ORIGINAL ARTICLE

Design and Evaluation of Losartan Potassium Controlled Release Microcapsules

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Abstract

Objective: The objective of the present work is to formulate and evaluate Losartan potassium (LP) controlled release microcapsules using gum karaya and polyethylene oxide as polymers, sodium alginate, and calcium chloride as encapsulating material and cross-linking agent. **Materials and Methods:** LP controlled release microcapsules were prepared by ionic gelation method. The prepared microcapsules were characterized by flow properties such as angle of repose, compressibility index, particle size, and encapsulation efficiency and drug release profiles. **Results:** All the prepared microcapsules were spherical and exhibited good flow properties. LP is an antihypertensive drug which comes under the class of angiotension antagonist and it was greatly encapsulated with gum karaya and polyethylene oxide (Water soluble resin 303). The Fourier transform infrared spectroscopy and differential scanning calorimetry studies were conducted for pure drug, polymers and optimized formulations, the studies revealed that they were no incompatibilities between drug and polymers used in the present study. Scanning electron microscopy analysis showed that the microcapsules were uniform and spherical in nature with good surface characteristics. Among all the LP controlled release microcapsule formulations. **Conclusions:** The optimized formulation (L14) prepared with equal proportion of polymers gum karaya and polyethylene oxide was found to extend the release of drug up to 12 h.

Key words: Gum karaya, ionic gelation method, losartan potassium, polyethylene oxide (Water soluble resin 303) microcapsules

INTRODUCTION

Microparticles, microspheres, and microcapsules are frequent constituents of multiparticulate drug delivery systems, and their application is suited for convenient and tolerable drug administration through numerous routes due to their structural and functional characteristics.[1] These carrier systems are widely employed to disguise the taste and odor of therapeutic molecules, prolong drug release, improve drug stability, and increase bioavailability.[2-4]

Compounds are difficult to administrate due to features such as insolubility, volatility, reactivity, hygroscopicity, and physical state. Microcapsules can help to structure such molecules.[5] They may also help to protect the encapsulated contents against degradation caused by external environmental variables including oxygen, light, heat, and humidity, which can harm any labile chemical. Because it is delivered orally, microcapsules may be necessary to protect it from the severe conditions of the upper gastrointestinal tract.[6-8] Furthermore, if the cells are identified as antigen, the immune system of the host fights the transplanted cells, resulting in rejection and unwanted side effects. Immunoprotection and immunoisolation, which are required for *in vivo* administration and implantation of cells such as stem cells for tissue and cell engineering applications, are made

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possible by microcapsules. In many disease states such as Type I diabetes, Parkinson's disease, Alzheimer's disease, and other illnesses, the ability of microcapsules to function as immune protection has been extensively elucidated.[9-12] Microcapsules might also be used to allow for the controlled release of encapsulated contents, which could be controlled by chemical, physical, and mechanical aspects. It may also control the encapsulated product's release at the desired time, rate, dose, and site of action.

Ionic gelation was used to make microcapsules in the current investigation.[13] Losartan potassium (LP) is an efficient antihypertensive medication, although it binds heavily to plasma proteins and can cause gastrointestinal problems, neutropenia, acute hepatotoxicity, migraines, and pancreatitis.[14] Because of these factors, it is preferable to provide this medication in a sustained-release dose form. The goal of this work was to develop LP microcapsules using the ionic gelation process and to investigate the effect of the production method on the physical attributes and drug release patterns of LP microcapsules.

MATERIALS AND METHODS

Materials

LP is a gift sample from Aurobindo Pharma limited, Hyderabad (India). Gum Karaya and poly ethylene oxides were commercially procured from Yarrow Chemical Products, Mumbai. Sodium alginate and calcium chloride were commercially procured from Colorcon chemicals Asia Pvt., Ltd., Mumbai.

Preparation of LP controlled release microcapsules by ionic gelation method

The ionic gelation method was used to prepare LP controlled release microcapsules. A magnetic stirrer was used to dissolve sodium alginate (2 percent w/w) in 25 ml of distilled water. To achieve a homogenous mixture, LP and polymers were added to the sodium alginate mixture and agitated for 5–10 min at 1000 rpm. The mixture was set aside until all of the air bubbles had vanished, and then it was extruded drop by drop into a 50 mL solution of 5% calcium chloride. The calcium chloride solution was decanted after 1 h of curing time, and the beads were filtered and air dried. The composition of LP controlled release microcapsules is given in Table 1.

