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Formulation and Evaluation of Calcium Channel Blocker Lercanidipine Loaded Hollow Microspheres

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Abstract

The purpose of the study is to create and assess hollow microspheres filled with Lercanidipine. Ethyl cellulose, Polyethleneoxide, Hydroxypropyl cellulose K15M, and Eudragit L 100 were used as polymers, together with dichloromethane and ethanol as solvents, to create Lercanidipine -loaded hollow microspheres. The physicochemical characteristics, in-vitro drug release, and in-vitro buoyancy of the produced hollow microspheres were assessed. The hollow microspheres were studied using Fourier transform infrared spectroscopy and differential scanning calorimetry. The *in vitro* experiments showed that the largest amount of medication was released from hollow Lercanidipine microspheres made with ethyl cellulose and HPMCK15M in a 2:1 ratio (F2).

Keywords*:* Lercanidipine, Hollow microspheres, Quasi emulsion diffusion, Tween 80, Polyethylene oxide

1. Introduction

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration [1]. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion [2]. Drugs that are easily absorbed from the GIT and having a short half-life are eliminated quickly from the blood circulation. To avoid these problems oral controlled drug delivery systems have been developed as they release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time. However, incomplete release of the drug and a shorter residence time of dosage forms in the upper gastrointestinal tract, a prominent site for absorption of many drugs, will lead to lower bioavailability. Efforts to improve oral drug bioavailability have grown in parallel with the pharmaceutical industry. As the number and chemical diversity of drugs has increased, new strategies are required to develop orally active therapeutics. Thus, gastro retentive dosage forms, which prolong the residence time of the drugs in the stomach and improve their bioavailability, have been developed [3]. Gastroretentive Drug Delivery Systems / Gastroretentive Dosage Forms (GRDFS) One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to

control the gastric residence time i.e. Gastro retentive Dosage Forms (GRDFs) These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in absorption of drug for the intended duration of time. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs. Thus, control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drug exhibiting an 'absorption window' in the GI tract [4]. The intimate contact of the DDS with the absorbing membrane and also the potential to maximize drug absorption may influence the rate of drug absorption. These considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities. Drug may not be absorbed uniformly over the length of the gastrointestinal tract, because dosage form may be rapidly transported from more absorptive upper regions of the intestine to lower regions where the drug is less absorbed and drug absorption from colon is usually erratic and inefficient. Moreover, certain drugs are absorbed only from the stomach or the upper part of small intestine [5].

Lercanidipine is an antihypertensive (blood pressure lowering) drug. It belongs to the dihydropyridine class of calcium channel blockers, which work by relaxing and opening the blood vessels allowing the blood to circulate more freely around the body. This lowers the blood pressure and allows the heart to work more efficiently. [6]

The drug acts more slowly than older dihydropyridines. It probably has fewer adverse effects, but a comparatively high potential for drug interactions.

MATERIALS AND METHODS

Materials

Lercanidipine was gift sample from "Matrix Lab Hyderabad" as a model drug, HPMCK15M, Eudragit L100, Polyethylene oxide, Ethyl cellulose

METHODS

Construction of Calibration Curves

Standard graph of Lercanidipine in 0.1N HCl

Stock solution of the Lercanidipine was prepared by transferring an accurately weighed amount of 100mg of into 100 ml volumetric flask, containing 0.1N HCl to dissolve. Then, the volume was made up to the mark with 0.1N HCl. From this stock solution, necessary dilutions were made to give concentration ranging from 0-15µg/ml. The absorbance of each test solution was measured at λ_{max} of i.e., 234nm using UV/ Visible spectrophotometer against 0.1 N HCl as blank and and plotted graphically to give the standard graphs.

Preparation of hollow microspheres

Floating microspheres with a central hollow cavity were prepared by using a modified Quasi-emulsion diffusion technique. Weighed quantities of Lercanidipine, Ethyl cellulose, polyethylene oxide and hydroxy propyl methyl cellulose (HPMC K15M) were dissolved in a mixture of ethanol and dichloromethane (1:1 solvent ratio) at room temperature in a magnetic stirrer at 50 rpm for 50 min. This solvent was poured drop wise into 100mL distilled water containing 2mL of Tween 80 maintained at a

temperature of 50 ± 2°C. The resultant solution was stirred with a pitched-blade-type impeller type agitator at 1100 rpm for 3h to allow the volatile solvent to evaporate. This resulted in the formation of microspheres. Different ratios of polymers were used to prepare the microspheres.

