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FORMULATION AND INVITRO EVALUATION OF LOSARTAN POTASSIUM OSMATIC CONTROLLED MATRIX TABLETS

H. Padmalatha
Gyana Jyothi College of Pharmacy

Abstract:

The aim of the present study was to develop a controlled porosity osmotic tablet of Losartan potassium and to evaluate the in vitro release of the drug from the system. The osmotic tablet is developed such that it delivers 8 mg of Losartan potassium over a period of 24 hours. Drug – Excipient compatibility study was carried out using FTIR study. The results showed that there was no interaction between them. Calibration curves of Losartan potassium were constructed in three different pH; Acid buffer pH 1.2, Acetate buffer pH 4.5 and phosphate buffer pH 6.8. Wet granulation produced excellent flow and the granules were compressed on 9/32 concave punches into tablets. The tablets were then coated with a controlled porosity semipermeable membrane of CA with sorbitol as pore former. The post compression parameters namely uniformity of weight, thickness, diameter, hardness, drug content and uniformity of content were evaluated for the coated and uncoated tablets and were found to be within limits. To describe the mechanism of drug release, the optimized formulation was fitted to various models. The drug release was found to follow zero order and Hixson Crowell release. The accelerated stability testing was carried out for 3 months and showed no change inthe appearance, hardness, diameter, thickness, friability, drug content and in vitro release.

Key words: *Formulation, Evaluation, Losartan potassium, Osmatic controlled, matrix tablets*

Corresponding author:
H. Padmalatha,
Principal,
Gyana Jyothi College of Pharmacy
Gyana Jyothi Nagar, Uppal, Hyderabad
Telangana, India.
E-mail: Padmalatha.malthar@gmail.com

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INTRODUCTION:

The delivery of drugs has changed over time with drugs targeting specific tissues like cancer tissue or sustained and controlled rates of drug delivery [1]. Nowadays, novel drug delivery systems are continuously replacing conventional drug delivery systems. Recently, controlled release systems have been tremendously popular. They avoid multiple dosing and as well as prolonged delivery of drugs, which has importance for scientists as well the pharmaceutical industry [2]. Controlled release (CR) systems offer constant release for a longer duration with improved compliance [3]. A perfect drug delivery system has two good basic aspects; that is, providing the required drug content and being target-specific. Conventional and controlled release dosage forms have the same systemic availability as well as therapeutic effects when prepared in different dosages, but the only difference observed was the single dosage for controlled release forms [4]. It is well known that controlled release devices have predictability and reproducibility in release kinetics [5]. In another study, metformin HCl matrices were developed with various polymers to sustain the drug release rates [6]. Flurbiprofen controlled release matrix tablets were prepared to extend the drug release rates, with Eudragit as a rate-controlling agent [7]. Matrix tablets are well-known controlled release dosage forms, releasing the drug either by dissolution or diffusion mechanism. Drug and rate-controlling agents are mixed homogeneously, and rate-controlling agents can be hydrophilic, mineral, lipid, or plastic, among others [8]. Carbamazepine controlled release tablets were also developed with polymers such as HPMC of various grades, using the wet granulation technique and some using the direct compression method. They found that the drug was efficiently extended by HPMC [9]. Glipizide controlled release matrices were prepared by direct compression technique and used Eudragit and HPMC as polymers, and evaluated its physicochemical characteristics and noted that drug release was extended [10]. Losartan potassium belongs to the group of angiotensin 2 receptor blockers and is mostly used in the management of high blood pressure. Its half-life is about 2 h and it is available in off-white crystalline powder [11]. It is freely soluble in phosphate buffer 6.8 pH [12]. Sustained release losartan potassium matrices were developed by the direct compression method using polymers ethylcellulose, eudragit RSPO, and eudragit RLPO, and it was noted that drug release rates were more extended with ethylcellulose when used in combination than polymers used alone [13]. The authors of [14] prepared sustained release matrix tablets of losartan potassium with xanthan gum by direct compression methods and evaluated the in vitro dissolution as well pharmacokinetics. In another study, controlled release matrices were developed with synthetic and non-synthetic polymers and evaluated for physic-chemical characteristic, and it was found that polymeric combination attained 24 h release of the drug [15]. The authors of [16] developed sustained release matrices of losartan potassium with gum prosophis juliflora as a rate-altering agent, and the authors noted that the polymeric material sustained the drug release rates. Losartan potassium sustained release matrices were prepared with xanthan gum, ethylcellulose, and HPMC and evaluated for in vitro dissolution, and it was observed that formulation F3 sustained drug release rates up to 10 h [17]. Directly compressed controlled release matrices of losartan potassium were prepared with the following polymers: sodium alginate, pectin, and xanthan gum, and dissolution studies were performed for drug release. It was noted that drug release was in controlled fashion from the matrices [18].

MATERIALS AND METHODOLOGY:

MATERIALS

Losartan Potassium was obtained as gift sample from M/S AUROBINDO Pharma Ltd, Hyderabad. Hydroxy propyl methyl cellulose (Methocel/HPMCK15M) was obtained as gift sample from M/S Colorcon Asia Pvt. Ltd, Mumbai. Microcrystalline Cellulose (Tabulose) and Mannitol was obtained as Gift Sample from M/S Matrix Pharma Ltd, Hyderabad. Talc and magnesium stearate were obtained commercially from Loba Chemie Pvt. Ltd, Mumbai. Ethyl cellulose-7cps was obtained commercially from S.D.Fine Chem. Ltd, Mumbai. Poly Ethylene Glycol-4000 was obtained as gift sample from Sisco Research Laboratories Pvt. Ltd, Mumbai.

METHODOLOGY

PHYSICAL COMPATIBILITY STUDY

The physical admixture of the drug and excipients so as to reflect those expected to be present in the final product were taken in 2 ml glass vials and sealed. These glass vials were kept at room temperature and at $40^{\circ} \pm 2$ºC / 75% ± 5% RH for 1 month. At the end of 10 days, the samples were withdrawn and analyzed for colour change.

FTIR STUDY- IDENTIFICATION AND COMPATIBILITY OF DRUG ANDPOLYMER

Infrared Spectroscopy was conducted using FTIR spectrophotometer and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing the sample (drug alone, mixture of drug and excipients and the optimized formulation) in KBr and compressed into discs by applying a pressure of 5 Tons for 5minutes in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded.

STANDARD CURVE FOR LOSARTAN POTASSIUM

Standard curve in 0.1 N Hydrochloric Acid Buffer pH 1.2

50 mg of Losartan potassium was weighed, transferred to 50 ml standard flask and dissolved in equal proportions of methanol(25ml) and 0.1N Hydrochloric Acid buffer pH 1.2 (25ml) to geta concentration of 1mg/ml. From the stock solution 10ml was taken and diluted to 100ml with 0.1N Hydrochloric Acid buffer pH 1.2 to get a concentration of 100mcg/ml. The above solution was further diluted with to get a concentration of 2, 4, 6,8,10 mcg/ml. The absorbance of the resulting solution was measured at 376nm using UV-Visible Spectrophotometer taking 0.1N Hydrochloric acid acid buffer pH1.2 as blank.

Standard curve in Acetate Buffer pH 4.5

50 mg of Losartan potassium was weighed, transferred to 50ml standard flask and dissolved in equal proportions of methanol(25ml) and Acetate buffer pH 4.5 (25ml) to get a concentration of 1mg/ml. From the stock solution 10ml was taken and diluted to 100ml with Acetate buffer pH 4.5 to get a concentration of 100mcg/ml. The above solution was further diluted to get concentrations of 2, 4, 6,8,10 mcg/ml. The absorbance of the resulting solution was measured at 376nm using UV-Visible Spectrophotometer taking Acetate buffer pH 4.5 as blank.

Standard curve in Phosphate Buffer, pH 6.8

50 mg of Losartan potassium was weighed, transferred to 50ml standard flask and dissolved in equal proportions of methanol (25ml) and Phosphate buffer pH 6.8 (25ml) to get a concentration of 1mg/ml. From the stock solution 10ml was taken and diluted to 100ml with Phosphate buffer pH 6.8 to get a concentration of 100mcg/ml. The above solution was further diluted to get a concentration of 2, 4, 6,8,10 mcg/ml. The absorbance of the resulting solutionwas measured at 376nm using UV-Visible Spectrophotometer taking Phosphate buffer pH 6.8as blank.

