A Review on: Novel Approach in Development of Bi-Layer Tablet

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Abstract- *The novel drug delivery systems with altered pharmacokinetic charracters (specially tablets) have shown more promising results in drug delivery system and easy manufacturing techniques helps to add advantage to the pharmaceutical industry. In recent years, bilayered tablets have grown in popularity. A bilayer pill is more effective in releasing two active components at the same time. The bilayered tablet technique allows two or more different drug compounds to be delivered in respective sites, with one Immediate layer provide instant release as ainitial dose and the other providing sustained release as a maintenance dose. This article discusses the various bilayer tablet procedures, development techniques and why they are necessary for reducing common bilayer issues such as layer separation, insufficient hardness, inaccuracy in individual layer weight control, cross-contamination between layers, and lower yield.*

Keywords- Bilayer Tablet, Patient Compliance, Incompatiblity, Sustained Release

I. INTRODUCTION

Many medications are carried in bilayer formulations, each of which is distributed at its own rate, with no pharmacokinetic or dynamic interactions (immediate, timed or sustained). The advantages of bilayer tablet technology outnumber those of single-layered tablet technology.(1) Typically, traditional monotherapy with single drug-containing tablets results in frequent dosing and a large range of drug concentration fluctuations in the blood and tissues, resulting in unacceptable toxicity and poor efficacy for medicines with shorter half-lives [1,2hr]. Combination drug delivery systems were born out of the need for repetitive dosage and inconsistent absorption from tablets. By localising the drug at the site of action, lowering the amount necessary, or delivering consistent drug delivery, the purpose of constructing sustained or controlled delivery systems is to minimise dosing frequency or boost drug effectiveness.The main goal of sustained release drug delivery is to maintain patient safety while also increasing treatment efficacy and compliance. Bilayer tablets are ideal for the sequential release of two medications in combination, separating two incompatible substances, and creating a sustained release tablet with one layer serving as the initial dose and the second serving as the maintenance dose (2).The bilayer tablet is made using several processes, such as a single compress or a dubble press, which aids in the compaction of loose powder layers using novel active ingredients accessible in the pharmaceutical industry. At this time, numerous pharmaceutical companies are producing bilayer tablets.

The mechanical structures of this drug delivery system have become rather elaborate, requiring more durable binders, advanced super disintegrants, as well as difficult tablet geometries and patient-friendly administration, which offer severe problems to pharmaceutical scientists.

Need of Bilayer tablet(8)

- Managing the rate at which a single active pharmaceutical ingredient or two active pharmacological components are administered
- Alter the overall surface area available for API layer by sandwiching with one or two active layers to achieve swellable/erodible barriers for modified release.
- To separate incompatible active pharmaceutical ingredients (APIs) and use the functional feature of the other layer to control API release from one layer (such as, osmotic property).
- Longer drug product life cycle, buccal/mucoadhesive delivery systems; develop new drug delivery methods for gastro-retentive drug delivery, such as chewing devices and floating tablets

BI-LAYER APPLICATION(2,9)

- Physical separation helps to avoid chemical incompatibilities between APIs.
- Allows for the simultaneous release of two medicines.
- Traditional dose forms require repetitive dosing, which can be avoided with a bilayer tablet.
- In comparison to traditional dosage forms, a lower drug dose is necessary.

- It is the most popular and practical method of administration.
- Chemical and microbiological stability are higher than in other oral dose formulations.
- Bilayer floating tablets have two layers, one of which is the floating layer and the other is the drug's instant release layer.
- Two distinct medications with different release profiles are delivered using bilayer tablets.

General Properties of Bi-Layer Tablet Dosage Forms(2)

- A bi-layer tablet should have a sophisticated product identity and be devoid of flaws such as cracks, chips, contamination, and discolouration.
- It must be strong enough to withstand mechanical shock during manufacture.
- It must be chemically and physically stable in order to retain its physical properties throughout time.
- Chemical stability shelf life is required

Advantages of Bi-Layer Tablet Dosage Forms(2,3)

- When compared to other oral dose forms, the cost is cheaper.
- Compact and lighter.
- Packaging and stripping is the simplest and cheapest option.
- Easy to swallow with minimal hang-up potential.
- Coating method can disguise unpleasant odours and bitter tastes.
- Large-scale production is possible.
- They are unit dosage forms that have the most capabilities of any oral dosage form in terms of dose precision and content variability.
- When using an embossed and/or monogrammed punch face, product identification is simple and quick, needing no additional processes.

