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An Emerging Formulation Tablet in Tablet: An Overview

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Abstract:- In recent years, the Pharmaceutical industry has witnessed remarkable advancements in drug delivery technologies, a trend expected to continue. Among the various dosage forms, tablets remain one of the most preferred options due to their practicality, ease of administration, and patient compliance. Innovations in tablet formulations have opened doors to enhanced customization of therapeutic agents, optimizing their effectiveness. Numerous novel drug delivery systems have been developed, providing improved therapeutic outcomes and addressing challenges associated with traditional formulations. This review highlights one such innovative approach, tablet-in-tablet systems. These systems offer significant advantages, such as sustained release of active pharmaceutical ingredients (APIs) and improved safety profiles, while ensuring better patient adherence. By transforming conventional drug delivery methods, such as injectables or oral solid dosage forms, into advanced formulations, tablet-in-tablet technology holds immense potential to revolutionize drug administration practices.

Keywords:- *Tablet-in-Tablet Systems, Sustained-Release Tablets, Innovative Drug Delivery Systems, Dual-Layer Tablets.*

I. INTRODUCTION

The oral route remains the most widely preferred method for drug administration due to its convenience, patient acceptance, cost-effectiveness, ease of use, and accurate dosing. It is also the most investigated route for sustained-release drug delivery systems. Tablet formulation involves the use of various excipients such as binders, diluents, glidants, granulating agents, and lubricants, which play critical roles in ensuring efficient production. Coating tablets with polymers not only improves their ease of swallowing but also enables controlled release of the active pharmaceutical ingredients (APIs).

The development of diverse tablet formulations stems from the need for simple and cost-efficient drug delivery systems. Tablets can vary in size, shape, and weight based on the amount of active ingredient and the intended route of administration. Approximately 70% of all medicines are dispensed as tablet dosage forms.

➢ *Advantages of Tablet Dosage Forms:*

- Tablets offer precise dosing, being unit dosage forms.
- They do not require sterile environments, simplifying manufacturing and storage.
- Large-scale production is feasible compared to other dosage forms.
- Coatings enhance organoleptic properties, improve stability, and extend shelf life by reducing moisture content.
- Various types of tablets, such as buccal, floating, effervescent, dispersible, mouth-dissolving, and chewable forms, cater to different therapeutic needs.
- Tablets are lightweight, compact, and economical compared to other dosage forms.
- Sustained-release formulations are achievable with the use of specific polymers.

➢ *Definition:*

A tablet is a solid unit dosage form prepared by compressing a drug or a mixture of drugs, with or without excipients, into flat or biconvex shapes. Tablets are traditionally circular or disk-shaped but are now also available in various shapes, including oblong forms. According to the *Indian Pharmacopoeia*, pharmaceutical tablets are solid preparations that differ in size and weight depending on the quantity of the medicinal substance and the mode of administration.

➢ *Disadvantages of Tablet Dosage Forms:*

- **Difficulty in Swallowing:** Tablets can be challenging for children, elderly individuals, or unconscious patients to swallow.
- **Slow Onset of Action:** Tablets often have a slower onset of action compared to parenteral formulations, capsules, or liquid oral forms.
- **Formulation Challenges:** Drugs with poor wettability, slow dissolution rates, or compression resistance can be difficult to formulate into tablets.
- **Gastrointestinal Irritation:** Certain tablets can irritate the stomach lining, causing discomfort if not taken with adequate water or food. Drugs with high acidity or specific excipients may exacerbate these effects.
- **Fixed Dosages:** Tablets are generally manufactured in fixed doses, limiting flexibility. Dividing tablets can alter drug release profiles, particularly for sustained-release or enteric-coated formulations.

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- **Taste and Odor:** Bitter-tasting drugs or those with objectionable odors may require encapsulation or coating for improved palatability.

➢ *List of Some Tableting Techniques Currently Used by Pharma Companies*

- **OSDrC Tablet Concept**: One-step dry compression coating technology.
- **Accu-Break Technology**: Used for controlled-release tablets.
- **DiffCORE Technology**: Designed for modified-release tablets.
- **GEOMATRIX Technology**: A technology for multi-layered tablets with controlled-release properties.
- **Tablet-in-Tablet Technology**: An innovative method for layered drug delivery systems.

