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A REVIEW ON CAPSULES ITS ADVANCES IN FORMULATIONS

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ABSTRACT
Advancements in capsule technology demonstrate the pharmaceutical industry's commitment to improving treatment effectiveness, patient satisfaction, and adaptable drug formulations. With increasing complexity in drug compounds and a growing emphasis on personalized medicine, capsules continue to play a vital role in contemporary drug delivery systems.

Keywords: Capsules. Types, Evaluation, Formulations, Testing Procedures, Standards

INTRODUCTION

Capsules and Their Advances in Formulation

Capsules are **solid dosage forms** designed to contain one or more medicinal substances within a **shell or container**, typically made from **gelatin** or other biocompatible materials. They offer a versatile platform for delivering both solid and liquid medications effectively.

Classification of Capsules

1. **Hard Gelatin Capsules (HGC)**
2. **Soft Gelatin Capsules (SGC)**
3. **Modified-release Capsules**
4. **Gastro-resistant (Enteric-coated) Capsules**
5. **Liquid-filled Capsules (LFHC or LSGC)**

1. Hard Gelatin Capsules (HGC)

Overview:

Hard gelatin capsules are solid, two-part dosage forms consisting of a **cap and a body**, typically made from **animal-derived gelatin**. These are primarily used to deliver **dry formulations** such as **powders, pellets, or granules**.

Composition:

- **Gelatin** (from bovine or porcine sources)
- May contain **colorants**, **opacifying agents** (e.g., titanium dioxide), and **preservatives**
- **Vegetarian alternatives** use **HPMC (Hydroxypropyl Methylcellulose)**

Common Uses:

- Widely used in **prescription and OTC medications**
- Can accommodate **powders**, **beads**, **mini-tablets**, or even **smaller capsules** (for dual-drug delivery)

Benefits:

- Simple to manufacture at scale
- Can **mask unpleasant tastes or odors**
- Allows **precise control over dosage**
- Supports **custom release profiles** via multiparticulate systems

Limitations:

- Incompatible with **water-based or hygroscopic** substances
- Can become **brittle** in low humidity environments

2. Soft Gelatin Capsules (SGC)

Overview:

Soft gelatin capsules are **single-unit, flexible capsules**, made by blending gelatin with a **plasticizer** to give elasticity. They are used primarily for **liquids**, **suspensions**, or **semi-solids**.

Composition:

- **Gelatin**
- **Plasticizer** (e.g., glycerin, sorbitol)
- **Water**
- May include **flavors**, **colors**, or **preservatives**

Common Fill Types:

- Oils (e.g., fish oil, essential oils)
- Solutions or suspensions of active ingredients
- Lipid-based delivery systems

Benefits:
- Ideal for delivering **lipophilic or oily drugs**
- Enhanced **absorption** and **bioavailability**
- **Tamper-resistant** due to sealed design
- **Easy to swallow**, patient-friendly form

Limitations:
- Higher production cost and complexity
- Sensitive to **temperature and moisture**
- Not suitable for **water-containing** solutions due to potential shell degradation

3. Modified-Release Capsules

Overview:

These capsules are engineered to release the drug over a **specific duration or at a specific site**, rather than immediately after ingestion. They are tailored for **controlled**, **sustained**, or **pulsatile** drug delivery.

Types:
- **Extended-release (ER)** – slow, continuous release
- **Delayed-release (DR)** – released after a predefined lag (e.g., post-gastric emptying)
- **Pulsatile-release** – periodic, time-based release

Technologies Used:
- **Coated pellets or mini-tablets** inside the capsule
- **Osmotic pumps**
- **Polymer coating systems** like **ethyl cellulose** or **Eudragit**

Benefits:
- Maintains **stable drug levels** in blood
- Reduces **dosing frequency** and improves compliance
- Minimizes **side effects** related to drug spikes

Challenges:
- Requires **precise formulation** and advanced manufacturing control
- **Batch-to-batch consistency** can be difficult to maintain

4. Gastro-resistant (Enteric-coated) Capsules

Overview:

Gastro-resistant capsules are specially designed to **resist stomach acid** and only dissolve once they reach the **alkaline pH** of the intestine. This protects drugs that degrade in acidic environments or cause gastric irritation.