Table 1: formulation chart of Lercanidipine hollow microspheres

Formulation code	Ethyl Cellulose gm	Polyethylene oxide gm	HPMC K15M gm	Eudragit L100 gm	Drug mg
F1	2	1.5	1.5	2	10
F2	1	1.5	1.5	1	10
F3	1.5	1.5	1	2	10
F4	2	1	1.5	1.5	10
F5	1.5	2	1.5	1	10
F6	1.5	2	1	1.5	10
F7	1.5	1.5	1	1	10
F8	1	2	1.5	1.5	10
F9	1	1.5	1	1.5	10
F10	1.5	1	1.5	1	10
F11	2	1.5	1.5	1	10
F12	2	1.5	2	1.5	10
F13	1	1.5	1.5	2	10
F14	1.5	2	1.5	2	10
F15	1.5	1	1	1.5	10
F16	1.5	1	1.5	2	10
F17	1.5	1.5	2	2	10
F18	2	1.5	1	1.5	10
F19	1	1.5	2	1.5	10
F20	1	1	1.5	1.5	10
F21	1.5	1.5	2	1	10
F22	1.5	1	2	1.5	10
F23	1.5	2	2	1.5	10
F24	2	2	1.5	1.5	10

Drug-Excipients Compatibility Studies

Fourier Transform Infrared Spectroscopy

The Fourier transform infrared (FT-IR) spectra of samples were obtained using FT-IR spectrophotometer (Shimadzu, 8400 S, Japan). About 2–3 mg of samples was mixed with dried potassium bromide of equal weight and compressed to form a KBr disc. The samples were scanned from 400 to 4,000 cm−1wave number [7].

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) experiments were carried out to characterize the physical state of RSM in microspheres as well as to find out the presence of any interaction among drug and the excipients. Lercanidipine, Ethyl cellulose, polyethylene oxide and HPMC K15M samples were put in aluminium pan and hermetically sealed. The heating rate was 10°C/min; nitrogen served as purged gas and the system was cooled down by liquid nitrogen. The differential thermal analyzer was used for this purpose.

Surface Morphology

The surface morphology of the microspheres was examined by scanning electron microscopy operated at 15kVon samples gold-sputtered for 120 s at 10 mA, under argon at low pressure [8].

Evaluation Tests

Micromeritic properties of microsphere Particle size, Angle of repose, Tapped bulk density and Floating Characteristics In vitro buoyancy of microspheres, In vitro drug release study was performed.

Characterization of microspheres

Percentage Yield

The Percentage yield of microspheres of various formulations were calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of microspheres.

***In-vitro* Buoyancy:**

Floating behaviour of hollow microspheres was studied using a USP dissolution test apparatus II. The microspheres (50 mg) was spread on 900mL of 0.1M HCl containing 0.02% Tween 80 as surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 12 hours, both the floating and the settled portions of microspheres were collected separately. The microspheres were dried and weighed and the percentage of floating microspheres was calculated [9].

Particle size:

The particle size of the microspheres was measured using an optical microscope and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer.

Angle of Repose:

It is the maximum angle possible between the surface of pile of powder and the horizontal plane. The angle of repose was determined by the fixed funnel method. The accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated using the following equation [10].

Density

The Bulk Density (BD) and Tapped Density (TD) of microspheres were determined. Two grams of microspheres was introduced into a 10 ml calibrated measuring cylinder. After noting down the initial volume, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 inch at 2 seconds intervals. The tapping was continued until no further change in volume was noted.

Drug Loading and Entrapment Efficiency:

The drug loading was calculated from following equation. For the determination of drug entrapment efficiency, accurately weighed the quantity of 50 mg of microspheres. Crushed it by using mortar and pestle, add the crushed powder into 100ml volumetric flask. Then add some quantity of double distilled water to the volumetric flask and sonicate the resulting solution for 30 min. on Ultrasonicator. Further make up volume with double distilled water. Make up the suitable dilutions of resulting solution so that to obtained the solution of desired drug concentration. The drug entrapment efficiency was measured spectrophotometrically at 234 nm for lercanidipine.