II. TABLET-IN-TABLET TECHNOLOGY

The tablet-in-tablet technology involves formulating tablets with two distinct parts: an internal core and an external coating. The core is completely enclosed by the surrounding layer, creating a single tablet that houses another within it. This technique has gained significant attention in recent years, especially for modified-release formulations. It involves compressing granular material around the core tablet during manufacturing.

This technology offers several benefits, including protection for hygroscopic, oxidative, photosensitive, and acid-labile drugs. While compression coating is relatively simple and cost-effective for small-scale production, large-scale manufacturing requires specialized equipment. It is widely accepted in the pharmaceutical industry as it uses conventional manufacturing processes.

➢ *Types of Tablet-in-Tablet Formulations*

- *Inlay Tablets:*

✓ A type of layered tablet where the core tablet is not completely coated. The top surface of the core remains exposed (see Figure 1).
✓ During manufacturing, only the bottom part of the die cavity is filled with the coating material to form a "cup." The core tablet is placed on top, and compression forces displace the coating material, binding the entire tablet together.

- *Tablet-in-Tablet Technique:*

✓ In this type, the inner core is fully surrounded by an external coat, appearing as a single tablet from the outside (see Figure 2).
✓ This technique is ideal for modified-release products and involves compressing the outer material around the inner core tablet.

➢ *Advantages of Tablet-in-Tablet Technology*

- Enables rapid onset of action followed by sustained drug release.
- Reduces the frequency of dosing.
- Allows for higher drug-loading capacity.
- Facilitates the administration of two different drugs in a single dosage form.
- Prevents interactions between two incompatible drugs.
- Improves patient compliance.
- Avoids the issue of layer separation, common in bilayer tablets.
- Supports the combination of immediate-release and delayed-release formulations in one tablet.

➢ *Disadvantages of Tablet-in-Tablet Technology*

- The manufacturing process is more complex compared to conventional tablets.
- Production costs are higher due to the need for specialized equipment and processes.

➢ *Manufacturing Process of Tablet-in-Tablet Technology*

The tablet-in-tablet technology involves the formulation of a tablet with two distinct layers: an inner core and an outer coated layer. The process begins with the compression of the inner core, which is a smaller tablet. This core serves as the primary layer. Subsequently, a larger die is utilized to produce the final tablet.

During this process, the coating material is added to the die cavity surrounding the core. Once the cavity is filled, compression is applied to bind the coating material with the core, resulting in the final tablet (see Figure 3). The inner core layer typically provides the initial dose of the drug, while the outer layer facilitates sustained drug release. This configuration is particularly useful in scenarios where controlled release is critical, such as minimizing the risk of dose-related toxicity.

The inclusion of enteric polymers in the core can help inhibit the premature release of the drug in acidic environments. The outer layer ensures that the required initial dosage is delivered efficiently. Additionally, tablets can be manufactured with subdivisions using flat punches and dies, which allow for direct compression of granules.

➢ *Evaluation of Tablet-in-Tablet Technology*

The quality of compression-coated tablets must be evaluated through various tests to ensure safety, efficacy, and consistency.

- *General Appearance*

✓ **Shape**: The tablet's shape should be uniform, such as round, oval, or caplet, with consistent outlines.
✓ **Size and Thickness**: Tablets must maintain uniform dimensions and thickness to ensure accurate dosage. These parameters are typically measured using a caliper or micrometer, with variations limited to within ±5% of the standard value.

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- ✓ **Colour and Texture**: Tablets should exhibit consistent colour and surface texture. Any irregularities, such as discoloration or uneven finishes, may indicate suboptimal manufacturing processes or stability issues.
- ✓ **Odour**: Tablets should be odourless unless specified by the formulation, as unexpected odours may impact consumer perception.
- ✓ **Organoleptic Properties**: Characteristics such as taste and overall sensory appeal are also evaluated for consumer acceptability.

- *Mechanical Strength*

- ✓ **Hardness**: This refers to the force required to crush or break the tablet. Adequate hardness is essential for withstanding mechanical stress during handling, packaging, and transport, while still allowing for quick disintegration upon ingestion.
- ✓ **Friability**: Friability measures the tablet's resistance to crumbling under mechanical stress. Tablets should not lose more than 1% of their weight during this test, as higher friability may indicate poor formulation or insufficient compression force.

