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Original Article

Formulation and Evaluation of Sustained Release Matrix Tablets of Losartan

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ABSTRACT

A selective and sensitive stability-indicating high-performance liquid chromatographic method was developed and validated for the determination of losartan. The λmax of the two ingredients i.e. losartan , were found to be 210 nm and 225 nm respectively in methanol as solvent system. Accurately weighed 100 mg of losartan was transferred to 100 ml volumetric flask. About 40 ml of HPLC grade methanol was added and sonicated to dissolve. The volume was made up to mark with same solvent. Then 10 ml of the above solution was diluted to 100 ml with the solvent system. Mobile phase was prepared by taking Potassium dihydrogen phosphate buffer+Dipotassium hydrogrn phosphate (0.01 M, pH 3.0): acetonitrile (30:70). Mobile phase was filtered through 0.45 m membrane filter and degassed under ultrasonic bath prior to use. The mobile phase was pumped through the column at a flow rate of 1.0 ml/min. The HPLC system was set with the optimized chromatographic conditions to run the standard solution of losartan for 15 min. The retention time were found to be 2.03 min and 9.93 min respectively

Keywords: Losartan, RP-HPLC, Acetonitrile (30:70). & Retention time.

1. INTRODUCTION

In recent years in association with progress and innovation in the field of pharmaceutical technology there has been an increasing effort to develop prolonged release dosage forms. The prolonged release dosage forms have many advantages in safety and efficacy over immediate release products in that frequency of dosing can be reduced drug efficacy can

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be prolonged and the incidence of adverse effects can be decreased. Extended release drug formulations have been used since 1960's. These formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improves patient convenience and compliance, by incorporating the dose in a unit dosage form from which the drug is slowly released for 24 hr. This formulation helps to avoid the side effects associated with low concentration and high concentrations. The ideal drug delivery system should show a constant zero order release rate and maintain the constant plasma concentrations.

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. Unlike angiotensin-converting enzyme (ACE) inhibitors, ARBs do not have the adverse effect of dry cough. Losartan may be used to treat hypertension, isolated systolic hypertension, left ventricular hypertrophy and diabetic nephropathy. It may also be used as an alternative agent for the treatment of systolic dysfunction, myocardial infarction, coronary artery disease, and heart failure.

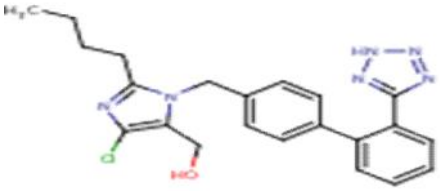


Fig 1: Structure of Losartan

2. MATERIAL & METHODS

2.1 Preformulation Study

A. Colour, odor, taste and appearance:

The drug sample was evaluated for its colour and odor. The results are shown in Table.

B. Melting point determination: Melting point of the drug sample was determined by capillary method by using melting point apparatus.

*C. Determination of solubility***:** The solubility of the Losartan potassium was determined by adding excess amount of drug in the solvent and equilibrium solubility was determined by taking supernatant and analyzing it on Perkin Elmer Lambda35, double beam spectrophotometer.

D. Ultraviolet Visible (UV-visible) spectroscopy:

Construction of Calibration Curve:

Standard Stock solution:

Accurately weighed 100 mg of Losartan potassium was dissolved in 100 ml of 6.8pH phosphate buffer. The resultant solutions were having concentration of 1000 µg/ml (1.1 mg/ml). 10 ml of this solution was further diluted up to 100.0 ml with 6.8pH phosphate buffer and to give a solution of Concentrations 100 µg/ml. This resultant solution is used as working stock solution for further study. Further dilutions were prepared from the same solution.

