IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

RECENT ADVANCES AND INSIGHTS INTO BILAYER TABLETS FORMULATIONS: STATE OF THE ART FOR DEVELOPMENT

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ABSTRACT

The bi-layer tablet represents a new era in the development of controlled release formulations with a variety of characteristics to ensure effective medication delivery. Bilayer layer tablets feature two layers: a gradual release layer and an instant release layer. In addition, enhanced useful technology has been developed to solve the shortcomings of single layer tablets. Due to different incompatible active pharmaceutical ingredients (APIs) for each other, bilayer tablet formulations were required. The compressibility and consolidation of bilayer tablet materials are both important. OROS® push pulls Technology, EN SO TROL Technology, L-OROSTM Technology, DUROS Technology, and DUREDASTM Technology are some of the processes used to make bilayer tablets. The numerous kinds of bilayer tablet presses now on the market, the various methodologies utilised in bilayer tablet systems, and the characterization and assessment of the bilayer tablet system are all discussed. Pioglitazone, Atenolol, Aspirin, Isosorbide 5-mono-nitrate, Nifedipine, Clopidogrel, Losartan, Atorvastatin, Trimetazidine, Gliclazide, and other bilayer tablets are now available.

Keywords: Bilayer, Tablets, Sustained release, Technology, Preparation, Challenges

INTRODUCTION

Based on these concerns, we have presented a bilayer tablet in which one layer is prepared to provide quick drug release with the goal of achieving a high serum concentration in a short period of time. The second layer is a hydrophilic controlled-release matrix that is meant to maintain an effective plasma level for a long time. The pharmacokinetic advantage is based on the fact that drug release from the rapid releasing layer causes a dramatic increase in blood concentration. However, once the medication is removed from the sustaining layer, the blood level remains constant. Multi-layer tablet dosage forms were created for a variety of reasons, including controlling the delivery rate of either one or two different active pharmaceutical ingredients (API),

separating incompatible APIs from one another, controlling the release of API from one layer by utilising the functional property of the other layer (such as osmotic property), and modifying the total surface area available for API layer either by sandwiching with one or two inactive layers in order to increase the total surface area available for API layer. When compared to monolayer tablets, bilayer tablets offer a few important benefits. Such tablets, for example, are often employed to eliminate chemical incompatibilities of formulation components by physical separation. Furthermore, by mixing layers with different release patterns or combining slow-release and immediate-release layers, bilayer tablets have permitted the creation of controlled distribution of active medicinal components with specified release profiles. However, due to the poor mechanical and compression characteristics of the constituent materials in the compacted adjacent layers, elastic mismatch of the layers, insufficient hardness, inaccurate individual mass control, cross contamination between the layers, reduced yield, and their tendency to delaminate at the interface between the layers, these drug delivery devices are mechanically complicated to design/manufacture and harder to predict their long-term mechanical properties. As a result, the primary challenge to be addressed is to fully comprehend the origins of these issues at micro and macroscales, as well as to create remedies to address them throughout solid dose administration design.

Applications

1. A bi-layer tablet is ideal for the simultaneous release of two medicines.
2. Separate two substances that are incompatible.
3. Sustained release tablet has an instant release initial dosage and a maintenance dose on the second layer.
4. Encouraging Patient Compliance and Convenience.
5. A bilayer tablet is an enhanced technology that addresses the shortcomings of a single-layered tablet.
6. Bilayer tablets give both the loading and sustained doses of the same or distinct medicines.
7. Bilayer floating tablets are made up of two layers, one of which is the floating layer and the other is the drug's instant release layer.
8. Two distinct medicines with varying release patterns are delivered using bilayer tablets.

Advantages

1. They are employed as an add-on to existing technologies.
2. Single-entity feed granules might be used.
3. Separation of components that is incompatible.
4. Patient compliance improves, resulting in better treatment regimen effectiveness.
5. In comparison to conventional delivery systems, patient comfort is increased since fewer daily doses are needed.
6. Keep physical and chemical stability under check.
7. Maintain potency and dosing precision.

Disadvantages

1. It adds complexity to the process, and dual rotary presses are costly.
2. Inadequate hardness, layer separation, and decreased yield.
3. Inaccurate weight management of separate layers.
4. There is a risk of cross-contamination between the layers.