- *Content Uniformity*

- ✓ **Weight Variation Test**: Ensures that individual tablets contain consistent amounts of the active pharmaceutical ingredient (API) within acceptable limits.
- ✓ **Disintegration Test**: Measures the time taken for a tablet to break down into smaller particles under specific conditions, ensuring it meets pharmacopeial standards.
- ✓ **Dissolution Test**: Evaluates the rate at which the API is released and dissolved in the body, ensuring bioavailability.

- *Size and Shape*

The dimensional properties of the tablet, including size and shape, are controlled to ensure consistency. Thickness is a critical parameter, and it is measured using a vernier caliper or similar device. The thickness should remain within ±5% of the standard value to ensure proper dosing and patient acceptability.

➢ *Unique Identification Marking*

Unique identification marking on tablets involves techniques such as debossing, embossing, or printing on the dosage form. These markings help in product identification and often include the company name, logo, product name, or product code. This ensures proper traceability and prevents counterfeit production.

➢ *Organoleptic Properties*

Organoleptic properties pertain to the tablet's physical and sensory characteristics, such as color, odor, taste, and overall appearance.

- **Color**: The color distribution should be uniform without any mottling or patchy effects.
- **Odor**: The tablet should have no unusual smell unless a characteristic odor is part of the formulation.
- **Taste**: For orally administered tablets, taste is compared with a standard sample to ensure consistency.
- **Appearance**: Tablets should exhibit a smooth and polished surface to enhance consumer acceptability.

➢ *Mechanical Strength of Tablets*

The mechanical strength of a tablet is crucial to ensure it withstands handling, transportation, and storage without breaking or crumbling. It is evaluated using two main tests:

- *Hardness Test*

- ✓ **Definition**: Hardness refers to the force required to break or crush the tablet.
- ✓ **Significance**: Tablets need sufficient hardness to endure mechanical shocks during manufacturing, packaging, and transportation while disintegrating easily upon ingestion.

- *Friability Test*

- ✓ **Procedure**: Friability is measured using a Roche Friabilator. Tablets are placed in a rotating plastic chamber that drops them from a height of 6 inches. The chamber revolves at 25 rpm for 100 revolutions.
- ✓ **Evaluation**: Tablets are weighed before and after the test. The acceptable weight loss to pass the friability test is less than 0.1–0.5%.
- ✓ **Significance**: Excessive weight loss indicates poor formulation or inadequate compression, leading to failure during handling.

➢ *Content Uniformity*

Content uniformity ensures that each tablet in a batch contains an accurate and consistent amount of the active pharmaceutical ingredient (API).

- *Procedure:*

- ✓ Select 30 tablets randomly.
- ✓ Assay 10 tablets individually for drug content.
- ✓ Acceptance criteria: At least 9 out of the 10 tablets must contain between 85% and 115% of the labeled content, with the 10th tablet containing between 75% and 125%.
- ✓ If the criteria are not met, assay the remaining 20 tablets individually.

➢ *Weight Variation Test (USP)*

This test determines whether tablets have uniform weights within a batch.

- *Procedure:*

- ✓ Weigh 20 tablets individually.
- ✓ Calculate the average weight.
- ✓ Compare each tablet's weight to the average.
- ✓ Acceptance criteria: No more than 2 tablets should deviate from the specified percentage limit, and none should deviate by more than twice the limit.

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➢ *Disintegration Test*

The disintegration test assesses the time required for a tablet to break into smaller particles in a liquid medium.

- *Apparatus:*

The test uses a USP disintegration apparatus, which consists of six glass tubes open at the top and fitted with a mesh (#10) at the bottom.

- *Procedure:*

✓ Place one tablet in each tube.
✓ Submerge the basket assembly containing the tubes into a beaker filled with water, simulated gastric fluid, or intestinal fluid at 37 ± 2°C.
✓ Move the basket up and down through a distance of 5–6 cm at a frequency of 28–32 cycles per minute.
✓ Add perforated plastic discs on top of each tablet to prevent floating during the test.

- *Acceptance Criteria:*

✓ For uncoated tablets: Disintegration time should be between 5 and 30 minutes.
✓ For coated tablets: Disintegration time should be between 1 and 2 hours.
✓ For tablets with an immediate-release outer layer in tablet-in-tablet formulations, the outer layer must disintegrate within the specified time.

- *Significance:*

The test ensures that tablets disintegrate properly, allowing the API to be released and absorbed efficiently in the body.

➢ *Dissolution Test*

The dissolution test evaluates the rate and extent at which the active pharmaceutical ingredient (API) is released from the tablet into a dissolution medium. It is performed using two types of apparatus as specified by the United States Pharmacopeia (USP).

