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FABRICATION AND CHARACTERIZATION OF LERCANIDIPINE HYDROCHLORIDE LOADED HOLLOW MICROSPHERES

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ABSTRACT
The goal of this research is to treatment of hypertension by developing hollow microspheres that are loaded with Lercanidipine hydrochloride. The purpose of developing hollow microspheres loaded with Lercanidipine hydrochloride is to extend the drug's gastrointestinal retention time over currently available sustained release solutions, hence reducing the frequency of dose and improving bioavailability. The following polymers were used: cellulose acetate, Eudragit RS 100, polyethylene oxide, Hydroxypropyl cellulose K15M, ethyl cellulose, and Eudragit RL100. These microspheres were manufactured using solvents such as dichloromethane and ethanol. Hollow microspheres that contain Lercanidipine hydrochloride were produced by modifying quasi-emulsion diffusion techniques. Preformulation tests for hollow microspheres loaded with Lercanidipine hydrochloride showed that all formulations have acceptable flow characteristics. SEM analysis investigated that the surface of hollow microspheres was found to be slightly porous, smooth, and spherical in shape. FTIR spectra studies confirmed that there is compatibility between the drug and excipients. By using buoyancy tests and the maximum amount of drug released within 12 hours, the formulation design was optimised. In vitro tests shown that Lercanidipine hydrochloride hollow microspheres composed of Eudragit RL 100 and Eudragit RS 100 at a ratio of 1:2 (F7) exhibited the most efficient sustained release of drug. Therefore, there is potential for a novel treatment of hypertension with the optimised formulation (F7) of hollow microspheres containing Lercanidipine hydrochloride.

Keywords: Lercanidipine hydrochloride, Hollow microspheres, Polyvinyl alcohol, Eudragit RS 100, Polyethylene oxide, Quasi emulsion diffusion.

INTRODUCTION
The most used method of drug administration is oral administration. Gastric emptying can impact the in-vivo efficacy of drug delivery systems, demanding frequent dosage of these medications to attain appropriate therapeutic action [1]. Hollow microspheres are spherical, empty, coreless particles that may remain a considerable amount of time in the stomach area. Based on a non-effervescent mechanism, hollow microspheres are gastro-retentive drug delivery methods in the stomach. These particles are free-flowing and vary in diameters between 1 and 1000 mm [2]

Lercanidipine hydrochloride, a calcium channel blocker used to treat hypertension, is classified under biopharmaceutical classification system II. Chemically lecanidipine hydrochloride (LCP) is 1, 4-Dihydro-2,6-dimethyl -4-(3-nitrophenyl) 3,5-dicarboxylic acid pyridine 2- [Methyl (3,3-diphenyl propyl) HCl of amino]-1,1-dimethylethylmethyl ester. Because of substantial first pass metabolism, the

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drug has a 44% oral bioavailability. Due to its lower dose range and shorter half-life, LCP is ideally suited for drug delivery systems that target the stomach [3]

MATERIALS AND METHODS:

Lercanidipine Hydrochloride was purchased from hetero laboratories Limited Hyderabad. Eudragit RS 100, Eudragit RL 100, HPMC K15M, Ethocel, Cellulose acetate, Polyethylene oxide, Ethanol, Dichloromethane and Polyvinyl alcohol. All the "chemicals are of Laboratory-grade and purchased from SD Fine Chemicals" Private Limited.

METHODOLOGY

Formulation of lercanidipine hydrochloride floating hollow microspheres

A modified version of the quasi-emulsion diffusion method was employed to fabricate hollow-core floating microspheres. The drug, hydroxypropyl methylcellulose (HPMC K15M), ethyl cellulose, Eudragit RL 100, Eudragit RS 100, polyethylene oxide and cellulose acetate were weighed in various ratios. These polymers and the drug were dissolved in a mixture of methylene chloride and ethanol (1:1) at 37°C for 50 minutes with stirring at 500 revolutions per minute using a magnetic stirrer. The resulting solvent solution was then added dropwise to spinning solution of 1% PVA [4].The solution was stirred at 500 rpm for 6 hours using a magnetic stirrer until complete evaporation of the volatile solvent occurred, resulting in the formation of hollow microspheres. Table 1 in the formulation details various polymer ratios utilized for microsphere design. After collection, the hollow microspheres must be thoroughly rinsed with water to remove any residual substances. Subsequently, the collected microballoons should be air-dried at room temperature before further evaluation [5]

Table 1: Composition of Lercanidipine hydrochloride Loaded hollow microspheres.

