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Formulation and Evaluation of Sustained Release 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. Post compression parameters such as hardness were found to be 5.46 to 7.21 kg/cm2 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.

Keywords: Bilayer Tablet of Losartan Potassium,

1. Introduction

The oral route of drug delivery is considered as the preferred and most patient convenience 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 represents unit dosage forms in which hone usual dose of the drug has been accurately placed. Layer tablets are composed of two 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.

The multilayered tablet concept has long been utilized to developed 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 consist 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 consist of super disintegrant which releases its drug within first one hour and sustain release layer maintain its therapeutic level up-to 12 hours by releasing constant amount of drug slowly shown in Figure.

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 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 sustain release bilayer tablets of Losartan Potassium using different synthetic and natural polymers Losartan potassium possess short biological half-life (1.5-2hrs), which demands frequent administration usually thrice a day leading to patient noncompliance exposing him to risk of side effects. In order to overcome this, Losartan potassium sustained release dosage forms are 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 his 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 classify as eitherprimary (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 remaining5–10% 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 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 vaso-constrictive 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.

MATERIALS

Drug	Obtained sources
Losartan potassium	
Polymer	
Carbopol 971	Noveon Chemicals, Bangalore
Hydroxypropyl methyl cellulose	Noveon Chemicals, Bangalore
Chemicals	
Dibasic calcium phosphate	Enar Chemicals Ltd., Ahmedabad
Sodium starch glycolate	Sujata Chemicals, Ahmedabad
Polyvinyl pyrollidone	Loba Chemie Pvt. Ltd. Mumbai
Talc	Loba Chemie Pvt. Ltd. Mumbai
Magnesium stearate	Finar Reagents, Mumbai
Hydrochloric acid	S.D. Fines Chemicals, Mumbai

Sodium hydroxide	S.D. Fines Chemicals, Mumbai
Potassium dihydrogen orthophosphate	S.D. Fines Chemicals, Mumbai
Instruments	
Compression machine (10 stations)	Electrolab, Mumbai
Digital weighing balance	Electrolab, Mumbai
Dissolution test system	Electrolab, Mumbai
Friabilator, EF- 2 (USP)	Electrolab, Mumbai
Hardness tester	Sartorius, Switzerland
pH –meter	Lab India, Baroda
Stability chamber	Thermolab, Mumbai
Tap density tester (USP)	JEL , Ahmedabad
Vernier calipers	Mahr Instruments, Ahmedabad
UV Spectrophotometer	Shimadzu

4. 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.

A. Dose Calculation

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.

Dt = Dose (1 + 0.693 × t/$t_{1/2}$) Where, Dt = Total dose, Dose = Immediate release dose, t = Total time period for which sustained release is required, $t_{1/2}$ = 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.

B. Formulation of the IR Layer

The IR ingredients (Table 1) 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.

C. Formulation of the 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.

D. 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/cm^2). 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.

5. Determination of λ max and development of calibration curve of losartan potassium

Maximum absorbance (**λ max**) of losartan potassium were measured at pH 1.2 (hydrochloric acid buffer) and pH 6.8 (phosphate buffer) using UV/Vis spectrophotometer. 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

The *in vitro* dissolution was carried out using USP Dissolution testing apparatus type-II. 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 rota ting 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. Drug concentrations in the sample were determined from standard calibration curve.

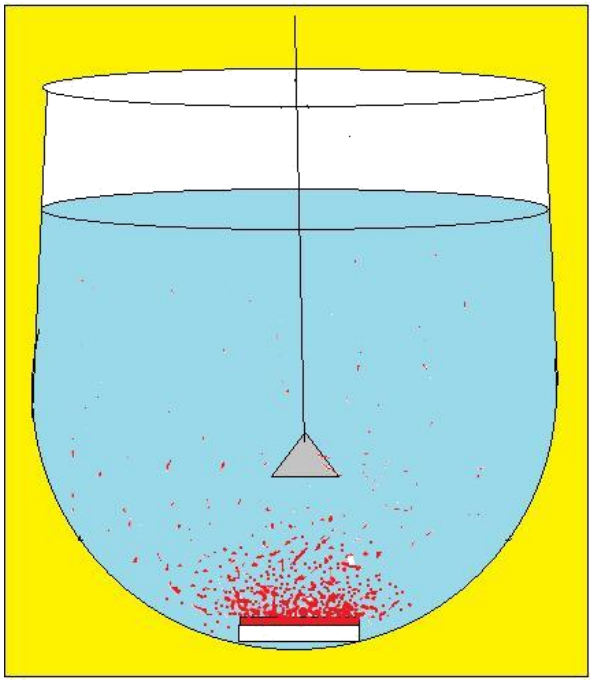


Fig 1: *In-Vitro* dissolution study.

Graph of Losrtan Potassuim in various Liquid.