➢ *Apparatus 1: Basket Type*

- ***Design****: This apparatus features a small wire mesh basket attached to the end of a rotating shaft, driven by a variable-speed motor.*

- ***Procedure****:*

✓ A single tablet is placed in the basket.
✓ The basket is immersed in a dissolution medium held in a 1000 mL vessel.
✓ The vessel is maintained at a constant temperature of 37 ± 0.5°C using a water bath or heating system.
✓ The motor rotates the basket at a specified speed, as outlined in the drug monograph.
✓ At predetermined intervals, samples of the dissolution medium are withdrawn to measure the amount of drug released into the solution.

➢ *Apparatus 2: Paddle Type*

- ***Design****: Similar to Apparatus 1, but the basket is replaced with a paddle.*
- ***Procedure****:*

✓ The tablet is placed at the bottom of the dissolution vessel, which contains the specified medium.
✓ The paddle is rotated at a controlled speed as defined in the drug monograph.
✓ The dissolution medium, volume, rotation speed (rpm), and duration of the test are defined in the USP.
✓ Samples are collected at regular intervals to determine the drug release profile.

➢ *Key Parameters for Both Apparatus*

- **Dissolution Medium**: The type of liquid used, such as water, simulated gastric fluid, or intestinal fluid, is specified in the monograph.
- **Temperature**: The medium is maintained at 37 ± 0.5°C to simulate physiological conditions.
- **Volume**: Typically, 900–1000 mL of medium is used, depending on the test requirements.
- **Sampling Intervals**: Fluid samples are withdrawn at specified time intervals for analysis of drug release.
- **Rotation Speed**: The speed of the basket or paddle is predetermined and varies depending on the drug formulation.

