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Review Article

Bilayer Tablets in Pharmaceutical Technology: An Insight into Innovation and Development

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ABSTRACT

A new and improved pharmaceutical dosage form called a bilayer tablet was created to get around some of the drawbacks of traditional single-layer tablets. Because of their two separate layers, incompatible medications can be physically separated, and various release profiles, such immediate and sustained release, can be combined into a single device. By administering an initial loading dose and a maintenance dose, this dual-layer method improves therapeutic efficacy and is particularly helpful for disorders that call for both quick and sustained action. Bilayer tablets not only increase patient compliance but also provide versatility in creating fixed-dose combinations, allowing for sequential or synchronized medication administration. The method is especially useful for decreasing the frequency of doses and attaining regulated release. Bilayer tablets are a substantial improvement in drug distribution, with promise future uses in a variety of therapeutic areas, despite certain manufacturing and stability issues.

INTRODUCTION

For the majority of medications, oral administration is still preferred because it is a well-known, practical, and painless substitute for injections. When used orally, the practicality of Maximum patient compliance can be achieved by the oral route, self-administration features, and the high degree of dosing regimen flexibility offered. [1]. A pharmaceutical dosage type called a bilayer tablet is made to include two different medications or pharmacological formulations. It is made up of two distinct layers, each with a unique composition, function, and goal. These tablets are frequently used to combine several drugs in a single dose, improve therapeutic efficacy, or increase compliance by achieving controlled or

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immediate drug release patterns. Drugs with distinct release mechanisms may be present in the two layers: one layer for sustained release for longer-lasting impact and one for instant release for quick therapeutic benefits. This structure aids in improving drug stability, lowering side effects, and decreasing the frequency of dosages. Bilayer tablet manufacturing calls for specific methods, including compression, to guarantee that the layers hold together and don't mix while being made or stored. Bilayer tablets can be used to treat illnesses that need more than one medication or where a sequential drug release is necessary. [2,3] Bilayer tablets, which are regarded as one of the alternatives to address the oral delivery issues of medications, such as those faced with traditional or matrix tablets, can offer unique product performance in terms of drug delivery and patient compliance. When rapid drug release is needed to alleviate disease symptoms, a bilayer tablet is required. [4]

1. Types of bilayer tablets:

Bilayer tablets consist of two distinct layers, which can be either the different (heterogeneous) or same (homogenous)

Homogenous type

Homogenous bilayer tablets are preferred when dual drug release profiles are required or when the release patterns of the active ingredients differ. This design enables controlled modification of dissolution rates and drug release characteristics. Typically, the first layer serves as an immediate release dose for rapid drug action, while the second layer deliver a delayed or extended release for sustained therapeutic effect.

Heterogenous type

Heterogeneous bilayer tablets are ideal for the sequential release of two different drugs or for separating incompatible substances within a single dosage form. This design ensures the stability and effectiveness of the combined formulation. [5]

2. Various approaches to bilayer tablets

a. Floating drug delivery system
b. Intra gastric bilayer floating tablets
c. Multiple unit types floating tablets
d. Polymeric bio-adhesive system
e. Swelling system

a. Floating drug delivery system:

These types of floating bilayer tablets are manufactured for having lower density so that allowing it to float on gastric fluid after administration. This system remains buoyant until the systems either break down or absorbs enough fluid to reduce its buoyancy, enough it to pass through the stomach via motility waves that facilitate gastric emptying. Bilayer tablets system which mainly consists of two layers: one layer provides an immediate drug release for rapid onset of action, while the other layer serves as the floating layer, ensuring the prolonged retention in the stomach.