***In-vitro* Drug Release:**

The drug release was studied using a USP dissolution apparatus type II at 100 rpm in 0.1N HCl solution as dissolution medium (900 ml) maintained at 37±5°C. A sample (10 ml) of the solution was withdrawn up to 12 hour from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered and diluted to a suitable concentration with 0.1N HCl solution. Absorbance of these solutions was measured 234nm using UV spectrophotometer. Percentage drug release was calculated using an equation obtained from a standard calibration curve.

RESULTS AND DISCUSSION

Construction of Standard Graph of Lercanidipine in Acidic Buffer (0.1N Hcl) P^H 1.2

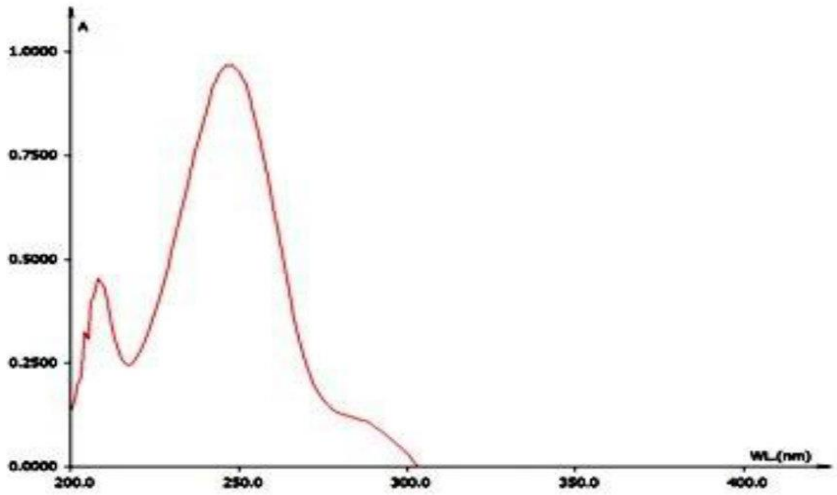

Figure 1: UV-Spectrum of Lercanidipine

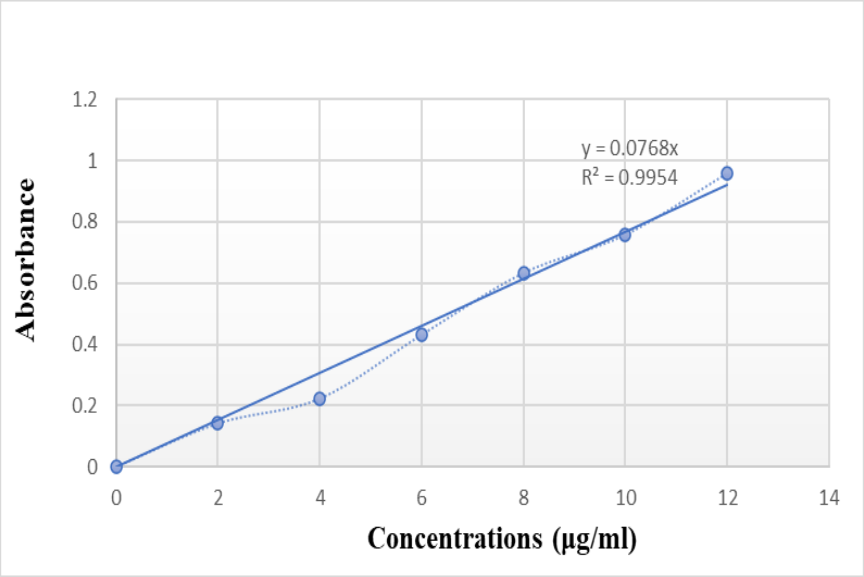

Figure 2: standard curve of Lercanidipine in acidic buffer P^{H} 1.2

Table 2: Various Flow Properties of Formulations

Formulation Code	Parameters				
	Angle of Repose (θ)	Bulk Density (gm/cm3)	Tapped Density (gm/cm3)	Hausner's Ratio (HR)	Carr's Index (%)
F1	11.26 ±1.23	0.1422 ±0.023	0.1324 ±0.05	1.143 ±0.3	13.68 ±1.54
F2	12.27 ±1.32	0.1242±0.032	0.1433 ±0.06	1.155 ±0.6	12.33 ±1.54
F3	13.24 ±1.43	0.1135 ±0.043	0.1535 ±0.07	1.153 ±0.8	12.55 ±1.76
F4	12.24±1.42	0.1432± 0.035	0.1543 ±0.06	1.167 ±0.7	13.33 ±1.85
F5	16.34±1.32	0.1342 ±0.032	0.1435 ±0.07	1.135 ±0.8	11.43±1.75
F6	15.24 ±1.54	0.1324 ±0.032	0.1346±0.09	1.135 ±0.7	12.64 ±1.32
F7	13.34±1.42	0.1432± 0.045	0.1324 ±0.07	1.154 ±0.3	14.45 ±1.65
F8	14.86 ±1.65	0.1325 ±0.032	0.1345 ±0.08	1.153 ±0.2	12.73 ±1.73
F9	17.53 ±1.43	0.1643 ±0.042	0.1543±0.05	1.135 ±0.3	14.44 ±1.24
F10	23.43 ±1.43	0.1324 ±0.045	0.1531 ±0.08	1.143±0.2	12.64 ±1.85
F11	13.26±1.25	0.1432± 0.035	0.1543 ±0.07	1.154 ±0.7	13.86 ±1.74
F12	11.24±1.62	0.1312 ±0.032	0.1586 ±0.06	1.187 ±0.8	11.36±1.32
F13	14.56±1.45	0.1354 ±0.032	0.1597 ±0.07	1.132 ±0.7	12.26 ±1.64
F14	12.35±1.84	0.1482± 0.045	0.1537 ±0.06	1.125 ±0.3	14.95 ±1.43
F15	12.94±1.48	0.1492± 0.035	0.1437 ±0.07	1.126 ±0.2	12.24 ±1.32
F16	13.64±1.45	0.1232 ±0.065	0.1337±0.09	1.167 ±0.7	14.52±1.64
