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FORMULATION AND EVALUATION OF FLOATING MICROSPHERES OF LERCANIDIPINE HYDROCHLORIDE

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ABSTRACT

Floating Lercanidipine Hydrochloride microparticles using polymer ethyl cellulose, HPMC, Poly vinyl pyrrolidine and Eudragit RS 100 was developed by solvent evaporation method and it was found to be a suitable floating oral drug delivery system in terms of particle size distribution, drug loading capacity and Sustained release Lercanidipine Hydrochloride microparticles obtained was spherical in shape, discrete and free flow in nature. Polymer-drug ratio influence the particle size as well as drug release pattern of microsphere. Entrapment efficiency of drug loaded batches F1 to F9 were determined and it was found that F2 and F9 had a better drug entrapment efficiency of 95% and 96% Drug loading efficiency was better with F9 showed 96%. *In-vitro* drug release from all the formulations was found to be slow and sustained over the period of 8 hours was found to be 96.89%.

KEYWORDS: Lercanidipine hydrochloride, HPMC, microsphere, In-vitro.

Floating drug Delivery System

Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased Gastric retention time and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.

Matrix type system

Release profile of the drug from the matrix type of the device critically depends on the state of the dug whether it is dissolved or dispersed in the polymer matrix. In case of the drug dissolved in the polymeric matrix, the amount of drug and the nature of the polymer affect the release profile.

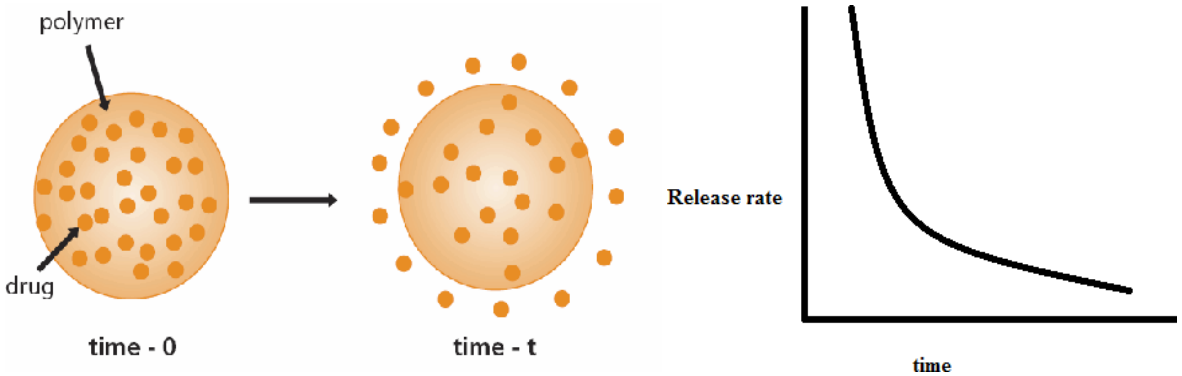


Figure 1: monolithic device and typical plot of drug release rate vs. time.

Reservoir type system

Drug release from the reservoir type system with rate controlling membrane proceeds by first penetration of water through the membrane followed by dissolution of the drug in the penetrating dissolution fluid. The dissolved drug after partitioning through the membrane diffuses across the stagnant diffusion layer.

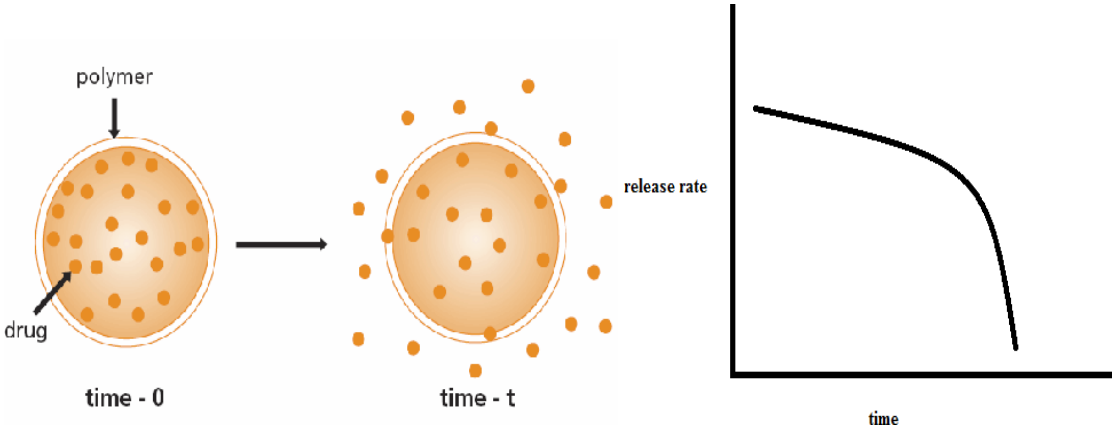


Figure 2: Reservoir device and typical plot of drug release rate Vs time.

HYPERTENSION

Hypertension is a chronic medical condition in which the blood pressure is elevated. It is also referred to as high blood pressure or shortened to HT, HTN or HPN. The word "hypertension", by itself, normally refers to systemic, arterial hypertension.

Hypertension can be classified as either essential (primary) or secondary, Essential or primary hypertension means that no medical cause can be found to explain the raised blood pressure. It is common. About 90-95% of hypertension is essential hypertension. Secondary hypertension indicates that the high blood pressure is a result of (i.e., secondary to) another condition, such as kidney disease or tumours (adrenal adenoma or pheochromocytoma).

Angina pectoris

Angina pectoris, or just angina, is temporary chest pain or discomfort caused by decreased blood flow to the heart muscle. Because of the decreased flow of blood, there is not enough oxygen to the heart muscle resulting in chest pain. Coronary artery disease, which can result in narrowing of the coronary arteries that carry blood and oxygen to the heart muscle, is one of the most common causes of angina. While angina is not a heart attack, it does signal an increased risk for a heart attack. Seek immediate medical attention if you experience any chest pain or discomfort.

DRUG PROFILE

LERCANIDIPINE HYDROCHLORIDE

Chemical formula

3-Ethyl 5-methyl ?(4RS-2-[(2-aminoethoxy)]-4-(2-chlorophenyl-6-methyl-1,4- dihydropyridien-3,5-dicariboxtlate benzensulphate.

