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Formulation and Evaluation of Modified Release Inlay Tablets of Losartan Potassium

Y. Bhuvana Teja*, V. Shanmugam[1] and P. Parimala[2]

[*1]Dept of Pharmaceutics, Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupathi- 517503, India.

[2]Formulation & Development, KAPL, Banglore, India.

ABSTRACT

The aim of this present work is to design an inlay tablet consists of Losartan potassium to improve the oral therapeutic efficacy. Losartan potassium is an angiotensin-II antagonist used in the treatment of hypertension. The formulation has been designed which contains of one drug losartan potassium but dual releases. The present investigation is to design and characterize a quick / slow delivery dosage form as a inlay tablet in which the coat (immediate release of drug) to attain onset of action and the core (central tablet) provide a slow and sustained release as maintained dose. Different concentration of polymers has been used to develop formulation and evaluated for weight variation, angle of repose, Bulk density, compressibility index, drug content and were subjected to 12 hour *invitro* dissolution studies using 0.1N hydrochloric acid for first 2 hours, phosphate buffer pH 6.8 as a dissolution medium for next 10 hours. The sustained core tablets contains HPMC K100M and Eudragit RS 100 combination shows good drug release i.e 96.86% as well as follows zero order kinetics. The outer coat immediate release showing with 97.68 % of drug release due to disintegration agent more concentration of sodium starch glycollate and cross povidone. This modified release inlay tablets also reduced dosing frequency, increase the bioavailability and provide better patient compliance.

Keywords: Losartan potassium, Hpmc K100, Eudragit RS, Sodium starch glycolate, Zero order.

INTRODUCTION

For every disease or disorder condition of the patient, proper medication is of major importance to maintain the patient in good health. In conventional oral dosage forms drug dosage must be taken numerous times which results in fluctuating drug levels in plasma. This disadvantage of conventional dosage form can be overcome through formulation of modified release dosage forms which provides drug release in an amount sufficient to continue the therapeutic drug level over extended period of time (Rudnic ME *et al*., 2000).

In this type of dosage forms, a sufficient amount of drug is initially made available to the body to cause desired pharmacological response. The remaining fraction is released periodically and is required to maintain the maximum initial pharmacological activity for some desirable period of time in excess time expected from usual single dose (Aulton ME, 2002).

***Corrosponding author**

Y. Bhuvana Teja
Email id: reddy.hruthika4@gmail.com

MODIFIED RELEASE DOSAGE FORMS

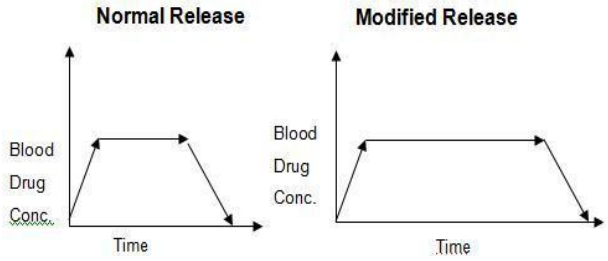
Modified-release dosage forms have been developed to distribute drug to the part of the body where it will be absorbed, to shorten dosing schedules, and to assure that concentration of drug is maintain over an appropriate time interval. Drugs that are not intrinsically long lasting require multiple daily dosing to achieve the desired therapeutic effects (Shargel L *et al*., 1999).

Advantages

1. Increased time within the Therapeutic Window due to lesser peak plasma concentration and shallower slope
2. Has kinetics similar to IV infusion, with the ease of a tablet
3. Decrease dosing frequency

Disadvantages

1. If a toxic dose is given, it will stay toxic for a long time
2. Takes a long time to treat patient
3. Strong first pass effect by staying below the metabolizing enzymes saturation point



INLAY TABLETS

A type of layered tablet in which instead the core tablet being completely surrounded by coating, top surface is completely exposed. Tablet compressing was done with core rod tooling in which only one surface of core is expose to outside and other drug is incorporated in cup portion. While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it (Jantzen GM *et al*., 1995; Rajalakshmi R *et al*., 2011).