Table 1: Angle of Repose, Carr's Index and Hausner's Ratio

Flow Property	Angle of repose (θ in degrees)	Carr's Index (CI in %)	Hausner's Ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>66	>38	>1.60

FORMULATION DEVELOPMENT

Preparation of Losartan potassium granules and compaction into tablets:

The Losartan potassium tablets were prepared with varying ratios of the osmogen (Mannitol). Drug and all the ingredients except lubricants were weighed and passed through sieve no. 20. The powders were mixed together. To the resultant powder mixture, PVP dissolved in isopropyl alcohol was added to form a coherent mass. Then the coherent mass was passed through 16 mesh screen to form granules. The wet granules were dried at 50^0C for 15 minutes. The dried granules were passed through sieve no. 20 to break the lumps and to get uniform particle size of granules. The lubricant was passed through sieve no. 40 and mixed with the dried granules.
The lubricated granules were compressed into tablets using 11/32 inches (8.0mm) standard concave punches on a 27 station rotary tablet punching machine.

Table 2: COMPOSITION OF CORE TABLETS

S.No	Ingredients	F01(mg)	F02(mg)	F03(mg)	F04(mg)
1	Losartan potassium	8	8	8	8
2	SLS	12	12	12	12
3	Tromethamine	25	25	25	25
4	Mannitol	0	50	100	150
5	Lactose	187	137	87	37
6	Povidone K30	12	12	12	12
7	Isopropyl alcohol	q.s	q.s	q.s	q.s
8	Magnesium Stearate	2.5	2.5	2.5	2.5
9	Talc	2.5	2.5	2.5	2.5
10	Aerosil	1	1	1	1
Total Weight		**250 mg**			

RESULTS AND DISCUSSION:

The physical compatibility study was performed visually. The results show thatthe drug and the excipients were physically compatible with each other.

The identification of drug and the compatibility between the drug and the different excipients was carried out using FTIR. The FTIR spectrum of the pure drug, drug – excipientsmixtures and final formulation were shown in figures

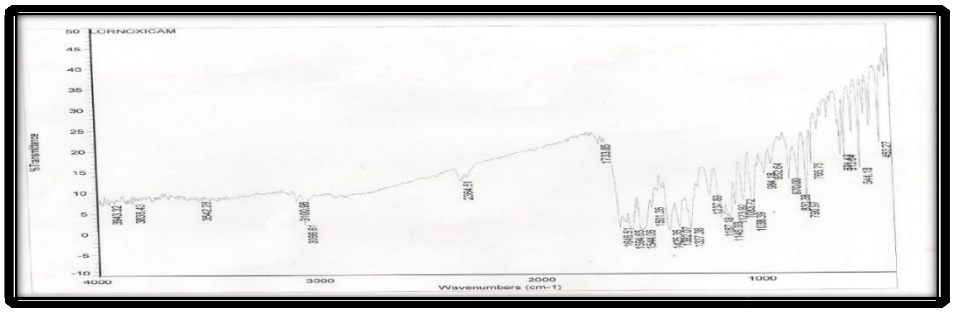

Fig. 1: FTIR Spectrum of Losartan potassium

Table 3: IR Interpretation of Losartan potassium

Wave Numbers (cm^{-1})	Interpretation
3066.61	Aromatic C-H Stretching
1425.35	C=C Stretching
1501.35	C=N Stretching
3100.96	N-H Stretching
3542.28	O-H Stretching
1646.51	C=O Stretching
1382.07	SO_2 Stretching
870	S-N Stretching
765.75	C-S Stretching

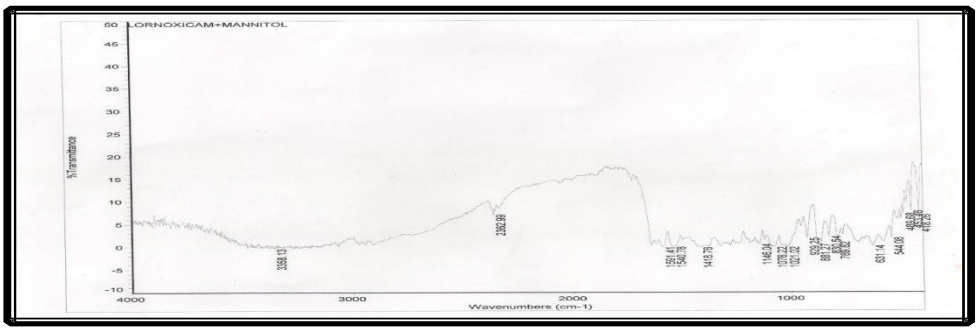

Fig. 2: FTIR Spectrum of Losartan potassium and Mannitol

Table 4: IR Interpretation of Losartan potassium and Mannitol

Wave Numbers (cm^{-1})	Interpretation
3066.00	Aromatic C-H Stretching
1418.76	C=C Stretching
1540.70	C=N Stretching
3100.00	N-H Stretching
3542.00	O-H Stretching
1591.41	C=O Stretching
1382.00	SO_2 Stretching
881.27	S-N Stretching
789.82	C-S Stretching

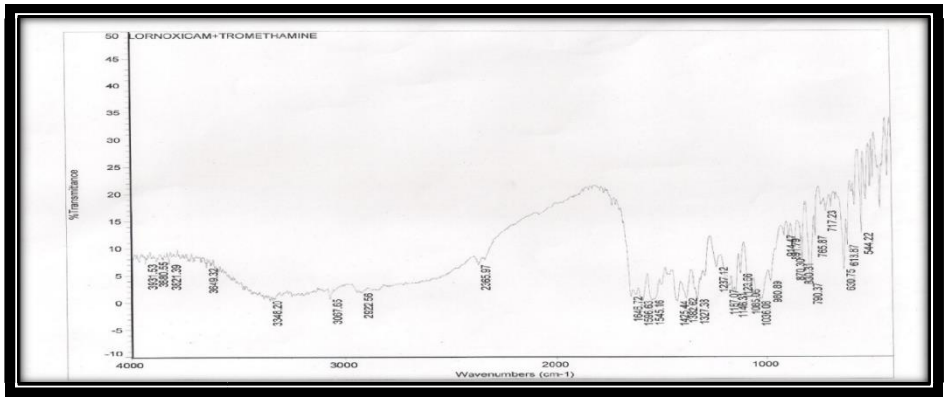

Fig. 3: FTIR Spectrum of Losartan potassium and Tromethamine

Table 5: IR Interpretation of Losartan potassium and Tromethamine

Wave Numbers (cm^{-1})	Interpretation
3067.65	Aromatic C-H Stretching
1425.44	C=C Stretching
1501.00	C=N Stretching
3067.65	N-H Stretching
3649.32	O-H Stretching
1646.72	C=O Stretching
1382.62	SO_2 Stretching
870.03	S-N Stretching
765.87	C-S Stretching

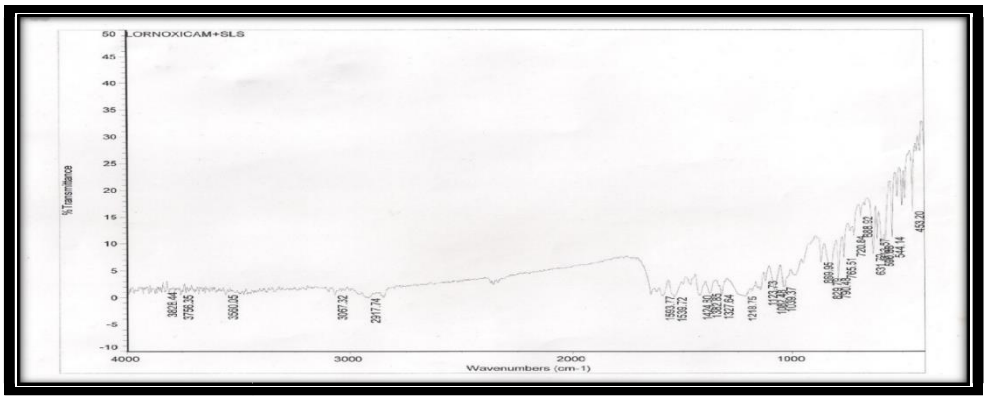

Fig. 4: FTIR Spectrum of Losartan potassium and SLS

Table 6: IR Interpretation of Losartan potassium and SLS

Wave Numbers (cm^{-1})	Interpretation
3067.32	Aromatic C-H Stretching
1424.50	C=C Stretching
1539.72	C=N Stretching
3100.00	N-H Stretching
3560.05	O-H Stretching
1646.00	C=O Stretching
1382.85	SO_2 Stretching
869.95	S-N Stretching
765.51	C-S Stretching

