WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 13, 316-335. Review Article ISSN 2277–7105

A COMPREHENSIVE REVIEW ON THE FORMULATION, MANUFACTURING, AND EVALUATION OF PHARMACEUTICAL CAPSULES

Kavya S. U.*, Annapoorna T., S. Umme Shifa, Prashant H. K., Rohan Ahmmod, Mehebub Alom

Department of Pharmaceutics, SCS College of Pharmacy, Harapanahalli-583131, Karnataka, India.

Article Received on 27 May 2026,
Article Revised on 17 June 2026,
Article Published on 01 July 2026,

https://doi.org/10.5281/zenodo.21023877

***Corresponding Author**

Kavya S. U.

Department of Pharmaceutics, SCS College of Pharmacy, Harapanahalli-583131, Karnataka, India.

How to cite this Article: Kavya S. U.*, Annapoorna T., S. Umme Shifa, Prashant H. K., Rohan Ahmmod, Mehebub Alom (2026). A Comprehensive Review On The Formulation, Manufacturing, And Evaluation Of Pharmaceutical Capsules. World Journal of Pharmaceutical Research, 15(13), 316–335.

ABSTRACT

Capsules are widely utilized in oral drug delivery due to their ease of administration, formulation adaptability, and manufacturing efficiency. This review provides a detailed overview of hard and soft gelatin capsules, including their raw materials, shell composition, production processes and structural characteristics. The physicochemical properties of gelatin, particularly the influence of moisture content on mechanical strength, shell flexibility, integrity and stability, are examined critically. Distinctions between hard and soft gelatin capsules in terms of formulation design and functional applications are outlined. Standard evaluation procedures, including disintegration testing, moisture analysis, weight uniformity assessment, and structural integrity testing, which are essential for ensuring product performance and regulatory compliance, are discussed. The influence of environmental factors such as temperature and humidity on capsule stability is also addressed. The review further highlights recent advancements in capsule technology aimed at improving formulation, performance and regulatory compliance. Collectively, these considerations underscore the importance of integrated formulation and quality control strategies in ensuring consistent therapeutic effectiveness and product reliability.

KEYWORDS: Hard gelatin capsule, Soft gelatin capsule, Capsule manufacturing, Excipients, Quality control, Non-gelatin capsules.

INTRODUCTION

Drugs: A drug is a chemical substance or molecule introduced into the body to trigger a specific biological response. It works by altering normal biochemical pathways, typically by binding to a cellular receptor or changing how a specific enzyme functions.[1]

Dosage form: Dosage forms are the final, ready-to-use pharmaceutical products that combine active drug molecules with inactive excipients. They are precisely formulated into specific doses and can be manufactured as solid, liquid or semisolid preparations, depending on their intended physiological target. Common examples include tablets, capsules, and therapeutic syrups. Ultimately, the type of dosage form dictates the route of administration for the medication.[2]

Capsule: Capsules are unit solid dosage forms containing drugs in small gelatin shells. The word capsule comes from the Latin word "capsula" which simply means small container. Capsules are considered as primary oral dosage form due to the ease of manufacturing process compared to other dosage forms.[3]

History: In 1830 Joseph Gerard Auguste Dublanc and Francois Achille patented the first capsule, which was formulated from soft gelatin. Similarly, in 1846, a two-piece hard capsule was patented by Jules Lehuby.[4]

Advantages

- Medicines can be administered in a tasteless and odorless manner by enclosing them in a capsule shell.[4]
- The quick release of medicine in the stomach is made possible by gelatin's solubility at gastric pH.[4]
- Capsules are manufactured, packed and shipped at a lower cost with less damage than liquid form.[4]
- They are cost effective and simple to handle and transport.[5]
- Manufacturer's name and product code are carved or imprinted on their surface, making them easily recognizable.[4]
- To provide light shielding, the shells are tinted or opacified (using titanium dioxide).[5]

Disadvantages

- Liquids that dissolve gelatin, including aqueous or hydroalcoholic solutions are incompatible with capsules.[6]
- Concentrated solutions that need to be diluted previously are not ideal for capsules because they cause GI irritation.[5]
- Deliquescent materials may dry the capsule shell to brittleness.[6]
- Effervescent materials may cause the capsule to soften.[6]
- Hygroscopic medications should not be filled into capsules because they will absorb the water in the capsule shell, making it extremely brittle.[5]