HYPERTENSION

Hypertension means high blood pressure (tension) in the arteries. Normal blood pressure is below 120/80. 120 correspond to systolic blood pressure; represent the pressure in the arteries as the heart contracts and pumps blood forward into the arteries. 80 corresponds to diastolic pressure, represents the pressure in the arteries as the heart relaxes after the contraction.

CLASSIFICATIONOF HYPERTENSION

There are two major types of hypertension and four less frequently found types.

- Primary hypertension
- Secondary hypertension

The other types include:

- Malignant hypertension
- Isolated systolic hypertension
- White Coat Hypertension
- Resistant Hypertension
- Resistant Hypertension

MATERIALS AND METHODS

Materials

Losartan potassium, Hpmc K100, Hpmc K4, Eudragid RSPO, Sodiumstarch glycolate, Starch, Magnesium Stearate, Lactose, Microcrystalline cellulose, Pvpk-30.

Determination of λ max of losartan potassium in acidic 0.1N Hcl

Standard stock solution was prepared by dissolving100mg drug in 100ml of 0.1N HCl to get concentration of 1000mcg/ml. This solution was subjected to scanning between 200 – 400 nm and absorption maximum was determined. From the spectra of drug λ max of losartan potassium 207 nm was selected for the analysis.From the standard stock solution, 1 ml of the stock solution was further diluted to 100 ml with 6.8 phosphate buffer into a 100 ml volumetric flask and diluted up to the mark with 6.8 phosphate buffer Aliquots of 0.2, 0.4, 0.6, 0.8, upto 1.4ml of stock solution were pipette out into 10ml volumetric flasks. The volume was made up to the mark with phosphate buffer. The absorbance was measured in the UV spectrophotometer at 207 nm (Jayesh Parmar *et al*., 2009).

Determination of λ max of losartan potassium in phosphate buffer pH 6.8

Standard stock solution was prepared by dissolving100mg drug in 100ml of 6.8 phosphate buffer to get concentration of 1000mcg/ml. This solution was subjected to scanning between 200 – 400 nm and absorption maximum was determined. From the spectra of drug λ max of losartan potassium 207 nm was selected for the analysis. From the standard stock solution, 1 ml of the stock solution was further diluted to 100 ml with 6.8 phosphate buffer into a 100 ml volumetric flask and diluted up to the mark with 6.8 phosphate buffer Aliquots of 0.2, 0.4, 0.6, 0.8, upto 1.4ml of stock solution were pipette out into 10ml volumetric flasks. The volume was made up to the mark with phosphate buffer. The absorbance was measured in the UV spectrophotometer at 207 nm.

PREPARATION OF INLAY TABLET

The Inlay tablets of losartan potassium were prepared by the direct compression method.

a. 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 distributionof the drug in formulation. The blend was mixed with aerosil and magnesium stearate.

b. Formulation of the 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.

EVALUATION

Evaluation of Granules (Brahmankar HA *et al*., 2000)

i. Bulk Density (D_b)

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

$$D_b = M / V_b$$

ii. Tapped Density (D_t)

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 as

ontinued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by,

$$D_t = M / V_t$$

Where, M is the mass of powder, V_t is the tapped volume of the powder.

iii. Angle of repose (Θ):

The rubbing forces in a loose powder can be measured by the angle of repose. It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

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

iv. Compressibility index:

It indicates the flow properties of powders. It is expressed in percentage and is give by,

$$\text{Compressibility\%} = [(TD-BD)/ TD] \times 100$$

iv. Hausner ratio:

It is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Evaluation of Tablets

1. Uniformity of weight

According to the official test, twenty tablets from each batch were selected randomly & weighed individually using a highly sensitive electronic balance. The mean weight was calculated for each batch. The percent deviation was calculated using the following formula.

2. Tablet Hardness

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness (diametric crushing strength). The hardness of 6 tablets of each formulation was measured by using Monsanto hardness tester.

3. Friability

For each formulation, 20 tablets were weighed.The tablets were placed in a friabilator (Roche Friabilator) and subjected to 100 rotations in 4 minutes. The tablets were then dedusted and reweighed. The friability was calculated as the percentage weight loss.