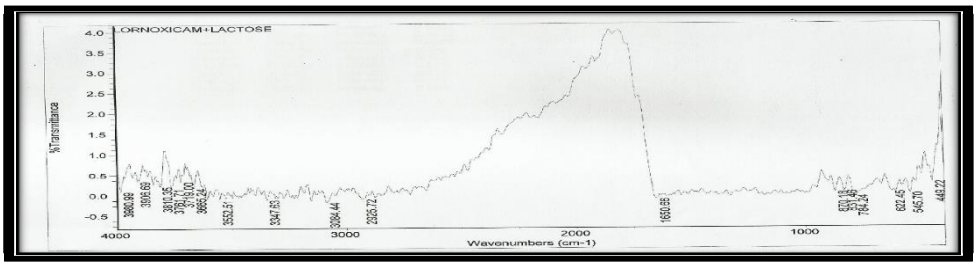

Fig. 5: FTIR Spectrum of Losartan potassium and Lactose

Table 7: IR Interpretation of Losartan potassium and Lactose

Wave Numbers (cm^{-1})	Interpretation
3067.32	Aromatic C-H Stretching
1427.00	C=C Stretching
1543.00	C=N Stretching
3093.00	N-H Stretching
3526.00	O-H Stretching
1643.00	C=O Stretching
1382.85	SO_2 Stretching
869.95	S-N Stretching
765.51	C-S Stretching

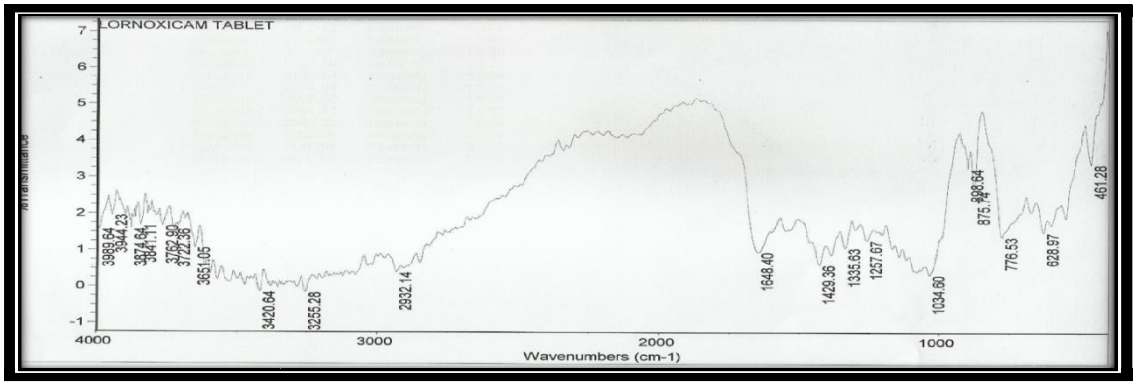

Fig. 6: FTIR Spectrum of Losartan potassium Tablet

Table 8: IR Interpretation of Losartan potassium Tablet

Wave Numbers (cm^{-1})	Interpretation
2932.14	Aromatic C-H Stretching
1429.36	C=C Stretching
1500	C=N Stretching
2932.14	N-H Stretching
3420.64	O-H Stretching
1648.40	C=O Stretching
875.74	SO_2 Stretching
1335.83	S-N Stretching
776.53	C-S Stretching

From the FTIR spectra, it is clearly evident that the physical mixtures of Losartan potassium with different excipients showed the presence of Losartan potassium characteristics bands at their same wave number. This indicated the absence of chemical interaction between the drug and the excipients.

STANDARD CURVE OF LOSARTAN POTASSIUM

The UV Spectrophotometric method was used to analyze LOSARTAN POTASSIUM. The absorbance of the drug in various buffers: 0.1 N HCl buffer pH 1.2, acetate buffer pH 4.5 and phosphate bufferpH 6.8 was measured at a wavelength of 376 nm.

Table 9: Standard Curve of Losartan potassium

S. No.	Concentration(mcg/ml)	Absorbance at 376 nm		
		pH 1.2	pH 4.5	pH 6.8
1	2	0.0971	0.0874	0.0786
2	4	0.1861	0.1705	0.1477
3	6	0.2698	0.2536	0.2214
4	8	0.3490	0.3366	0.2950
5	10	0.4280	0.4095	0.3680

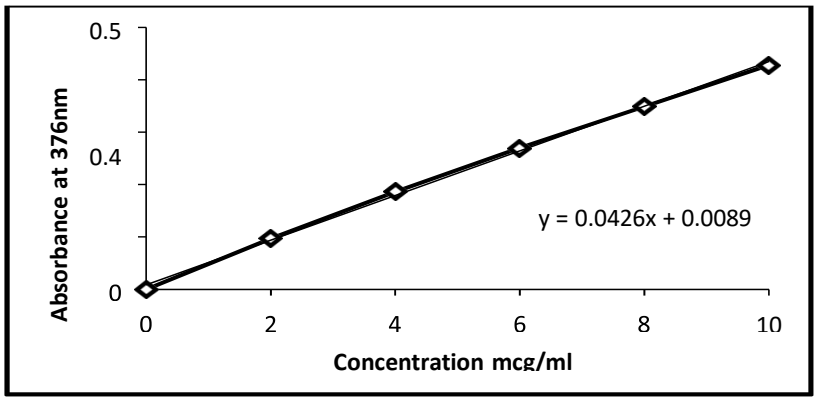

Fig. 7: Standard Curve of Losartan potassium in Acid buffer pH 1.2

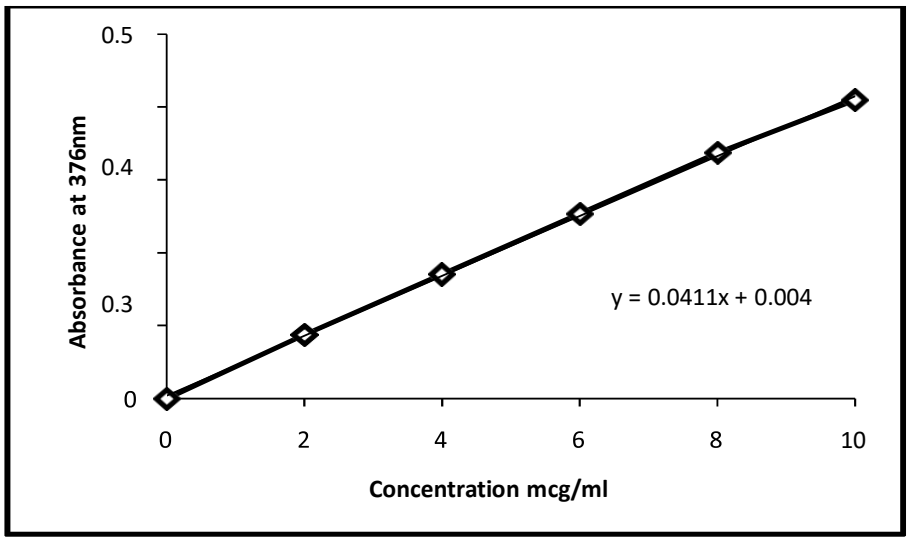

Fig. 8: Standard Curve of Losartan potassium in Acetate buffer pH 4.5

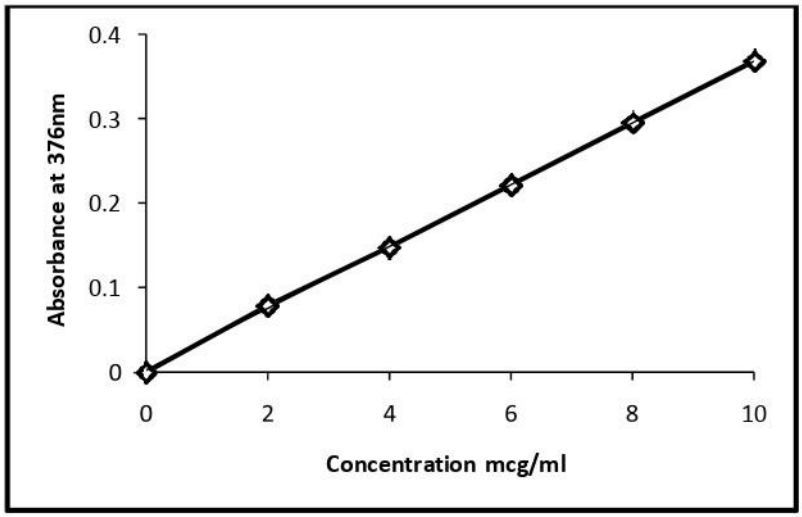

Fig. 9: Standard Curve of Losartan potassium in Phosphate buffer pH 6.8

The standard curve of Losartan potassium in buffers pH 1.2, 4.5 and 6.8 are linear, starting from theorigin. The curve obeys Beer Lambert law.[51]