Chemical structure

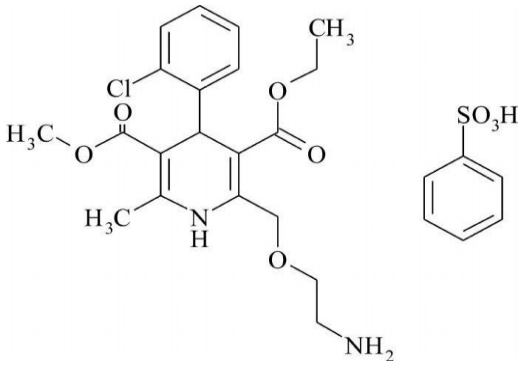


Figure 3: Structure of Lercanidipine Hydrochloride.

LITERATURE REVIEW

Swethakallepu, et al., have been reported a work on the Formulation and evaluation of Gastro Retentive Floating Microsphere of Nimodipine, The microsphere was prepared by solvent evaporation method. The result of *in-vitro* dissolution study. Microsphere was characterized for their micromeritic properties, floating behavior, entrapment efficiency, scanning electron microscopy (SEM), X-ray diffraction, differential scanning colorimetry, and *in-vitro* drug release it showed good flow properties. Size ranges of (90±1.02)-(145±1.34)µm. Microsphere were capable to float for 12 h. It can be concluded that the developed formulation is potential dosage form for nimodipine.

Joselinjoseph, et al, have been studied the formulation and evaluation of floating microsphere of pantoprazole sodium. The floating microsphere of pantoprazole sodium werepreprared by solvent evaporation method using HPMC K 15 and ethyl cellulose as polymer. Seven different formulations were developed. The developed floating microspheres were evaluated for, percentage yield, particle size, entrapment efficiency, *in-vitro* buoyancy, scanning electron microscopy and drug release. Results show that as the concentration of

polymer ethyl cellulose increase it affects the particle size, percentage yield, in vitro buoyancy and drug release of microsphere. The floating microsphere of pantoprazole sodium cane successfully designed for controlled drug delivery dosage forms.

AIM AND SCOPE OF STUDY

- The purpose of this research work was to develop a novel retentive floating microsphere of Lercanidipine Hydrochloride.
- The main aim of the present study is to develop sustained release Lercanidipine Hydrochloride Microsphere using Ethylcellulose, HPMC, PVP, Eudragit RS100 polymers by solvent evaporation method and to evaluate the suitability and potentiality of this sustained release drug delivery system through the determination of drug loading capacity, entrapment efficiency, flow properties and *in-vitro* release characteristic studies.

PLAN OF WORK

I. PREFORMULATION STUDIES

(i) Determination of solubility profile of Lercanidipine Hydrochloride.

(ii) Compatibility studies (FT-IR)

II. FORMULATION OF LERCANIDIPINE HCL FLOATNG MICROPARTICLE

III. EVALUATION OF LERCANIDIPINE HCL FLOATING MICROPARTICLE

1. Determination of Percentage yield
2. Micromertic Properties

(i) Angle of Repose

(ii) Bulk Density and Tapped Density

(iii) Compressibility Index

(iv) Hausner's Ratio

3. Particle Size and Morphology Analysis (SEM)
4. Swelling Index (%)
5. Percentage of Drug content/ Drug loading amount (%)
6. Percentage of Drug entrapment (%)
7. *In-vitro* Buoyancy studies
8. *In-vitro* Drug Release

IV. STABILITY STUDIES

Stability studies for initial and after one month at 40^{o} C$\pm$ 2 and 75 % $\pm$ 5 % RH.

MATERIALS AND EQUIPMENTS

Table 1: Materials.

S.NO	CHEMICAL/MATERIAL	SOURCE
1	Lercanidipine Hydrochloride	GIFT SAMPLE, Sai Meera Pharma, Chennai.
2	Ethylcellulose	S.D fine chemicals Ltd.
3	HPMC	S.D fine chemicals Ltd.
4	PVP	S.D fine chemicals Ltd.
5	Eudragit RS 100	S.D fine chemicals Ltd.
6	Ethanol	S.D fine chemicals Ltd.
7	Sodium lauryl sulphate (0.1%)	S.D fine chemicals Ltd.
8	Dichloromethane	S.D fine chemicals Ltd.

Table 2: Equipments.

S.NO	NAME OF THE INSTRUMENT	COMPANY
1	Mechanical stirrer	Remi equipment
2	UV spectrophotometer	Jasco V530
3	Optical microscope	Olympus
4	FT-IR Spectrophotometer	Karunya university, coimbatore
5	Scanning electron microscopy	Karunya university, coimbatore
6	Magnetic stirrer	Remi equpiments, Mumbai
7	Dissolution apparatus	Veego, VDA 6DR USP apparatus

METHODOLOGY

I. PREFORMULATION STUDIES

a. Solubility Profile

Determination of solubility profile of Lercanidipine Hydrochloride. The solubility profile of the selected drug (Lercanidipine Hydrochloride) was determined. Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.

b. Fourier transform Infra-red spectroscopy

I.R. spectroscopy can be used to investigate and predict any physiochemical interactions between difference components in a formulation and therefore it can be applied to the selection of suitable chemically compatible excipients.

The aim of the present study was to find out the possible interaction between selected polymer, ethylcellulose, HPMC, PVP, Eudragit RS 100 and the drug Lercanidipine Hydrochloride and also identify the compatibility between the drug and polymer.

10 mg of sample and 40 mg of KBr was taken in a mortar and triturated. A small amount of triturated sample was taken into a pellet marker and was compressed at 10 kg/cm^2 using hydraulic press. The

pellet was kept in a sample holder and scanned from 4000 cm-1 in Perkin Elmer FT-IR spectrophotometer.

Samples were prepared for pure polymer, pure drug, physical mixture of drug and polymer and drug loaded microparticles. The spectra obtained for these samples were compared and interpreted for the shifting of major functional peaks and disappearance of functional peaks if any.

II. FORMULATION OF AMLODOIPINE HCL FLOATING MICROPARTICLES

In this present study, solvent evaporation technique was employed for preparation microsphere formulation. Lercanidipine Hydrochloride microparticles were prepared by dissolving polymer ethylcellulose and HPMC in ethanol and dichloromethane. Then the drug Lercanidipine Hydrochloride was added to the polymer solution. The resulting mixture was then added drop by drop into 0.1% sodium lauryl sulphate while stirring continuously. Stirring rate was constant at 900 rpm and continued for 30 minutes until organic solvent evaporated completely.

The dispersed drug and polymer were transferred into fine droplets, which subsequently solidified into rigid microparticles due to solvent evaporation. The microparticles formed were collected by filtration, and washed 4 to 5 times with distilled water and dried at room temperature for 24 hours.

Nine batches of drug loaded microparticles were prepared by keeping drug ratio constant altering the different polymer with different ratio and formulations code as F1,F2,F3,F4,F5,F6,F7,F8,F9.

