World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Research Article
ISSN: 2583-6579
SJIF Impact Factor: 5.111
Year - 2024
Volume: 3; Issue: 5
Page: 440-453

FORMULATION AND EVALUATION OF BILAYER TABLET OF ANTIHYPERTENSIVE DRUG

Madhu Rajak*[1], A. Amal Raj[2], Rajendra Singh Dhakad[3] and Hakim Singh Rajput[4]

[1,2,3]Shri Ramnath Singh Institute of Pharmaceutical Science & Technology, Sitholi, Gwalior 474005, Madhya Pradesh India.

[4]Oriental University Indore 453555, Madhya Pradesh India.

Article Received: 19 August 2024 | | ***Article Revised: 08 October 2024*** | | ***Article Accepted: 30 October 2024***

***Corresponding Author: Madhu Rajak**
Shri Ramnath Singh Institute of Pharmaceutical Science & Technology, Sitholi, Gwalior 474005, Madhya Pradesh India.
DOI: https://doi.org/10.5281/zenodo.14050790

How to cite this Article: Madhu Rajak, A. Amal Raj, Rajendra Singh Dhakad and Hakim Singh Rajput. (2024). FORMULATION AND EVALUATION OF BILAYER TABLET OF ANTIHYPERTENSIVE DRUG. World Journal of Pharmaceutical Science and Research, 3(5), 440-453. https://doi.org/10.5281/zenodo.14050790

ABSTRACT

The aim of present study is to prepare bilayer tablets of Losartan Potassium with an immediate release and a sustained release layer. The immediate release layer was prepared using super disintegrant sodium starch glycolate and sustained release layer is formulated with different polymers. The bilayer tablets of losartan potassium were prepared by the direct compression method. The drug, polymers and other excipients used for both immediate (IR) and sustained release (SR) layers were passed through sieve #80 before their use in the formulation. The immediate dose of drug was calculated from total dose of losartan potassium extended release tablet, which is 50 mg. Losartan potassium can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg. *in vitro* dissolution was carried out using USP Dissolution testing apparatus type-II (Paddle method; Veego Scientific VDA-8DR, Mumbai, India). Different batches of tablets were prepared varying the different sustaining components that were considered to have significant effect on drug release. These bilayer tablets as well as the powder blends were subjected to various *in-process* quality control tests for evaluation of their different physical parameters. The release of losartan potassium from fast releasing layer was analyzed by plotting the cumulative percentage of drug release Vs time. It shows an effective initial burst effect from IR layer and released from this layer was completed within 10 minutes. Bi-layer tablet is improved beneficial technology to overcome the limitation of the single layered tablet.

KEYWORDS: Bilayer tablets, Drugs, Losartan potassium, sodium starch glycolate.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs. The goal of any drug delivery system is to provide a therapeutic amount of the drug at the site an effective throughout the entire duration of therapy and then maintain the desired drug concentration.[1] Conventional dosage form produces wide range of fluctuation in drug concentration in the blood stream and tissues which leads to reduction or loss in drug effectiveness or increased incidence of side effects with subsequent undesirable toxicity and poor efficiency. However, sustained or controlled drug delivery systems can decrease the frequency of the dosing and also increases effectiveness of the drug by localization at the site of action, reducing the dose required and providing uniform drug delivery.[2]

Different approaches have been proposed to formulate sustained release tablets for retaining dosage form in stomach. These include bioadhesive or mucoadhesive systems[3], swelling and expanding systems[4,5] floating systems[6,7] and other delayed gastric emptying devices.