Fig 2: λ max of losartan potassium in acidic pH 1.2

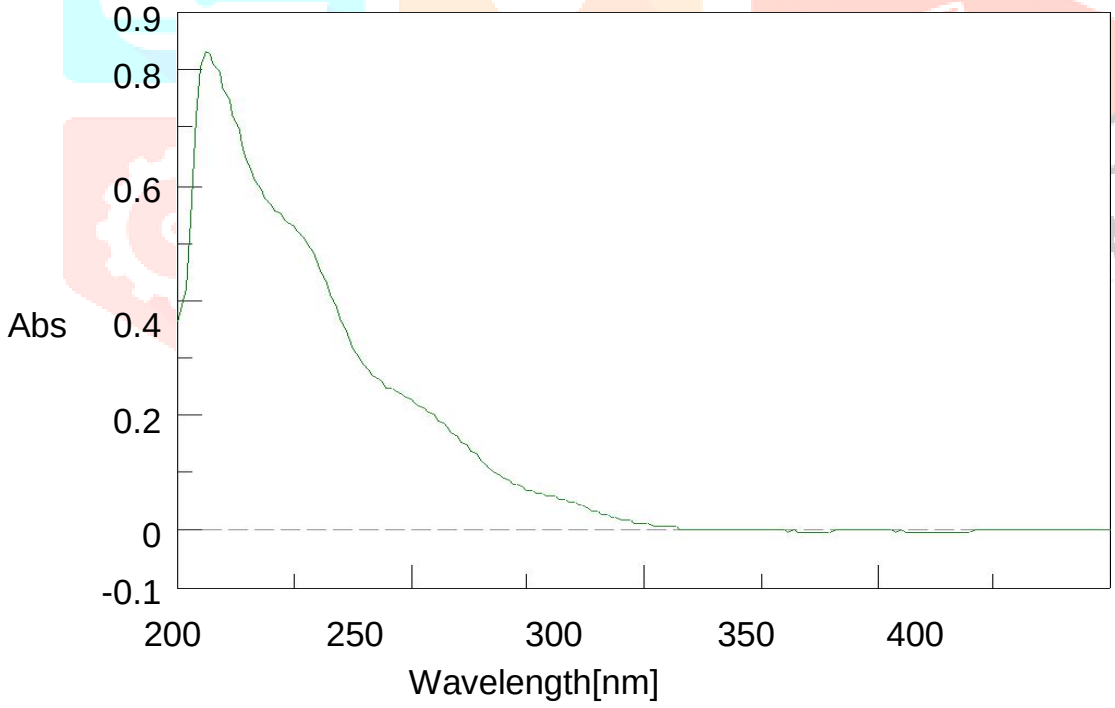


Table 1: Determination of Standard calibration curve of losartan potassium in acidic Ph 1.2:

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

Fig 3 : Standard calibration curve of losartan potassium in acidic Ph 1.2:

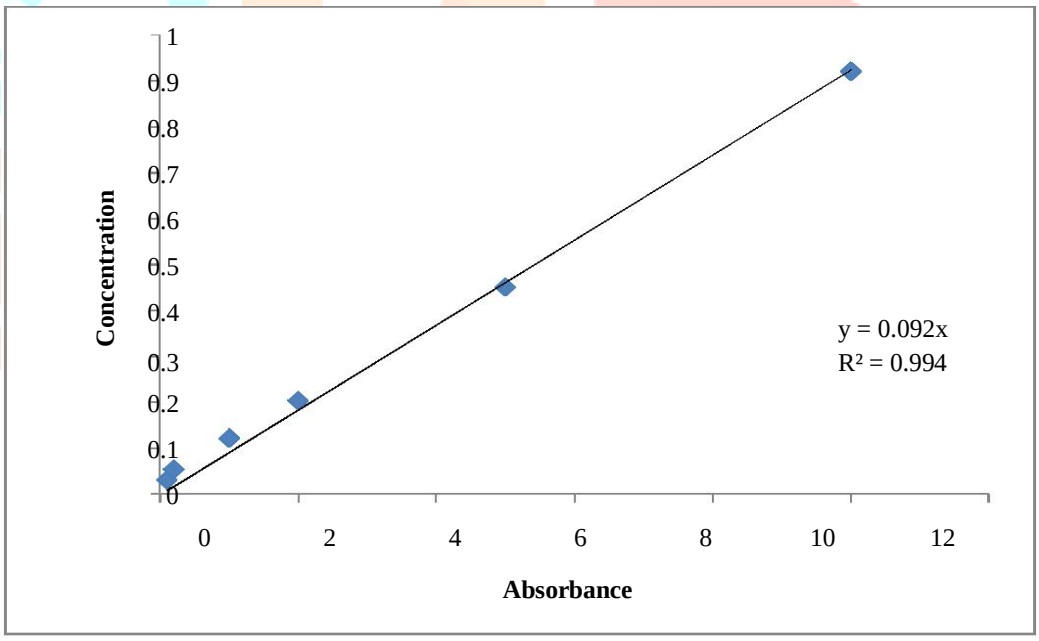


Fig 4: λ max of losartan potassium in distille

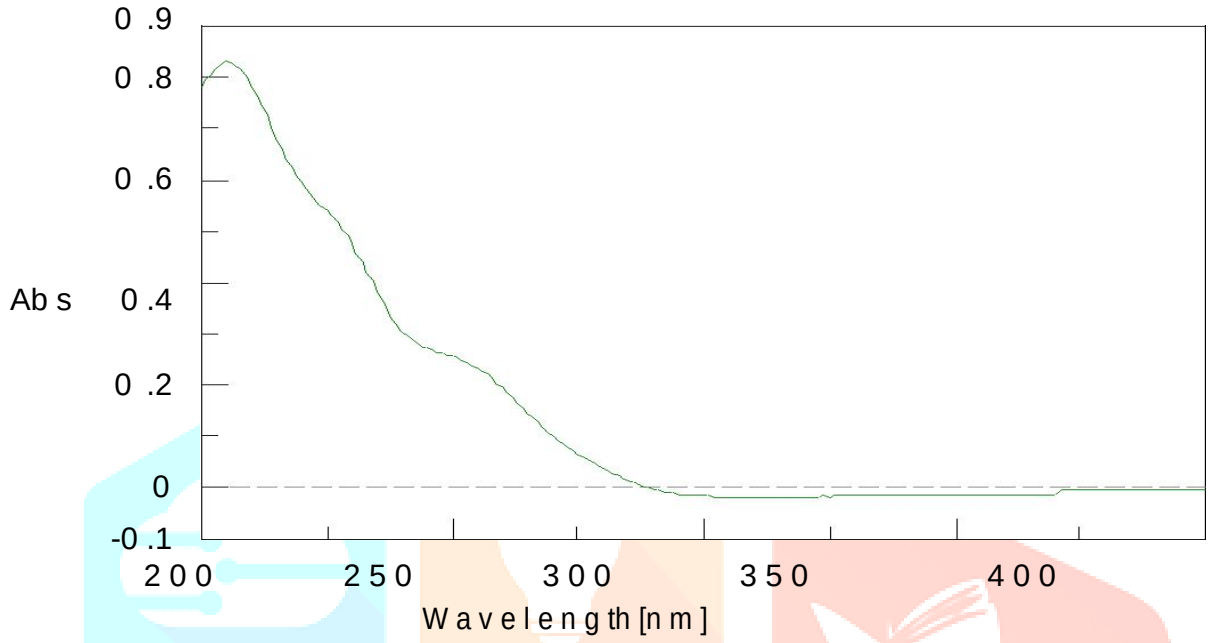


Table 2: Determination of Standard calibration curve of losartan potassium in distilled water:

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

Fig 5 : Standard calibration curve of losartan potassium in distilled water:

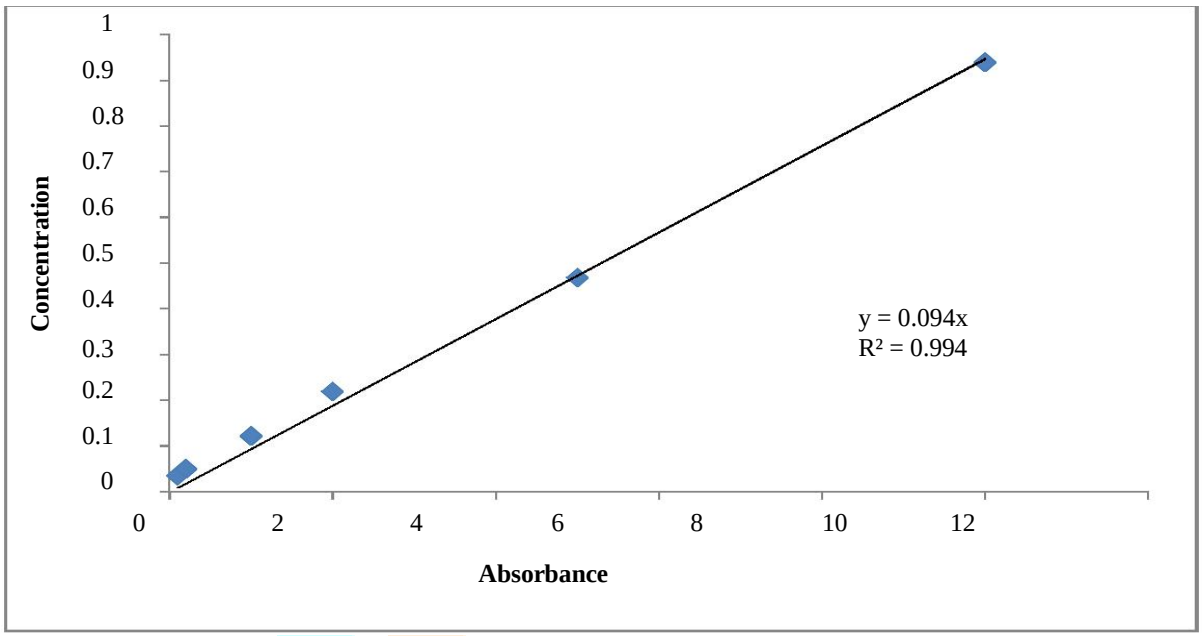


Fig 6 : λ max of losartan potassium in phosphate buffer pH 6.8

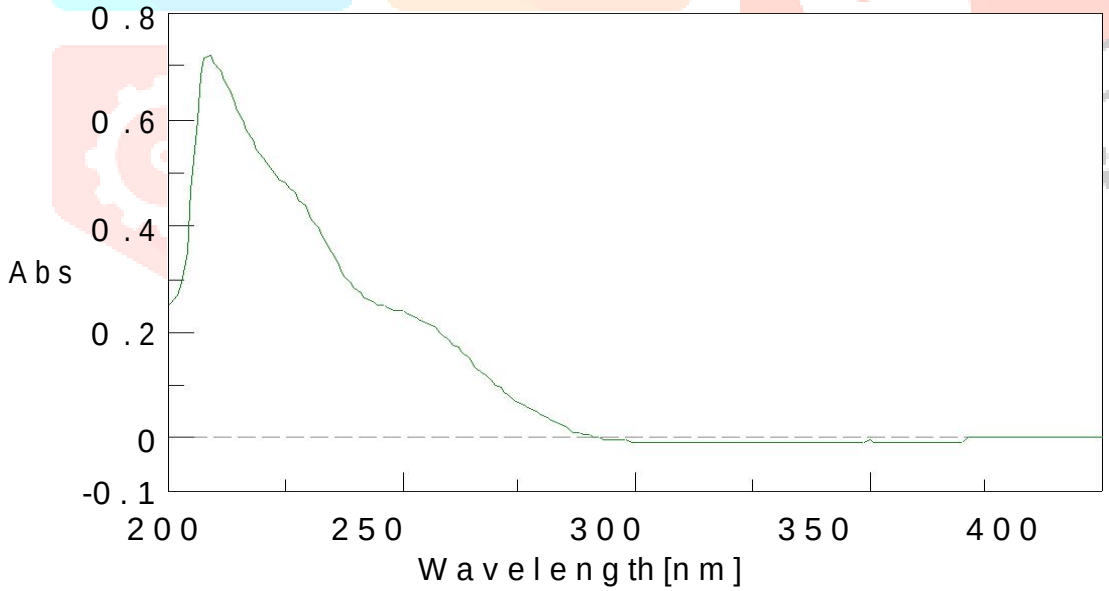


Table 3: Determination of Standard calibration curve of losartan potassium in phosphate buffer pH 6.8:

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

Fig 7 : Standard calibration curve of losartan potassium in phosphate buffer pH 6.8:

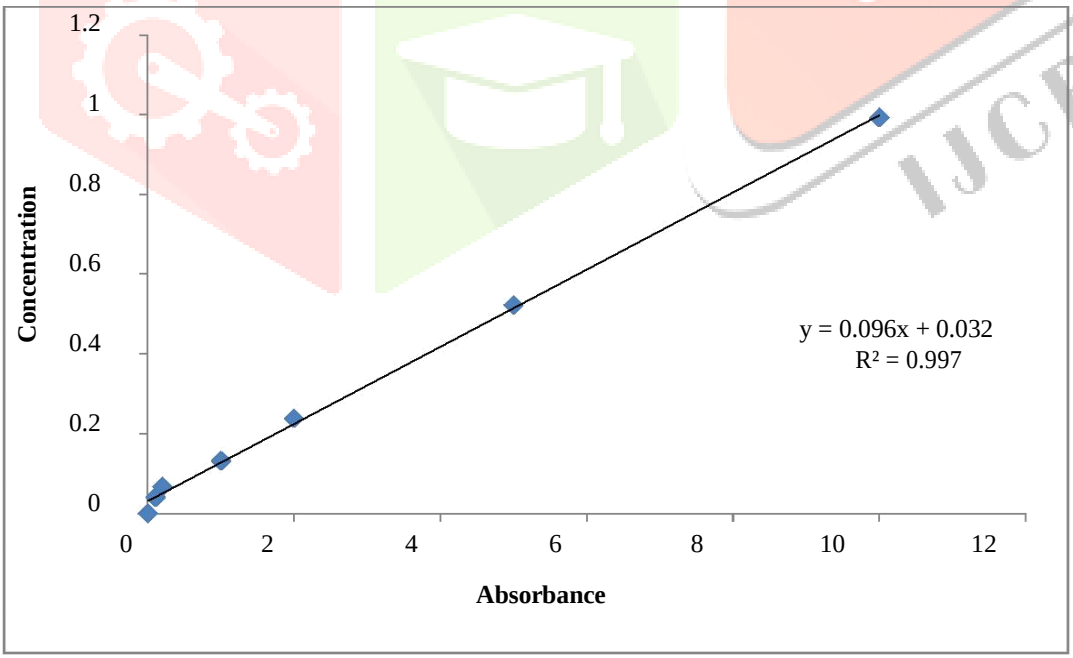


Table 4: Formulation details during primary development and optimization of immediate release layer using sodium starch glycolate.

Formulation	Weight per tablet (mg)							
Code	Drug	SSG	PVP-K30	DCP	Mg-stearate	Talc	Colour	Total Wt.
MI1	5	4	10	28.99	1	1	0.01	50
MI2	5	8	10	24.99	1	1	0.01	50
MI3	5	12	10	20.99	1	1	0.01	50

SSG= Sodium starch glycolate, PVP= Polyvinylpyrrolidone, DCP= Di-calcium phosphate

Table 5: Formulation details during primary development and optimization of sustained release layer using HPMC-K4M and carbopol 940-P.

Formulation	Weight per tablet (mg)							
Code	Drug	HPMC K4M	Carbopol 940-P	PVP-K30	DCP	Mg - stearate	Talc	Total Wt.
MS1	44	80	-	20	54	2	2	200
MS2	44	70	10	20	54	2	2	200
MS3	44	60	20	20	54	2	2	200
MS4	44	50	30	20	54	2	2	200
MS5	44	40	40	20	54	2	2	200

HPMC= Hydroxypropylmethylcellulose.

Table 6: Formulation details during primary development of sustained release bi-layer layer tablets using sodium starch glycolate, HPMC-K4M and carbopol 940-P.

Sr. no.	Ingredients (mg/tab) For IR layer	ME1	ME2	ME3	ME4	ME5
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
8	Total Wt.	50	50	50	50	50
	For SR layer					
8	Losartan potassium	45	45	45	45	45
9	HPMC K4M	80	70	60	50	40
10	Carbopol 940 -P	-	10	20	30	40
11	D.C.P.	51	51	51	51	51
12	PVP-K30	20	20	20	20	20
13	Mg-stearate	2	2	2	2	2
14	Talc	2	2	2	2	2
16	Total Wt.	250	250	250	250	250

Table 7: Micrometric 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

Table 8: Post-compression parameter of sustained release bilayer tablets

Code	Dimension		Hardness (kg/cm^2)±S.D	Friability (%)±S.D	Weight Variation(gm) ±S.D	Drug Content (%w/w)±S.D
	Diameter (mm)±S.D	Thickness (mm)±S.D				
ME1	9.48±0.035	3.43±0.023	6.34±0.061	0.22±0.017	248±1.44	99.8±0.3
ME2	9.52±0.024	3.45±0.033	7.92±0.045	0.14±0.018	250±1.36	100.1±0.4
ME3	9.53±0.022	3.47±0.026	7.61±0.034	0.21±0.021	249±1.48	99.4±0.2
ME4	9.51±0.015	3.46±0.021	7.11±0.032	0.24±0.012	251±1.46	100.3±0.5
ME5	9.49±0.038	3.44±0.031	7.10±0.047	0.33±0.015	249±1.45	99.6±0.4

Table 9 : Cumulative percentage release (mean±SD) from immediate release at pH 1.2