Common Enteric Polymers:
- **Eudragit L100/S100**
- **Cellulose Acetate Phthalate (CAP)**
- **Hydroxypropyl Methylcellulose Phthalate (HPMCP)**

Applications:
- Delivery of **acid-sensitive drugs** (e.g., enzymes, probiotics)
- Drugs that can **irritate the stomach lining** (e.g., NSAIDs)
- Targeting the **small intestine or colon** for specific absorption

Benefits:
- Ensures **site-specific release**
- Protects **drug stability** in the stomach
- Can improve **absorption** and reduce **GI side effects**

Limitations:
- **Delayed therapeutic effect** due to lag in release
- Coating process requires **high precision and quality control**

5. Liquid-Filled Capsules (LFHC / LSGC)

Overview:

These capsules (either hard or soft) are filled with **liquid or semi-solid drug formulations**, particularly beneficial for drugs with **low water solubility** or those requiring **rapid absorption**.

Types:
- **Liquid-Filled Hard Capsules (LFHC)** – rigid gelatin or HPMC shells
- **Liquid-Filled Soft Gelatin Capsules (LSGC)** – flexible shells with plasticizers

Common Fill Materials:
- **Lipid-based carriers** (e.g., medium-chain triglycerides)
- **Self-emulsifying systems (SEDDS/SMEDDS)**
- **Non-aqueous solvents**
- **Surfactants** to enhance solubility

Benefits:
- Greatly enhances **bioavailability** of poorly soluble APIs
- Suitable for **low-dose, potent compounds**
- Can be used for **controlled-release** formulations

- Protects **oxygen- or moisture-sensitive drugs**

Challenges:

- Requires **specialized filling equipment**
- Compatibility between **fill material and shell** must be ensured
- Higher production costs than standard powder-filled capsules

Table

Capsule Type	Structure	Best For	Key Advantage
Hard Gelatin Capsules (HGC)	2-piece, rigid	Powders, granules, pellets	Widely used, easy manufacturing
Soft Gelatin Capsules (SGC)	1-piece, flexible	Liquids, oils, lipid-based drugs	Better solubility and patient compliance
Modified-Release Capsules	Varies	Controlled, sustained, pulsatile release	Consistent therapeutic effect and compliance
Gastro-resistant Capsules	Coated/enteric	Acid-sensitive or irritating drugs	Site-specific release, protects API in stomach
Liquid-filled Capsules	1- or 2-piece	Poorly soluble or low-dose drugs	Enhances absorption and stability

Recent Innovations in Capsule Formulation

With growing pharmaceutical demands, capsule formulations have progressed significantly, transforming them into sophisticated systems for **targeted and controlled drug delivery**. Below are key innovations:

1. Liquid-Filled Hard Capsules (LFHCs)

These are hard-shell capsules filled with liquid or semi-solid drug formulations.

Benefits:

- Improves absorption of poorly water-soluble drugs
- Suitable for delivering potent compounds at low doses
- Supports modified or sustained drug release

Recent Developments:

- Use of **lipid-based systems** such as **Self-Emulsifying Drug Delivery Systems (SEDDS)** and **SMEDDS**
- Enhanced solubility and absorption through in-capsule emulsification

2. Modified-Release Capsules

Types:

- **Extended-release (ER)**
- **Delayed-release (DR)**
- **Pulsatile-release**

Formulation Techniques:

- Incorporation of **multi-particulate systems** (e.g., coated granules or pellets)
- Use of **polymer coatings** (like HPMC, ethyl cellulose)
- Advanced **osmotic systems** for steady drug release

Benefits:

- Targeted delivery to specific GI tract regions
- Reduced dosing frequency
- Better patient adherence

3. Gastro-resistant (Enteric-Coated) Capsules

Purpose:

To protect the drug from stomach acid and enable release in the intestine.