Mucoadhesive bilayer tablet is new concept for successful development of sustained release formulation along with various features to provide a way of successful drug delivery system that include an immediate release (IR) layer and an Sustained release (SR) layer. Immediate release layer provide therapeutically effective plasma drug concentration for a short period of time and Sustained release (SR) layer maintain uniform drug levels over a sustained period to reduce dosing intervals and side effects, increase the safety margin for highly-potent drugs and thus offer better patient compliance. It also includes bimodal drug delivery profile (fast release / slow release / fast release).[8] This type of system is used primarily when maximum relief needs to be achieved quickly and it is followed by a sustained release phase to avoid repeated administration. Suitable candidate drugs for this type of administration include nonsteroidal anti-inflammatory drugs (NSAIDs) and antihypertensive, antihistaminic, and antiallergic agents, antipsychotics, hypnotics.[9]

In many therapies, extended-release preparations are considered desirable but for many drugs, significant daily variations in pharmacokinetics and/or drug effects have been demonstrated on human beings. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and absorption varies along the gastrointestinal (GI) tract.[10]

A constant plasma concentration may not be obtainable even though a dosage form with a zero order *In-vitro* release is administered. It is conceivable that a delivery system that can provide a release profile with an initial burst of release followed by a relatively steady release or an accelerated release at a late stage may offer a better solution. Such a release profile, namely pseudo zero-order release with initial burst or bimodal release may compensate for the lower absorption rate in the stomach and the large intestine.[11,12]

On the basis of these considerations, a new oral delivery device was proposed, in the form of a double-component tablet, one portion is formulated to obtain a prompt release of the drug with the aim of reaching a high serum concentration in a short period of time. The second portion is a prolonged-release layer which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing component leads to a sudden rise in the blood concentration.

However, the blood level is maintained at steady state as the drug is released from the sustaining layer.

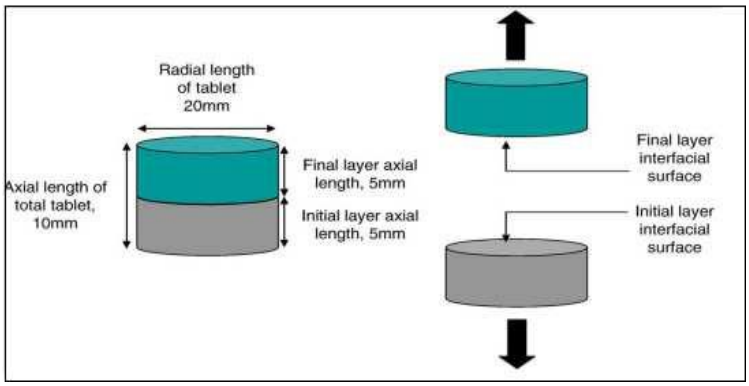

Fig 1: Diagram showing the definitions of the axial lengths, radial length and interfacial fracture surfaces.

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. Bilayer tablets have been developed to achieve controlled delivery of different drugs with predefined release profiles. In the last decade interest in developing a combination of two or more API's in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance. Several pharmaceutical companies are presently developing bi-layer tablets, for a variety of reasons patent extension, therapeutic, marketing to name a few. To decrease capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. This article explains about different techniques of bi-layer tablet and why development and production of quality bi-layer tablets need to be carried out on purpose built tablet presses to conquer common bilayer problems, such as layer separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, reduced yield etc. There are various applications of the bi-layer tablet consists of monolithic partially coated or multilayered matrices.

The primary target of any drug delivery is to provide therapeutically active agent at a proper site with maximum efficacy and minimum side effects. To achieve it, drug delivery is designed in such that it should deliver drug at predicted rate required by the body over the specified period. The basic objective of designing dosage has to control the release of drug in the face of uncertain fluctuation in the in vivo environment in which drug release take place.

MATERIALS AND METHODS

Table 1: Chemicals to be used.

Name	Manufacturer/supplier
Losartan potassium	Macleods pharmaceuticals Ltd., Mumbai
Carbopol 971	Macleods pharmaceuticals Ltd., Mumbai
Hydroxypropyl methyl cellulose	Macleods pharmaceuticals Ltd., Mumbai
Dibasic calcium phosphate	Macleods pharmaceuticals Ltd., Mumbai
Sodium starch glycolate	Macleods pharmaceuticals Ltd., Mumbai
Polyvinyl pyrollidone	Macleods pharmaceuticals Ltd., Mumbai
Talc	S.D Fines Chemicals Ltd., Mumbai
Magnesium stearate	S.D Fine Chemicals Ltd., Mumbai
Hydrochloric acid	S.D Fine Chemicals Ltd., Mumbai
Sodium hydroxide	S.D Fine Chemicals Ltd., Mumbai
Potassium dihydrogen orthophosphate	S.D Fine Chemicals Ltd., Mumbai

Table 2: Equipments to be used.