Time(t) Minutes	% Drug release(MI1) ±SD (n=3)	%Drug release(MI2) ±SD (n=3)	%Drug release(MI3) ±SD (n=3)
5	8.98±0.49	18.04±0.67	38.23±0.97
10	18.76±1.58	27.12±3.12	51.56±1.65
15	28.79±5.44	36.93±4.48	62.89±1.42
20	38.5± 6.29	46.61±5.45	73.54±3.11
25	47.9± 5.77	55.57±2.25	82.81±1.22
30	58.68±4.09	65.75±3.38	91.25±2.35

Table 10: Cumulative percentage release (mean±SD) from sustained release bilayer tablets

Time (minute)	ME1	ME2	ME3	ME4	ME5
5	7.75657±0.46	8.17105±0.31	10.3263±0.65	9.7105±0.65	9.39078±0.54
10	10.0733±0.62	13.1546±0.53	13.9244±0.32	13.7789±0.32	11.6100±0.42
15	13.4922±1.81	13.8787±1.32	15.8370±0.71	14.9801±0.71	12.2900±0.64
20	15.4732±0.93	14.5354±0.65	19.1453±1.03	15.3705±1.03	14.5366±0.83
25	16.1858±2.02	15.9769±1.98	20.4938±0.86	15.7745±0.86	15.9663±1.03
30	17.4467±0.081	16.9760±1.65	22.8440±1.58	17.1039±2.58	17.1786±0.96
60	20.8219±1.51	22.3617±2.55	24.7567±2.54	20.394±1.65	20.3036±2.55
120	28.7628±1.63	28.3690±1.78	27.1174±1.09	27.4917±1.09	24.7837±1.83
180	37.2654±1.92	32.8690±1.22	30.3029±1.22	32.3469±2.21	30.1245±0.82
240	40.4626±2.38	34.8124±0.87	33.3877±0.53	33.6055±3.53	31.5871±2.54
300	41.6879±3.31	36.3283±2.98	36.1556±1.87	34.3735±2.87	32.205±1.42
360	42.3986±1.43	37.1182±1.90	37.1908±1.60	34.7193±1.60	32.9682±0.52
420	44.0838±2.77	38.7413±1.75	38.5015±1.44	36.630±1.44	33.5696±5.15
480	44.9491±2.54	39.8757±0.78	39.2743±2.43	36.9760±1.43	34.1505±2.58
540	46.7779±1.22	40.7200±1.44	40.4538±1.52	36.3882±3.52	34.9475±1.57
600	48.0069±2.03	43.2501±2.73	42.1021±2.86	38.2143±2.86	36.3978±3.41
660	51.2668±1.22	45.2142±1.64	43.1657±1.11	38.3655±2.11	37.1261±1.39
720	53.6383±2.64	46.5370±2.09	44.4721±2.10	39.6437±2.17	38.3886±3.11
780	55.3236±3.11	48.6601±3.88	45.8564±4.15	40.1471±6.15	39.6223±1.52
840	56.8873±1.43	49.6813±1.41	46.9163±1.81	41.9675±1.81	41.8098±0.71
900	58.9444±1.01	51.1694±2.47	48.2420±0.52	43.3357±1.52	43.4525±2.76
960	60.0529±1.41	54.2756±1.33	50.6758±0.83	44.3913±4.83	45.3998±1.88
1020	61.1548±1.65	56.9603±3.21	52.1278±1.45	47.7379±1.45	49.4178±1.62
1080	62.3922±3.22	58.3920±2.05	53.5634±1.91	52.0026±3.91	52.8300±2.81

1140	63.3986±2.15	61.0269±1.11	55.4800±2.88	55.7811±2.88	57.0775±1.33
1200	65.2623±1.25	61.9821±1.72	56.3288±1.80	58.5142±1.80	59.0623±4.71
1260	68.1538±2.47	63.6876±3.86	57.9157±2.51	60.6457±2.51	60.926±1.85
1320	69.3313±1.32	66.8465±2.24	58.7172±4.62	64.9198±4.62	63.5941±1.96
1380	70.9878±1.55	68.8731±0.76	61.0735±1.43	68.4351±1.42	67.4238±2.64
1440	72.5759±3.65	69.8913±2.51	62.6020±3.85	69.8152±3.85	70.9400±1.57
1500	73.1645±2.88	72.0040±3.32	64.6340±1.47	73.6144±2.47	75.0710±1.93
1560	74.02±1.87	72.6480±0.65	66.4249±3.61	78.6942±1.46	80.2065±3.18
1620	75.9582±6.76	74.0509±4.25	69.8790±0.97	83.4890±2.97	85.8286±1.22
1680	76.4611±1.54	75.9694±1.82	71.9607±3.15	87.5393±4.55	92.368±3.41
1740	77.2971±2.25	78.6434±2.11	76.3145±2.31	91.8828±2.51	97.5101±2.97
1800	78.1482±2.32	81.2598±1.32	83.8649±2.11	95.4434±2.11	100.1559±1.84

