

# Development and Evaluation of Bilayer Tablets of Losartan Potassium

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**Abstract:** The aim of present study is to prepare bilayer tablets of Losartan Potassium with an immediate release and a controlled release layer. The immediate layer was prepared using super disintegrant sodium starch glycolate and controlled release layer is formulated with polymer guar-gum and HPMC K15M, individually in different concentrations and in combinations. The values of pre-compression parameters evaluated were within prescribed limits. (Angle of repose 17.66-26.10, Carr's index 18.05-20.17 % and hausners ratio of 1.19-1.29 indicated good flow property). Post compression parameters such as hardness were found to be 5.46 to 7.21 kg/cm<sup>2</sup> sufficient enough to withstand the mechanical stress condition while handling. In all the formulations, the friability value is less 1% and meets the Indian Pharmacopoeial limits. The percentage drug content of all the tablets was found to be almost are nearer to 100%, swelling index of matrix tablets were directly proportional to the concentration of the polymer. Formulation (F5) containing combination of guar-gum and HPMC K15M showed better swelling index than that of other formulation. In vitro drug release from the controlled release layer increased with an increase in the polymer concentration because of increase in the thickness of the layer, which retarded drug diffusion out of tablets. Formulation (F5) containing combination of guar-gum and HPMC k15M in equal proportions showed the drug release up to 24hrs. Kinetic release studies of optimized formulation F5 showed zero order release.

**Keywords:** immediate release, controlled release, polymers, bilayer tablet

## 1. Introduction

The oral route of drug delivery is considered as the preferred and most patient convenient means of drug administration. Consequently, much effort is directed during drug discovery to identify orally active candidates that will provide reproducible and effective plasma concentration in vivo. The oral route of drug administration is the most important method of administering drugs for systemic effects. At least 90% of all the drugs used to produce systemic effects is administered by the oral route. Of drugs that are administered orally, solid oral dosage forms preferred class of product. Tablets represent unit dosage forms in which one usual dose of the drug has been accurately placed. Layer tablets are composed of two or three layers of granulation compressed together. They have the look of a sandwich because the edges of each layer are uncovered. This dosage form has the benefit of separating two incompatible substances with an inert barrier between them. Two layer tablets need fewer materials than compression coated tablets. Monograms and other distinguishing markings may be intimidated in the surfaces of the multilayer tablets. Coloring the divide layers provides various possibilities for unique tablet identity. Analytical work may be simplified by a separation of the layers prior to assay.

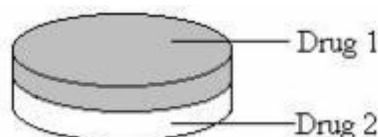


Figure 1: Bilayer tablet

The multilayered tablet concept has long been utilized to develop sustained release formulations. Multilayered tablet has a fast releasing layer and may contain two or three layers to sustain the drug release. A fast releasing granules lead to sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug release

from the sustaining granules. Bilayer tablet consists of two layers of tablet in a single unit. This approach can be used for the treatment of various diseases which require not only single drug but also combination of drugs. Bilayer tablet consists of two layers first fast release layer consists of super disintegrant which releases its drug within first one hour and sustain release layer maintains its therapeutic level up to 12 hours by releasing constant amount of drug slowly shown in Figure no. 2.

