# FORMULATION AND IN VITRO EVALUATION OF BILAYER TABLETS

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**Abstract**

According to the study , the Formulation of bilayer tablets are suitable for constant release of two drugs in which one layer is immediate release layer and the second layer as extended release layer . Bilayer tablets have been developed to achieve immediate and extended delivery of different drugs with pre-defined release profiles. In the previous 10 years from today, interested in to design or formulate a combination of two or more active pharmaceutical ingredients (API) in a single fixed dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance[1]. Bilayer tablet is suitable for sequential release of two drugs in combination or to incorporate of two incompatible substances in same tablet. Bilayer Tablets were prepared by using different grades of HPMC ( HPMC K4M and HPMC K 100 M) for extended layer and use of different super disintegrants ( Sodium Starch glycolate and PVP K-30 ) for immediate layer. Tablets were evaluated for physico chemical properties such as hardness, friability , thickness , weight variation and drug- content uniformity. FTIR studies revealed that there was no interaction between the drug and polymers used in study. *In vitro* drug release studies were performed using USP type II paddle type apparatus. The formulation gave an initial burst effect of immediate layer within half an hour and followed by extended release of drug for 12 hrs. The optimized formulations shows no significant changes on stability studies when stored at 40ºC /70% RH, for 3 months.

**Keywords**: Bilayer tablet, Immediate release , extended release layer , HPMC , .PVP K-30

## INTRODUCTION

Oral route is the most common route for administration of drug. Tablets are the most suitable oral dosage form and favored by patient and physicians. Bilayer tablet is convenient for subsequent release of two drugs in combination in which one layer is sustained release and another layeris immediate release.[2]Bilayer tabletshave some important benefits compared to regulate monolayer tablets.

Bi-layer tablets can be a primary option to avoid chemical incompatibilities between APIS by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). Bi-layer tablet is suitable for sequential release of two drugs in combination it is also capable of separating two incompatible substances

and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablets contain immediate and sustained release layers. The immediate release layer delivers the initial dose, it contains superdisintegrants which promotes drug release rate and attains the onset of action quickly (loading dose) whereas sustained release (maintenance dose) layer releases drug in sustained manner for prolonged time period.

Diabetes is metabolic disorder characterized by hyperglycaemia, glycosuria, hyperlipemia.There are two types of Diabetes mellitus therefore Type 1 and Type 2 Diabetes mellitus.Type 1 is Insulin dependent diabetes mellitus and Type 2 is Non-insulin dependent diabetes mellitus.Type 2 diabetes mellitus is generally onset after the age of 35 years[3].

Type 2 diabetes mellitus and hypertension are both the most usual chronic non communicable diseases .Lifestyle and genetic factors is the major cause for diabetes mellitus and hypertension. The prevalence of type 2DM has increase from 1.2% to 11% over last three decades. A patient who suffers from type 2DM has 2–4 times possibility of death from cardiovascular causes than the patient without suffering from diabetes mellitus. The most common reason of death inthe diabetic patient is heart disease. In addition, peripheral vascular disease, end-stage renal disease, blindness, and amputations are usual comorbidities in diabetic patients. Hence, combination therapy is important for the avoidance of diabetes in patients with hypertension.[4]

Hypertension is one of the prime risks related with heart disease. Hypertensionis the major cause of stroke; an important risk factor for coronary artery disease and its related complications, myocardial infarction and sudden cardiac death. The prevalence of hypertensionriseswithincreasing age;forexample, about50%ofpeoplebetween theagesof 59 and 70 years old suffer from hypertension, and the prevalence is further raised above age 72.[5,6]

The ojective of present study was to develop formulation of bilayer tablet were evaluated for Thickness, Hardness, Friability,Weight variation, Disintegration, Dissolution

