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Development and evaluation of controlled porosity osmotic pump tablet of losartan potassium

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ABSTRACT

The aim of the present work was to prepare and evaluate controlled porosity osmotic pump tablets of Losartan potassium to prolong the release of drug oral administration. Losartan potassium is an anti-hypertensive drug and it acts as an angiotension II receptor antagonist. The tablets were prepared by the wet granulation method using mannitol as an osmogen and polymers like polyox N-80, polyox N-205 at different concentrations. The tablets were coated with opadry CA upon contact with water it results in an *in situ* formation of a micro porous structure. Total twelve (F1-F12) were formulated and the tablets were evaluated for various parameters such as compatibility studies, drug content, weight variation, hardness, thickness, friability, *in vitro* drug release studies and release rate kinetics. The drug-polymer interaction was also studied by conducting FTIR. The *in vitro* release kinetics studies reveal that all formulations fits well with Zero order, followed by Korsmeyer-Peppas and the mechanism of drug release follows super case II transport. After analysis of different evaluation parameters and drug release kinetics, formulation code F9 was selected as a promising formulation for delivery of Losartan potassium as a controlled porosity osmotic pump tablet with 99.82 % *in vitro* drug release at 24th hour. The stability studies were carried out at 40°C/75% RH for 90 days. There was no significant change in the physical property during the study period.

Keywords: Losartan Potassium, Controlled porosity osmotic pump tablet, Anti-hypertensive, Zero order and Korsmeyer-Peppas equation.

INTRODUCTION

The oral route for drug delivery is the most popular, desirable, and most preferred method for administrating therapeutically agents for systemic effects because it is a natural, convenient, and cost effective to manufacturing process. In these systems, drug dose and dosing intervals are optimized to maintain the drug concentration within the therapeutic range, thus ensuring efficacy with minimum toxic effects. Osmotically controlled drug release formulations deliver drug due to the

difference in osmotic pressure within and outside the osmotic pump [1].

The release rate from this system is not affected by gastric pH and other hydrodynamic conditions. Also, release characteristic can be easily adjusted by optimizing the release parameters. To maintain the drug concentration within the therapeutically effective range, it is often necessary to take these types of dosage forms several times a day. Controlled drug delivery has taken an important place in pharmaceutical development, improving the tolerability and patient compliance with prescribed dosing regimens. Despite the predominant use of polymer-based systems, alternatives have been developed to decrease the influence of the various physiological factors that occur following food intake or that are dependent on patient age [2].

One of the most promising technologies is the oral osmotically driven system (OODS). Osmotic devices are the most reliable controlled drug delivery systems (CDDS) and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these systems to release the drug in a controlled manner. Osmotic pump tablet (OPT) generally consists of a core including the drug, an osmotic agent, other excipients and semi-permeable membrane coat [3].

MATERIALS & METHODS

Materials

Losartan Potassium (BP/USP) was the active pharmaceutical ingredient obtained as a Yarrow chem. Products, Mumbai. Polyox N80, Polyox N205, & Opadry CA were used a excipents to design Controlled porosity osmotic tablets obtained from Colorcon, Goa. Microcrystalline cellulose (Avicel PH-101), Mannitol, Poly Vinyl Pyrolodione (PVP K -30), Potassium dihydrogen ortho phosphate, Sodium hydroxide, Magnesium stearate and Talc were procured from S.D Fine chemicals (Mumbai, India). Isopropyl alcohol, Acetone and all the other chemicals used in the study were of analytical grade.

Method

Preparation of tablet core

The core tablets of Losartan Potassium were prepared by wet granulation. All the ingredients of tablet core except PVP K 30, talc, & magnesium stearate were passed through 80 mesh sieve, accurately weighed and thoroughly mixed. The mixture was then granulated by using required quantity of PVP K 30 dissolved in sufficient quantity of isopropyl alcohol and the resulting wet mass was passed through 10-mesh sieve[4].

The granules were dried at 50^{o}C for 30 mins in hot air oven. Finally the dried granules were blended with magnesium stearate and talc for 10 mins in a polybag and were compressed into tablets having average 250mg using a single stroke tablet punching machine (Cadmach, India) fitted with a 8mm round concave punches with a pressure was 6 kg/cm^2 – 8 kg/cm^2.