Table 3: Formulation of Lercanidipine Hydrochloride Microparticles.

S. No	Incredients	Formulation code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	**Drug**	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g	0.5 g
2	**Ethylcellulose**	0.5 g	4 g	0.3g	0.3	0.3 g	-	2 g	-	1 g
3	**HPMC E 50**	0.3g	0.3g	4 g	-	-	4 g	-	1 g	-
4	**Chitosan**	-	-	-	-	2 g	2 g	-	-	-
5	**PVP**	-	-	-	-	-	-	-	2 g	2 g
6	**Eudragit RS 100**	-	-	-	-	-	-	0.5 g	-	-
7	**Ethanol**	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml
8	**Dichloromethane**	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml	15 ml
9	**Sodium lauryl sulphate (0.1%)**	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml

III. PREPARATION OF STANDARD GRAPH OF LERCANIDIPINE HYDROCHLORIDE USING PHOSPHATE BUFFER pH 7.4

Preparation of stock solution

10 mg of accurately weighed drug was dissolved and diluted to 100 mil with phosphate buffer pH 7.4 to produce 100 µg/ml.

Preparation of sample solution

Different dilutions of stock solution with phosphate buffer were made to obtain solution having concentration 5,10,15,20,25,30 µg/ml. absorbance was measured at 360 nm against phosphate buffer pH 7.4 as blank, using UV systronics-2202 spectrophotometer.

IV. EVALUATION OF LERCANIDIPINE HYDROCHLORIDE MICROPARTICLES

Actual drug content of microparticles was determined by UV-spectrophotometer (systronics-2202) 50 mg equivalent of drug loaded microsphere were dissolved in chloroform and extracted with 50 ml of phosphate buffer 7.4 and then analyzed at 360nm

a. Entrapment efficiency (%) = $\frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$

Buoyancy test

Microparticles (0.3g) were spread over the surface of a USP dissolution apparatus (type II) filled with 900 ml 0.1 mol. Hcl containing 0.01 % Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 8 hrs. The floating and the settled portion of floating microparticles were recoverd separately. The floating microparticles were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the floating microparticles that remained flaoting and the total mass of the floating microparticles.

$$\text{Percentage buoyancy} = \frac{\text{Microparticles remained floating}}{\text{Total mass of floating microparticles}} \times 100$$

$$\text{Drug loading (\%)} = \frac{\text{Actual drug content}}{\text{Weight of Microsparticles}} \times 100$$

$$\text{Percentage yield (\%)} = \frac{\text{Weight of Microsphere}}{\text{Total expected weight of Drug and polymer}} \times 100$$

Particle size and Morphology analysis

The particle size of microparticles was determined using optical microscopy method. Approximately 100 microparticles were counted for particle size using a calibrated optical microscope Surface morphology of microsphere was determined by Scanning Electron Microscope (SEM). The microparticles were coated uniformly with gold-palladium by using Sputter Coater, after fixing the sample in individual stabs.

Swelling Index

The swelling indexes of the formulated microparticles were performed pH 1.2 and phosphate buffer pH 7.4 at 37.5 ± 0.5°C for 8 hours. Drug loaded microparticles were equilibrated in different test tubes and at every one hour interval; microparticles were withdrawn filterd transferred into a small beaker and the weighed.

The swelling ratio was calculated from the followed expression,

$$\text{Swelling index} = \frac{Wf - W0}{W0} \times 100$$

Where, W1 = weight of micro particle observed at every time interval W0 = initial weight of micro particles.

Micromeritic properties

i. Angle of repose

Flow properties of microsphere were determined by this method. Angle of repose of different formulation was measured according to a fixed funnel standing method.

$\Theta = \tan^{-1} h/r$

Where Θ is angle of repose, r is radius and h is the height

Table 4: Relationship between Flow properties and Angle of Repose.

Angle of repose	Flow Property
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

ii. Bulk density and Tapped density

Bulk and tapped densities were measured by using 10 ml of graduated cylinder. The sample was poured in graduated cylinder and tapped mechanically for 100 times, then tapped volume was noted down and bulk density and tapped density were calculated.

iii. Carr's index

Compressibility Index (CI) or Carr's index value of microparticles was computed according to the following equation:

$$\text{Carr's index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

iv. Hausner's ratio

Hausner'ratio of microsphere was determined by comparing the tapped density to the bulk density using the equation

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

Table 5: Relationship between Hausner's ratio and Flowability.

Hausner's ratio	Flowability
<1.25	Good
>1.25	Poor
1.25-1.5	Very

v. *In-vitro* dissolution study of Lercanidipine Hydrochloride microsphere

Drug release from the microsphere was performed using the rotating basket method as specified in USPXXIV. *In-vitro* release profile was examined in Phosphate buffer pH 7.4 from 1- 8 hours.

Microparticles equivalent to 100 mg of drug were placed in the basket and the medium was maintained at 37°C and was kept at a rotation of 750 rpm. An aliquot of 10 ml were withdrawn periodically at intervals of one hour and same volume of fresh medium was replaced.

The concentration of drug released at time intervals was determined by measuring the absorbance at 360nm using UV spectrophotometer.

vi. Stability studies

The stability studies indicates the significant difference between the release patterns of microsphere at 40°C and RH for one month.

The stability studies were carried out at and optimized formulation, i.e, from F9 forumulation. The formulation was store at (40°C±2°C at 75% RH ± 5 %) for 1 months. Sample were withdrawn and retested for drug release and was compare with the formulation diffusion profile.

OBSERVATION DATA

Table 6: Solubility Profile of Lercanidipine Hydrochloride.

S.NO	SOLVENT	SOLUBILITY
1	WATER	Slightly soluble
2	2,PROPANOL	Slightly soluble
3	METHANOL	Freely soluble
4	ALCOHOL	Sparingly soluble

Table 7: Physical observation test for drug polymer compatibility studies.