Evaluation of LP controlled release microcapsules

The prepared microcapsules were evaluated for flow properties such as angle of repose and compressibility index, the drug content, encapsulation efficiency, and particle size were also evaluated. The results are given in Table 2.

Angle of repose

The powder flow parameters were investigated to establish if the material flow was good or bad. The powder was placed in a funnel, which was then poured through. A graph sheet was placed beneath this to produce a heap-like structure, the radius and height of which were measured. The angle of repose was computed using the formula based on these:

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

Compressibility index

By comparing the poured density and the tapped density of a powder, as well as the pace at which it is packed down, a simple test was utilized to evaluate the flow ability of a powder.

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Poured density}}{\text{Tapped density}} \times 100$$

Drug content

The drug content of microcapsules was evaluated by crushing a known amount of microcapsules in a mortor and triturating with a pestle before soaking in 100 ml of 6.8 pH phosphate buffer for 60 min with continuous stirring. The microcapsules swelled and burst completely as a result of this. After suitable dilution with 6.8 pH phosphate buffer, the resulting dispersion was filtered through a 0.45 m membrane filter, and the concentration of medication in the solution was measured spectrophotometrically.

Encapsulation efficiency

LP microcapsules were chosen at random from a batch and crushed to a fine powder. The powdered substance was placed in a 100 mL volumetric flask, which was then filled with 70 mL of 6.8 pH phosphate buffer. The volume was increased to 100 ml by adding 6.8 pH phosphate buffer and shaking it occasionally for about 30 min. A portion of the solution from the volumetric flask was centrifuged, yielding around 10 mL. The centrifuge tube's supernatant solution was collected and filtered again with a millipore filter. The filtrate was then diluted, and the absorbance at 254 nm was measured. For each batch of microcapsules, this test was done 6 times ($n = 6$).

Particle size determination

The size distribution of microcapsules is crucial in influencing their release characteristics. The average particle size of microcapsules was determined using the microscopic technique. A calibrated optical microscope was used to count the particle size of 100 microcapsules for these tests.

Table 1: Composition of losartan potassium controlled release microcapsules

Ingredients (mg)	Formulations													
	L1	L 2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13	L14
Losartan potassium	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Karaya Gum	-	-	-	10	20	30	40	50	-	-	-	-	-	25
Polyethylene Oxide (WSR303)	-	-	-	-	-	-	-	-	10	20	30	40	50	25
Sodium Alginate	15	25	50	50	50	50	50	50	50	50	50	50	50	50
Calcium Chloride (5% w/w)	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Water (ml)	50	50	50	50	50	50	50	50	50	50	50	50	50	50

*QS: Quantity sufficient, WSR: Water soluble resin

Table 2: Evaluation of losartan potassium controlled release microcapsules

S. No	Formulation	Angle of repose (θ)	Compressibility index (%)	Drug content* (mg) (mean±S.D)	Encapsulation efficiency (%)	Particle size (μm)
1	L1	21.52	11.33	98.99±0.11	59±0.02	177
2	L2	24.56	12.52	97.55±0.01	60±0.06	185
3	L3	23.66	13.65	98.36±0.18	59±0.08	190
4	L4	25.11	14.21	98.88±0.21	61±0.09	187
5	L5	22.63	12.66	99.36±0.31	60±0.02	179
6	L6	21.69	13.88	98.74±0.41	62±0.03	188
7	L7	25.63	12.77	99.36±0.13	61±0.05	189
8	L8	24.22	14.52	98.45±0.21	60±0.09	177
9	L9	21.99	13.69	97.66±0.01	61±0.02	169
10	L10	24.88	14.44	98.88±0.81	63±0.01	170
11	L11	25.41	15.20	99.63±0.21	64±0.07	175
12	L12	24.87	13.78	98.32±0.51	62±0.08	180
13	L13	23.99	14.00	98.36±0.11	61±0.09	186
14	L14	24.74	14.88	99.11±0.51	68±0.08	196