Coating of tablet core

The core tablets of Losartan Potassium were coated with opadry CA in a modified automated pan coating machine (Cemach, Ahmadabad, India). The compositions of the coating solution used for coating of core tablets are given in Table1

All the tablets were coated with varying concentrations of opadry CA in coating solution. Various components of the coating solution were added to the solvent mixture in a sequential manner. The component added first was allowed to dissolve before the next component was added. The rotating speed of the pan was kept 20rev/min.

The coating was performed using spray gun with nozzle diameter 1mm and the spray rate of 3 - 5 ml/min. Coating was continued until desired weight gain (10%) was obtained on the active tablets. In all the cases, active tablets were dried at 50^{o}C for 10 h before further evaluation.

Table 1: Formulation table for Controlled porosity osmotic pump tablets

S.No.	Ingredients (mg)	Formulation Code											
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
1	Losartan potassium	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
2	Polyox Leo N 80 WSR	45	49	53	57	61	65	-	-	-	-	-	-
3	Polyox Leo N 205 WSR	-	-	-	-	-	-	45	49	53	57	61	65
4	Mannitol	50	50	50	50	50	50	50	50	50	50	50	50
5	Micro Crystalline Cellulose	30	26	22	18	14	10	30	26	22	18	14	10
6	Poly Vinyl Pyrolidone K-30	15	15	15	15	15	15	15	15	15	15	15	15
7	Iso Propyl alcoshol (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
8	Talc	5	5	5	5	5	5	5	5	5	5	5	5
9	Magensium Sterate	5	5	5	5	5	5	5	5	5	5	5	5
Coating Solution													
10	Opadry CA (%w/V)	5	5	5	5	5	5	5	5	5	5	5	5
11	Acetone (ml)	95	95	95	95	95	95	95	95	95	95	95	95
12	Water (ml)	5	5	5	5	5	5	5	5	5	5	5	5
13	% Weight gain (%)	10	10	10	10	10	10	10	10	10	10	10	10
14	Total Weight (mg)	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

