STM JOURNALS

International Journal of
Antibiotics

https://journals.stmjournals.com/ijab

ISSN: 2584-2986
Volume 2, Issue 1, 2025
January–June
DOI (Journal): 10.37591/IJAB

Review IJAB

Advancing Capsule Technology: A Comprehensive Review of Formulation Strategies

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Abstract

Capsules are a popular and versatile oral dosage form used in drug delivery, offering benefits, such as ease of swallowing, taste masking, and improved stability of active pharmaceutical ingredients (APIs). They can be made from gelatin or non-gelatin materials like Hydroxypropyl Methylcellulose (HPMC), Polyvinyl Alcohol (PVA), and starch, catering to dietary, cultural, and sustainability needs. Capsules can be engineered for controlled, sustained, or targeted release, enhancing bioavailability, particularly for poorly soluble drugs. They can hold powders, granules, liquids, and even combination therapies, offering flexibility in drug formulation and delivery. The manufacturing process of capsules involves precision, with hard gelatin capsules produced using the dip-coating method, and soft gelatin capsules made via plate, rotary die, or seamless techniques. Strict quality control ensures the capsules meet standards for weight, content uniformity, and disintegration. Non-gelatin capsules also cater to specific needs, offering plant-based or eco-friendly alternatives without compromising on drug delivery. Technological advances in capsule manufacturing, such as controlled release, biodegradable materials, and 3D printing, are improving patient compliance and therapeutic outcomes. Capsules remain a vital and adaptable tool in modern drug delivery systems, offering solutions for a wide range of therapeutic applications.

Keywords: Capsules, formulation, gelatin, manufacturing, quality control tests

INTRODUCTION

Capsules are a form of solid dosage used for delivering medications, typically consisting of small containers (shells) made from gelatin that enclose a precisely measured amount of the active pharmaceutical ingredient(s). The word "capsule" comes from the Latin term *capsula*, meaning a small container. Capsules have a prominent role in drug development and are often considered a primary oral dosage form due to the efficiency of their manufacturing process compared to other dosage forms. Gelatin is commonly used to create the capsule shell because it dissolves upon contact with water, allowing the complete release of the medication. However, alternatives to gelatin, such as denatured gelatin, methyl cellulose, and polyvinyl alcohol [1].

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Received Date: December 14, 2024
Accepted Date: January 03, 2025
Published Date: January 07, 2025

Citation: Mohd. Wasiullah, Piyush Yadav, Shashikant Maury, Mohammad Aquif Sheikh. Advancing Capsule Technology: A Comprehensive Review of Formulation Strategies. International Journal of Antibiotics. 2025; 2(1): 44–56p.

TYPES OF CAPSULES

There are several types of capsules used in the pharmaceutical industry, including soft gelatin capsules**,** hard gelatin capsules**,** Hydroxypropyl methylcellulose (HPMC) capsules**,** Polyvinyl Alcohol (PVA) capsules**,** and starch capsules**.** These capsules can be broadly divided into two categories: gelatin-based capsules and non-gelatin-based capsules.

Gelatin Capsules

Gelatin capsules, which are made primarily from gelatin, are a popular choice in drug formulation. They can be further classified into two main types: soft gelatin capsules and hard gelatin capsules.

Soft Gelatin Capsules

Soft gelatin capsules were first introduced in the 19th century, primarily to mask the unpleasant taste and odor of certain medications. Over time, their use has expanded beyond pharmaceuticals to include health and nutrition products, cosmetics, and even recreational items like paintballs.

In the pharmaceutical industry, soft gelatin capsules are gaining preference for several reasons:

- *Product Line Extension:* They offer flexibility in creating different formulations.
- *Technological Advantages:* Soft gelatin capsules provide excellent content uniformity, particularly for low-dose drugs, ensuring accurate dosing.
- *Safety:* They help reduce the risk of operator and environmental contamination when handling potent or cytotoxic substances.
- *Consumer Convenience:* Many people find soft gelatin capsules easier to swallow compared to other dosage forms.

Recent innovations in soft gelatin capsules focus on improving their performance, especially with liquid and semi-solid fillings. These advancements aim to enhance bioavailability, which refers to how effectively the drug is absorbed into the bloodstream. By improving the solubility of the drug and using techniques to boost absorption, these capsules help ensure that the drug performs better in the body, reducing variability in drug levels and improving therapeutic outcomes [2].

