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FORMULATION AND EVALUATION OF LOSARTAN POTASSIUM MICROSPHERES BY SOLVENT EVAPORATION METHOD

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ABSTRACT

Losartan Potassium loaded microspheres were prepared by solvent evaporation method with combination of hydroxy propyl methyl cellulose and Carbopol polymers in various proportions. A total of nine formulations were prepared. The particle size of all the formulations were ranged between 112±0.02 and 183±0.01µm. The entrapment efficiency was ranged between 68.38±0.01 and 93.16±0.01 All formulations were evaluated for further studies like micromeretic properties, swelling index and in-vitro release profile. It was confirmed with the results of micromeretic property that all the selected formulations showed good flow property. A microsphere was found to be sustained over 12 hours. Hence, it can be concluded that the Formulation prepared by solvent evaporation method, has potential to deliver LosartanPotassium in a controlled manner in a regular fashion over extended period of time in Comparison to all other formulations and can be adopted for a successful oral delivery of Losartan potassium for safe management of hypertension. The Losartan potassium microspheres were prepared successfully by solvent evaporation technique using combination of novel polymers and the in vitro release studies have shown that better release profile with combination of polymers especially with increase in Carbopol concentration.

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INTRODUCTION

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. More precisely, sustained drug delivery can be defined as "Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects. The efficiency of any drug therapy can be described by achieving desired concentration of the drug in blood or tissue, which is therapeutically effective and non toxic for a prolonged period.This goal can be achieved on the basis of proper design of the dosage regimen. [1,2] Microspheres have potential to deliver drug in a controlled fashion. Losartan potassium is an effective antihypertensive drug but is extensively bound to plasma proteins and also causes gastrointestinal disorders, neutropenia, acute hepatotoxicity, migraine and pancreatitis It may therefore be more desirable to deliver this drug in a sustained release dosage form. Microspheres provide sustained release over a prolonged period of time and better bioavailability than conventional dosage forms which reduces dosing frequency, side effects and thereby increases patient compliance.[3] The smaller size and spherical shape of microspheres increases the surface area which increases the bioavailability of the dosage form. It also has advantage over the microparticles and nano particles as they tend to accumulate at the site of action but microspheres due to its smaller size (i.e. micron size) and spherical shape can be injected and hence shows better bio-availability. Microspheres are defined as spherical microscopic particles having a size range of 1- 1000µm[4,5] We can also define it as a monolithic sphere or therapeutic agent distributed throughout the matrix.[6] One of the very common and suitable method to prepare these polymeric microspheres is solvent evaporation method because it facilitates sustained release of a drug which has many clinical advantages as well as it provides compatibility to use more than one novel polymers like hydroxyl propyl methyl cellulose, Carbopol as encapsulation matrix .[6,7]

Microspheres have potential to deliver drug in a controlled fashion. Losartan potassium is an effective antihypertensive drug but is extensively bound to plasma proteins and also causes gastrointestinal disorders, neutropenia, acute hepatotoxicity, migraine and pancreatitis. It maytherefore be more desirable to deliver this drug in a sustained release dosage form. The present study was focused on development of sustained release Losartan microspheres using solvent evaporation method and to study the effect of method of preparation on physical properties and drug release profile of Lorsatan potassium microspheres The purpose of this work is to develop sustained release drug delivery system of Losartan potassium, a low soluble drug, to improve the bioavailability with reduction in dosing frequency along with good patient compliance.

MATERIALS AND METHOD

MATERIALS

The following drugs, excipients/polymers and chemicals were used for the formulation and evaluation of microspheres by solvent evaporation method.

Table: 1 List of Materials.

S.No.	MATERIALS	VENDOR
1	Losartan Potassium	MSN Libratory Private Limited, Hyderabad
2	HPMC	S.D. Fine Chem. Ltd, Mumbai, India
3	Carbopol	S.D. Fine Chem. Ltd, Mumbai, India
4	Salbutamol sulphate	S.D. Fine Chem. Ltd, Mumbai, India
5	Dicloro methane	S.D. Fine Chem. Ltd, Mumbai, India
6	Methanol	S.D. Fine Chem. Ltd, Mumbai, India
7	Sodium lauryl sulphate	S.D. Fine Chem. Ltd, Mumbai, India

METHOD

Losartan Potassium microspheres were prepared using HPMC, Carbopol and distilled water as continuous phase by solvent evaporation technique. Initially dichloromethane (DCM) and methanol was mixed uniformly at room temperature, then HPMC and Carbopol in various proportions was dissolved in the above solution. To this mixture, a drug solution corresponding to 500 mg was added and mixed thoroughly and injected drop wise in to the continuous phase consisting of 100 mL of 0.2% (w/v) SLS (sodium lauryl sulphate) at 250 rpm. The microspheres obtained was washed for 2-3 times with distilled water and dried at room temperature.[8] Different concentrations and ratios of polymers used in the formulation of microspheres are mentioned in Table 2.

