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Review on Tablet in Tablet Techniques

Aher Akshay H[1], Dr. Rajendra K. Surawase[2], Wagh Rakesh M[3], Khairnar Darshan B[4], Gangurde Lalit H[5]

[1,2,3,4,5]Department of Pharmaceutics, Loknete Dr. J. D. Pawar College of Pharmacy, Manur.

ABSTRACT

Tablet-in-tablet technology is an innovative pharmaceutical approach designed to enhance drug delivery efficiency and patient compliance. This technique involves compressing an inner drug-containing core with an outer coating layer, allowing for biphasic or controlled release. It offers several advantages, including the ability to separate incompatible drugs, protect sensitive ingredients, and provide targeted or delayed drug release. This method also reduces the pill burden by combining multiple drugs into a single dosage form. Additionally, it employs solventless coating techniques, making it an eco-friendly alternative to traditional coating methods. Tablet-in-tablet technology is widely used in the treatment of chronic conditions such as cardiovascular diseases, diabetes, and cancer due to its flexibility in drug release profiles and improved therapeutic outcomes.

Keywords: Tablet-in-tablet, Drug delivery system, Solventless coating.

1. INTRODUCTION

The oral route is the most preferred way to deliver drugs because it is easy to use, convenient for patients, and allows for flexible formulation. Tablets are the most common solid form used for oral drug delivery. Pharmaceutical tablets often have exterior coatings, which serve various purposes, such as controlling or improving the release of the active pharmaceutical ingredient (API) or simply masking the bitter taste of the API [2]. These coatings can improve the tablet's colour, texture, mouthfeel, and flavour. However, this coating technology has some limitations that need to be addressed. One of the best alternatives for controlled release is the tablet-in-tablet formulation,[3] where the medicine is present in both the core and the outer shell. This method is also used to achieve a biphasic release, with both fast and slow release of the drug.

Tablets are the most commonly used dosage form because they are easy to administer, cost-effective to produce, and have an elegant appearance [13]. The aesthetic qualities, such as colour, texture, mouthfeel, and taste masking, depend on the coating techniques used. However, coating technology has certain limitations. To overcome these drawbacks, the tablet-in-tablet formulation is considered one of the best alternatives.

Coating provides both physical and chemical protection to the drug. It also helps modify the drug's release pattern. In the 19th century, sugar coating was introduced in pharmaceuticals to mask the bitter taste of medicines. However, sugar coating had several drawbacks. It required a long processing time of 6 to 7 days and involved multiple steps (sealing, sub-coating, smoothing, colouring, polishing, etc.), which needed skilled operators. Other issues included the lack of automation, weight gain of the tablets, and the sugar solution being prone to bacterial growth. These limitations led to the development of new coating

techniques.

Film coating significantly reduced the processing time compared to sugar coating. In 1954, Abbott Laboratories introduced the first film-coated tablet. Film coating brought a major revolution in coating technology by offering batch-to-batch consistency in formulation, suitability for different dosage forms, and easier process control with automation.

Film coating uses either aqueous- or organic-based polymer solutions, but both have disadvantages. Organic solvents used in film coating can be flammable, toxic, and leave residual solvents in the film, making the process costly. On the other hand, aqueous film coating requires more heat and a longer drying time, which increases the overall manufacturing cost.

Compression coating, first introduced by Noyes in a patent in 1896, is another coating technique. It is considered one of the best alternatives in modern drug delivery systems and is regarded as a novel coating technology [2].

To overcome the challenges of film and sugar coating, the tablet-in-tablet or compression coating technique was introduced as an alternative. It is also known as dry coating or press coating and was one of the first solvent-free coating methods. A tablet-in-tablet or compression-coated tablet generally consists of two parts: an inner drug core and an outer coating shell. The outer layer covers the inner core and mainly controls the coating strength, drug release, and stability [15].

1.1. Types of Solventless Coating:

There are seven techniques of solvent less coating of tablets that include

1. Compression coating / Tablet in tablet
2. Magnetically assisted impaction coating (MAIC)
3. Hot melt coating
4. Supercritical fluid coating/microencapsulation
5. Electrostatic Dry Coating
6. Powder/dry coating
7. Photo curable coating

1. Compression Coating

Compression coating is a dry process in which an external layer of powder-based excipients is compacted around a core tablet using specialized tablet presses. This method is commonly used in the development of tablet-in-tablet dosage forms and controlled-release formulations.