Technological Improvements:

- Use of pH-sensitive polymers such as:
  - **Eudragit L/S (methacrylic acid copolymers)**
  - **Cellulose acetate phthalate (CAP)**
- HPMC-based capsules with **enteric coatings** for acid resistance

4. Vegetarian and Plant-Based Capsules

Materials:

- **HPMC (Hydroxypropyl Methylcellulose)**
- **Pullulan**
- **Modified starch**

Applications:
- Ideal for **thermolabile** (heat-sensitive) and **moisture-sensitive** drugs
- Widely accepted in the **nutraceutical** and **vegan markets**

Innovations:
- Improved **moisture protection** and **oxygen barrier**
- Enhanced **dissolution** and **mechanical properties**

5. Capsules with Advanced Fill Materials
Fill Forms:
- Powders, granules, pellets, beads
- Microcapsules, liposomes, nanoparticles

Advantages:
- Enables combination therapy within one capsule
- Better protection and controlled release
- Target-specific delivery

Example:
Coated pellets offering **dual or multi-phase release** from a single capsule

6. Capsule-in-Capsule (Double Capsules)
Design:
An inner capsule enclosed inside a larger one.

Use Cases:
- Separate incompatible ingredients
- Provide **sequential** or **pulsed release**
- Enhance therapeutic outcomes through time-staggered delivery

7. Capsules for Biologics and Macromolecules
Challenge:
Large biomolecules like peptides and proteins are easily degraded in the GI tract.

Solutions:
- Use of **protective encapsulation techniques** like nanoparticles or bioadhesive polymers
- Enteric coating to bypass gastric degradation
- Applied in **oral delivery of insulin**, **vaccines**, and even **gene therapies**

8. Smart and 3D-Printed Capsules
Features:
- Customized drug release profiles using 3D printing
- Multi-layer or multi-compartment designs for precision delivery

Applications:
- **Personalized therapies**
- Delivery of multiple drugs with distinct release kinetics
- Treatment of diseases requiring time-specific dosing (e.g., **chronotherapy**)

9. Capsule Banding and Sealing Technologies
Techniques:
- **Band sealing** with gelatin or HPMC
- **Thermal** and **ultrasonic liquid sealing**
- Designed to be tamper-evident and leak-resistant

Benefits:
- Improves product **stability and safety**
- Prevents **leakage, contamination**, or **counterfeiting**
- Ensures **dosage integrity**

10. Targeted and Site-Specific Capsule Delivery
🧿 **Goal:**
To deliver medication to a specific site such as the colon, small intestine, or even the brain.

Methods:
- Use of **pH-dependent polymers** for GI targeting
- **Microbial-triggered systems** for colon-specific release
- Investigational approaches like **magnetically guided capsules**

Capsule formulations have gone far beyond traditional roles, now serving as **intelligent drug delivery systems** that improve:
- **Drug solubility**
- **Stability**
- **Bioavailability**
- **Precision targeting**
- **Patient compliance**

Role of Capsule Formulation in Enhancing Drug Performance

Capsules serve not only as convenient oral dosage forms but also as sophisticated drug delivery platforms designed to tackle various challenges in pharmaceutical therapy. This section highlights how capsules can improve drug **solubility**, **stability**, **bioavailability**, **targeted delivery**, and **patient compliance**.

1. Enhancing Drug Solubility

Relevance:

A significant number of active pharmaceutical ingredients (APIs), especially new chemical entities, suffer from **poor aqueous solubility**, which impairs their absorption in the gastrointestinal tract and limits therapeutic efficacy.