Table 2: Composition of various Losartan Potassium microspheres formulations.

FORMULAIONS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan Potassium (mg)	500	500	500	500	500	500	500	500	500
HPMC (mg)	900	800	700	600	500	400	300	200	100
Carbopol (mg)	100	200	300	400	500	600	700	800	900
Dicloro methane (mL)	10	10	10	10	10	10	10	10	10
Methanol (mL)	10	10	10	10	10	10	10	10	10
Sodium lauryl sulphate (mg)	100	100	100	100	100	100	100	100	100

EVALUATION PARAMETERS

1. Drug polymer Interaction (FTIR) study

FTIR spectroscopy was performed on Fourier transform infrared spectrophotometer The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min and the spectra were scanned in the wave number range of 4000- 600 cm-1. FTIR study was carried on Losartan Potassium, physical mixture of Losartan Potassium and polymer.[9]

2.Differential Scanning Calorimetery (DSC)

The physical state of drug in the Losartan Potassium microspheres was analyzed by DSC. The thermograms of Losartan Potassium, Losartan Potassium microspheres with different polymers were obtained at a scanning rate of 10°C/min conducted over a temperature range of 25–350ºC, respectively[9,10]

3. Particle size analysis and percentage yield

Particle sizes of the Losartan Potassium microspheres were determined using an optical microscope. Around 250 microspheres were randomized and their diameters were measured. Percentage yield was calculated by using the following formula. [10,11]

$$\text{Percentage yield} = \frac{\text{Actual weight of microspheres}}{\text{Weight of starting materials}} \times 100$$

4. Determination of percentage drug entrapment efficiency

Efficiency of drug entrapment for each batch was calculated in terms of percentage drug entrapment as per the following formula[12,13]

$$\text{percentage drug entrapment efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Theoretical drug content was determined by calculation assuming that the entire Losartan Potassium present in the polymer solution used gets entrapped in Losartan Potassium microspheres, and no loss occurs at any stage of preparation of Losartan Potassium microspheres.

Practical drug content was analyzed by using the following procedure

Weighed amount of Losartan Potassium microspheres equivalent to 100 mg of Losartan Potassium was dissolved in 100 ml of water. This solution was kept overnight for the complete dissolution of the Losartan Potassium in water. This solution was filtered and further diluted to make a conc. of 10 µg/ml solution. The absorbance of the solutions was measured at 206 nm using double beam UV-Visible spectrophotometer against distilled water as blank and calculated for the percentage of drug present in the sample.

Calibration curve of Losartan potassium

Scanning of Losartan potassium by UV-spectrophotometer in water Standard stock solution of Losartan potassium was prepared by dissolving accurately weighed 10 mg of Losartan in water in 100 ml volumetric flask. The volume was then made up mark by using water, so as to get the solution of 100 µg/ml.

Procedure for Calibration curve of Losartan potassium in water max 206 nm

From the Losartan potassium standard stock solution (100µg/ml). From this solution, aliquots of 2, 4, 6, 8 and 10.0 ml were transferred to the series of 10 ml volumetric flasks and final volume is made with water, so as to get drug concentrations of 2 to 10.0 µg/ml respectively. The absorbance of these drug solutions were estimated at max 206 nm. This procedure was performed in triplicate to validate the calibration curve.

5.Swelling Index

The swelling of microspheres were carried out in phosphate buffer (pH 6.8) for 30 hrs. The excess liquid drops adhered to surface were removed by blotting and the swollen microspheres were weighed. The microspheres were then dried in hot air oven at 400C for 60 hrs until there was no change in dried mass of sample. The swelling index was calculated from the following equation.[14]

$$\text{Swelling Index} = \frac{\text{Mass of swollen microspheres - Mass of dry microspheres}}{\text{Mass of dry microspheres}}$$

6. Scanning Electron Microscopy (SEM)

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation.Dry Losartan Potassium microspheres were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of Losartan Potassium microspheres were taken by random scanning of the stub.[15]