Types of capsules

A. Soft gelatin capsule: Soft gelatin capsules are single-unit solid dosage forms made out of an elastic outer shell that is sealed and contains liquid or semisolid content. They are also called one-piece capsules. The delivery of a liquid in a solid oral dosage form is made possible by soft gelatin capsules.[7]

Shape and size: The soft gelatin capsules are available in various shapes, sizes and designs. The shape, size and design of these capsules depend on the die roll. Generally, they are available in round, oval, oblong and tube-like shapes. These capsules have no specific size range but their capacity is stated in minims.[9, 10]

B. Hard gelatin capsule: It is also called two-piece capsule or dry filled capsule. They are made up of a body and a cap and are less flexible. Gelatin, water and sugar are combined to create the basic hard gelatine capsule shells. The capsules are transparent, colorless and essentially flavorless.[8]

Shape and size: Hard gelatin capsules are available in eight different sizes (000, 00, 0, 1, 2, 3, 4, and 5). The size “000” is the largest size, which has a capacity of about 1.37 ml. The size “5” is the smallest size, having a capacity of about 0.13 ml. The hard gelatin capsules are generally cylindrical in shape.[9, 10]

Table 1: Difference between hard gelatin capsules and soft gelatin capsules.[11]

Hard gelatin capsule	Soft gelatin capsule
It consists of a body and a cap.	The two halves are sealed together to make a single unit
These are mostly available in cylindrical	These capsules come in round, oval or tube-

shapes.	like shapes.
The mixture of drug and excipients is filled in the form of powders, beads or granules.	The fill materials are in the form of liquids or solids dissolved in excipients.
These capsules are generally prepared using gelatin, titanium dioxide, colorants and plasticizers.	These capsules are generally prepared using gelatin, plasticizer, and preservative.
They are sealed after filling to ensure protection during handling.	Filling and sealing is done simultaneously during manufacturing.

Applications of capsules[12]

- **Targeted drug delivery:** Capsules are designed to deliver drug content to the target site within the gastrointestinal tract, reducing side effects and enhancing medication effectiveness.
- **Inhalation therapy:** Respiratory conditions like asthma and COPD are treated using capsules in dry powder inhalers. The capsule is punctured and the drug is released in the form of fine powder.
- **Nutritional supplements:** These capsules are used to deliver vitamins, herbal products and dietary supplements.
- **Personalized medicine:** These capsules are a part of new advanced technology. These medicines are personalized according to specific requirements of individual patients.
- **Diagnostic kits:** Reagents in diagnostic kits are delivered using capsules to ensure precision and convenient application.
- **Capsules containing ophthalmic ointments:** These are sterile preparations and thus they are required to be filled in single dose containers. The capsule is punctured with a sterile needle, the medicament is applied into the eye and the shell is discarded.
- **Rectal capsules:** Pear-shaped soft gelatin capsules are used as an alternative for rectal and vaginal suppositories.
- **Enteric coated capsules:** These capsules are coated with cellulose acetate phthalate and a combination of waxes containing fatty acids or esters.
- **Sustained release capsules:** Pellets are prepared from fine powdered drug and coated with special protective coatings to delay drug release. These capsules contain 30% coated pellets (drug release in 8 hours), 30% uncoated pellets (drug release in 4 hours) and 10% neutral pellets to fill the capsule.

Gelatin: Gelatin is a major component used for preparation of capsules. Any polymer replacement for gelatin also requires the same basic properties as gelatin. It is non-toxic, soluble in biological fluids and has a good flexible film-forming property.[13]

Types of gelatin by production method

- **Type A gelatin:** It is prepared by acidic pretreatment of collagen.[14] It has an isoelectric point of pH 9.0 approximately.[15]
- **Type B gelatin:** It is prepared by alkaline pretreatment (liming) of collagen.[14] It has an isoelectric point of pH 4.7 approximately.[15]

Production of gelatin

From bones: This process starts by crushing dry bones. The crushed bones are then treated with 4-7% HCl for 10 to 14 days. This acid treatment yields dicalcium phosphate along with a substance called ossein. This ossein is then treated with 5-15% lime for 3-8 weeks. After the lime treatment it is washed and the lime is removed. In the next step, pH is adjusted to make the mixture sour (acidic). This is done by acids such as HCl, H_2SO_3, H_3PO_4, or H_2SO_4. Once the pH is adjusted the material undergoes extraction and filtration. The filtrate is then concentrated to 12-25% and dried at 32-60℃ under controlled humidity. The final product is then crushed and Type B gelatin is obtained.[16]