*SD: Standard deviation, (n=6)

In vitro dissolution studies

For each batch of microcapsules, dissolution studies were conducted in a calibrated eight station dissolution test apparatus (LABINDIA DS 8000), equipped with paddles (USP apparatus II method) using 900 ml of 6.8 pH phosphate buffer as the dissolution medium. Up to 12 h of samples were taken at regular intervals. To maintain a consistent volume throughout the experiment, fresh medium was replaced with the same volume. The amount of drug released was assessed using an ELICO double beam spectrophotometer at 254 nm after the samples were diluted using the same dissolution media. Various *in vitro* dissolving parameters, such as first order, Higuchi, and Korsmeyer Peppa's constant, were determined based on the data. The *in vitro* drug release profile of various LP controlled release microcapsules is shown in Figures 1 and 2.

Characterization studies

Based on the results obtained on dissolution studies, the optimized formulations were selected, and Fourier Transform Infrared (FTIR), Differential Scanning Calorimetry (DSC) studies were performed to observe the drug-polymer interactions. Scanning electron microscopy (SEM) analysis was performed on LP pure drug, polymers such as gum karaya, polyethylene oxide sodium alginate, and optimized formulation to know the surface characteristics. The results are shown in Figures 3-17.

RESULTS AND DISCUSSION

Preparation of LP controlled release microcapsules by ionic gelation method

In the present investigation, LP controlled release microcapsules were prepared by ionic gelation method. Gum karaya and polyethylene oxide were used as controlled release coating polymeric material for the preparation of microcapsules. Sodium alginate and calcium chloride were used as encapsulating and cross-linking agents. The compositions of various LP controlled release microcapsules are given in Table 1.

Evaluation of physical parameters of LP controlled release microcapsules

The prepared microcapsules were evaluated for angle of repose, compressibility index, % drug content, encapsulation efficiency, and particle size. Angles of repose values for various microcapsules ranged from 21.52° to 25.41°, indicating that microcapsules have good flow characteristics. The compressibility indexes for all microcapsules were ranged from 11.33% to 15.20%, indicating good flow of microcapsule characteristics. The average particle size was assessed using a simple microscopic method, and all of the formulations were between 170 and 196 um. The drug content of microcapsules manufactured using the ionic gelation process ranged from 97.55 ± 0.01 to 99.63 ± 0.21 mg, depending on the polymeric concentration. The encapsulation efficiency of LP controlled release microcapsules was found to be in the range of 59–68%. The physical parameters evaluated for various microcapsules are given in Table 2.

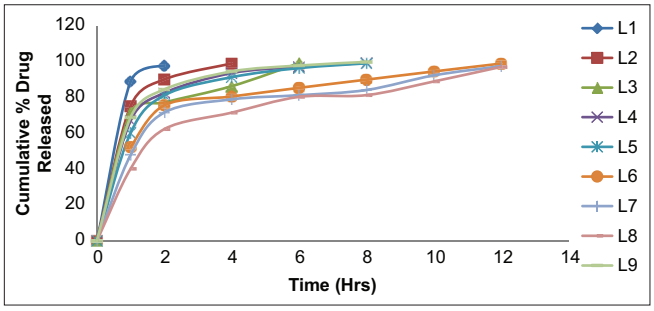

Figure 1: *In vitro* drug release profiles of losartan potassium controlled release microcapsules (L1 to L9) (mean ± S.D; *n* = 3)

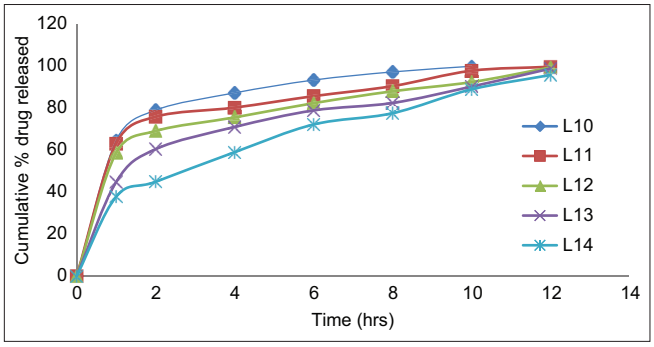

Figure 2: *In vitro* drug release profiles of losartan potassium controlled release microcapsules (L10 to L14) (mean ± S.D; *n* = 3)