F17	12.84±1.84	0.1424 ±0.087	0.1337 ±0.07	1.188 ±0.8	13.52 ±1.82
F18	12.65±1.62	0.1252± 0.038	0.1537 ±0.07	1.153 ±0.7	11.45±1.78
F19	12.48±1.24	0.1195 ±0.098	0.1536 ±0.06	1.132 ±0.8	12.24±1.78
F20	12.64±1.64	0.1623 ±0.025	0.1425 ±0.07	1.139 ±0.7	14.75 ±1.47
F21	13.24±1.84	0.1424 ±0.032	0.1373±0.09	1.153 ±0.3	12.98 ±1.26

F22	12.34±1.24	0.1224 ±0.036	0.1373 ±0.07	1.152 ±0.2	14.36 ±1.33
F23	16.34±1.45	0.1432± 0.026	0.1337 ±0.08	1.162 ±0.7	13.27 ±1.65
F24	13.24±1.95	0.1325 ±0.021	0.1522 ±0.07	1.131±0.8	11.26±1.75

Table 3: Various Evaluation Parameters of Formulations

Formulation Code	% Yield	Mean Particle Size (µm)	Drug Entrapment Efficiency (%)	Drug Loading (%)	Buoyancy percentage (%)
F1	75.67±0.1	53±0.1	76.39 ±2.45	38.73± 2.34	63.76±2.35
F2	86.35±0.2	43±0.2	75.54 ±2.53	49.33± 2.25	67.54±1.43
F3	79.25±0.3	49±0.3	81.52 ±2.15	33.43±2.33	63.42±2.35
F4	77.69±0.21	52±0.2	79.66 ±2.65	35.54± 2.66	61.43±2.64
F5	78.45±0.2	50±0.5	88.67 ±2.64	47.43± 2.43	64.43±2.54
F6	77.14±0.3	49±0.5	75.35 ±2.74	33.24± 2.32	69.76±2.34
F7	82.45±0.2	47±0.6	74.95 ±2.54	45.45± 2.23	62.54±2.15
F8	85.25±0.3	45±0.7	75.54 ±1.43	33.46± 2.76	61.24±2.65
F9	84.25±0.5	44±0.8	76.55 ±1.53	35.25± 2.45	61.76±1.67
F10	83.69±0.5	49±0.4	77.87 ±1.23	37.43± 2.44	58.47±2.98
F11	76.43±0.9	51±0.1	82.15 ±2.76	32.56±2.33	62.51±2.32
F12	78.68±0.4	52±0.2	75.27 ±2.42	35.14± 2.76	63.24±2.35
F13	81.45±0.1	48±0.3	87.75 ±2.65	42.15± 2.35	63.54±2.26
F14	82.58±0.2	47±0.2	79.26±2.73	32.17± 2.21	68.25±2.76
F15	83.68±0.3	48±0.5	72.85 ±2.14	46.31± 2.87	61.51±2.25
F16	84.75±0.3	49±0.5	73.27 ±1.14	31.25± 2.43	62.61±2.26
F17	83.5±0.2	48±0.65	77.75 ±1.14	32.54±2.31	62.62±2.86
F18	77.48±0.1	52±0.68	82.37 ±2.74	32.12± 2.54	63.14±2.27
F19	80.14±0.2	47±0.45	71.25 ±2.15	43.24± 2.14	62.51±2.86
F20	81.75±0.3	46±0.11	86.26 ±2.54	33.24± 2.41	66.24±2.27
F21	83.25±0.5	45±0.2	72.75 ±2.25	41.24± 2.54	63.54±2.16
F22	81.02±0.6	47±0.3	73.47 ±2.15	33.24± 2.22	62.51±2.98
F23	83.47±0.6	46±0.1	78.26 ±1.25	31.54±2.43	63.25±2.31
F24	79.64±0.2	51±0.2	71.78 ±1.73	32.15± 2.25	62.51±2.54