There are mainly two approaches to developing floating dosage forms:

- Intra-gastric bilayer floating tablets
- Multiple-unit types floating pills

b. Intra gastric bilayer floating tablets

These tablets are mainly consists of two compresses layers. The one layer, known as the immediate release layer, is designed to deliver a rapid therapeutic effect. The second laye, referred to as the sustained release or extended- release

layer, which affect the target after the completion of first layer occure.

c. Multiple-unit types floating pills

These pills feature an extended or sustained-release as seeds encapsulated by double layers. The inner layer is chemically composed of effervescent agents, while the outer layer consisting of a swellable membrane. When such type of pills is exposed to a solution at normal body temperature, the pill initially sinks to the bottom before expanding like a balloon due to its low density, hence allowing it to float on the surface.

d. Polymeric bio-adhesive system

These formulations are designed in such a way that they absorb the fluid after they are administered. Then, causing the outer layer to become viscous and adhesive, allowing it to stick to the gastric mucosal layer. This adhesion will be helpful for prolong gastric retention until the bond weakens over time. These tablets consist of two layers: one layer for immediate release of the drug and the other layer with a bio-adhesive properties. However, this dosage form has only been administered into animals and is not used in humans due to the differences in physiology of the human and animal body, wherein the amount and consistency of mucous differ largely.

e. Swelling system

These formulations are designed to be considerably small on being administered for easing the dose administration. After administration, they disintegrate, swell, or rapidly unfold to a size that prevents passage through the pylorus, until the progression of the drug release to the desired level. The system remains in the stomach until it gradually erodes or breaks down into smaller bits. The simple bilayer tablet in this system mainly consists of one layer for the immediate release of the drug and the second layer for the extended or controlled release. [6]

Techniques for bilayer tablets:

a. OROS push pull technology
b. L-OROS tm technology
c. EN SO TROL technology
d. DUROS Technology
e. DUREDAS Technology

a. OROS push pull technology

This system primarily consists of two or three layers, in that one or more layers are essential of the drug and other layers are consists of push layer. The drug layer contains the active pharmaceutical ingredient along with two or more different agents. So, this drug layer comprises of drug which is in poorly soluble form. To enhance its performance an osmotic agent is also included. The tablet core is surrounded by a semi permeable membrane.

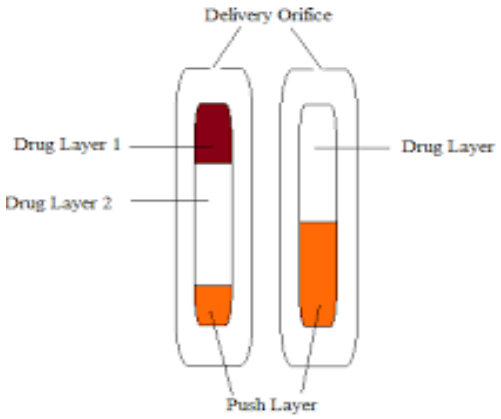

Fig 1. Bilayer and trilayer OROS push pull technology

b. L-OROS tm technology

This system is mainly used for the solubility issue Alza developed the L-OROS system. In this system a lipid soft gel containing the drug in a dissolved state is first manufactured and then coated with a barrier membrane, and then osmotic push layer and then a semi permeable, drilled with an orifice.

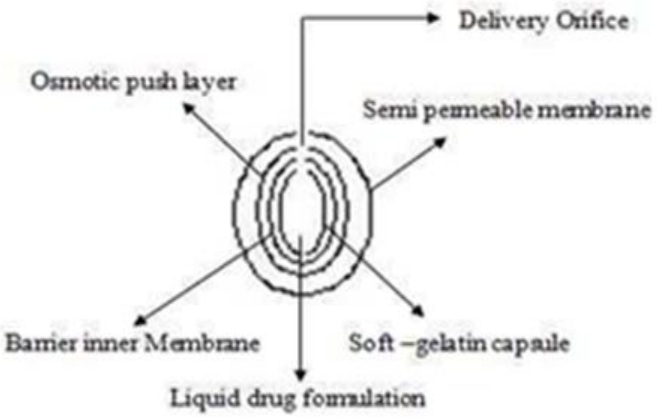

Fig 2. L-OROS tm technology

c. EN SO TROL Technology

Solubility enhancement of an order of magnitude or to develop an optimized dosage form, shire laboratories employ an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.