S. No	polymer	Drug: polymer ratio	First day		After one week		After three week	
			25°C	40°C	25°C	40°C	25°C	40°C
1	Ethylcellulose	1:1	NC	NC	NC	NC	NC	NC
2	HPMC	1:1	NC	NC	NC	NC	NC	NC
3	PVP	1:1	NC	NC	NC	NC	NC	NC
4	Ethylcellulose HPMC	1:1:1	NC	NC	NC	NC	NC	NC

FOURIER TRANSFORM INFRARED SPECTROSCOPY

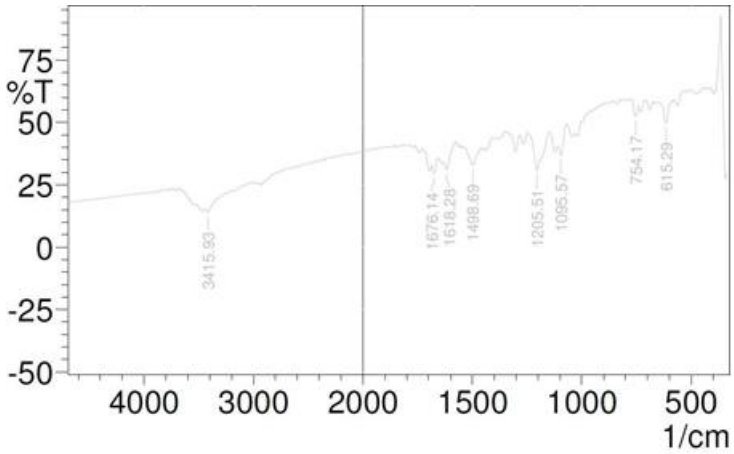


Figure 4: FT-IR Spectra of Lercanidipine Hydrochloride.

Table 6: Solubility Profile of Lercanidipine Hydrochloride.

S. No	Polymer	Drug: polymer ratio	First day		After one week		After three week	
			25°C	40°C	25°C	40°C	25°C	40°C
1	Ethylcellulose	1:1	NC	NC	NC	NC	NC	NC
2	HPMC	1:1	NC	NC	NC	NC	NC	NC
3	PVP	1:1	NC	NC	NC	NC	NC	NC
4	Ethylcellulose HPMC	1:1:1	NC	NC	NC	NC	NC	NC

Table 8: FT-IR Spectra of Lercanidipine Hydrochloride.

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	615.29	49.807	8.675	650.01	578.64	18.18	1.56
2	754.17	52.441	5.04	777.31	740.67	9.306	0.594
3	1095.57	36.867	6.635	1111	1066.64	16.678	1.139
4	1205.51	30.914	15.075	1247.94	1147.65	41.19	7.372
5	1498.69	32.808	6.312	1535.34	1469.76	29.02	2.341
6	1618.28	31.129	5.02	1635.64	1571.99	28.06	1.17
7	1676.14	29.653	4.095	1685.79	1658.78	13.429	0.822
8	3415.93	13.913	1.841	3437.15	3188.33	179.432	-2.763

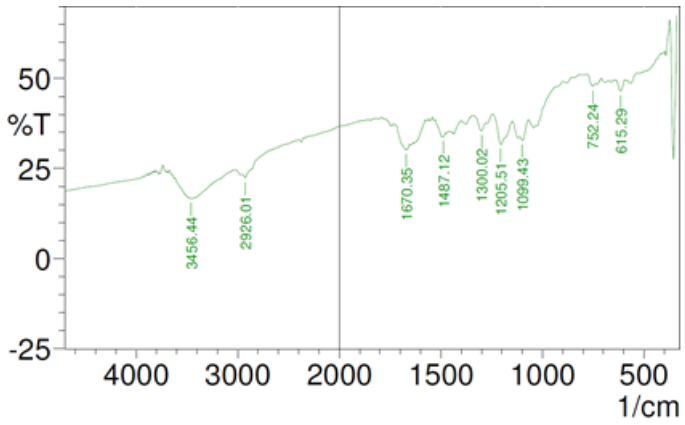


Figure 5: FTIR spectra of Lercanidipine Hydrochloride + Ethyl cellulose + Poly Vinyl Pyrolidone.

Table 9: FTIR spectra of Lercanidipine Hydrochloride + Ethyl cellulose + Poly Vinyl Pyrolidone.

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	615.29	46.512	3.043	636.51	596	12.967	0.616
2	752.24	47.88	1.616	779.24	736.81	13.146	0.311
3	1099.43	32.778	2.289	1111	1068.56	19.389	0.602
4	1205.51	31.664	7.657	1246.02	1147.65	44.445	4.361
5	1300.02	35.456	2.875	1338.6	1280.73	24.723	0.844
6	1487.12	33.802	0.362	1490.97	1475.54	7.182	0.033
7	1670.35	30.177	0.191	1672.28	1666.5	3.004	0.01
8	2926.01	22.425	1.583	2958.8	2517.1	243.977	-5.386
9	3456.44	16.647	1.005	3618.46	3427.51	140.243	4.197

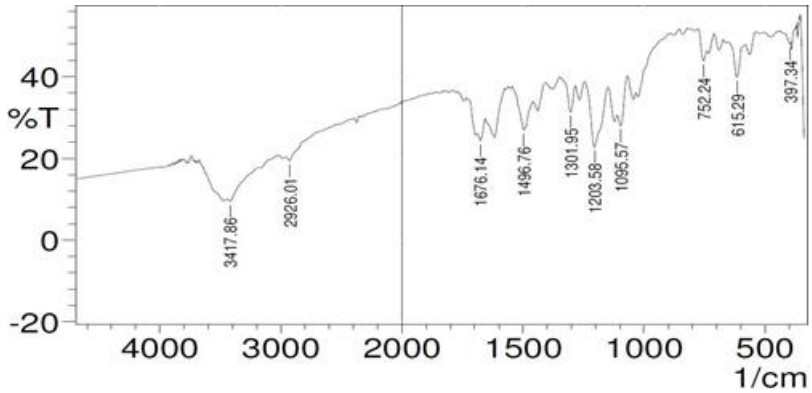


Figure 6: FTIR spectra of Lercanidipine Hydrochloride + Ethyl Cellulose.

Table 10: FTIR spectra of Lercanidipine Hydrochloride + Ethyl Cellulose.

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	397.34	48.057	0.744	416.62	393.48	7.145	0.081
2	615.29	39.898	8.315	651.94	580.57	24.645	2.039
3	752.24	43.86	4.45	775.38	738.74	12.174	0.803
4	1095.57	27.968	6.113	1111	1068.56	20.875	1.562
5	1203.58	22.785	15.46	1246.02	1147.65	51.235	10.055
6	1301.95	31.41	6.961	1348.24	1284.59	28.073	1.934
7	1496.76	26.873	7.014	1543.05	1473.62	34.985	3.081
8	1676.14	24.329	3.182	1689.64	1654.92	20.171	0.897
9	2926.01	19.428	1.579	2964.59	2519.03	270.63	-5.352
10	3417.86	9.512	1.118	3439.08	3182.55	220.227	-4.597

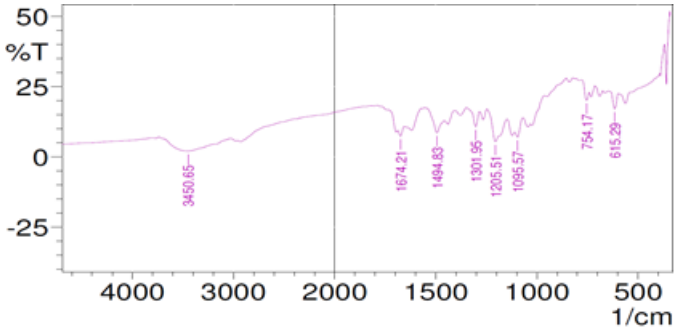


Figure 7: FTIR spectra of Lercanidipine Hydrochloride + Ethyl Cellulose + Hydroxy Propyl Methyl Cellulose.

