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FORMULATION AND EVALUATION OF GASTRORETENTIVE LOSARTAN FLOATING TABLETS

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ABSTRACT

The objective of this research was to formulate and evaluate hydrodynamically balanced controlled drug delivery system of Losartan. This dosage form is associated with many advantages especially increased bioavailability and reduction in dosing frequency. The formulation was designed adopting optimization technique, which helps in setting up experiments in such a manner that the information is obtained as efficiently and precisely as possible. Initially, considering buoyancy as the main criteria, blank tablets were compressed for different formulae with various polymers like HPMC, MC and EC. The formula selected for design had a combination of Losartan, HPMC, EC and MC. The tablets were prepared by direct compression method and evaluated for Losartan content, in vitro release profile and buoyancy. The dissolution study was carried out in simulated gastric fluid using USP dissolution test apparatus employing paddle stirrer. Duration of buoyancy was observed simultaneously when the dissolution has carried out. The variation in weight was within the range of ±4% complying with pharmacopoeial specifications (±7.5%). The drug content of Losartan floating tablet 8.455±0.0085 mg in of optimized formulations indicating content uniformity. The buoyancy of the tablets was range 15.345±0.1321 hrs the maximum buoyancy was seen in P6, which has a high level of drug to polymer ratio. The *in-vitro* release was found to be in the range between the 79.12% to 90.45%.. The formulation P6 has an in vitro release of 79.12%, showed the release of the drug in the controlled manner. The optimized formulation P6 exhibited responses that were comparable with that of the predicted values of the design in optimization technique. This indicates the suitability of the technique chosen for the present dosage form.

INTRODUCTION

Dosage forms with a prolonged gastric residence and controlled drug delivery are called as GRDDS. Thus, these dosage forms significantly extend the period of time over which the drugs may be relased in comparison on other CRDDS. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment[1].

The strategies for delaying drug transit through the GIT fall into one of the three categories-

I. **Pharmacological approach:** It involves co-administration or incorporation of a drug into the dosage forms that delay either gastric emptying e.g. antimuscarinic agents such as propantheline or a drug that retards gastric motility e.g. loperamide.

II. **Physiological approach:** Use of natural materials or fat derivatives such as triethanolamine myristate which stimilate the duodenal recelptors to slow gastric emptying. Use of large amounts of volume filling polymer such as polycarbophil can slow gastric emptying.

III. **Pharmaceutical approach:** The first two approaches are not used beacause of toxicity problems. The various pharmacetical approaches or systems used for gastroretentive can be classified as follows

1. Low density systems/ Floating dosage forms: It have a bulk density less than of gastric fluids and so remain buoyant in the stomach. Such systems are also called as **hydrodynamically balanced systems (HBS)**. Floating can be achieved through

a. Effervescent systems/ gas generating systems.

b. Non-effervescent systems: It can be further classified into

i. Swelling or expanding systems.

ii. Inherently low density systes.

2. High density systems: It are retained in the bottom of the stomach.
3. Modified shape systems: Which unfold to a large size that limits passage through pyloric sphincter.
4. Muucoadhesive systems: which adhere to the gastric mucosa.

Hydro dynamically balanced drug delivery systems[2]: A hydro dynamically balanced gastrointestinal drug delivery system, in either capsule or tablet form, is designed to prolong GI residence time in an area of the GI tract to maximise drug reaching its absorption site in the solution state and, hence ready for absorption. It is solution state and, hence ready for

absorption. It is prepared by incorporating a high level (20-75% w/w) of one or more gel forming hydrocolloids eg. Hydroxy ethyl cellulose, hydroxyl propyl cellulose, hydroxy propyl methyl cellulose and sodium carboxy methyl cellulose into the formulation and then compressing these granules into a tablet or encapsulating capsules.On contact with the gastric fluid, the hydrocolloid in the hydro dynamically balanced drug delivery system becomes hydrated and forms a colloidal gel barrier around its surface with thickness increasing with time. This gel barrier controls the rate of solvent penetration in to the device and the rate of the drug release from it. The mechanism of the drug release follows matrix diffusion controlled release process[7]. Gastric retention systems are important for drugs that are degraded in the intestine, drugs with local action in the stomach, drugs with poor solubility in intestine due to alkaline pH, drugs with rapid absorption from gastrointestinal tract to produce transient peaks in serum drug levels. Losartan is an angiotensin II receptor antagonist drug used mainly to treat high blood pressure (hypertension). It was the first angiotensin II antagonist to be marketed. Losartan is a selective, competitive angiotensin II receptor type 1 (AT_1) receptor antagonist, reducing the end organ responses to angiotensin II. Losartan administration results in a decrease in total peripheral resistance (afterload) and cardiac venous return (preload). All of the physiological effects of angiotensin II, including release of aldosterone, are antagonized in the presence of losartan[8]. Reduction in blood pressure occurs independently of the status of the renin-angiotensin system. Losartan is a uricosuric. Because it can cause hyperkalemia, potassium supplements or salt substitutes containing potassium should not be used without appropriate monitoring by a physician.