NEED OF BILAYER TABLETS

1. To administer fixed dosage combinations of multiple APIs, lengthen the drug product life cycle, buccal/mucoadhesive delivery systems; manufacture innovative drug delivery systems, such as chewing devices and floating tablets for gastro-retentive drug delivery
2. Managing the rate of administration of a single active pharmaceutical ingredient or two separate active pharmacological components
3. To produce swellable/erodible barriers for modified release, adjust the overall surface area accessible for API layer by sandwiching with one or two active layers.
4. To segregate incompatible active pharmaceutical ingredients (APIs) and to regulate API release from one layer using the functional attribute of the other layer.

CHALLENGES IN BILAYER MANUFACTURING

Bilayer tablets may be thought of as two single-layer tablets rolled into one. There are certain manufacturing obstacles in practise.

Delamination

When the two parts of a tablet do not entirely bind, the tablet will come apart. When crushed, the two granulations should stick together.

Cross-contamination

Cross-contamination happens when the granulation of the first layer mixes with the granulation of the second layer, or vice versa. It has the potential to defeat the bilayer tablet's entire goal. Cross contamination may be greatly reduced with proper dust collection.

Production yields

Dust collection is necessary to avoid cross contamination, which results in losses. As a result, bilayer tablets produce less than single-layer tablets.

Cost

For numerous reasons, bilayer tableting is more costly than single layer tableting. To begin with, the tablet press is more expensive. Second, in bilayer mode, the press normally runs slower. Third, two compatible granulations must be developed, which requires extra time for formulation creation, analysis, and validation. These elements, if not effectively controlled/optimized, will have an influence on bilayer compression in general and the quality features of bilayer tablets in some manner (sufficient mechanical strength to maintain its integrity and individual layer weight control). As a result, gaining insight into the fundamental reasons is vital in order to build a solid product and process.

TYPES OF BILAYER TABLET PRESS

Single sided press

A single-sided press with both chambers of the doublet feeder separated is the simplest design (**Figure 1**). The two distinct layers of the tablets are produced by gravity or forced feeding each chamber with various powers. The first layer powder is put into the die as it travels through the feeder, followed by the second layer powder. The tablet is then compacted in one or two stages.

Figure 1. Single sided tablet press.

Limitations of single sided press

1. Individual layer weight monitoring and control is not possible.
2. There is no apparent distinction between the two levels.
3. Due to the tiny compression roller, the first layer dwell time is very short, potentially resulting in poor de-aeration, capping, and hardness issues.

Dwell time

Dwell time is defined as the amount of time while the compression force is greater than 90% of its highest value. Longer dwell durations are crucial in making a high-quality tablet, particularly when compressing a complex recipe.

Compression force

To maintain the capacity to connect with the second layer, many bilayer formulations need a first layer compression force of less than 100 daN. This capacity may be lost over 100daN, and bonding between the two layers may be insufficient, resulting in poor bilayer tablet hardness and separation of the two layers.

Double sided tablet press

Compression force is used to monitor and manage tablet weight in most double-sided tablet presses with automated production control (**Figure 2**). The control system measures the effective peak compression force applied on each individual tablet or layer at the layer's major compression. The control system uses this measured peak compression force to reject out-of-tolerance tablets and modify the die fill depth as necessary.

Figure 2. Double sided tablet press.

Bilayer tablet press with displacement

The concept of displacement tablet weight management is significantly different from the compression force method. The sensitivity of the control system for monitoring displacement is determined by the applied pre-compression force rather than the tablet weight (**Figure 3**).

Figure 3. Bilayer tablet press.

PREPARATION OF BILAYER TABLETS

The first layer of a bilayer tablet is meant to release the medicine immediately, while the second layer is designed to release the drug subsequently, either as a second dosage or in an extended release form. Separate layers of each medicine may also be compressed to decrease the area of contact between two layers, resulting in bilayer tablets containing two incompatible pharmaceuticals. An extra layer of inert material may be used as an intermediary layer. Certain conditions, such as appropriate mechanical strength and the proper drug release profile, must be satisfied in order to develop an acceptable tablet formulation. Because of poor flow and compatibility characteristics of the medication, which will result in capping and/or lamination, it may be difficult for the formulator to attain these parameters, particularly in bilayer tablet formulation when double compression method is used. The compressibility and consolidation of a material are both factors in compaction.