From skin: This process begins by washing the raw pig skin with water for 3 hours at 20℃, followed by removal of visible fat. After the removal of fat the skin is washed again for 10 hours at 20℃. Now the material is introduced to a swelling step using 3% HCl for 20 hours, followed by washing again with water for 15 hours at 20℃. The resulting material undergoes extraction using hot water at 60-80℃. The extracted material is then filtered, concentrated and cooled at 5℃ for 12 hours. Finally, the product is air-dried for 12 hours and ground to a desirable size (specifically 10 mesh size).[17]

Pre-formulation studies

Preformulation is a critical phase which provides information about physical properties and drug-excipient compatibility.[18] The main goal of preformulation studies is to collect data that can be used to formulate a stable and bioavailable dosage form that can be produced in large scale. Understanding the physicochemical properties and their biological effect helps in selecting the lead compounds and identify drug delivery problems early. Basically, preformulation studies help check if a molecule actually has good “drug-ability”. Therefore, it is a very important step for making decisions during both the drug discovery and development phase.[19]

Core study components

Solubility analysis: Drug must have good solubility to be therapeutically active. If the substances are insoluble, it can cause incomplete absorption. Preformulation involves the study of drug-solvent interactions that may occur during administration of drug. There may be bioavailability issues for medications having an aqueous solubility less than 1%.[20]

Ionization constant: The measurement of pKa or ionization constant is important in preformulation, especially because most of the drugs are either weak bases or weak acids. The ability of acidic and alkaline substances to dissolve depends upon the pH of the medium. When the pKa and pH become equal, a balance of 50% ionization and 50% unionization of the substance can be observed.[20]

Solid-state stability: Solid state reactions are difficult to determine as they are slower than solution state reactions. It happens due to a lower number of molecular contacts between drug and excipient molecules. It is done by storing sample for 1-3 weeks at a specified storage condition and then physically assessing the samples for any caking, liquefaction, odor, discoloration and gel formation.[21]

Solution state stability: This test is generally easier to perform compared to the solid state reaction. This test is done by placing the solution in additives and autoclaving the sample to determine susceptibility to oxidation, heavy metal, and exposure to light. Compatibility with ethanol, glycerin, preservatives, sucrose, and buffers are carried out in case of oral liquids.[21]

Particle engineering and micromeritics: Suitable particle size and good flow properties are very important. Small-sized particles enhance the surface area for dissolution but they can also increase cohesiveness and interfere with flow.Tools like Angle of repose and Carr's index are used to obtain necessary data required to ensure the powder flows uniformly into the capsule body.[22]

Drug-excipient compatibility: This information for known drugs is already available, but for new drugs, this test must be done for compatibility screening of new drug with excipient of each class. These classes include binders, disintegrants, lubricants and many more. Any physical or chemical drug-excipient interaction may affect the bioavailability and stability of drug and hence this study can help maximize stability.[21]

Fill excipients: Excipients are the inert substances used as medium to deliver medicaments. It helps in converting the active pharmaceutical ingredients to a suitable dosage form, ensuring its safety and efficacy. It also ensures weight consistency and volume required for administration of active pharmaceutical ingredients.[23]