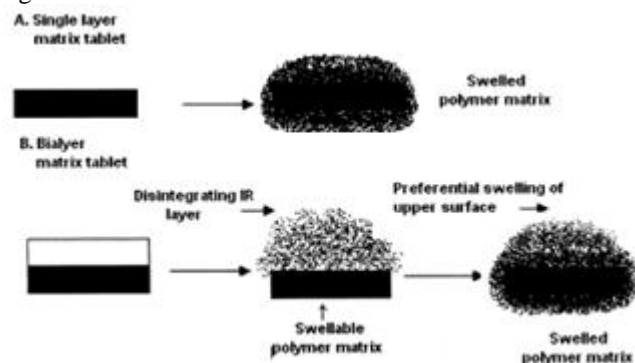


Figure 2: Bimodal drug release

The concept of Bilayer tablet technology is utilized to develop sustained release and immediate formulation for a single drug or combination of drugs. Bilayer tablets are preferred in some cases because they maintain uniform drug levels, reduce dose, side effects, increase the safety margin for high-potency drugs and thus offer better patient compliance. Losartan potassium is an anti-hypertensive drug which acts by controlling antagonizing effect on the angiotensin II receptors. The aim of this investigation is to formulate and evaluate the sustained release bilayer tablets of Losartan Potassium using different synthetic and natural polymers. Losartan potassium possesses a short biological half-life (1.5-2 hrs), which demands frequent administration usually thrice a day leading to patient non-compliance exposing him to risk of side effects. In order to overcome this, Losartan potassium sustained release dosage forms are

Volume 9 Issue 4, April 2020

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formulated as bilayered tablet which comprises of two layers among which the first layer is immediate release layer and the second layer is sustained release layer. The immediate release portion ensures quicker onset of action by eliciting MEC in less time while the same levels offering once a day convenient dosing. The current research is to formulate and evaluate an ideal bilayer matrix tablet of sustained release profile by using suitable methods by using different polymers. (2)

### Advantages of Bilayer tablets

- 1) Bilayer tablet in FDCs: Fixed dose combination with two or more ingredients to be formulated together in spite of actives having different physico-chemical characteristics and active-active incompatibility.
- 2) Bilayer tablet can be manufactured in such a way that one layer provides sustained release and second later provides immediate release of the medicament. This approach is beneficial for providing initial loading dose and then maintenance dose within therapeutic window so it avoids frequent dosing of the drug.
- 3) Bilayer tablet can be formulated as buoyant dosage form (floating bilayer tablet) which is helpful to increase residence time in the stomach and also to enhance the therapeutic effect.

Hypertension or high blood pressure is a chronic medical condition in which the systemic arterial blood pressure is elevated. It is the opposite of hypotension. It is classified as either primary (essential) or secondary. About 90–95% of cases are termed "primary hypertension", which refers to high blood pressure for which no medical cause can be found. The remaining 5–10% of cases (Secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart, or endocrine system.

Losartan is an angiotensin-receptor blocker (ARB) that may be used alone or with other agents to treat hypertension. Losartan and its longer acting metabolite, E-3174, lower blood pressure by antagonizing the renin-angiotensin-aldosterone system (RAAS); they compete with angiotensin II for binding to the type-1 angiotensin II receptor (AT1) subtype and prevents the blood pressure increasing effects of angiotensin II. Losartan competitively inhibits the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. Losartan is metabolized to its active metabolite, E-3174, which is 10 to 40 times more potent than losartan and acts as a noncompetitive AT1 antagonist. Inhibition of angiotensin II binding to AT1 inhibits its AT1-mediated vasoconstrictive and aldosterone-secreting effects and results in decreased vascular resistance and blood pressure. Losartan is 1,000 times more selective for AT1 than AT2. Inhibition of aldosterone secretion may increase sodium and water excretion while decreasing potassium excretion. Losartan is effective for reducing blood pressure and may be used to treat essential hypertension, left ventricular hypertrophy and diabetic nephropathy. The systemic bioavailability of losartan is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3–4 hours, respectively. 99.7% protein bound, primarily to albumin. Following oral administration of losartan, 35% of

the dose is recovered in the urine and about 60% in the feces. Following an intravenous dose, 45% is recovered in the urine and 50% in the feces.

## 2. Materials and Methods

Losartan potassium was obtained from Vijashree chemicals. Pvt. Ltd. Hyderabad. The excipients such as microcrystalline cellulose, Sodium starch glycolate, guar gum, HPMC, magnesium stearate, Talc of analytical grade were obtained from S.D. fine chemicals. India.

