Review Article

Bilayer Tablets in Drug Delivery: A Concept of Modified Release

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ABSTRACT

The potential of Bilayer tablets as novel drug delivery system is a promising platform for successful combination therapy. Bilayer tablets are modified release system in which one layer serves as loading dose and the other layer serves as maintenance dose to enhance the bioavailability or to avoid the interaction between the incompatible substances by separating them physically. Several pharmaceutical companies are currently developing bi-layer tablets for a variety of reasons: patent extension, therapeutic, and marketing purposes. Bilayer tablets are advancing helpful technologies to overcome the disadvantages of single-layered tablets. The goal of this review article is to discuss different approaches, criteria for immediate and sustained release dosage form, manufacturing techniques, advanced techniques, evaluations, and therapeutic applications of bilayer tablet technology.

Keywords: Modified release, combination therapy, loading dose, maintenance dose.

INTRODUCTION

Now-a-days various developed and developing countries move towards a combination therapy for the treatment of various diseases and disorders requiring long term therapy such as hypertension, diabetes and cardiovascular diseases. 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.[1]

Solid orals are the preferred route of drug administration because of better patient compliance and ease manipulation in the dosage regimen. Several novel drug delivery systems have gained acceptance and researchers still show interest in modified tablets such as controlled/sustained release tablets, delayed release tablets, compression coated tablets and oral osmotic pumps. [2]

The dual release technique is the easiest way to successfully develop a cost-effective controlled release formulation. Bilayer tablet is more successful than the traditionally used dosage forms due to their suitability for sequential release of drugs in combination and it also has characteristics of separating incompatible substances, the best example is a sustained release tablet or controlled release tablet in which one layer is as initial dose (immediate release) and the second layer is maintenance dose (controlled release). In a few cases, bilayer tablets have two sustained-release layers of different drugs. The immediate release layer contains super disintegrants which promote drug release rate and attains the onset of action (quick release) as a loading dose whereas the sustained release contains low viscosity polymers (maintenance bioavailability of drug) which help to releases the drug in a sustained manner for a prolonged time period. [3]

Figure 1: Same drug with different release

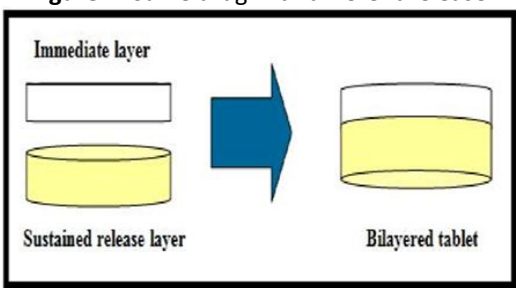

Figure 2: Different drug with different release

RATIONALE OF DEVELOPING BILAYER TABLETS

- To deliver fixed dose combinations of different APIs, prolonging the drug product life cycle, developing buccal/ mucoadhesive delivery systems or development of floating tablets for gastro-retentive drug delivery.
- Controlled release drug delivery of either single or two different active pharmaceutical ingredient(s).
- To achieve modified drug release either by sandwiching drug with one or two inactive layers with swellable/erodible barriers.

- To separate incompatible drugs from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).[4]

Advantages

- Two chemically incompatible active pharmaceutical ingredients (APIs) can be formulated in a bilayer configuration. In some cases, depending on the magnitude of the incompatibility between the two APIs, an intermediate layer needs to be added to provide physical separation between the two layer.
- Two APIs or the same API with different release profiles can be delivered as a single bilayer tablet (e.g. drugs with extended release and immediate release profiles.)
- Combining two or more APIs in a single bilayer tablet reduces the dosing unit burden thereby improving patient compliance.
- As most bilayer tablets are developed as part of a Life Cycle Management program, the bilayer technology provides possibility of prolonging patent life of a drug product.
- Increased efficacy of the active components due to their synergistic effect.

Limitations

- Inaccurate individual layer weight between the layers.
- Cross contamination between the layers.
- Elastic modulus mismatch between the adjacent layers.
- Reduced production yield and the propensity to delaminate (distinct layers separation) at the non-planer interface between the adjacent compacted layer.
- Disproportionate layers weight ratio coupled with low drug load.
- Insufficient bilayer tablet hardness.
- Long term physical and chemical integrity throughout shelf life.
- Large tablet size, which can impact the swallowability of the unit dose.
- Impact of high temperature and humidity on layer adhesion upon storage.[5]

General properties of bilayer tablet dosage forms

- Bilayer tablet should have elegant product identify while free of defect like chips, cracks, discoloration and contamination.
- It should have sufficient strength to withstand mechanical shock during its production, shipping and dispensing.
- It should have chemical and physical stability to maintain its physical attributes over time.
- The bilayer tablet must be able to release the medicinal agents in a predictable and reproducible manner.[6]