4. Content Uniformity

Twenty uncoated tablets were randomly selected & average weight was calculated. Tablets were crushed in a mortar individually and accurately weighed amount of tablet triturate from each blend was taken. Samples were transferred to twenty different volumetric flasks and were diluted up to the mark with purified water. The content was shaken well for some time and kept for 30 minutes for dissolving of drug completely. The mixtures were filtered and appropriate dilutions were made. The drug content in each tablet was estimated at λ max 207nm against blank reference and reported.

5. In vitro drug release

In vitro drug release studies were carried out using USP – type I dissolution apparatus (Basket type) at 100 rpm. The dissolution medium consisted of 1000 ml purified water maintained at 37 + 0.5 °C. The collected samples were analyzed at 207 nm using phosphate buffer solution pH 6.8 as a blank. The cumulative percentage drug release was calculated.

6. Drug release kinetics

To study the release kinetics, data obtained from *In-vitro* drug release studies were plotted in various kinetics models:

Zero order- cumulative percentage of drug released Vs. time,

First order- log cumulative percentage of drug remaining Vs. time,

Hixson-Crowell- Cube root of % of drug remaining in the tablet Vs. time,

Higuchi model- square root of time Vs. percentage of drug release.

Accelerated stability studies

The optimized formulation of metformin hydrochloride were packed in strips of 0.04mm thick aluminium foil laminated with polyvinyl chloride by strip packing and these packed formulation were stored in ICH certified stability chambers (thermo labs) maintained at 40 ˚C and 75% RH for 3 months (zone III conditions as per ICH Q1 guidelines). The samples were withdrawn and evaluated for their hardness, content uniformity and for *invitro* drug release.

Table.1 Formulation of Losartan potassium Sustained release granules

S.No	Ingredients	F1 Mg	F2 Mg	F3 mg	F4 mg	F5 mg	F6 mg	F7 mg	F8 mg	F9 mg	F10 Mg
1	Losartan potassium	50	50	50	50	50	50	50	50	50	50
2	Lactose	73	73	70	70	43	77.5	67	59.5	59.5	59.5
3	HPMC K100	15	15	22.5	-	22.5	-	-	15	-	15
4	HPMC K4	-	-	-	22.5	22.5	-	-	-	15	15
5	Eudragid RSPO	-	-	-	-	-	15	22.5	15	15	-
6	Starch	7.5	-	-	-	-	-	-	-	-	-
7	PVP K30	-	7.5	3	3	7.5	3	6	6	6	6

8	Aerosil	3	3	3	3	3	3	3	3	3	3
9	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Total	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Table.2 Formulation of losartan potassium immediate release granules

S.No	Ingredients	F1 Mg	F2 mg	F3 mg	F4 mg	F5 mg	F6 Mg	F7 Mg	F8 mg	F9 Mg	F10 mg
1	Losartan potassium	25	25	25	25	25	25	25	25	25	25
2	MCC	109	109	113.5	115	112	110.5	117.5	115	113.5	112
3	PVP K30	-	7.5	3	1.5	3	3	1.5	1.5	1.5	1.5
4	Starch	7.5	-	-	-	-	-	-	-	-	-
5	Sodium starch glycolate	3	3	3	3	4.5	6	1.5	3	-	-
6	Cross povidone	-	-	-	-	-	-	1.5	3	4.5	6
7	Talc	3	3	3	3	3	3	3	3	3	3
8	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
9	Brilliant blue	1	1	1	1	1	1	1	1	1	1
	Total	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

EVALUATION OF POWDER BLENDS

Table.3 Precompression parameters of losartan potassium Immediate release granules

Formulation	Angle of Repose (θ)	Tapped Density (g/cc)	Bulk Density (g/cc)	Compressibility Index (%)	Hausner's Ratio
F1	22.47	0.5578	0.5007	10.23	1.114
F2	21.62	0.5858	0.5202	11.98	1.126
F3	22.83	0.5793	0.5148	11.34	1.125
F4	20.09	0.5852	0.5178	11.51	1.130
F5	20.74	0.5384	0.4773	11.34	1.128
F6	23.24	0.5715	0.5072	11.25	1.126
F7	22.84	0.5535	0.4847	12.42	1.141
F8	21.52	0.5821	0.5146	11.59	1.131
F9	21.47	0.5941	0.5274	11.22	1.126
F10	20.16	0.5846	0.5171	11.54	1.130