- **Diluents:** Diluents are also called fillers.These are used to increase the bulk of the powder mix when the API dose is very low.This helps for accurate mechanical filling and uniform unit dosing.Lactose monohydrate is commonly used because of its properties like solubility, good compatibility, and cost-effectiveness.Microcrystalline cellulose is preferred for its dry-binding and flow properties. Dibasic calcium phosphate is used for its low moisture content and compatibility with moisture-sensitive APIs.[24]
- **Binders:** Binders are added to give cohesive properties to powders.The addition of binders helps in the preparation of strong granules that stay intact during filling, handling, and storage. Povidone is a commonly used binder (synthetic) that works in both aqueous and organic granulations.Hydroxypropyl methylcellulose is used in wet granulation and can also affect release. Starch is also used as a natural binder.[24]
- **Disintegrants:** Disintegrants are used to increase the rate of decomposition of the drug contents in gastrointestinal fluids, ensuring that the API is released for dissolution and absorption. Superdisintegrants such as croscarmellose sodium (which expands 4-8 times its volume), sodium starch glycolate, and crospovidone are particularly effective at low concentration.[24]
- **Lubricants:** Lubricants are used to reduce friction between the fill material and the capsule filling machine's metal surfaces to ensure smooth powder flow. These lubricants reduce adhesion and help in complete ejection of the filled dose. While adding lubricant, it must be kept in mind that excess addition may slow down the dissolution process. Magnesium stearate is the most commonly used lubricant; generally 0.25–2.0% w/w. Stearic acid and sodium stearyl fumarate can also be used as they have a low hydrophobic effect on dissolution.[24]
- **Glidants:** These are used to achieve better flow property of the powder by reducing interparticle friction and cohesion. This is important for obtaining a uniform die filling and consistent fill weight in high-speed automatic capsule filling machines. Colloidal silicon dioxide (0.1-0.5% w/w) is used due to its small particle size and large surface area. Talc (1-2% w/w) acts as a glidant and anti-adherent.[24]
- **Buffering agents:** Buffers are usually mixtures of weak acid or weak base and one of its salts.[24] These are the agents that allow a solution to maintain its pH when dissolved in a

solvent. These agents help in withstanding pH changes that may be caused by addition of acid or alkali. The majority of buffer systems depend on carbonate, citrate, gluconate, lactate and tartrates.[25]

- **Preservatives:** In the past, preservatives like parabens were added to hard gelatin capsules to prevent microbial contamination, but at present manufacturers follow good manufacturing practice guidelines and thus stopped using preservatives. In the finished product the moisture content is not enough to support bacterial growth. But in soft gelatin capsules preservatives such as methyl paraben, propyl paraben are used.[8]

Manufacturing process of hard gelatin capsules[3]

Step 1. Preparation of gelatin solution (dipping solution): Gelatin is dissolved in demineralized water which has been heated to 60-70℃ in a jacketed pressure vessel to form concentrated solution of gelatin. The solution contains 30-40% w/w of gelatin and it is highly viscous and thus air bubbles are formed as a result of air entrapment. The presence of bubbles would produce capsules of inconsistent weight. These bubbles may also cause problems during filling and storage. Hence vacuum is applied to remove the bubbles. Finally, colorants and pigments are added to get desired capsule appearance also sodium lauryl sulfate is added to reduce surface tension. The solution viscosity is measured and adjusted by adding hot demineralized water.

Step 2.Dip coating the gelatin solution on to metal pins: Steel pins arranged in rows on metal base are dipped in aqueous gelatin solution (25-30% w/w) maintained at 50℃ in jacketed heat pan to manufacture capsule shells. If the moulds are below gelling temperature gelatin begins to form a thin gelatin layer on mould. Pins are arranged in such a way that the caps and the bodies are formed simultaneously.

Step 3. Rotation of dip-coated pins: The base containing pins is removed after absorption of gelatin solution and rotated many times so that the solution is distributed uniformly. Uniform distribution is important for accuracy of capsule wall thickness and dome strength.

Step 4. Drying of gelatin coated pins: A blast of cool air is used to set the gelatin on the mould. The gelatin is dried and the pins are further moved for several drying stages in order to get desired moisture content.

Step 5. Stripping and trimming: Once the gelatin is dried properly and the desired moisture content is achieved the capsules are stripped off the moulds and trimmed to obtain a proper and required length.

Step 6. Joining of trimmed capsule shells: After trimming, the cap and the body are joined using a pre-lock mechanism. Here, printing is done if needed before packing in cartons for shipping.

Step 7. Printing: Capsule shells are printed for easy identification. This includes information such as product name, code number, manufacturers name, logo and dosage details. This can be done using one or two colors. This reduces the risk of product confusion between manufacturers, pharmacists, nurses, doctors, caregivers and patients.

Filling of hard gelatin capsules: Capsule filling method depends on the dose of material measured into the capsule body. Filling can be done by using the following methods.

- Very small-scale manual filling (e.g., Feton capsule filling machine).
- Intermediate scale semi-automatic filling.
- Large scale fully automatic filling.
- Hard gelatin capsule can also be hand filled one at a time manually.