Table 11: FTIR spectra of Lercanidipine Hcl + Ethyl Cellulose + Hydroxy Propyl Methyl Cellulose.

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	615.29	17.06	5.855	644.22	597.93	31.877	2.348
2	754.17	20.158	4.243	779.24	742.59	23.247	1.259
3	1095.57	7.015	3.623	1111	1068.56	43.41	2.807
4	1205.51	5.409	10.048	1247.94	1147.65	101.441	19.019
5	1301.95	10.771	5.701	1350.17	1284.59	54.706	3.87
6	1494.83	8.556	6.234	1544.98	1458.18	79.125	7.542
7	1674.21	7.374	2.626	1687.71	1656.85	32.706	1.93
8	3450.65	1.992	3.491	3678.25	3184.48	741.806	113.644

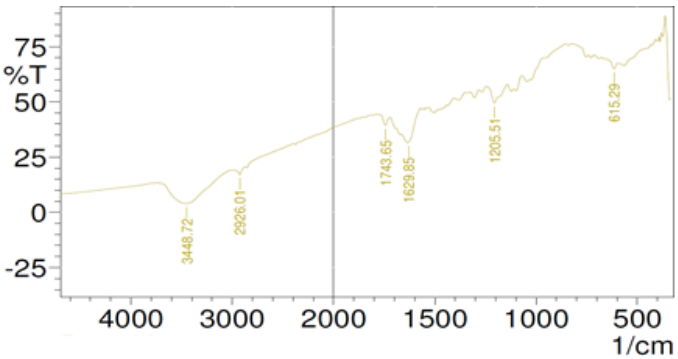


Figure 8: FTIR spectra of Lercanidipine Hydrochloride + Hydroxy Propyl Methyl Cellulose.

Table 12: FTIR spectra of Lercanidipine Hydrochloride + Hydroxy Propyl Methyl Cellulose.

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	615.29	65.013	3.109	655.8	597.93	9.904	0.406
2	1205.51	49.579	7.788	1246.02	1141.86	28.032	2.979
3	1629.85	31.602	1.061	1633.71	1573.91	24.882	0.198
4	1743.65	39.413	4.064	1770.65	1720.5	18.99	0.871
5	2926.01	17.12	2.79	2980.02	2870.08	79.614	2.552
6	3448.72	3.934	11.371	3695.61	3008.95	717.478	168.541

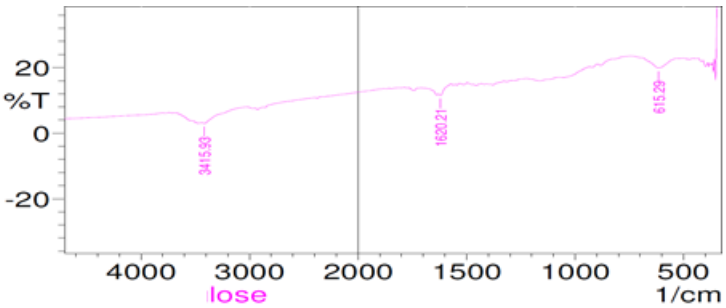


Figure 9: FTIR spectra of Ethyl Cellulose.

Table 13: FTIR spectra of Ethyl Cellulose.

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	615.29	19.88	3.06	690.52	536.21	103.3	4.62
2	1620.21	11.49	0.92	1627.92	1570.06	50.54	0.18
3	3415.93	2.88	0.54	3435.22	3016.67	517.08	-25.39

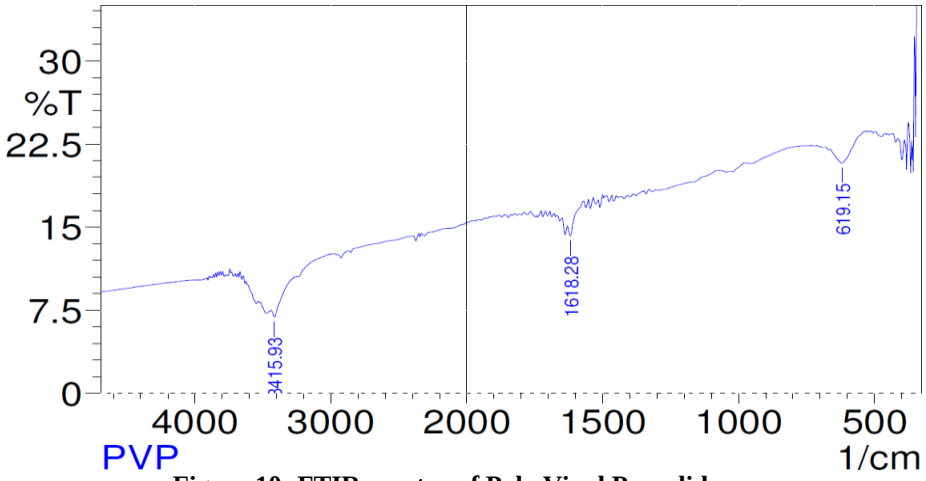


Figure 10: FTIR spectra of Poly Vinyl Pyrrolidone.

Table 14: FTIR spectra of Poly Vinyl Pyrrolidone.

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	619.15	20.77	1.81	661.58	534.28	83.81	2.16
2	1618.28	14.21	1.35	1629.85	1571.99	46.35	0.59
3	3415.93	6.89	1.01	3439.08	3265.49	183.58	1.01

STANDARD CALIBRATION CURVE OF LERCANIDIPINE BESILATE IN PHOSPHATE BUFFER pH 7.4

Table 15: Standard graph of Lercanidipine Hydrochloride.