Drug and excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Drug(mg)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K15M (mg)	100	100	100	200	300	--	--	--	--	--	--	--	--	--	--
Ethyl cellulose(mg)	100	200	300	100	100	--	--	--	--	--	--	--	--	--	--
Eudragit RL 100	--	--	--	--	--	100	100	100	200	300	--	--	--	--	--
Eudragit RS 100	--	--	--	--	--	100	200	300	100	100	--	--	--	--	--
Polyethylene oxide	--	--	--	--	--	--	--	--	--	--	100	100	100	200	300
Cellulose acetate	--	--	--	--	--	--	--	--	--	--	100	200	300	100	100
Ethanol(ml)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Dichloromethane (ml)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Drug to polymer ratio	1:1:1	1:1:2	1:1:3	1:2:1	1:3:1	1:1:1	1:1:2	1:1:3	1:2:1	1:3:1	1:1:1	1:1:2	1:1:3	1:2:1	1:3:1

Drug Excipient Compatibility Study

FTIR Spectroscopy

FTIR studies were carried out using a Shimadzu instrument and the KBr pellet method to assess the compatibility between drugs and polymers. Both an optimized formulation and pure drug samples underwent analysis via FTIR. The aim of these compatibility studies was to explore possible interactions between the excipients in the formulations and Lercanidipine hydrochloride. IR spectra ranging from 4000 to 400 cm^{-1} were examined for pure Lercanidipine hydrochloride, and the optimized preparation [6].

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Evaluation of Lercanidipine hydrochloride loaded hollow microspheres

Micromeritic properties

The micromeritic properties of the hollow microspheres, including bulk density, tapped density, Hausner's ratio, and Carr's compressibility index, were evaluated. Tapped density was determined employing the tapping method, while both bulk and tapped densities were measured using a graduated measuring cylinder. Initially, the sample was introduced into the cylinder, and its bulk volume was recorded. Then, the cylinder underwent 100 taps to attain the final tapped volume. For tap density determination, the cylinder was tapped until no measurable change in volume was observed. This ensured that the powder particles had reached a stable, maximally compacted state within the cylinder [7].

$$\text{Tapped density} = \text{“}V_b - Vt / V_b \times 100\text{”}$$

Here, V_b and V_t are bulk & tapped volume resp.

Hausner's ratio and Carr's compressibility index for the microspheres were calculated using the following formulas:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

$$\text{Carr's Index} = \frac{\text{Tapped denisty} - \text{Bulk density}}{\text{Tapped density}} \text{x100}$$

Angle of repose (AOR)

The angle of repose for the hollow microspheres was determined using the fixed funnel method. This angle represents the highest angle that can be formed between a pile of freely flowing microspheres and the horizontal plane. To measure the angle of repose, a conical pile of hollow microspheres was allowed to flow freely through a funnel until it reached the tip of the funnel. The funnel was positioned with its end attached to graph paper and placed at a fixed height on a horizontal flat surface [8].

The angle of repose can be calculated using the following formula.

$$\text{Tan}\theta = \frac{h}{r}$$

Where r = Cone base radius, h = Height of cone

Measurement of Particle Size

The particle size of the manufactured hollow microspheres was assessed using an optical microscope. This method involved measuring the size of one hundred particles with an ocular micrometer, from which the mean particle size was calculated [9].

Scanning Electron Microscope (SEM) analysis

The surface morphology of the optimized formulation was examined using SEM (Scanning Electron Microscopy). Hollow microspheres were scanned and analyzed using an electron microscope with a fine coat of Ion sputter. The sample was placed into a "Copper sample holder" and then spatter coated with gold and Carbon to enhance conductivity and imaging quality during SEM analysis [10].

Percentage Yield

To calculate the percentage yield, divide the weight of the dried hollow microspheres by the total initial weight of all ingredients used in the formulation [11] (including the drug and non-volatile excipients), and then multiply by 100 to express the result as a percentage.

CAHIERS MAGELLANES-NS
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http://magellanes.com/

The following formula is used to calculate it:

$$\text{Percentage Yield} = \frac{\text{Weight of dried hollow microspheres}}{\text{Total amount of the dru} \quad \text{non volatile substances}} \text{X } 100$$

Entrapment Efficiency (EE)

To determine the quantity of drug trapped in the floating hollow microspheres, the following steps were taken:

1. Preparation of Samples: One dose equivalent of floating hollow microspheres was taken and washed using 0.1N Hydrochloric acid to remove any free drug on the surface and unentrapped drug.
2. Dispersing the Formulation: 20 mg of the washed formulation was precisely weighed and dispersed in 10 mL of 0.1M Hydrochloric acid. The mixture was then stirred for approximately 12 hours using a magnetic stirrer to ensure thorough mixing of the polymer and to extract the entrapped drug.
3. Filtration: Both the whole and unentrapped drug solutions were filtered using a Whatman filter to separate the drug from the microspheres and any unentrapped drug.
4. Drug Concentration Measurement: The drug concentration in both the whole and unentrapped drug solutions was measured spectrophotometrically at 234 nm after appropriate dilution with 0.1N Hydrochloric acid [12]

By comparing the drug concentration in the whole solution before and after filtration, and accounting for any dilutions, the quantity of drug trapped in the floating hollow microspheres can be compute

EE (%) was evaluated by the methodology below.

