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A Review of Bilayer tablets

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ABSTRACT
Bilayer tablet is a new era for the successful development of controlled release formulation along with various features to provide a way of the successful drug delivery system. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles like the immediate release with extended release. Bilayer tablet is a very different aspect of anti-inflammatory and analgesic. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet is improved beneficial technology to overcome the short coming of the single layered tablet. There are various applications of the player tablet, it consists of monolithic partially coated or multilayered matrices.

Keywords: Bilayer tablets, Preparation, Characterization, Various presses.

I. INTRODUCTION

Solid oral dosage forms are mostly preferred over other routes for many drugs and are still the most widely used formulations. The controlled-drug delivery systems typically require more demanding mechanical testing, characterization, and monitoring techniques with faster response times than those possible with traditional measurement approaches.(1)Over 90% of the formulations manufactured today are ingested orally. It shows that this class of the formulation is the most popular worldwide and the major attention of the researcher is towards this direction. The major aim of controlled drug delivery is to reduce the frequency of dosing (2). The objective of sustained release is to ensure safety and also to improve efficacy of drugs and patient compliance. Bilayer tablet is a fixed dose combination (FDC) intended for oral application. It consists of two layers first layer have immediate release part of single; next layer is controlled release part of single or multiple actives. They are called as “Bilayer tablets”.

For the identification of two drugs various colors were used. Bilayer tablet is a very improved technique to overcome the single layered tablet. Bilayer tablets contain immediate, sustained release layers, and the immediate release layer delivers the initial dose. It includes super disintegrates, that increases the release rate of the drug and also attains the onset of action quickly. Whereas sustained release (maintenance dose) layer releases the drug in a sustained manner for a prolonged period of time by using various polymers as release in retardants. Diabetes, antihypertensive, antihistamines, analgesics, antipyretics and antiallergenic agents are mainly suitable for this type of drug delivery (3).Bilayer tablets have advantage as compared to conventional monolayer tablets. These tablets are commonly used so as there is less use of chemical incompatibilities of formulation components by physical separation. Moreover, bilayer tablets have also enabled the development of controlled delivery of an API by combining slow-release with immediate-release layers

However, such drug delivery devices are complicated mechanically to manufacture and also difficult to judge their long term properties as they have poor mechanical and compression of the materials in the adjacent layers which is compacted, insufficient hardness, inaccurate individual mass control, reduced yield, cross contamination between the layers and their potency to delaminate at the interface while on various stages of compaction process. The major problem, that has to be overcome, is to find out in detail the sources of these problems at lower scales and to find out remedies to solve them.A major challenge is lack of appropriate bonding at the interface between the adjacent compacted layers. When the compacted layers are beyond a certain limit soft or hard, they might not bond appropriately with each other and that can lead to compromised mechanical integrity. Challenges during development also includes layer weight ratio, establishing the order of layer sequence, first layer tamping force, elastic mismatch of the adjacent layers and cross contamination between layers(4,5)

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NEED OF BILAYER TABLETS [6-8]

- For the administration of fixed dose combinations of different APIs, prolong the drug product life cycle, buccal/mucoadhesive
- delivery systems; fabricate novel drug deliver systems such as chewing device and floating tablets for gastro-retentive drug delivery.
- Controlling the delivery rate of either single or two different active pharmaceutical ingredients
- To modify the total surface area available for API layer either by sandwiching with one or two in active layers in order to achieve swellable/erodible barriers for modified release.
- To separate incompatible Active pharmaceutical ingredient (APIs) from each other, to control the release of API from onelayer by utilizing the functional property of the other layer (such as, osmotic property

General Properties of Bi-Layer Tablet Dosage Forms

- A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
- Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
- Should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.
- Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

ADVANTAGES(9)

1. Release of both drugs starts immediately.
2. Combination of incompatible drugs.
3. Combination of different release profiles.
4. Reduce the side effects by using a combination of one drug for this patient.
5. Treat different ailments in the same patient, at the same time and with one pill.
6. Increased patient compliance.
7. Self-administration is possible.
8. Easy to transport from one place to another place.
9. Good physical and chemical stability compared to liquids

Disadvantages [10)

1. Adds complexity and bilayer rotary presses are expensive.
2. Insufficient hardness, layer separation, reduced yield.
3. Inaccurate individual layer weight control. Cross contamination between QA
4. Bitter tasting drugs, drugs with an objectionable
5. odor or drugs that are sensitive to oxygen may require encapsulation or coating.
6. Difficult to swallow in case of children and unconscious patients.