Applications of GRDDS

1. Effective in delivery of sparingly soluble and insoluble drugs having low solubility at intestinal pH eg. Diazepam
2. Effective in the therapy of local disease such as *H.pylori* infection with drugs such as antibiotics treatment with antiacids and misoprostol.
3. Suitable for administering drugs having absorption window in stomach or upper part of small intesting eg. Gabapentine, metformin, levodopa, etc.
4. Suitable reduction in variability in drug absorption which is commonly due to differences in gastric transit time[9].

MATERIAL & METHODS

Losartan is the gift sample Micro labs Pvt. Ltd, Pondicherry, India; Methyl cellulose was purchased from Otto Kemi, Mumbai, India. Ethyl cellulose, micro crystalline cellulose, and aerosil were obtained from Shasun drugs and chemicals, Pondicherry. Hydroxypropyl methyl cellulose (SD Fine Chemicals, Boisar, Maharashtra, India). Magnesium stearate was obtained from Burgoyne Uribiges & Co, Mumbai, India and Sodium bicarbonate was obtained from Spectrum Chemicals and Reagents, Cochin, India.

Design of formulation and evaluation[3]

The formulations were designed based on 2 full factorial designs for the formula. This model was found good to predict the response desired. The different factors chosen were:

A. Drug to total polymer content ratio (1:14 and 1:16)

B. Polymer mixture to ethyl cellulose ratio (4:1 and 0:1)

C. HPMC to Methyl cellulose (2:1 and 4:1)

The drug to total polymer content ratio was chosen as factor A. The drug content was calculated as 15 mg based on the biological half life and peak plasma concentration and elimination rate constant, so that the dosage form can be used. The drug to total polymer content ratio was chosen from 1:14 and 1:16. This factor signifies the role of the polymer. Polymer mixture to ethyl cellulose was chosen as factor B where polymer mixture is the combination of HPMC and MC. Ethyl cellulose is used as retardant. HPMC to MC was chosen as factor C where HPMC imparts the floating property to the dosage form and MC for binding property and also for gelation. A two level full factorial design was considered with factors. According to the model totally 6 experiments have to be conducted, one more experiment at the centre point, a total of nine experiments have to be conducted. The actual and coded levels of the factors are as follows.

Table 1. Actual and coded values for the factor

Factors	Actual values		Coded values	
	Low level	High level	Low level	High level
Factor A	1:10	1:12	-1	+1
Factor B	3:1	9:1	-1	+1
Factor C	1:1	1:3	-1	+1

The coded values are calculated using the following formula:

$$\text{Level} = \frac{\text{X} - \text{the average of two levels}}{\text{Half the difference}}$$

The tablet weight was fixed to 300 mg in order to maintain tablet weight constant, microcrystalline cellulose was used as diluents, which does not interfere with the floating property of the tablet due to its low bulk density.

Table 2. Optimized formula

Ingredients	L 1 (mg)	L 2 (mg)	L 3 (mg)	L 4 (mg)	L 5 (mg)	L 6 (mg)
Losartan	15	15	15	15	15	15
HPMC	110	100	110	115	120.34	135.23
EC	35	50	45	50	53	38.3
MC	60	50	45.67	49.5	37.7	42.60
MCC	60	60	60	45	50	45
Sodium bi carbonate	20	20	20	20	20	20
Magenesium stearate	5	5	5	5	5	5
Total	300	300	300	300	300	300

Formulation of HBS tablets[4]: The tablets were prepared by direct compression method. All the ingredients except Losartan were passed through # 80 mesh prior to mixing. The ingredients were weighed separately and mixed to get a uniform polymer mixture. The drug was then mixed with the polymer mixture in geometric dilution for a period of 30 minutes to ensure uniform mixing of the drug. These powder mixtures were lubricated with magnesium stearate and compressed to obtain tablets.

Evaluation of HBS tablets

The formulations were evaluated for the Losartan content, duration of buoyancy and drug release rate profiles.

Estimation of Losartan in tablets

Ten tablets were selected in random and average weight was calculated. The tablets were then triturated to get a fine powder. From the resulting triturate, weight equivalent to 15 mg of the drug was transferred into 100 ml volumetric flask and add 50 ml of methanol, and placed in an ultrasonic bath for 15 mins. Diluted with buffer volume, and placed in the ultrasonic bath for an additional 15 minutes. Filtered through a solvent resistant filter. The absorbance of the resultant solution was measured at 238 nm[5].The same procedure was followed for all formulations.