EE (%) = "Total drug content - unentrapped drug x100
Total drug content"

Invitro Buoyancy studies

To conduct the in-vitro buoyancy studies for floating microspheres, a USP type II dissolution apparatus was utilized. Specifically, 20 mg of microspheres were positioned atop 900 mL of 0.1N HCl (pH 1.2) and stirred at 50 rpm for a duration of 12 hours. Following this period, filtration was employed to differentiate the layer of buoyant microspheres from those that settled. The separated particles were then thoroughly dried and weighed individually [13].

The following formula was used to compute the buoyancy of microsphere

$$\text{Buoyancy}(\%) = w_F/(w_F+w_S)\times 100$$

Here, w_S and w_F= weight of settled and floating Hollow microspheres respectively.

Drug Content

UV Spectrophotometry was used to determine the amount of drug in respectively formulation equivalent to a unit dose (20 mg).Each formulation was removed and pulverised to a fine powder in a glass mortar before being dissolved for 6 hours in a 0.1N HCl solution. After filtering the solution, the absorbance at 236 nm was measured [14]

In vitro Drug Release studies

The release of lercanidipine hydrochloride from the hollow microspheres was evaluated using a USP Type 2 dissolution tester. Dissolution tests were performed in 900 mL of 0.1 N HCl as the dissolution medium, with a rotation speed of 50 rpm and a temperature maintained at 37 ± 0.5 °C. Sample solutions of 5 mL were withdrawn at predetermined 12-hour intervals to analyze the release profile [15]. To maintain sink conditions, an equal volume of dissolution media was replenished after each withdrawal. The samples were subsequently analyzed using a UV spectrophotometer at a wavelength of 236 nm. All experiments were conducted in triplicate.

CAHIERS MAGELLANES-NS
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Statistical Analysis

One-way analysis of variance was used to compare the cumulative drug release data for each formulation, which corresponded to various polymers and their ratios (ANOVA). The statistical software tool Minitab 21.4.2 was used to perform this analysis [16]

Stability studies:

In accordance with the standards of the International Conference on Harmonisation (ICH), stability studies were conducted out. The optimised Microballoons (F7) were placed in a desiccator with a saturated sodium chloride solution (75% relative humidity) after being covered with polyethylene [17]. For three months, the dessicator was kept at 40°C. Microballoons were assessed for their physical characteristics, drug content, and percentage of drug release for a 12-hour period at the end of each month [18].

RESULTS AND DISCUSSION

Drug Excipient Compatibility Study

FTIR Spectroscopy

The drug-excipient compatibility study was carried out using Fourier transforms infrared spectroscopy. FTIR spectra indicated peaks at 3346, 1591,1516, 1414, 1259,1020 and 711 cm-1, attributable to stretching of the C-H, N-H, N-O, -OH, C-O, C-N and meta-substituted benzene respectively shown in Figure 1. Peaks of 3357, 1608, 1523, 1451, 1235,1023 and 702 cm-1 were visible in the FTIR spectrum of polymer. In Figure 2 the FTIR spectrum of the optimized formulation revealed both peaks associated with the drug and the polymer, showing no interaction with the drug polymer