7. In vitro Dissolution Studies

The release rate of Losartan Potassium microspheres was determined by employing Dissolution apparatus by rotating basket method. The dissolution test was performed using 900 ml PH 7.4, in 37 ± 0.5°C at 50 rpm. Losartan Potassium microspheres equivalent to 50 mg were placed in a basket to avoid floating of microspheres. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were passed through Whatmann filter paper and the absorbance of these solutions was measured at 206 nm. Dissolution profiles of the formulations were analyzed by plotting drug release versus time plot. Data obtained was also subjected to kinetic treatment to understand release mechanism.[15,16]

8. Micromeretic Properties

Bulk density

Bulk density was determined by the following formula[17]

Bulk density= Sample weight/Sample volume

Tapped density

The tapped density was determined by tapping method, in which the cylinder containing known amount (M) of microspheres was subjected to a fixed number of taps (approximately 100) until the bed of microspheres had reached the minimum. The final volume after tapping 'Vo' was recorded and the tapped density was calculated by the following equation[17]

Tapped density (Pp) = M/Vo

Compressibility index (CI), Haussner's ratio and Angle of repose

Carr's index (% compressibility index), Hausner ratio and Angle of repose were determined to predict flowability and these can be determined by following equations.[17]

$$CI = \frac{\text{(Tapped density- Bulk density)}}{\text{Tapped density}} \times 100$$

Haussner's ratio = Tapped density/Bulk density

Angle of repose is measured by passing the samples through funnel on the horizontal surface. The height (h) and radius (r) of the cone funnel was measured. The angle of repose (θ) was given by the following formula,[17]

Angle of repose (θ) = tan-1 h/r

RESULT AND DISCUSSION

Drug polymer interaction (FTIR) study

From the spectra of Losartan potassium and physical mixture of Losartan potassium , it was observed that all characteristic peaks of Losartan potassium were present in the combination spectrum, thus indicating compatibility of the Losartan potassium and polymer.

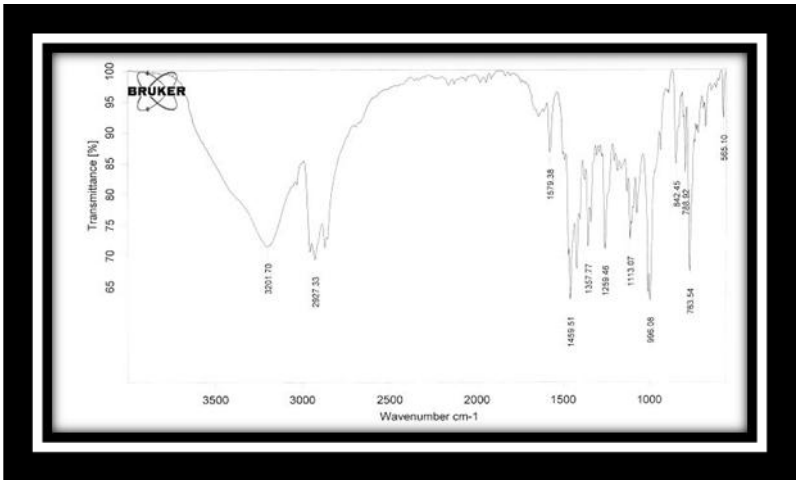

Fig No.1 F IR of Losartan Potassium.

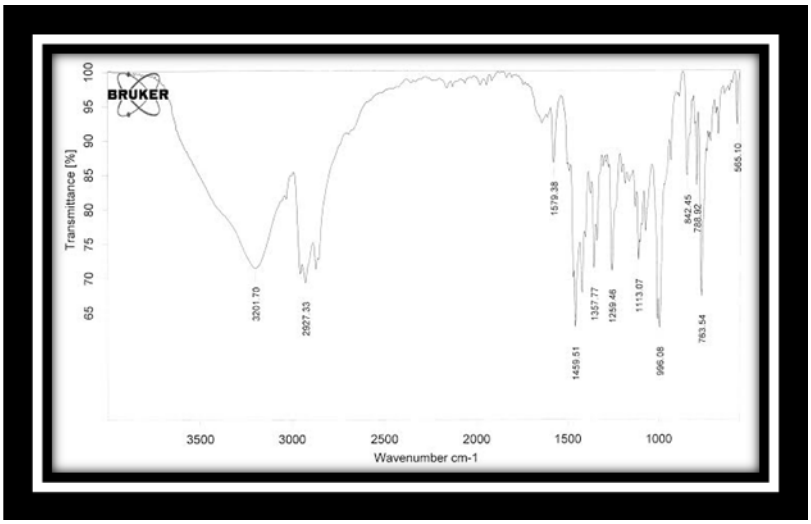

Fig No.2 FTIR of Losartan Potassium Physical Mixture.