TYPES OF BILAYER TABLET PRESS [11-12)

A. Single sided tablet press.
B. Double sided tablet press.
C. Bilayer tablet press with displacement monitoring.

I. Single sides press the simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or forced fed with different powers, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is at first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps

II. Double sided tablet press Most double-sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at the main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablets and correct the die fill depth when required.

III. Bilayer tablet press with displacement the displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre-compression force

Preparation of bilayer tablets (22,23,24)

Quality and Good manufacturing practice (GMP) requirements of bi-layer tablets12:

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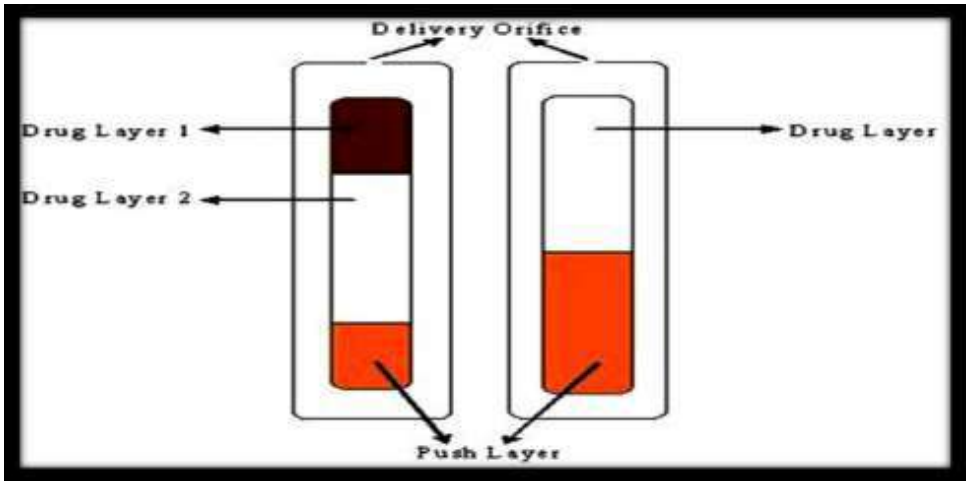
1. To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:
2. Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.
3. Providing sufficient tablet hardness.
4. Preventing cross-contamination between the two layers.
5. Producing a clear visual separation between the two layers.
6. High yield.
7. Accurate and individual weight control of the two layers

TECHNIQUES OF BILAYER TABLETS (13,14)

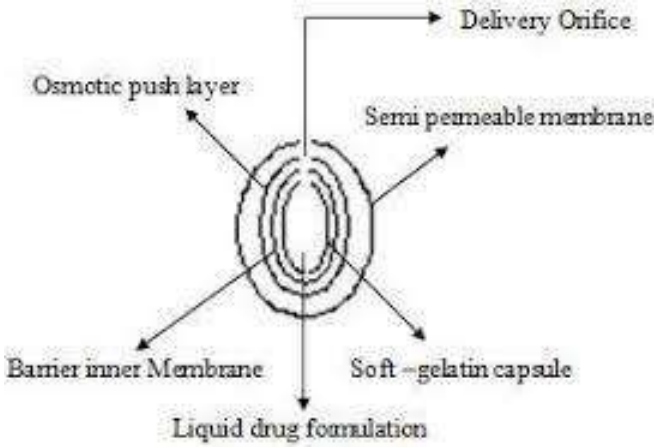
1. O R O S®push p u l l technology -

It includes two or three layers amongst which the one-layer inessential of the drug and other layer is push layer. The drug layer consists of drug along with two or more various agents. So, this drug layer comprises of drug which is in poorly soluble form. Suspending agent and osmotic agents can also be added. A semi permeable membrane surrounds the tablet core



2. L-ORO time technology

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



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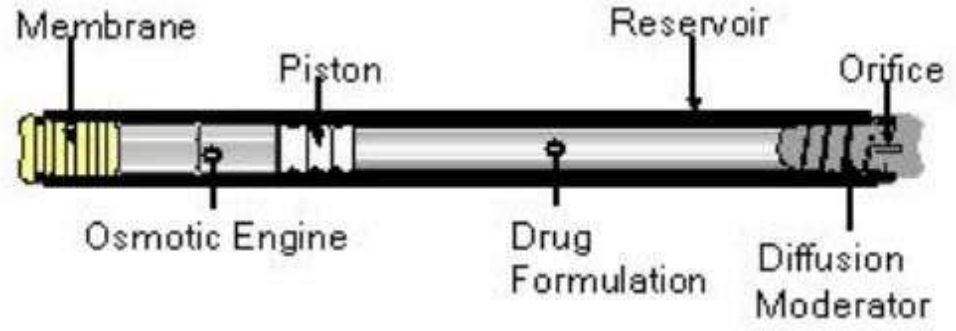
3. ENSOTROL technology

Solubility enhancement of an order of magnitude or creates optimized dosage forms hire laboratory use an integrated approach to drug delivery, focusing on identification and incorporation of the identified enhancer into controlled release technologies

4. DUROS Technology

The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and regions minute quantity of concentrated form in continuing and consistent from over months or years.