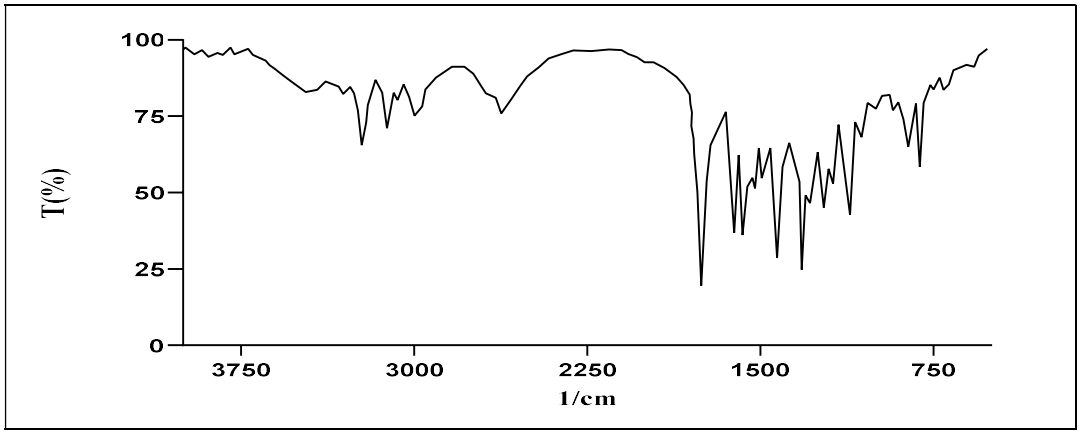
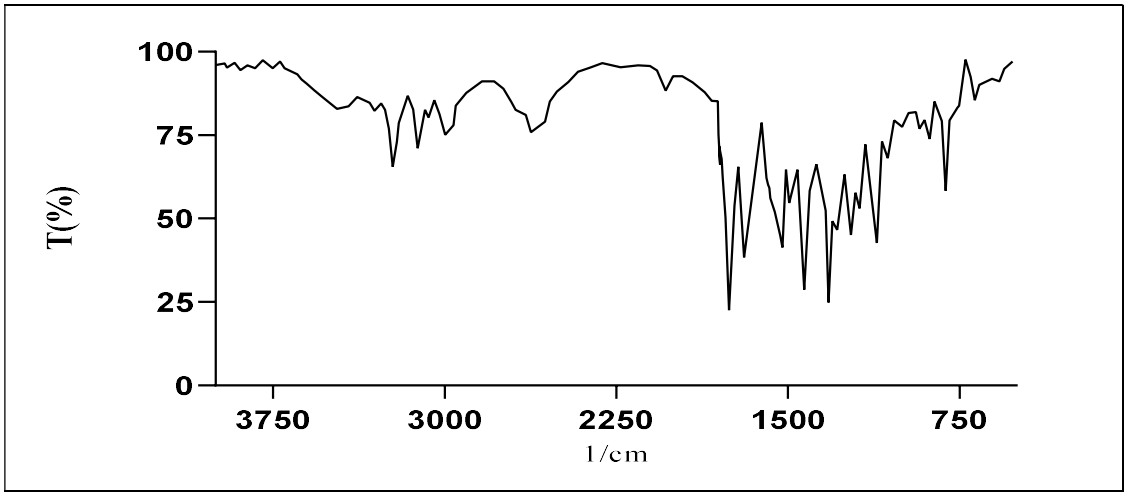


Figure 1: FTIR spectra of Lercanidipine hydrochloride pure drug.



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http://magellanes.com/

Figure 2: FTIR spectra of optimized formulation(F7).

Micromeritic Properties

The measured Hausner's ratio, Carr's index, and angle of repose were all within acceptable ranges, indicating adequate flow properties. All parameter values are provided Table 2. Microscopic image of optimized formulation(F7) shown in Figure 3.

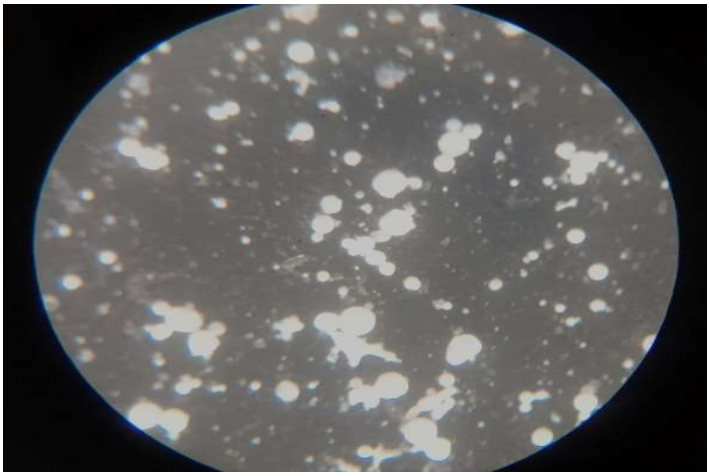

Figure 3: Microscopic image of optimized formulation(F7).

Table 2: Micromeritic Properties of all Formulations.

"Formulation Code"	Parameters				
	"Angle of Repose (θ)"	"Bulk Density (gm per cm3)"	"Tapped Density (gm per cm3)"	"Hausner's Ratio (HR)"	"Carr's Index (%)"
F1	22.36±1.11	0.142±0.52	0.162±0.88	1.14±0.84	12.34±0.56
F2	23.32±0.98	0.122±0.49	0.139±0.74	1.13±0.93	12.23±0.58
F3	25.97±0.94	0.133±0.58	0.152±0.83	1.14±0.85	12.51±0.42
F4	22.34±0.85	0.144±0.51	0.161±0.81	1.11±0.55	10.59±0.62
F5	26.13±0.76	0.132±0.48	0.149±0.79	1.12±0.87	11.40±0.59
F6	25.99±1.01	0.161±0.55	0.183±0.72	1.13±0.66	12.02±0.57
F7	25.03±0.99	0.177±0.61	0.199±0.91	1.12±0.42	11.05±0.63
F8	26.78±0.93	0.166±0.57	0.189±0.93	1.13±0.85	12.16±0.72
F9	27.14±1.15	0.173±0.45	0.195±0.88	1.12±0.71	11.28±0.58
F10	26.45±0.94	0.169±0.43	0.191±0.76	1.13±0.77	11.51±0.83
F11	24.52±0.88	0.158±0.47	0.178±0.82	1.12±0.65	11.23±0.55
F12	25.11±0.79	0.167±0.40	0.189±0.77	1.13±0.73	11.64±0.64
F13	26.25±0.81	0.156±0.62	0.181±0.73	1.16±0.64	13.81±0.54
F14	25.07±0.91	0.163±0.69	0.185±0.71	1.13±0.96	11.89±0.89
F15	27.48±0.84	0.176±0.54	0.204±0.75	1.15±0.90	13.72±0.90