Disadvantages of Bi-Layer Tablet Dosage Form(4,34)

- Because of their amorphous structure and low density, some medications defy compression into dense compacts.
- Drugs that have a bitter taste, an unpleasant odour, or are oxygen-sensitive may require encapsulation or coating.
- Children and unconscious individuals may find it difficult to swallow.
- Drugs with poor wetting properties, slow dissolution properties, and optimum absorption high in the GI tract may be challenging to design or manufacture as a tablet while still providing appropriate or full drug bioavailability.

MANUFACTURE OF MULTILAYER TABLETS

Multilayer tablet manufacturing has been successful for over 60 years. Formulation development scientists are currently researching a new drug delivery system with increased efficacy and safety, reduced dose frequency, and improved patient compliance. For drugs with shorter half lives, single layer tablets lead to frequent dosing and unpredicted drug plasma levels. A number of diseases, such as diabetes and hypertension, require immediate drug release for immediate effect to manage panic attacks at their onset, and then drug concentration must be Frontiers in Pharmacology. Sustain release bilayer pill for the drug's impact to last longer. The multilayered tablet concept has been used to address the need for such disease situations (7).Metformin was supplied via the controlled release layer, while glimepiride was delivered via the rapid release layer. A blend of hydrophobic and hydrophilic polymers made up the controlled release layer, while a disintegrant and glimepiride9 made up the immediate release layer. This stresses the importance of these systems in the treatment of chronic diseases including hypertension and diabetes. For the concurrent treatment of hypercholesterolemia, Nirmal and colleagues created a bilayered tablet containing atorvastatin calcium for quick release and nicotinic acid for delayed release.The combination of these two medications has been demonstrated to result in significant reductions in low density lipoprotein cholesterol as well as beneficial changes in high density lipoprotein cholesterol. The polymeric matrix for nicotinic acid was Methocel® K100M, and the quick release layer containing atorvastatin calcium was made with croscarmellose sodium, a super disintegrant. The findings of 12 hour drug release trials showed that these tablets were successful in delivering two types of medicines at the same time (2).

VARIOUS METHODS USEDFOR BILAYER TABLET

OROS® Push Pull Technology (10)

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. The drug layer is made up of the drug and 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.

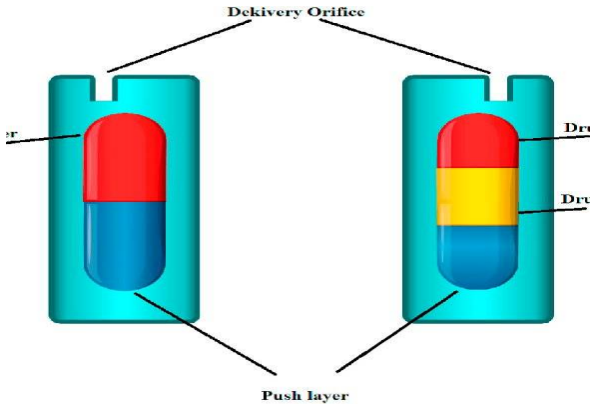

Figure 1: Bilayer And Trilayer OROS Push Pull Technology

L-OROS TM Technology(11)

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 condition with a barrier membrane, then an osmotic push layer, and finally a semi permeable membrane drilled with an exit orifice.

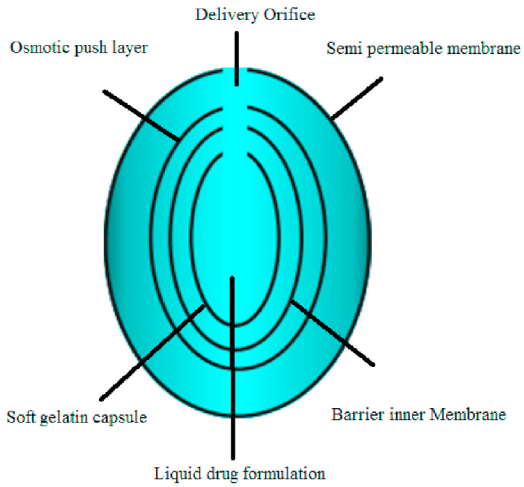

Figure 2: L-OROS TM Technology

EN SO TROL Technology (11)

Shire laboratory uses an integrated strategy to drug delivery concentrating on identification and implementation of the identified enhancer into controlled release technologies to improve solubility by an order of magnitude or to generate optimum dosage forms.