Key Ingredients in Soft Gelatin Capsule Shells

Soft gelatin capsules are carefully crafted from a variety of ingredients that work together to form a flexible, functional, and effective capsule. Below are the essential components used in their production:

- *Gelatin:* The primary material in soft gelatin capsules is gelatin, like hard gelatin capsules. The gelatin used is typically alkali-processed (Type B), making up about 40% of the gel mass. In some cases, acid-processed (Type A) gelatin may also be used. The properties of the gelatin shell, including its flexibility, strength, and durability, can be modified by selecting different gelatin types and adjusting the concentration of plasticizers.
- *Plasticizers:* To ensure the capsule shell is flexible and not too brittle, plasticizers are incorporated into the gelatin mixture. These substances interact with gelatin molecules, reducing the temperature at which the shell becomes rigid (the glass transition temperature, or Tg) and improving moisture retention.
- *Glycerol:* is the most common plasticizer used, though sorbitol, mannitol, and polypropylene glycol may also be used in combination to achieve the desired level of flexibility and moisture retention.
- *Water:* Water plays a vital role in the formulation of soft gelatin capsules, typically accounting for 30–40% of the wet gel mass. It is essential for both the manufacturing process and maintaining the capsule’s flexibility after production. The water-to-gelatin ratio is typically between 0.7 and 1.3 parts of water per part of dry gelatin, and the exact amount depends on the gelatin’s viscosity.
- *Preservatives:* To prevent microbial growth and ensure the stability of the gelatin solution during storage, preservatives are added to the formulation. Common preservatives include potassium sorbate and various forms of hydroxybenzoates (such as methyl, ethyl, and propyl hydroxybenzoate), which protect the capsules from bacteria and mold.
- *Colorants and Opacifiers:* To enhance the appearance of the capsule or protect sensitive ingredients from light, colorants and opacifiers are added. Colorants can include soluble dyes or insoluble pigments, while opacifiers, such as titanium dioxide are used to block light, which is particularly important for protecting light-sensitive drugs. Generally, the capsule shell is darker in color than the substance inside.

- *Other Excipients:* Additional excipients may be used in certain formulations, though they are less common. These may include:
- Flavorings and sweeteners to improve taste, especially in capsules designed for children or patients with difficulty swallowing.
- Acid-resistant polymers produce enteric-coated capsules that release the drug in the intestines rather than the stomach.
- Chelating agents, like ethylenediaminetetraacetic acid (EDTA)**,** to prevent the degradation of sensitive drugs by binding to trace metals like iron in the gelatin.

These ingredients work synergistically to create soft gelatin capsules that are stable, effective, and easy to consume, providing a reliable delivery system for oral medications [3].

Hard Gelatin Capsules

Hard gelatin capsules are one of the most common and widely used forms of capsules in the pharmaceutical industry. These capsules are made up of two parts: a long cylindrical body and a shorter cap, which fit together securely.

The core ingredients in hard gelatin capsule shells typically consist of a blend of gelatin**,** sugar, and water, resulting in clear, colorless shells that are virtually tasteless.

Once produced, these empty capsules are supplied to the pharmaceutical industry by capsule shell manufacturers. The next step involves filling the body of the capsule with the active ingredients, after which the cap is sealed onto the body to complete the capsule.

For almost a century, hard gelatin capsules have been the go-to option in the pharmaceutical field due to the excellent properties of gelatin. However, it’s important to recognize that gelatin, derived from animal sources, can be susceptible to chemical instability. Additionally, there is a potential risk related to transmissible spongiform encephalopathy (TSE); a condition associated with certain animal-based products [4].

Key Ingredients in Hard Gelatin Capsule Shells

Here’s a breakdown of the main ingredients that make up hard gelatin capsules:

- *Gelatin:* Gelatin is the primary material used in the production of hard gelatin capsules. It is a mixture of purified proteins extracted from animal sources, such as skin**,** bones, and connective tissue. This protein is processed through hydrolysis, which converts collagen into a gelatinous form. Gelatin is favored for its ability to form solid, stable, and easily dissolvable shells.
- *Plasticizers:* To ensure the capsule shell is not too stiff and is flexible enough to handle, plasticizer**s** are added to the gelatin. Glycerin and polyhydric alcohols (like sorbitol) are common examples of plasticizers that improve the shell’s elasticity. Water also naturally acts as a plasticizer, as it is inherent in the gelatin matrix and helps in maintaining the right balance of flexibility.
- *Colorants:* To enhance the appearance of the capsules and assist with product identification, colorants are often added. These can include synthetic dyes, such as azo dyes or xanthene dyes, or pigments like iron oxide. The colorants used must comply with the regulatory standards in the regions where the capsules will be sold.
- *Opacifying Agents Opacifiers:* Such as titanium dioxide, are used to turn the otherwise transparent gelatin into an opaque form. This is particularly useful for protecting sensitive drugs from light or simply to hide the contents of the capsule. Opaque capsules can also be used to create a more polished and visually appealing product.
- *Preservatives:* In the past, preservatives like paraben esters were added during capsule manufacturing to prevent microbial growth. However, under modern Good Manufacturing Practice (GMP) guidelines, their use has been phased out. Today, the moisture content in finished

hard gelatin capsules typically ranges between 12% and 16%. This moisture is tightly bound within the gelatin, creating a low water activity that is insufficient for bacteria to thrive.

Together, these ingredients form a capsule that is not only functional and stable but also safe and effective for delivering oral medication [5].

SPECIAL TYPES OF HARD GELATIN AND SOFT GELATIN CAPSULES

Modified Release Capsules

Capsules can be designed to modify the rate at which their contents are released, depending on the drug's properties and the excipients used in the formulation. For drugs that are highly soluble in water and need to be released quickly, hydrophilic (water-attracting) and neutral excipients are typically used. On the other hand, hydrophobic (water-repelling) excipients can slow down the release, allowing for a more controlled, sustained release. For water-insoluble drugs, hydrophilic excipients can speed up the release, while hydrophobic ones slow it down. For ultra-rapid release, methods like puncturing the capsule or adding agents like sodium bicarbonate and citric acid (which release carbon dioxide) can help open the capsule quickly.

Coated Capsules

Capsules are often coated for various reasons, including improving their appearance, masking unpleasant tastes, and controlling where the medication is released in the gastrointestinal tract. Enteric coatings are applied to prevent the drug from being released in the stomach, ensuring it reaches the intestines instead. These coatings require specialized techniques and equipment to ensure they function correctly and release the drug at the intended site.

Sustained Release Capsules

Traditional medications often require multiple doses throughout the day, leading to fluctuations in drug levels in the bloodstream. To address this, sustained-release capsules are used to provide a steady release of the drug over time. These capsules are typically filled with multiple coated pellets that release the drug gradually. Each pellet might have a different coating thickness to control the timing of its release. For example, a capsule could contain pellets designed to release the drug immediately, after 4 hours, 8 hours, and so on, providing consistent blood levels and reducing the need for frequent dosing.

Liquid-Filled Hard Gelatin Capsules

Many new chemical entities (NCEs) have poor water solubility, making traditional solid capsules less effective for absorption. Liquid-filled hard gelatin capsules offer a solution by enclosing a liquid or semi-solid formulation, often using oils or lipids to dissolve the drug. This approach can improve drug absorption and bioavailability compared to solid dosage forms.

Non-Gelatin Capsules

While gelatin has traditionally been the material of choice for capsule shells, *non-gelatin capsules* have been developed to meet specific needs, such as dietary or cultural preferences. Examples of non-gelatin capsules include those made from HPMC (Hydroxypropyl Methylcellulose)**,** PVA (Polyvinyl Alcohol), and starch.

HPMC Capsules

HPMC Capsules are a popular alternative to gelatin-based capsules, especially for individuals with dietary restrictions. These capsules are made from plant-derived cellulose and are non-cross-linked, offering similar dissolution characteristics to gelatin. They are compatible with most excipients and are preferred in markets where gelatin is not acceptable for religious, vegan, or vegetarian reasons. HPMC capsules dissolve in the stomach and release the active ingredient in a controlled manner, making them a reliable option for many pharmaceutical applications.

PVA Capsules

Polyvinyl alcohol (PVA) is another non-gelatin option for capsule production. PVA capsules are typically produced using preformed plasticized films, which are then shaped into capsules using specialized equipment. These capsules have the advantage of being less hygroscopic (less likely to absorb moisture) than gelatin capsules, which helps improve the stability of the contents. PVA capsules are also useful for substances that need to be shielded from moisture. Unlike gelatin, PVA doesn't forms a gel when exposed to water, making it a viable alternative for certain formulations.