All the values are represented as Mean ± SD (n=3)

Particle Size

The microsphere formulations (F1-F15) were observed to have a mean particle size that ranged from 72 to 133 µm

SEM

SEM analysis revealed that floating microspheres (F7) were found to be smooth, spherical, and slightly

CAHIERS MAGELLANES-NS
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porous. The surface of microsphere was formed smooth due the increase the concentration of Eudragit RS 100 seen in Figure 4

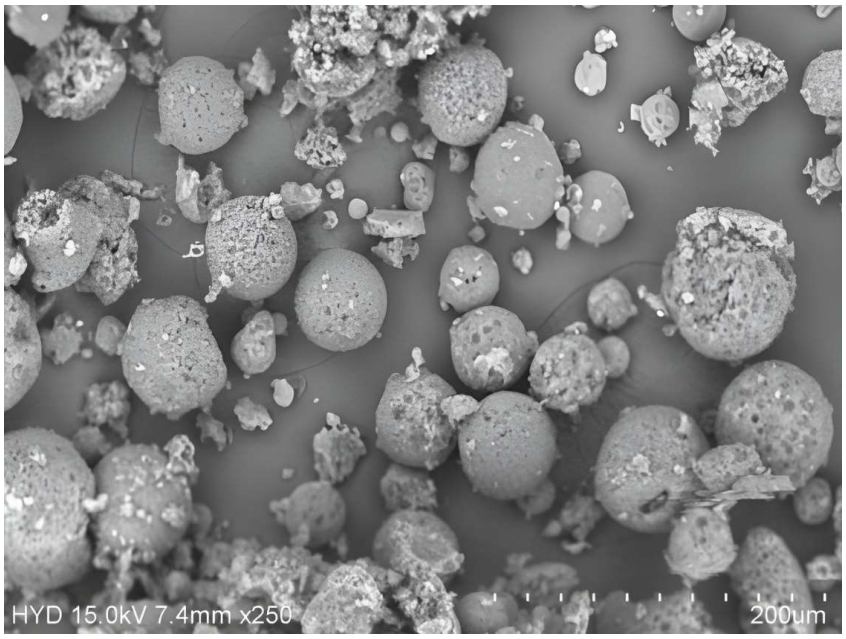

Figure 4: SEM image of optimized formulation F7.

Percentage yield

The % yield of the all formulated microballoons was calculated. Table.4 shows percentage yield outcomes. For all formulations, the percentage yield ranged from 50 to 85 %. With HPMCK15 and ethyl cellulose, the yield was less i.e 62%, and for the optimised formulation, the yield was 80.56%

Table 3: Various Evaluation Parameters of Formulations.

"Formulation Code"	"% Yield"	"Mean Particle Size (µm)"	"Drug Entrapment Efficiency" (%)	Buoyancy percentage (%)	Drug content
F1	50.64±1.99	125.36±0.64	78.41±2.01	67.52±0.87	91.11±1.01
F2	55.19±1.83	132.57±0.51	81.33±2.13	70.35±0.79	93.03±1.36
F3	59.47±1.91	129.44±0.55	83.65±1.95	73.96±0.81	94.24±1.29
F4	63.27±1.85	130.51±0.63	76.56±1.99	65.19±0.90	90.67±1.25
F5	65.42±1.88	128.68±0.59	73.53±2.04	63.66±0.85	87.96±1.14
F6	73.53±1.96	73.82±0.47	88.45±2.21	83.14±0.77	94.36±1.09
F7	80.56±1.87	74.31±0.71	93.09±2.19	88.52±0.73	97.88±1.18
F8	81.49±1.85	72.09±0.76	94.38±1.93	89.05±0.76	98.14±1.24
F9	83.61±1.90	67.45±0.73	84.62±2.08	79.46±0.91	92.25±1.30
F10	85.97±1.83	87.63±0.69	80.22±1.91	84.73±0.88	95.18±1.25
F11	62.13±1.81	112.42±0.65	76.34±2.21	64.85±0.85	88.56±1.20
F12	68.55±1.84	98.58±0.64	80.15±2.14	67.62±0.95	91.49±1.17
F13	72.43±1.80	100.04±0.59	83.66±1.96	71.05±0.77	93.64±1.26
F14	74.99±1.79	108.69±0.72	73.83±2.11	62.38±0.72	85.77±1.31
F15	75.93±2.01	103.44±0.78	76.19±2.15	65.74±0.83	89.63±1.29