Compression

It is described as a method of reducing bulk volume by removing voids and bringing particles closer together (**Figure 4**).

Consolidation

It is the property of a material in which mechanical strength is improved as a result of interparticulate contact (bonding). The compressive stress on layer 1 was discovered to be a significant influence in tablet delamination.

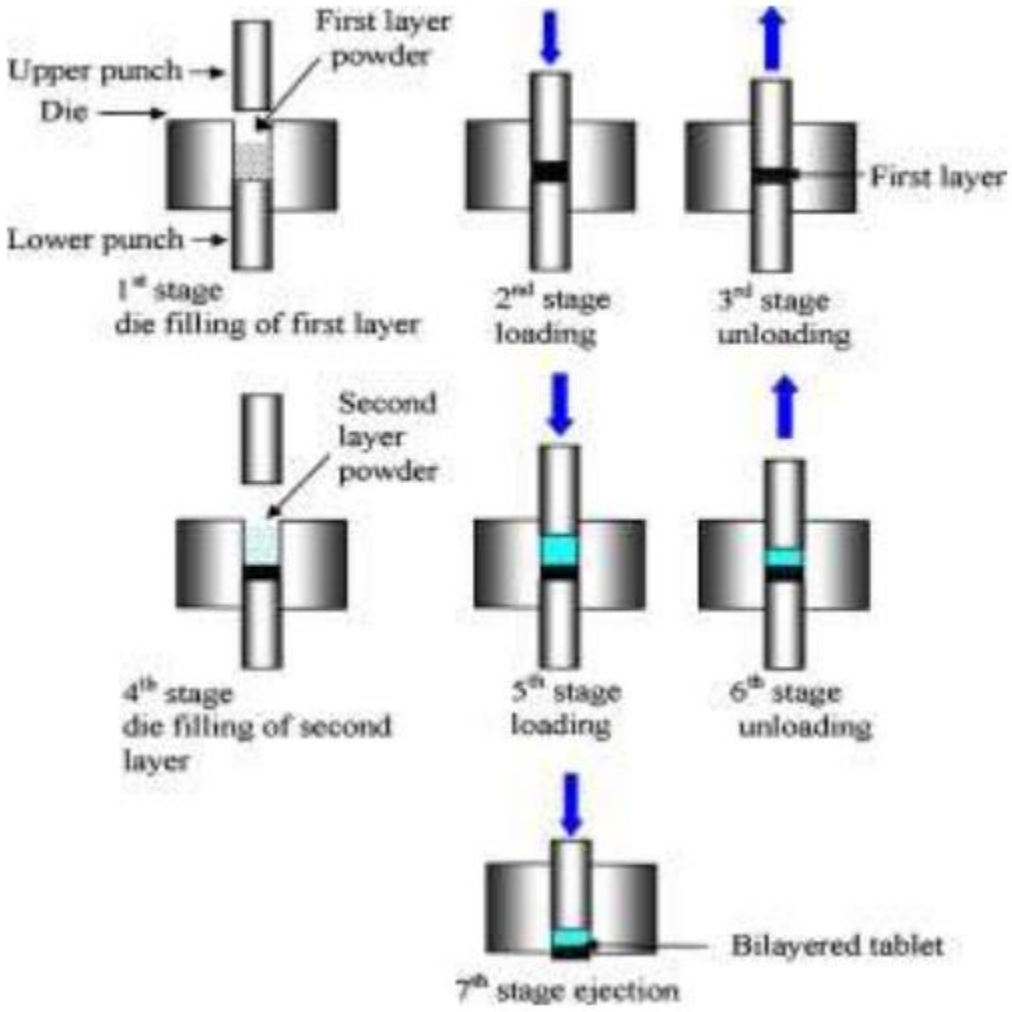

Figure 4. Bilayer tablet compaction.

General properties of Bi-Layer Tablet Dosage Forms

1. A bi-layer tablet should have a sophisticated product identity that is devoid of flaws such as chips, fractures, discoloration, and contamination.
2. Must be strong enough to endure mechanical stress during manufacturing, packing, shipping, and dispensing.
3. It must be chemically and physically stable in order to keep its physical properties throughout time. The therapeutic chemicals must be released in a predictable and repeatable way by the bi-layer tablet.
4. Must have a chemical stability shelf-life so that the therapeutic agents do not change.