Preparation of calibration curve for Losartan potassium: Appropriate aliquots were pipetted out from the standard stock solution in to a series of 10 ml volumetric flasks. The volume was made up to the mark with 6.8pH phosphate buffer to get a set of solutions having the concentration range of 2, 4, 6, 8 and 10 µg/ml for Losartan potassium. Absorbances of the above solutions were measured at 250 nm and a calibration curve of absorbance against concentration was plotted and the drug follows the Beer's & Lambert's law in the concentration range of 2-10

µg/ml. The regression equation and correlation coefficient was determined.

E. Bulk density, Tapped density, % Compressibility index & Hausners ratio:

1) Apparent Bulk Density: The bulk density was determined by transferring the accurately weighed sample of powder to the graduated measuring cylinder. The initial volume and weight was noted. Ratio of weight of the sample was calculated by using the following formula.

Density = Mass/Volume

2) Tapped Density: Weighed powder sample was transferred to a graduated cylinder and was placed on the tap density apparatus, was operated for fixed number of taps (200). The tapped density was determined by the following formula.

Density = Mass/Tapped Volume

3) Percentage Compressibility (or) Carr's index (%): Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.

Carr's index (%) = [(Tapped Density-Bulk Density) / Tapped Density] X 100

Table 1: % Compressibility limits with respect to flowability

S.No	%Compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair
4	23-25	Poor
5	33-38	Very poor
6	More than	Very very poor

4) Housner's Ratio: It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density.

Hausner ratio = Tapped density/Bulk density

Table 2: Hausner ratio limits.

Hausner's ratio	Type of flow
< 1.25	Good flow
> 1.25	Poor flow

All these results are shown in Table.

5) Angle of Repose: The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Angle of repose= $\tan^{-1}$ (h/r)

Where, h = height r = radius

Procedure:

- 20gms of the sample was taken
- The sample was passed through the funnel slowly to form a heap.
- The height of the powder heap formed was measured.
- The circumference formed was drawn with a pencil on the graph paper.
- The radius was measured and the angle of repose was determined. This was repeated three times for a sample

Table 3: Flow properties of tablets

Flow properties	Angle of repose (θ)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very very poor	> 66

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability and invitro-dissolution characters.

1. Physical Appearance: The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot

uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

2. Size & Shape: It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

3. Weight variation test: This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests.. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Method:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Table 4: Limits for Tablet Weight variation test:

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
> 324	5 %

4. Content Uniformity: The drug content of the matrix tablets was determined by standards and it meets the requirements if the amount of the active ingredient in each of 10 tested tablets lies within the range of 90% to 110% of the standard amount.Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 10mg of Losartan potassium was transferred to 100ml volumetric flask containing 70ml of 7.2 pH phosphate buffer. It was shaken by mechanical means for 1hr then it was filtered through Watsmann filter paper (no.1) and diluted to 100ml with 7.2 pH phosphate buffer. From this resulted solution 1ml was taken, diluted to 50ml with 7.2 pH phosphate buffer and absorbance was measured against blank at 227nm.

Friability: Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Method:

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

% friability = $(W_1-W_2) / W_1 X 100$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

***In vitro* drug release study:**

In vitro drug release was studied using USP II apparatus, with 900 ml of dissolution medium maintained at 37±1°C for 15 h, at 50 rpm. 0.1 N HCl (pH 1.2) was used as a dissolution medium for the first 2 h, followed by pH 6.8 phosphate buffers for further 10 h. 5ml of sample was withdrawn in different time intervels, and was replaced by an equal volume of fresh dissolution medium of same pH. Collected samples were analyzed spectrophotometrically at 271 nm, and cumulative percent drug release was calculated. The study was performed in triplicate.

Kinetic-models:

In order to describe the DS release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models:

Zero order, first order, and Higuchi respectively.

$Qt = Q0 + K0\ t$…….. (3)

where, Qt is the amount of drug released at time t; Q0 the amount of drug in the solution at t = 0, (usually, Q0 = 0) and K0 the zero order release constant.

$\log Qt = \log Q\alpha + (K1/2.303)\ t$…….. (4)

Qα being the total amount of drug in the matrix and K1 the first order kinetic constant.