Response evaluation

***In-vitro* release profile**

The dissolution study was carried out in the simulated gastric fluid using USP dissolution test USP XXII paddle apparatus employing paddle stirrer. In this study, one tablet containing 15 mg of Losartan was placed inside 750 ml dissolution medium and speed of the paddle was set at 50 rpm. Samples were (5ml) withdrawn at a time interval of 1 hr and same volume of fresh medium was replaced[6]. The samples were analyzed for the drug content against simulated gastric fluid as a blank at λmax 238 nm. Drug content was determined by UV-Visible spectrophotometer (Schimazdu UV 1700 E 23) at238nm. The release studies were conducted in triplicate.

Duration of buoyancy

Duration of buoyancy was observed simultaneously when the dissolution has carried out. The time taken by the tablet to rise to the surface of the media (lag time) and the time for it to sink to the bottom was noted, which gives the buoyancy of the tablets[7].

RESULTS AND DISCUSSION

The tablets were formulated based on 2 full factorial design and estimated for the drug content, evaluated for response like thickness, friability, hardness, weight variation, drug content, duration of buoyancy and release profile.

From the results obtained, the angle of repose was in the range of $26^{0}56$, the formulation P6 were found to be $27^{0}25$ and $30^{0}15$ indicates good flow property. Bulk density values ranges of 0450±0.0015 gm/ml and tapped density values ranged between 0.553±0.0040 g/ml indicates good flow property. Hausner ratio was found to be in the range of 1.230±0.004. Carr's index was ranges of 18.32±0.320 % and these indicate the prepared granules exhibited good flow properties.

Thickness of formulated tablets was arranged between 3.04±0.0163mm to 3.09 ±0.019mm and hardness for different formulations were found to be 3.055±0.005 kg/cm2 indicating satisfactory mechanical strength. The friability was below 1.5 % for all formulations which is an indication of good mechanical resistance of the tablets. The variations in weight were within the range of ±4% complying with pharmacopoeial specifications (±7.5%). The drug content varied varied in the range of 8.455±0.0085 mg in different formulations indicating content uniformity. The buoyancy of the tablets was ranges of 15.345±0.1321 hrs, the maximum buoyancy was seen in P6, which has a high level of drug to polymer ratio. The *in-*

vitro release was found to be in the range of 79.12% to 90.45%. The formulation P6 has an *in-vitro* release of 79.12%, showed that release of the drug in the controlled manner.

From the results obtained the formulation P6 was found to be best among all formulation; Optimized formula.