All the values are represented as Mean ± SD (n=3)

CAHIERS MAGELLANES-NS
Volume 06 Issue 1
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Entrapment efficiency

The entrapment efficiency of floating microballoons was calculated, and the results are summarized in Table 3. The optimized formulation exhibited an entrapment efficiency of 93%, while the range varied from 73% to 94% for all formulations. Formulations containing HPMCK15 and ethylcellulose, polyethylene oxide and cellulose acetate showed minimal entrapment efficiency. A comparison of percentage yield, particle size, and entrapment efficiency is illustrated in Figure 5

Figure 5: Comparison of %Yield, Entrapment efficiency and Mean particle size for all formulations

In vitro Buoyancy

To examine the buoyancy of produced microspheres, an In vitro buoyancy test was conducted. The table below displays the floating ability for the formulations (F1 to F15). The results also indicated that a microsphere's ability to float increased with size. All these parameters are shown in Table 3. The Polyethylene oxide and cellulose acetate formulations had slightly less amount of buoyancy. All formulations obtained percentage buoyancy between 62 and 89%; the optimized formulation had a percentage buoyancy of 83 %.

Drug content

The drug content of all prepared formulations falls within the range of 85% to 98.0%. These values are within acceptable limits. The specific values obtained are represented in Table 3.

In vitro drug release studies

All formulations were dissolution tested using a USP paddle type dissolution apparatus. Different formulations dissolution profiles were compared. Tables 4, 5, 6 show the cumulative % drug releases of F1-F15 at the end of 12 hours, while Figures 6 to 8 depict the dissolution profile.

Table 4: Percentage drug release data of Lercanidipine hydrochloride loaded hollow microspheres F1-F5.

Time (hr)	F1	F2	F3	F4	F5
0	0	0.00	0	0	0
1	13.00±2.11	12.60±2.77	11.3±2.36	14.7±2.94	16.3±2.16

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2	24.60±2.14	19.00±2.68	17.7±2.84	28.1±2.86	31.4±2.57
4	36.60±2.37	33.20±2.79	28.3±2.63	38.4±2.75	42.6±2.81
6	48.00±2.64	43.60±2.57	40.8±2.15	51.2±2.66	56.24±2.93
8	61.70±2.77	58.90±2.34	52.3±2.44	63.6±2.41	65.23±2.82
10	72.60±2.33	65.40±2.76	60.5±2.37	74.87±2.63	76.47±2.47
12	80.50±2.42	73.26±2.55	71.3±2.39	83.04±2.58	85.2±2.23

Table 5: Percentage drug release data of Lercanidipine hydrochloride loaded hollow microspheres F6-F10.

Time (hr)	F6	F7	F8	F9	F10
0	0±0	0±0	0±0	0±0	0±0
1	18.2±3.03	10.7±2.48	7.3±2.22	22.6±3.17	25.4±2.43
2	36.7±2.98	21.1±2.21	17.6±3.06	44.5±2.97	53.2±2.64
4	64.9±2.77	37.8±2.51	33.2±3.64	70.9±3.08	76.4±2.57
6	81.8±2.89	58.1±2.73	49.1±2.94	83.2±3.22	94.6±2.49
8	90.4±2.54	77.5±2.24	72.2±2.67	93.7±3.11	99.4.0±3.17
10	99.9±3.21	94.9±2.84	84.1±2.96	99.7±3.55	
12		99.8±2.21	93.7±3.12		

Table 6: Percentage drug release data of Lercanidipine hydrochloride loaded hollow microspheres F11-F15.

Time (hr)	F11	F12	F13	F14	F15
0	0	0	0	0	0
1	10.98±2.66	8.47±2.16	6.1±2.25	12.42±2.75	14.55±3.18
2	21.72±3.98	18.63±2.44	15.07±2.38	24.11±2.9	32.59±3
4	34.27±2.87	31.75±2.31	29.45±2.44	43.18±2.21	65.23±3.08
6	40.23±2.66	38.64±2.69	36.19±2.09	58.69±2.42	86.24±2.97
8	53.67±2.71	49.71±2.83	46.28±2.47	80.66±2.68	99.86±2.86
10	78.12±2.59	76.35±2.94	70.67±2.63	99.77±2.57	
12	95.21±3.01	92.16±2.16	88.93±2.71		