PRECOMPRESSION STUDIES OF THE DRUG, BLENDS AND GRANULES

The result of precompression parameters for the drug and the formulated blends

Table 10: Precompression Study of Drug and Formulated Blends

Drug & Formulation	Bulk Density* (g/ml)	Tapped Density* (g/ml)	Compressibility Index*(%)	Hausner's Ratio*	Angle of Repose*(θ)
Drug	0.711±0.002	1.103±0.002	35.53±0.16	1.55±0.06	30.15±0.23
F01	0.663±0.007	0.768±0.008	13.67±0.10	1.15±0.08	31.32±0.23
F02	0.674±0.004	0.783±0.012	13.92±0.12	1.16±0.09	28.44±0.29
F03	0.622±0.005	0.730±0.009	14.79±0.14	1.17±0.12	35.44±0.28
F04	0.678±0.012	0.797±0.014	14.93±0.11	1.17±0.05	28.44±0.26

***Mean ± SD (n=5)**

The Angle of Repose of the blend ranged from 28.44^0 to 35.44^0. The Hausner's ratio ofthe formulated blends ranged from 1.15 to 1.17. The formulation blends showed poor – passable flow property.[76] Hence the wet granulation technique was used.

PRECOMPRESSION STUDIES OF DRUG AND GRANULES:

The result of pre compression studies of various formulations

Table 11: Precompression Study of Drug and Granules

Drug & Formulation	Bulk Density* (g/ml)	Tapped Density* (g/ml)	Compressibility Index*(%)	Hausner's Ratio*	Angle of Repose*(θ)
F01	0.510±0.004	0.585±0.007	12.82±0.21	1.14±0.03	19.44±0.16
F02	0.489±0.002	0.560±0.002	12.67±0.24	1.14±0.07	17.28±0.64
F03	0.479±0.003	0.534±0.006	10.29±0.28	1.11±0.05	19.43±0.17
F04	0.489±0.005	0.560±0.008	12.67±0.34	1.14±0.09	17.35±0.28

***Mean ± SD (n=5)**

The Angle of repose of the blend ranged from 17.28^0 to 19.44^0 .The Hausner's ratio ofthe formulated blends ranged from 1.11 to 1.14. The flow property of granules is excellent.

EVALUATION OF LOSARTAN POTASSIUM CORE TABLETS

Uniformity of weight

Table 12: Uniformity of weight of Losartan potassium core tablets

Formulation	Average weight of tablet*(g)
F01	0.249±0.002
F02	0.249±0.001
F03	0.252±0.003
F04	0.249±0.001

***Mean ± SD (n=5)**

The core tablets were uniform in weight

Thickness

Table 13: Thickness of Losartan potassium Core Tablets

Formulation	Thickness*(mm)
F01	3.27±0.0
F02	3.27±0.0
F03	3.28±0.0
F04	3.27±0.0

***Mean ± SD (n=5)**

The thickness of core tablets is found to be 3.27mm and 3.28 mm. The tablets haveuniform thickness.

Diameter

Table 14: Diameter of Losartan potassium Core Tablets

Formulation	Diameter*(mm)
F01	8.76±0.0
F02	8.76±0.0
F03	8.77±0.0
F04	8.76±0.0

***Mean ± SD (n=5)**

The diameter of all the formulations was found to be 8.76mm and 8.77 mm. The tabletshave uniform diameter.

Hardness

Table 15: Hardness of Losartan potassium core tablets

Formulation	Hardness* (kg/cm^2)
F01	3.0±0.0
F02	3.1±0.0
F03	3.0±0.0
F04	3.0±0.0

***Mean ± SD (n=5)**

The hardness of Losartan potassium core tablets was found to be between 3 kg/cm^2 and 3.1 kg/cm^2. Hence the tablets have enough hardness to withstand stress during transport andhandling.

Friability

Table 16: Friability of Losartan potassium core tablets

Formulation	%Friability*
F01	0.16±0.023
F02	0.10±0.012
F03	0.12±0.025
F04	0.12±0.019

***Mean ± SD (n=5)**

The percentage friability of various formulations ranged from 0.10% to 0.16%. Hence thepercentage friability complies with the official standard.[77]

EVALUATION OF LOSARTAN POTASSIUM COATED TABLETS

Uniformity of weight

Table 17: Uniformity of weight of Losartan potassium coated tablets

Formulations	Average weight of tablet*(g)
F01C1	0.278±0.003
F01C2	0.277±0.004
F01C3	0.277±0.002
F02C1	0.278±0.002
F02C2	0.277±0.003
F02C3	0.277±0.003
F03C1	0.277±0.002
F03C2	0.277±0.003
F03C3	0.276±0.002
F04C1	0.275±0.002
F04C2	0.276±0.002
F04C3	0.277±0.003

***Mean ± SD (n=5)**

The coated tablets were uniform in weight[77] and the weight ranged between 0.275g and 0.278 g.

Thickness

Table 18: Thickness of Losartan potassium coated tablets

Formulations	Thickness*(mm)
F01C1	3.542±0.014
F01C2	3.538±0.028
F01C3	3.568±0.019
F02C1	3.560±0.025
F02C2	3.546±0.016
F02C3	3.574±0.008
F03C1	3.542±0.034
F03C2	3.580±0.015
F03C3	3.568±0.013
F04C1	3.566±0.005
F04C2	3.570±0.033
F04C3	3.566±0.005

***Mean ± SD (n=5)**

The thickness of coated tablet was between 3.538mm and 3.580 mm. The table haveuniform thickness.

Diameter

Table 19: Diameter of Losartan potassium coated tablets

Formulations	Diameter*(mm)
F01C1	8.966±0.020
F01C2	8.952±0.031
F01C3	8.956±0.020
F02C1	8.946±0.048
F02C2	8.912±0.042
F02C3	8.950±0.010
F03C1	8.954±0.023
F03C2	8.952±0.032
F03C3	8.960±0.010
F04C1	8.934±0.040
F04C2	8.966±0.015
F04C3	8.960±0.007

***Mean ± SD (n=5)**

The diameter of coated tablet was found to be 8.912mm to 8.966 mm. The tablets haveuniform diameter.

Hardness

Table 20: Hardness of Losartan potassium Coated Tablets

Formulation	Hardness* (kg/cm^2)
F01C1	5.7±0.273
F01C2	5.7±0.447
F01C3	5.6±0.418
F02C1	5.7±0.273
F02C2	5.5±0.353
F02C3	5.6±0.418
F03C1	5.5±0.353
F03C2	5.2±0.570
F03C3	5.9±0.273
F04C1	5.3±0.447
F04C2	5.8±0.570
F04C3	5.5±0.500

***Mean ± SD (n=5)**

The hardness of coated tablet ranged between 5.2 kg/cm^2 and 5.8 kg/cm$^{2.}$ Hencethe tablets have enough hardness to withstand stress during transport and handling.[29]

Friability

Table 21: Friability of Losartan potassium Coated Tablets

Formulations	Friability (%)
F01C1	0.10±0.023
F01C2	0.16±0.021
F01C3	0.15±0.019
F02C1	0.15±0.022
F02C2	0.14±0.026
F02C3	0.13±0.021
F03C1	0.12±0.028
F03C2	0.22±0.024
F03C3	0.18±0.021
F04C1	0.62±0.022
F04C2	0.71±0.027
F04C3	0.70±0.023

***Mean ± SD (n=5)**

The friability of osmotic tablet ranged between 0.10% and 0.71 %. Hence thetablets have enough hardness to withstand stress during transport and handling.[77]

Drug Content

The content of active ingredients of various formulations was analyzed using UVspectrophotometer at 376 nm.

Table 22: Drug content

Formulations	Drug Content* (%w/w)
F01C1	100.84±1.403
F01C2	95.61±0.894
F01C3	97.33±0.976
F02C1	100.91±0.955
F02C2	99.08±1.110
F02C3	97.29±0.998
F03C1	95.26±0.987
F03C2	99.46±1.098
F03C3	97.15±1.143
F04C1	95.98±0.987
F04C2	98.33±1.056
F04C3	99.05±1.123

***Mean ± SD (n=5)**

The percentage of drug content of all the formulations ranged from 95.61% w/w to100.91%w/w. All the formulations comply with the official standards.

Uniformity of content

The content of active ingredients of various formulations was analyzed using UVspectrophotometer at 376 nm.

