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Review Article

Formulation, Optimization and Evaluation of Bilayer Tablet of Antihypertensive Drug

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ABSTRACT

Hypertension or high blood pressure occurs when the high cardiac output exerts pressure on the arterial wall as the blood flow increases. Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, either as second dose or in an extended release manner. Bi-layered tablet is suitable for sequential release of two drugs in combination, separate 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 tablet is suitable for sequential release of two drugs in combination, separate 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. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs.

Keywords: Hypertension, Bi-layered tablet, Enalapril, Immediate release and Sustained release.

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1. INTRODUCTION:

Hypertension or high blood pressure occurs when the high cardiac output exerts pressure on the arterial wall as the blood flow increases. The present available conventional dosage form used in the treatment of hypertension cannot produce the desired therapeutic effect for prolonged period of time and thus dose fluctuation and missing of dose chances are more.¹

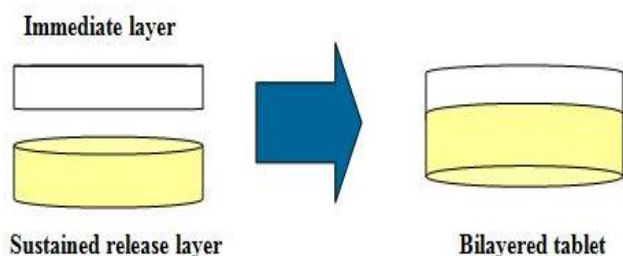


Figure 1: Bi-layered tablet

Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, either as second dose or in an extended release manner. Bi-layered tablet is suitable for sequential release of two drugs in combination, separate 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. The basic goal of therapy is to achieve a steady state drug in blood level for an extent period of time².

1.1 Advantage of Bi-layered tablets³⁻⁴

- Bi-layered execution with optional single-layer conversion kit.
- Cost is lower compared to all other oral dosage form.
- Greatest chemical and microbial stability over all oral dosage form.
- Objectionable odor and bitter taste can be masked by coating technique.
- Flexible concept.
- They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- Easy to swallowing with least tendency for hang-up.
- Suitable for large scale production.

1.2 Disadvantage of Bi-layered tablets^{5,6}

- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character,
- Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating.

- Difficult to swallow in case of children and unconscious patients.
- Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate as a tablet that will still provide adequate or full drug bioavailability.

1.3 Advantage of Bi-layered tablets over conventional tablets⁷:

- Blood level of a drug can be held at consistent therapeutic level for improved drug deliver, accuracy, safety and reduce side effects.
- Reduction of adverse effect can be accomplished by targeting the drug release to the absorption site as well as controlling the rate of release, enabling the total drug content to be reduced.
- Patient convenience is improved because fewer daily doses are required compared to traditional systems. Patient compliance is enhanced leading to improved drug regimen efficacy.
- Bi-layered tablets readily lend themselves to repeat action products; where in one layer provide initial dose, the other layer provide maintenance dose.
- Separate physically or chemically incompatible ingredients.

2. TYPES OF BI-LAYERED TABLET PRESS⁸⁻¹²

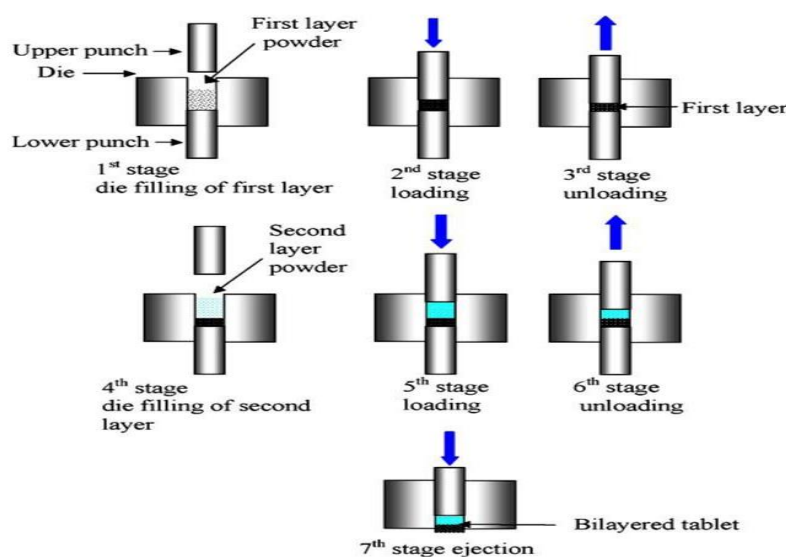


Figure 2: Stages of Bi-layered tablet manufacturing

3. ANTI-HYPERTENSIVE DRUGS WITH BRAND NAME¹³:

- Enalapril (Vasotec)
- Captopril (Capoten)
- Lisinopril (Zestril and Prinivil)
- Benazepril (Lotensin)
- Quinapril (Accupril)
- Perindopril (Aceon)
- Ramipril (Altace)
- Trandolapril (Mavik)

- Single sided tablet press.
- Double sided tablet press.
- Bi-layered tablet press with displacement monitoring.