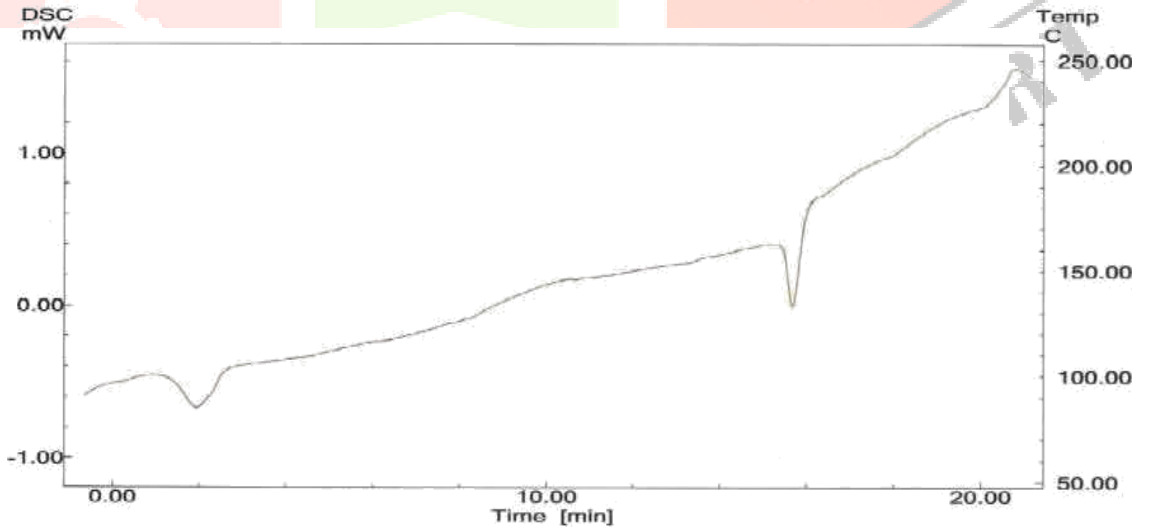


Fig 8 : Differential Scanning Colorimetry (DSC) result of Losartan potassium.

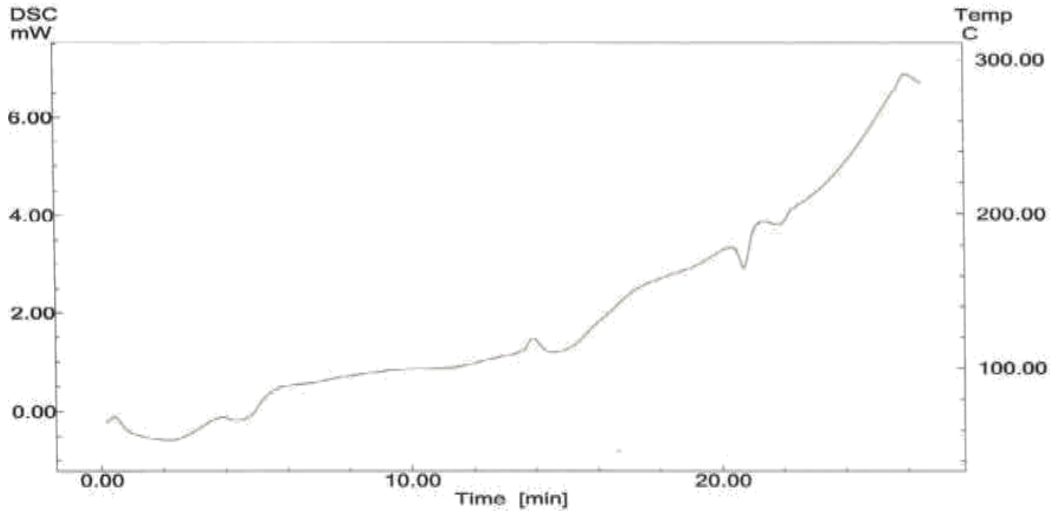


Fig 9: Differential Scanning Colorimetry (DSC) result of Losartan potassium + HPMC K4M.

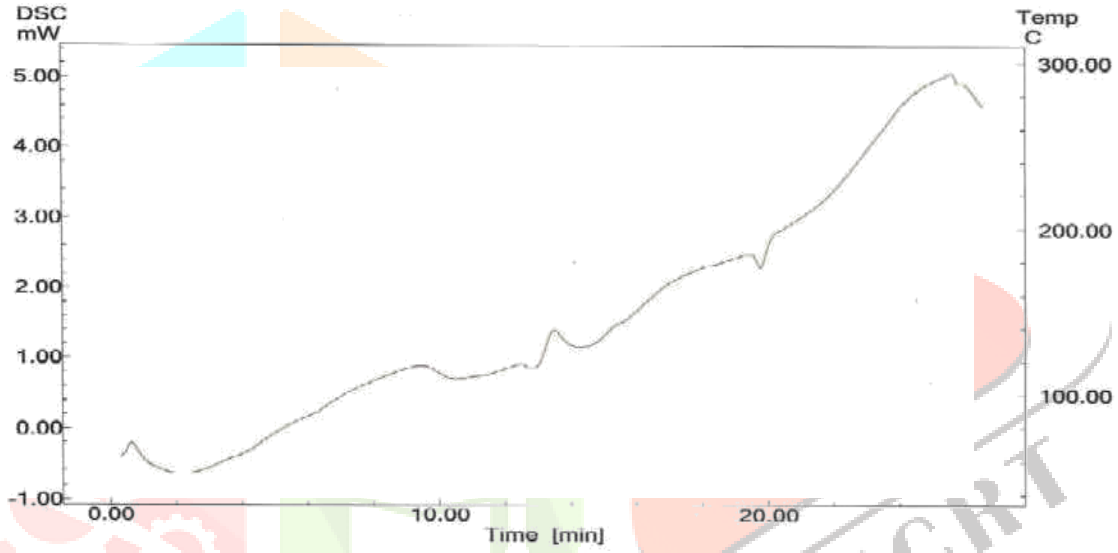


Fig 10: Differential Scanning Colorimetry (DSC) result of Losartan potassium + Carbopol 940P.