Table.4 Preformulation parameters Losartan potassium Sustained release core granules

Formulation	Angle of Repose (θ)	Tapped Density (g/cc)	Bulk Density (g/cc)	Compressibility Index (%)	Hausner's Ratio
F1	21.54	0.5852	0.5007	14.43	1.168
F2	23.86	0.5623	0.4902	12.82	1.147
F3	22.65	0.5914	0.5148	12.95	1.148
F4	21.47	0.5518	0.4878	11.59	1.131
F5	22.85	0.5978	0.5273	11.79	1.133
F6	21.46	0.5724	0.5072	11.39	1.128
F7	20.62	0.5537	0.4847	12.46	1.142
F8	21.41	0.5764	0.5146	10.72	1.120
F9	20.62	0.5814	0.5174	11.20	1.123
F10	22.45	0.5935	0.5171	12.87	1.147

Table.5 Post compression parameters of losartan potassium inlay tablets

Batch Code	% Weight Variation	Hardness (Kg/cm^2)		Thickness (mm)	Friability (%W/W)	Drug Content	Disintegration Time (sec)
		core	Cup				
F1	300±0.04	5.8±0.06	2.1±0.09	3.4±0.06	0.19±0.02	98.24	49
F2	300±0.02	5.5±0.11	2.4±0.21	3.2±0.01	0.16±0.04	98.41	58
F3	301±0.08	5.3±0.09	1.9±0.18	3.5±0.05	0.21±0.01	97.42	45
F4	301±0.06	6.1±0.21	2.3±0.37	3.1±0.09	0.16±0.05	99.25	54
F5	302±0.08	5.6±0.06	2.0±0.09	3.4±0.02	0.20±0.03	97.24	46
F6	302±0.04	5.9±0.26	2.2±0.26	3.3±0.09	0.18±0.02	98.54	52

F7	301±0.07	5.4±0.21	1.9±0.09	3.6±0.01	0.23±0.01	98.51	43
F8	301±0.02	5.7±0.06	1.8±0.24	3.6±0.06	0.26±0.04	99.27	40
F9	300±0.07	5.8±0.24	2.5±0.24	3.1±0.09	0.14±0.03	98.32	62
F10	301±0.01	5.3±0.16	2.1±0.08	3.3±0.02	0.17±0.02	98.96	48

Table.6 *In vitro* drug release data for Losartan potassium Inlay Tablets

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0.25	31.33±2.1	29.54±2.6	31.2±2.3	34.93±2.1	35.87±2.1	39.56±2.4	38.97±2.4	**41.25±2.1**	38.58±2.5	40.54±2.34
0.5	53.62±1.9	57.82±3.4	55.47±4.1	54.75±2.4	53.21±3.5	55.27±2.7	58.98±2.8	**56.96±2.7**	56.12±3.9	57.65±2.64
0.75	78.58±2.7	76.39±2.9	71.32±3.5	83.24±4.6	89.19±2.6	81.87±3.5	72.86±2.1	**83.95±2.4**	87.23±4.1	89.84±3.1
1	89.26±3.5	91.8±3.5	93.81±2.5	91.25±3.4	93.97±2.8	98.92±2.8	85.04±3.5	**97.68±3.1**	96.29±2.8	99.56±4.2
2	23.74±2.9	21.47±2.8	21.92±3.2	22.48±3.3	20.62±2.5	19.96±2.4	16.12±±2.6	**14.28±3.5**	17.35±2.4	13.14±2.8
3	33.34±3.8	36.85±2.4	34.42±2.6	37.19±2.7	49.26±3.7	41.63±3.2	43.74±4.8	**29.32±2.9**	29.54±3.6	27.6±53.5
4	41.32±4.2	50.83±4.3	45.83±3.2	48.32±2.8	56.47±4.3	55.82±2.7	50.96±3.7	**38.26±2.1**	36.21±4.3	35.78±2.7
5	54.06±3.5	61.23±2.7	57.21±2.8	56.76±3.1	64.29±4.8	64.25±4.6	57.39±2.8	**47.61±3.5**	42.78±3.8	42.21±2.6
6	79.51±3.5	78.37±3.5	64.25±4.2	65.51±2.6	71.26±2.4	69.29±5.1	62.23±2.3	**54.32±3.8**	53.57±3.5	51.35±3.1
7	88.31±3.4	89.16±5.4	73.62±4.8	76.31±4.2	79.94±2.7	76.96±2.4	71.48±3.4	**69.96±2.6**	62.85±2.7	59.78±2.9
8	94.34±4.8	95.92±3.1	82.65±2.6	84.35±2.8	84.23±2.6	81.23±3.5	82.23±2.6	**73.52±3.3**	71.47±4.3	66.85±3.2
9	98.21±5.1	101.24±3.9	91.24±2.1	96.73±2.4	89.26±2.1	86.47±3.7	88.56±2.1	**80.17±2.6**	82.14±2.4	77.67±4.1
10			96.57±2.9		93.78±2.8	93.47±2.5	91.54±3.3	**89.23±3.1**	89.21±3.2	83.87±2.8
11					95.52±2.5			**96.86±2.5**	94.74±2.5	95.56±2.6