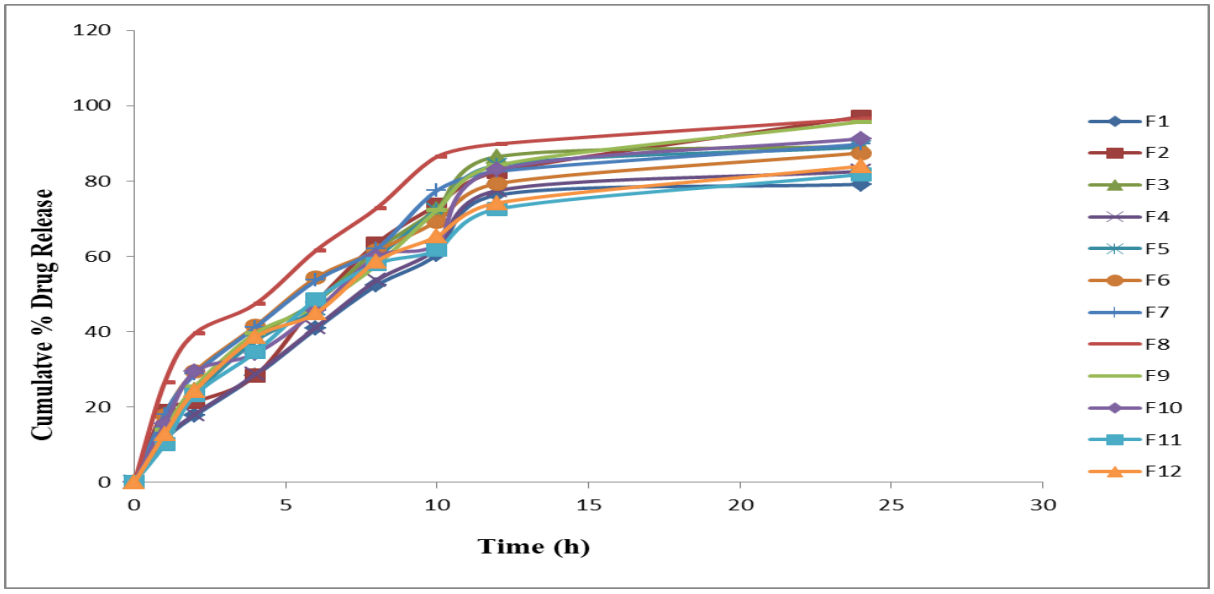

Figure 3: Cumulative percent drug release of formulations F1-12

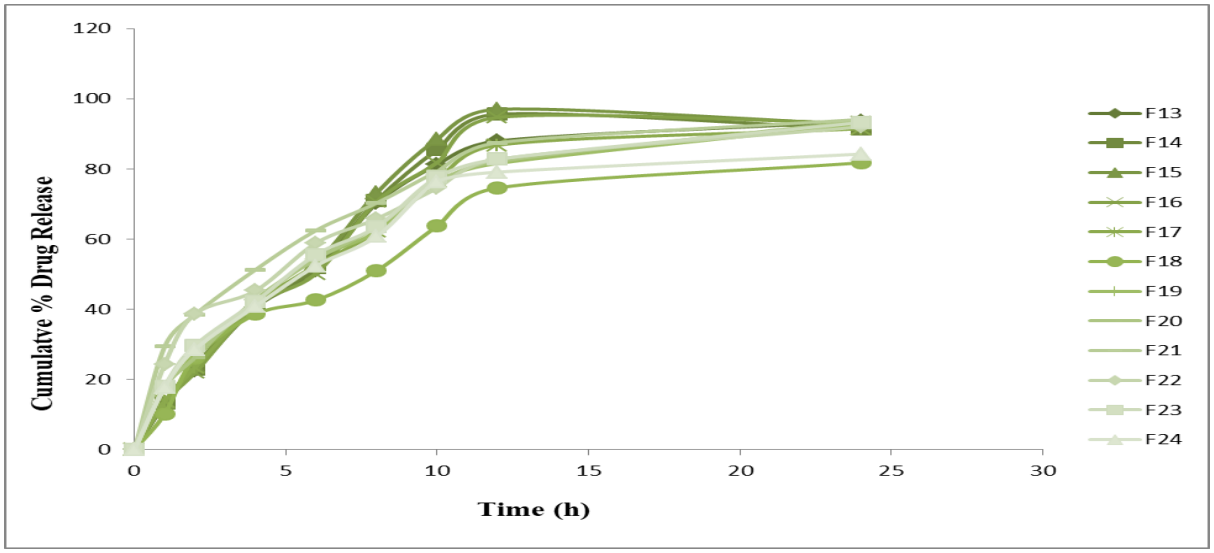

Figure 4: Cumulative percent drug release of formulations F13-F24

***In- vitro* Buoyancy:**

The in-vitro buoyancy test was carried out to investigate buoyancy of prepared microspheres. The formulations (F1 to F24) floating ability is shown in table. Result also showed that longer the size of microsphere more the ability to float.

Percentage Yield:

The percentage yield of floating microspheres was varied according to concentration of polymer. As the polymer concentration increases the percentage yield of floating microsphere decreases.

Particle Size:

The mean particle size of the microsphere's formulations (F1 to F24) was found to be in range of 43.48±1.06 to 59.67±2.45. The result showed that as the polymer concentration increases the particle

size also increases. The viscosity of the solution increases as the polymer concentration increases which result in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities, hence the particle size increases.

Micromeritic Properties:

The Bulk Density, Tapped Density and Hausner's ratio of formulation (F1 to F24) was in range of 0.1000 to 0.1424. The Carr's index was in range of 10.3% to 15.8% and angle of repose was between 10.34o to 25.26.

Drug Loading and Entrapment Efficiency:

The Drug Loading and Drug Entrapment Efficiency of formulation (F1 to F24) were found to be in range of 72.5% to 87.7% respectively