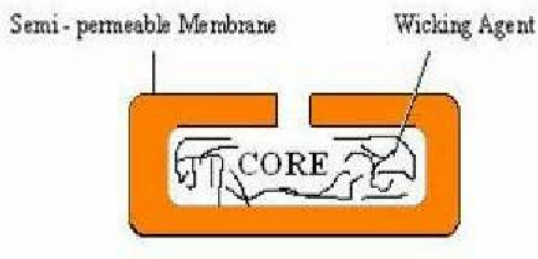

Figure 3: EN SO TROL Technology

DUROS Technology (12)

An exterior cylindrical titanium alloy reservoir makes up the system. The drug molecules are protected from enzymes by this reservoir, which has a high impact strength. The DUROS technology is a small medicine delivery system that works like a miniature syringe, administering a constant and consistent amount of concentrated form across months or years.

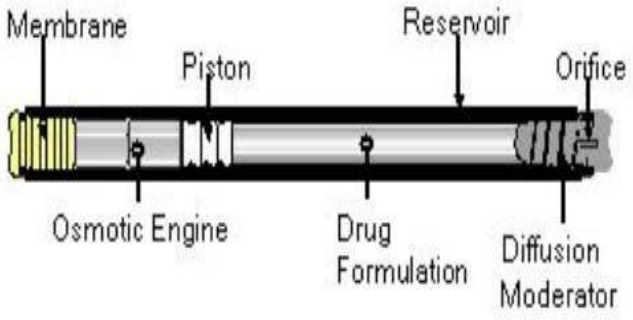

Figure 4: DUROS Technology

ELAN.DrugTechnologies(2,36,21)

The Dual Release Drug Delivery System (DUREDASTM Technology) is a bilayer tablet that can deliver two medications simultaneously or at differing release rates in one dose form. Within one tablet, the tabletting technique can offer different layers of immediaterelease granulate and modified-release hydrophilic matrix complex. A mixture of hydrophilic polymers provides the dosage form's modified-release features.

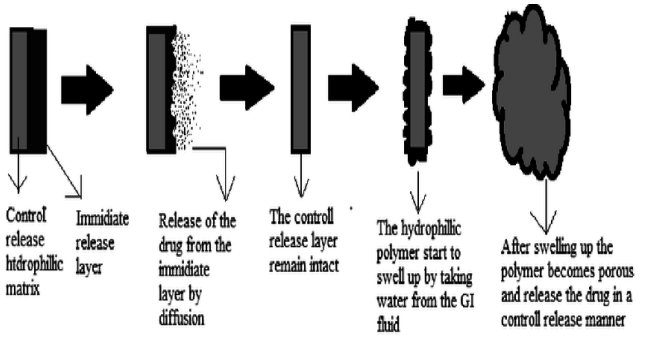

Figure 5: DUREDAS technology consists of control release and immediate release layer

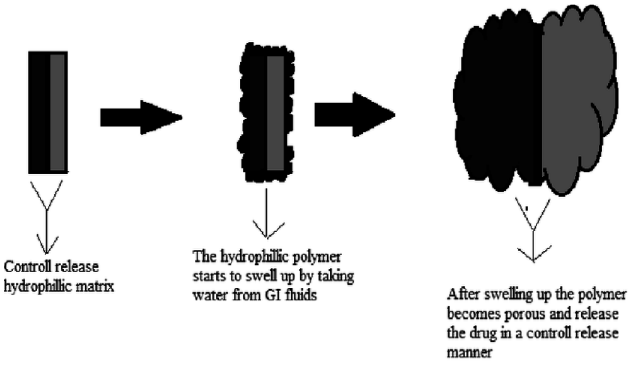

Figure 6: DUREDAS technology consist of two control release layers

Benefits offered by DUREDAS™ Technology

- Technology for bilayer tabletting
- Two medication components have different release rates.
- Combination of two distinct CR formulas
- The possibility to combine immediate and modified release components in a single tablet
- Presentation of unit dosage tablets

Types of bilayer tablet press

Single sided tablet press (13)

A single-sided press with both chambers of the doublet feeder separated is the simplest design. The two layers of tablets are produced by gravity or forced feeding with varied power in each chamber. The first layer powder is fed 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 7: Single sided tablet press

Limitations of the single sided press

- Individual layer weight monitoring and control are not available.
- There is no clear visible distinction between the two levels.
- Problems with capping and hardness

Double Sided Tablet Press(14,19)

Each layer has its own fill station, pre-compression, and primary compression on a double-sided press. Before being evacuated from the press, the bi-layer tablet will go through four compression steps. Compression force is used to monitor and control tablet weight in most double-sided tablet presses with automated production control. The control system measures the effective peak compression force exerted on each individual tablet or layer at main compression. The control system uses this measured peak compression force to reject out-of-tolerance tablets and modify the die fill depth when necessary.