RESULTS

Drug-Excipients compatibility study

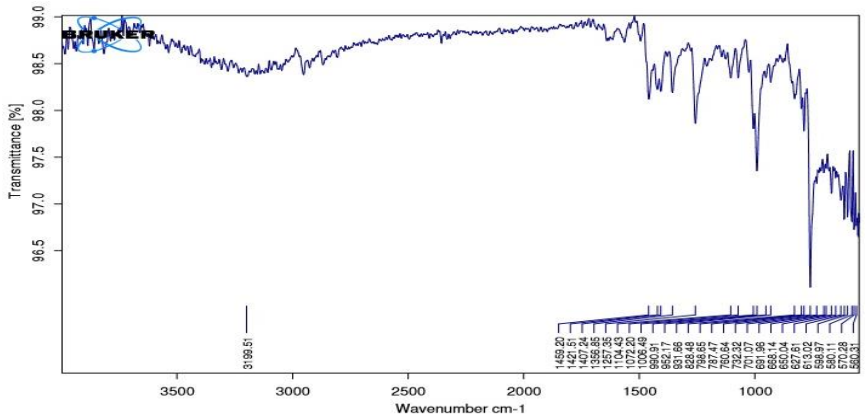

Fig.1: FTIR Spectra of Losartan Potassium Drug Sample

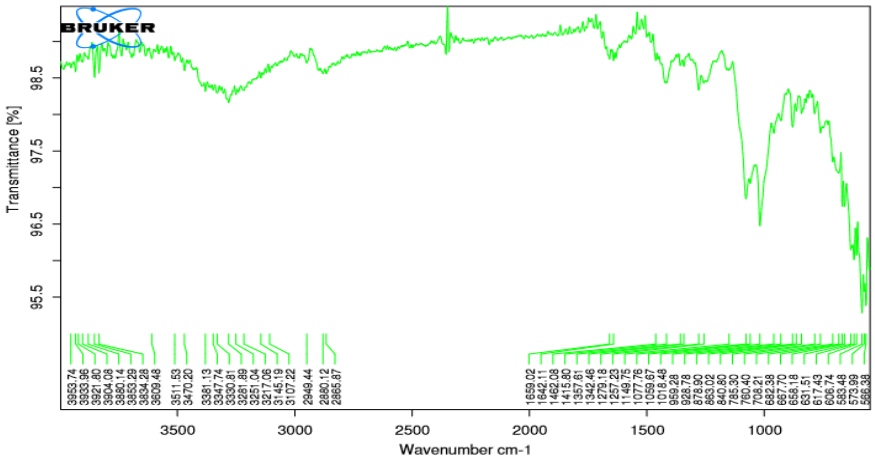

Fig.2: FTIR Spectra of Optimized Formulation (F9)

Micrometric Properties of Granules

Table 1: Micrometric Properties of Granules (Pre-compression Data)

Formulation Codes	*Angle of Repose (°)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	23°.67±0.06	0.53±0.04	0.61±0.04	13.34±0.03	1.08±0.94
F2	21°.54±0.02	0.51±0.07	0.65±0.05	12.12±0.04	1.06±0.84
F3	24°.15±0.04	0.58±0.02	0.66±±0.04	12.23±0.02	1.09±0.86
F4	22°.91±0.03	0.61±0.03	0.52±0.07	11.00±0.07	1.09±0.89
F5	21°.93±0.05	0.64.±0.05	0.68±0.03	12.20±0.06	1.10±0.91
F6	20°.54±0.04	0.55±0.05	0.62±0.04	13.00±0.05	1.09±0.93

Table 2: Micrometric Properties of Granules (Pre-compression Data)

Formulation Codes	*Angle of Repose (°)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
F7	23°.91±0.06	0.54±0.03	0.64±0.02	11.20±0.07	1.15±0.87
F8	24°.91±0.01	0.58±0.06	0.61±0.07	14.34±0.06	1.12±0.85
F9	**20°.91±0.05**	**0.62±0.07**	**0.68±0.05**	**11.11±0.06**	**1.03±0.92**
F10	23°.24±0.07	0.50±0.04	0.54±0.05	12.12±0.02	1.14±0.83
F11	22°.93±0.05	0.57±0.02	0.62±0.03	12.23±0.05	1.10±0.89
F12	24°.34±0.02	0.63 ±0.06	0.66±0.04	09.34±0.03	1.11±0.93

*All the values represented as mean ± Standard Deviation (SD), n=3

Post-Compression Evaluation Tests

Table 3: Post compression evaluation of Controlled Porosity Osmotic Pump Tablet System (CPOP) of Losartan Potassium before Coating

Formulation Codes	‡ Weight Variation (mg)	* Thickness (mm)	* Hardness (kg/cm^2)	Friability (%)	Drug Content Uniformity (%)
F1	250.0±0.87	4.3±0.09	6.03±0.15	0.56±0.08	97.53±0.16
F2	250.5±1.15	4.4±0.07	6.09±0.15	0.37±0.05	97.91±0.10
F3	250.0±0.966	4.3±0.04	6.06±0.15	0.51±0.05	98.75±0.10
F4	251.5±1.17	4.3±0.03	6.1±0.17	0.49±0.02	97.84±0.06
F5	250.5±1.03	4.2±0.09	6.13±0.15	0.45±0.10	98.40±0.06
F6	250.0±1.08	5.1±0.09	5.96±0.20	0.54±0.02	98.95±0.10
F7	249.4±0.88	4.6±0.07	6.02±0.11	0.51±0.005	97.56±0.06
F8	250.12±0.94	4.6±0.05	6.01±0.17	0.42±0.02	97.01±0.14
F9	**250.02±0.95**	**4.6±0.01**	**6.4±0.16**	**0.40±0.08**	**99.56±0.06**
F10	250.1±1.05	4.1±0.18	6.4±0.16	0.49±0.02	98.76±0.11
F11	249.6±0.74	4.5±0.05	6.04±0.13	0.45±0.10	98.15±0.06
F12	249.99±1.06	4.1±0.04	6.3±0.12	0.54±0.02	97.25±0.16

* All the values represented as mean ± Standard Deviation (SD), n=3.