Table 23: Uniformity of content

Formulation	Drug Content* (%w/w)
F01C1	99.04±0.989
F01C2	97.23±0.709
F01C3	100.23±0.231
F02C1	99.87±0.897
F02C2	98.99±1.110
F02C3	95.90±0.289
F03C1	97.12±0.678
F03C2	99.98±0.092
F03C3	98.95±1.076
F04C1	98.98±0.678
F04C2	97.34±1.897
F04C3	100.23±1.021

***Mean ± SD (n=10)**

The drug content from all the formulations ranged from 95.90%w/w to 100.23%w/w. Allthe formulations comply with the test for uniformity of drug content[77].

***In vitro* release study of the tablets:**

Table 24: *In vitro* release of the tablets

Dissolution Medium	Time in Hours	Cumulative percentage drug release*											
		F01C1	F02C1	F03C1	F04C1	F01C2	F02C2	F03C2	F04C2	F01C3	F02C3	F03C3	F04C3
Acid Buffer pH 1.2	0	0	0	0	0	0	0	0	**0**	0	0	0	0
	1	0.17 ±0.04	0.50 ±0.40	3.50 ±0.4	3.76 ±0.48	0.20 ±0.02	2.76 ±0.02	5.90 ±0.08	**9.00 ±0.05**	0.23 ±0.03	3.29 ±0.56	10.70 ±0.16	12.09 ±0.91
	2	2.78 ±0.32	6.14 ±0.56	7.15 ±0.56	7.49 ±0.69	2.78 ±0.21	6.14 ±0.36	8.46 ±0.03	**11.50 ±0.49**	3.01 ±0.18	8.65 ±0.28	15.02 ±0.23	18.68 ±0.56
Phosphate Buffer pH 6.8	3	9.02 ±0.55	15.20 ±0.96	18.38 ±0.58	19.98 ±0.21	11.96 ±1.04	15.32 ±0.16	17.52 ±0.08	**21.63 ±0.26**	11.15 ±0.72	18.68 ±0.33	25.73 ±0.54	35.04 ±0.97
	4	11.73 ±0.45	18.19 ±0.23	22.78 ±0.53	23.77 ±0.98	16.61 ±0.29	19.32 ±0.15	28.73 ±0.04	**30.52 ±0.53**	16.02 ±0.04	24.04 ±0.52	34.96 ±0.05	43.31 ±0.69
	5	14.76 ±0.58	21.90 ±0.55	27.36 ±0.89	27.69 ±0.43	18.88 ±0.33	25.07 ±0.22	33.81 ±0.04	**39.60 ±0.59**	19.67 ±0.33	29.15 ±0.43	44.17 ±0.54	48.90 ±0.17
	6	18.33 ±0.55	26.82 ±0.50	33.08 ±0.21	32.82 ±0.55	24.76 ±0.24	31.29 ±0.02	37.82 ±0.08	**43.82 ±0.81**	27.53 ±0.21	35.13 ±0.07	51.30 ±0.05	55.37 ±1.62
	7	22.26 ±0.49	28.76 ±0.47	37.48 ±0.56	37.60 ±0.59	29.54 ±1.46	37.46 ±3.42	41.97 ±0.03	**47.76 ±0.89**	35.13 ±0.10	41.24 ±0.47	58.04 ±0.20	62.59 ±1.30
	8	26.42 ±0.87	33.28 ±0.45	41.35 ±0.53	41.29 ±0.59	32.29 ±0.71	41.95 ±0.20	47.30 ±0.30	**57.43 ±0.59**	39.91 ±0.01	48.71 ±0.40	62.45 ±0.89	68.06 ±0.15
	9	29.13 ±0.64	36.86 ±0.98	45.55 ±0.58	46.02 ±0.95	39.82 ±1.09	47.90 ±0.20	49.74 ±0.04	**61.49± 0.41**	44.05 ±0.77	56.70 ±0.40	65.64 ±0.51	74.72 ±0.51
	10	35.21 ±0.89	39.65 ±0.44	48.83 ±0.44	52.41 ±0.69	44.88 ±0.89	52.40 ±0.40	57.53 ±0.50	**68.45 ±0.23**	50.78 ±0.10	62.31 ±0.17	73.32 ±0.94	79.08 ±0.93
	24	45.81 ±0.66	49.38 ±0.85	55.98 ±0.48	59.94 ±0.65	52.89 ±0.16	63.59 ±0.30	86.18 ±0.02	**99.14 ±0.63**	58.04 ±0.20	76.39 ±0.45	97.43 ±0.11	99.01 ±1.00

***Mean ± SD (n=3)**

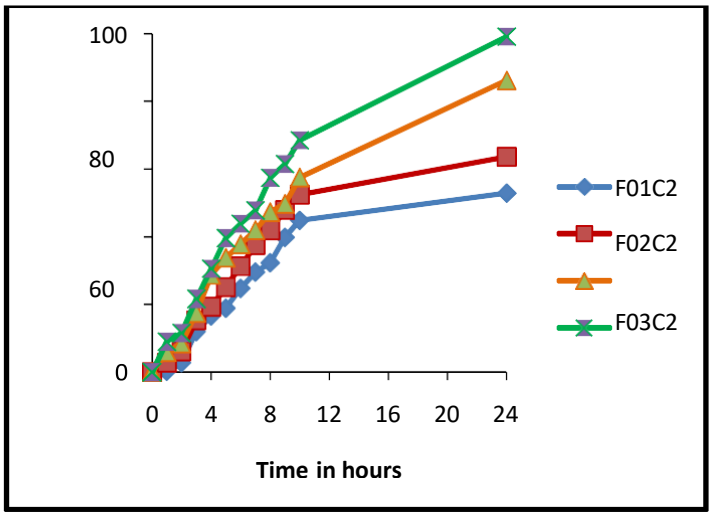

Fig. 10: *In vitro* release study of the tablets

***In vitro* Release Study of Optimized Formulation (F04C2)**

The *in vitro* release study of optimized formulation

Table 25: *In vitro* Release of Optimized Formulation (F04C2)

S. No	Time in hours	Cumulative percentageDrug Release*
1	0	0
2	1	9.22±0.026
3	2	15.89±0.067
4	3	21.11±0.078
5	4	27.21±0.038
6	5	33.90±0.067
7	6	38.75±0.087
8	7	45.21±0.028
9	8	52.03±0.078
10	9	55.90±0.065
11	10	62.01±0.042
12	12	68.89±0.067
13	14	74.23±0.029
14	16	83.89±0.098
15	24	99.13±0.023

***Mean ± SD (n=3)**

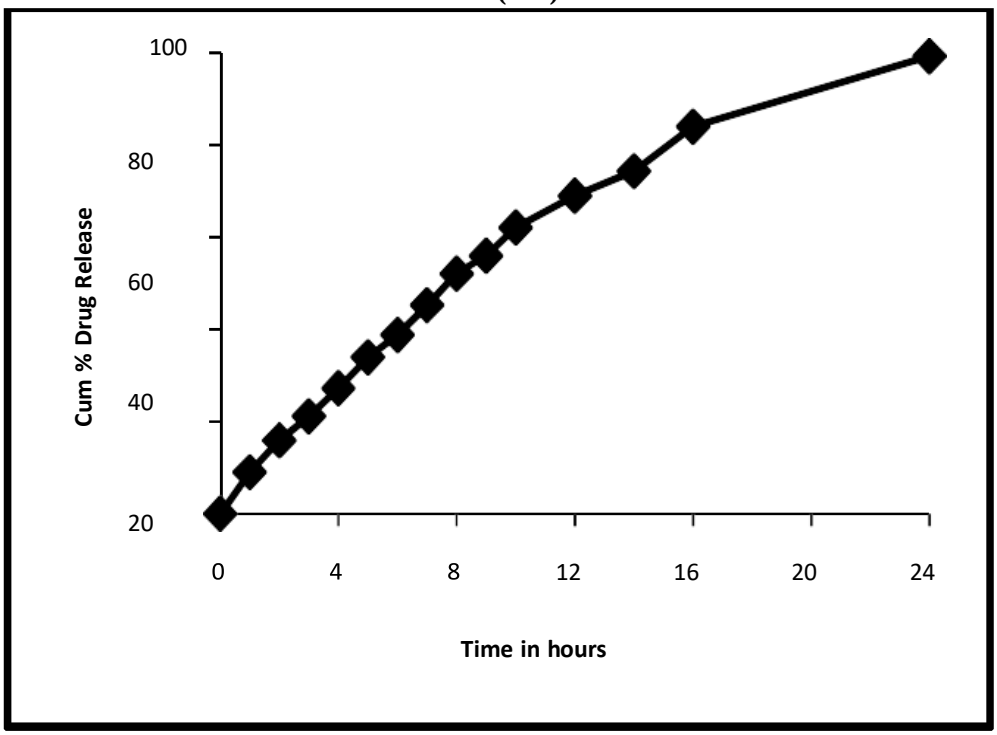

Fig. 11: Release study of optimized formulation (F04C2)

The formulating F04C2 produced the drug release for 24 hours.