Figure.1 Inlay tablet

Figure.2 Formulation of Inlay tablet

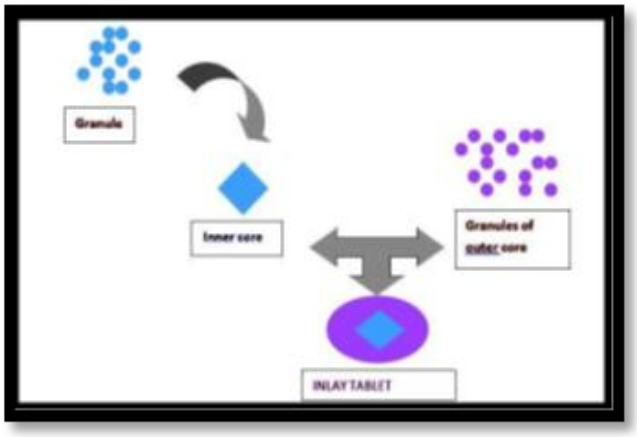


Figure.3 FTIR Graph For Pure Drug Of Losartan Potassium

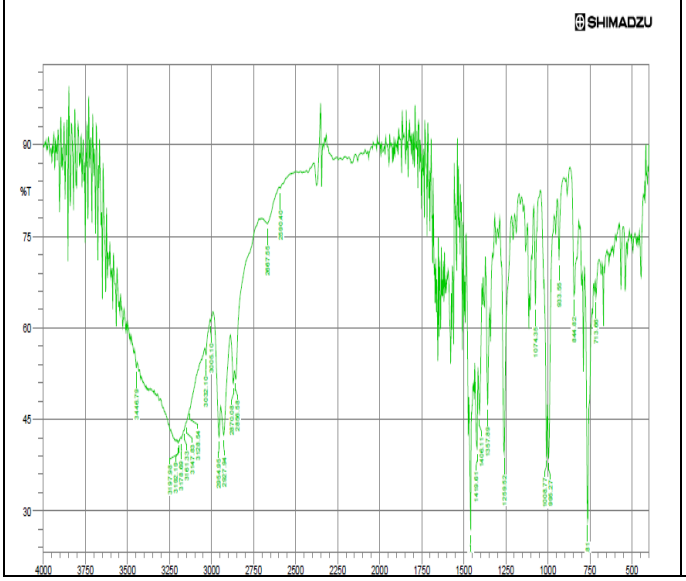


Figure.4 FTIR Graph For Eudragit RS 100

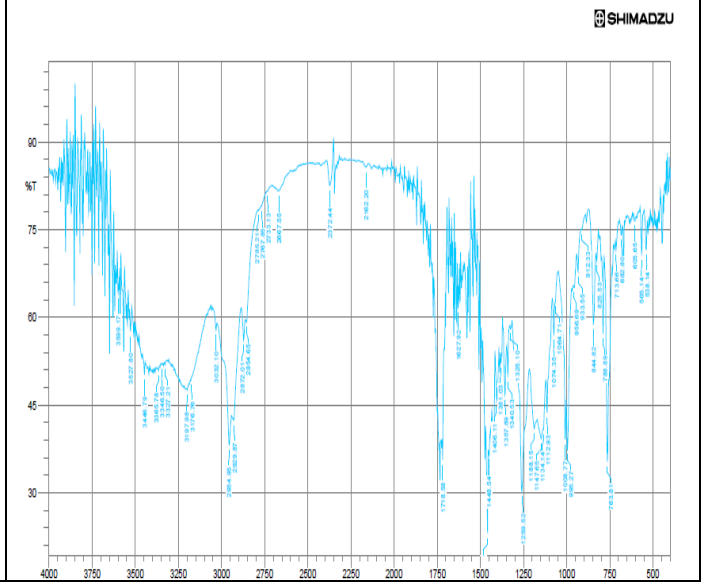