Starch Capsules

Starch-based capsules are another alternative to gelatin, especially when dealing with issues like moisture sensitivity or when a more sustainable option is desired. Starch capsules are made by combining starch with plasticizers like glycerol and sorbitol, which are then processed into capsules using extrusion methods. These capsules have a high level of mechanical stability and elasticity, making them resistant to breakage. They are also less sticky under humid conditions, which is an advantage in storage and handling. However, they may face challenges when used with hydrophilic (water-attracting) fills, as they tend to swell when exposed to moisture.

Some starch-based capsules use potato starch, combined with plasticizers, glidants, and disintegrants, to improve their properties further. These capsules are biodegradable and serve as an environmentally friendly alternative to traditional gelatin-based products [6].

IMPORTANCE OF CAPSULE IN DRUG DELIVERY SYSTEM

Capsules play a critical role in drug delivery systems, offering several advantages for both patients and pharmaceutical companies. Here are some key points regarding their importance:

- *Enhanced Patient Compliance:* Ease of Swallowing: Capsules, especially soft-gelatin types, are generally easier to swallow than tablets, reducing discomfort and improving adherence. Taste and Odor Masking: Capsules can effectively mask the taste and odor of drugs, enhancing patient experience and compliance [7].
- *Protection of Active Ingredients:* Barrier to Environmental Factors: Capsules can protect sensitive active pharmaceutical ingredients (APIs) from moisture, light, and oxygen, improving stability and extending shelf life. Minimizing Drug Degradation: Encapsulation prevents premature degradation of the drug in acidic or enzymatic environments, particularly beneficial for sensitive drugs and biologicals [8].
- *Controlled Release and Targeted Delivery:* Immediate, Sustained, and Controlled Release: Capsules can be engineered for various release profiles, allowing for immediate or delayed release depending on therapeutic needs. Site-Specific Delivery: Capsules can be designed to release drugs at specific sites in the gastrointestinal (GI) tract, such as enteric-coated capsules that release in the intestine, reducing gastric irritation and improving absorption [9].
- *Improved Bioavailability:* Enhanced Absorption: Certain formulations, such as liquid-filled capsules or self-emulsifying drug delivery systems (SEDDS), improve the solubility and absorption of poorly soluble drugs, increasing bioavailability. Optimization of Lipophilic Drug Delivery: Capsules allow for lipid-based formulations, which are effective for delivering drugs that are poorly soluble in water.
- *Versatility in Formulation:* Compatibility with a Wide Range of Formulations: Capsules can contain powders, granules, liquids, and even mini tablets, allowing for greater flexibility in drug formulation. Multiple APIs: Capsules can accommodate combination therapies, where multiple APIs are needed in a single dose, facilitating complex regimens.
- *Reduced Manufacturing Complexity:* Simplified Production for Certain Drugs: Capsules can simplify the manufacturing process by allowing liquid filling or encapsulation of sensitive drugs without extensive compaction or heat processing.

- *Potential for Innovation and Personalization:* 3D Printing and Customization: Capsule technology has the potential to enable personalized medicine, with innovations like 3D printing allowing precise dosages tailored to individual patient needs. Smart Drug Delivery Systems: Advances in capsule technology, such as “smart” capsules with sensors or controlled release based on physiological triggers, are enabling more responsive drug delivery [10].
- *Global Acceptance and Accessibility:* Established Patient Preference and Trust: Capsules are widely accepted globally, and their versatility makes them suitable across age groups and for various healthcare settings. Addressing Allergies and Dietary Restrictions: Vegetarian and allergen-free capsules have increased accessibility, accommodating a broader range of patient need [11].

Capsule Formulation

Hard Gelatin Capsule Formulation

Hard gelatin capsules are one of the most widely used types of dosage forms in the pharmaceutical industry, being produced at a rate significantly higher than soft gelatin capsules. These capsules are provided empty by manufacturers to pharmaceutical companies, who then fill them with the required active ingredients. The production process for these capsules involves several precise and controlled steps to ensure product quality and consistency [12].

Manufacture of Hard Gelatin Capsules

Hard gelatin capsules are typically produced using a dip-coating method, which involves several steps:

Preparation of the Gelatin Solution

The first step in capsule production involves preparing a concentrated gelatin solution. Gelatin is dissolved in demineralized water, then heated to 60–70°C. The solution, typically containing 30%–40% gelatin by weight, is highly viscous. To prevent the formation of air bubbles, which can cause inconsistent capsule weights, a vacuum is applied. Additives, such as colorants or surfactants may also be incorporated at this stage to enhance the appearance and processing characteristics of the gelatin.