Capsule-Based Solutions:

- **Liquid-Filled Capsules**: Incorporating **lipid-based vehicles** (such as medium-chain triglycerides, PEG, or surfactants) into capsules allows dissolution of hydrophobic drugs, promoting better dispersion upon ingestion.
- **Self-Emulsifying Systems (SEDDS/SMEDDS)**: These systems form fine emulsions in the GI tract, enhancing solubility and facilitating drug uptake across the intestinal membrane.
- **Soft Gelatin Capsules (SGCs)**: SGCs are especially suited for lipophilic compounds, offering a pre-dissolved formulation that enables faster absorption.
- **Nanoparticles and Cyclodextrin Complexes**: Use of nanosized drug particles or cyclodextrin inclusion complexes inside capsules enhances wettability and water compatibility, improving solubility.

Outcomes:

- Faster drug dissolution
- Improved absorption for BCS Class II and IV drugs
- Enhanced therapeutic performance of low-solubility compounds

2. Improving Drug Stability

Relevance:

Many APIs degrade when exposed to **moisture, heat, oxygen**, or **acidic pH**, which can lead to reduced potency and shorter shelf life.

Stability-Enhancing Strategies:

- **Protective Capsule Shells**: Capsules made from **HPMC or pullulan** offer superior resistance to environmental moisture compared to conventional gelatin shells. Use of **opaque materials** also protects light-sensitive substances.
- **Hermetically Sealed Units**: **Softgels** form airtight containers, while **liquid-filled hard capsules** (LFHCs) use non-aqueous carriers to minimize degradation reactions.
- **Enteric Coatings**: Coated capsules remain intact in the acidic stomach and disintegrate in the higher pH of the intestines, shielding acid-sensitive drugs.

Outcomes:

- Increased formulation shelf life
- Enhanced protection from environmental factors
- Preservation of drug potency through gastrointestinal transit

3. Maximizing Bioavailability

Relevance:

Bioavailability reflects the portion of an administered drug that reaches systemic circulation and is available at the site of action. Factors such as **poor dissolution**, **enzyme degradation**, and **first-pass metabolism** often compromise it.

Bioavailability-Boosting Techniques:

- **Lipid-Based Drug Carriers**: By dissolving the drug in a lipid matrix, capsules can **enhance solubilization** and **facilitate lymphatic uptake**, bypassing hepatic metabolism.
- **Advanced Release Profiles**: Capsules may contain **coated pellets or matrix-based systems** that allow

controlled or delayed release, leading to sustained blood drug levels.

- **Particle Size Reduction**: Incorporation of **micronized** or **nanocrystalline drug particles** increases surface area, accelerating dissolution and improving absorption.

Outcomes:

- Enhanced drug absorption rates
- Reduced inter-patient variability
- Lower dosage requirements with consistent effects

4. Precision Targeting of Drug Release

Relevance:

Targeting drug release to specific regions of the gastrointestinal tract or synchronizing it with disease patterns (e.g., chronotherapy) improves treatment efficiency and minimizes side effects.

Targeting Techniques in Capsules:

- **Enteric-Coated Capsules**: These resist stomach acid and release contents in the **duodenum or intestine**, protecting acid-sensitive APIs.
- **Time-Delayed and Pulsatile Release Systems**: Capsules can deliver drugs at specific times or intervals using **layered coatings** or **multiparticulate systems**, suitable for diseases with circadian patterns (e.g., asthma, arthritis).
- **Colon-Targeted Systems**: Capsule formulations designed to degrade via **colonic enzymes** enable site-specific treatment for conditions like **ulcerative colitis** or **Crohn's disease**.
- **Smart Capsules (Under Development)**: Advanced designs may use **magnetic fields**, **sensors**, or **micro-motors** to control movement and drug release within the GI tract.

Outcomes:

- Focused delivery to desired GI regions
- Reduction of systemic side effects
- Improved therapeutic management of localized diseases

5. Improving Patient Compliance

Relevance:

Medication adherence is critical for therapeutic success. Complex regimens, unpleasant taste, or difficulty swallowing often reduce compliance, particularly in chronic treatments.