$Qt = KH.\ t^{1/2}$……. (5)

where, KH is the Higuchi rate constant.

Further, to better characterise the mechanism of drug release from matrices, dissolution data were analyzed using the equation proposed by Korsmeyer and Peppas.

$Q\ (t-l)/Q\alpha = KK\ (t-l)n$……. (6)

where, Qt corresponds to the amount of drug released in time t, *l* is the lag time (*l* = 2 hours), Qα is the total amount of drug that must be released at infinite time, KK a constant comprising the structural and geometric characteristics of the tablet, and n is the release exponent indicating the type of drug release mechanism. To the determination of the exponent n, the points in the release curves where $Q\ (t-l)/Q\alpha > 0.6$, were only used. If n approaches to 0.5, the release mechanism can be Fickian. If n approaches to 1, the release mechanism can be zero order and on the other hand if $0.5<n<1$, non-Fickian (anomalous) transport could be obtained. Anomalous (non-Fickian) transport generally refers to the drug release by the summation of both diffusion and erosion of the polymeric matrix. The criteria employed to select the ‘‘best model’’ was the one with the highest coefficient of determination (r2).

Stability studies:

Selected Formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for Stability Testing.

1. 25^0C/60% RH analyzed every month for period of three months.
2. 30^0C/75% RH analyzed every month for period of three months.
3. 40^0C/75% RH analyzed every month for period of three months.

FORMULATION DEVELOPMENT

Procedures: The Purpose of key ingredients included in the formulation.

Table 5: Composition of losartan potassium sustained release matrix tablets

S.no.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
1	Losartan potassium	50	50	50	50	50	50	50	50	50
2	Eudragit rlpo	50	100	---	---	---	---	30	30	40
3	Eudragit- l100	---	---	50	100	---	---	30	40	30
4	Ethyl cellulose	---	---	---	---	50	100	40	30	30
5	Microcrystalline Cellulose	140	90	140	90	140	90	90	90	90
6	Pvp k-30	5	5	5	5	5	5	5	5	5
7	Magnesium stearate	3	3	3	3	3	3	3	3	3
8	Talc	2	2	2	2	2	2	2	2	2
8	Iso propyl alcohol	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
	Total wt	250	250	250	250	250	250	250	250	250

Preparation of Formulation:

1. Drug and polymer (EUDRAGIT RLPO, EUDRAGIT L100 and ETHYL CELLULOSE combination) pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes.
2. Binder (PVPK-30) dissolved in isopropyl alcohol which is used as a granulating agent.
3. Above drug-polymer blend is granulated by using binder solution.
4. Add other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) and Lubricant (Talc) to the above blend mix it for 2min.
5. Compressed the above lubricated blend by using 8mm round punches.

3. RESULTS

Standard graph:

Table: 6 Standard graph of Losartan potassium in 0.1 N HCL 1.2 pH buffer at λ_{max}= 250 nm

S. NO.	CONCENTRATION(µG/ML)	ABSORBANCE
1	0	0
2	2	0.125
3	4	0.225
4	6	0.326
5	8	0.442
6	10	0.543

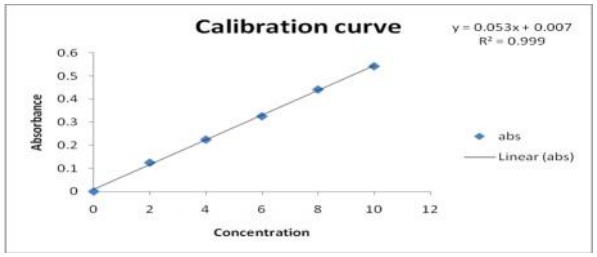


Fig 1: Standard graph of Losartan potassium in 0.1N HCl (1.2 pH)

Table: 7 Standard graph of Losartan potassium in 6.8 pH Phosphate buffer at λ_{max}= 250 nm