Name of equipment	Manufacturer
Tablet punching machine	Spinex Pvt. Ltd.
Digital weighing balance	Dolphin, Mumbai
Dissolution test apparatus	Veego instruments corporation, Mumbai
Disintegrator	Dolphin, Mumbai
Friability tester	Dolphin, Mumbai
Hardness tester	Rolex
pH –meter	Elico Ltd.
UV Spectrophotometer	Shimadzu

DRUG PROFILE

DRUG NAME

Losartan potassium

IUPAC NAME

2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl-phenyl) benzyl]-imidazole-5-methanol monopotassium salt.

CHEMICAL FORMULA

C22H22ClKN6O

MOLECULAR WEIGHT

461.01g/mol

MELTING POINT

184°C

CATEGORY

Angiotensin II receptor (type AT1) antagonist

HALF LIFE

The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours.

BIOAVAILABILITY

Losartan's bioavailability is about 32%.Following oral administration, 6% of losartan is excreted unchanged in the urine.

PROTEIN BINDING

99.7 % (primarily albumin)

SOLUBILITY

It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

APPEARANCE

White to off-white free-flowing crystalline powder.

DOSE

Losartan potassium can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

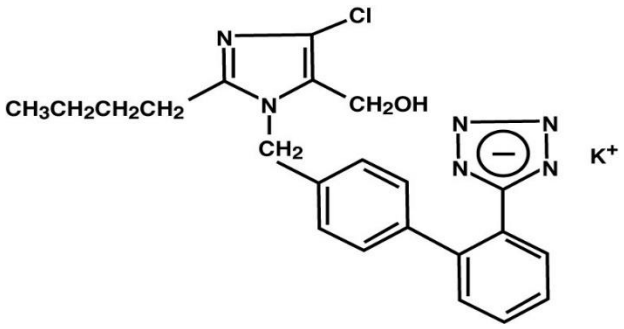

Fig-2.

PHARMACOKINETICS

Losartan is well absorbed following oral administration and undergoes significant first-pass metabolism to produce 5-carboxylic acid metabolite, designated as EXP3174. This metabolite is a long-acting (6 to 8 hr), noncompetitive antagonist at the AT1 receptor, and contributes to the pharmacological effect of losartan. EXP3174 is 10-40 times more potent in blocking AT1 receptors than losartan. Losartan's bioavailability is about 32% [13]. Metabolism is primarily by cytochrome P450 isoenzymes CYP2C9 and CYP3A4. Peak plasma concentrations of losartan and E-3174 occur about one hour and three to four hours, respectively, after an oral dose. Both losartan and E-3174 are more than 98% bound to plasma proteins. Losartan is excreted in the urine, and in the feces via bile, as unchanged drug and metabolites. About 4% of an oral dose is excreted unchanged in urine, and about 6% is excreted in urine as the active metabolite. The terminal elimination half-lives of losartan and E-3174 are about 1.5 to 2.5 hours and 3 to 9 hours, respectively.

MECHANISM OF ACTION

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)] is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT1 receptor and have much greater affinity (about 1000-fold) for the AT1 receptor than for the AT2 receptor. In vitro binding studies indicate that losartan is a reversible, competitive inhibitor of the AT1 receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT1 receptor. Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

PARTITION COEFFICIENT

Between time that a drug is administered and the time is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid like barriers.

A major criteria in evaluation of the ability of a drug to penetrate these lipid membranes is its apparent oil / water partition coefficient defined as:

$$K = C0/CW$$

Where,

Co = Equilibrium concentration of all forms of the drug e.g. ionized and unionized in an organic phase at equilibrium.