Basic steps in filling hard gelatin capsule include: rectification of capsules, separation of cap from the body, dosing of fill material.

Locking and sealing of hard gelatin capsules: For capsules filled manually or by hand filled machines, locking and sealing is necessary to prevent the detachment of caps and bodies during packaging, carrying, and storage. This also prevents loss of capsule contents.

Different methods used are mentioned below.

- Banding method
- Moistening method
- Spot welding method
- Thermal welding method
- By using Coni-Snap capsules.

Manufacturing process of soft gelatin capsules[26]

Plate process: In this process a warmed sheet of gelatin is kept on a die plate which has a number of die pockets. With the help of vacuum the sheet is drawn into the die pockets. A

suitable amount of liquid medicament is poured over it. Another plate of mould is placed over and both are combined by applying pressure. Simultaneously, capsules are shaped, filled, sealed and then cut. This method is used for small scale production of soft gelatin capsule.

Rotary die process

Step 1.Production of gelatin mass which provides the soft gel shell: Gelatin is dissolved in water at 80℃ under vacuum and then plasticizer is added to prepare gel mass. After dissolving gelatin completely, coloring agents, opacifiers, flavoring agents and preservatives are added. The hot gel mass is supplied to the encapsulation machine through heated transfer pipe and by a method called casting, the two separate gelatin ribbons are formed. The gelatin is filled in metering device which controls the flow of mass into air-cooled rotary drum. During casting process gelatin passes through softgel transformer. Thickness is maintained to ± 0.1 mm. Two gel ribbons are carried by rollers for the encapsulation. Each ribbon gives one half of the softgel.

Step 2. Fill matrix: The liquid fill matrix which contains active drug substance is manufactured separately. Active fill material is manufactured using conventional mixture homogenizer, by dissolving or dispersing the drug substance in non-aqueous liquid vehicle. They also break the agglomerates of solids. Oxygen sensitive drugs can be protected by mixing under vacuum or inert gas or addition of antioxidants.

Step 3. Rotary die: It consists of two side-by-side cylinders and in each cylinder half moulds are cut. Rotary machine can produce up to 25000 to 30000 capsules per hour with accuracy of ± 1%.

Step 4. Encapsulation: Liquid gelatin is forwarded to continuous ribbons by rotating drum and brought together between two rotating dies. The gel between ribbons is forced to expand into the pockets of die to give its proper shape and size. Mechanical press is applied on die rolls and heating of ribbons is done to seal the capsule. IR drying is done and they are separated on the tray and stacked in tunnel dryer which supplies 20% relative humidity air.

Reciprocating die process: It is similar to rotary process but different in encapsulating process. Gelatin ribbons are filled between vertical dies which continuously open and close to form the rows of the pockets in gelatin ribbons. These pockets are then filled with medicines and are sealed, shaped, and cut.

Accogel process: It is another rotary process which involves measuring roll, die roll, and sealing roll. Measuring roll rotates over the die and the pockets in two rolls are aligned with each other.

The pockets contain powder or granular fill material under vacuum. Plasticized sheet is drawn into die pocket. The measuring roll and die roll rotates simultaneously and the measured doses are transferred into the pockets of die roll. The second gelatin sheet is applied to complete other half of the capsule as the continuous rotation of filled die converges with sealing roll. The pressure between the two rolls caused the capsules to cut out.

Seamless gelatin capsules: It is a modern method to prepare soft gelatin capsules. It consists of two concentric tubes, medicament flows through inner tube and gelatin flows through surrounding outer tube. Medicament and gelatin together form a spherical drop, which is ensured by allowing the drop to form in liquid paraffin in which gelatin is insoluble. Regular induced pulsation causes drops of correct size and temperature of 4℃ ensures gelatin shell is rapidly congealed. Capsules are then degreased and dried.

Manufacturing defects of capsules[10]

- **Misshapen capsules:** This defect arises due to sudden transfer of capsules from an environment of high temperature to low temperature. It can be prevented by maintaining empty capsules at a temperature ranging 15-30℃ and humidity ranging 40-65%. Also exposure to direct light source and heat must be avoided.
- **Improper rectification:** This defect occurs due to improper orientation of capsules.
- **Failure to separate:** Due to vacuum sometimes cap and body of the capsule fail to separate. This defect can be avoided by maintaining capsule filler gauge at a range of 15-18 inches of mercury. Certain other factors are also responsible for this defect; the factors include cleanliness of filter bag and the gaps between machine's cap and body segment.
- **Dented capsules:** Dents can be formed due to improper setup, capsule overfilling or application of excessive pressure by the machine.
- **Telescoping:** This defect arises due to body and cap misalignment and the capsule body splits. This problem can be solved by ensuring that all the capsules are perfectly round. It is also important to ensure that the body and cap bushings or segments are perfectly aligned; this can be done using a gauge specially designed for this purpose.