In vitro dissolution studies of LP controlled release microcapsules

All of the microcapsules were tested *in vitro* dissolution test apparatus equipped with paddles and 900 ml of 6.8 pH phosphate buffer as the dissolution medium.[13] Without polymers, formulations L1 through L3 released 99.33% of the drug within 12 h and failed to extend the drug release. Formulations L4 to L8 containing gum karaya at concentrations ranging from 10 to 50 mg exhibited 99% drug release for 8–12 h. The drug release of formulations L9 to L13 prepared with polyethylene oxide at concentrations ranging from 10 to 50 mg was 99.11% for 8–12 h. Formulation L14 showed about 95.74% of drug release over a period of 12 h and was found to be suitable for extending drug release up to 16 h. The drug release profiles for various microcapsules are shown in Figures 1 and 2. The dissolution profiles indicated that as the equal propositions of gum karaya and polyethylene

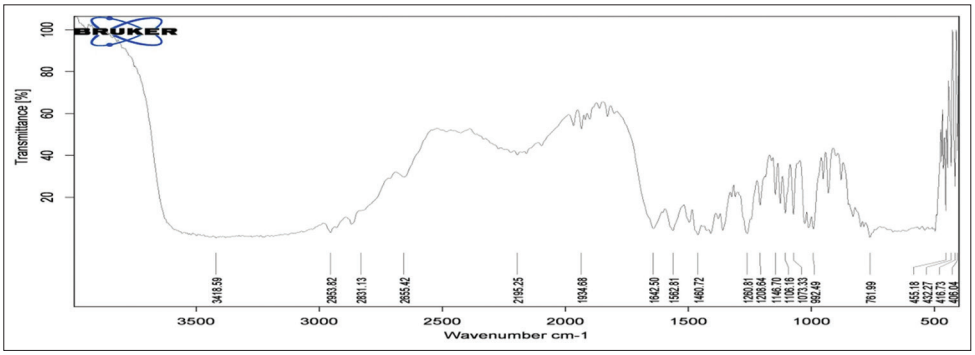

Figure 3: Fourier transform infrared spectrum of losartan potassium pure drug