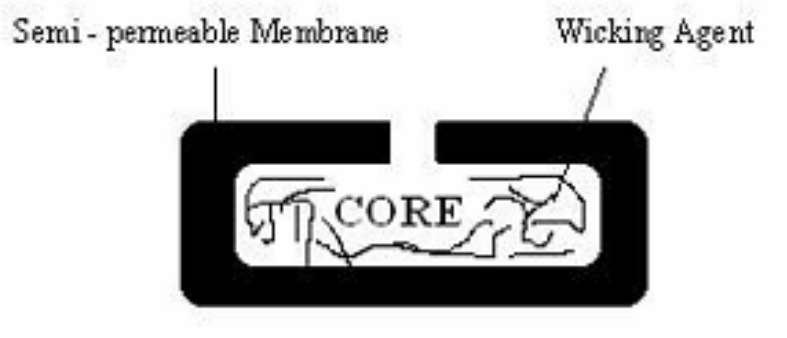

Fig 3. EN SO TROL Technology

d. Durose technology

The system consists an outer cylindrical titanium alloy reservoir. This reservoir offering high impact strength and protect the drug from enzymatic degradation. The DUROS technology functions as a miniature drug delivery system that opposes like a miniature syringe and release minute quantity of concentrated form in continuous and consistent from over months or year.

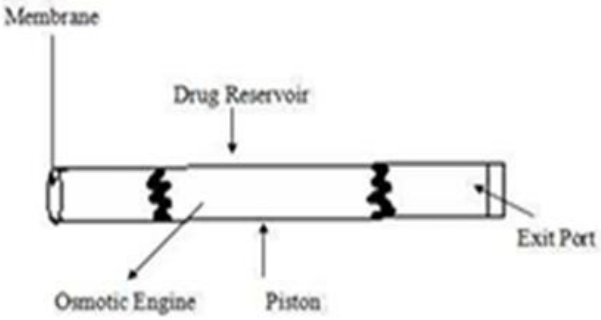

Fig 4. Durose Technology

e. Duredas Technology

DUREDAS Technology utilize bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. This tableting process can provide an immediate release granulate and a modified–release hydrophilic matrix complex as separate layers within the single tablet. The modified- release properties of the dosage form are achieved through a combination of hydrophilic polymer [7].

Preparation of bilayer tablet

Bilayer tablets are specially designed with two layers. The first layer typically contains the drug for immediate release, which providing an initial dose. The second layer is formulated to release the drug later, either as a second dose or in an extended-release form, thus it provides a sustained effect over time. This innovative design allows for controlled release of the medication, enhancing its therapeutic efficacy. The bilayer tablets containing two incompatible drugs can be prepared by compressing separate layers of each drug to minimize contact between the layers. Additionally, an intermediate layer of inert material may be included in order to separate the two drug layers and prevent interaction. This

approach ensures that each drug will retain its stability and efficacy within the tablet formulation.

Method of preparation

Bilayer tablets are prepared by wet granulation and direct compression techniques for both sustained release layer and immediate release layers. Method of preparation involves three major steps.

1. Formulation of immediate release layer

Active pharmaceutical ingredients (API), super disintigrants like sodium starch glycolate, croscarmellose and diluents like microcrystalline cellulose are screened using #25 mesh screen and mixed well. Then, glidants like talc and lubricant like magnesium stearate are sifted and mixed. The exact formulation and mixing parameters may vary depending on the desired characteristics of the tablet and the equipment used in manufacturing process.

2. Formulation of sustained release layer

The method involves mixing the drug along with polymers and diluents such as sodium CMC, Hydroxy propyl methyl cellulose, povidone K30 and Xhantan gum through #80 sieve, following uniform mixing. Granulation can be achieved by using the binder such as PVP K30 and solvent such as isopropyl alcohol to form a dough mass and which is then passed through a #10 sieve. The produced granules are dried at 50℃ and then sieved through #20 sieve. Finally, add and mix glidant such as Talc and lubricant such as magnesium stearate.

3. Compression of bilayer tablet

Accurately weigh the sustained release powder mixture and it is feed into the die cavity. And, this layer is compressed at mild compression force. After words accurately weigh immediate release power mixture and place it over sustained release layer and then compressed.