Capsule Features that Promote Adherence:

- **Swallowability**: Capsules, especially **softgels**, are smooth and easier to swallow than large, coated tablets.
- **Taste and Odor Masking**: Enclosed drug content prevents unpleasant flavors and smells from affecting the patient experience.
- **Reduced Dosing Frequency**: **Extended-release capsules** allow once-daily or twice-daily dosing, reducing regimen complexity.
- **Tamper Evidence and Dose Accuracy**: Capsules offer **unit-dose precision** and can be **band-sealed** to prevent tampering.
- **Cultural and Dietary Acceptance**: Use of **vegetarian capsules (HPMC, starch-based)** ensures suitability for individuals with religious or ethical restrictions.

Outcomes:

- Improved patient comfort and cooperation
- Higher treatment adherence rates
- Better long-term treatment outcomes

Table

Performance Parameter	Capsule-Based Formulation Benefits
Solubility	Lipid systems, SEDDS, nanoparticles improve dissolution of hydrophobic drugs
Stability	Protective shell materials, inert fillers, and enteric coatings extend shelf life and prevent degradation
Bioavailability	Enhanced absorption via lipid carriers, modified-release profiles, and size-reduction technologies

Performance Parameter	Capsule-Based Formulation Benefits
Precision Targeting	Targeted coatings, time-release systems, and microbiota-triggered capsules enable site-specific action
Patient Compliance	Better swallowability, taste masking, reduced dosing, and dietary-friendly options enhance adherence

Capsule dosage forms, whether **hard gelatin** or **soft gelatin**, undergo comprehensive **quality control tests** to ensure they meet the required pharmaceutical standards. These tests are typically categorized as **physical**, **chemical**, and **performance-related evaluations**.

1. Visual Inspection

Objective:

To detect **physical or cosmetic defects** in the capsule's appearance.

Parameters Checked:

- Uniform color and smooth surface
- Absence of cracks, spots, or pinholes
- Sealing integrity in softgel capsules
- Proper closure of body and cap in hard capsules

Importance:

A basic but essential test to identify **manufacturing inconsistencies or damage**.

2. Weight Variation Test

Objective:

To ensure **uniform filling** of each capsule.

Procedure (for Hard Gelatin Capsules):

1. Weigh 10 capsules individually.
2. Empty each and weigh the shells.
3. Subtract shell weight from total to find net fill weight.
4. Compare individual fill weights with the average.

USP Acceptance Limits:

- Not more than 2 capsules may vary by ±10% from the average.
- No capsule may deviate by more than ±20%.

Importance:

Ensures **consistent dosing** and reduces variability between units.

3. Content Uniformity Test

Objective:

To verify the **accuracy and consistency** of the active ingredient in each capsule.

Procedure:

- Randomly select 10 capsules.
- Analyze each using a validated method (e.g., UV, HPLC).
- Determine the percentage of drug content relative to the labeled claim.

USP Criteria:

- Each unit must contain **85%–115%** of the labeled amount.
- Relative Standard Deviation (RSD) must be within acceptable limits.

Importance:

Essential for **potent or low-dose** formulations to ensure therapeutic safety and efficacy.

4. Disintegration Test

Objective:

To assess the **time required for capsules to break apart** in a simulated physiological environment.

Procedure:

- Use a **disintegration tester** at 37 ± 2°C with appropriate medium (e.g., water or simulated gastric fluid).
- Place 6 capsules in the apparatus.
- Record the time taken for complete disintegration (usually ≤ 30 minutes for hard capsules).

Importance:

A key test to ensure the drug is **released in the GI tract** as intended.

5. Dissolution Test

Objective:

To evaluate the **rate and extent** of drug release from the capsule.

Procedure:

- Use USP Apparatus I (basket) or II (paddle) at 37°C.
- Select appropriate dissolution medium (e.g., 0.1N HCl or phosphate buffer).
- Withdraw samples at specified time points (e.g., 5, 10, 30 min).
- Analyze using UV or HPLC.