Mechanism

- A specific quantity of coating material is added to the tablet die.
- The core tablet is positioned within the coating material.
- Additional coating powder is added to completely cover the core.
- The entire assembly is compressed into a single unit, ensuring strong adhesion between the layers.

Advantages

- No solvents required, eliminating risks associated with residual solvents.
- Enables separation of incompatible drugs within a single dosage form.
- Protects the active ingredient from environmental degradation.
- Supports controlled drug release by modifying the composition of the coating layer.

Limitations

- Requires specialized tablet compression equipment.

- Achieving uniform coating thickness can be challenging.[6]

2. Magnetically Assisted Impaction Coating (MAIC)

MAIC is a dry coating technique that utilizes magnetic particles to facilitate the application of a coating layer onto the tablet's surface. This method is ideal for delicate pharmaceutical ingredients that cannot withstand heat or excessive mechanical forces.

Mechanism

- Magnetic particles are added to a processing chamber containing the core tablets and coating powder.
- An electromagnetic field generates movement of the magnetic particles, creating high-speed collisions.
- These collisions transfer energy to the coating powder, facilitating uniform attachment to the tablet surface.
- The result is a dry-coated tablet with a firmly adhered layer of coating material.

Advantages

- No need for heat, making it suitable for temperature-sensitive drugs.
- Produces a thin and uniform coating layer.
- Reduces degradation of active ingredients due to minimal mechanical stress.

Limitations

- Requires specialized magnetic processing equipment.
- Coating thickness is difficult to control.[12]

3. Hot Melt Coating

Hot melt coating involves applying a molten coating material onto the tablet's surface, which solidifies upon cooling. It is primarily used for taste masking, controlled drug release, and moisture protection.

Mechanism

- A lipid or polymer-based material is heated to its melting point.
- The molten coating is sprayed or poured onto the tablet.
- The coated tablet is cooled rapidly, solidifying the coating layer.

Advantages

- No solvents are used, making the process environmentally friendly.
- Short processing time due to rapid cooling.
- Cost-effective as it reduces energy consumption.

Limitations

- Requires high processing temperatures, which may not be suitable for heat-sensitive drugs.
- Limited choice of coating materials, as only lipids, waxes, and certain polymers can be used.[12]

4. Supercritical Fluid Spray Coating

This advanced coating technique uses supercritical carbon dioxide (CO_2) as a medium to apply a coating material onto pharmaceutical tablets. It is an alternative to solvent-based methods while providing precise control over coating thickness.

Mechanism

- The coating material is dissolved in supercritical CO_2 under controlled temperature and pressure.
- The tablets are placed in a coating chamber where the solution is sprayed onto their surface.

- The pressure is gradually reduced, causing the CO_2 to evaporate, leaving behind a uniform coating layer.

Advantages

- Eco-friendly process since it eliminates harmful organic solvents.
- Allows for controlled deposition of coating materials.
- Ideal for heat-sensitive and moisture-sensitive drugs.

Limitations

- High equipment cost due to the need for specialized pressure chambers.
- Limited solubility of certain coating materials in supercritical CO_2.

5. Electrostatic Dry Coating

Electrostatic dry coating applies an electrically charged powder onto a tablet's surface without the need for solvents. The process is widely used in paint and food industries and has been adapted for pharmaceutical coatings.

Mechanism

- A fine powder consisting of coating polymers is electrically charged using a spray gun.
- The charged particles are attracted to the grounded tablet surface.
- The coated tablet is then exposed to heat or UV light to fuse the particles into a uniform film.

Advantages

- Does not require solvents or liquid carriers.
- Precise and even coating distribution due to electrostatic attraction.
- Can apply different colours to create unique tablet appearances.

Limitations

- Requires specialized electrostatic spray equipment.
- The coated particles must be fused using heat, limiting use for heat-sensitive drugs.[11]

6. Dry Powder Coating

This advanced coating technique the direct application of powdered excipients onto a tablet, followed by a fusion step that binds the coating to the tablet surface.

Mechanism

- The powdered coating material is uniformly dispersed over the tablet surface.
- The tablet is subjected to controlled heat or pressure, promoting adhesion of the powder.
- The process may involve compaction, mechanical forces, or sintering to solidify the coating.