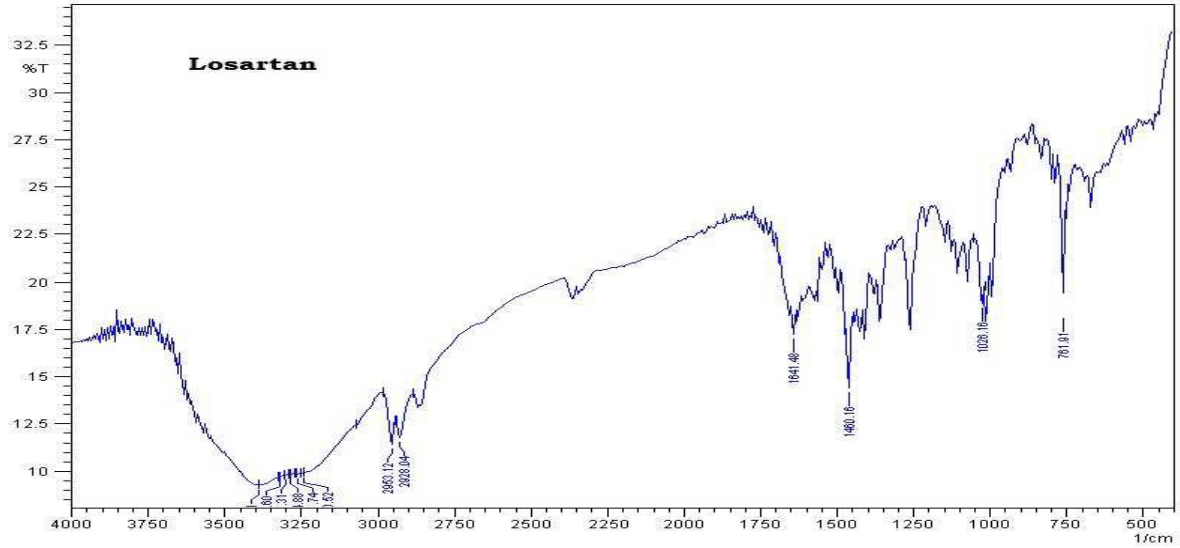


Fig :1 FT IR Data of Pure Losartan

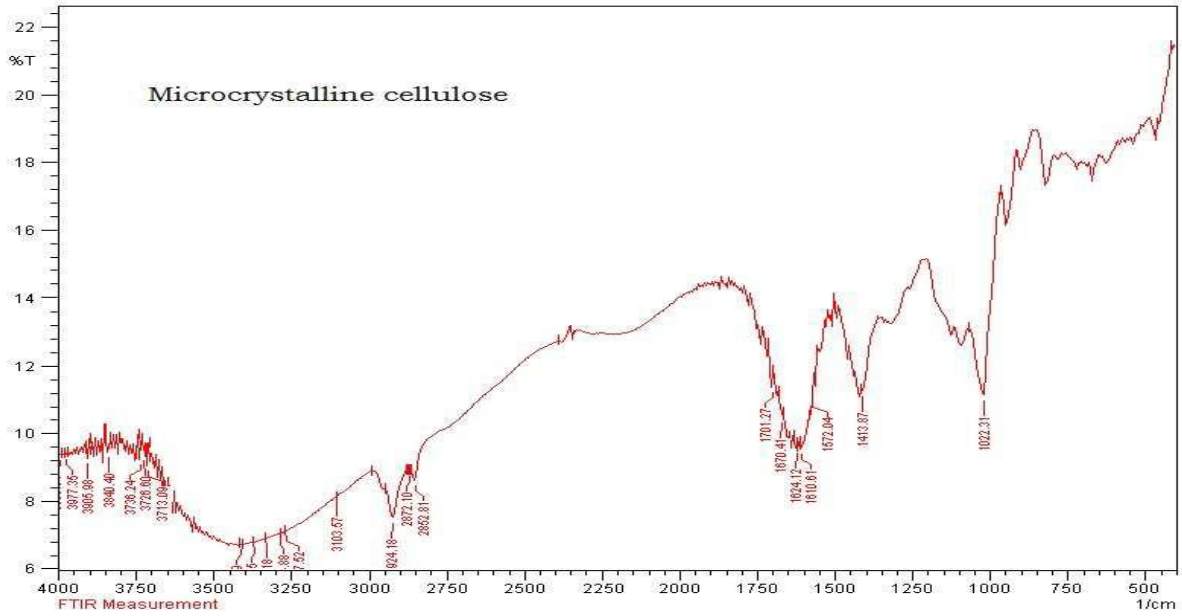


Fig : 2 FT IR Data of MCC

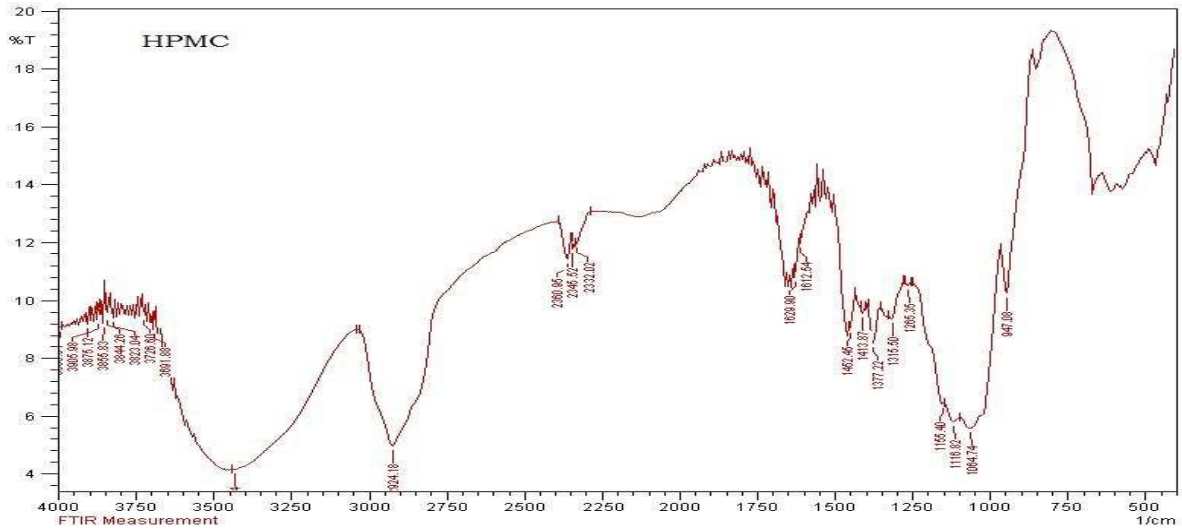


Fig : 3 FT IR Spectrum of MCC

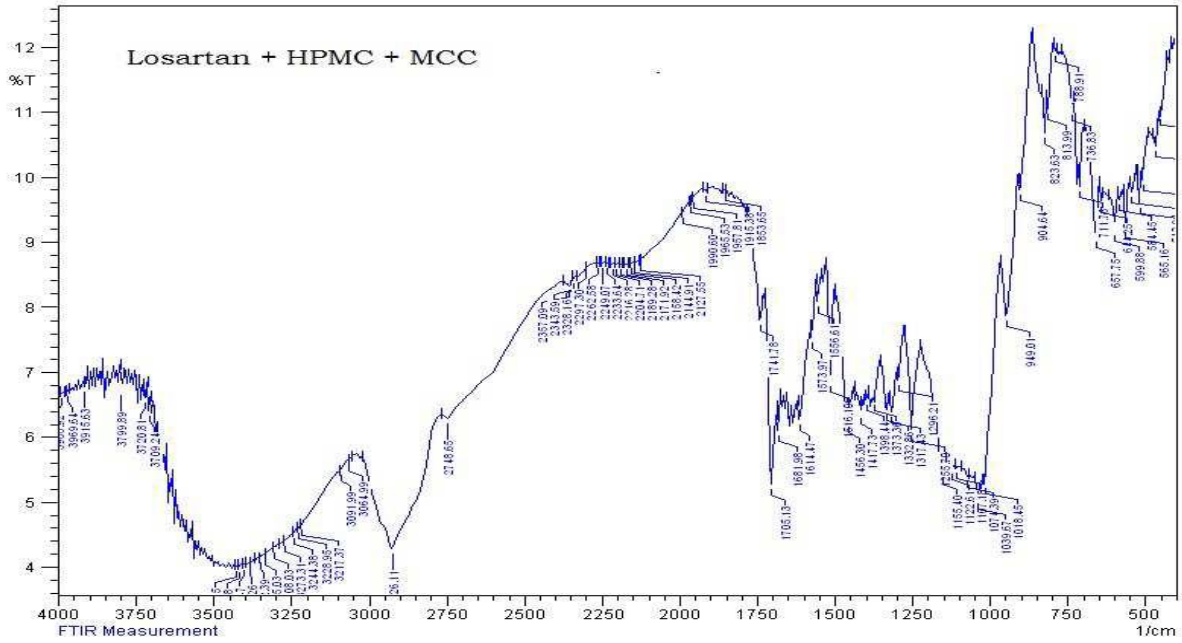


Fig :4 FT IR Spectrum of MCC

Table No. 3 Interpretation of FTIR Spectrums for Pure drug and Excipients

IR Absorption bands cm^{-1}		Bond	Functional groups
Observed peak	**Characteristic peak**		
Losartan +HPMC +MCC			
565.166,599.88, **611.25,788.91** **813.90,901.64,** **1018.45,1074.39** **1107.18,1155.10,** **1296.21,1332.86**	500-600 600-800 600-900 900-1300 1200-1500	C-Br Stretch C-I Stretch C-Cl Stretch C-H Bend out of plane C-H Rocking C-H Stretch	Alkanes Nitrocompounds

1417.73,1556.61 1681.98,1705.13 1853.65,1957.81 2127.55	1300-1500 1500-1700 1600-1900 1600-1700 2100-2400	C-H Bend in lane C-C Stretch C=O Stretch C=N Stretch C=C Stretch N-H Bending	Alkenes Aromatic rings Aldehydes Ketones Esters Nitriles Amines
2158.12,2328.16 2357.09,3091099 3228.95,3799.89 3969.61	2700-3300 2100-2400 3300-3600 3000-3700	C-H Stretch C=O Stretch C=N Stretch C=C Stretch O-H Stretch	Alkanes Alkenes Alkynes Aromatic rings Aldehydes Monomeric alcohols and phenols Htdrogen bonded Alcohols and phenols Amines