Cw = Equilibrium concentration of all forms in aqueous phase.

In general, drugs with extremely large values of 'K' are very oil soluble and will partition into membrane quite readily. According to Haunch correlation, the logarithm of the activity of a drug or its ability to be absorbed and the logarithm of its partition coefficient having parabolic relationship. The explanation for this relationship is that the activity of a drug is a function of its ability to cross membranes and interact with the receptor. The more effectively a drug crosses membranes, the greater its activity. The optimum partition coefficient value of a drug in which it most effectively permeates membranes and thus shows the greatest activity.

The value of K at which optimum activity is observed is approximately 1000/1. Drugs with a partition coefficient that is higher or lower than the optimum is, in general, poorer candidates for formulation into controlled-release dosage forms.

BULK DENSITY (Db)[14]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in gm/ml and is given by

$$Db = M/ Vb$$

Where, M and Vb are mass of powder and bulk volume of the powder respectively.

TAPPED DENSITY (Dt) [15]

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 was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in gm/ml and is given by

$$Dt = M / Vt$$

Where, M and Vt are mass of powder and tapped volume of the powder respectively.

HAUSNER'S RATIO

Hausner's Ratio[16, 17] is an ease of index of powder flow. It is calculated by using the following formula:

Hausner's Ratio = Tapped Density/ Bulk Density

COMPRESSIBILITY INDEX

The compressibility index of the power was determined by Carr's compressibility index:

Carr's index (%) = {(Dt – Db) X 100}/Dt

Table 3: Carr's Index values.

Carr's Index	Type of flow
5-15	Excellent
15-18	Good
18-23	Fair to passable
23-35	Poor
35-38	Very poor

ANGLE OF REPOSE

Funnel method was used to measure the angle of repose of powder. The accurately weighed powders 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 powder (2.0 cm above hard surface). The powders 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 the following equation:

Angle of Repose **θ = tan-1 H/R**

Where, H = Height of the powder cone,

R = Radius of the powder cone

Table 4: Angle of Repose values.

Angle of repose	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

PREPARATION OF BILAYER TABLET

The bilayer tablets of losartan potassium were prepared by the direct compression method. The drug, polymers and other excipients used for both immediate (IR) and sustained release (SR) layers were passed through sieve # 80 before their use in the formulation.

DOSE CALCULATION[18]

For sustained drug release up to 30 hours, the immediate dose of drug was calculated from total dose of losartan potassium extended release tablet, which is 50 mg. According pharmacokinetic data[41]

Dt = Dose (1 + 0.693 × t/t1/2)

Where, Dt = Total dose, Dose = Immediate release dose, t = Total time period for which sustained release is required, t1/2 = Half-life of drug. Half-life of losartan potassium ranges from 1.5 to 2.5 hr.

For example,

i. Losartan potassium: 50 = Dose [1+ (0.693 ×30)/1.5)], Dose = 3.36 mg propranolol hydrochloride.

ii. Losartan potassium: 50 = Dose [1+ (0.693 ×30)/2.5)], Dose = 5.37 mg propranolol hydrochloride.

According to dose calculation, IR dose of drug can be taken in between range of 3.36 mg to 5.37 mg for the preparation of bilayer tablets; thus 5 mg of Losartan potassium was taken in IR layer and 45 mg of Losartan potassium was taken in SR layers.

FORMULATION OF IR LAYER

The IR ingredients were accurately weighed and added into the blender in ascending order. The powder mixture was blended for 20 minutes to obtain uniform distribution of the drug in formulation. The blend was mixed with talc and magnesium stearate for 2 minutes and kept in a desiccators until further used.

FORMULATION OF SR LAYER

The SR ingredients were accurately weighed and added into the blender in ascending order. The powder mixture was blended for 20 minutes to obtain uniform distribution of the drug in formulation and subjected for pre-formulation studies.