Advantages

- No use of solvents, making it environmentally sustainable.
- Fast processing time with minimal energy consumption.
- Can be combined with sub-coating techniques to enhance adhesion.

Limitations

- Requires specific powder formulations to achieve adequate adhesion.
- Not suitable for all types of pharmaceutical coatings.[6]

7. Photocurable Coating

This cutting-edge technology involves the use of UV or visible light to trigger a chemical reaction that hardens a liquid monomer into a solid coating.

Mechanism

- A liquid photopolymer (such as acrylic siloxane) is applied to the tablet's surface.
- The tablet is exposed to UV or visible light, causing the polymer to cure and form a durable film.
- The resulting coating is mechanically strong, flexible, and moisture-resistant.

Advantages

- Extremely fast curing process, taking only seconds.
- No heat is required, making it ideal for temperature-sensitive drugs.
- Provides high-quality, defect-free coatings.

Limitations

- Requires light-sensitive coating materials.
- Exposure to light must be carefully controlled to prevent premature polymerization.[11]

1.2. Multiple Compressed Tablets

1. Tablet in tablet
2. Inlay tablet
3. Layered tablet

Tablet in tablet:

Tablet-in-tablet technology is an advanced pharmaceutical formulation. This technology allows better control of drug release and improved combination therapy. It offers enhanced patient compliance by combining multiple drugs in a single tablet.[5]

Modern techniques like OSDrC® make production more efficient and precise.

TiT is widely used for cancer, cardiovascular, and diabetic treatments due to its flexible release capabilities.[3]

Advantages of Tablet-in-Tablet Dosage Form

- Separation of incompatible materials: The core and outer shell can separate incompatible materials.
- Modified release products: This form can be used to develop delayed-release products.
- Targeted release: Two different drugs can be targeted to different areas of the gastrointestinal tract.
- No separate coating process needed: The press coating process eliminates the need for a separate coating process [2].
- Environmentally friendly: This process is solventless, making it non-hazardous to the environment.
- Avoids drug interactions: This form can avoid pharmacokinetic interactions between drugs by creating a time interval in their release.
- Protects sensitive drugs: This form protects hygroscopic or thermo-liable drugs [10].
- Improved bioavailability: This form can improve bioavailability of drugs that are mainly absorbed in the upper part of the gastrointestinal tract.
- Local action: This form can provide local action for stomach pathologies.
- Combination therapy: This form can achieve immediate and sustained release of a single drug or combination of drugs. [9]

- Using different polymeric excipients to formulate tablets in tablet dosage form that have different release times can prevent the pharmacokinetic interaction between the two simultaneously delivered drugs.[4]
- Increased patient compliance: By combining multiple drugs into a single tablet, patients are more likely to adhere to their medication regimen.
- Reduced pill burden: Tablet-in-Tablet dosage form can reduce the number of pills patients need to take, making it easier to manage their medication.
- Improved stability: The outer shell can protect the inner core from environmental factors, such as moisture and light, improving the stability of the drug.
- Masking unpleasant taste: The outer shell can mask unpleasant tastes or odors of the inner core, making the medication more palatable.
- Controlled release: The Tablet-in-Tablet dosage form can provide controlled release of the drug, reducing peak-to-trough fluctuations and improving therapeutic outcomes.
- Reduced side effects: By controlling the release of the drug, the Tablet-in-Tablet dosage form can reduce side effects associated with peak plasma concentrations.
- Increased bioavailability: The Tablet-in-Tablet dosage form can increase bioavailability by protecting the drug from degradation in the gastrointestinal tract.
- Flexibility in formulation: The Tablet-in-Tablet dosage form offers flexibility in formulation, allowing for the combination of different drugs, release profiles, and tablet sizes.

Challenges in Tablet-in-Tablet Technology

- Layer contamination risk: There's a possibility of contamination between the layers, which can affect the quality of the tablet.
- Layer attachment problems: The different layers may not stick together properly due to differences in their physical properties, leading to weak bonds between them.
- Stability issues: It's challenging to maintain the physical and chemical properties of the tablet over time, especially during storage.
- Difficulty in swallowing: The large size of the tablet can make it hard for patients to swallow [1].
- Inconsistent coating performance: If the core tablet is not centred, the coating may not be applied evenly, affecting the tablet's performance [2].
- Manufacturing complexity: The process of creating a Tablet-in-Tablet is more complex than traditional tablet manufacturing, requiring specialized equipment and expertise.
- Material selection: Selecting the right materials for the different layers of the Tablet-in-Tablet product can be challenging due to the need for compatibility and stability.