Bilayer Tablets: Quality And GMP-Requirements

To produce a quality bilayer tablet, in a validated and GMP-way, it is important that the selected press is capable of:

- Preventing capping and separation of the two individual layers that constitute the bilayer tablets.
- Providing sufficient tablet hardness.
- Preventing cross-contamination between the two layers.
- Producing a clear visual separation between the two layers.
- High yield, accurate and individual weight control of the two layers. [7]

MECHANISM OF DRUG RELEASE

Bilayer tablet consists of a matrix core containing the active drug along with one or more barriers. (Fig 3) These modulating layers result in delaying the interaction of active solute with dissolution medium, by limiting the surface available for the drug release. At the same time, results in controlling solvent penetration rate and protect core for some duration. Thus, burst effect can be achieved in desired range and the release can be maintained at a relatively constant level during the swelling and erosion process of barriers. (Fig 4) After this phase, the swollen barriers are erosion dominated and the surface available for drug release slowly increases and decrease in delivery rate due to the increase of diffusion path-length (saturation effect). This effect is counterbalanced by the simultaneous increase of the area available for drug release [8]

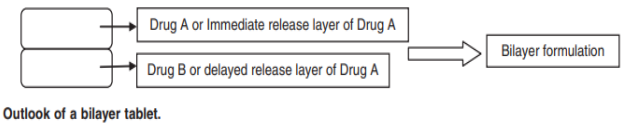

Figure 3: Outlook of bilayer tablet

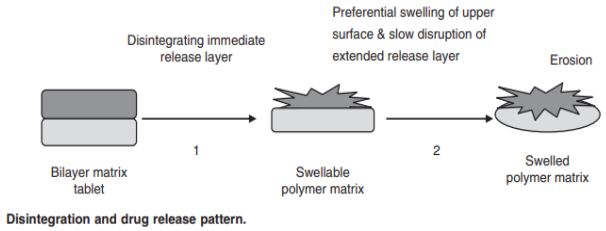

Figure 4: Disintegration and drug release pattern

VARIOUS APPROACHES TO BILAYER TABLET

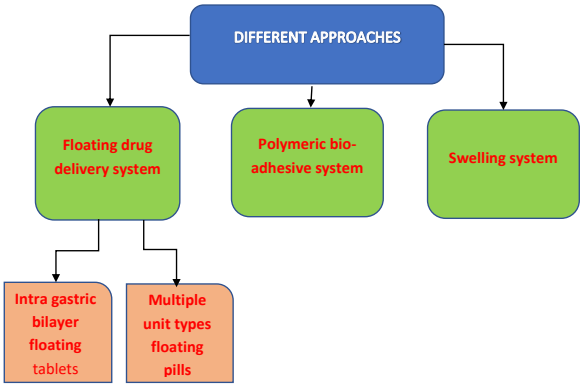

Figure 5: Various approaches to bilayer tablet

1. Floating Drug Delivery System

The bilayer tablet is made such that one of its layers provides an instant dose of the drug, giving faster action onset and the other layer is the floating layer that floats inside the stomach.

Approaches to design Floating Drug Delivery System:

The following approaches have been applied to the design of floating dosage forms of single- and multiple-unit systems.

a) Intra gastric bilayered floating tablets These tablets consist of two major layers which are in compressed form, one layer is termed as an immediate layer, which is employed to quickly affect the target area, whereas the second layer, is termed as the sustained release or expanded release, which affects the target after the completion of first layers occurs.

b) Multiple unit type floating pills

These pills consist of expanded/sustained release as seeds encapsulated by double layers. The inner layer is chemically composed of effervescent agents, while the outer layer has the composition of the swellable membrane layer. When such type of pills is dissolved in a solution at normal body temperature, the first sink to the bottom and then swell up like a balloon due to its low density, and therefore, floats on the surface.

2. Polymeric bio-adhesive system

These contain one layer for immediate dosing and the other having the bio-adhesive property. However, this type of dosage has only been administered into animals and has been avoided to use for humans.

3. Swelling system

These are manufactured to be considerably small on being administered for easing the dose ingestion. After being ingested, these disintegrate, swell, or unfold rapidly to a size that stops the pylorus passage until the progression of the drug release to the desired level .[9]

ADVANCED TECHNIQUES USED IN PREPARATION OF BILAYER TABLET

Oro's Push Pull Technology: This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So, this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.