Differential Scanning Calorimetery (DSC)

The pure drug Losartan Potassium shown as an endothermic peak at 260.91oC. The peak neither is nor shifted in the case of DSC of the Losartan Potassium microspheres formulation containing Losartan Potassium. The DSC of physical mixture of the Losartan Potassium showed an endothermic peak at 260.91oC. The DSC spectra as shown in Fig 3 & 4.

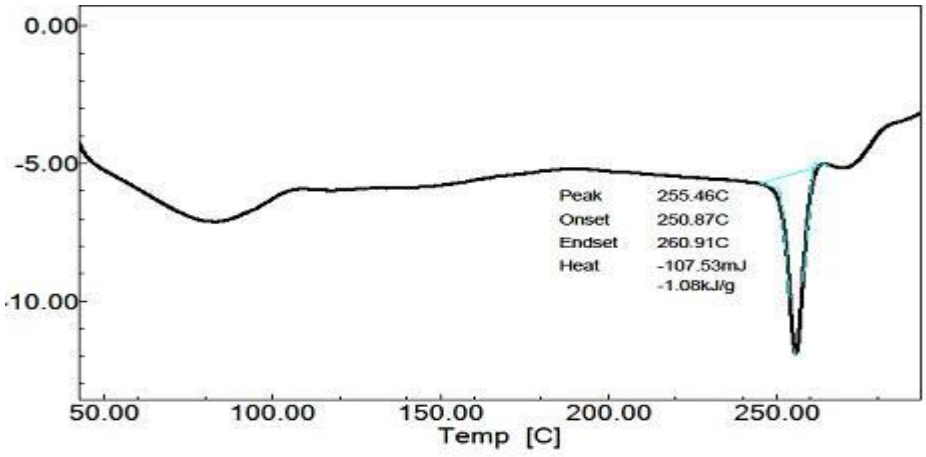

Fig. 3 DSC of Losartan Potassium.

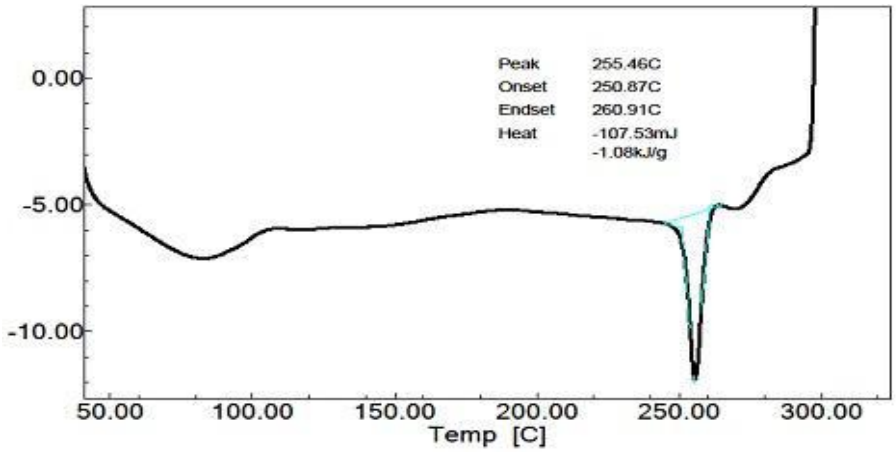

Fig. 4 DSC of Losartan Potassium with Physical mixture.

Particle size analysis

Physicochemical characteristics of the SS microspheres are shown in Table 3. The particle size of the medicated microspheres ranged between 112±0.02 and 183±0.01µm. It was noticed that the particle size of the microspheres increased with increased concentration of Carbopol and this may be due to high viscosity of Carbopol which increases the droplet size and results in increase in particle size.

Percentage yield

The percentage yields of the formulations were ranged between 56.12±.002and 97.78±0.01% are shown in Table 3.

Entrapment efficiency

The entrapment efficiency is increased with lower HPMC concentration and this may be due to the diffusion of drug into the aqueous phase because of decrease in interfacial tension by HPMC between drug and aqueous phase are shown in Table 3.