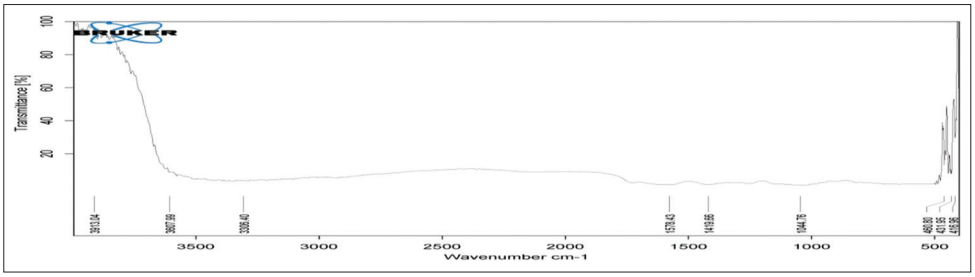

Figure 4: Fourier transform infrared spectrum of gum karaya

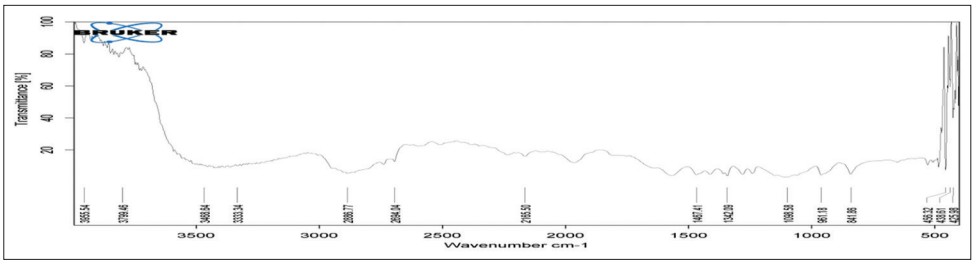

Figure 5: Fourier transform infrared spectrum of polyethylene oxide

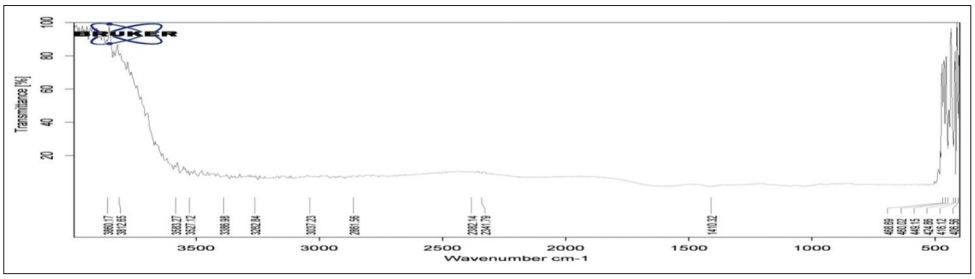

Figure 6: Fourier transform infrared spectrum of sodium alginate

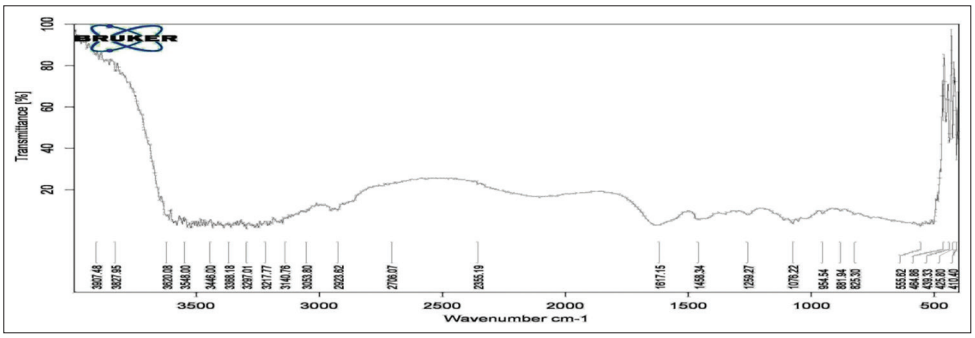

Figure 7: Fourier transform infrared spectrum of optimized formulation (L14)

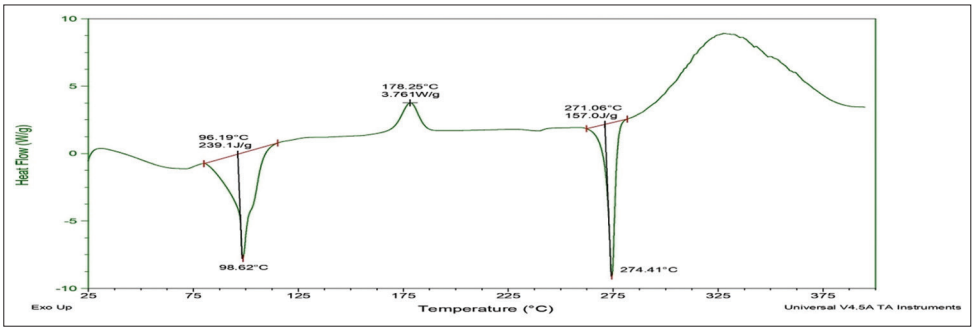

Figure 8: Differential scanning calorimetry thermogram of losartan potassium pure drug

oxide increases, the drug release is extended over prolong period of time. Past studies also revealed that the drug release was delayed on incorporation of PEO water soluble resin 303 into the formulation.[14] The drug release from the microcapsule formulations was by diffusion mechanism. The drug from the polymeric matrix diffused followed by erosion of the polymer. The drug also gets diffused from the channels formed on the coatings.[15] The dissolution profiles are indicated in Figures 1 and 2.

