch. The fundamental constituents of these capsules include gelatin, plasticizers, colorants, opacifying agents, preservatives, water, thickening agents, flavoring agents, and sweetening agents. Hard gelatin capsules are produced using a dip-coating technique, while softgels are manufactured using methods such as the plate process, rotary die process, reciprocating die process, accogel process, and seamless process. Soft gelatin manufacturing and filling occur simultaneously. The quality control process includes in-process testing, finished product testing, and shelf-life testing. In-process tests focus on parameters such as gel ribbon thickness and uniformity, softgel seal thickness during encapsulation, fill weight and consistency between capsules, shell weight and consistency between capsules, and moisture level of the capsule shell before and after drying. Finished product quality control tests assess permeability and sealing, potency and impurity content, weight variation, content uniformity, disintegration time, dissolution rate, moisture content, moisture permeation, and microbial content. Shelf-life testing involves stability assessments of capsules Packaging filled capsules is crucial to protect them against contamination and prevent moisture gain or loss during extended storage periods. They are typically enclosed in plastic blister packs, aluminum foil strips, or glass containers, designed to shield the capsules from excessive humidity exposure. Long-term storage requires meticulous temperature and humidity control to maintain capsule integrity over time.

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