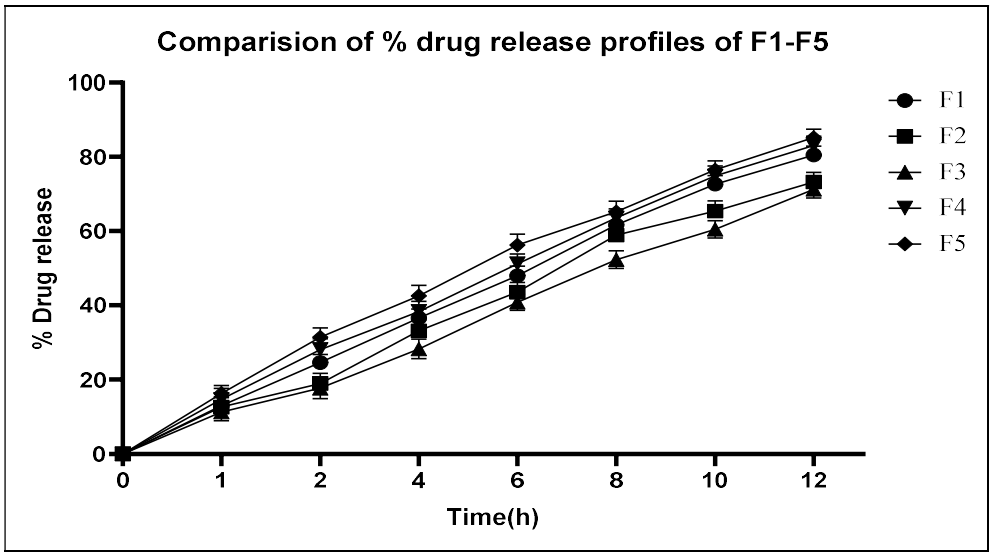

Figure 6: In-vitro drug release of Lercanidipine hydrochloride loaded hollow microspheresF1-

ISSN:1624-1940
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F5.

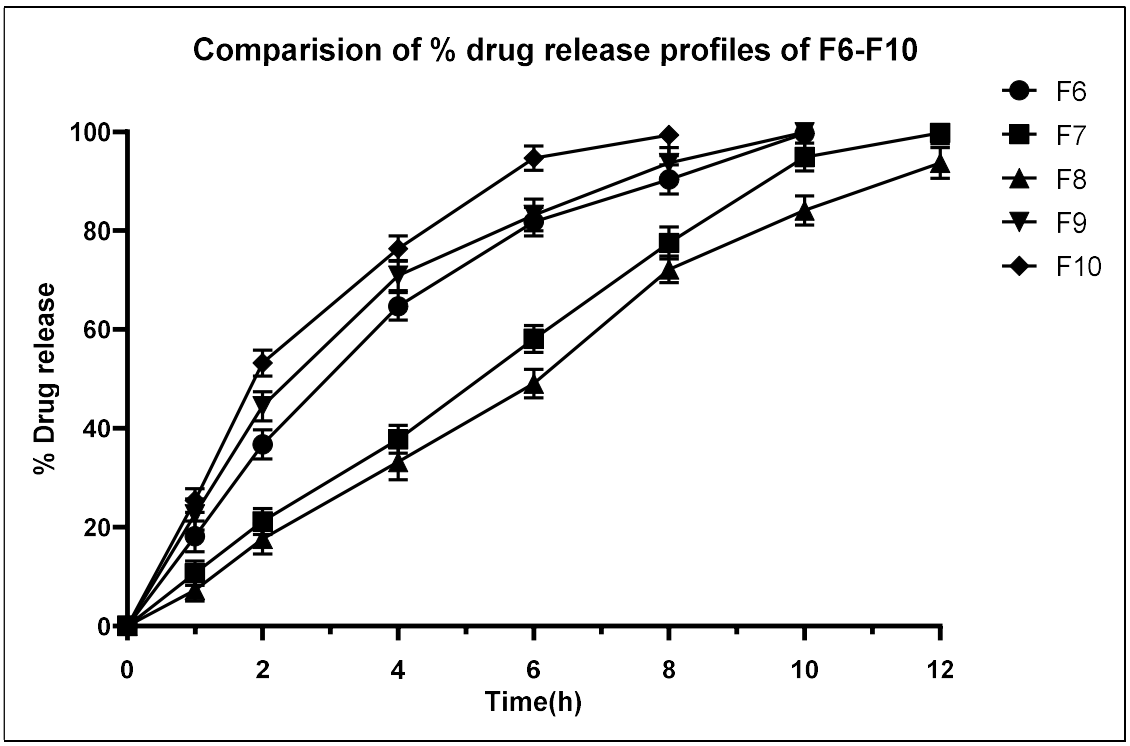

Figure 7: In-vitro drug release of Lercanidipine hydrochloride loaded hollow microspheres F6-F10.