Figure 8: Double Sided Tablet Press

Bilayer Tablet Press With Displacement(15,30,32)

The principle of displacement pill weight management is significantly different from the compression force principle. The sensitivity of the control system when monitoring displacement is independent of the operating point. However, it is contingent on the applied precompression force. In fact, the lower the precompression force, the more the monitoring control mechanism is activated, which is optimal for bilayer tablet interlayer bonding.

EVALUATION(16,17,18)

General Appearance

Consumer acceptance is dependent on a tablet's overall appearance, visual identity, and overall "elegance." Size, shape, colour, aroma, taste, surface texture, physical faults, and consistency and readability of any identifying marking are all factors to consider**.**

Tablet Thickness and Size

Tablet thickness and diameter were critical for tablet size consistency. A venire calliper was used to measure thickness and diameter.

Tablet thickness(22)

Tablet thickness is a crucial factor in both duplicating look and counting with filling equipment. The consistent thickness of the tablets is used as a counting mechanism in some filling equipment. A micro metre was used to measure the thickness of ten pills.

Weight variation:

Standard procedures are followed as described in the official books.

Friability(31)

The forces that cause tablets to chip, cap, or break are friction and shock. The friability test is related to tablet hardness and is used to assess a tablet's ability to tolerate abrasion during packaging, handling, and shipping. The Roche friabilator is commonly used to measure it. Abrasion loss is used to determine the tablet's friability. The percentage represents the value. During the friability test, a maximum weight loss of not more than 1% of the weight of the tablets being tested is regarded acceptable, and any broken or smashed tablets are not picked up. Friability values are normally not calculated when capping occurs. A thick tablet may have a lower tendency to cap, whereas small tablets with a big diameter commonly have extensive capping, indicating that thicker tablets have less internal tension.

Dissolution test(22,23)

In vitro drug release tests in simulated stomach and intestinal fluids were performed on bilayer tablets to determine their potential to offer the necessary controlled medication delivery. Since the usual gastric emptying duration is about 2 hours, drug release tests were conducted using USP dissolution test apparatus I at 100 rpm, 370.5°C, and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours. The dissolution liquid was changed with 900 mL of pH 6.8 phosphate buffer and the experiment was continued for another 10 hours. 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolving media at various time intervals. The removed samples were analysed with a UV spectrophotometer in multi component mode.

Stability Study(27)

A stability study is carried out in a stability chamber at 25°C/60 percent RH and 40°C/75 percent RH to assess the change in storage. At regular intervals, samples are taken. Hardness,thickness, disintegration time, and in vitro release experiments are all used to evaluate the formulation.

Table No. 1: Various advancements in the field of bilayer tablets(19,20)

Drug(s)	Dosage Form	Rationale
Atorvastatin, Atenolol	Bilayer gastroretentive matrix Table	Treatment of hypertension and hypercholesterolemia
Nifedipine	Gastroretentive floating bilayer tablets	Treatment of hypertension and angina pectoris
Aspirin, Isosorbide 5-mono-nitrate	Sustained bilayer tablets	Treatment of pain, fever and other inflammatory conditions
Pioglitazone HCl, Gliclazide	Bilayer Tablets	Treatment of Type II Diabetes
Losartan potassium	Bilayer tablet	Treatment of hypertension
Trimetazidine Hcl, Clopidogrel bisulphate	Bilayer tablets	Cytoprotective anti-ischemic, platelet inhibitor in acute coronary syndromes,
Diclofenac, Cyclobenza-prine	Bilayer tablets	Synergistic effect in pain
Granisetron HC1	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects
Metformin HC1,Glimipiride	Bilayer tablets	Synergistic effect in diabetes
Indomethacin	Bilayer floating tablets	Biphasic drug release
Metformin HC1, Atorvastatin Calcium	Bilayer tablets	To develop polytherapy for the treatment of NIDDS &hyperlipidemia
Cefixime Trihydrate, Dicloxacilline Sodium	Bilayer tablets	Synergistic effect in bacterial infections
Piracetam, Vinpocetin	Bilayer tablets	Synergistic effect in Alzheimer disease
Metformin Hcl, Pioglitazone	Bilayer tablets	Synergistic effect in diabetes mellitus
Atenolol	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration
Cefuroxime Axetil Potassium Clavulanate	Bilayer tablets	Synergistic effect against microbial infections and to minimize dose dependent side effects
Amlodipine Besilate Metoprolol Succinate	Bilayer tablets	Synergistic effect in hypertension
Diclofenac Sodium, Paracetamol	Bilayer tablets	Synergistic effect in pain

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