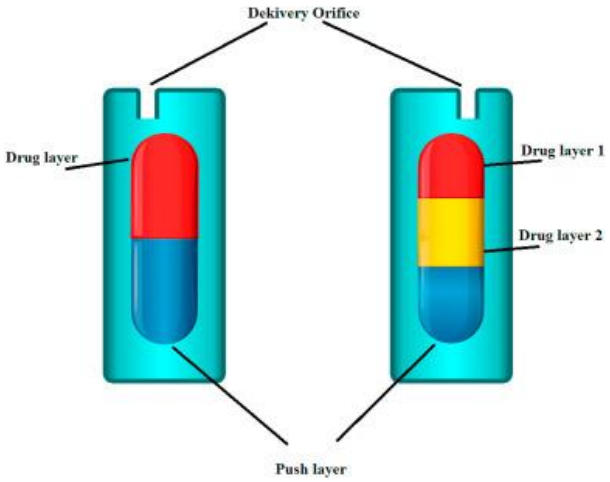

Figure 6: Oro's Push Pull Technology

L-OROS Technology: This system used for the solubility issue Alza developed the L-OROS system. This system is mainly used for solubility problem, where a lipid soft gel product containing drug in a dissolved condition initially prepared and then coated with barrier membrane then osmotic push layer and then semi permeable membrane drilled with exit orifice for drug release.

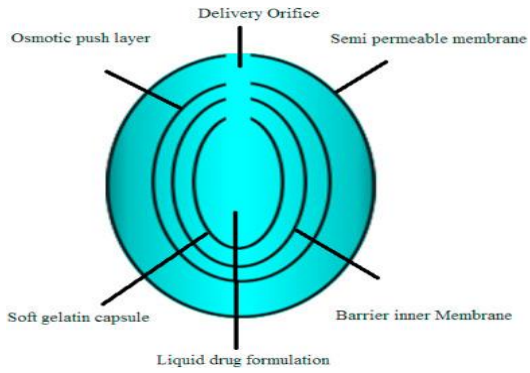

Figure 7: L-OROS Technology

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 release minute quantity of concentrated form in continues and consistent from over months or year.

En So Trol Technology: Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery

focusing on identification and incorporation of the identified enhancer into controlled release technologies.[10]

Duredas™ Technology: Dual Release Drug Absorption System (Elan Corporation) utilizes bilayer-tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. [11]

FORMULATION OF BILAYER TABLETS

Bilayer tablet is formulated by mainly three methods: -

1. Direct compression method
2. Wet Granulation
3. Dry Granulation [12]

Table 1: An outline of various steps involved in the manufacturing of tablets by different methods is mentioned below:

Wet Granulation	Dry Granulation	Direct Compression
1. Milling and Mixing of Drug and Excipients		
2. Preparation of binder solution	2. Compression into slugs or roll compaction	2. Compression of Tablet
3. Wet massing by addition of binder solution	3. Milling and screening of slugs or compacted powder	
4. Screening of wet mass	4. Mixing with lubricant and disintegrant	
5. Drying of wet granules	5. Compression of tablets	
6. Screening of dry granules		
7. Blending with lubricant		
8. Compression of tablet		

COMPRESSION CYCLE FOR BI-LAYER TABLET

Bi-layer tablets are made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two or three layers. [13]

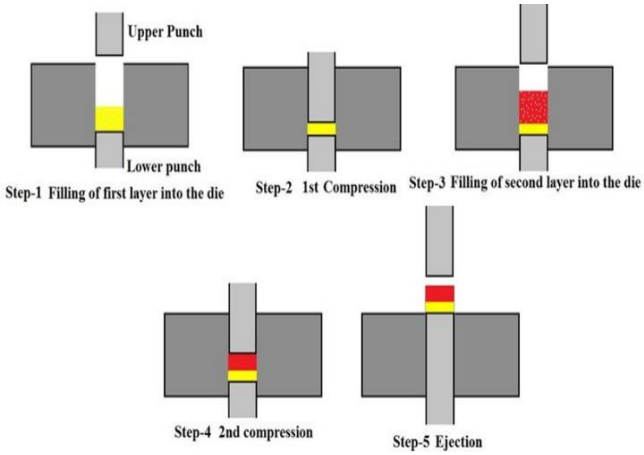

Figure 8: Steps involved in Compression cycle

Immediate Release Dosage forms: Immediate release tablets are invented to disintegrate and release their dosage form with no special rate controlling features, such as special coatings and other techniques. Immediate release tablets are those which disintegrate swiftly and get dissolved to release the medicaments.[14]

Desired Criteria for Immediate Release Drug Delivery System:

Immediate release dosage form should-

- ✓ In the case of solid dosage, it should dissolve or disintegrate in the stomach within a short period.
- ✓ In the case of liquid dosage form it should be compatible with taste masking.
- ✓ Be portable without fragility concern.
- ✓ Have a pleasing mouth feel.
- ✓ It should not leave minimal or no residue in the mouth after oral administration
- ✓ Exhibit low sensitivity to environmental condition as humidity and temperature.
- ✓ Be manufactured using conventional processing and packaging equipment at low cost.
- ✓ Rapid dissolution and absorption of drug, which may produce rapid onset of action.[15]