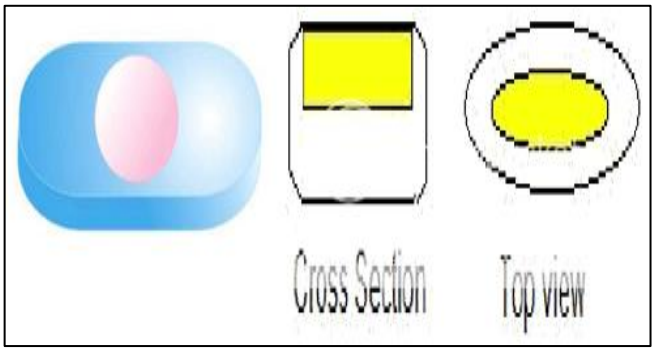

Fig 1 Inlay Tablet

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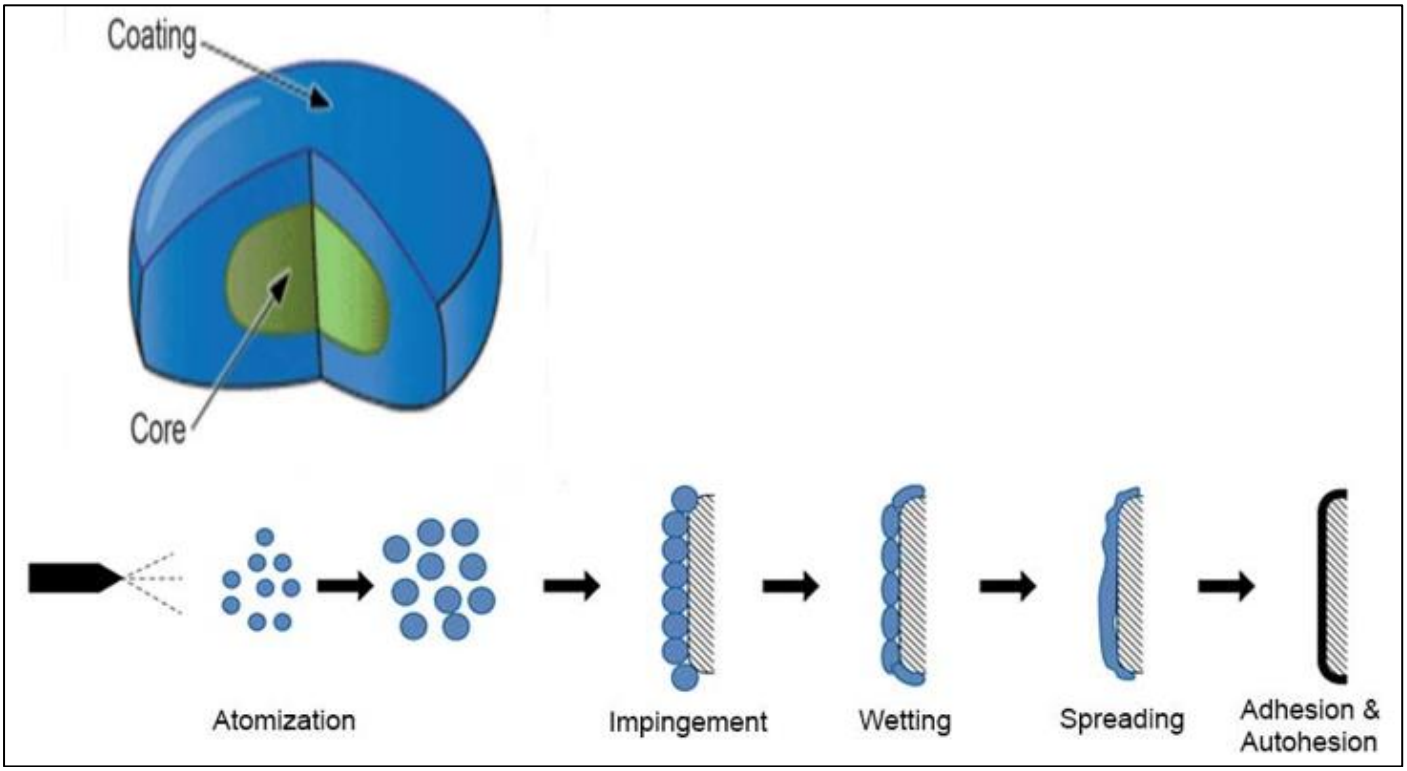