S. NO.	CONCENTRATION(µG/ML)	ABSORBANCE
1	0	0
2	2	0.105
3	4	0.216
4	6	0.336
5	8	0.434
6	10	0.539

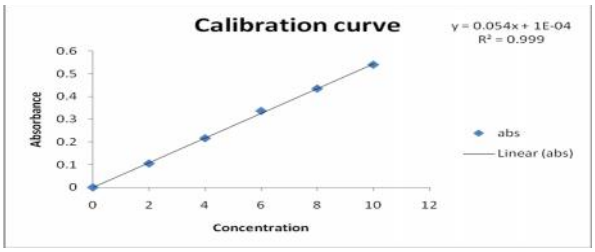


Fig 3: Standard graph of Losartan potassium in 6.8 pH Phosphate buffer

5.2 Pre compression Studies of Losartan potassium

Table 7: Table Pre compression Studies of Losartan potassium:

parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angleof repose	$26^0$43 ’±0.1	$27^0$46 ’±0.2	$24^0$31 ’±0.1	$28^0$89’ ±0.17	$29^0$14 ’±0.1	$28^0$14 ’±0.2	$29^0$12 ’±0.1	$27^0$14 ’±0.4	$23^0$21 ’±0.1
Bulk density	1.041 ±0.3	1.02± 0.4	1.01± 0.2	1.02±0 .28	0.96± 0.24	0.95± 0.24	0.94± 0.2	1.041 ±0.3	0.96± 0.2
Tapped density	1.16± 0.1	1.12± 0.2	1.11± 0.1	1.11±0 .21	1.03± 0.27	1.03± 0.27	1.03± 0.2	1.16± 0.1	1.04± 0.2
%Compressibility	11.4	9	9	8	7	9.5	9	11.4	8
Hausner’s ratio	1.114	1.09	1.09	1.08	1.07	1.095	1.095	1.114	1.08

Post compression Evaluation studies of Losartan potassium:

Table 8: Average thickness of the formulations

S.NO	Formulation code	Thickness
1	F1	2.01±0.06
2	F2	2.04±0.01
3	F3	2.06±0.04
4	F4	2.03±0.01
5	F5	2.01±0.02
6	F6	2.05±0.03
7	F7	2.01±0.02
8	F8	2.05±0.05
9	F9	2.05±0.02

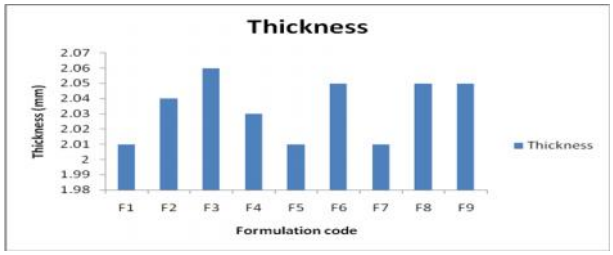


Fig 4: Average thickness of the formulations

Table 8: Average Weight variation of the formulations

S.NO	Formulation code	Weight variation
1	F1	250±0.4
2	F2	249±0.4
3	F3	249±0.7
4	F4	250±0.1
5	F5	249±0.3
6	F6	250±0.2
7	F7	249±0.9
8	F8	250±0.8
9	F9	250±0.1

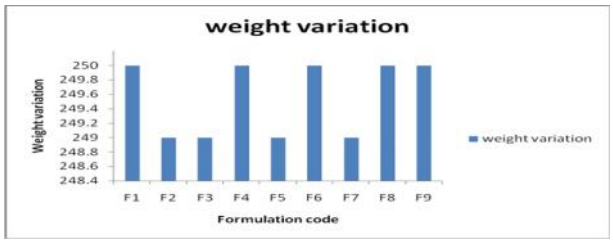


Fig 5: Average Weight variation of the formulations

S.NO	Formulation code	Hardness
1	F1	8.9±1.4
2	F2	7.4±1.2
3	F3	8.2±1.2
4	F4	6.9±0.9
5	F5	8.4±1.9
6	F6	8.1±1.7
7	F7	8.2±1.5
8	F8	8.3±1.6
9	F9	8.2±1.4