‡ All the values represented as mean ± Standard Deviation (SD), n=20.

Coating of the core tablets

Core tablets containing osmogen and varying proportion of polymers were coated with coating solution Opadry CA. The tablets were coated until a desired weight gain (10%) was achieved.

The tablets were then dried at 50^0C for 10hr. The tablets were then evaluated for post compression evaluation parameters. The results which are discussed as below from table 4.

Table 4: Post compression evaluation of Controlled Porosity Osmotic Tablet System (CPOP) of Losartan Potassium after coating

Formulation Codes	‡ Weight Variation (mg)	* Thickness (mm)	* Hardness (kg/cm^2)	Friability (%)
F1	275.0±0.87	4.5±0.09	6.13±0.15	0.76±0.08
F2	275.5±1.15	4.6±0.07	6.23±0.15	0.47±0.05
F3	275.0±0.966	4.5±0.09	6.2±0.15	0.61±0.05
F4	276.5±1.17	4.5±0.03	6.2±0.17	0.59±0.02
F5	275.5±1.03	4.4±0.09	6.3±0.15	0.65±0.10
F6	275.0±1.08	5.3±0.09	6.1±0.20	0.64±0.02
F7	274.4±0.88	4.3±0.06	6.05±0.05	0.55±0.08
F8	275.12±0.94	4.9±0.05	6.12±0.11	0.62±0.005
F9	**275.02±0.95**	**4.8±0.07**	**6.4±0.17**	**0.56±0.08**
F10	275.1±1.05	4.3±0.01	6.5±0.16	0.76±0.08
F11	274.6±0.74	4.6±0.18	6.2±0.16	0.59±0.02
F12	274.99±1.06	4.4±0.05	6.4±0.13	0.65±0.10

* All the values represented as mean ± Standard Deviation (SD), n=3.

‡ All the values represented as mean ± Standard Deviation (SD), n=20.

In vitro drug release studies

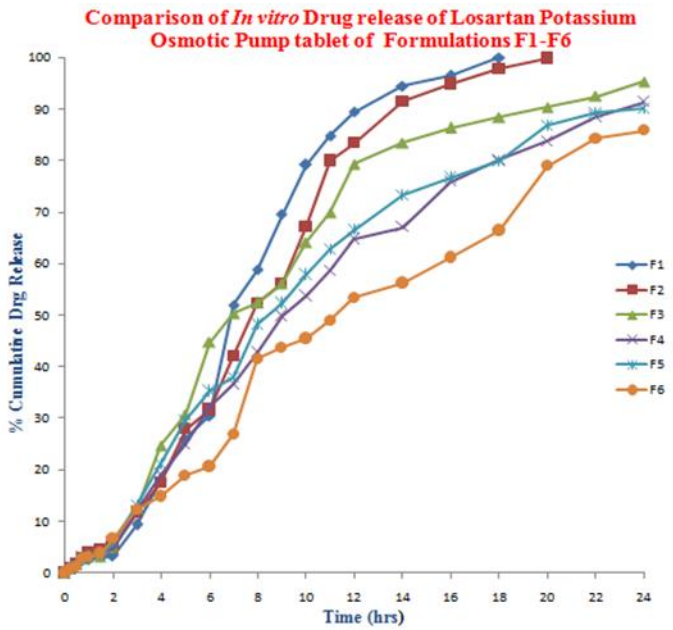

Fig.4: comparison of *In vitro* Drug release of Losartan potassium osmotic pump tablet of formulation F1 to F6