Dip-Coating the Gelatin Solution onto Molds

Pairs of metal pins are dipped into the gelatin solution to form the capsule body and cap. These molds are maintained at a temperature below the gelling point, ensuring the gelatin solidifies into a thin film. This process is carried out in a controlled environment to ensure uniformity.

Rotation of the Pins

After the gelatin solution has been applied, the molds are rotated to ensure the gelatin coats the pins evenly. This rotation is critical to achieving consistent wall thickness and dome shape for the capsule shells.

Drying the Gelatin-Coated Pins

Once the gelatin has been applied, it must be dried to remove excess moisture. The drying process is carefully controlled to avoid under- or over-drying, both of which can impact the structural integrity of the capsules.

Stripping and Trimming

After drying, the gelatin capsule shells are carefully removed from the molds (a process known as "stripping") and then trimmed to the desired length. This ensures that both the cap and body of the capsule fit together properly.

Joining the Capsule Shells

The cap and body of each capsule are brought together using a mechanism that ensures they fit securely. In some cases, printing may be applied at this stage for identification purposes, such as product codes or dosage information.

Printing

Once the capsule shells are formed, printing is done to add important product details, including the manufacturer's logo, product name, and dosage instructions. This step helps to prevent confusion in both handling and use [13].

Filling of Hard Gelatin Capsules

The filling of hard gelatin capsules is a well-established procedure, with various equipment options available depending on the scale of production:

- Manual Filling Machines are commonly used for small-scale or custom formulations, often in compounding pharmacies.
- Semi-automatic Machines are used for medium-scale production.
- Fully automatic machines are typically employed for large-scale manufacturing.

Regardless of the method, the basic principle involves measuring the correct amount of active ingredients and filling them into the capsule body [14].

Filling Liquids and Semisolid Formulations

There is a growing trend toward using liquid or semisolid formulations to improve the solubility and bioavailability of poorly soluble drugs. These formulations may include oils, solvents, or surfactants. The viscosity of these formulations must be closely monitored to ensure they can be filled into the capsules effectively. Typically, the viscosity is maintained between 50 and 1000 CP, and the formulation should not exceed 70°C during the filling process [15].

Locking and Sealing of Capsules

To prevent leakage and ensure that the capsule cap stays securely attached to the body, a sealing process is employed. Different methods can be used to achieve a tight seal:

- *Banding:* A gelatin band is applied around the seam of the capsule.
- *Moistening:* A small amount of moisture is applied to the edges to help the cap and body stick together.
- *Spot Welding:* Heat is applied at specific points to melt and seal the gelatin.
- *Thermal Welding:* A uniform heat treatment is used to fuse the cap and body.
- *Coni-Snap:* A specialized locking mechanism that ensures a secure closure [16].

Manufacturing Soft Gelatin Capsules

Soft gelatin capsules, also known as soft gels, are widely used in the pharmaceutical, nutraceutical, and dietary supplement industries to encapsulate active ingredients in liquid, semi-solid, or even solid forms. The production of these capsules requires specialized techniques and equipment to ensure the soft, flexible capsule shells that contain the active ingredient are formed and sealed with precision [17]. There are several methods for manufacturing soft gelatin capsules, with the following being the most common:

PLATE PROCESS

The plate process is one of the simplest methods for manufacturing soft gelatin capsules. It is most used for small to medium-scale production, especially when customized capsule sizes are needed.

How the Plate Process Works

- *Gelatin Preparation:* The first step is preparing a gelatin mass by mixing gelatin, plasticizers (like glycerin or sorbitol), and water. This mixture is heated and blended until it becomes a smooth, homogeneous solution.
- *Film Formation:* A thin layer of the gelatin mixture is spread across large plates or molds, where it is left to set. As the gelatin solidifies, it forms a soft, flexible sheet.
- *Filling:* Once the gelatin film has formed, it is cut into individual pieces. The active ingredients (whether in liquid, semi-solid, or powdered form) are placed in the center of each piece.
- *Sealing:* The filled pieces of gelatin film are then folded over the active ingredient, and the edges are sealed together using heat or pressure. This forms a complete soft gelatin capsule.
- *Drying:* Finally, the capsules are dried to remove excess moisture, ensuring they are firm yet flexible.

The plate process is ideal for small batches or when a specific size and shape are needed. It is cost-effective and relatively easy to implement for specialized or custom formulations [18].