COMPRESSION OF BILAYER TABLET

In the present study bilayer tablet was prepared manually using single station punching machine (Rimek mini press-1 Karnavati Engineering Ltd, Mehsana, Gujarat).Accurately weighed amount of SR powder mixture was fed manually into die cavity. SR layer was compressed at mild compression force (2-3 kg/cm2). After that accurately weighed IR powder mixture was manually fed into the die on SR layer and compressed using 9-mm circular punches (Rimek mini press-1 Karnavati Engineering Ltd, Mehsana, Gujarat). Both the layers were identified on the basis of color since the immediate release layer had pink color and the sustained release layer has white color.

DETERMINATION OF λMAX AND DEVELOPMENT OF CALIBRATION CURVE OF LOARTAN POTASSIUM

Maximum absorbance (**λmax**) of losartan potassium were measured at pH 1.2 (hydrochloric acid buffer) and pH 6.8 (phosphate buffer) using UV/Vis spectrophotometer (JASCO V-550).

Calibration curves were prepared using concentration ranges of 1–25 mcg/ml for pH 1.2 and 1-30 mcg/ ml for pH 6.8.

***IN-VITRO* DISSOLUTION STUDIES[19,20]**

The *in vitro* dissolution was carried out using USP Dissolution testing apparatus type-II (Paddle method; Veego Scientific VDA-8DR, Mumbai, India). The tablets were placed in the 0.1N hydrochloric acid for first 2 hours and pH 6.8 phosphate buffers for next 28 hours respectively, then the apparatus was run at 37°C±0.5°C and a rotating speed of 50 rpm in a 900 ml dissolution medium. The 5 ml aliquots were withdrawn at intervals of 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 1 hour, 2 hours,3 hours,4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours,11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours,21 hours, 22 hours, 23 hours, 24 hours, 25 hours, 26 hours, 27 hours, 28 hours, 29 hours, 30 hours and replacement was done each time with equal amounts of fresh dissolution medium maintained at same temperature. Each 5 ml aliquot was filtered through Whatmann filter paper (No.41). 1 ml of sample was diluted to 9 ml 0.1N HCL for first 2 hours and then with pH 6.8 phosphate buffers for next 28 hours and absorbance was measured at 206 nm using UV spectrophotometer (JASCO V-550). Drug concentrations in the sample were determined from standard calibration curve.

Details of Dissolution test

- ✓ Apparatus : USP type II
- ✓ Volume of medium : 900 ml
- ✓ Temperature : 37± 0.5^{0}C
- ✓ Paddle speed : 50 rpm
- ✓ Dissolution mediun used : 0.1 N HCL
- ✓ Aliquot taken at each time interval : 5 ml

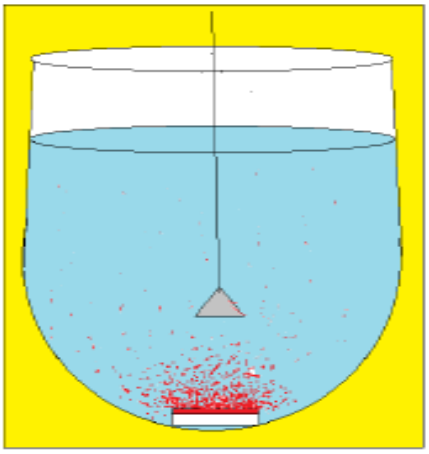

Fig 3: *In-Vitro* dissolution study.

RESULT DISCUSSION

DETERMINATION OF λ MAX OF LOSARTAN POTASSIUM

Figure 1 and Figure 2 exhibits the UV Spectrum of losartan potassium scanned according to the procedure. The absorbance spectra are characterized by maxima at 206 nm in both acidic and phosphate buffer (pH 1.2 and pH 6.8 medium).