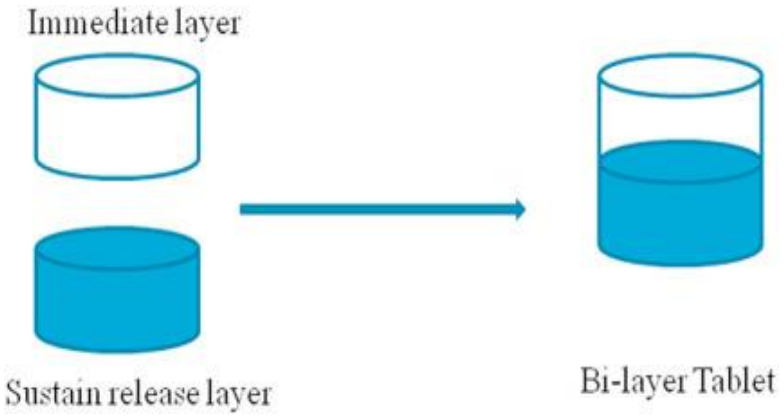

Fig 5: Bilayer Tablet

Steps involved in the bilayer tablet press

1. Filling of the first layer (sustained release layer) into the die cavity.

2. Mild compression of the first layer.

3. Filling of the second layer (immediate release layer) into the die cavity.

4. Compression of first layer.

5. Ejection of the bilayer tablet [8].

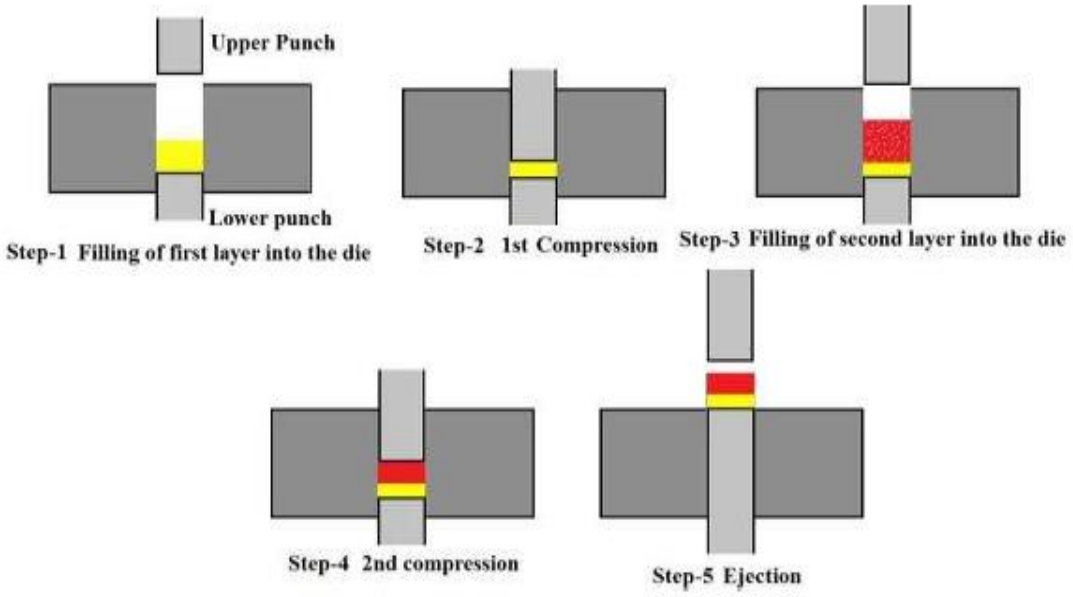

Fig 6. Steps involved in bilayer tablet formulation [9]

Types Of Bilayer Tablet Press

a. Single sided tablet press

b. Double sided tablet press

c. Bilayer tablet press with displacement monitoring

a. Single sided press

Over the year, various types of bilayer presses have been developed. The simplest design is the single sided press with two feeders, where each feeder is separated from each other. These feeders are either gravity fed or forced fed with different powders, thus producing the two individual layers of the tablet. As the die moves beneath the feeder, it is first loaded with the first-layer power, followed by the second layer powder. The entire tablet is then compressed in one or two steps that is pre compression and main compression. The two layers in the die get mix slightly at the interface, and in most of the cases bond sufficiently so that there is no layer-separation occurs when the tablet is produced. This method represents the simplest way of producing a bilayer tablet.

b. Double sided tablet press

Double-sided tablet presses are specifically designed and developed for the production of the quality bi-layer tablets and provide:

- Precise weight control through ‘displacement’ for accurate and independent weight control of each layer.
- low compression force is exerted on the first layer in order to prevent capping and layer separation.
- Extended dwell time at pre-compression of both first and second layers, to provide adequate hardness at maximum turret speed.
- Maximum cross contamination prevention between the two layers
- Clear visual separation between the two layers.
- Maximized production yield for improved efficiency.

c. Bilayer tablet press with displacement monitoring

The design of this press is mainly based on displacement monitoring and the principle on which it works is fundamentally different from the principle based on compression force. The press design is highly sensitive when measuring displacement and it depends on the applied pre-compressed force unless the tablet weight [10].