Figure.5 FTIR graph for HPMC K100

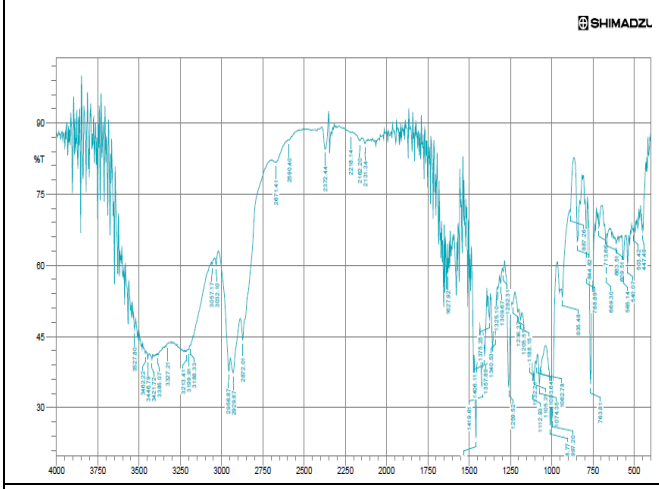


Figure.6 FTIR graph for HPMC K4

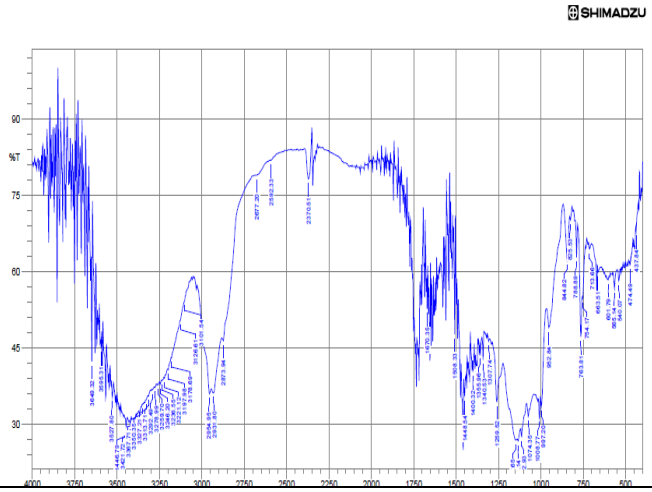


Figure.7 *In Vitro* Drug Release Graphs For Formulation F1-F3

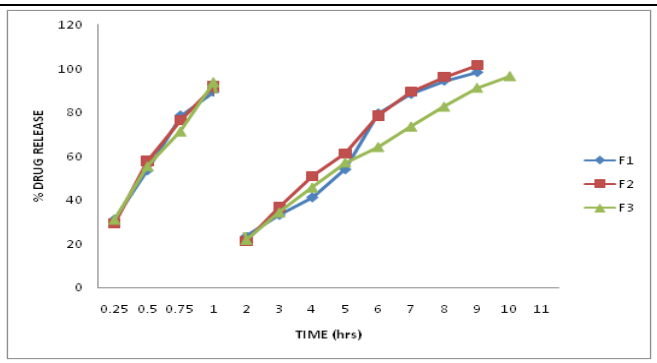