## 3. Formulation of Bilayered Tablets

Bilayered tablets were prepared by direct compression technique. All the ingredients of immediate and controlled release layer are passed through standard sieve 40#. Controlled release layer containing xanthum gum, gum karaya and HPMC k4M in different concentrations and combinations was compressed into tablets using 11mm flat round punch set. On this tablet the immediate release layer is compressed.

**Table 1:** Composition of bilayer matrix tablets of Losartan Potassium

Ingredients for immediate Release Layer						
S.No.	Formulation Code	F1	F2	F3	F4	F5
1	Losartan	10	10	10	10	10
2	SSG	3	3	3	3	3
3	MCC	36.5	36.5	36.5	36.5	36.5
4	Mg. Stearate	0.5	0.5	0.5	0.5	0.5
Ingredients for Controlled Release Layer						
S.No.	Formulation Code	F1	F2	F3	F4	F5
5	Guar-gum	160	160			90
6	HPMC K15M			160	180	90
7	MCC	142	122	142	122	122
8	PVP	20	20	20	20	20
9	Talc	4	4	4	4	4
10	Mg. Stearate	4	4	4	4	4

## 4. Pre-compressional Evaluation

### 4.1 Bulk density

It is the ratio total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) in to a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume.

$$\text{Bulk density BD} = (M/V) \text{ g/cc}$$

### 4.2 Tapped density

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume.

$$\text{Tapped density Td} = \text{Mass/Tapped volume}$$

### 4.3 Hausner's ratio

Hausner's ratio is an index of ease of powder flow: it is calculated by following formula.

$$\text{Hausner's ratio} = \text{Tapped density/Bulk density}$$

#### 4.4 Carr's Index

Tapped and bulk density measurements can be used to estimate the Carr's index of a material. Carr's index was determined by  $C.I. (\%) = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$

#### 4.5 Angle of repose

It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$$\Theta = \tan^{-1} (h/r)$$

### 5. Evaluation of bilayered tablets

#### 5.1 Weight Variation

20 tablets were selected randomly from the lot and weighed individually to check for weight variation. The individual weighed is then compared with average weight for the weight variations.

#### 5.2 Hardness

The strength of tablet is expressed as tensile strength (kg/cm<sup>2</sup>). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester). Three tablets from each formulation batch were tested randomly and the average reading were noted.

#### 5.3 Friability

Friability of the tablets was determined using Roche Friabilator. This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 min dropping the tablets at a distance of 6 inches with each revolution. Pre-weighed sample of 20 tablets was placed in the friabilator and reweighed. The friability (F %) is given by the following formula

$$F (\%) = (1 - W_0 / W) \times 100$$

Where,  $W_0$  is weight of the tablets before the test  $W$  is the weight of the tablets after test.

#### 5.4 Swelling studies

One tablet from each formulation was weighed and kept in Petri dish containing 20 ml of phosphate buffer of pH 6.8. At the end of specified time intervals tablets were withdrawn from Petri dish and excess buffer blotted with tissue paper and weighed. The % weight gain by the tablet was calculated by following formula.

$$R = \frac{w_a - w_b}{w_b} \times 100$$

where,  $w_a$  = weight of tablet after absorption  
 $w_b$  = weight of tablet before absorption.

#### 5.5 In-Vitro disintegration time

The disintegration time was measured using a paddle method originally proposed by Sunadaetal. The vessel filled with 500ml of 6.8 PH buffer at 37°C. The paddle was rotated at 100rpm.

The tablet was placed inside the sinks and the time at which it passes completely through the mesh of sinker was taken as the disintegration of the tablets.