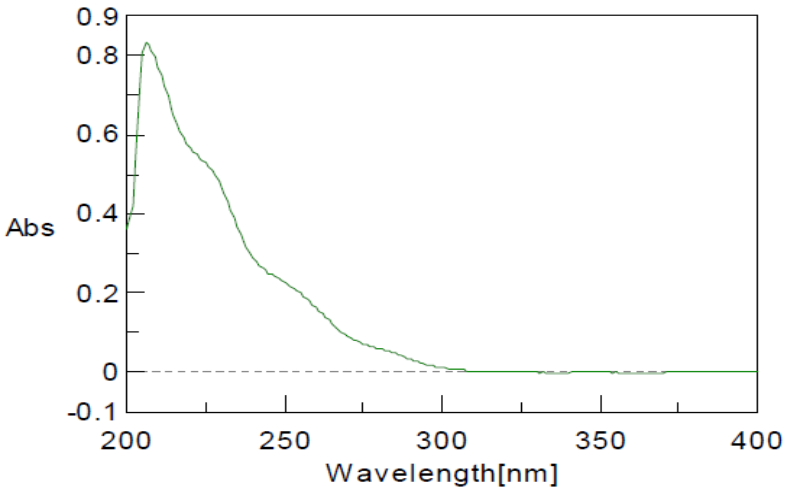

Fig 4: λ max of losartan potassium in acidic pH 1.2

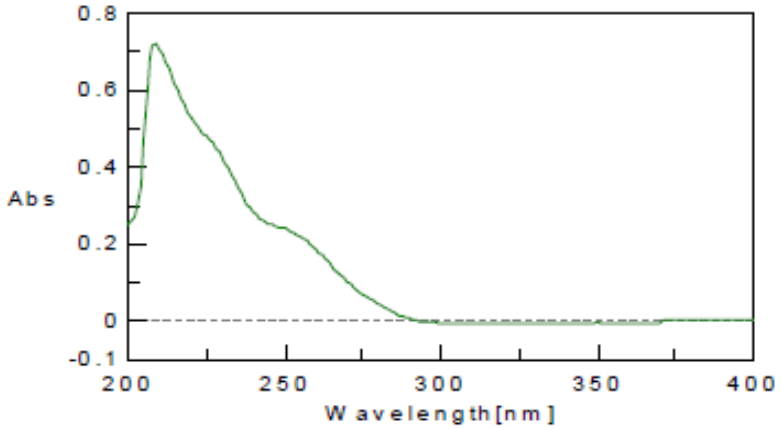

Fig 5: λ max of losartan potassium in phosphate buffer pH 6.8.

PREPARATION OF CALIBRATION CURVE FOR LOSARTAN POTASSIUM

Figure 3 and Figure 4 shows the calibration curves of losartan potassium, which was obtained when concentration in mcg/ml (**Table 5 - 7**) was plotted against absorbance. It gave straight line that passes through the origin in both pH 1.2 and pH 6.8 mediums. The correlation coefficient has been determined and found to be 0.994 and 0.997 respectively.

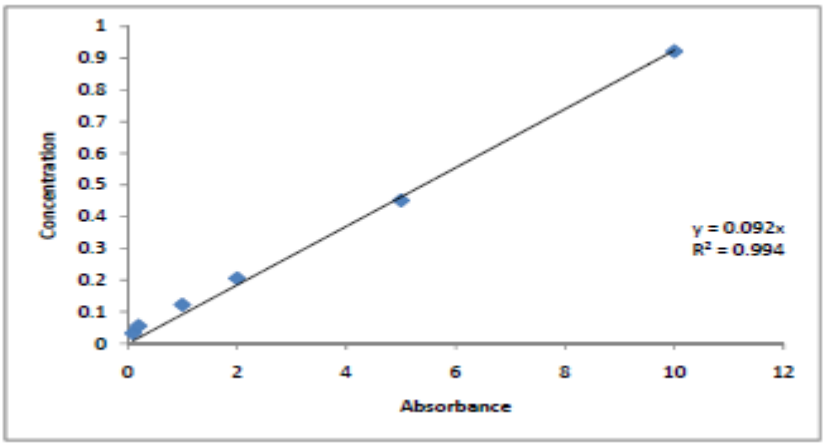

Fig 6: Standard calibration curve of losartan potassium in acidic Ph 1.2.