***In vitro* drug release**

The cumulative percentage drug releases of F1–F24 at the end of 24h

Drug - Excipient compatibility studies

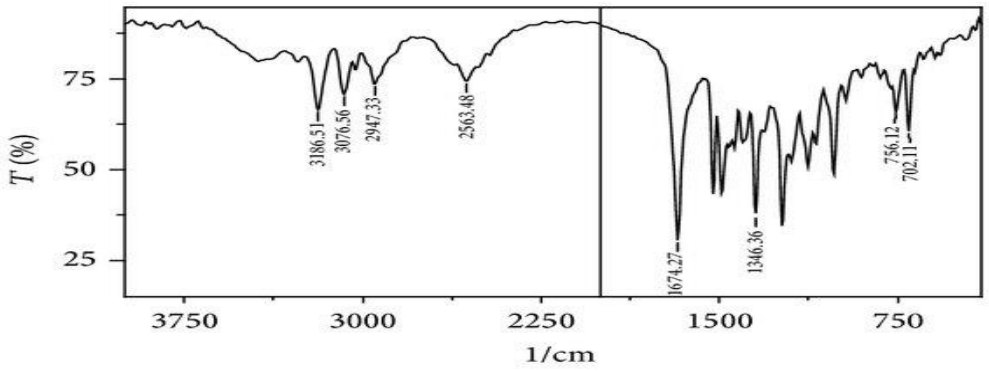

Figure 5: FTIR spectrum Lercanidipine pure drug

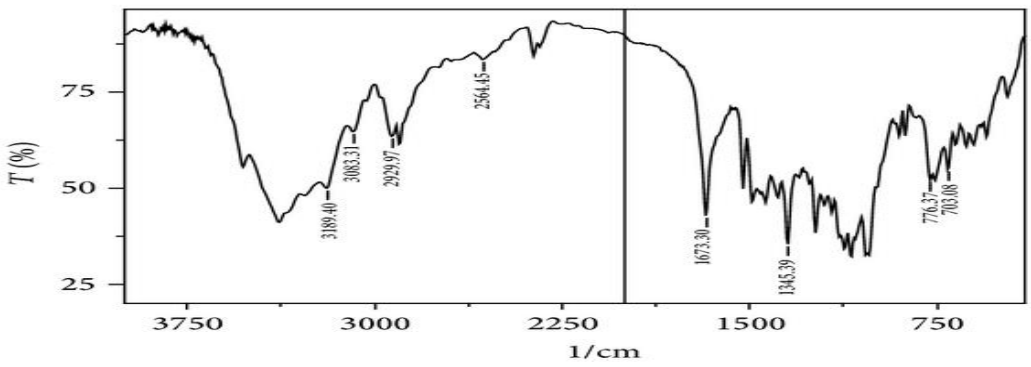

Figure 6: FTIR spectrum of Drug and Polymers

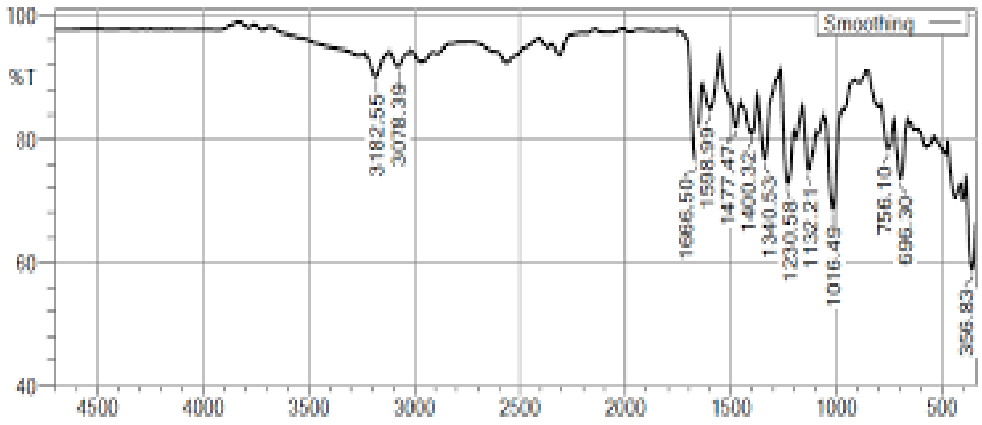

Figure 7: FTIR spectrum of Lercanidipine optimized formulation F2

FTIR spectra of Lercanidipine showed peaks of 3410, 2941, 1629, 1530, 1400 and 1060 cm^{-1}due to –OH stretching, C-H stretching, C=O stretching, N-H bending, C-H bend in plane and C-C stretching respectively. FTIR Spectra of HPMC K 1500 PH PRM showed peaks of 2929, 1462, 1163, 1022, 947 and 850 cm^{-1} due to C-H stretching, O-H stretching and C-C stretching respectively. FTIR spectra of optimized formulation showed both characteristics peaks of drug and polymer indicating no drug-polymer interaction.