5DUREDAS™ Technology

Dual Release Drug Delivery System DUREDAS™ Technology is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tableting process can provide an immediate release granulate and a modified release hydrophilic matrix, complex as separate layers with in the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers.

Challenges in bilayer manufacturing (15,16) :

Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In Practice, there are some manufacturing challenges.

Delamination

Tablet falls apart when the two halves of the tablet do not bond completely. **Cross-contamination**

When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, crosscontamination occurs. Proper dust collection can prevent crosscontamination.

Production yields

In order to prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single-layer tablets.

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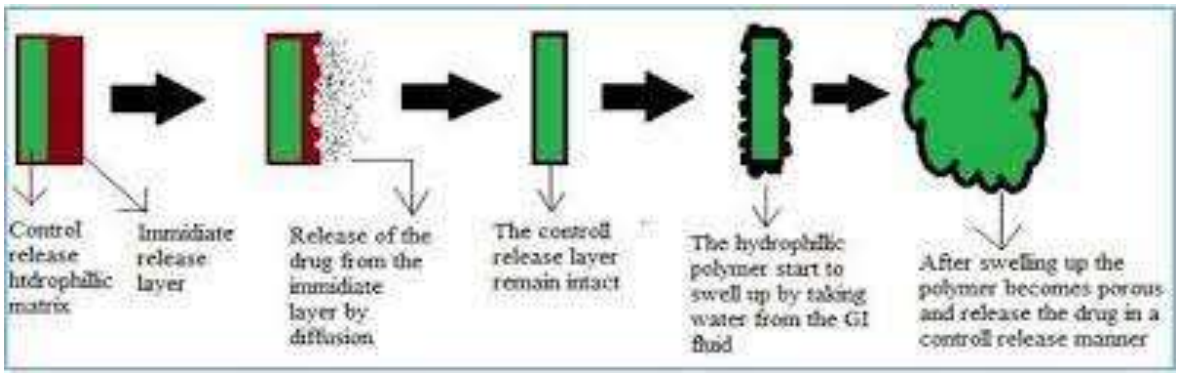
Cost

Bilayer tableting is expensive than single layer tableting for several reasons. The tablet press costs more.The press generally runs slowly in bilayer mode. Third, development of two compatible granulations is mandatory, which means more time spent on formulation development, analysis and validation.



Various approaches used in bi layer tablet preparation(17)

1. Floating drug delivery
2. Bio adhesive systems
3. Swelling systems

- In floating drug delivery system, polymers having low density that's why it was floated in gastro intestinal fluid.
- Bio adhesive systems having viscous material which is having tacky property that's why these systems attached to mucous layer and releases the drug.
- Swelling systems having swellable polymers, by using diffusion procedure these systems release the drug for long time.

Evaluation of Bilayer Tablets:

1. General Appearance(18): It includes its visual identity; "elegance" is required for consumer acceptance. Other parameters are tablet's size, colour, shape, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.
2. Size and Shape: The size and shape of the tablet can be dimensionally described, monitored and controlled.
3. Tablet thickness: Tablet thickness is an important characteristic when it comes to reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism.
4. Weight variation (19) : Standard procedures are followed as described in the official books.
5. Friability (19) : The friability test relates to hardness of tablet and is planned to test the ability of the tablet to withstand abrasion in all the processes like packaging. It is measured by the Roche friabilator. Tablets are placed in the apparatus after they are weighed where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. It continues for after four minutes or 100 revolutions. The loss occurring due to abrasion is measured by tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap whereas thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress the loss in the weight of tablet is the measure of friability and is expressed in percentage as:% Friability = 1- (loss in weight / Initial weight) X 100
6. Hardness (Crushing strength) (20): The hardness of the tablet will be carved out using Monsanto type hardness tester. The hardness of the tablet is measured in Kg/Cm2 . The hardness is considered as an important parameter which helps to overcome resist the tablets to shipping or breakage under conditions of storage.
7. Stability Study (Temperature dependent): The bilayer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

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APPLICATION (21)