Figure.8 *In vitro* Drug Release Graphs For Formulation F4-F6

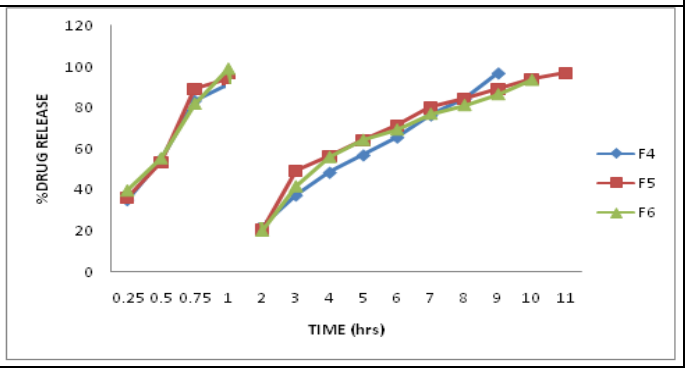


Figure.9 Invitro Drug Release Graphs For Formulation F7-F10

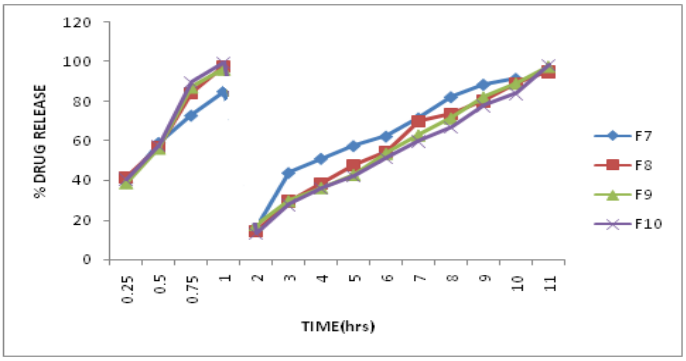
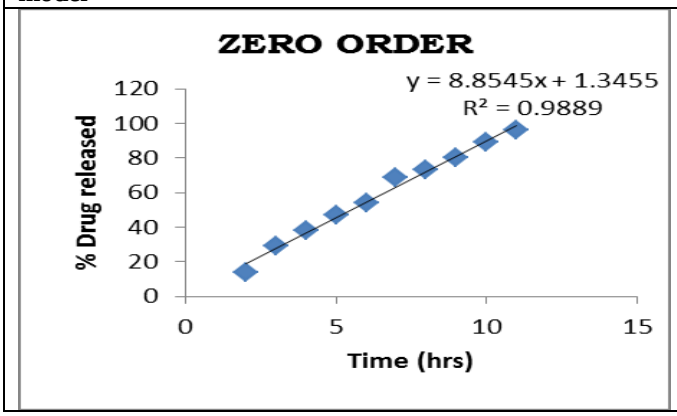
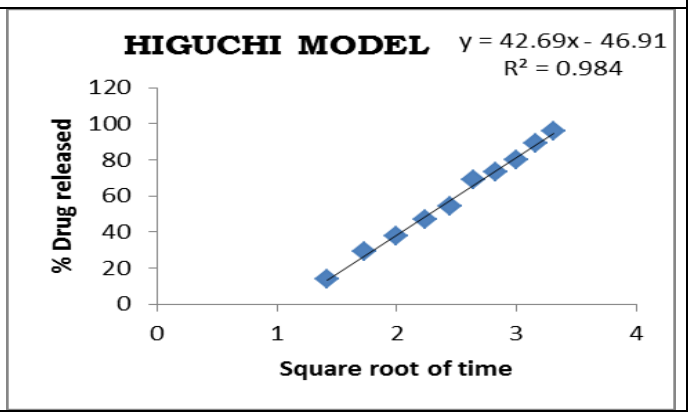