Fig 2 Tablet in Tablet

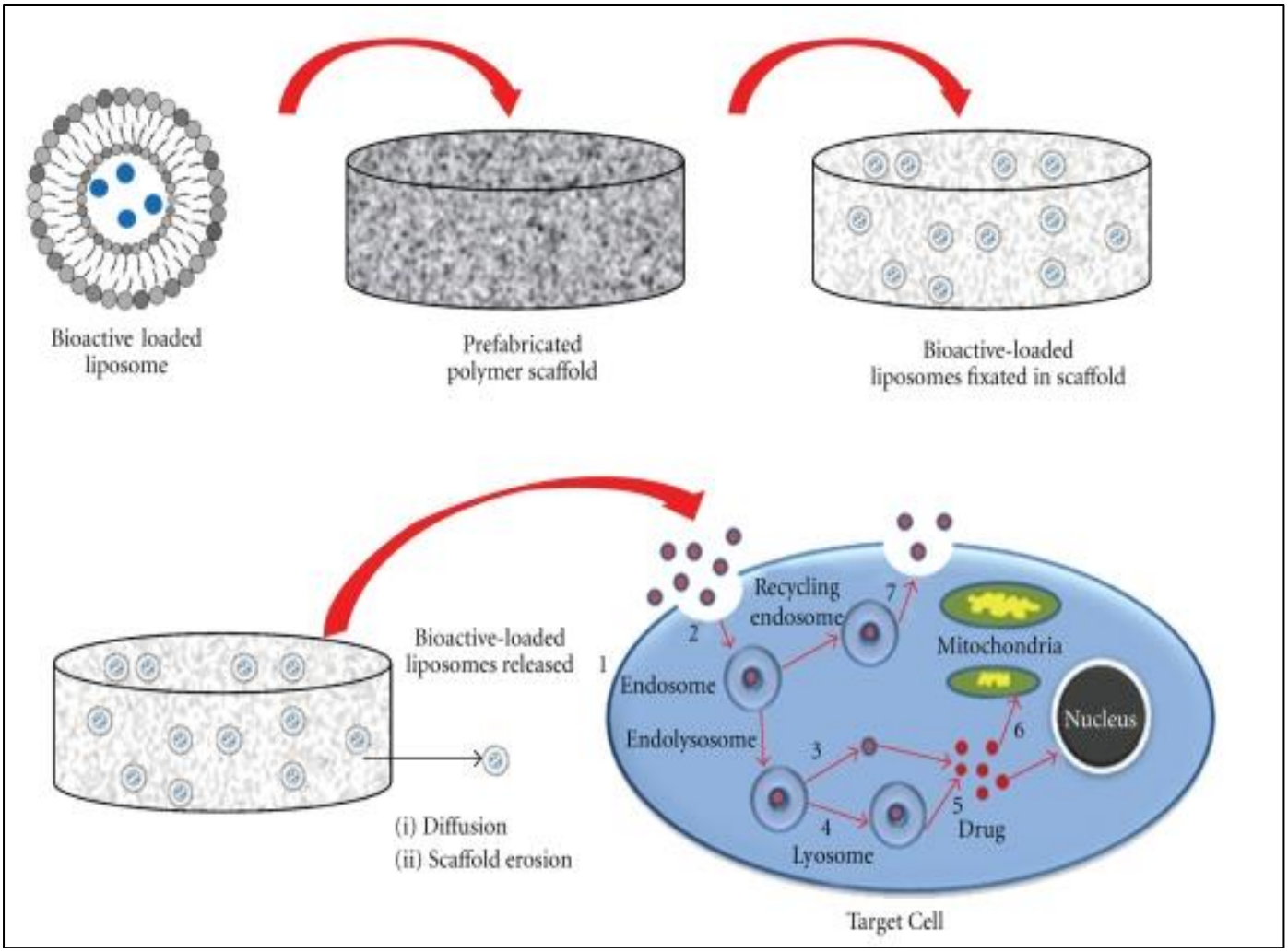

Fig 3 Manufacturing Process of Tablet in Table [6]

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III. RELEASE AND BIOAVAILABILITY (FOR CERTAIN DRUGS)

➢ *Bioavailability*

For drugs with narrow therapeutic indices, maintaining consistent bioavailability is crucial. Bioavailability refers to the extent and rate at which the drug is absorbed into the systemic circulation after administration.

- **Clinical Observations**: Pharmacokinetic studies are conducted to analyze how the drug behaves in the body following ingestion of the tablet.
- **Importance**: Ensuring stable drug bioavailability is essential for achieving the desired therapeutic effect and minimizing risks of under-dosing or overdosing.

➢ *Mechanism of Drug Release*

The release of a drug from the "Tablet-in-Tablet" dosage form occurs in three distinct stages:

- *Penetration of Dissolution Medium:*

✓ The dissolution medium enters the tablet, causing the outer coating to swell or thicken.

- *Erosion of the Outer Coating:*

✓ The outer coating barrier erodes as the dissolution liquid penetrates rapidly.
✓ The internal pressure created by the expanding core leads to the breakdown of the outer layer.

- *Drug Release from the Core Tablet:*

✓ After the outer layer breaks, the internal core tablet dissolves, releasing the drug rapidly.
✓ This final stage ensures the release of the drug in a controlled or sustained manner based on the tablet's formulation.

➢ *Erosion and Absorption Studies*

Modified-release formulations, such as "Tablet-in-Tablet," undergo erosion and absorption tests to evaluate their performance.

- *Methodology:*

✓ Gravimetric analysis is conducted using USP Type-II dissolution apparatus.
✓ Tablets are placed in a dissolution basket immersed in 900 mL of buffer solution at 37 ± 0.5°C.
✓ At specific intervals, tablets are removed, excess surface liquid is gently blotted off using filter paper, and their weight is recorded.
✓ Tablets are then dried in a hot-air oven at 60°C until their weight becomes constant.

- *Monitoring:*

✓ Six tablets are analyzed at each time point. A fresh tablet is used for every time point to maintain consistency.

- *Erosion and Swelling:*

✓ **Remaining Mass (RM)**: The erosion of the tablet is calculated based on its weight loss over time.
✓ **Swelling Ratio (SR)**: Water absorption and the subsequent expansion of the tablet are measured using the swelling ratio formula.

$$RM(\%) = \frac{Wr}{W0} \times 100$$
$$SR(\%) = Wt - Wr \backslash Wr \times 100$$

Where, W0 is the dry tablet's starting weight; At time t, Wr is the wg of the leftover dried tablet after penetrating the medium; Wt is the wg of the tablet excluding water on the surface.