Swelling index

It was seen that microspheres with more Carbopol concentration showed more swelling compared to those with HPMC are shown in Table 3.

Table 3. Characteristics of Losartan Potassium microspheres.

Formulation code	Particle size(µm) Mean±SD	Entrapment efficiency (%)	Percentage yield%	Swelling index
F1	112±0.02	68.38±0.01	56.12±.003	0.919±.001
F2	118±0.04	71.60±0.01	61.23±.004	0.920±.003
F3	140±0.06	78.41±0.01	68.45±.007	0.939±.001
F4	167±0.02	80.30±0.01	74.85±.006	0.949±.002
F5	171±0.01	83.31±0.01	79.01±.001	0.951±.004
F6	172±0.03	85.21±0.01	84.23±.002	0.969±.006
F7	174±0.07	88.12±0.01	88.32±.007	0.979±.004
F8	178±0.02	91.14±0.01	94.17±.002	0.982±.002
F9	183±0.02	93.16±0.01	97.78±.003	0.989±.001

Scanning Electron Microscopy (SEM)

SEM of the selected formulations is shown in Fig 5 Allthe selected microspheres were smooth, almost spherical in shape and non porous. Due to the presence of HPMC some microspheres showed rough surface.

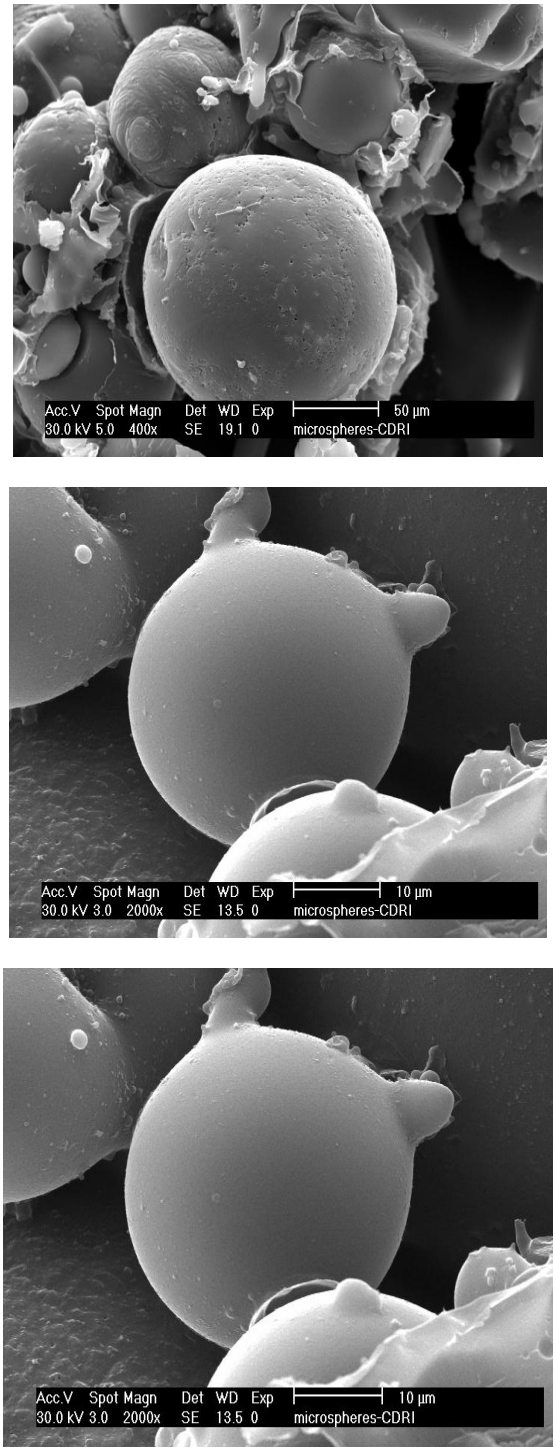

Figure 5: SEM photographs of Losartan Potassium microspheres.

In vitro Dissolution Studies

The drug release is decreased with decreasing concentration of HPMC and it showed controlled release of drug with increasing Carbopol concentration. This may be due to increase in viscosity which will increase the particle size and decrease the surface area. Increase in viscosity may also increase the diffusional path length which might also be the reason for reduction in drug release.

Table 4: In vitro release data of Losartan potassium microspheres.