S.No	Concentration µg/ml	Absorbance
1	0	0
2	5	0.071
3	10	0.143
4	15	0.221
5	20	0.274
6	25	0.351
7	30	0.423

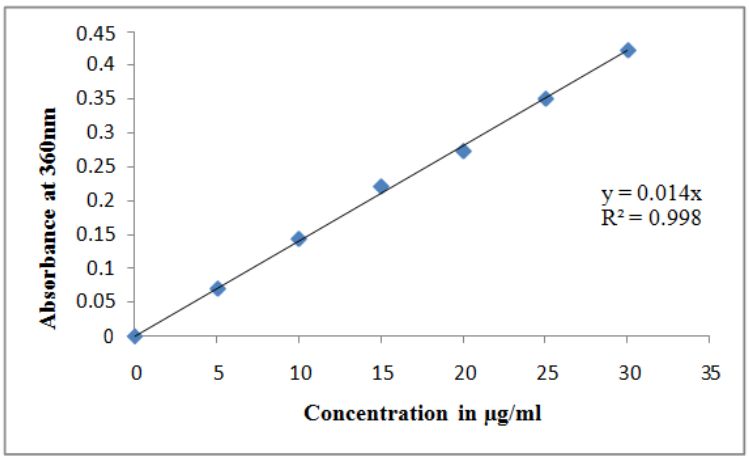


Figure 11: Standard graph of Lercanidipine Hydrochloride.

Table 16: Percentage Yield of Lercanidipine Hydrochloride Microparticles.

S.NO	FORMULATION CODE	PERCENTAGE YIELD (%)
1	F1	45
2	F2	95
3	F3	53
4	F4	65
5	F5	70
6	F6	75
7	F7	78
8	F8	82
9	F9	96

(±S.D.and no. of determinations = 3)

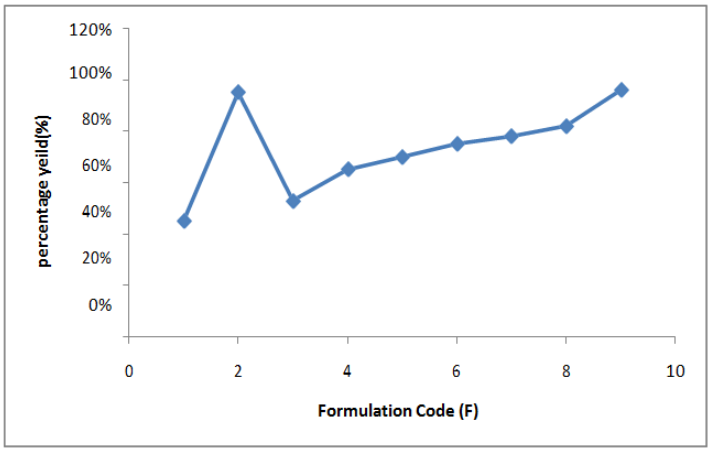


Figure 12: Percentage yield of Lercanidipine Hydrochloride Microparticles.

Table 17: Micromeritic Properties of Lercanidipine Hydrochloride Microparticles.

S.NO	Form. code	Angle Of Repose	Bulk Density	Tapped Density	Carr'S Index	Hausner'S Ratio
1	F1	20.42±0.20	0.78±0.64	0.84±0.73	10.1±0.84	1.05±0.54
2	F2	26.82±0.80	0.51±0.042	0.49±0.012	9.52±0.026	1.078±0.32
3	F3	20.66±0.36	0.79±0.62	0.83±0.72	7.73±0.29	1.14±0.011
4	F4	19.66±0.20	0.62±0.30	0.68±0.36	10.1±0.84	1.17±0.046
5	F5	19.11±0.20	0.73±0.46	0.67±0.32	10.05±0.54	1.16±0.032
6	F6	28.40±0.21	0.625±0.068	0.724±0.058	12.67±0.049	1.10±0.013
7	F7	32.00±0.63	0.641±0.52	0.769±0.074	16.65±0.064	1.15±0.018
8	F8	25.60±0.05	0.54±0.32	0.56±0.012	10.13±0.41	1.12±0.015
9	F9	24.92±0.32	0.49±0.013	0.55±0.014	9.12±0.012	1.122±0.032

(±S.D.and no. of determinations = 3)

Table 18: Particle Size of Lercanidipine Hydrochloride Microparticles.

S.NO	Formulation Code	PARTICLE SIZE µM
1	F1	185
2	F2	195
3	F3	253
4	F4	281
5	F5	321
6	F6	354
7	F7	343
8	F8	389
9	F9	482

(±S.D.and no. of determinations = 3)

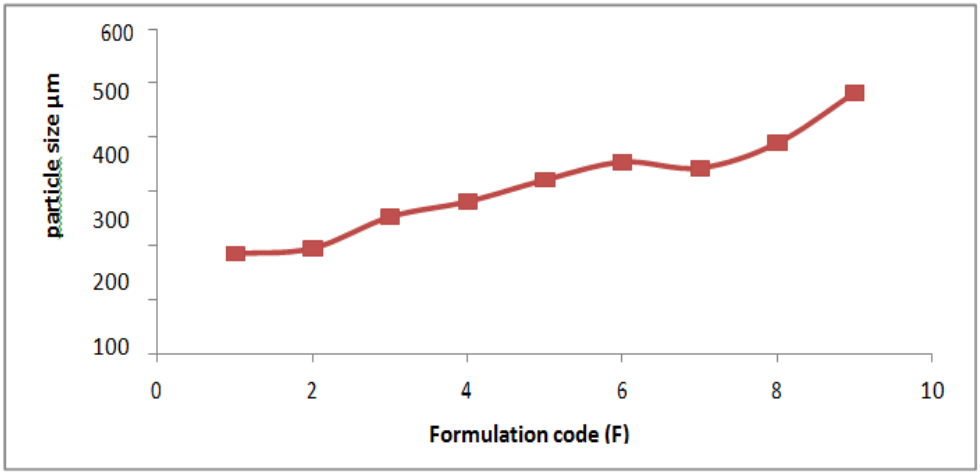


Figure 13: Particle Size of Lercanidipine Hydrochloride Microparticles.

Table 19: Swelling Index(%) of Lercanidipine Hydrochloride Microparticles.