Example Acceptance:

- At least **80% drug release in 30 minutes** (Q = 80%).

Importance:
Crucial for determining **bioavailability, therapeutic equivalence, and regulatory compliance**.

6. Hardness or Mechanical Strength Test
Objective:
To measure the **resistance of soft gelatin capsules** to external pressure.

Procedure:
- Use a **texture analyzer** or hardness tester.
- Apply pressure until the capsule ruptures.

Importance:
Ensures **capsule durability** during handling, packaging, and storage.

7. Friability Test *(for multiparticulate capsule fills)*
Objective:
To assess the **fragility** of granules, pellets, or beads inside the capsule.

Procedure:
- Place sample in a **friabilator**.
- Rotate for a set period (typically 4 minutes at 25 rpm).
- Weigh before and after; **weight loss should be ≤1%**.

Importance:
Ensures the **integrity of capsule contents** during manufacturing and handling.

8. Moisture Content Determination
Objective:
To determine **residual moisture**, which can affect drug stability and capsule integrity.

Methods:
- **Loss on Drying (LOD)**
- **Karl Fischer titration** (more precise)

Ideal Ranges:
- Hard gelatin capsules: **12–16%**
- Soft gelatin capsules: **6–10%**

Importance:
Maintaining optimal moisture prevents **shell brittleness, microbial contamination**, and **drug degradation**.

9. Seal Integrity Test *(for soft or liquid-filled capsules)*
Objective:
To ensure the capsule is **properly sealed** and free from leaks.

Methods:
- **Dye ingress test** under vacuum
- **Vacuum leak detection**
- **High-voltage leak detection** (non-destructive)

Importance:
Essential for **liquid or semi-solid capsules** to prevent leakage and preserve dose integrity.

10. Stability Testing
Objective:
To evaluate how the **capsule formulation behaves over time** under various conditions.

Conditions:
- **Accelerated:** 40°C ± 2°C / 75% RH ± 5% (6 months)
- **Real-time:** 25°C ± 2°C / 60% RH ± 5% (12–24 months)

Importance:
Helps define **shelf life**, storage guidelines, and **packaging needs**.

Table

Test	Objective	Applies To
Visual Inspection	Detect cosmetic/physical defects	All capsules
Weight Variation	Ensure uniform capsule fill	Mostly hard capsules
Content Uniformity	Confirm accurate API dosage	All capsules
Disintegration	Check capsule breakdown in GI fluid	All capsules

Test	Objective	Applies To
Dissolution	Evaluate drug release rate and extent	All capsules
Hardness Test	Assess shell strength/resistance	Mostly soft capsules
Friability Test	Check robustness of internal granules/pellets	Multiparticulate capsules
Moisture Content	Determine water content in shell/fill	Hard & soft gelatin capsules
Seal Integrity	Prevent leakage of contents	Soft & liquid-filled capsules
Stability Testing	Assess quality over time	All capsules

CONCLUSION

Capsule technology has advanced considerably, enhancing key aspects like drug solubility, stability, controlled-release mechanisms, and targeted delivery systems. Breakthroughs such as liquid-filled capsules, enteric coatings, and multiparticulate formulations have broadened the scope of drugs that can be effectively administered. Improvements in capsule materials—including vegetarian-friendly and moisture-resistant shells—have also contributed to better patient compliance and product durability.Looking to the future, capsule formulations are poised to integrate cutting-edge innovations like sensor-based and magnetically guided capsules, paving the way for highly precise drug delivery tailored to individual patient requirements. The rise of personalized medicine will further encourage the creation of bespoke capsule dosages and release profiles. Additionally, the adoption of environmentally sustainable capsule materials is expected to become increasingly important in pharmaceutical manufacturing.In summary, capsules will remain a vital and adaptable dosage form, merging ease of use with advanced drug delivery capabilities to meet evolving healthcare demands.

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