- **Popping:** Sometimes after capsule filling, the capsules may open up or get elongated. This happens due to overfilling or excessive locking pressure. Weak locking mechanism is also a rare cause of this defect.
- **Brittleness:** Capsules become brittle due to loss of moisture and improper storage condition. Presence of any hygroscopic drug or excipient in the finished product can also cause brittleness. Capsules made from HPMC have a higher ability to overcome this defect.

Evaluation tests for capsules

Moisture content: This test is done to determine the amount of moisture in the capsuleshell and its contents. Presence of excess moisture can affect the stability and integrity of the capsule.[12] The test is done by Karl Fischer titrimetry, which enables correlation of water content with the degradation profile or drug release characteristics of capsules.[8]

Moisture permeability: The USP recommends containers to be evaluated for moisture permeability to verify if they are suitable for capsule packaging. To measure moisture permeability, the dosage unit is loaded with a color-revealing desiccant pellet and then exposed to known relative humidity for a particular time period. The desiccant pellets are then checked for any color change which indicates moisture absorption, and finally compare pre-test and post-test weights.[8]

Bloom strength of gelatin: In this test, a 6.67% solution of gelatin is prepared by mixing it with water in a standard Bloom bottle. This solution mixture is then stirred and set aside to rest for about 3 hours at room temperature. Then this bottle is placed in a water bath at 65℃ for 20 minutes and allowed to cool for 5 minutes at room temperature. It is then conditioned for 16 hours in water bath at 10℃.[26] The conditioned gelatin is tested using a Bloom gelometer or texture analyzer.

Disintegration test: To perform this test, the standard tablet disintegration apparatus is used. Guiding discs are generally avoided except in cases where the capsules float on surface of water. A single capsule is added into each tube. The tubes are then suspended within beakers, moving up and down for 30 minutes (unless a different time period is mentioned in specific monograph).

This test is considered successful if the tube's mesh No. 10 screen doesn't retain any drug residue (except fragments of capsule shells).[8]

Dissolution test: Dissolution of drug at absorption site is very important for a drug to be absorbed and physiologically available. This test measures exactly how fast and how much of the drug is dissolved from the capsules. This test ensures that every batch delivers drug consistently. It also verifies that every batch has the same dissolution behavior as the original batch that was proven to be clinically effective.[8]

Content uniformity: This test is only performed when the content is mentioned in the individual monographs and the capsules fail the weight variation test. This test is optional if the capsules are completely full. Unless otherwise specified in the individual monograph, the drug content determined by assay should be between 85% and 115% of the labelled amount for at least 9 out of 10 capsules tested, and no single capsule should contain less than 75% or more than 125% of the labelled drug content. Some other tests are also recommended in case 2 or 3 units are out of specified range but within the same stated extremes.[8]

Weight variation test: For this test, 20 capsules are taken randomly and weighed. Their average and individual weight is calculated and noted. If the individual weights fall within 90-110% of average weight the test is considered to pass. Net content weight is determined if this requirement is not met. Soft gelatin capsule contents are taken out by cutting the shell, squeezing out, and washing the shell with suitable solvent. Similarly, contents of hard gelatin capsule are taken out by pouring out or using a small brush. The empty shells are then dried and weighed to calculate the individual content weight. The batch passes if not more than 2 capsules differ more than 10% from average content weight and no capsule differs more than 25% in any case.[27]

Microbial content: Test for microbial content is performed to ensure the capsules are free of bacteria and mold. These tests are done by incubating the capsule contents in a suitable growth medium and then counting the colonies that develop after a specific time period. The accuracy and success of this method for evaluating microbial contamination depends on the growth medium, test duration, and maintenance of aseptic conditions throughout the procedure.[8]