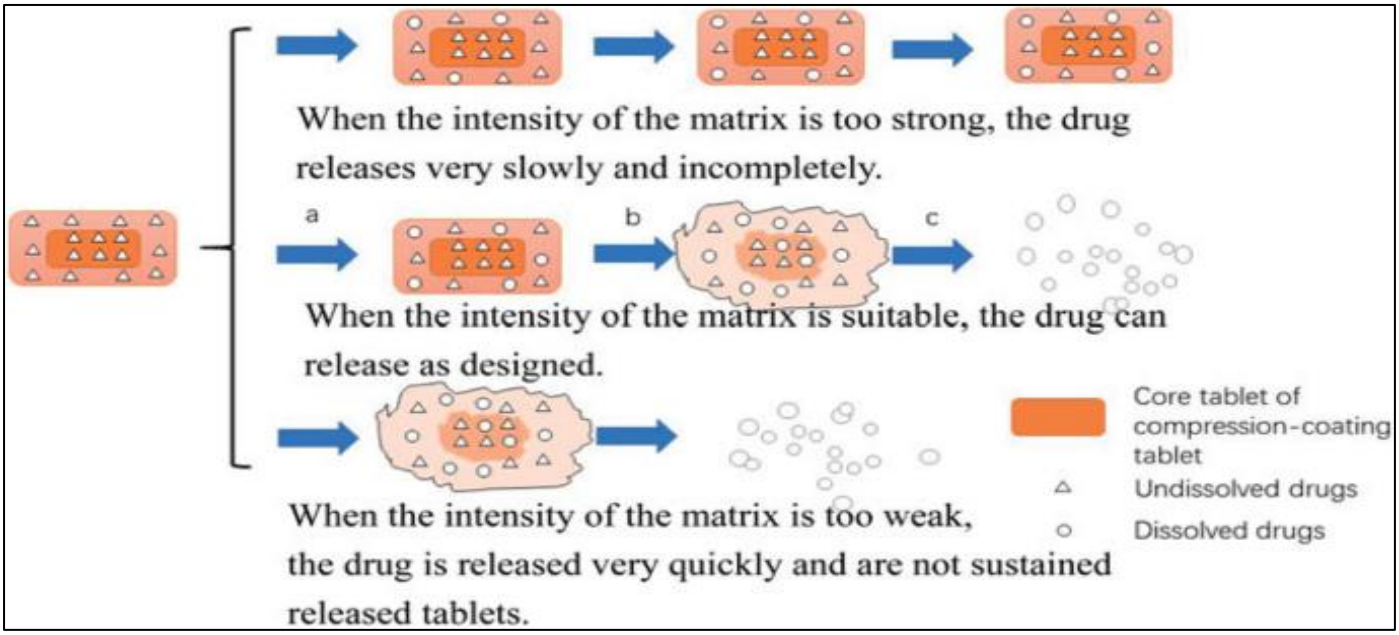

Fig 4 Mechanism of Release

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➢ *Application of Tablet-in-Tablet Technique in Pharmaceutical Formulation*

The tablet-in-tablet technique, also known as compression coating, was initially employed between 1950 and 1960 to manage incompatible drug combinations. Over the past two decades, this method has gained significant popularity due to several advantages:

- **No Solvent Requirement**: This approach eliminates the need for solvents, making it a safer and more environmentally friendly option.
- **Efficient Production**: The production process is relatively fast compared to other coating methods.
- **Increased Core Tablet Weight**: Compression coating allows for a greater weight ratio of the inner core tablet compared to conventional coating methods.

➢ *Pharmaceutical Applications:*

- *Protection of Sensitive Drugs:*

✓ Used to safeguard drugs that are sensitive to moisture, light, oxygen, or acidic environments.

- *Separation of Incompatible Drugs:*

✓ Helps in formulating dosage forms where two or more drugs need to be separated to avoid interaction.

- *Controlled Drug Release:*

✓ Enables the modification of drug release profiles to achieve sustained, immediate, or delayed release as required.

IV. CONCLUSION

The tablet-in-tablet dosage form is an advanced pharmaceutical approach that combines an active ingredient in the core tablet with a sustained-release profile and an outer layer with an immediate-release profile. Key benefits of this technique include:

- **Zero-Order Drug Release**: Ensures a consistent release rate of both soluble and insoluble drugs in dissolution media.
- **Enhanced Efficacy for Highly Soluble Drugs**: Reduces the dosing frequency while maintaining therapeutic efficacy.
- **Minimized Drug Interactions**: Prevents compatibility issues and burst release effects, making it suitable for combining various drugs.
- **Improved Patient Compliance**: Reduces the need for frequent dosing and simplifies drug regimens.

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