VARIOUS TECHNIQUES FOR BILAYER TABLET

OROS® push pulls Technology

This system is made up of two or three layers, with one or more layers being necessary to the medicine and the other layer being a push layer (**Figure 5**). The drug layer contains mostly of the drug, as well as two or more distinct agents. As a result, this drug layer contains a medication that is poorly soluble. A suspending agent and an osmotic agent are also included. The tablet core is surrounded by a semi-permeable membrane.

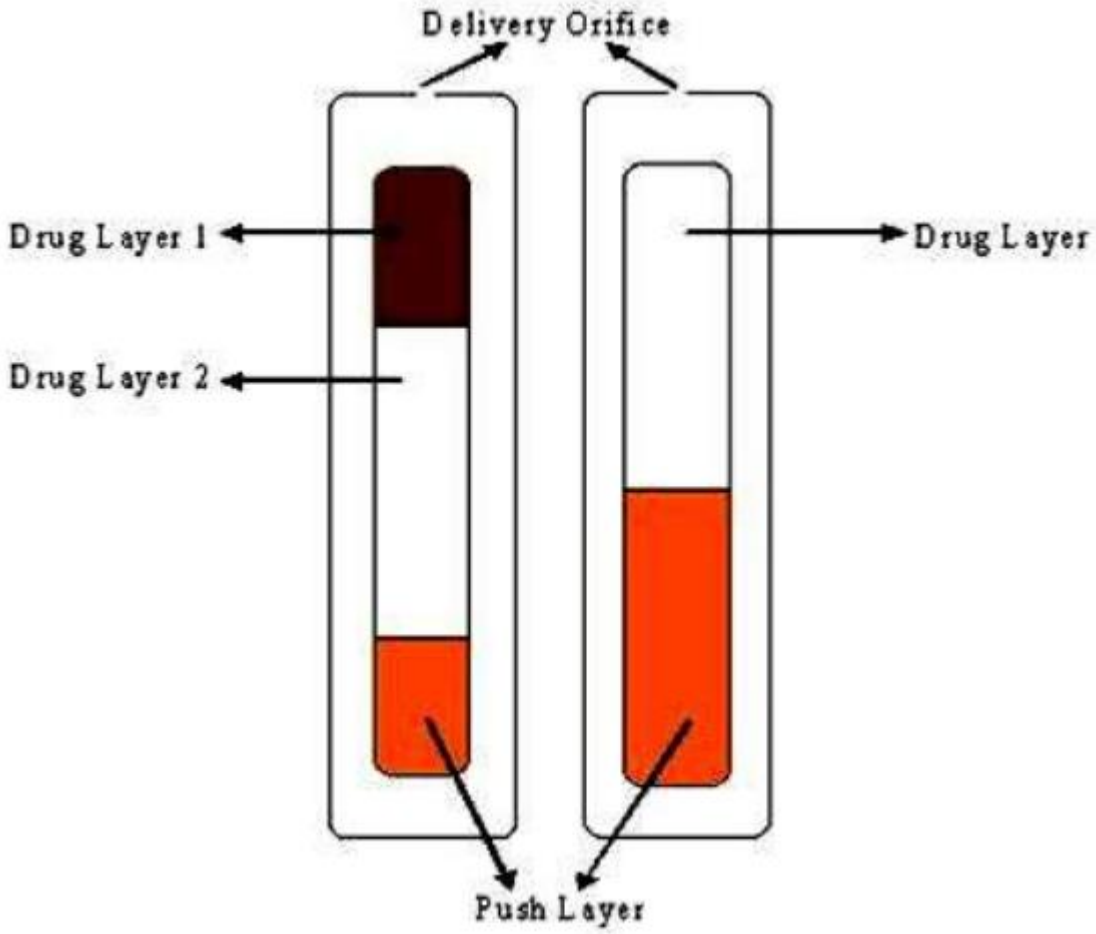

Figure 5. Bilayer OROS push pull technology.

L-OROSTM Technology

This system was used to solve the solubility problem. Alza created the L-OROS system, which involves coating a lipid soft gel product containing medicine in a dissolved form with a barrier membrane, then an osmotic push layer, and finally a semi permeable membrane drilled with an exit hole (**Figure 6**).