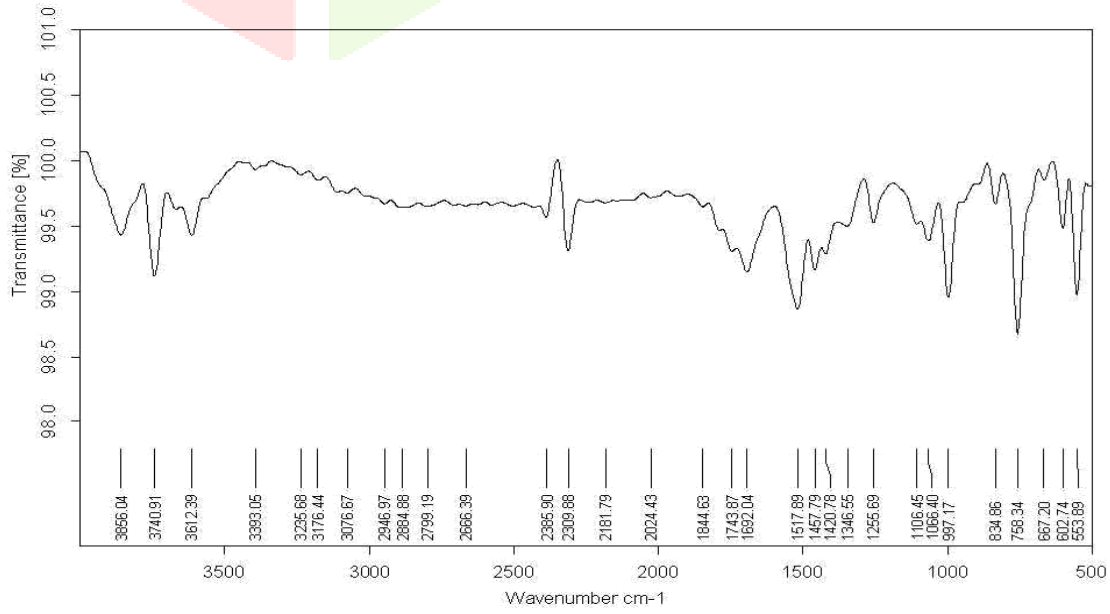


Fig 11: ATR-FTIR Curve of Losartan potassium.

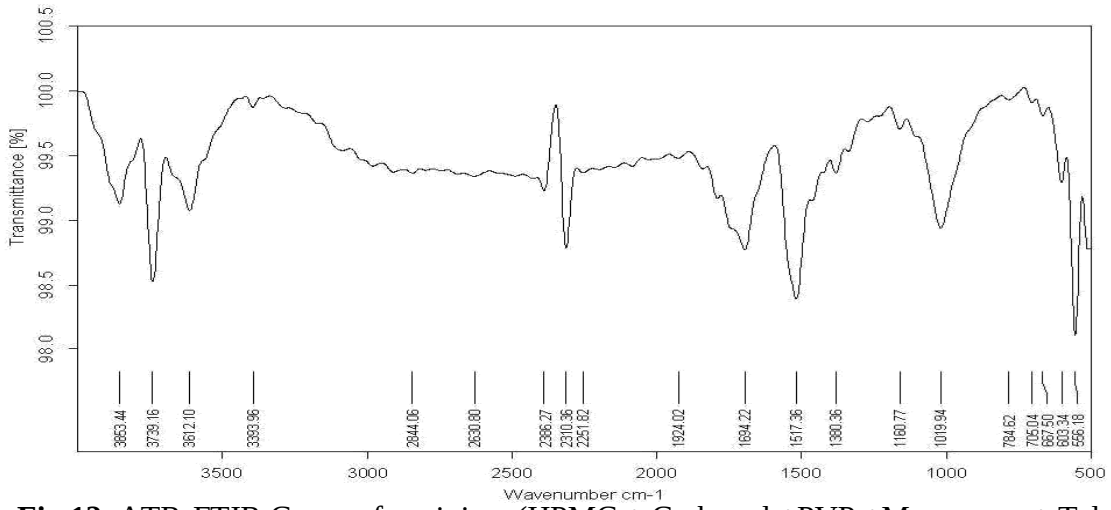


Fig 12: ATR-FTIR Curve of excipient (HPMC + Carbopol +PVP +Mg.stearate+ Talc)

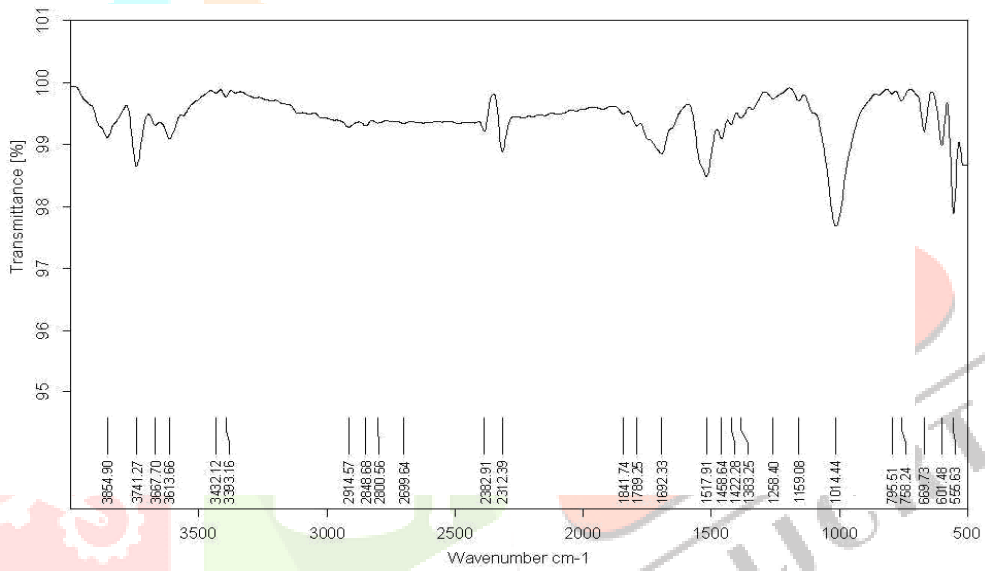


Fig 13: ATR-FTIR Curve of formulation ME5 (Drug+excipients)

6. Result and Discussion:

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 superdisintigrant, 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.** 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

A. Bulk Density and Tapped Density

Bulk density and Tapped density of the losartan potassium of the optimized batches were determined as per the procedure described in Chapter IV.