With R2 values ranging from 0.911 to 0.991, all microcapsule formulations were found to be linear with first-order release rate. As a result, all of the microcapsule formulations' drug release rates were concentration dependent and linear with a first order release rate constant (K1). The Higuchi constant was found to be linear in all microcapsule formulations, with R2 values ranging from 0.931 to 0.994. As a result, all of the microcapsule formulations' drug release rates were determined by diffusion. For all of the microcapsule

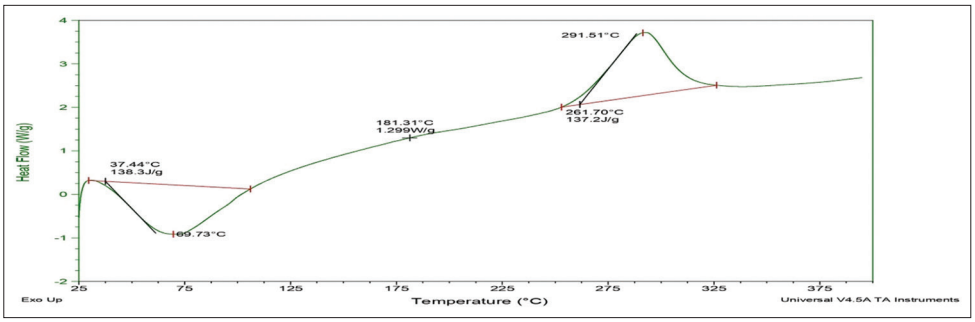

Figure 9: Differential scanning calorimetry thermogram of gum karaya

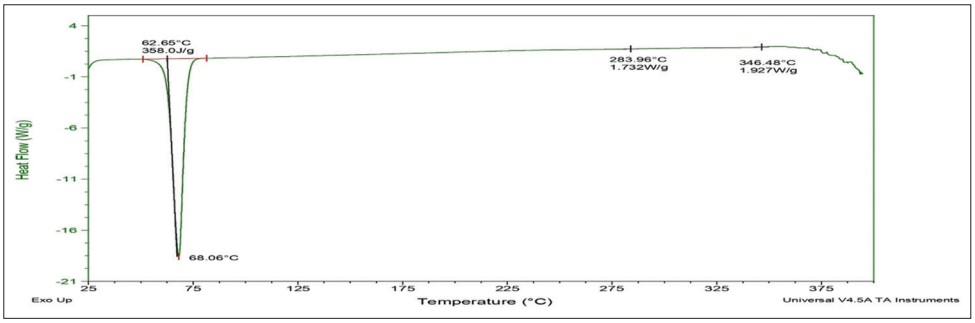

Figure 10: Differential scanning calorimetry thermogram of polyethylene oxide

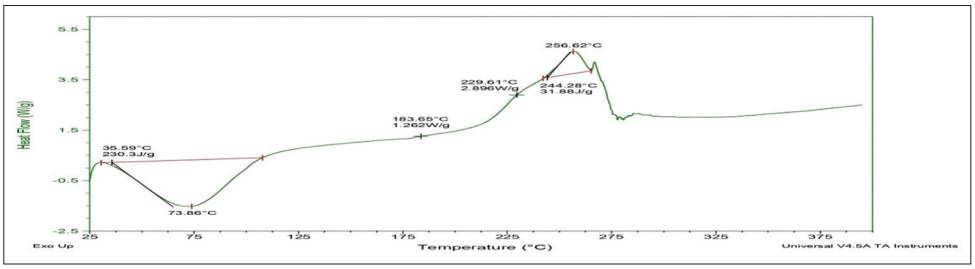

Figure 11: Differential scanning calorimetry thermogram of sodium alginate

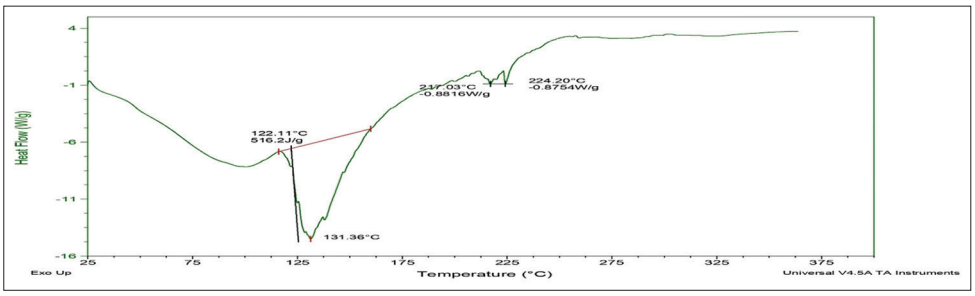

Figure 12: Differential scanning calorimetry thermogram of optimized formulation (L14)

formulations, the release exponent (n values) derived from Peppa's plot was in the range of 0.5–0.8, showing that drug release was by erosion. The dissolution parameters are given in Table 3.