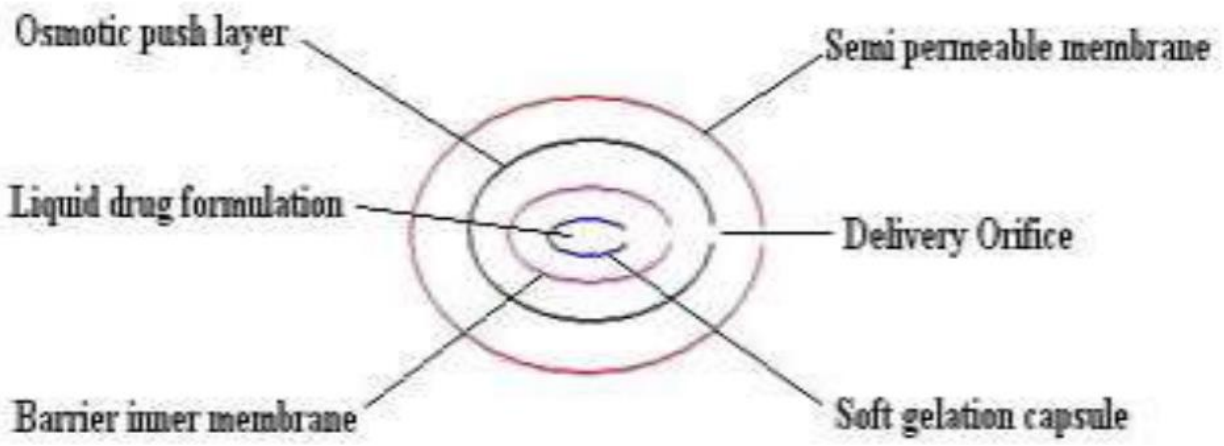

Figure 6. L-OROSTM Technology.

EN SO TROL Technology

Shire laboratory uses an integrated strategy to drug delivery concentrating on discovery and implementation of the discovered enhancer into controlled release technologies to improve solubility by an order of magnitude or to generate optimum dosage forms (**Figure 7**).

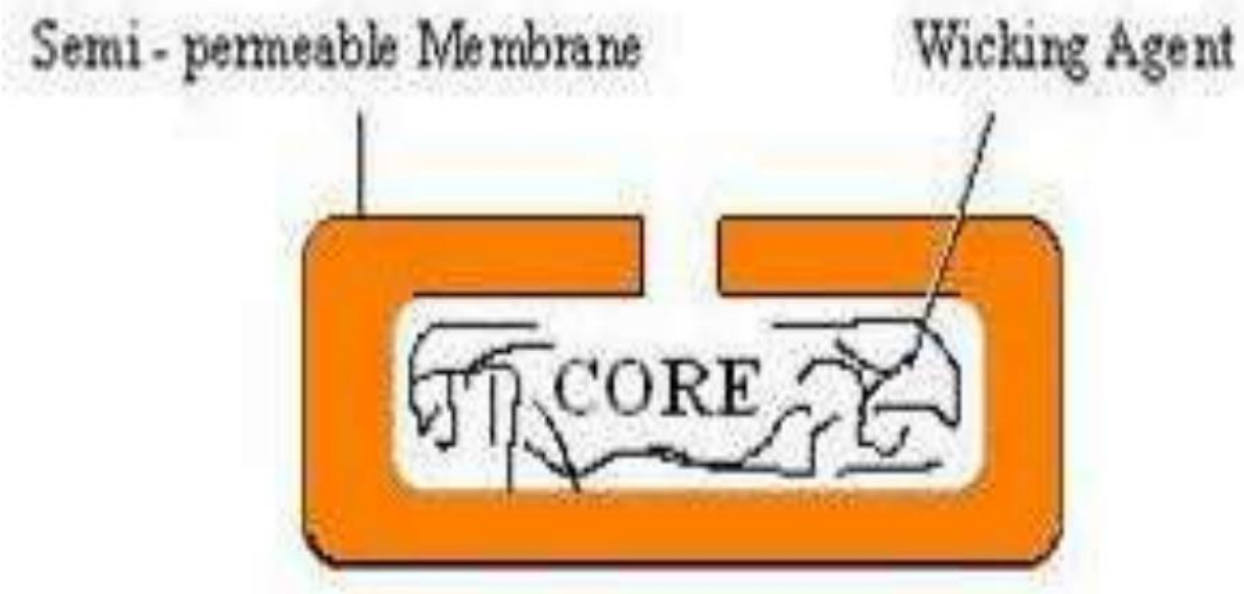

Figure 7. EN SO TROL Technology.