### 6. Results and Discussions

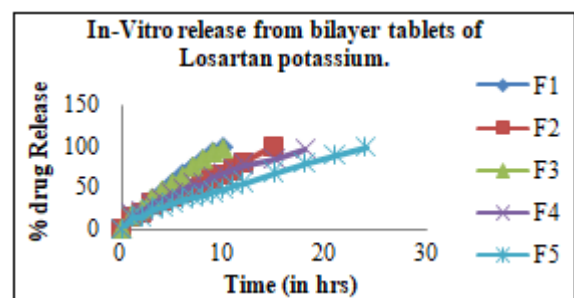
In the present study, five formulations of bilayered tablets of Losartan Potassium were prepared, in them ingredients of the immediate layer were kept constant and the controlled release layer ingredients like guar-gum, HPMC K15M were used in different concentrations and in combinations.

**Table 2:** Preformulation parameters of precompressional blend

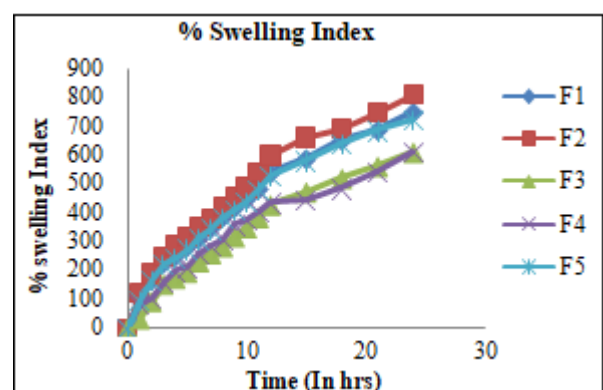
Formulation Code	Angle of repose( $\theta$ )	Carr's index(%)	Hausner's ratio
F1	41.22 $\pm$ 0.16	31.19 $\pm$ 0.14	1.45 $\pm$ 0.07
F2	17.66 $\pm$ 0.32	18.25 $\pm$ 0.09	1.22 $\pm$ 0.02
F3	18.41 $\pm$ 0.15	19.37 $\pm$ 0.02	1.24 $\pm$ 0.01
F4	19.33 $\pm$ 0.87	18.05 $\pm$ 0.14	1.22 $\pm$ 0.02
F5	26.10 $\pm$ 0.94	19.72 $\pm$ 0.18	1.24 $\pm$ 0.01

**Table 3:** Post compressional parameters of bilayeral tablets. All values are expressed as mean of three readings.

Formulation Code	Hardness (kg/cm <sup>2</sup> )	Friability (%)	Thickness (mm)	Drug content (%)	Weight Variation
F1	5.46	0.31	4.47	98.21	2.33
F2	5.48	0.28	4.52	98.01	1.72
F3	5.71	0.22	4.47	98.45	1.38
F4	5.64	0.34	4.44	98.32	1.22
F5	7.2	0.21	4.52	99.91	1.53



**Figure 3:** In-Vitro release from bilayer tablets of Losartan potassium



**Figure 4:** % Swelling Studies of bilayer tablets

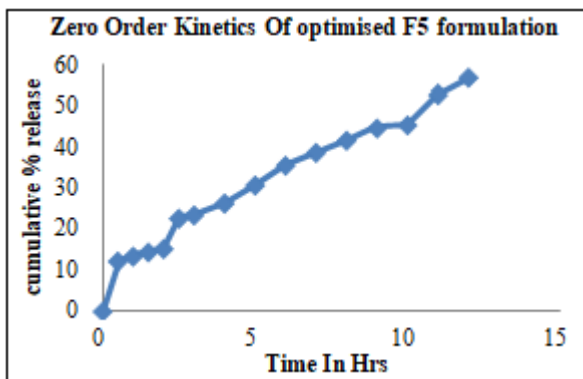


Figure 5: Release Kinetics

## 7. Conclusion

The pre-formulation studies of formulation showed good flow properties and feasibility for direct compression. The compressed bilayered tablets were evaluated for hardness, friability, weight variation, drug content uniformity and in vitro drug release. Formulation contained combination of guar gum & HPMC K15M was optimized which showed prolonged release of Losartan Potassium for about 24hr.

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