Sustained release dosage forms

Sustained release are used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[16]

Ideal properties of drug suitable for SRDDS

- ✓ It should be effectively absorbed by oral route and stable in gastro-intestinal (GI) fluid. II.
- ✓ Drugs that have short half-lives (2-4 hrs.) are ideal drug candidate for formulation into SR dosage forms e.g. Captopril, Salbutamol sulphate. III.
- ✓ The dose of drug should not be less than 0.5gm and maximum dose of drug for designing SRDDS is 1.0 gm e.g. Metronidazole. IV.
- ✓ The therapeutic range of the drug should be high in SRDDS for drug should have wide therapeutic range enough such that variation in the release does not

result in concentration beyond the minimum toxic levels.[17]

EVALUATIONS OF BILAYER TABLET

1. **Appearance** The general appearance of bilayer tablet was identified visually in terms of shape, size, color, presence or absence of odor, taste and surface texture.
2. **Weight variation** Weigh 20 tablets accurately. Determine average weight of tablets. The individual weight of each tablet was compared with average tablet weight.
3. **Thickness** Randomly tablet was selected and its thickness was measured by using vernier caliper scale.
4. **Hardness** The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet can be determined with the help of Monsanto hardness tester. The hardness was measured in kg.
5. **Friability:** Friability is a measure of tablet strength. Friability can be determined with the help of Roche friabilator. Twenty tablets are weighed accurately and placed in tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 minutes the tablets are weighed and percentage loss in tablet weight is calculated.

% loss = initial weight of tablets – final weight of tablets/ initial weight*100

6. **Disintegration time**: 6 tablets are taken in disintegration apparatus with distilled water or suitable medium at 37^{o}C. Calculate time at which tablet gets converted to soluble particles. Disintegration time for immediate release tablets and bilayer tablets was determined.
7. **Dissolution time:** Dissolution profile is evaluated with the help of USP paddle apparatus. 900ml of suitable dissolution mediums are taken in vessel maintained at 370C at 75rpm. The dissolution was carried out for about 12 hrs. 5ml of sample was withdrawn at regular time intervals, and 5ml of fresh medium is inserted in vessel. Absorbance is recorded for each sample at specific lambda maxima for the combination drugs. [18]

8. Stability studies

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.[19]

Table 2: Different stability study with storage conditions and duration

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

THERAPEUTIC APPLICATIONS OF BILAYER TABLET

Table 3: Applications of Bilayer Tablet as Combination Therapy

Drug(s)	Dosage Form	Rationale	Reference
Atorvastatin, Atenolol	Bilayer Gastroretentive matrix tablet	Hypercholesterolemia and hypertension treatment	[20]
Nifedipine	Gastro-Retentive floating bilayer tablets	Angina pectoris and hypertension treatment	[21]
Aspirin, Isosorbide 5-mono-nitrate	Sustained bilayer tablets	Pain, fever, and other inflammatory disorders treatment	[22]
Granisetron HCl	Bilayer buccal tablet	For overcoming the bioavailability issues and decreasing the side effects	[23]
Atorvastatin, Calcium	Bilayer buccal tablets	For overcoming the bioavailability issues, decreasing side effects and administration frequency	[24]
Atenolol, Lovastatin	Bilayer floating tablets	Synergistic effect for biphasic release profile and hypertension	[25]
Diclofenac sodium and Ranitidine HCl	Sustained release	Reduces symptoms of ulcer	[26]
Metformin HCl Pioglitazone	Bilayer Tablets	Synergistic effects in diabetic mellitus	[27]
Rosuvastatin Calcium, Atenolol	Bilayer Tablets	Hyperlipidemia and hypertension	[28]

CONCLUSION

The bilayer tablet is improved beneficial technology to overcome the shortcoming of the single-layered tablet. These days, bilayer tablets are made for combination therapy, which involves an initial layer that releases the drug instantly, followed by a prolonged release that keeps the plasma level at an effective level for a long time. Bilayer tablets are manufactured for combination therapy, which aims to maintain an effective plasma level for a long time by achieving an initial drug release from the immediate layer followed by a sustained release over a longer period of time. The main purpose of this drug delivery system is to guarantee that the drug is effective, has the fewest side effects, and is properly manufactured, keeping in view all GMP parameters, to maintain its quality throughout its shelf life. The manufactured tablet is evaluated both physically and chemically to ensure its effectiveness and stability throughout its shelf life.

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