Stability testing: The goal of stability testing of capsules is to determine the intrinsic stability of the active drug molecule, the physicochemical stability of the drug substance in the final drug product under specified package and recommended storage conditions, and the effects of environmental factors (temperature, humidity, and light) on the closure system, the container, and the formulation components.The battery of tests for stress, long-term stability, and accelerated stability helps identify the ideal storage conditions and the product's estimated shelf life.[8]

Packaging and storage of capsules: Capsules are generally packed in well-closed glass or plastic containers and stored at temperature not more than 30℃. These containers protect capsules against dust and moisture, and provide transportation convenience better than cardboard boxes. In strip packing, the capsule is hermetically sealed within strips of plastic or aluminum foils, and the blister packs utilize a press to force the capsule through a backing strip.[4] To prevent capsules from shaking and breaking, a small piece of cotton is placed at the top and bottom of the container. For capsules having hygroscopic properties, a small packet of silica gel or calcium chloride is added to keep them dry.[27]

Packaging and storage of hard gelatin capsules

Storage conditions: Hard gelatin capsules require a moisture content of 13-16% to maintain physical integrity, below 12% shells become brittle and above 18% shells soften or lose shape. The bulk of this moisture is physically bound and depending on relative hygroscopicity it can transfer between the shell and its contents. Therefore, it is critical to avoid extreme temperatures and maintain 40-60% relative humidity during handling.[8]

Packaging requirements: Hard gelatin capsules are packaged in strip or blister packs to protect them from moisture, oxygen, and physical damage. These packaging materials must be heat-stable, moisture-resistant, and durable enough for mechanical handling. Proper enclosure ensures the capsules remain stable and prevents gelatin cross-linking.[15]

Packaging and storage of soft gelatin capsules

Storage conditions: Due to the presence of high-water content, soft gelatin capsules require extra caution during storage. They should be stored in air-conditioned areas where the relative humidity is maintained at 45% and temperatures between 21℃ and 24℃. Maintaining these specific environmental controls is necessary to prevent the shells from absorbing excess moisture or losing their defined shape.[4]

Packaging requirements: The packaging of soft gelatin capsules must be carefully designed to keep them stable. Soft gelatin capsules are sensitive because moisture from air can leak into the outer shell or the liquid inside. While testing the shelf-life stability, it must be analyzed if the plasticizers or residual water moves into the fill or if a part of volatile components evaporates into the atmosphere. Stability testing for these packages determines the best storage conditions and the length of study required for specific formulations to test thermal stability and solvent loss.[8]

Special types of capsules (non-gelatin): Non-gelatin capsules are considered as alternatives for conventional gelatin capsules. Different non-gelatin capsule materials have been developed and are discussed in the literature.

Hydroxypropyl methylcellulose capsules (HPMC): Hydroxy Propyl methyl cellulose capsules are semi-synthetic, inert, viscoelastic polymer. These are used as ophthalmic lubricants, excipients, and controlled delivery component in oral medicaments.[6] These capsules are hydrophilic biodegradable and biocompatible polymers having a wide range of application in the pharmaceutical industry. These capsules are also used in cosmetic, textile, and agricultural industries. HPMC capsules are less hygroscopic and have low moisture content as compared to gelatin capsules.[28]

Starch capsules: Starch is used as a gelatin alternative to produce capsules. Starch is a commonly available biopolymer having biodegradable properties. It is inexpensive and can be easily extracted from various plant sources like rice, potato, corn and many more. Starch has thermoplastic properties and increased film flexibility when added with plasticizers but cannot provide an effective barrier against humidity and oxygen.[28]

PVA Copolymer capsules: Macrogol 400 absorbs moisture and causes the capsule shell to become brittle easily and thus cannot be filled in conventional gelatin capsule shell. To overcome this problem PVA copolymer capsules are prepared by copolymerizing acrylic acid (AA) and methyl methacrylate (MMA) on PVA as a skeleton. The obtained PVA copolymer is used to prepare capsule shells and fill macrogol 400. Dosage forms of insoluble drugs can be developed with macrogol 400 to improve solubility.[29]

Alginate capsules: Alginate is obtained from some species of bacteria and marine sources (brown algae). It is non-toxic and biodegradable natural polysaccharide.[13] Alginate capsules

are vegetarian alternatives to gelatin capsules. These capsules are easy to manufacture and are 30% smaller than the traditional gelatin capsules. Additionally, it is sugar and gluten free and provides protection from oxidation, enhancing product life cycle.[29]