Characterization of bilayer tablets

General Appearance and Organoleptic Features: Bilayer tablets' overall look is crucial for guaranteeing patient adherence. To guarantee patient acceptability, important factors such tablet size, shape, color, odor, taste, and surface texture must be thoroughly assessed. The dimensions and form of the tablet should be precisely described.

Bi-layer tablet thickness: A micrometer device for ten tablets or a normal slide calliper are used to measure the tablet thickness. To guarantee the content homogeneity and consistency of applied compressional force for every unit of bilayer tablets, the thickness must be uniform within the statistical limit.[11]

Weight variation: Standard processes outlined in the official literature must be adhered to for the weight variation evaluation procedure. An approximate level of content consistency is ensured by the study's proper outcome. [12]

Friability: The ability of bilayer tablets to maintain their structural integrity or resistance to weight loss from shock and friction during handling and transit is known as friability. The usual approach outlined in official texts is utilized to determine the friability using the Roche friabilator. Weight loss of less than 1% of starting weight after taking 20 pills for four minutes is the acceptability threshold. [13]

Hardness: The tablet's ability to withstand capping, abrasion, and breakage during handling, transportation, and storage can be evaluated by conducting a hardness test. For this, hardness testers from Pfizer and Monsanto are utilized. This aids in figuring out how much compression force needs to be changed at various stages of the bilayer tablet production process. The pill shouldn't be very rigid since this could prevent it from dissolving and cause the immediate release layer's medication to release slowly. The Indian Pharmacopoeia states that a tablet's permissible hardness is 4 kg/cm2. [14]

Dissolution: According to the official monograph for that specific drug, dissolution is defined as the percentage of drug that dissolves per unit time in a given solvent system under specific conditions. One or more pharmacological substances may be present in the two layers of bilayer tablets. At least three duplicates of the study are conducted, and the standard deviation is used to express the results.[15]

Drug content: After dissolve is complete, a sample of the solvent used for the dissolution research can be taken to ascertain the drug content of the drug compounds present in various layers. During dissolution research, the right amount is calculated to make up for sampling loss. At least three duplicates of the study are conducted, and the standard deviation is used to express the results. [16]

Stability: The proper conditions for long-term stability testing of pharmaceutical goods are specified by ICH guidelines. The bilayer tablets are examined for physical characteristics, such as hardness, drug content, dissolution, and friability,

following a 15-day storage period in these settings. [17]

Sustained Release Drug Delivery System

The oral route of drug administration is the most commonly used route because of its convenient dosage form, design and patient care. Before formulating sustained release dosage form several parameters must be considered, such as variations in the gastro-intestainal p^H, motility, and enzyme system and its effects on the dosage form and drug. Most of the sustained release formulations follow the mechanisms such as diffusion, dissolution or combination of both, in order to ensure slow release of drug at predetermined rate. The plasma drug concentration time profiles differ between conventional tablets or capsules, zero order sustained release formulations and sustained release formulations.

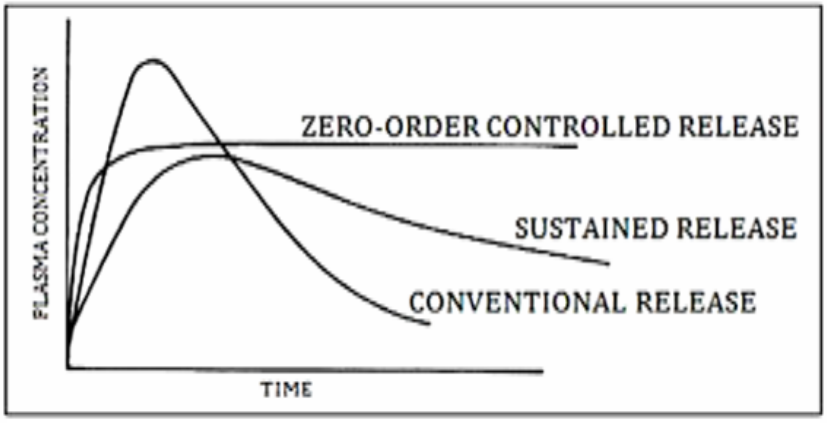

Fig 7. Plasma drug concentration profile for conventional release, sustained release and zero order controlled release formulations