ROTARY DIE PROCESS

The rotary die process is a highly automated and efficient method used for large-scale production of soft gelatin capsules. This process can produce a high volume of capsules with consistent quality and is widely used in industry.

How the Rotary Die Process Works

- *Gelatin Preparation:* Like the plate process, gelatin is dissolved in water and plasticizers to create a gelatin mass. The solution is kept at a temperature of around 60–70°C to maintain its consistency.
- *Film Formation:* The gelatin solution is fed onto two continuous sheets of gelatin film, which are passed through rollers. This forms a continuous layer of gelatin that is kept warm to prevent it from hardening too quickly.
- *Filling:* As the gelatin film moves through the rotary die machine, the active ingredients (typically in liquid or semi-solid form) are injected into the center of the capsule shape.
- *Die Cutting and Sealing:* The machine uses rotary dies to cut the gelatin film into the desired shape for the capsule body and cap. The two halves are then sealed together with heat and pressure, forming a complete capsule.
- *Drying:* After the capsules are formed, they undergo a drying process to remove moisture and ensure the capsules reach the proper consistency for storage and use.

The rotary die process is the most used method for large-scale soft gelatin capsule production due to its efficiency, high output, and consistent quality [19].

RECIPROCATING DIE PROCESS

The reciprocating die process is like the rotary die process but involves back-and-forth movement, rather than continuous rotation. This method is generally used for smaller production runs or when specific formulations are required.

How the Reciprocating Die Process Works

- *Gelatin Preparation:* Just like the other processes, gelatin is mixed with plasticizers and water to form a uniform solution.
- *Gelatin Film Formation:* Instead of using two continuous gelatin sheets, the reciprocating die process uses a single band of gelatin that moves back and forth through a reciprocating die machine.
- *Filling:* The active ingredients (liquid or semi-solid) are introduced into the gelatin film as it passes through the machine, filling each capsule shape.
- *Die Cutting and Sealing:* The die then cuts the gelatin film into capsule shapes, and the two parts (body and cap) are sealed together with heat and pressure, much like the rotary die process, but with a back-and-forth motion.

- *Drying:* The capsules are dried to remove excess moisture, ensuring they maintain their shape and integrity.

The reciprocating die process is useful for producing smaller batches or when a customized capsule is needed. It's also ideal for formulations that may require slight modifications to the production process [20].

ALCOGEL PROCESS

The Alcogel process is an advanced technique used to produce soft gelatin capsules, particularly for encapsulating high-viscosity liquids or semi-solid formulations. This process allows for better encapsulation of difficult-to-handle liquids and oils, enhancing bioavailability and solubility.

How the Alcogel Process Works

- *Gelatin Preparation:* Like other methods, gelatin is dissolved with water and plasticizers to form a gel-like mass. The solution is heated to a temperature around 60–70°C.
- *Formation of Alcogel:* The gelatin mass is combined with a mixture of alcohol (usually ethanol) and water to form an Alcogel. The alcohol modifies the viscosity of the gelatin, making it easier to encapsulate viscous or semi-solid active ingredients.
- *Filling*: The prepared formulation (liquid, semi-solid, or oil-based) is filled into the capsule, with the Alcogel allowing for smooth and controlled encapsulation.
- *Drying and Solidification*: The capsules are then dried to remove the alcohol and any excess moisture, ensuring the gelatin shell hardens into its final form.
- *Sealing*: As with other methods, the cap and body of the capsule are sealed to prevent leakage.

The Alcogel process is particularly beneficial for encapsulating poorly water-soluble substances, helping to improve the bioavailability of drugs and active ingredients [21].

SEAMLESS PROCESS

The seamless process eliminates the need for traditional cap-body sealing, resulting in soft gelatin capsules that are formed without seams. This technique enhances the stability and integrity of the capsule, making it ideal for products that require enhanced performance, such as controlled-release formulations or those containing sensitive ingredients [22].

How the Seamless Process Works

- *Gelatin Preparation:* Gelatin is mixed with plasticizers and water to create a uniform mass.
- *Film Formation:* The gelatin mass is fed into a forming machine that shapes it into a continuous sheet or ribbon.
- *Encapsulation:* In the seamless process, both the capsule body and cap are formed simultaneously. Active ingredients are injected directly into the molten gelatin ribbon as it moves through the machine, which eliminates the need to join the two parts of the capsule afterward.
- *Sealing and Shaping:* The gelatin forms a smooth, uninterrupted capsule without seams. The continuous film encapsulates the active ingredients in one seamless structure, minimizing the risk of leaks or weak spots.
- *Drying and Hardening:* The capsules are dried to remove moisture, allowing them to harden and maintain their stability.
- *Finishing:* After drying, the capsules are inspected for quality, and if needed, printing or labeling is applied for identification [23].