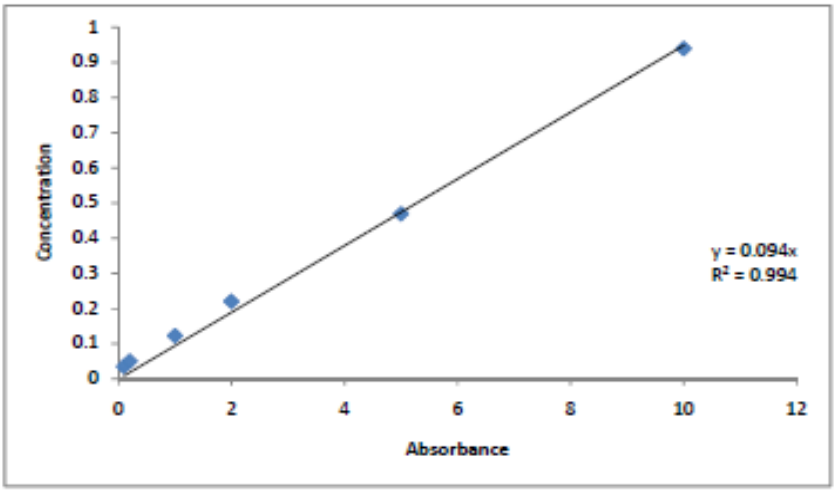

Fig 7: Standard calibration curve of losartan potassium in distilled water.

Table 5: Determination of Standard calibration curve of losartan potassium in acidic pH 1.2.

Concentration (mcg/ml)	Absorbance (nm)
0.1	0.0318
0.2	0.0554
1	0.1221
2	0.2051
5	0.4511
10	0.9218

Table 6: Determination of Standard calibration curve of losartan potassium in distilled water.

Concentration	Absorbance
0.1	0.0358
0.2	0.0611
1	0.1229
2	0.2206
5	0.4695
10	0.9398

Table 7: Determination of Standard calibration curve of losartan potassium in phosphate buffer pH 6.8.

Concentration (mcg/ml)	Absorbance (nm)
0.1	0.0414
0.2	0.0680
1	0.1331
2	0.2390
5	0.5239
10	0.9932

PREPARATION OF LOSARTAN POTASSIUM BILAYER TABLETS AND EVALUATION OF DIFFERENT PHYSICAL PARAMETERS

Bilayer tablets contain losartan potassium as active ingredient, PVP-K30 as a binding agent, Sodium starch glycolate as superdisintegrant, HPMC K4M and Carbopol 940-P as sustaining material and to retain the structure of tablets, DCP as filler, Mg-stearate and talc as lubricant and glidant. The composition of the different bilayer tablets are shown in (**Table 8)**. Different batches of tablets were prepared varying the different sustaining components that were considered to have significant effect on drug release. These bilayer tablets as well as the powder blends were subjected to various *in-process* quality control tests for evaluation of their different physical parameters. These *in-process* quality control tests are very much important not only because these parameters determine the uniformity of flow properties of powders and uniformity of tablets in respect to weight, size, shape & content but also they determine the suitability of tablets for further processing like *in-vitro* release studies.

Table 8: Formulation details during primary development of sustained release bi-layer layer tablets using sodium starch glycolate, HPMC-K4M and carbopol 940-P.

S.NO.	Ingredients (mg/tab)	ME1	ME2	ME3	ME4	ME5
For IR layer						
1	Losartan potassium	5	5	5	5	5
2	Sodium starch glycolate	12	12	12	12	12
3	PVP-K30	10	10	10	10	10
4	D.C.P.	20.99	20.99	20.99	20.99	20.99
5	Mg-stearate	1	1	1	1	1
6	Talc	1	1	1	1	1
7	Color	0.01	0.01	0.01	0.01	0.01
	Total Wt.	50	50	50	50	50