Losartan			
761.91,1026.16, 1460.16,1641.48 2953.12,3150.52 3250.31,3271.88 3330.60	800-830 800-1200 1300-1500 900-1300 1600-1900 2100-2400 1000-1400 3000-3700	C-H Stretch C-H Bend in plane C-H Bend out of plane C-C Stretch C=O Stretch C=N Stretch O-H Stretch N-H Stretch	Alkenes Alkynes Akanes Aromatic rings Aldehydes Alcohos Ethers Monomeric alcohols and phenols Hydrogen bonded
Microcrystalline cellulose			
1022.31,1413.87 1572.04,1670.41 2872.10,3103.57, 3260.18,3713.09, 3840.40,	1300-1500 1000-1400 1200-1500 1500-1700 1600-1900 3000-3700	C-H Stretch C-H Bend in plane C-C Stretch C=O Stretch C=C Syretch C=N Stretch C-F Stretch O-H Stretch N-H Stretch N-H Bending	Alkenes Alkanes Alkynes Aromatic rings Aldehydes Monomeric alcohos and phenols Amines Nitriles Nitrocompounds
HPMC			
947.08,1116.82, 1315.50,1377.22 1452.45,1629.90, 2345.52,3450.54 3823.04,3875.12, 3905.98	800-1200 1300-1500 900-1300 1600-1900 2100-2400 1000-1400 3000-3700	C-H Bend in plane C-H Bend out of plane C-C Stretch C=O Stretch C=N Stretch O-H Stretch N-H Stretch	Alkenes Alkynes Akanes Aromatic rings Aldehydes Alcohos Ethers Monomeric alcohols and phenols