OBJECTIVE

- Protecting drugs sensitive to moisture, light, oxygen, or acidity
- Separating incompatible drugs to prevent adverse interactions
- Achieving controlled release of drugs
- Targeted Drug Delivery
- Increased Bioavailability
- Improved Patient Compliance

APPROACHES

The tablet-in-tablet system employs different drug release strategies based on the coating and core design. Here are the major approaches:

1. Multiphasic Release (Two-Step Release)

- The tablet releases the drug in two phases:
- Fast release → Provides immediate relief.
- Slow release → Continues to release the drug over time for long-lasting effects.
- Example: A painkiller tablet that offers quick pain relief but also reduces inflammation for several hours.

2. Delayed Release (Time-Gap Release)

- The drug release is delayed for a specific time after swallowing.
- This is achieved by coating the inner tablet with a layer that dissolves slowly.
- Used for drugs that need to bypass the stomach and release in the intestine or colon.
- Example: Tablets for colon diseases, which need to release the drug only after passing through the stomach.

3. Time-Controlled Release (Scheduled Release)

- The tablet releases the drug at a fixed time after being swallowed.
- Example: Tablets for high blood pressure that release the drug early in the morning when blood pressure spikes.

4. pH-Controlled Release (Stomach or Intestine-Specific)

- This approach uses a special coating that dissolves only at certain pH levels.
- Since the pH is different in the stomach and intestine, the tablet can be designed to release the drug only at the target site.
- Coating with enteric polymers ensures the tablet dissolves only in specific pH environments (e.g., intestine or colon).
- Example: Tablets for Crohn's disease, which need to release the drug in the intestine, not the stomach.[7]

5. Microbial-Controlled Release (Bacteria-Triggered)

- This method targets the colon, where specific bacteria break down the outer coating.
- Once the coating is broken, the drug is released.
- Polymers like alginates, amylase, and cellulose are used, which are broken down by bacterial enzymes.
- Example: Tablets for ulcerative colitis, where the drug needs to act only in the colon. [7]

6. Controlled Release Systems

Compression-coated tablets are designed to control the release of drugs. how they work:

Core: The core of the tablet can be designed for fast disintegration or modified release.

Barrier: A solid barrier is compressed onto the core. This barrier can contain:

- Polymeric materials
- Diluents (to modify release)
- Drugs (for extended release)

Modified Release Patterns

By adjusting the drug distribution and type of controlling polymer used in the core and coat, different release patterns can be achieved:

- Extended Release: Drug is released slowly over a longer period.
- Delayed Release: Drug is released after a specific time, pH, or microbial trigger.
- Targeted Release: Drug is released in a specific region of the gastrointestinal tract [8].

TABLET IN TABLET MANUFACTURING PROCESS

Tablet-in-Tablet Manufacturing Process: Inner Core Tablet Formulation

- Weighing and Sieving: Accurately weigh each ingredient and pass it through a mesh #60 sieve to ensure uniform particle size.
- Blending: Blend the mixture with lactose (or a suitable diluent) for 10 minutes using a mortar and pestle.
- Granulation: Gradually add granulating liquid to form a damp mass, then pass it through a mesh #18 sieve to form granules.
- Drying: Dry the granules at 60°C until they reach the desired moisture content.
- Lubrication and Sieving: Lubricate the dried granules and pass them through a mesh #12 sieve.
- Compression: Compress the final granules into core tablets using a rotary tablet compression machine with 6 mm round concave punches.