Pullulan capsule: These capsules are prepared by fermentation of starch by eco-friendly fungus *Aureobasidium pullulans*. Pullulan has 250 times more oxygen barrier properties compared to conventional capsules. They undergo rapid dissolution and increase bioavailability. They possess clear appearance and are also tasteless and odorless.[30]

AI in capsule formulation: It is an emerging technology in pharmaceutical process development. AI applies various algorithms across a wide range of circumstances and overcomes challenges like poor powder flowability, manufacturing stability and chemical degradation. The algorithms include linear regression, logistic regression, decision tree, Random Forest, K-Nearest Neighbors (KNN), LightGBM, XGBoost, and Support Vector Machine. Six AI techniques for capsule formulation identify defects in physical stability, dissolution rate, and dissolution profile. Specifically, algorithms like KNN, SVM, and CNN detect defects in capsules and pellet forms present inside them.[30]

Recent advances

Sustained release capsules: These capsules are prepared by encapsulating finely powdered drugs as pellets to control drug release. They provide a steady and prolonged therapeutic effect by releasing medications over an extended period. Due to this mechanism the frequency of drug dosing is reduced overcoming the disadvantages of conventional dosage form and increasing patient compliance.[30]

Liquid filled hard gelatin capsules: These capsules are prepared by encapsulating liquid or semi-solid drug substances along with some excipient. These capsules are ideal for drugs having low melting points and poor bioavailability. These capsules have properties like moisture resistance, faster action, superior stability, ease of production and highly transparent in appearance.[30]

Novel floating ring capsules: These are formulated for stomach specific targeting. These capsules extend medication presence to significantly improve overall therapeutic efficacy. These are developed using polymers like sodium CMC and HPMC to control drug release.[30]

Telemetric capsules: These capsules are ingestible, non-invasive therapeutic and diagnostic devices equipped with standard cylindrical forms, sensors, transmitters and lithium batteries. They can detect abnormalities at an early stage by monitoring physiological properties in real time. However, their accessibility is highly restricted due to sensitive transmission data security issues and extensive production cost.[30]

Codas technology: The Chronotherapeutic Oral Drug Absorption System utilizes a schedule release mechanism perfectly aligned with circadian rhythm. It can delay drug release for 4 to 5 hours. This unique property can effectively treat asthma and hypertension by preventing excessive dosing at inappropriate times.[30]

Sodas technology: The Spheroidal Oral Drug Absorption System optimizes performance by providing immediate action followed by sustained release. It uses uniform spherical beads containing drugs coated with product-specific controlled-release polymers. It is an advanced system which can enhance bioavailability and therapeutic efficacy. It can also provide customized dosage flexibility and facilitates target release.[30]

Capsule in capsule technology: This new approach allows nesting an inner capsule in an outer liquid-filled capsule, and can deliver both immediate and sustained release phases using the internal solution. It increases bioavailability, but has certain limitations like high production cost, inflexible dosing schedule, and dose dumping risk.[30]

Tablet in capsule: This method encapsulates directly compressed mini tablets into hard gelatin capsule shells. This technology initially gives rapid therapeutic effect followed by extended release, protecting sensitive drugs from degradation.[30]

Self-pressurized gelatin capsules for oral biologic delivery: Researchers from Georgia Institute of Technology developed a hard gelatin capsule that builds internal pressure by effervescent reaction. This was designed to administer biologics orally which normally requires injections. It improves patient compliance (because of no injection) and increases the use of capsules into biologics.[15]

CONCLUSION

Capsules remain an essential element of oral medication administration, providing remarkable adaptability and patient compliance. This review has thoroughly examined the entire formulation process of hard and soft gelatin capsules, from raw material selection and

detailed production procedures to structural and functional variations. It is clear that maintaining a precise balance of physicochemical parameters, particularly moisture content, is crucial to preserve shell integrity and stability. Formulators can ensure product safety and therapeutic efficacy by conducting standard evaluation procedures and managing environmental conditions. Furthermore, the incorporation of modern technological advances demonstrates the ongoing evolution of this traditional dosage form. Finally, mastering both the fundamental formulation principles and new developments assures that capsules will continue to supply dependable, high-quality therapeutic solutions in the pharmaceutical sector.

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