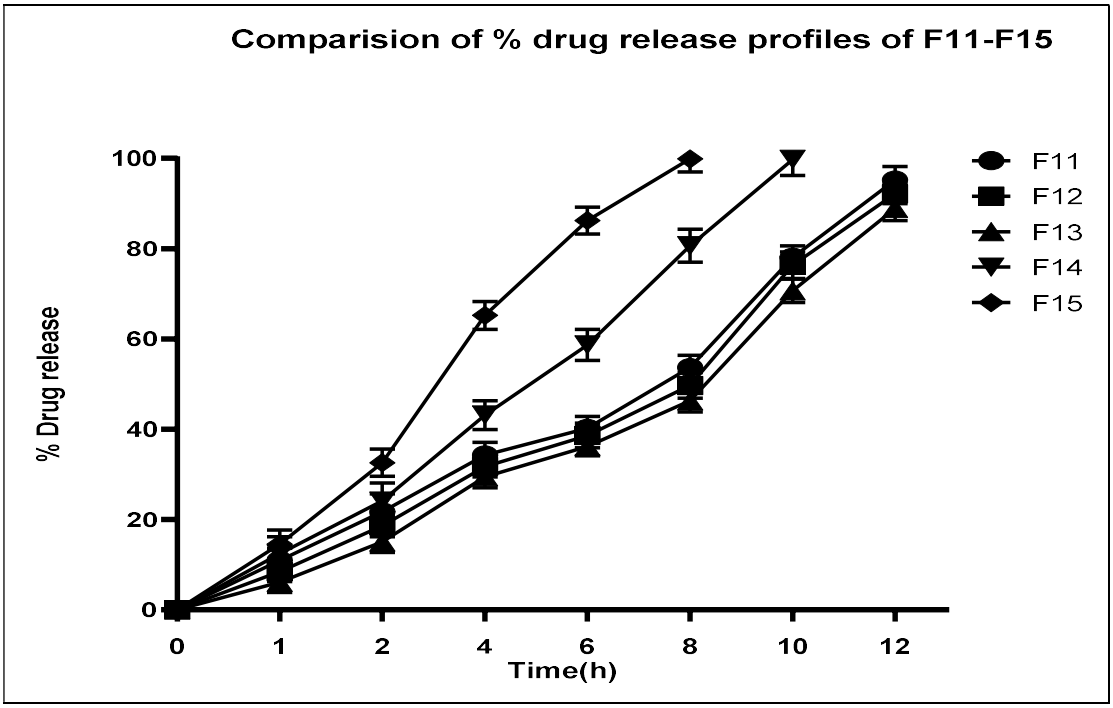

Figure 8: In-vitro drug release of Lercanidipine hydrochloride loaded hollow microspheres F11- F15.

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Stability analysis

In vitro drug release and drug content (%) studies observed no variation throughout the optimal formulation storage, as shown in Table 7. The optimized formulation was shown to be stable based on the results.

Table 7: Parameters after Accelerated Stability analysis of optimized Formulation F7.

Parameters	Temperature kept at 40±2^{0}C; RH kept at 75%±5%RH			
	Initial	After one month	After three months	After six months
In vitro Drug Release (%)	99.76±1.34	99.71±1.52	99.69±1.33	99.60±1.25
Drug Content (%)	97.10±0.64	97.01±0.53	96.98±0.66	96.93±0.62

Statistical analysis

ANOVA was performed using Minitab version 21.4.2 software trial version (Minitab Inc., State College, PA, USA) for Drug release of all formulations and the values are shown in Table 8. Based on ANOVA there is no significant differences between all formulations.

Table 8: ANOVA of %Drug release values for the fifteen formulations.

Source	Degree of freedom	Sum square	Mean square	F value
Factor	14	5751.68	410.83	0.37
Error	98	109489.63	1117.24	
Total	112	115241.3		

CONCLUSION

In the current work, hollow microspheres loaded with lercanidipine hydrochloride have been manufactured using polymers such as Eudragit RS 100, HPMC K15M, Ethyl cellulose, Polyethylene oxide, celluolose acetate and Eudragit RL 100. The quasi-emulsion diffusion technique can effectively produce hollow microspheres, as per the study's findings. Upon an FTIR drug-excipient compatibility investigation, it was concluded that the drug was compatible with all excipients used in the study. The following tests were performed on all manufactured hollow microspheres: drug content, entrapment efficiency, percentage yield, tapped density, particle size measurement, micromeritic properties, and in vitro buoyancy, drug content, all test results fit within the Pharmacopoeia parameters, and the microballoons in 0.1NHCl remained buoyant for almost 12 hours. According to the in vitro tests, hollow microspheres developed with a 1:2 ratio of Eudragit RL 100 to Eudragit RS 100 released the highest amount of drug release within 12h (F7). It therefore appears to be the best formulation. Therefore, compared to the conventional dosage form, the optimised formulation (F7) of lercanidipine hydrochloride hollow microspheres shows good potential for innovative treatment of hypertension.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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