DUREDAS™ Technology

Elan pharma technologies' Dual release drug delivery system is another name for this device. DUREDASTM Technology is a bilayer tablet that may provide instant or sustained release of two medications in one dose form, or differing release rates of the same drug. Within a single tablet, the tableting technique may produce an instant release granulate and a modified release hydrophilic matrix complex as distinct layers. A mixture of hydrophilic polymers provides the dosage form's modified-release features.

DUROS Technology

An exterior cylindrical titanium alloy reservoir makes up the system. The drug molecules are protected from enzymes by this reservoir, which has high impact strength. The DUROS technology is a small medicine distribution mechanism that works like a micro syringe to continuously and consistently deliver minute amounts of concentrated dosage over months or years (**Figure 8**).

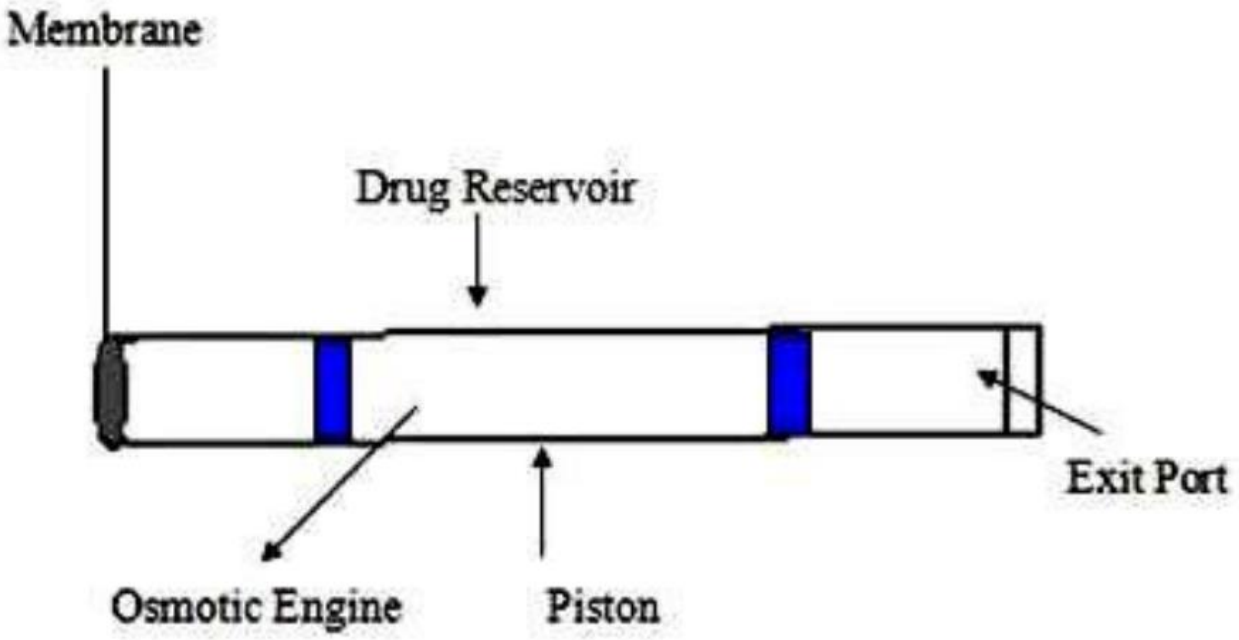

Figure 8. DUROS Technology.

Characterization of bilayer tablet

Particle size distribution

A sieving technique will be used to determine the particle size distribution.

Photo-microscope study

A photomicroscope will be used to capture the images (X450 magnifications).

Angle of repose

The angle of repose was estimated using the following equation after measuring the diameter of the powder cone.

Tan ø=h/r

Where, h = Height, r = Radius of the powder cone.

Moisture sorption capacity

Moisture Sensitive medicines are affected by all disintegrates' ability to absorb moisture from the environment. 1 g of disintegration was used to test moisture sorption capacity. For 2 days, uniformly dispersed in petri-dishes were maintained in a stability chamber at 37°C1°C and 100 percent relative humidity, and the quantity of moisture absorption was measured by the change in weights.

Density

The following formulae were used to estimate and compute the loose bulk density (lbd) and tapped bulk density (tbd).