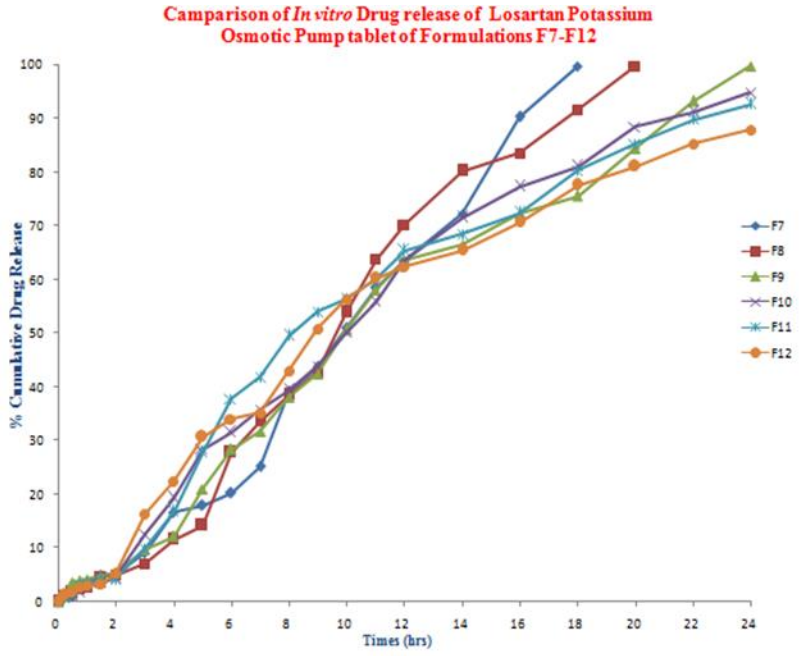

Fig.5: comparison of *In vitro* Drug release of Losartan potassium osmotic pump tablet of formulation F7 to F12