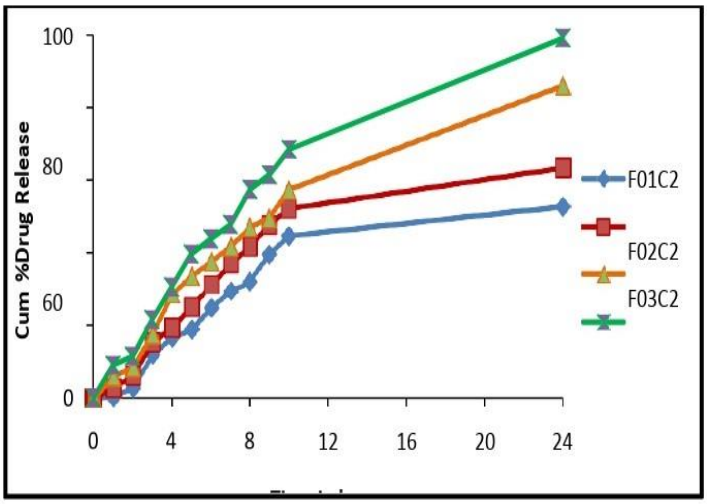

Fig. 12: Effect of osmogen concentration on drug release

Effect of amount of osmogene on drug release:
Increase in concentration of mannitol increases the drug release. Higher the amount of osmogen, greater is the driving force to release the drug. This is because increase in osmogen concentration increases the osmotic pressure inside the tablet and thus the rate of drug release is increased.

Effect of concentration of pore forming agents on drug release

To study the effect of concentration of pore forming agent(sorbitol), core tablet F04 with three different coatings C1, C2, C3 (Formulation F04C1, F04C2, F04C3) containing various concentration of sorbitol were selected.

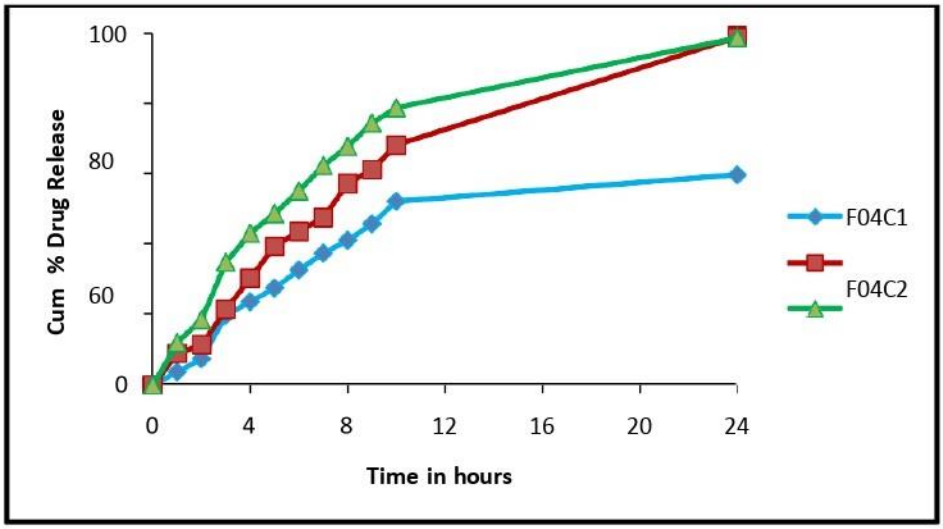

Fig. 13: Effect of concentration of pore forming agents on drug release

The formulation F04 with C1 coating showed only 52.41% of drug release at the end of

10 hours due to lack of pore forming agent (0% sorbitol). The formulation F04 with C2 coating(10% sorbitol) showed drug release of 68.45% at the end of 10 hours. The formulationF04 with C3 coating (20% sorbitol) showed faster drug release of 79.08% at the end of 10 hours. This shows that the level of pore former increases the membrane porosity resulting in faster drug release.

EVALUATION OF OPTIMIZED FORMULATION

Effect of Agitation Speed on the drug release

Drug release under different agitation rates was conducted in order to investigate theinfluence of agitation rate on drug release

Table 26: Effect of Agitation Speed on drug release

Dissolution Medium	Time in hours	Cumulative % drug release*		
		Speed of rotation of the paddle		
		50 rpm	100 rpm	150 rpm
Acid buffer pH 1.2	0	0	0	0
	1	9.29±0.56	8.45±0.55	10.45±0.78
	2	13.06±0.83	14.10±1.11	13.77±0.44
Phosphate buffer pH 6.8	3	21.33±0.88	21.05±1.63	21.48±1.41
	4	26.30±1.6	26.15±0.85	26.58±0.62
	5	31.54±0.50	31.33±1.11	31.86±0.14
	6	38.14±0.86	38.11±0.89	38.74±1.26
	7	45.35±0.64	43.73±0.87	48.50±0.40
	8	50.12±0.45	50.98±1.02	51.61±0.84
	9	57.91±1.09	57.40±0.60	57.44±0.90
	10	67.69±0.52	66.72±2.18	68.40±1.04
	24	99.10±0.13	99.32±0.49	99.50±0.28

***Mean ± SD (n=3)**

The speed of rotation doesn't have much effect on drug release. Therefore the mobility of gastrointestinal tract might scarcely affect the drug release.[29]

Effect of Osmotic Pressure on drug release

Drug release under different osmotic pressure was conducted in order to investigate the influence of osmotic pressure of release medium on drug release.

Table 27: Effect of Osmotic Pressure on drug release

DissolutionMedium	Time in hours	Cumulative % drug release*		
		Osmotic Pressure of the medium		
		1.5 atm.	3 atm.	4.5 atm.
Acid buffer pH 1.2	0	0	0	0
	1	5.70±0.58	3.76±0.80	3.12±1.12
	2	7.87±0.36	8.72±0.51	6.93±0.41
Phosphate bufferpH 6.8	3	20.38±0.73	19.96±1.27	18.29±1.61
	4	24.11±0.89	22.11±1.10	23.20±1.01
	5	30.09±2.01	28.03±1.18	26.01±1.00
	6	38.02±1.07	35.98±0.25	33.81±0.19
	7	43.22±1.67	43.44±0.79	37.40±0.81
	8	53.45±0.77	48.08±0.95	42.66±0.55
	9	58.98±00.23	56.01±1.20	47.66±1.01
	10	67.94±0.27	61.44±1.46	49.81±2.18
	24	86.85±1.15	72.22±2.78	57.53±1.47

The drug release from the formulation decreased with increase in osmotic pressure of the dissolution medium. This confirms that the mechanism of drug release is by osmotic pressure.[29]

Effect of pH on drug release

In order to study the effect of pH on drug release the optimized formulation (F04C2) was subjected to drug release study in different dissolution medium like acid buffer pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8.

Table 28 : Effect of pH on drug release

Time inhours	Cumulative % drug release*		
	Acid Buffer pH1.2	Acetate BufferpH 4.5	Phosphate Buffer pH 6.8
0	0	0	0
1	9.93±1.07	9.46±1.53	10.16±2.82
2	14.80±1.40	14.86±0.35	14.92±0.42
3	21.29±0.61	21.10±1.90	23.73±2.26
4	28.47±0.83	29.06±1.17	29.01±1.11
5	33.09±1.41	35.01±1.37	36.21±1.78
6	38.2±4.20	38.69±0.54	42.35±0.86
7	44.84±0.00	44.42±1.47	47.73±1.05
8	52.63±0.63	51.34±0.78	54.47±0.86
9	58.73±0.07	58.40±0.83	59.06±2.17
10	67.61±0.20	65.33±1.79	65.55±1.45
24	99.45±0.45	99.13±0.63	99.21±0.36