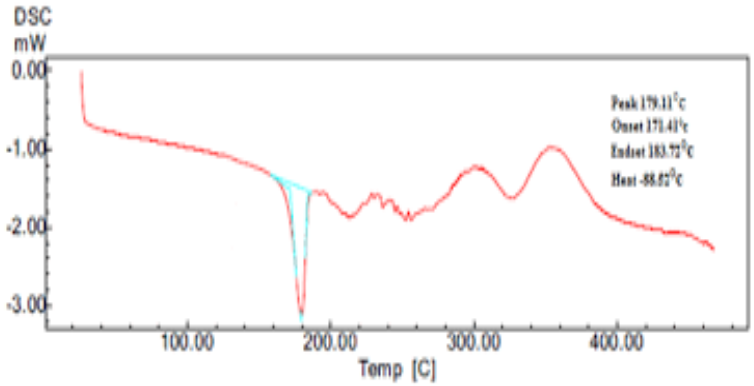

Figure 8: DSC thermogram of pure Lercanidipine

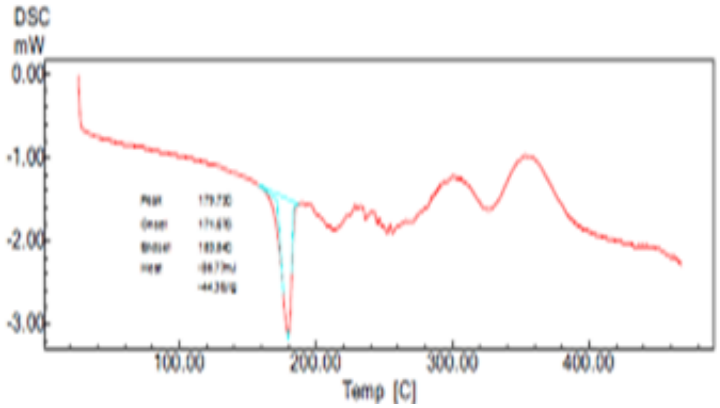

Figure 9: DSC thermogram of optimized formulation mixer

Compatibility studies by DSC:

Sharp endothermic peak was observed at 179.71 ^{0}C the melting point of Lercanidipine. In formulation mixer the peak was found at 178.35 ^{0}C indicating that the formulation was stable up to 69^{0}C. All are shown in figure.

Scanning Electron Microscopy

Developed floating microspheres (F2) were found to be porous, spherical having smooth surface as evident in figure. The perforated microsphere was formed at high stirring speed of 1600 it may be due to the fact that rapid evaporation of solvent takes place which results in void formation. The high floating time of 10h obtained for formulation (F2) would be due to the porous structure of microspheres which makes the microspheres light weight and less dense.

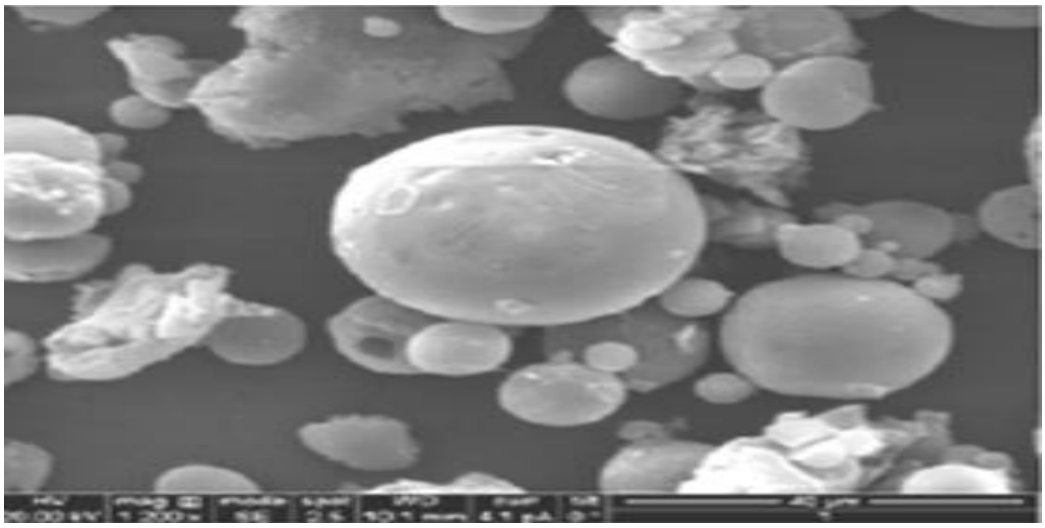

Figure 10: Scanning Electron microscopy image of optimized formulation F2

Conclusion:

In the current work, Eudragit L 100, HPMC K15M, Polyethylene Oxide, and ethyl cellulose polymers were used to create Lercanidipine -loaded hollow microspheres. According to the study's findings, Lercanidipine hollow microspheres can be successfully prepared using the quasi-emulsion diffusion approach. The drug was determined to be compatible with all of the excipients utilised in the study after a drug-excipient compatibility analysis was conducted using DSC & FTIR. The *in vitro* experiments showed that the largest amount of medication was released from hollow Nisoldipine microspheres made with ethyl cellulose and HPMCK15M in a 2:1 ratio (F2).

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