1. Bi-layer tablet is suitable for sequential release of two drugs in combination.
2. Separate Two Incompatible Substances.
3. Sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose.
4. Promoting Patient Convenience and Compliance.
5. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet
6. Bilayer tablets are used to deliver the loading dose and sustained dose of the same or different drugs.
7. Bilayer tablets are used for bilayer floating tablets in which one layer is floating layer another one is immediate release layer of the drug.
8. Bilayer tablets are used to deliver the two different drugs having different release profiles

Drugs	Dosage form	rationale
Atorvastatin, Atenolol(25)	Bilayer Gastroretentive Matrix Tablet	Treatment of hypertension and hypercholesterolemia
Nifedipine(26)	Gastro-Retentive Floating Bilayer Tablets	Treatment of hypertension and angina pectoris
Aspirin, Isosorbide 5-Mono-nitrate(27)	Sustained Bilayer tablets	Treatment of pain, fever and other inflammatory conditions
Pioglitazone HCl, Gliclazide(28)	Bilayer Tablets	Treatment of Type II Diabetes
Losartan potassium(29)	Bilayer tablet	Treatment of Type II Diabetes
TrimetazidineHCl, clopidogrel bisulphate(30)	Bilayer tablets	Cytoproctive anti ischemic, platelet inhibitor in acute coronary syndromes
Diclofenac, Cyclobenza-prine(31)	Bilayer tablets	Synergistic effect in pain
GranisetronHCl **(32)**	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects
Metformin HCl, Glimipiride (33)	, Bilayer tablets	Synergistic effect in diabetes,
Indomethacin(34)	Bilayer floating tablets	Biphasic drug release
Metformin HC1, Atorvastatin Calcium(35)	Bilayer tablets	To develop polytherapy for the treatment of NIDDS & hyperlipidemia
CefiximeTrihydrate, Dicloxacilline Sodium (36)	Bilayer tablets	Synergistic effect in bacterial infections

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Metformin HCl, Pioglitazone(37)	Bilayer tablet	Synergistic effect in diabetes mellitus
Atenolol (38)	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration
Cefuroxime Axetil Potassium Clavulanate(39)	Bilayer tablets	Synergistic effect against microbial infections and to minimize dose dependent side effects
Amlodipine Besilate Metoprolol Succinate(40,41)	Bilayer tablets	Synergistic effect in hypertension
Diclofenac Sodium, Paracetamol (42)	Bilayer tablets	Synergistic effect in pain
Ibuprofen, Methocarba-mol(43)	Bilayer tablets	Synergistic effect of drugs in back pain
Atorvastatin Calcium (44)	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration
Paracetamol Diclofenac (45)	Bilayer tablets	Synergistic effect of drugs in pain
Losartan (46)	Bilayer tablets	Biphasic release profile
Metformin HCl, Pioglitazone (47)	Bilayer tablet	Synergistic effect in diabetes mellitus
Guaifenesin (48)	Bilayer tablets	Biphasic release profile
Tramadol, Acetaminophen (49)	Bilayer tablets	Synergistic effect of drugs in pain
Atenolol, Lovastatin (50)	Bilayer floating tablets	Synergistic effect in hypertension and biphasic release profile
Montelukast, Levocetrizine (51)	Bilayer tablets	To improve the stability of drugs in combination
Salbutamol, Theophylline (52)	Bilayer tablets	Synergistic effect of drugs in asthma
Glipizide, Metformin HCl (53)	Bilayer tablets	To avoid interaction b/w incompatible drugs
Telmisartan Hydrochlor-thiazide (54)	Bilayer tablets	To minimize contact b/w hydrochlorothiazide & basic component of telmisartan

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Amlodipine, Atenolol (55)	Bilayer tablets	To improve the stability of drugs in combination
Misorostol, Diclofenac (56)	Bilayer tablets	To minimize contact b/w drugs

II. CONCLUSION

Bi-layer tablet is selected for sequential release of two drugs in combination or separate two substances which are incompatible, for sustained release tablet where one layer is immediate release and second layer is maintenance dose. Bi-layer tablets give an opportunity for producers to improve their products' efficacy, and protect against impersonator products. Bi-layer tablet GMP requirements can differ widely. When a bi-layer tablet requires to be developed along with accurate weight control of the two layers, compression force-controlled presses are limited as their insufficient sensitivity and thus lack of accuracy at low compression forces required to secure interlayer bonding. Accurate individual layer weight monitoring/control at high speed and in combination with reduced layer separation risk can be achieved with the displacement weight control system based presses. Bilayer tablet has been done with various or various combination, which is useful for various ailments. Thus bilayer formulation is convenience dosage form, safe and possesgreater advantages to both patient and clinician that it may be administered as a single tablet in once a day. Bilayer tablet is quality and GMP requirements can vary widely

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