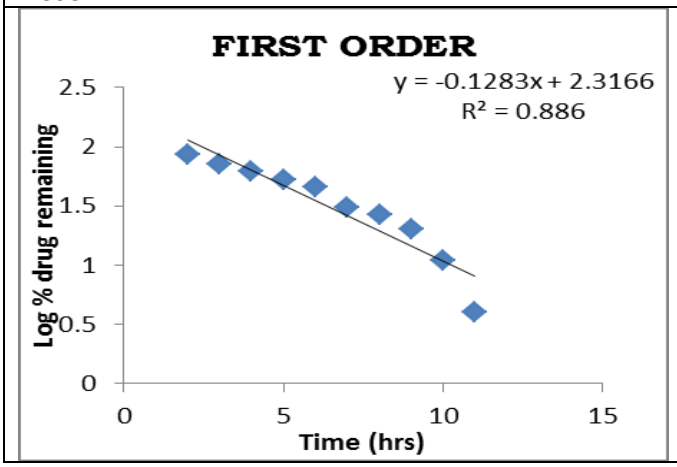
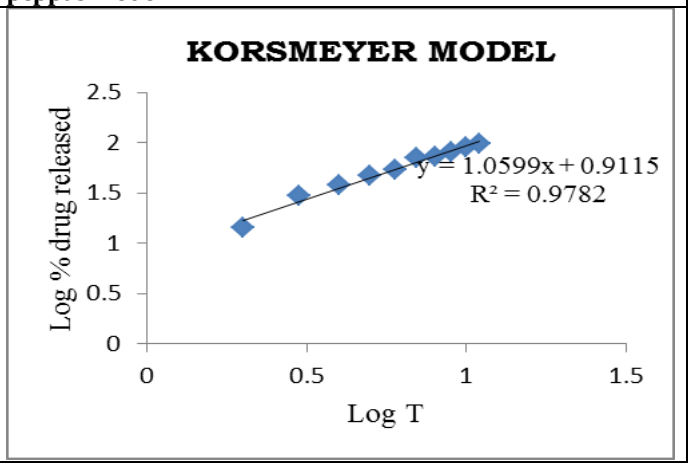
Figure.10 Kinetic Studies For Optimised Formulation (F8)

Kinetic release of losartan potassium for Zero order model



Kinetic release of losartan potassium for Higuchi model



Kinetic release of losartan potassium for First order model	Kinetic release of losartan potassium for Korsmeyer peppas model
	

RESULTS

Drug excipient compatibility study

FT-IR studies: I.R spectra of pure drug losartan potassiumand combination of losartan potassium and excipients were obtained. All the characteristic peaks of losartan potassium were present in Spectra thus indicating compatibility between drug and excipients.

CONCLUSION

Both immediate release and sustained release formulation are prepared by direct compression techniques and contain in a single dosage form usingsuper disintegrant sodium starch glycolate for fast release layer and combination of HPMC K100M, HPMC K4M and Eudragit RS 100 for sustaining release layer. The prepared tablets were evaluated for weight variation, hardness, friability, thickness, drug content and *in-vitro* drug release stdies. The sustained core tablets contains HPMC K100Mand Eudragit RS 100combination shows good drug release i.e 96.86% as well as follows zero order kinetics. The outer coat immediate release showing with 97.68 % of drug release due to disintegration agent more concentration of sodium starch glycollate and cross povidone.

REFERENCES

Aulton ME. Eds. Pharmaceutics: The science of dosage form design. 2nd edn., Churchill Livingstone, New York, 2002, 487-488, 492-495.

Brahmankar HA, Jaiswal SB, Biopharmaceutics and Pharmacokinetics A Treatise, Vallabh Prakashan, 2000, 337, 348-357.

Guidelines Subcommittee, World Health Organization-International Society of Hypertension. Guidelines for the Management of Hypertension. *J Hypertens*. 1999;17:151-183.

Hypertension Society of Southern Africa. Guidelines for the management of hypertension at primary health care level. *S Afr Med J*. 1995;85:1321-1325.

Jantzen GM, Robinson JR, Sustained and controlled-release drug delivery systems, in Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, 3rd ed., Marcell Dekker, Inc. New York, 72, 1995, 575-609.

Jayesh Parmar, Manish Rane. Tablet Formulation Design and Manufacture: Oral Immediate Release Application. *Pharma Times*. 2009;41(4):21-29.

R. Rajalakshmi, A. Sireesha, S. Mohana Lakshmi. Inlay tablets – A novel approach. *International Journal of Advanced Pharmaceutics*. 2011;1(1).

Rudnic ME, Joseph D. Oral solid dosage form. In: Gennaro AR, editor. Remington: the science and practice of pharmacy. 20th ed. Philadelphia: Lippincott Williams & Wilkins; 2000. vol. 1 p. 858-62.

Shargel L, Yu ABC. Modified release drug products, Applied Biopharmaceutics and Pharmacokinetics. 4th ed. McGraw Hill, 1999, 169-171.