Classification of SR DDR

A. Diffusion sustained system

a. Reservoir type

b. Matrix type

B. Dissolution sustained system

a. Reservoir type

b. Matrix type

C. Methods using ion-exchange

D. Methods using osmotic pressure

E. pH independent formulation

F. Altered density formulation

A. Diffusion sustained system

Diffusion systems are characterized by the release rate of a drug is being dependent on its diffusion through an innert membrane barrier. Basically, the diffusion process involve the moment of drug molecule from the region of higher concentration to one of the lower concentration. The drug flux J(in amount/area-time), across a membrane in the direction of decreasing concentration, is governed by Fick's law.

$$J \frac{-Ddc}{dx} =$$

Where, D = Diffusion coefficient in area/time

dc /dx= change of concentration "c" with distance"x"

There are two types of diffusional systems are recognized:

a. Reservoir type

In this system, water insoluble polymeric material encapsulate a drug core. The drug will partition into the membrane and then exchange with the fluid surrounding the particle or tablet. As more drug enters the polymer, diffuse to the periphery and subsequently release into the surrounding media.

Advantages

- Zero order delivery is possible.
- Release rate can be varied based on polymer type.

Disadvantages

- The system must be physically removed from the implants site.
- It is difficult to deliver high molecular weight compounds.
- Potential toxicity of the system gets failed.

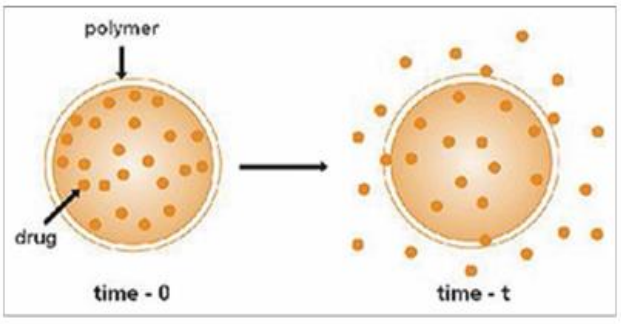

Fig 8. Representation of diffusion sustained drug release: Reservoir system

b. Matrix type

In a matrix system, the drug is dispersed as solid particles within a porous matrix made of a water insoluble polymer. Initially, the drug particles located at the surface of the release unit will get dissolved first and the drug get released rapidly. As the process continues, the drug particles located deeper within the matrix gradually dissolve and release by the diffusion in the pores to the exterior of the release unit. Thus, as the release process proceeds the diffusion distance of dissolved drug will increase.

Advantages

- It is easier to produce than the reservoir devices.
- It can deliver high molecular weight compounds.

Disadvantages

- Cannot obtain a zero-order drug release.
- Removal of remaining matrix is necessary for implanted system.

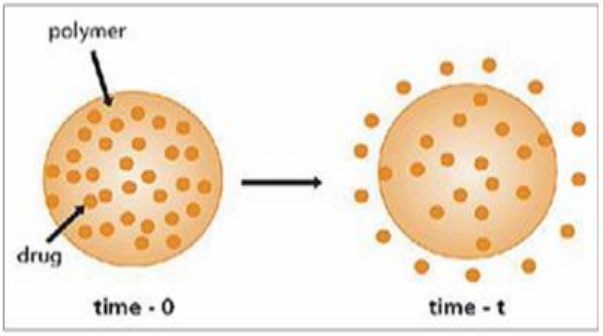

Fig 9. Representation of diffusion sustained drug release: Matrix type

B. Dissolution sustained system

A drug with a slow dissolution rate will demonstrate sustained release properties, since the release of the drug is controlled by the rate of dissolution. Sustained release(SR) formulations of the drugs can be developed by decreasing their rate of dissolution. This can be achieved through

several approaches, such as preparing suitable salts or derivatives, coating the drug with slowly dissolving materials or incorporating the drug in a tablet containing a slowly dissolving carrier. Dissolution sustained system can be made different techniques.