2.1 Single sided tablet press:

The single 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 power, producing the two individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

2.2 Double sided tablet press:

In 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 of layer is measured by the control system at main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required.

2.3 Bi-layered tablet press with displacement monitoring:

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.

4. PRE-FORMULATION STUDIES:

Pre-formulation testing is the first step in rational development of dosage forms of a drug substance. Pre-formulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the excipients that could affect drug performance and development of as efficacious, stable and safe dosage form. It provides a framework for the drug combination with pharmaceutical excipients in the dosage form.

4.1 Determination of λ_{\max} ¹⁴

APIs was dissolved in solvent further diluted with the same and scanned for maximum absorbance in UV Visible spectrophotometer.

4.2 Solubility¹⁵

The solubility of APIs was determined in distilled water, methanol, ethanol, acetone, chloroform and pH 6.8 phosphate buffer by shake flask method. Absorbance is measured by UV-Visible Spectrophotometer. The drug content is calculated by using the standard graph.

4.3 Melting point¹⁵

Melting point of the APIs was determined by capillary method in triplicate.

4.4 Standard Curve for APIs¹⁵

100 mg of APIs was accurately weighted and dissolved in 100 ml of solvent to prepare first stock solution. 10 ml of above solution was taken and diluted to 100 ml with the same solvent to prepare II stock solution. The aliquot amount of II stock solution was further diluted to get 5, 10, 15, 20, 25 and 30 g of drug per ml of the final solution. Then the absorbance was measured in a UV spectrophotometer.

4.3.5 Compatibility studies¹⁵

The compatibility studies of the drug with polymers are studies using FT-IR spectroscopy.

FT-IR Spectroscopy¹⁶

FT-IR spectroscopy was carried out to check the compatibility between drug and excipients. Infrared spectroscopy was conducted using a Thermo Nicolet FTIR and the spectrum was recorded in the region of 4000 to 400 cm^{-1} . The sample (drug and drug-excipient mixture in 1:1 ratio) in KBr (200-400mg) was compressed in to discs by applying a pressure of 5 tons for 5 min in hydraulic press. The interaction between drug-excipients was observed from IR-spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drug-excipients.

DSC Analysis for formulation¹⁷

Thermal properties of the pure drug and the physical mixture of drug and excipients were analyzed by Differential Scanning Calorimeter. The samples were heated in a thermally sealed aluminium pans. Heat runs for each sample were set from 25 to 350 °C at a heating rate of 10 °C / min, using nitrogen as blanket gas.

5. PARAMETER CONSIDER DURING FORMULATION DESIGN:

5.1 Calculation of dose¹⁸

The total dose of APIs for once daily formulation was calculated by the following equation, using available pharmacological data.

$$Dt = \text{Dose} (1 + 0.693 \times t / t_{1/2})$$

Where, Dt = Total dose of drug,

Dose = Dose of immediate release part.

t = Time in hr during which the sustained release is desired

$t_{1/2}$ = Half life of the drug

5.2 Formulation of Immediate release layer¹⁹:

Table 1: Formulation of Immediate Release Layer (IRL)

| S. No. | Ingredients |
|--------|----------------------------|
| 1 | APIs |
| 2 | Lactose |
| 3 | Croscarmellose sodium |
| 4 | Sodium starch glycolate |
| 5 | Microcrystalline cellulose |
| 6 | Ponceau 4R |
| 7 | Magnesium stearate |
| 8 | Talc |
| 9 | Total |

5.3 Formulation of sustained released layer¹⁹

Table 2: Formulation of Sustained Release Layer (SRL)

| S. No. | Ingredients |
|--------|----------------------------|
| 1 | APIs |
| 2 | Lactose |
| 3 | HPMC K4M |
| 4 | HPMC K100M |
| 5 | Microcrystalline cellulose |
| 6 | Magnesium stearate |
| 7 | Talc |
| 8 | Total |

5.4 Preparation of IRL²⁰:

IRL of APIs was prepared by wet granulation by using different Superdisintegrants such as SSG and Croscarmellose sodium. PVP K30 solution with containing coloring agent was used as binding solution. As DS was oily in characteristics, MCC was used as adsorbent. Manufacturing steps-Pass all the ingredients through sieve #80. Mix APIs with MCC geometrically and then mix with lactose. Add Superdisintegrants and mix for 10 to 15 min in mortar and pestle. Make wet mass using binding agent PVP K 30 solution containing color. Pass the cohesive mass through sieve # 16 to get uniform granules. Dry the granules at 50°C for 15 min in hot air oven. Lubricate the granules with lubricating agent and compressed into 250 mg each tablet weight by adjusting hardness.