Quality Control Tests for Capsules

In-Process Quality Control Tests for Capsule Drug Products

In-process quality control tests are conducted at specific stages during the manufacturing process of capsule drug products. These tests are carried out by production personnel, and the results are carefully documented in the batch records. If any issues or discrepancies are identified, they provide valuable information for adjusting the manufacturing process. These checks are essential for ensuring that the product meets the required quality standards throughout production [24].

For soft gelatin capsules, the following key parameters are closely monitored during the encapsulation process:

- *Gel Ribbon Thickness and Consistency:* The gelatin ribbon (the film that forms the capsule shell) must have a uniform thickness across its entire length. Any variation in thickness can lead to inconsistencies in the final capsule size and strength, affecting the product's quality.
- *Seal Thickness:* The seal where the capsule cap and body meet is crucial for preventing leakage or breakage. The thickness of this seal is carefully controlled during encapsulation to ensure it is strong enough to securely hold the filling material inside the capsule.
- *Weight of the Capsule Fill:* The amount of fill inside each capsule must be consistent. Variations in the fill weight from one capsule to another can result in dosing inaccuracies. These variations are closely monitored to ensure each capsule contains the correct amount of active ingredients.
- *Weight of the Capsule Shell:* The weight of the empty capsule shell must also be consistent. Differences in shell weight can indicate issues with the gelatin film, which could impact the capsule's strength and integrity.
- *Moisture Content of the Capsule Shell:* The moisture level of the gelatin shell is monitored both before and after the drying process. Too much moisture can weaken the capsule, while too little can make it brittle. Proper moisture content is essential for ensuring the capsule remains stable and performs well throughout its shelf life.

These in-process quality control checks help ensure that every batch of capsules is consistently manufactured to meet the desired specifications for performance, safety, and effectiveness [25].

Finished Product Quality Control Tests for Capsule Drug Products

After capsules are produced, they undergo a series of quality control tests to ensure they meet the required standards for safety, potency, and consistency. These tests are essential to determine whether the batch of capsules is fit for marketing or its intended use.

Here are the key tests typically performed on finished capsules:

- *Permeability and Sealing:* Soft gelatin capsules are visually inspected to check for physical integrity and confirm that there are no leaks. This ensures that the capsule shell remains intact and that the contents are securely enclosed. Hard gelatin capsules are also checked for any damage, such as cracks, splits, or separation between the cap and body. This step ensures the capsule remains intact during handling and storage.
- *Potency and Impurity Content:* Each batch of capsules is tested for drug potency, ensuring the active ingredient content matches the labeled amount. Potency is measured as a percentage of the label claim. In addition to potency, capsules are tested for related substances or impurities, which must fall within predefined limits. A batch will only be deemed acceptable if both the potency and impurity levels meet regulatory specifications.
- *Weight Variation Test:* To assess the uniformity of the capsule contents, the weight variation test is conducted. This test determines if the weight of the capsules is consistent across the batch. Here is how it's typically performed.

Weight Variation Test for Hard Gelatin Capsules

Ten hard gelatin capsules are individually weighed. The contents are then emptied, and the weight of the empty shells is measured. The net weight of the filling material is calculated by subtracting the weight of the shell from the total weight of the capsule. Based on the percentage of the active ingredient in the formulation, the content of the drug in each capsule can be determined.

Weight Variation Test for Soft Gelatin Capsules

For soft gelatin capsules, the process begins by weighing the gross weight of ten individual capsules. Each capsule is then carefully opened using a clean, dry tool, such as scissors, and the contents are extracted by rinsing with a solvent that dissolves the fill material but leaves the shell intact. After the solvent has evaporated (typically after 30 minutes), the washed shells are weighed. The net content is calculated by subtracting the weight of the empty shell from the gross weight of the capsule. This allows for the determination of the active ingredient content in each capsule, like the method used for hard gelatin capsules.

The variation in fill weight is often linked to factors like equipment setup and the filling process. To address this, automated machines are commonly used to ensure uniformity. These machines check the weight of each capsule and discard any that are overfilled or underfilled.