a. Reservoir type

The drug is coated with a given thickness coating, that dissolves slowly in GI tract. By altering layers of the drug with the rate controlling coatings, a pulsed delivery of the drug can be achieved. If the outer most layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be immidiately achieved with pulsed intervals.

b. Matrix type

The more common type of dissolution-sustained release dosage form involves either a drug impregnated sphere or tablet, which will be subjected to slow erosion.

C. Methods using ion exchange

Ion-exchange systems typically utilize resins composed of water-insouble cross-linked polymers. These polymers features salt forming functional groups in repeating sites on the polymer chain. The drug is attached to the resin and is released by exchanging with the appropriatrly charged ions that interact with the ion-exhange groups.

D. Methods using osmotic pressure

$$Resin^{+} - Drug^{-} + X^{-} \longrightarrow Resin^{+} - X^{-} + Drug^{-}$$

$$Resin^{-} - Drug^{+} + Y^{+} \longrightarrow Resin^{-} - Y^{+} + Drug^{+}$$

In this system, the flow of liquid into the release unit is mainly facilitated by the difference in the osmotic pressure between the inside and outside of the release unit is used as the release controlling process. In the osmotic sustained release system the following sequences of events are involved in the release of the drug.

- The liquid enters the release unit via the osmotic transport.
- The drug dissolution takes place inside the release unit.
- Convection transport of a saturated drug solution takes place by pumping of the solution through a single orifice or by pores in the semi-permeable membrane.

E. pH independent formulation

Most of the drugs are either weak acids or weak bases, the release of the drug from sustained release formulations is pH dependent. So that, the buffer such as salts of citric acid, amino acid, phthalic acid, phosphoric acid or tartaric acid can be added to the formulations to maintain a consistent internal pH resulting in the pH independent drug release. A buffered sustained release formulation is prepared by mixing a basic or acidic drug with one or more buffering agents, granulating the mixture with suitable pharmaceutical excipients, and coating it with a polymer film that is permeable to the GI fluid. When the GI fluid penetrates through the membrane, the buffering agents regulates the internal p^{H} to a stable level, enabling a controlled rate of drug release.

F. Altered density formulation

It is essential for a drug delivery system to remain near the absorption site untill the majority, if not all, of the drug is released in order to ensure its effectiveness. To this end, several approaches have been developed to extend the residence time of DDS in the gastrointestinal tract.

- High density approach
- low density approach

Merits

a) It provides better control over drug therapy.

b) It allows the modification of the rate and extension of drug absorption.

c) The frequency of drug administration is reduced.

d) Improved patient compliance.

e) Improve convenience in drug administration.

f) Maximizing the availability of drug with minimum dose.

g) It increases the safety margin for high potency drug.

Demerits

a) It does not permit immediate termination of therapy.

b) It limits flexibility in dose adjustment.

c) These dosage forms mainly designed on the basis of average biological half-life.

d) As compared to conventional dosage forms, they are more expensive.

Immediate Release Drug Delivery Systems

An immediate release (IR) dosage forms allows manufacturer to extend market exclusively, while providing patients with a convenient dosage form or regimen. Immediate release tablets are those tablets which are designed in order to disintegrate and release their medicament without any special rate controlling features, such as special coatings and other techniques. Recently, immediate-release tablets have started gaining popularity and acceptance as a drug delivery system, due to their ease of administration, rapid onset of action, and improved patient compliance. There are mainly three major factors that govern the rate and extent of drug absorption of immediate release (IR) solid oral dosage forms. They are,

a. Dissolution rate
b. Solubility
c. Intestinal permeability [18-22]

GMP Requirements for Bilayer Tablets

In order to produce a quality bilayer tablet, in a validated and GMP-way, it is essential to carefully select an appropriate bilayer tablet press. These requirements seem obvious but are not so easily accomplish. The selected press must be capable of:

1. Preventing capping and separation of the two distinct layers that constitute the bilayer tablet.

2. Avoiding the cross-contamination between the layers.

3. Ensuring adequate tablet hardness.

4. Maintaining accurate and individual weight control of the two layers.

5. Producing the clear visual separation between the layers.

6. Achieving the consistently high production yield [23]

Applications Of Bilayer Tablets

a. It helps to separate two incompatible substances.

b. Bilayer tablets are suitable for the sequential release of two drugs in combination.

c. Improve patient convenience and compliances.

d. Bilayer tablet in which one of the layers is immediate release as an initial dose and second layer as a maintenance dose.

e. Bilayer tablet is improved beneficial technology in order to overcome the shortcomings of the single layered tablets.

f. Bilayer tablets are designed to deliver the loading dose and sustained dose of the same or different drugs.

g. Bilayer tablets are also used for bilayer floating tablets in which one layer is floating layer and another layer is immediate release layer of drug.

h. Bilayer tablets are designed to deliver the two different drugs having different release profile. [24]

Advantages of Bilayer Tablets

a) **Dual drug delivery:** Allows for the mixing of two APIs with distinct therapeutic outcomes.

b) **With modified release profiles:** a tablet can have both sustained release (SR) and immediate release (IR) layers.

c) **Decreased Pill Weight**: blends several therapies into one unit, improving adherence.

d) **Reduced Drug Interactions:** Divides incompatible medications into distinct layers.

e) **Economical Efficiency:** Decreases manufacturing expenses in contrast to creating distinct dosage forms. [25]

Disadvantages Of Bilayer Tablets

a. Complex manufacturing process increases production costs and risk of layer layer separation or delamination during production or storage.

b. Bilayer tablets may not be suitable for certain medications due to difficulties in achieving desired release profiles.

c. There is a higher risk of dose dumping if one-layer dissolves too quickly.

d. Regulatory challenges may arise in demonstrating the compatibility, stability, and uniformity between layers.

e. Challenges in achieving uniform distribution and consistency of drug content between layers, leading to variation in therapeutic effects across batches.[26]

Difficulties In Bilayer Tablets Manufacturing

Bilayer tablets can be conceptualized as two. Tablets with a single layer squeezed into one. In Actuality, there are several difficulties in manufacturing.

Delamination:

The tablet breaks when the two halves don't stick together completely. The two granulations should adhere to one another when crushed

Cross-contamination:

When the granulation of the first layer combines with that of the second layer, or vice versa, this is known as cross-contamination. It might even negate the intended purpose of the dual-layer tablet. Appropriate dust collection is one of the best strategies to prevent cross-contamination.

Production Yields:

To avoid cross-contamination, which causes losses, dust collection is required. As a result, bilayer tablets produce less than single-layer tablets.

Cost:

Bilayer tableting is more costly than single layer tableting for several reasons. The tablet press is more costly, to start. Second, the press frequently runs slower when in bilayer mode. Third, in order to produce two formulations that are compatible, more effort needs to be devoted to formulation creation, analysis, and validation. If these factors are not adequately controlled or modified, they will have an impact on the bilayer compression process itself as well as the quality attributes of the bilayer tablets (enough mechanical strength to maintain its integrity and individual layer weight management). Therefore, understanding the fundamental causes is essential to enabling the development of a robust product and process. [27]

CONCLUSION:

By combining two different drug release profiles—immediate and sustained—into a single dose form, bilayer tablet technology marks a substantial leap in oral drug delivery systems. The separation of incompatible medications is made possible by this system, which also increases patient compliance and therapeutic efficacy. It is very helpful for illnesses that need to act for a long time and with a quick beginning. Methods like OROS, DUROS, and DUREDAS increase the adaptability and performance of bilayer systems even more. Layer separation, cross-contamination, and complicated production are still major obstacles in spite of the benefits. To overcome these challenges, advancements in tablet press technology and formulation science are essential. For fixed-dose combinations, bilayer tablets provide a calculated solution that minimizes dosing frequency and maximizes pharmacokinetics. Their expanding use in several therapeutic fields indicates their potential for use in tailored and focused treatments in the future. Bilayer tablets have the potential to become widely used in enhanced medication delivery once production and regulatory barriers are resolved.

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