5.5 Preparation of SRL²⁰:

Accurately weighed APIs and polymer and others ingredients were taken in mortar and pestle and mixed well. The powder were mixed with sufficient quantity for PVP K30 solution until wet mass formed. The cohesive mass obtained was passed through sieve # 16 and the granules were dried in a hot air oven at 50°C for 20 min. The dried granules again passed through sieve # 22 to break the large lumps. Then granules were mixed with talc and magnesium stearate and compressed into 300 mg each tablet by adjusting hardness.

5.6 Preparation of bi-layered tablet^{20,21}:

By the study of disintegration and drug release profile of IRL and SRL, best formulations of each layer were chosen and bi-layered tablet were prepared by double compression in single rotatory tableting machine.

6. EVALUATION OF PRE-FORMULATION PARAMETERS:

6.1 Angle of Repose²²

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using equation.

$$\tan\theta = \frac{h}{r}$$

Where, θ = the angle of repose, h = height of the heap of the powder, r = radius of the heap of the powder

Table 3: Angle of Repose

| S. No | Angle of Repose (θ) | Type of flow |
|-------|------------------------------|--------------|
| 1 | < 25 | Excellent |
| 2 | 25-30 | Good |
| 3 | 30-40 | Passable |
| 4 | > 40 | Very poor |

6.2 Determination of bulk density and tapped density²³

A quantity of 2 g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using following formulas. LBD and TDB were calculated using the following equations.

$$BD = \frac{\text{Weight of the powder blend}}{\text{Untapped Volume of the packing}}$$

$$TDB = \frac{\text{Weight of the powder blend}}{\text{Tapped Volume of the packing}}$$

6.3 Carr's Index / Compressibility Index²⁴

It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by;

$$\text{Carr's Index (\%)} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

6.4 Hausner's Ratio²⁵

Hausner's ratio is an indirect index of ease of powder flow. Hausner's ratio was measured by the ratio of tapped density to bulk density.

$$H = \frac{\rho T}{\rho B}$$

Where ρT = tapped density, ρB = bulk density

Table 4: Scale of flowability

| Flow Character | Compressibility Index (%) | Hausner's Ratio |
|----------------|---------------------------|-----------------|
| Excellent | < 10 | 1.00 - 1.11 |
| Good | 11 - 15 | 1.12 - 1.18 |
| Fair | 16 - 20 | 1.19 - 1.25 |
| Passable | 21 - 25 | 1.26 - 1.34 |
| Poor | 26 - 31 | 1.35 - 1.45 |
| Very poor | 32 - 37 | 1.46 - 1.59 |
| Extremely poor | > 38 | > 1.60 |

7. EVALUATION OF PREPARED FORMULATIONS:

7.1 Evaluation of APIS, IRL, SRL and Bi-Layered tablet²⁶⁻²⁹:

The tablets prepared were evaluated for the following parameters:

- Weight variation
- Hardness
- Friability
- Drug content
- In-vitro Dissolution Studies

7.1.1 Weight Variation Test:

To study weight variation, 20 tablets of each formulation were weighed using electronic balance and the test was performed according to the official method.

Table 5: Scale of flowability

| S. No. | Average Weight of Tablet (mg) | % of Deviation |
|--------|-------------------------------|----------------|
| 1 | < 80 | 10 |
| 2 | < 80 - 250 | 7.5 |
| 3 | ≥ 250 | 5 |

7.1.2 Hardness:

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/cm². 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

7.1.3 Friability:

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. 10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded. Percentage friability was calculated by using the formula.

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Weight Initial}} \times 100$$

7.1.4 Tablet thickness:

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation. Vernier caliper consists of metric and imperial scales. The main metric scale is read first then read "hundredths of mm" of imperial scale (count the number of division until the lines concedes with the main metric scale. The imperial scale number is multiply with 0.02. Then that number obtained from imperial scale added with main metric scale to get final measurement.

7.1.5 In Vitro dissolution studies:

The release rate of tablet (n=3) was determined using *The United States Pharmacopoeia* (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was

performed using 900 ml of 0.1 N HCl, at $37 \pm 0.5^\circ\text{C}$ and 75 rpm.

8. CONCLUSION:

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered Matrices. Bilayer tablet is suitable for sequential release of two drugs in combination, separate 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. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers. Bilayer tablet quality and GMP-requirements can vary widely.

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