LBD = weight of the powder = volume of the packing ð2þ

TBD = weight of the powder = tapped volume of the packing ð3þ

Compressibility

Carr's compressibility index was used to establish the disintegrate's compressibility index.

C = 100 × (1-þb/þt)

RECENT DEVELOPMENTS IN THE FIELD OF BILAYER TABLETS

The creation of pre-determined active ingredient release patterns and the combination of incompatible active ingredients into a single unit dosage form has been made possible by the advent of bilayer tablets into the pharmaceutical industry. In this area, a lot of work has been done (**Table 1**).

Table 1. Advances in bilayer tablet formulations.

DRUG	DOSAGE FORM	USES	REFERENCE
Amlodipine, Metoprolol	Bilayer tablets	Synergistic effect in hypertension	
Amlodipine, Atenolol	Bilayer tablets	To improve the stability of drugs in combination	
Atenolol	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration	
Atorvastatin	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects	

		and frequency of administration	
Atorvastatin, Atenolol	Bilayer Gastroretentive Matrix Tablet	Treatment of hypertension and hypercholesterolemia	
Aspirin, Isosorbide 5-mono-nitrate	Sustained Bilayer tablets	Treatment of pain, fever and other inflammatory conditions	
Cefixime, Dicloxacilline	Bilayer tablets	Synergistic effect in bacterial infections	
Cefuroxime, Potassium Clavulanate	Bilayer tablets	Synergistic effect in bacterial infections	
Diclofenac, Cyclobenzaprine	Bilayer tablets	Synergistic effect in pain	
Glipizide, Metformin	Bilayer tablets	To avoid interaction b/w incompatible drugs	
Granisetron	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects	
Guaifenesin	Bilayer tablets	Biphasic release profile	
Ibuprofen, Methocarbamol	Bilayer tablets	Synergistic effect of drugs in back pain	
Indomethacin	Bilayer floating tablets	Biphasic drug release	
Losartan	Bilayer tablets	Biphasic release profile	
Metformin, Glimipiride	Bilayer tablets	Synergistic effect in diabetes	
Metformin, Pioglitazone	Bilayer tablets	Synergistic effect in diabetes mellitus	
Metformin, Atorvastatin	Bilayer tablets	Polytherapy for the treatment of NIDDS and hyperlipidemia	
Misorostol, Diclofenac	Bilayer tablets	To minimize contact between drug	
Montelukast, Levocetrizine	Bilayer tablets	To improve the stability of drugs in combination	
Nifedipine	Gastroretentive Floating Bilayer Tablets	Treatment of hypertension and angina pectoris	
Paracetamol, Diclofenac	Bilayer tablets	Synergistic effect of drugs in pain	
Pioglitazone, Gliclazide	Bilayer tablets	Treatment of Type-II Diabetes	
Piracetam, Vinpocetin	Bilayer tablets	Synergistic effect in Alzheimer's disease	
Salbutamol, Theophylline	Bilayer tablets	Synergistic effect of drugs in asthma	
Telmisartan, Hydrochlorthiazide	Bilayer tablets	To minimize contact between hydrochlorothiazide and basic component of telmisartan	
Tramadol, Acetaminophen	Bilayer tablets	Synergistic effect of drugs in pain	
Trimetazidine, Clopidogrel	Bilayer tablets	Cytoprotective anti-ischemic, platelet inhibitor in acute coronary syndromes	

CONCLUSION

Manufacturers may use bi-layer tablets to set themselves apart from their rivals, increase the effectiveness of their goods, and protect themselves from imitators. A bilayer tablet, consisting of two layers, one of which is delayed release and the other of which is instant release, has been suggested, in which one layer is formulated to get immediate release of the drug, with the goal of attaining a high serum concentration in a short amount of time. The second layer is a hydrophilic regulating release matrix, which is designed to maintain an effective plasma level for a long time. Pioglitazone, Atenolol, Aspirin, Isosorbide 5-mono-nitrate, Nifedipine, Clopidogrel, Losartan, Atorvastatin, Trimetazidine, Gliclazide, and other bilayer tablets are now available.

CONFLICT OF INTEREST

No conflict of interest declared.

FUNDING INFORMATION

No agency provided any funding for this study.

ACKNOWLEDGEMENT

The authors acknowledge the help received from the college management.

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