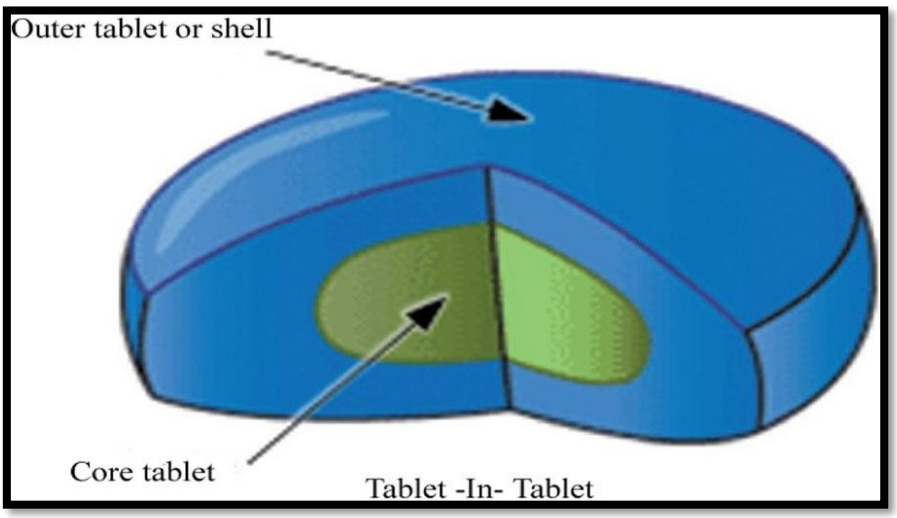

Fig.1 Tablet in Tablet

Tablet-in-Tablet Manufacturing Process

The tablet-in-tablet dosage form consists of two parts: an inner core and an outer coating. To create the internal core, a small concave tooling (6 mm) was used to make a tiny tablet. In contrast, larger tooling was used for the outer layer.

Preparation of Outer Tablet Shell

1. Weighing and Sieving: Each component listed in Table 2 was accurately weighed and passed through a #60 sieve to ensure uniformity in the powder blend.
2. Mixing: The powder blend was mixed on butter paper for 30 minutes to achieve uniformity.
3. API Addition: The Active Pharmaceutical Ingredient (API) was added to the mixture and geometrically blended for 10 minutes using a mortar and pestle.

Compression of Outer Tablet Shell

1. Lower Layer: 50% of the powder weight was placed as the lower layer in the 8 mm round concave punch die cavity.
2. Core Tablet Placement: The optimized core tablet (100 mg) was placed at the center of the die cavity.
3. Upper Layer: The remaining 50% of the outer tablet powder was weighed and manually added to the core tablet in the die cavity.

LIMITATIONS OF TRADITIONAL TABLET-IN-TABLET (TIT) MANUFACTURING

Conventional dry-coating methods for producing TiT tablets have several issues. The core tablet transport system can cause problems like:

- Missing cores (non-core)
- Double cores
- Off-centered cores
- Inlays

These issues limit the use of dry coating or TiT tablets compared to traditional tablets.

Innovative One-Step Dry-Coating (OSDrC) Method:

A new method developed in Japan creates TiT tablets in a single step, eliminating the core tablet transport system issues. Here's a simplified overview of the traditional method:

1. Filling the outer coating layer: The space created by the lower punches is filled with the outer coating layer powder.
2. Pre-compression: The powder is pre-compressed.
3. Creating space for the core: The punches are adjusted to create space for the core.
4. Filling and pre-compressing the core: The core powder is filled and pre-compressed.

The OSDrC method offers a more efficient and reliable way to produce TiT tablets.

Advantages of OSDrC®:

- More precise coating thickness.
- No need for separate core manufacturing.
- Improved tablet quality.[3]

INLAY TABLET:

An inlay tablet is a type of multilayer tablet where the core (inner portion) is partially exposed rather than being fully coated. Unlike tablet-in-tablet forms where the inner core is fully enclosed, in inlay tablets, one surface of the core is visible, while the other side is embedded in the outer layer.

Structure of Inlay Tablets

Core: Contains one active ingredient.

Outer Layer: Holds another active ingredient or protective layer.