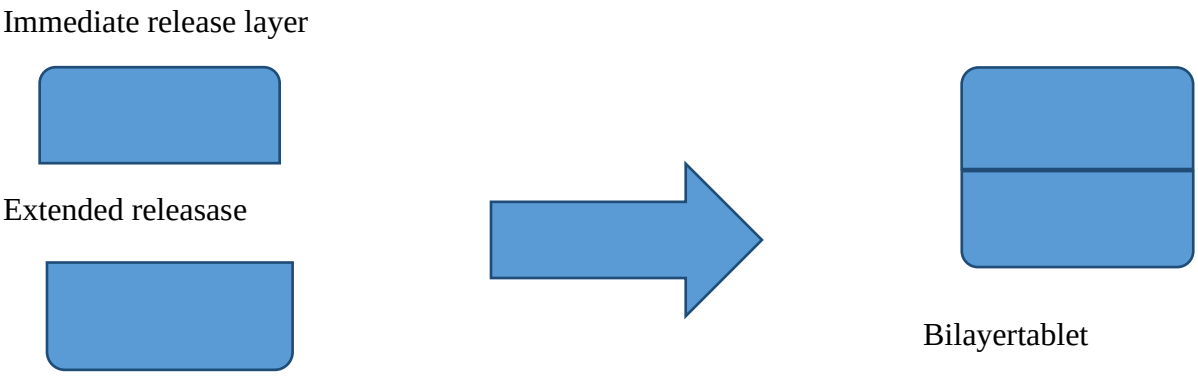


**Fig. No.1: Bilayer tablets (same drug with different release pattern)**

**Multi-layer tablet dosage forms are designed for variety of reasons [7]:**

1. To delivers the drug at a predetermined rate either single or two different active pharmaceutical ingredients.

2. To administer fixed dose combinations of different APIs, prolong the drug product life cycle.

3. To separate incompatible APIs from each other.

**Need of Bi-layer Tablet**

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

**Advantages of the Bi-layer Tablet[8]**

- Bi-layer execution with optional single layer conversion kit.
- Low cost compared to other dosage forms.
- Greatest chemical and microbial stability compared to other oral dosage form
- Objectionable odour and taste can be masked by coating technology.
- Offer greatest precision and the least content uniformity
- Easy to swallow with least hang up problems.
- Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximiz the efficacy of combination of two drug.

**Disadvantages of Bi-layer Tablet[7]**

- Ads complexity and bi-layer rotary presses are expensive.
- Insufficient hardness, layer separation, reduced yield.
- Imprecise individual layer weight control
- Cross contamination between the layers.
- Difficult to swallow in case of children and unconscious patients.

**Ideal Characteristics of Bi-layer Tablet**

- A bi-layer tablet should have elegant product identity while free of defects like chipping, cracks, discoloration and contamination.
- It should have sufficient strength to with stand mechanical shock during its production packaging, shipping and dispensing.
- It 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.

- It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

**Applications**[7]

- Bi-layer tablets are used to deliver the two different drugs having different release profile.
- Bi-layer tablets are used to deliver the loading dose and maintenance dose of the same or different drug.
- Bi-layer tablets are mainly used in combination for modified release.

**Types of Bilayer Tablet**

The term bilayered tablets containing subunits that may be either the same (homogeneous) or Different (heterogeneous).

**1. Homogenous type**

Bilayer tablets are preferred when the release profiles of the drugs are different from one Another. Bilayer tablets allows for designing and modulating the dissolution and release Characteristics .Bilayer tablets are prepared with one layer of drug for immediate release While second designed to release drug, later, either as second dose or in an extended release Manner

**2. Heterogeneous type**

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two Incompatible substance.

**Methods used for the preparation of bilayered tablets:**[7]

Example:

combination of Antihypertension and diabetic drugs was taken as a example. Bilayer tablets are prepared by direct compression and wet granulation technique for both immediate release Aliskiren and extended release Empagliflozin layer.