***Mean ± SD (n=3)**

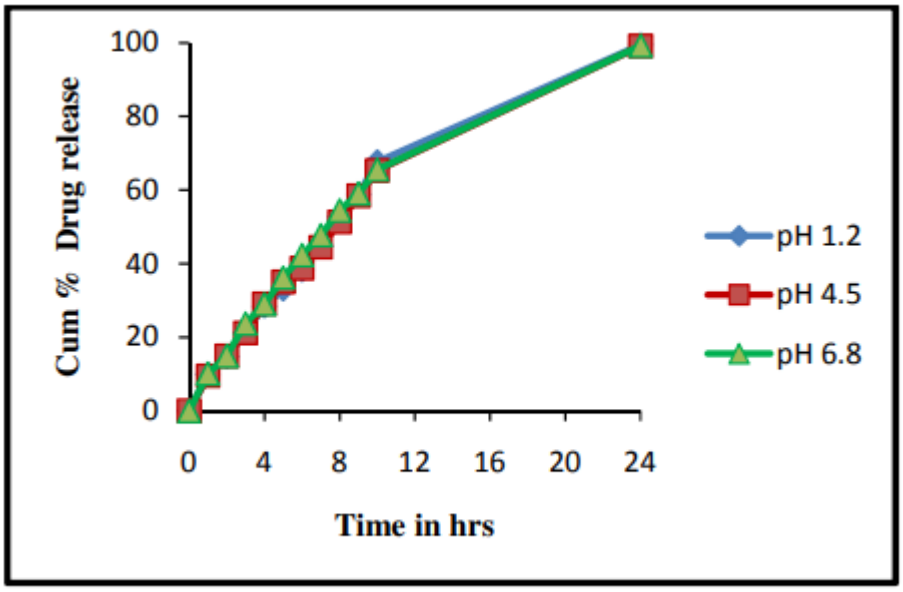

Fig 15: Effect of pH on drug release

The pH of release medium does not have significant effect on drug release. Thereforethe pH of gastrointestinal tract might scarcely affect the drug releaase.[22]

Membrane Morphology of porous Osmotic Tablets

Membranes obtained before and after dissolution was studied using scanning electron microscope. Membranes obtained before dissolution showed non porous region After 24 hours of dissolution the membrane showed pore formation owing to the dissoution of sorbitol from the membrane and thus the release of drug

takes place. Coating solution C2 containing 10% sorbitol was coated on the formulation F04 produced less pores compared to formulation F04 coated with the coating solution C3 containing 20% sorbitol.

a) Before Dissolution **b) After Dissolution**

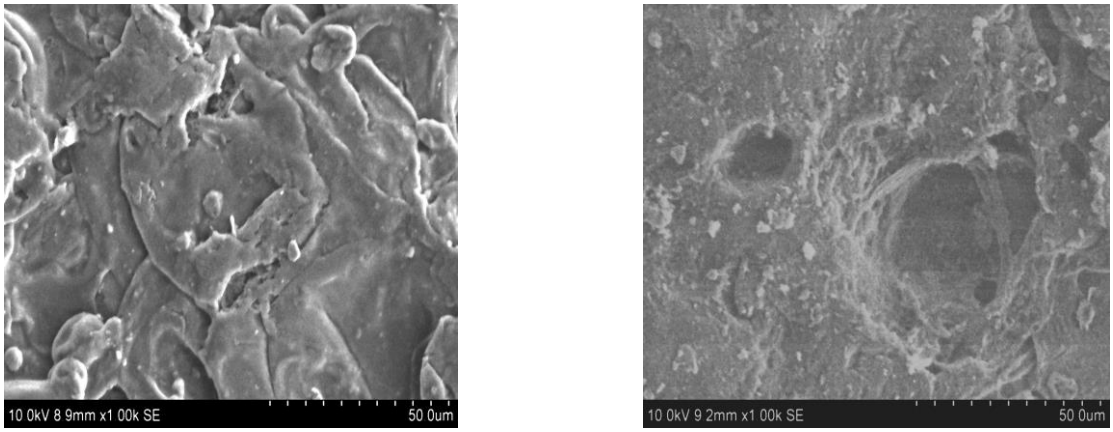

Fig. 16 : Membrane Morphology of Formultion F04C2 by ScanningElectron Microscope

a) Before Dissolution **b) After Dissolution**

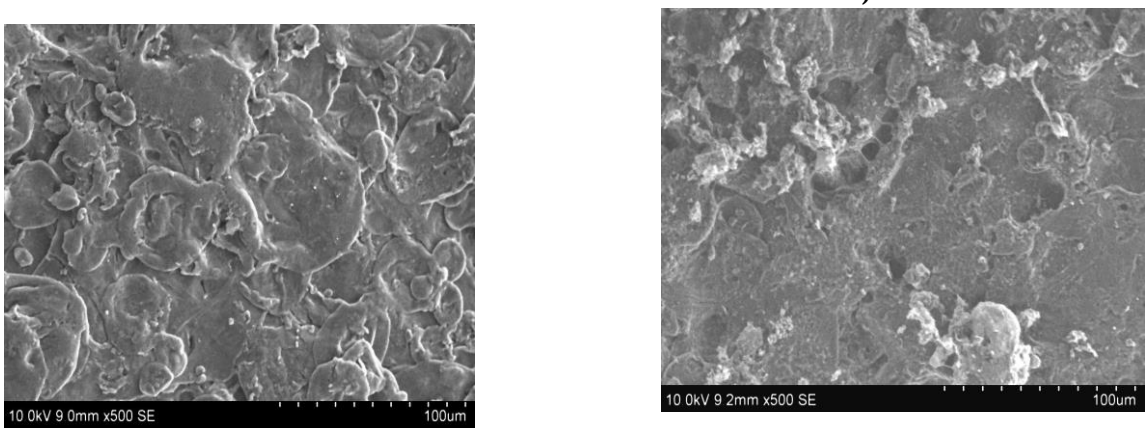

Fig. 17: Membrane Morphology of Formulation F04C3 by ScanningElectron Microscope

Release Kinetics of the Optimized Formulation

The dissolution data of the optimized formulation was fitted to various kinetic models

Table 29: Release Kinetics of the Optimized Formulation

Time (hours)	Log time (Hours)	Sq. root of time (hours)	Cum % drug release	Cum % Drug remaining	Log Cum %drug release	Log cum % drug remaining	Cube rootof cum % drug remaining
0	-	0	0	100	-	2.00	4.64
1	0	1	9.22	90.78	0.96	1.96	4.49
2	0.30	1.14	15.89	84.11	1.20	1.92	4.38
3	0.48	1.73	21.11	78.89	1.32	1.89	4.29
4	0.60	2.00	27.21	72.79	1.43	1.86	4.18
5	0.70	2.24	33.90	66.10	1.53	1.82	4.04
6	0.77	2.44	38.75	61.25	1.59	1.79	3.94
7	0.85	2.65	45.21	54.79	1.66	1.74	3.80
8	0.90	2.83	52.03	47.97	1.72	1.68	3.63
9	0.95	3.00	55.90	44.10	1.75	1.64	3.53
10	1.00	3.16	62.01	37.99	1.79	1.60	3.36
12	1.07	3.46	68.89	31.11	1.84	1.49	3.15
14	1.15	3.74	74.23	25.77	1.87	1.41	2.95
16	1.20	4.00	83.89	16.11	1.92	1.20	2.53
24	1.38	4.90	99.13	0.87	1.99	-0.06	0.95