Characterization of microcapsules

Based on the dissolution studies performed on all the formulations, the optimized formulations were selected and following characterization studies were done.

Fourier-transform infrared spectroscopic analysis

The FTIR spectra of LP exhibited principle peaks at wave numbers of 2953 cm^{-1} (C-H), 1642 cm^{-1} (C=C-), 3418 cm^{-1}(O-H Stretching), and 761.99 cm^{-1} (C-Cl bending). For gum karaya, the peaks were observed at 2970 cm^{-1} (C-H), 3376 cm^{-1} (O-H), 1252cm^{-1} (C-O-C), and 1578 cm^{-1}(C=O). For polyethylene oxide, the peaks were observed at 2886 cm^{-1} (C-H), 3426 cm^{-1} (O-H), and 1068.81 cm^{-1} (C-O-C). For sodium alginate, the peaks were observed at 2950 cm^{-1} (C-H), 3420 cm^{-1} (O-H), 1032 cm^{-1} (C-O-C), and 1650 cm^{-1} (C=O).

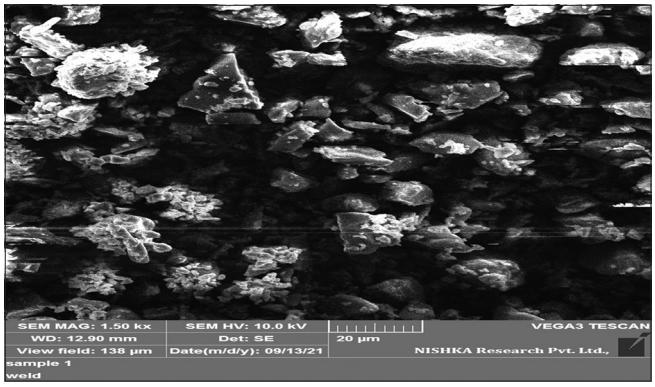

Figure 13: Scanning electron microscopy Image of losartan potassium pure drug

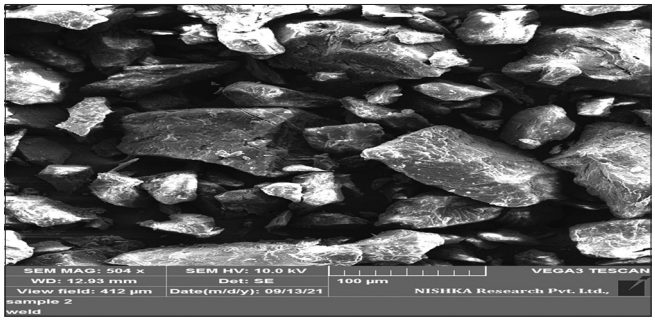

Figure 14: Scanning electron microscopy image of gum karaya

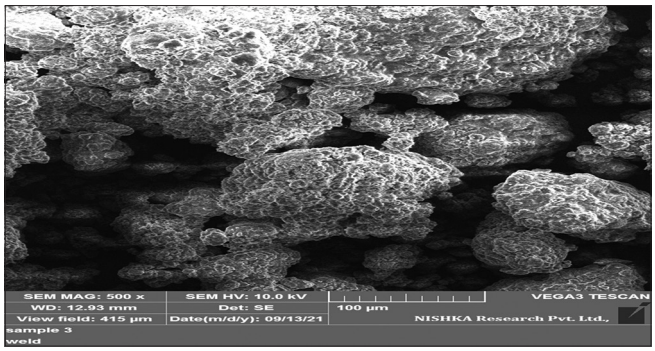

Figure 15: Scanning electron microscopy image of polyethylene oxide

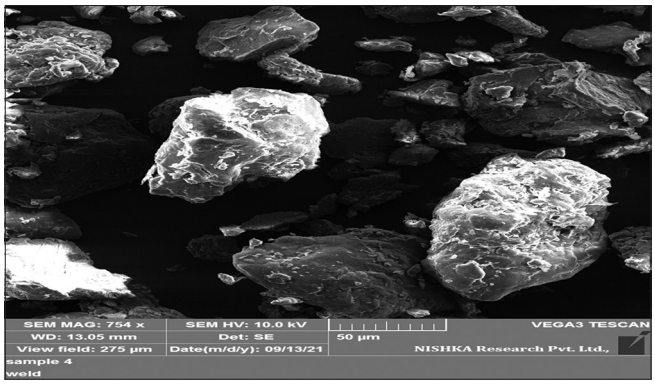

Figure 16: Scanning electron microscopy image of sodium alginate

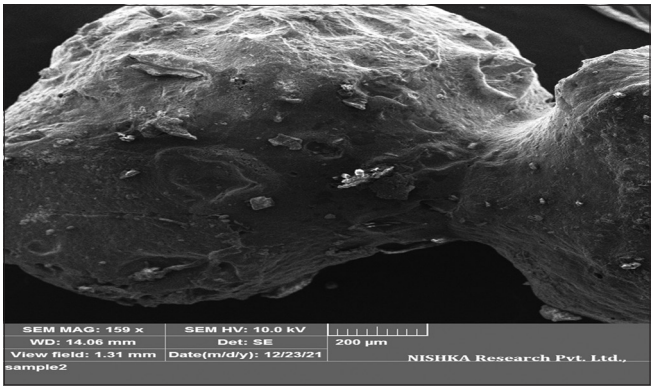

Figure 17: Scanning electron microscopy image of optimized formulation (L14)

Table 3: *In vitro* dissolution parameters of losartan potassium controlled release microcapsules

Formulation	First Order		Higuchi		Peppas	
	K_1 (h^{-1})	R^2	K_H (mg/$h^{1/2}$)	R^2	*n*	R^2
L1	0.222	0.911	35.86	0.931	0.777	0.976
L2	0.316	0.923	39.12	0.955	0.678	0.956
L3	0.454	0.925	32.45	0.967	0.556	0.965
L4	0.234	0.943	33.54	0.923	0.690	0.944
L5	0.333	0.976	36.11	0.965	0.732	0.978
L6	0.399	0.933	29.00	0.945	0.690	0.980
L7	0.400	0.956	27.32	0.936	0.756	0.966
L8	0.422	0.976	23.66	0.978	0.898	0.958