S.No	Formulation code	Swelling index (%)
1	F1	190
2	F2	195
3	F3	189
4	F4	175
5	F5	165
6	F6	182
7	F7	185
8	F8	186
9	F9	196

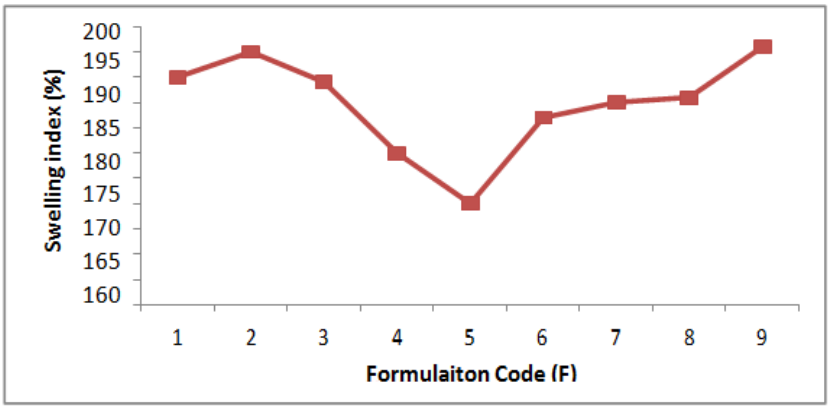


Figure 14: Swelling Index(%) of Lercanidipine Hydrochloride Microparticles.

Table 20: Percentage Drug Loading of Lercanidipine Hydrochloride Microparticle.

S. NO	FORMULATION CODE	DRUG LOADING (%)
1.	F1	80
2.	F2	95
3.	F3	75
4.	F4	89
5.	F5	90
6.	F6	85
7.	F7	85
8.	F8	90
9.	F9	96

(±S.D. and no. of determinations = 3)

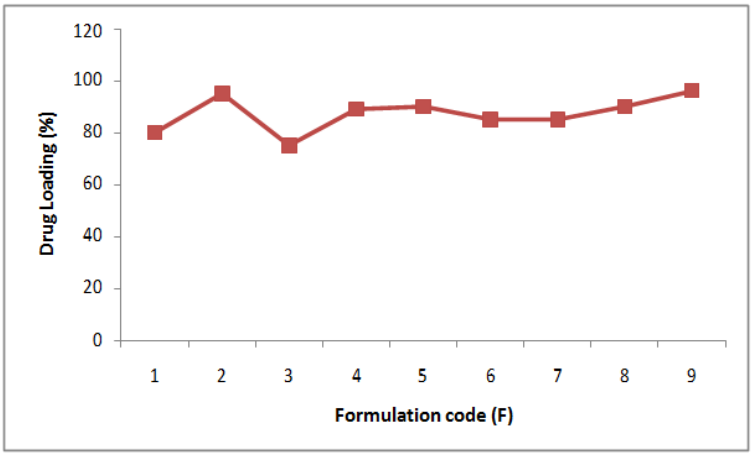


Figure 15: Percentage Drug Loading or Lercanidipine Hydrochloride.

Table 21: Entrapment Efficiency of Lercanidipine Hcl Microparticles.

S.NO	FORMULATION CODE	ENTRAPMENT EFFICIENCY (%)
1	F1	25
2	F2	95
3	F3	30
4	F4	44
5	F5	53
6	F6	58
7	F7	65
8	F8	80
9	F9	96

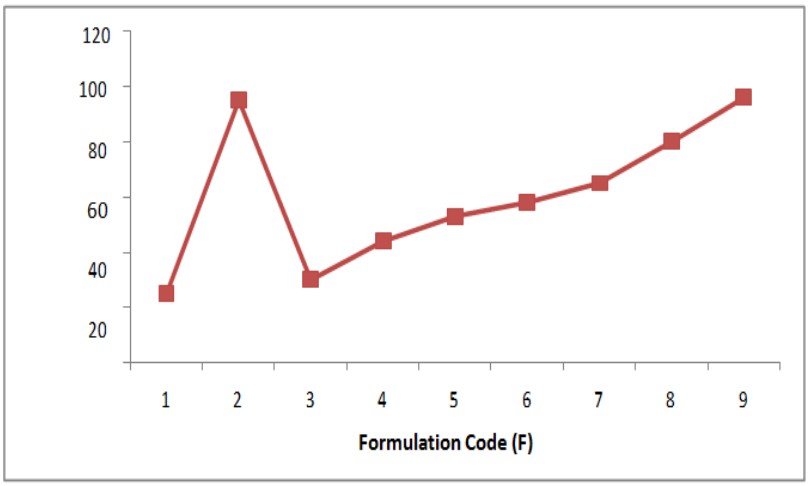


Figure 16: Entrapment Efficiency of Lercanidipine HclMicroparticles.

Table 22: *In-Vitro* Buoyancy (%) Studies.

S.No	Formulation code	Buoyancy (%)
1	F1	87.5
2	F2	96.0
3	F3	88.5
4	F4	83.5
5	F5	88.5
6	F6	88.2
7	F7	89.2
8	F8	91.21
9	F9	97.00

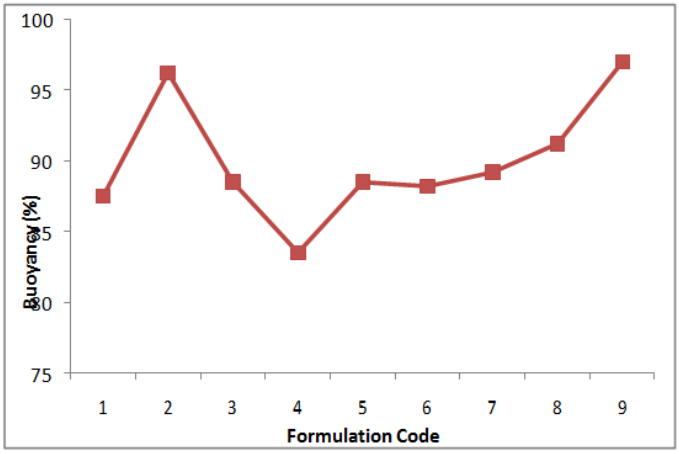


Figure 17: *In-Vitro* Buoyancy (%) Studies.

Table 23: *In-Vitro* Dissolution Profile of Lercanidipine Hydrochloride Microsphere Mean Cumulative Percentage Drug Release (%).