It was found from the results **Table** 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.

B. Angle of Repose

The method angle of repose described previously in Chapter IV 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.** The values range in between 24.88 to 28.24, indicating that the powders have good flowing properties.

C. Compressibility Index (I) and Hausner'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%.

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, indicating that the powders have free flowing properties.

D. Weight Variation Test

The maximum percentage weight variation that can be allowed for tablets according to USP is specified in **Table**. Accordingly, if the tablet weight is between 130- 324 mg, then the maximum % deviation allowed is ±7.5 %. shows the weight variation of the optimized batches. The % weight variation ranged between 1.36 to 1.48% and no tablets were found to be outside this range. So, the tablets were statistically significant with respect to weight.

Weight variation test is a satisfactory method of determining the drug content uniformity if the tablets were all or essentially all (90 to 95%) active ingredient, or if the uniformity of the drug distribution in the granulation or powder from which the tablets were made were perfect. Though the first criterion is not met in this study but every effort has been taken to uniformly mix the

drug with other excipients. So it is anticipated that the tablets which are uniform in respect to weight will also be uniform in respect to drug content.

E. Content Uniformity

This is an important test to ascertain the uniformity of tablets with respect to drug content. The % variation of drug content should be within ±15%. In all the prepared batches on which the content uniformity tests were carried out, the content variation was very less shown in **Table**, i.e. within the compendia limits. So, as it was anticipated, the tablets are very much uniform in respect to drug content.

F. Thickness

Crown thickness uniformity is necessary not only for consumer requirement but also for packaging. Usually ±5% variation is permissible. The thickness of all bilayer tablets were tested by the method described in Chapter IV. It was observed that thickness of all tablets ranged between 3.43-3.47as shown in **Table**.

G. Hardness

The hardness of all losartan potassium tablets was tested by the method described in Chapter IV. It was found that hardness of prepared losartan potassium bilayer tablets varied between 6 - 8 kg/cm^2 for all the batches.

H. Friability Test

During the compression of the powders, sufficient force was applied to get the final hardness of the tablet of around 6 - 8 kg/cm^2 hardness as measured in a Monsanto Tablet Hardness Tester. But tablet hardness is not an absolute indicator of tablet strength. Friability test is done to ascertain whether the tablets are resistant to chipping and cracking during handling and/or subsequent processing. Weight loss should be less than 1% for good tablets. This test was performed on all the optimized batches of tablets as per the procedure given in Chapter 2. The loss % for all the batches was found to fall within the range of 0.14 to 0.33 %.

I. Disintegration time of IR layer

The disintegration time of IR layer of all bilayer tablets were tested by the method described in Chapter IV. It was observed that disintegration time of all tablets ranged between 1 to 2 minutes.

J. Drug excipient compatibility studies

I. Fourier transforms infra-red (FTIR) spectroscopy.

Major functional groups present in losartan potassium show characteristic peaks in IR spectrum. Figure 1 shows peaks observed at different wave numbers and the functional group associated with these peaks for drug and drug with different polymer. The major peaks are identical to functional group of losartan potassium. Hence, it was confirmed that there was no incompatibility between drug and various polymers.

II. Differential scanning calorimetry (DSC).

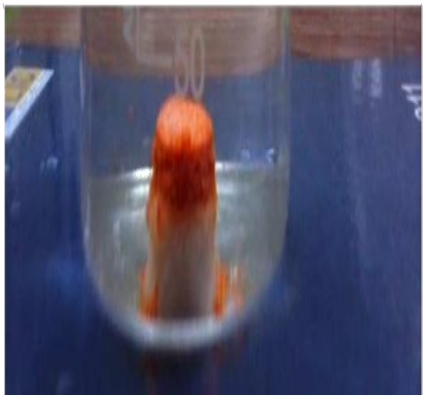
DSC was performed to characterize thermal changes in the melting behaviour of losartan potassium with other excipients present in different formulations. Fig. depicts the thermograms of heat verses temperature for pure losartan potassium, losartan potassium + HPMC, losartan potassium + Carbopol 940-P respectively. DSC thermogram showed that there was no any major difference in onset temperature and peak temperature, when compared with pure drug thermogram. Hence, it was confirmed that there was no incompatibility between drug and various polymers.

K. *In Vitro* drug release studies

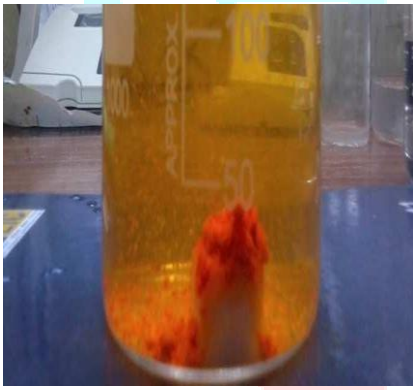
The release of losartan potassium from fast releasing layer was analyzed by plotting the cumulative percentage of drug release Vs time. It shows an effective initial burst effect from IR layer and released from this layer was completed within 10 minutes. Formulations ME1, ME2, ME3, ME4, and ME5 were 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.

After 2 minutes



After 5 minutes



After 10 minutes

After 15 minutes

Conclusion.

The success of any research work depends on the results obtained there from and conclusion drawn therein, which could bring out the revealed or unrevealed or unexplored scientific explanations. The findings from any research work may further lead to better understanding, explanation, and profound knowledge in any specific area. The present research was carried out to develop a bilayer tablet of losartan potassium using super disintegrant sodium starch glycolate for fast release layer and combination of HPMC K4M and carbopol 940-P for sustaining release layer. The tablets showed an initial burst release to provide the loading dose of drug followed by sustained release up to 30 hours. This modified release bilayer tablets also reduced dosing frequency, increase the bioavailability and provide better patient compliance. 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.

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