Time (hrs.)	Percent drug release at time (hr)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	50.20±0.9	49.2±0.6	44.31±0.3	46.21±0.9	43.21±0.6	42.13±0.3	43.12±0.2	40.11±0.3	38.56±0.3
2	55.10±0.3	54.21±0.2	53.20±0.9	52.41±0.4	51.23±0.5	49.21±0.5	48.32±0.2	45.23±0.3	42.78±0.6
3	60.01±0.34	59.01±0.1	57.23±0.3	56.14±0.3	55.32±0.4	54.25±0.5	53.23±0.1	49.25±0.3	48.78±0.6
4	68.87±0.32	63.02±0.69	61.35±0.2	60.54±0.1	59.24±0.2	58.36±0.5	56.32±0.2	55.32±0.4	52.36±0.3
5	75.58±0.7	67.58±0.6	63.21±0.7	62.30±0.5	61.25±0.2	60.87±0.6	59.23±0.2	58.24±0.5	56.63±0.1
6	79.58±0.7	72.71±0.1	71.03±0.9	70.21±0.2	69.58±.0.5	68.21±0.4	66.54±0.6	64.36±0.4	62.36±0.3
8	88.4±0.4	77.15±0.52	76.8±0.1	75.21±0.3	74.21±	73.89±0.4	72.36±0.2	70.61±0.5	69.21±0.3
9	98.52±0.2	88.14±0.3	85.74±0.3	84.33±0.4	83.25±0.5	82.54±0.4	79.56±0.5	77.23±0.2	74.89±0.2
10	---	98.23±0.2	92.69±0.5	91.36±0.3	89.72±0.3	82.31±0.4	81.36±0.3	80.36±0.6	81.63±02.
11	---	---	97.58±0.2	97.34±0.6	92.30±0.2	86.01±.012	85.63±0.1	84.36±0.4	89.54±0.6
12	---	---	---	---	98.51±0.3	97.31±0.7	96.86±.03	96.36±00.2	95.21±0.12

Micromeretic Properties

The microspheres were evaluated for various derived properties such as bulk density, tapped density and flowproperties such as angle of repose, Hausner's ratio and Compressibility index , all the results were shown in table 5.

Table 5: Flow Properties of Losartan Potassium Microspheres.

Formulation code (Avg. ± S.D.)	Bulk density (Avg. ± S.D.)	Tapped density (Avg. ± S.D.)	Compressibility index (Avg. ± S.D.)	Haussner's ratio (Avg. ± S.D.)	Angle of repose (Avg. ± S.D.)
F1	0.416 ± 0.02	0.339 ± 0.01	3.102 ± 0.02	1.034 ± 0.01	21.170 ± 0.14
F2	0.212 ± 0.01	0.391 ± 0.03	4.309 ± 0.03	1.049 ± 0.01	23.120 ± 0.17
F3	0.410 ± 0.02	0.329 ± 0.01	3.611 ± 0.01	1.036 ± 0.02	19.170 ± 0.15
F4	0.316 ± 0.01	0.345 ± 0.02	3.875 ± 0.01	1.049 ± 0.01	21.140 ± 0.12
F5	0.376± 0.02	0.337 ± 0.02	3.459 ± 0.02	1.044 ± 0.01	20.070 ± 0.11
F6	0.307 ± 0.02	0.421 ± 0.01	3.571 ± 0.02	1.047 ± 0.01	23.210 ± 0.18
F7	0.350 ± 0.03	0.385 ± 0.04	4.309 ± 0.02	1.048 ± 0.02	22.490 ± 0.14
F8	0.401 ± 0.02	0.428 ± 0.02	4.406 ± 0.01	1.033 ± 0.01	24.370 ± 0.16
F9	0.397 ± 0.01	0.442 ± 0.01	3.875 ± 0.01	1.031 ± 0.01	22.270 ± 0.19

CONCLUSION

All the drug and excipients obtained were of appropriate standards. From the IR and DSC studies it is concluded that the drug is compatible with excipients and there is no interaction between them. The Microspheres were evaluated for Encapsulation efficiency, Drug content, Drug release, FTIR, SEM, XRD & Particle size analysis.

The Losartan potassium microspheres were prepared successfully by solvent evaporation technique using combination of novel polymers and the in vitro release studies have shown that better release profile with combination of polymers especially with increase in Carbopol concentration.

ABBREVIATIONS

UV - ultra Violet Spectroscopy
DSC - Differential Scanning Calorimetry
XRD - X-Ray Diffraction
SEM - Scanning Electron Microscopy
IR - Infra Red Spectroscopy

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CONFLICT OF INTEREST

The authors do not report any conflict of interest

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