Table 9: Average Hardness of the formulations

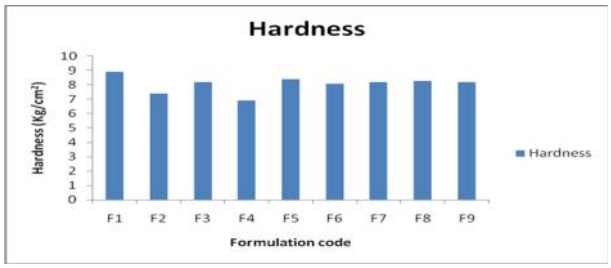


Fig 6: Average Hardness of the formulations

Table 10: Average Friability of the formulations

S.NO	Formulation code	Friability
1	F1	0.12%±0.2
2	F2	0.16%±0.23
3	F3	0.15%±0.19
4	F4	0.15%±0.26
5	F5	0.15%±0.22
6	F6	0.12%±0.1
7	F7	0.11%±0.4
8	F8	0.11%±0.5
9	F9	0.11%±0.3

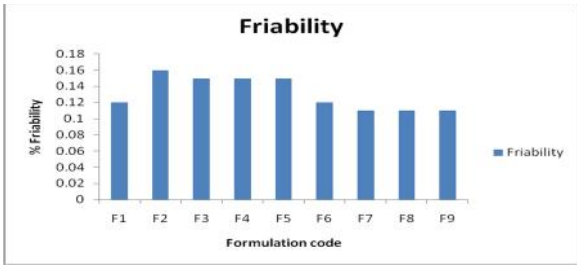


Fig 6: Average Hardness of the formulations

Table 11: Average Drug content of the formulations

S.NO	Formulation code	Drug content
1	F1	96.01%±0.2
2	F2	97.4%±0.4
3	F3	97.7%±0.3
4	F4	98.8%±0.2
5	F5	99.8%±0.3
6	F6	99.19%±0.2
7	F7	99.18%±0.2
8	F8	99.28%±0.2
9	F9	99.88%±0.2

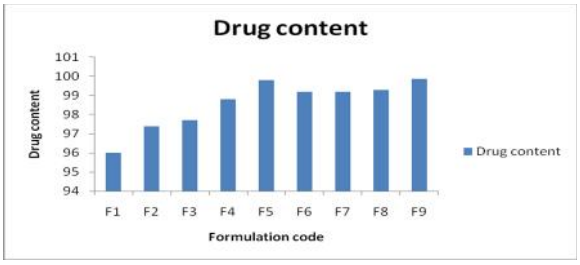


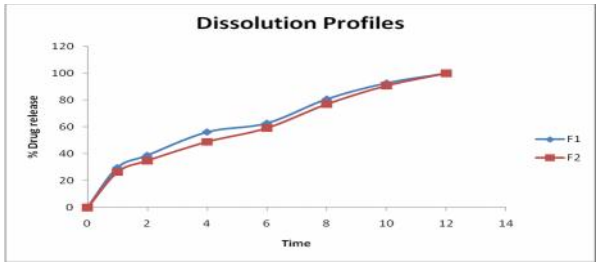
Fig 7: Average Drug content of the formulations

In-Vitro Dissolution Studies of Sustained Release Matrix Tablets of Losartan potassium