Differential Scanning Calorimetry (DSC): The pure drug Losartan shown as an exothermic peak at 158.3 ^{o}C & exothermic peak at 165.6 ^{o}C. The peak neither is nor shifted in the case of DSC of the formulation containing Losartan + HPMC + MCC and Mixtures. The DSC of HPMC showed an endothermic peak 248.3^{o}C & exothermic peak was 104.8^{o}C. The DSC of MCC showed an endothermic peak 106.9^{o}C & exothermic peak was 158.0^{o}C. The DSC of Mixtures shows the 102.8 ^{o}C which shown exothermic peak & endothermic peak was 151.8 ^{o}C there is no incompatibility exist in the formulation.

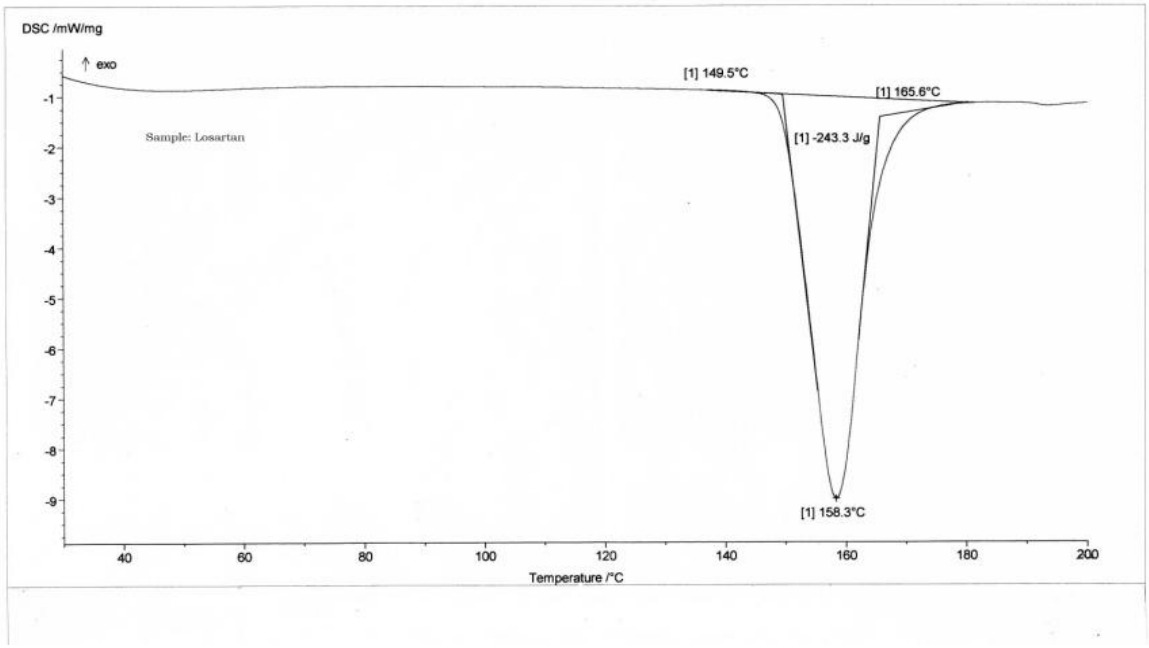


Fig. No. 5 DSC Spectrum of Pure drug

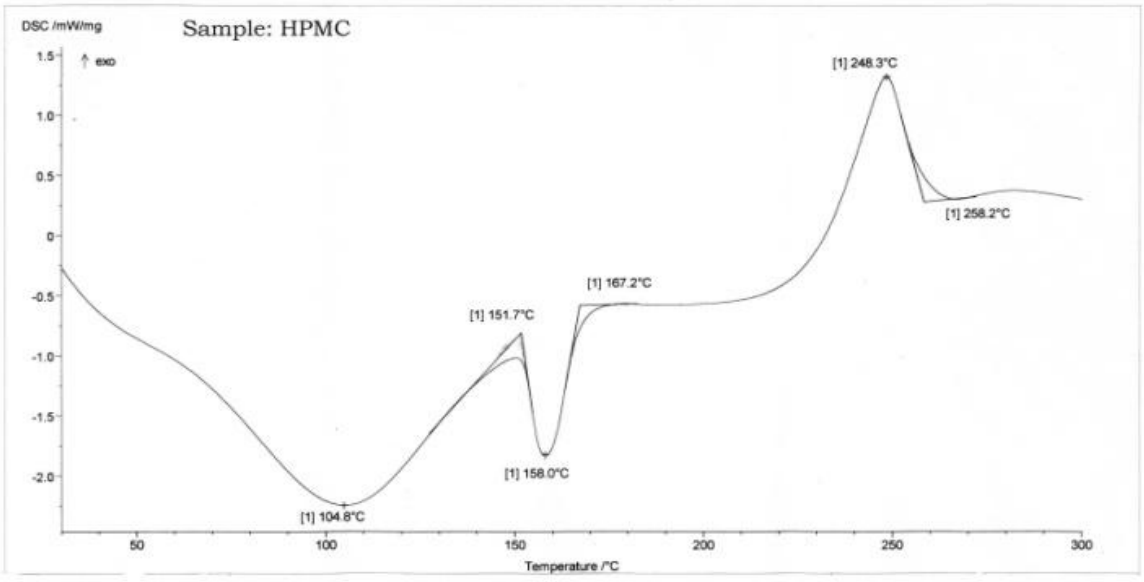


Fig. No.6 DSC Spectrum of HPMC