**Formulation of the immediate release layer:**

The immediate release layer were prepared by direct compression technique weigh accurately quantity of Aliskiren uniformly with sodium starch glycolate using PVP K-30 a as binder and added lactose and microcrystalline cellulose were screened using screen # 25. The screened powders were then transferred into the mixer and mixed for 10 mins.Magnesium stearate was sifted through screen # 40 and added above powder mix and mixed for 3 mins at20 rpm.

**Formulation of the extended release layer:**

The sustaining granules were formulated by the wet granulation technique, mixing Empagliflozin uniformly with HPMC K4M and HPMC K100M. Lactose and Micro Crystalline Cellulose was mixed with the above drug and polymer mixture. PVP K-30 was used as a binder . Further sustaining granules were also subjected to similar processing steps as the immediate releasing granules. The granules were mixed with magnesium stearate.

**Various steps involved in bilayer tablet formulation are as follows[8]:**

(1) Filling of first layer

(2) Compression of first layer

(3) Filling of second layer

(4) Compression of second layer

(5) Ejected fully bilayer tablet

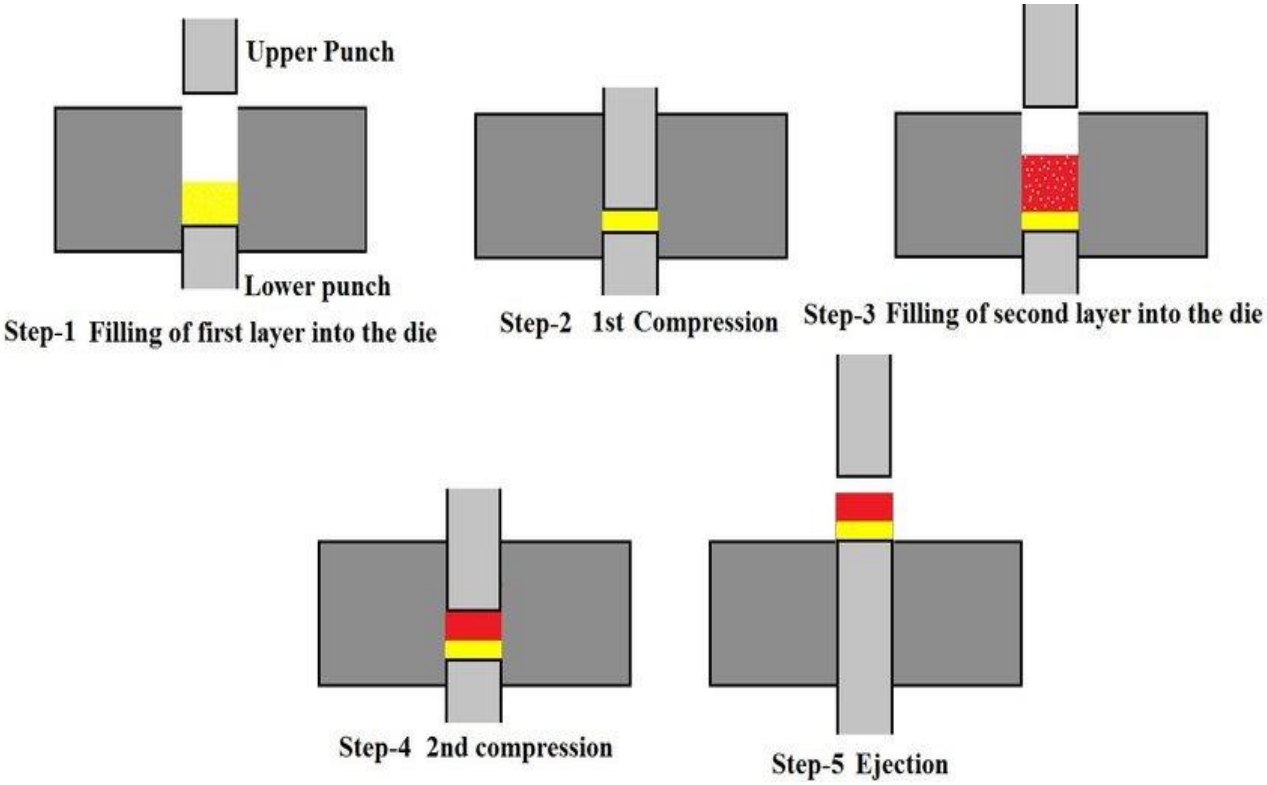


**Fig.No. 2: Steps in bilayer tablet formulation**

**Fig.No. 3: Bilayer and Trilayer tablets**

**Preformulation study**

**Melting point :**

Melting point of the Aliskiren and Empagliflozin were determined by capillary method in triplicate

**Bulk density:**

Density is defined as weight per unit volume. Bulk density is defined as the mass of the powder divided by the bulk volume and is expressed as gm/ ml. The sample of about 10 gm of powder was carefully introduced in to the 50 ml graduated cylinder.

**Tapped density:**

Tapped density was obtained by dividing the mass of powder by the tapped volume in ml. The sample of powder was carefully introduced in to the graduated cylinder. Tapped density of each formulation was then obtained by tapping for 100 tapping'manually, then dividing the weight of sample in gm by the final tapped volume in ml of the sample contained in the cylinder.

**Compressiblity Index:**

An indirect method of measuring powder flow from bulk density was developed by carr's index was calculated by below equation :

$$\% \text{ Compressibility} = \frac{\rho t - \rho 0}{\rho t} \times 100$$

**Hausner's Ratio:**

Hausner′ s Ratio is defined as a ratio of tapped density to bulk density .

**Angle of repose:**

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose $\text{Tan } \theta = h / r$