For SR layer						
1	Losartan potassium	45	45	45	45	45
2	HPMC K4M	80	70	60	50	40
3	Carbopol 940 -P	-	10	20	30	40
4	D.C.P.	51	51	51	51	51
5	PVP-K30	20	20	20	20	20
6	Mg-stearate	2	2	2	2	2
7	Talc	2	2	2	2	2
	Total Wt.	250	250	250	250	250

BULK DENSITY AND TAPPED DENSITY

Bulk density and Tapped density of the losartan potassium of the optimized batches were determined as per the procedure. It was found from the results (**Table 9**) that bulk densities of all batches examined varied in the ranges from 0.68 to 0.73 g/ml and the tapped densities ranged between 0.81 – 0.93 g/ml.

Table 9: Micromeritic properties of pre-compression powder blend.

Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
ME1	0.68	0.81	16.04	1.19	27.34
ME2	0.71	0.86	17.44	1.21	25.80
ME3	0.73	0.90	18.89	1.23	26.59
ME4	0.72	0.93	22.25	1.29	24.88
ME5	0.70	0.89	21.34	1.27	28.24

ANGLE OF REPOSE

The method angle of repose described previously in Chapter V is called a *dynamic angle* and is generally the preferred means of measurement because it more closely mimics the manufacturing situation, in which the powder is in motion. Value of Φ between 25 to 30 indicates good flow property. The Φ values of the optimized batches are shown in (**Table 9).** The values range in between 24.88 to 28.24, indicating that the powders have good flowing properties.

COMPRESSIBILITY INDEX (I) & HAUNER'S RATIO (R)

The flow ability of the powders was also indicated by compressibility index and Hausner's Ratio. Values of I below 15% usually give rise to good flow characteristics, the reading above 25% indicate poor flow ability (109). The I values of the optimized batches were found the range in between 16.04 % - 22.25% (**Table 9**).

Hauser Ratio (R) which is obtained as a ratio between tapped density and bulk density was found to fall in the range 1.19 to 1.29 (**Table 9**), indicating that the powders have free flowing properties.

***IN-VITRO* DRUG RELEASE STUDIES**

The release of losartan potassium from fast releasing layer was analyzed by plotting the cumulative percentage of drug release Vs time. It shows an effective initial burst effect from IR layer and released from this layer was completed within 10 minutes.

Formulations ME1, ME2, ME3, ME4, and ME5 were prepared by using HPMC K4M and carbopol 940-P. In each formulation the quantity of HPMC K4M and carbopol 940-P was varied to achieve the desired drug release profile. In formulation ME1, only 40% (w/w) HPMC K4M was used which gave the drug release just 78% after 30 hours. In order to achieve greater drug release in formulation ME2, the quantity of HPMC K4M was reduced to 35%w/w and 5% of carbopol 940-P was added, the drug release from the formulation (ME2) was found to 81% after 30 hours.

When the quantity of HPMC K4M was further reduced to 30%w/w, 25%w/w, 20%w/w and the carbopol 940-P was increased to 10%(w/w), 15%(w/w) and 20%(w/w) in formulation ME3, ME4 and ME5, the drug release from the formulation was found to 83%, 95% and 100% after 30 hours. The formulation ME5 containing 20% of HPMC-K4M and 20%w/w of carbopol 940-P was selected as the optimized batch since it showed the best drug release profile up to 30 hours as compared to the other formulations. In this selected formulation, the calculated regression coefficient for Higuchi and Peppas's models were 0.880 and 0.916 respectively. Higuchi's Plot, Peppas's Plot states that release followed the diffusion controlled mechanism. All the other parameters of the batch ME5 were found to be satisfactory.

CONCLUSION

The present research was carried out to develop a bilayer tablet of losartan potassium using superdisintegrant sodium starch glycolate for fast release layer and combination of HPMC K4M and carbopol 940-P for sustaining release layer. Finally, bi-layer tablet is improved beneficial technology to overcome the limitation of the single layered tablet. It 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.

CONFLICTS OF INTEREST

The authors state that they have no conflicts of interest.

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