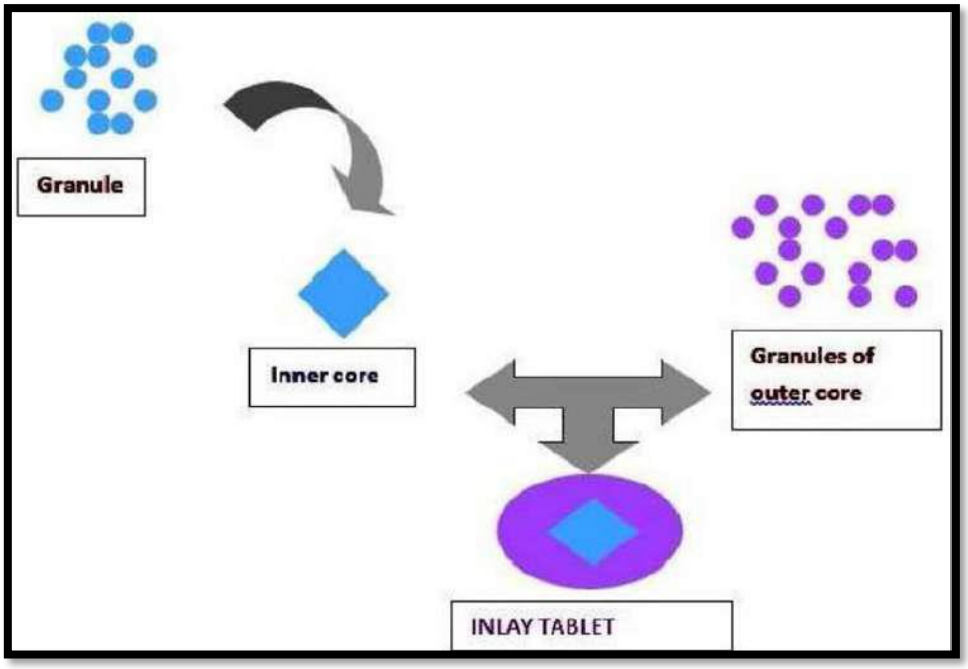

Fig. 2 Preparation of inlay tablets.

Benefits of Inlay Tablets

- Dual Drug Release: They can release two different drugs simultaneously but at different rates.
- Modified Release: The outer layer dissolves first, providing an immediate effect, while the core dissolves slowly for a sustained release.
- Prevents Drug Interaction: Keeps incompatible drugs separated.
- Enhanced Effectiveness: Helps maintain steady plasma concentration, reducing the risk of side effects.
- Avoids Burst Release: Prevents sudden high drug release, which could lead to toxicity.

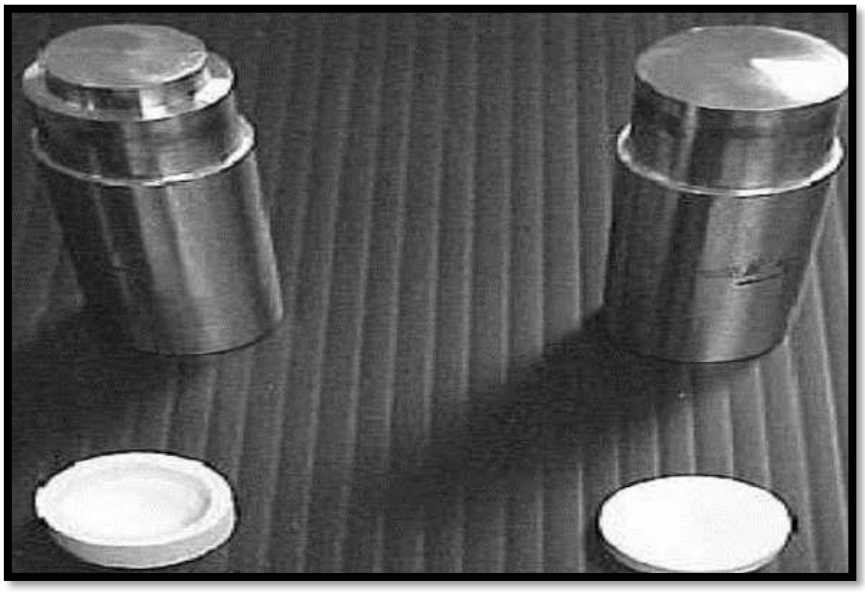

Fig. 3 The image shows the tools used to test and prove the idea, along with a cup and a fully prepared medication dose.

Examples of Inlay Tablets

Metformin (500mg) + Pioglitazone (15mg) → Used for diabetes management.

Disadvantages

- Complex Manufacturing: Requires specialized equipment.
- Costly Production: More expensive compared to regular tablets.
- Potential Core Displacement: The core tablet might shift during production, affecting drug release accuracy. [3]

LAYERED TABLET

Definition

A layered tablet consists of two or more layers of granulated material compressed together. It resembles a sandwich due to its visible layers. Each layer may contain different active pharmaceutical ingredients (APIs) or release mechanisms, making it ideal for delivering multiple drugs or controlling the drug release rate.

Types of Layered Tablets

1. Bilayer Tablet: Contains two layers, often used for combining two drugs with different release profiles. For example, one layer releases the drug quickly, while the other provides a slow release.
2. Triple Layer Tablet: Consists of three layers, usually for more complex drug delivery systems, such as separating interacting drugs.