**Evaluation of bilayer tablets:**

**General appearance :** The general appearance of tablets is visual identity and overall elegance is essential for consumer acceptance for the production process.

**Size and Shape :** The shape and diamensions of compressed tablets are determined by the type of tooling during the compression process.

**Thickness and diameter[7] :** The diameter of the tablets is determined with a Verneir Caliper (or) Screw Gauage.

**Weight variation test[7] :** For weight variation test, twenty tablets are selected randomly and the average weight is calculated thereafter the weight variation is calculated and weight variation is compared with IP standard.

**Friability[7] :** Friability will be measured by taking randomly 10 tablets which is weighed and placed in a Friabulator (Roche Friabilator) and rotated at 25rpm for a period of 4 mins. After resolution, the tablets can be dusted.then calculated it.

$$\% \text{ Friability} = \frac{\text{Initial wt - Final wt.}}{\text{Initial weight}} \times 100$$

**Hardness:[7]**

The resistance of tablets to shipping or breakage under condition of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in the terms of kg/cm 2 . 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

**In Vitro Dissolution Studies**

Medium: Phosphate buffer pH 6.8

Volume: 900ml

Apparatus: Dissolution apparatus type II of USP (paddle)

Rotating Speed: 45 rpm

Temperature: 37 0 C +0.5 0 C

Preparation of Phosphate buffer pH 6.8

Dissolve 68.0g of Potassium dihydrogen Phosphate and 9.0g of sodium hydroxide in 10 liters of water. Adjust pH to 6.8 with dilute ortho Phosphoric acid or dilute Sodium Hydroxide.

**Accelerated Stability Studies:**

The optimized formulation was subjected for two month stability study according to standard guidelines. The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. They were stored at 40 0C / 75% RH for 3 months and evaluated periodically.

**Conclusion**

In the present work bi-layered tablet of Aliskiren and Empagliflozin were prepared by direct compression method and wet granulation method, using superdisintegrants such as sodium starch glycolate and croscarmellose for immediate release layer and for extended release layer polymer like HPMC K4M and HPMC K100M was used.

Best formulations of each layer were selected for bi-layered tablet and bilayered tablet were prepared. Bi-layered tablet were subjected to hardness, weight variation, friability, drug content uniformity, in vitro drug release and drug polymer interaction.

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