L9	0.245	0.951	33.56	0.966	0.789	0.977
L10	0.344	0.966	24.78	0.955	0.623	0.971
L11	0.390	0.939	31.67	0.970	0.799	0.980
L12	0.457	0.970	32.77	0.978	0.811	0.971
L13	0.477	0.980	31.09	0.980	0.836	0.968
L14	0.387	0.991	25.11	0.994	0.787	0.992

The spectra of optimized microcapsules L14 exhibited all the principle peaks present in the LP pure drug. Thus, there was no appearance or disappearance of any characteristics peak which shows that there is no chemical interaction between the drug and the polymer used. The FTIR spectra of drug, polymers, and optimized formulation L14 are shown in Figures 3-7.

DSC

DSC thermographic peak for LP was observed at temperature 98.62°C as sharp endothermic peak. The DSC thermographic peak for gum karaya was observed at 69.73°C as broad endothermic peak. The DSC thermographic peak for polyethylene oxide was found at 68.03°C as sharp endothermic peak. The DSC thermographic peak for sodium

alginate was found at 73.86°C as broad endothermic peak. The DSC thermographic peak for optimized formulation L14 was found at 122.11°C as broad endothermic peak. The results revealed that there were no major interactions between the drug and the polymers during coating process. The DSC endothermic peaks are shown in Figures 8-12.

SEM

SEM analysis was performed for some of the microcapsules prepared by ionic gelation method. The microcapsules formulated were observed to be spherical and uniform. The SEM images are shown in Figures 13-17.

CONCLUSIONS

The concept of formulating microcapsules containing LP offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over an extended period of time. Thus, the microcapsules of LP were successfully prepared by ionic gelatin method using the different concentration of polymers gum karaya and polyethylene oxide.

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