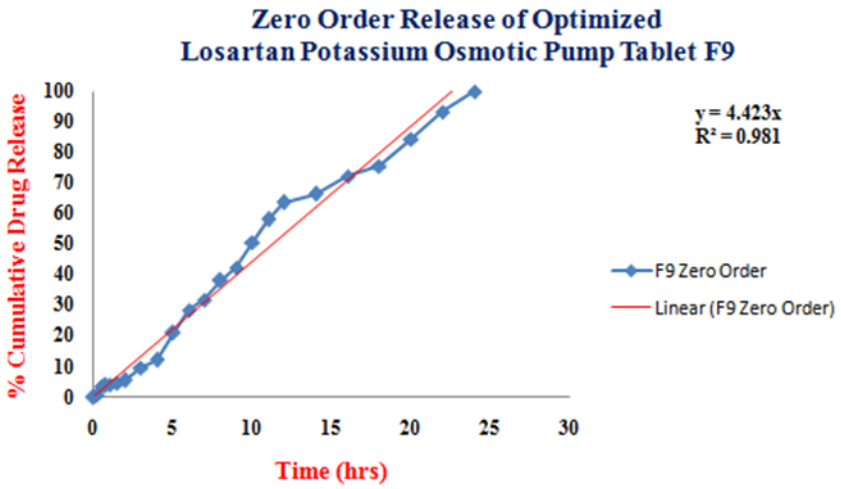

Fig.6: Zero Order Graph of Optimized Formulation F9

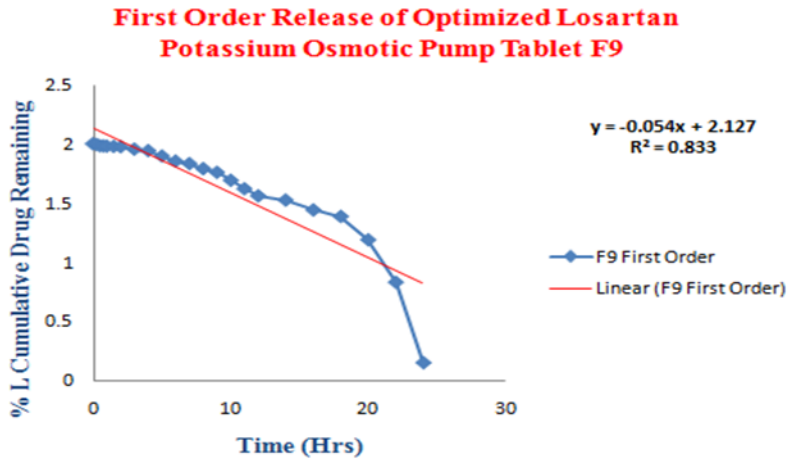

Fig.7: First Order Graph of Optimized Formulation F9

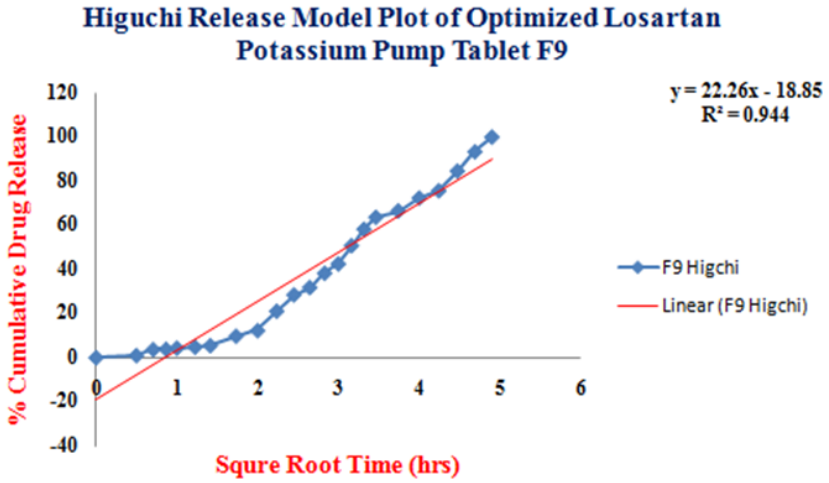

Fig.8: Higuchi Equation plot Graph of Optimized Formulation F9

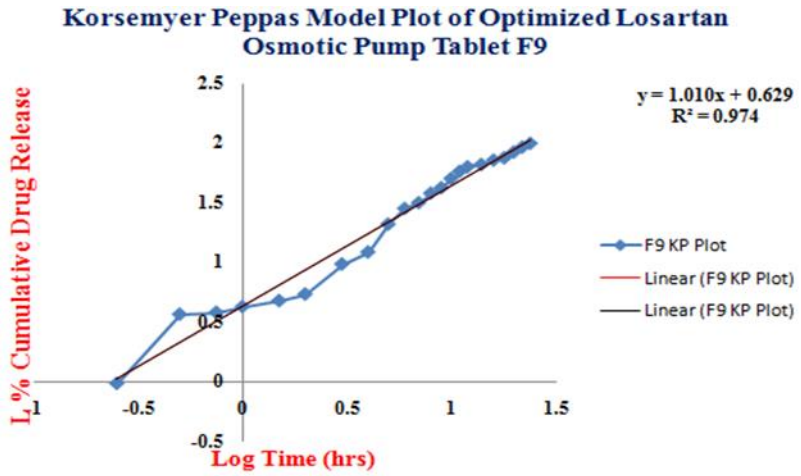

Fig.9: Korsemyer Peppas Graph of Optimized Formulation F9

DISCUSSION

In the present work, Losartan Potassium is an Antihypertensive used in the treatment of radiating of blood vessels, has been utilized as an active drug and it is soluble in water. An attempt has been made to Losartan Potassium present it in the form of osmotic tablet to provide a controlled release for prolonged period of time.

Before carrying out the formulation preformulation studies on Losartan Potassium were carried out the results of which are described as below.

PREFORMULATION STUDIES

Identification of Drug

The IR spectrum of pure drug was found to be similar to the reference standard IR spectrum of Losartan Potassium.

Table 5: IR data for estimation of Timlol Melate

S.No	Functional Group Present	Reference Peak (cm^{-1})	Observed Peak (cm^{-1})
1	Cyclic amines	**3200-3500**	**3250**
2	C-H stretching	**3000-2840**	**2950**
3	O-H bending	**1470-1395**	**1459.20**
4	C-Cl	**1000-925**	**990.91**

Melting Point

Melting point of Losartan Potassium was found to be in the range of **260 °C** as reported in literature, thus indicating purity of the drug sample.