These quality control tests help ensure that every batch of capsules meets the required standards for consistency, dosage accuracy, and physical integrity, providing assurance that the capsules will perform as intended in the patient population [26].

Uniformity of Content

This test is typically required only when the content is specified in the individual monographs, or when capsules do not pass the weight variation test. If the capsules are properly filled, the uniformity of content test is not necessary. However, if required, the assay should ensure that the amount of the active ingredient in each capsule is within the specified range. For a batch to pass this test, the amount of drug in nine out of ten capsules must fall within 85.0% to 115.0% of the label claim. Additionally, no capsule should have less than 75.0% or more than 125.0% of the labeled drug content. If two or three capsules fall outside the desired range but remain within these extremes, further testing may be required [27].

Disintegration Time Test for Capsules

The disintegration test is performed to ensure that both hard and soft gelatin capsules break down properly in the body, allowing the active ingredient to be released and absorbed. This test is critical for confirming that the drug substance will be available for dissolution and absorption in the gastrointestinal tract. The disintegration procedure for capsules follows the same guidelines used for tablets. Capsules are placed in a basket-rack assembly and submerged in a temperature-controlled fluid bath (typically set at 37°C), where they are subjected to a series of mechanical movements. The test monitors how long it takes for the capsules to break apart, ensuring they disintegrate within the required time frame, facilitating proper drug release [28].

CONCLUSIONS

Capsules continue to play a central and indispensable role in modern drug delivery systems, offering an unparalleled combination of versatility, precision, and patient-centric design. Whether in the form of hard gelatin, soft gelatin, or non-gelatin alternatives, such as HPMC (hydroxypropyl methylcellulose), PVA (polyvinyl alcohol), and starch-based capsules, provide a reliable and flexible platform for the formulation and delivery of a wide range of active pharmaceutical ingredients (APIs). These dosage forms are not only easy to swallow, improving patient compliance, but also enable accurate dosing, which is crucial for therapeutic effectiveness. Additionally, capsules have the unique advantage of being customizable to meet specific therapeutic needs, allowing for innovations, such as controlled or sustained release mechanisms, enteric coatings for targeted delivery, and liquid-filled capsules for improved bioavailability of poorly soluble drugs. This adaptability makes them suitable for a vast array of drug types, from conventional small molecules to complex biology.

The technological advancements in capsule manufacturing, such as the use of non-gelatin materials, reflect the growing demand for dietary flexibility, sustainability, and compliance with religious or cultural restrictions, further expanding their global appeal. These innovations not only offer viable alternatives for vegetarians and individuals with dietary restrictions but also contribute to more environmentally responsible drug delivery solutions, addressing the increasing focus on sustainability in the pharmaceutical industry. Moreover, the careful selection and incorporation of excipients – such as plasticizers, preservatives, and colorants–into capsule formulations ensure the stability, bioavailability, and aesthetic appeal of the final product, enhancing both the functionality and the patient experience.

In terms of production, the manufacturing of capsules, whether through the dip-coating method for hard gelatin capsules or the rotary die process for soft gelatin capsules, is highly specialized, requiring precision and strict adherence to quality control standards. Throughout the production process, rigorous in-process quality control tests, such as monitoring gelatin ribbon thickness, weight variation, and seal integrity, ensure that capsules meet the required specifications and that any potential discrepancies are identified and addressed promptly. Once the capsules are manufactured, finished product tests, including potency assays, disintegration tests, and uniformity of content, guarantee that the capsules deliver the correct dosage, maintain their physical integrity, and release their contents appropriately in the body, ensuring both safety and efficacy.

The continuing evolution of capsule technology, driven by advancements in materials, manufacturing processes, and innovations like 3D printing, underscores the ongoing potential for personalized medicine and the development of "smart" drug delivery systems. These innovations allow for even more precise dosing and targeted delivery, enhancing the therapeutic outcomes of drug therapies. As the pharmaceutical industry faces the challenges of an aging population, an increase in chronic diseases, and growing patient expectations for personalized treatment, capsules will undoubtedly remain at the forefront of drug delivery solutions, adapting to meet the dynamic needs of patients and the healthcare system. With the ongoing focus on enhancing bioavailability, improving patient adherence, and developing sustainable and efficient drug delivery methods, capsules will continue to be a cornerstone in pharmacotherapy, delivering both safety and efficacy to patients worldwide, while ensuring that their evolving role in modern medicine remains vital and impactful for years to come.

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