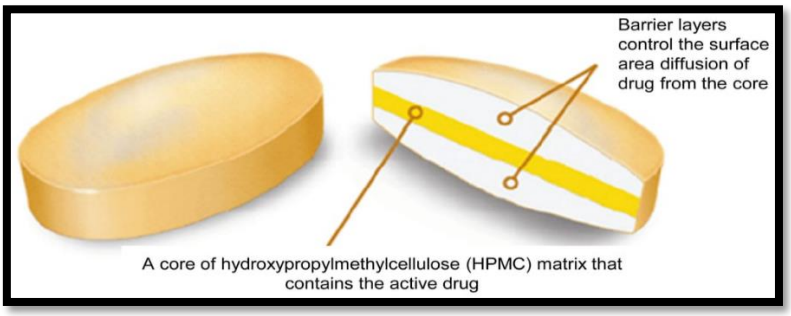

Fig.4 Triple Layered Tablets

3. Multilayer Tablet: Contains more than three layers, offering advanced controlled-release profiles.

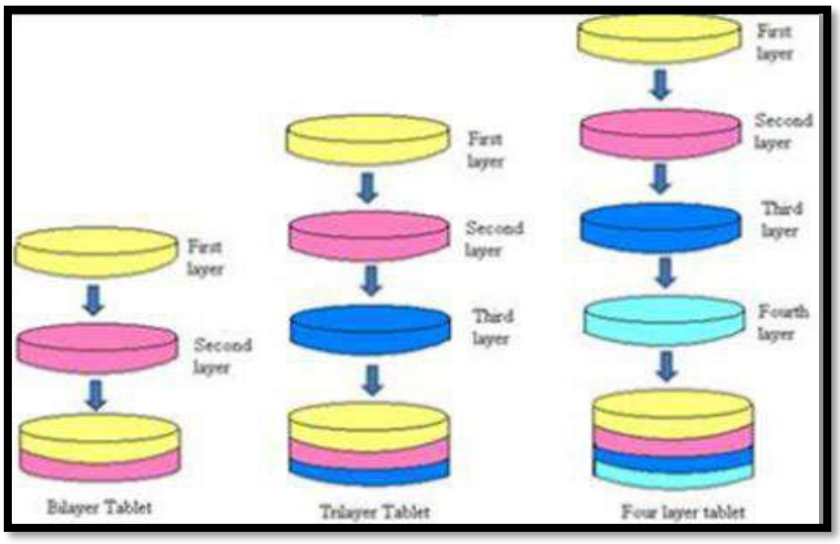

Fig. 5 Multilayer Layer Tablet

Examples of Layered Tablets

Metoprolol and Amlodipine: Used for hypertension with a combination of sustained and immediate release layers.

Advantages of Layered Tablets

1. Combination Therapy: Enables the delivery of two or more drugs in a single tablet, simplifying treatment for patients.
2. Controlled Release: Allows different release profiles for each layer, ensuring consistent or targeted drug delivery.
3. Reduced Dosing Frequency: Prolonged release reduces the need for multiple daily doses, improving patient compliance.
4. Enhanced Stability: Separates incompatible drugs into different layers, preventing interactions.
5. Cost-Efficient: Combines multiple drugs in one tablet, reducing production and packaging costs.

Disadvantages

1. Complex Manufacturing: Requires specialized machinery and precise formulation control.
2. Layer Separation Issues: Poor adhesion between layers can lead to splitting or uneven drug release.
3. Higher Cost: More expensive to produce compared to single-layer tablets.
4. Difficulty in Swallowing: Larger tablets may be harder for some patients to swallow.

CONCLUSION

Tablet-in-tablet technology represents a significant advancement in pharmaceutical formulation by offering enhanced drug delivery efficiency and patient convenience. Its ability to control the release rate, protect sensitive drugs, and separate incompatible ingredients makes it highly effective for combination therapies. The solventless coating methods make the process environmentally friendly and cost-effective. Despite some challenges, such as manufacturing complexity and stability concerns, this technology plays a vital role in modern drug delivery, particularly for chronic conditions requiring precise and sustained drug release. As research and technology continue to evolve, tablet-in-tablet systems are expected to become even more versatile and widely adopted in pharmaceutical practice.

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