LOSARTAN POTASSIUM + EUDRAGIT RLPO

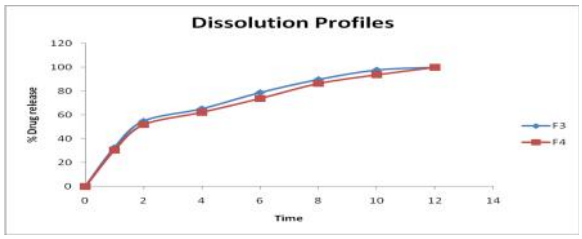
Time	F1	F2
0	0	0
1	29.67	26.36
2	38.91	34.92

4	56.24	48.92
6	62.84	59.21
8	80.78	76.93
10	92.72	90.72
12	100	99.92



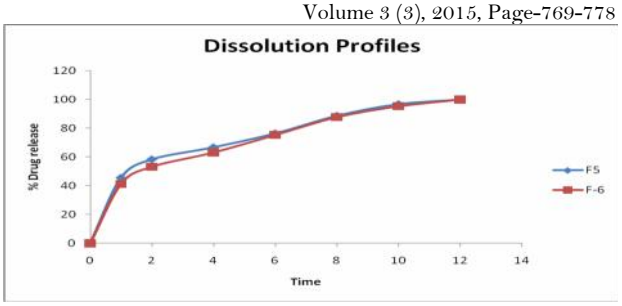
LOSARTAN POTASSIUM+EUDRAGIT L100

Time	F3	F4
0	0	0
1	32.67	30.62
2	54.91	51.83
4	65.24	62.26
6	78.84	73.87
8	89.78	86.38
10	97.72	93.71
12	100	100



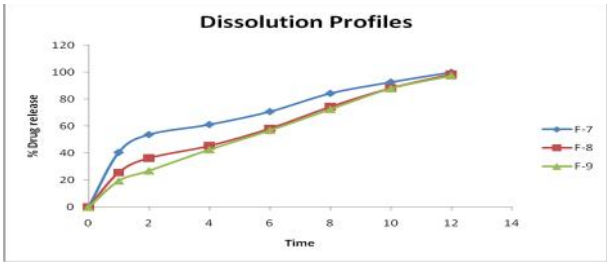
LOSARTAN POTASSIUM+ETHYL CELLULOSE

Time	F5	F-6
0	0	0
1	45.65	41.35
2	58.44	53.29
4	66.83	63.21
6	76.47	75.38
8	88.74	87.78
10	96.82	95.36
12	100	100



LOSARTAN POTASSIUM+EUDRAGIT RLPO+ EUDRAGIT L100+ETHYL CELLULOSE

Time	F-7	F-8	F-9
0	0	0	0
1	40.62	25.65	19.43
2	53.83	36.37	26.94
4	61.26	45.47	42.59
6	70.87	58.28	56.86
8	84.38	74.41	72.48
10	92.71	88.26	87.83
12	100	98.49	97.27



STABILITY STUDIES:

Table 12: Stability Studies of Optimized Formulation

S.No	Time in days	Physical changes	Mean % drug content ± SD	
			25°c	30°c
1.	01	No Change	97.27±0.49	97.24±0.49
2.	15	No Change	97.26 ± 0.45	97.20 ± 0.42
3.	30	No Change	97.22± 0.39	97.21 ± 0.37
4.	45	No Change	97.25 ± 0.76	97.21 ± 0.41
5.	60	No Change	97.21 ± 0.81	97.24 ± 0.37
6.	75	No Change	97.19 ± 0.31	97.18 ± 0.81
7.	90	No Change	97.17 ± 0.43	97.10 ± 0.91
8.	105	No Change	97.10± 0.51	97.10 ± 0.15

9.	120	No Change	97.12 ± 0.48	97.10 ± 0.27

4. CONCLUSION

Sustained release matrix tablets of Solbutamol were prepared using different Polymers. Polymers were used HPMC K4M, HPMC K100M, Eudragit L 100, Eudragit RLPO, Guar gum and Xanthan gum in 1:1 and 1:2 ratios were prepared. The compositions of the formulations are shown in Table No.3 and Table No.4 MCC was used as filler.

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