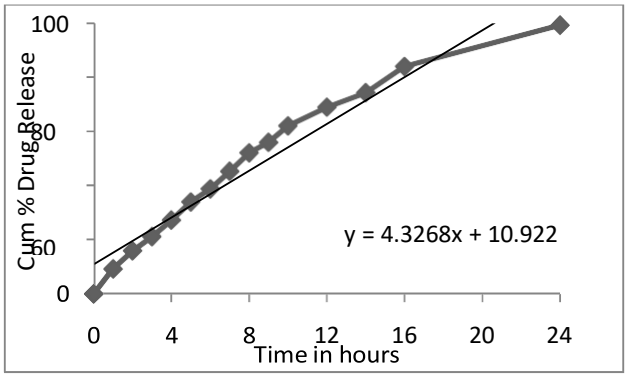

Fig. 18 : Plot of zero order kinetics

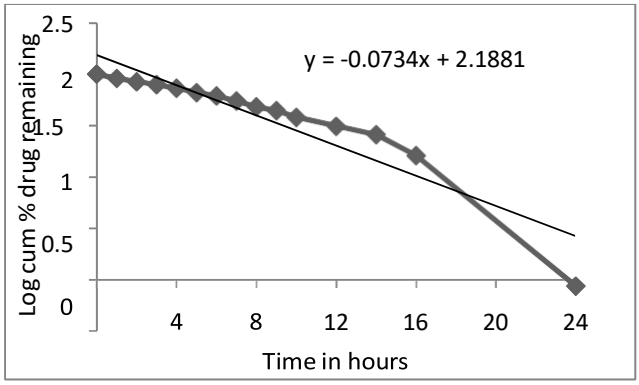

Fig. 19: Plot of first order kinetics

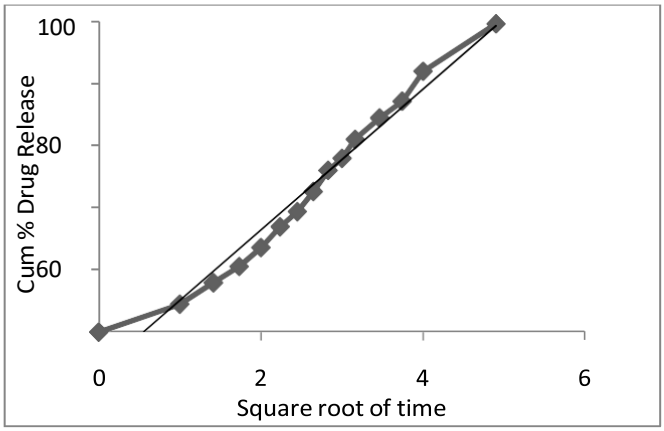

Fig. 20: A Plot of Higuchi kinetics

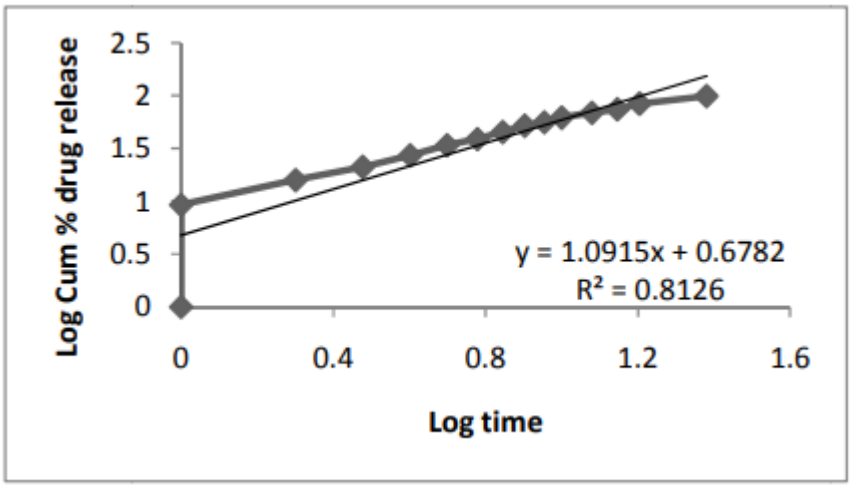

Fig. 21: Plot of Korsmeyer and Peppas Kinetics

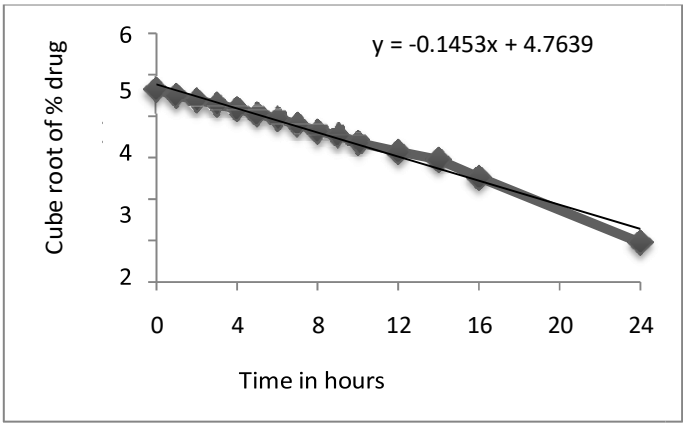

Fig. 22: Plot of Hixson-Crowell Kinetics

The coefficient of determination (R^2) was taken as criteria for choosing the mostappropriate model.

Table 30: R^2 values of various kinetic models

Kinetic model	Coefficient of determination(R^2)
Zero order	0.9443
First order	0.8639
Higuchi	0.9714
Korsemeyer and Peppas	0.8126
Hixson Crowell	0.9815

The *in vitro* drug release of the optimized formulation F04C2 was best explained by Hixson Crowell as the plots showed the highest linearity (R^2=0.9815) followed by zero order(R^2=0.9443). The Hixson Crowell plot indicated a change in surface area and diameter of thetablets with progressive dissolution of the tablet as a function of time.

STABILITY STUDY

After storage, the formulation F04C2 was subjected to evaluation of physical parameters,drug content and *in vitro* drug release.

Table 31: Stability Studies

Parameter	Initial	1st Month	2nd Month	3rd Month
Description	Yellow round concave coated tablets	Yellow round concave coated tablets	Yellow round concave coated tablets	Yellow round concave coated tablets
Diameter* (mm)	8.966±0.0151	8.952±0.0311	8.978±0.0356	8.954±0.0309
Thickness*(mm)	3.570±0.0330	3.542±0.0148	3.574±0.0190	3.570±0.0178
Hardness* (kg/cm^2)	5.8±0.5700	5.7±0.2738	5.7±0.5734	5.8±0.3209
Drug content*(%w/w)	98.33±1.123	99.08±1.098	98.34±1.134	99.18±1.1290

***Mean ± SD (n=5)**

Table 32: *In vitro* release study before and during stability study

Dissolution Medium	Time in hours	Cumulative % drug release*			
		Initial	1st Month	2nd Month	3rd Month
Acid bufferpH 1.2	0	0	0	0	0
	1	09.00±0.05	8.37±0.75	7.75±0.46	7.34±0.50
	2	11.50±0.49	12.05±1.84	12.10±0.21	12.89±0.19
Phosphate Buffer pH6.8	3	21.63±0.26	24.34±0.65	22.44±0.51	24.37±0.44
	4	30.52±0.53	30.02±1.10	29.83±0.68	29.71±0.39
	5	39.60±0.59	41.14±0.86	39.11±0.85	39.93±1.03
	6	43.82±0.81	43.75±1.06	44.07±0.12	44.77±0.51
	7	47.76±0.89	47.26±0.95	49.50±1.53	50.56±0.48
	8	57.43±0.59	56.21±1.79	56.40±0.42	57.41±0.42
	9	61.49±0.41	60.19±0.93	63.34±0.67	64.97±0.13
	10	68.45±0.23	69.71±0.31	69.82±0.57	69.79±0.70
	24	99.14±0.63	99.51±0.36	98.44±1.44	98.00±0.69

***Mean ± SD (n=3)**

When the osmotic tablets were stored at 40^{0}C±2ºC / 75±5% RH for 3 months there appeared no change either in physical appearance or in drug content. When the dissolution study was conducted in the simulated physiological environment of stomach (pH 1.2) and intestine (pH 6.8), not much difference was observed in the cumulative percentage release of Losartan potassium from F04C2.

SUMMARY AND CONCLUSION:

The aim of the present study was to develop a controlled porosity osmotic tablet of LOSARTAN POTASSIUM and to evaluate the *in vitro* release of the drug from the system. The osmotic tablet is developed such that it delivers 8 mg of LOSARTAN POTASSIUM over a period of 24 hours.

- Drug – Excipient compatibility study was carried out using FTIR study. The results showed that there was no interaction between them.
- Calibration curves of LOSARTAN POTASSIUM were constructed in three different pH; Acid buffer pH 1.2, Acetate buffer pH 4.5 and phosphate buffer pH 6.8.
- Wet granulation produced excellent flow and the granules were compressed on 9/32 concave punches into tablets. The tablets were then coated with a controlled porosity semipermeable membrane of CA with sorbitol as pore former.
- The post compression parameters namely uniformity of weight, thickness, diameter, hardness, drug content and uniformity of content were evaluated for the coated and uncoated tablets and were found to be within limits.
- The *in vitro* study was carried out for 2 hours in 0.1N HCl buffer pH 1.2 and for 22 hoursin phosphate buffer pH 6.8.
- Among the different formulations, F04C2 gave satisfactory results by releasing 99.13% of LOSARTAN POTASSIUM in 24 hours.
- The drug release was found to increase with increase in the osmogen content.
- Variation in the speed of rotation of the paddle did not alter the release to a greater extent. Increase in osmotic pressure of the medium decreased the drug release.

- The release study was conducted in different release medium like Acid buffer pH 1.2, Acetate buffer pH 4.5, and Phosphate buffer pH 6.8. Variation in pH does not affect the release to a greater extent.
- To describe the mechanism of drug release, the optimized formulation was fitted to various models. The drug release was found to follow zero order and Hixson Crowell release.
- The accelerated stability testing was carried out for 3 months and showed no change inthe appearance, hardness, diameter, thickness, friability, drug content and *in vitro* release.

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