Compatibility Studies

Compatibility studies of pure drug Losartan Potassium with all excipients were carried out prior to the preparation of osmotic pump tablets. I.R spectra of pure drug Losartan Potassium and combination of Losartan Potassium and excipients were obtained, which are shown in Figure No. 1 to 2. All the characteristic peaks of Losartan Potassium were present in Spectra thus indicating compatibility between drug and excipients. It shows that there was no significant change in the chemical integrity of the drug.

Calibration Graph Losartan Potassium

The standard graph of Losartan Potassium has shown good linearity with R^2 values 0.999 and 0.999 in 0.1N Hydrochloric acid and phosphate buffer pH 6.8 respectively, which suggests that it obeys the "Beer-Lambert's law" over this concentration range. The λ_{max} Losartan Potassium was found to be **223 nm** and **223nm** in phosphate buffer pH 6.8 and Ethanol-Water Mixture respectively.

Micrometric Properties of Granules

The Micrometric properties of granules for Controlled Porosity Osmotic Tablet System (CPOP) of Losartan Potassium were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio

- Angle of repose (**θ**) was found to be within 20° - 30° and Carr's index values were less than 21 for all granules of all formulations indicating good to fair flowability and compressibility.
- Hausner's ratio was found to be less than 1.25 for granules of all formulations indicating good flow properties.

Formulation development of osmotic tablet

The osmotic tablets of Losartan Potassium were prepared using wet granulation method. Then coated with opadry CA.

Post-Compression Parameters of Matrix Tablets

The results of the weight variation, hardness, thickness, friability and drug content of the prepared Osmotic tablets of Losartan Potassium are given in table 3.

- All the tablets of prepared formulations are compiled with the official requirements of weight variation as per I.P and U.S.P as their weights varied above 270mg i.e., ±5%.
- The hardness of the tablets ranged from 6-7 kg/cm^2 before coating and after coating and the friability values were found to be less than 0.8% indicating the prepared tablets were compact and hard thus they can withstand mechanical hazards.
- The thicknesses of the tablets were ranged from 3.31-4.95 mm.
- All the formulations satisfied the content of the drug as they contained 90-102 % of variation and good uniformity in drug content was observed.
- Thus all the physical attributes of the prepared osmotic tablets were found to be practically within control.

Coating of the core tablets

Core tablets containing varying proportions of osmoagen and other polymers were coated with coating solution opadry CA. The tablets were coated until a desired weight gain (10%) was achieved.

The tablets were then dried at 50°C for 10 h. the tablets were then evaluated for post compression evaluation parameters. The results of which are discussed as table 4.

In vitro drug release studies

The developed formulations of Losartan Potassium were subjected to ***in vitro*** dissolution studies using USP-Type II dissolution apparatus in two media i.e. 0.1N Hydrochloric acid pH 1.2 for 2 hrs and in Phosphate buffer pH6.8 (SIF) after 2 hrs in order to simulate the conditions prevalent in the gastrointestinal tract.

All the formulations released more than 50% of drug after 24 hrs and F9 showed the highest release amongst all, hence was considered as best optimized formulation and was further evaluated for effect of various formulation variables affecting drug release from the osmotic pump tablets which are discussed as Fig.4 to 5.

Kinetic Data of *In vitro* Dissolution Data

The release rate kinetics data for the **F9** is shown in figures 6-9, drug release was best explained by Zero-order equation, as the plots showed higher linearity ($r^2=0.981$), followed by Korsmeyer - Peppas ($r^2=0.974$) and Higuchi plot($r^2=0.944$) and first order ($r^2=0.833$). As the drug release was best fitted in the Zero order kinetics, indicating that the rate of drug release is concentration independent.

Mechanism of Drug Release

For Korsmeyer – Peppas equation indicated a good linearity ($r^2=0.974$). The diffusional exponent **"n"** was 1.010, which appears to indicating the release of drug polymer matrix formulations was

found to be **Zero Order & Super case II transport**.

Accelerated stability studies

The stability of this optimized formulation was known by performing stability studies for three months at accelerated conditions of 40^0C $\pm$ 75 % RH on optimized formulation **F9**. The formulation was found to be stable, with no change in the weight variation, thickness, and friability, hardness, drug content and *In vitro* drug release pattern.

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