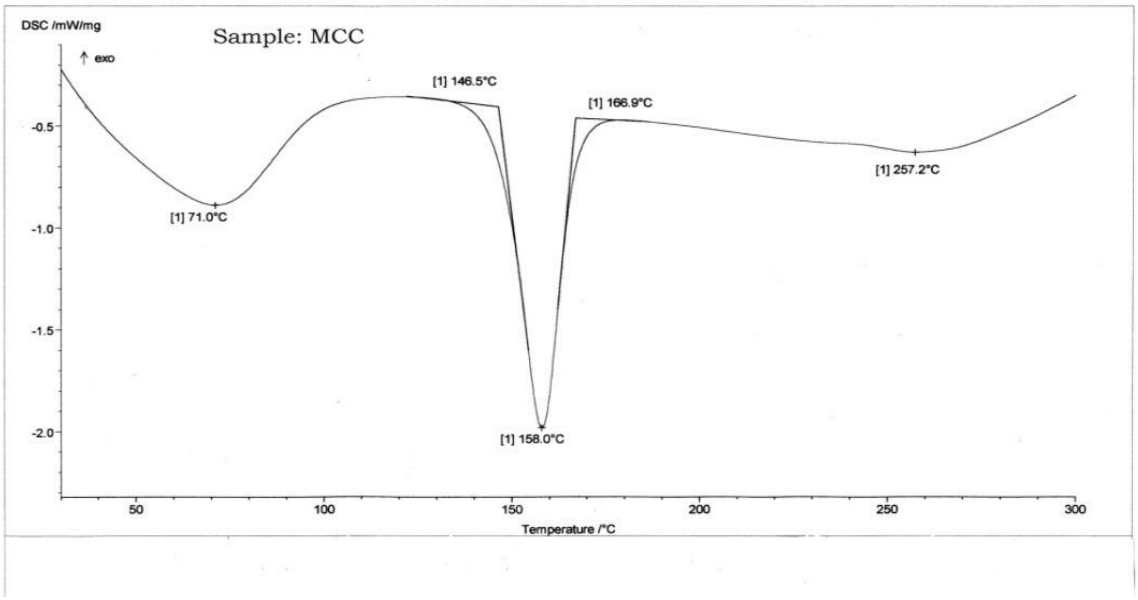


Fig. No.7 DSC Spectrum of MCC

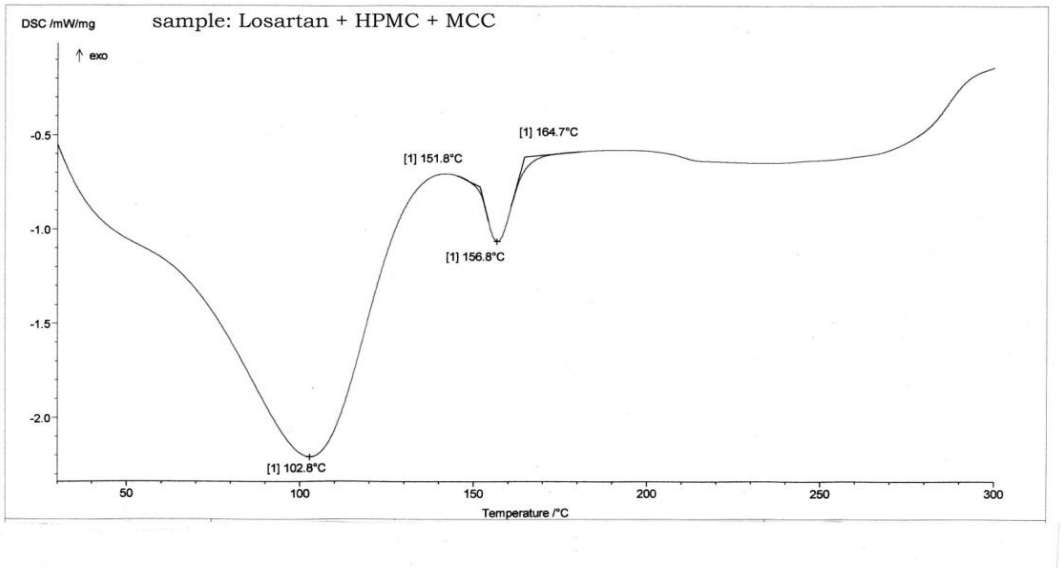
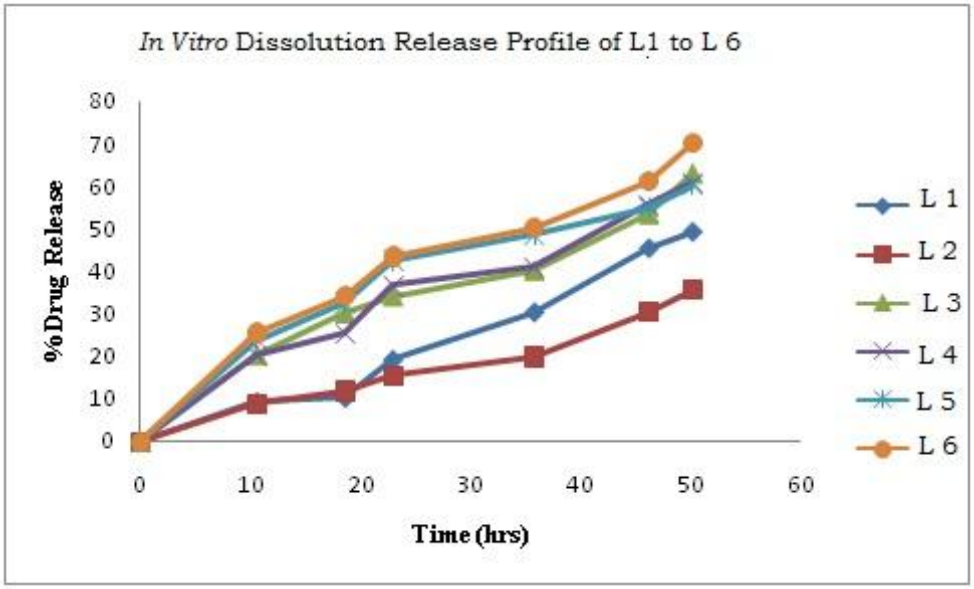


Fig. No.8 DSC Spectrum of Drug + HPMC + MCC

Table no. 4 Evaluation of the formulation P6

Parameters	Trial 2	Trial 3	Trial 3	Average ±S.D
Angle of Repose(^{0})	$27^0$23	$27^0$35	$26^0$56	$27^0$25
Bulk Density (g/ml)	0.450	0.445	0.446	0450±0.0015
TappedDensity (g/ml)	0.552	0.550	0.576	0.553±0.0040
Carr's Index (%)	18.40	18.34	19.50	18.32±0.320
Hausner ratio	1.23	1.25	1.24	1.230±0.004
Thichness (kg/cm^2)	3.04	3.64	3.05	3.055±0.005
Hardness(kg/cm^2)	3.9	4.0	4.2	4.055±0.187
Friability (%)	0.403	0.409	0.532	0.499±0.045
Buoyancy (hrs)	15.22	15.34	15.32	15.345±0.1321
Drug Content (mg)	98.435	8.345	8.456	8.455±0.0085

Fig No.9 *In vitro* release profile of L 1- L 6



CONCLUSION

Finally it can be concluded that hydrodynamically balanced controlled drug delivery systems offers a suitable and practical approach to obtain controlled release of Losartan with enhanced bioavailability and reduced dosing frequency. The methodology of factorial design helps in determining the relationship between the factors acting on the system and the response or properties of the system. The optimized formulation L6 exhibited responses that were comparable with that of the predicted values of the design in optimization technique. This indicates the suitability of the technique chosen for the present dosage form.

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