S.No	Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1	14.84	11.92	14.01	10.18	10.91	11.65	10.11	10.25	11.82
2	2	19.20	29.82	20.02	25.14	27.20	20.05	30.11	28.52	30.12
3	3	24.26	42.01	23.01	38.26	43.05	30.01	42.45	39.42	43.15
4	4	28.96	59.02	26.05	42.01	55.06	40.05	55.42	40.14	57.89
5	5	32.27	68.01	31.08	45.01	65.01	52.06	60.14	52.15	69.12
6	6	38.97	79.03	35.04	58.03	74.06	68.17	85.12	61.27	78.95
7	7	42.01	87.05	42.05	60.02	85.23	70.18	87.15	75.38	89.01
8	8	42.05	95.03	42.06	60.05	87.41	72.19	87.26	79.16	96.89

(±S.D.and no. of determinations = 3)

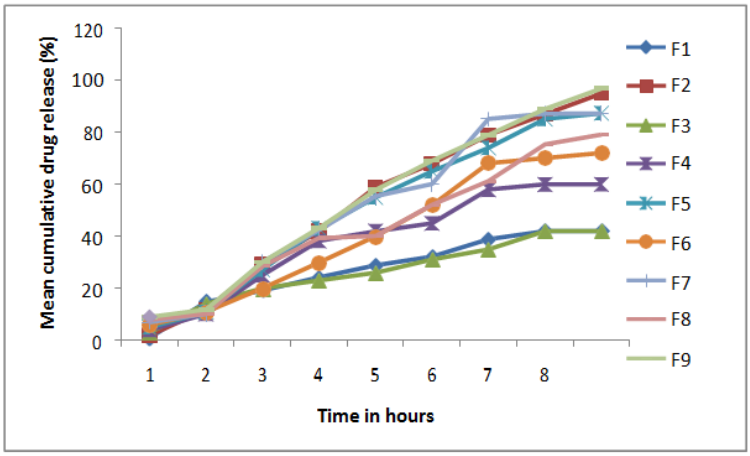


Figure 18: *In-vitro* Dissolution Profile of Lercanidipine Hydrochloride Microparticle mean Cumulative Percentage Drug Release (%)

RESULT AND DISCUSSION

The principle objective of this research study was to formulate and evaluate sustained release microparticles of Lercanidipine Hydrochloride using ethylcellulose, HPMC, Eudragit RS 100 and PVP polymer by solvent evaporation technique method. Various batches were made form batch (F1 to F9).

To achieve the above objective, ethylcellulose and Poly vinyl pyrrolidine was found to be suitable polymer due to its biocompatibility, good stability, and ease of fabrication.

Solvent evaporation method was employed to formulate microsphere due to its ease of fabrication without compromising the activity of the drug. Sustained release microspheres obtained by this method were found to be spherical, discrete and free flowing in nature.

The prepared Microspheres were evaluated for percentage yield, Micromeritic properties such as Angle of repose, Bulk density, Tapped density, compressibility

index, Hausner's ratio, particle size, Morphology analysis (SEM), swelling index (%), Drug content (%), Drug Entrapment efficiency(%), Buoyancy studies, *in-vitro* drug release and finally stability studies.

FOURIER TRANSFORM-INFRARED SPECTROSCOPY

FT-IR study was carried out to see whether there is any incompatibility between drug and polymer and also to know whether there is complete physical adsorption of drug on to the polymer matrix without any mutual interaction.

The results obtained from the IR studies are shown in Fig No.4 Lercanidipine showed prominent peaks. The same peaks were also observed in the physical mixture of drug & polymer and drug loaded Microspheres.

After interpretation through the above spectra it was confirmed that there was no major shifting of functional peaks between the spectra of drug, polymer, physical mixture of drug and polymer and drug loaded microspheres.

Drug excipients interaction study

Drug excipients interaction was studied using (FT-IR) fourier transformed infrared spectroscopy. The characteristic peaks of the drug (fig 4) were observed at wave numbers 615.29cm^{-1}, 754.17 cm^{-1}, 1095.57 cm^{-1}, 1205.01cm^{-1}, 1498.69 cm^{-1}, 1618.28 cm^{-1}, 1676.14 cm^{-1}, 3415.93 cm^{-1}, in the functional group region of the pure drug spectrum. These characteristic peaks in the spectrum correspond to 615.29 cm^{-1} for stretching vibration of functional groups (OH, CH, CH3, CH2OH). These characteristic peaks also appear in the spectrum of Lercanidipine microparticles formulation at the same wave numbers indicating that there was no interaction between the drug and formulation excipients.

PERCENTAGE YIELD

The low percentage yield in some formulation may be due to microspheres lost during the washing process. Percentage yield of all formulations varies from F1 to F9 which are shown in Table No.16 and indicates that F9 shows highest percentage yield of 96%

MICROMERITIC PROPERTIES

Angle of repose

Angle of repose value of all the formulations were in the range of 20.42±0.20 to 25.60±0.05, which shows free flow nature of the prepared microsphere, the results were shown in table no.17

Bulk density and Tapped density

It has been stated that, bulk density values less than 1.2 gm/cm^3 indicate good glow and values greater than 1.5 gm/cm3 indicate poor flow characteristic. It is seen from table No. 18 that the bulk density values are less than 1.2 gm/cm3 indicating good flow characteristics of the microspheres.

Compressibility index

The Carr's index of all the formulations was less than 20, i.e from 10.1±0.84 to 10.13±0.41, which inidicates good flow properties and compressibility.

Hausner's ratio

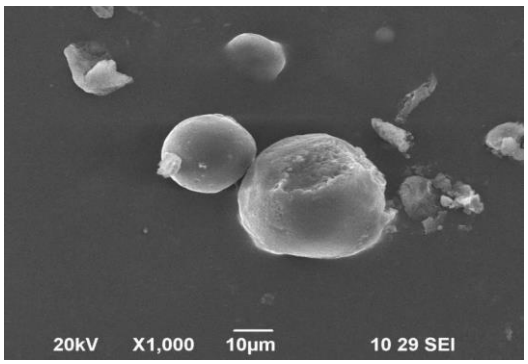
Hausner's ratio was ranging from 1.05±0.54 to 1.12±0.015 i.e., all the preparation showed that they had good flow properties. The improvement in flow properties suggests that the microspheres can be easily handled during processing. The results were shown in table no.17

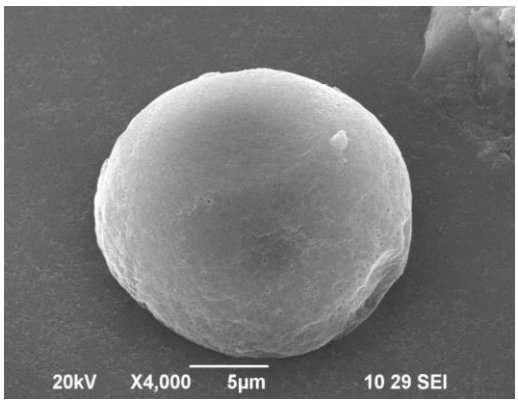
PARTICLE SIZE AND MORPHOLOGY ANALYSIS (SEM)

Here, keeping drug ratio constant and varied polymer ratio as the polymer concentration increases, viscosity increases, which influences the interaction between disperse phase and dispersion medium and affects the size concentration, there was increase in relative viscosity so as resulted in an increase in mean particle size. The particle size of drug loaded batches, ranges from 185 to 489µm. The mean particle size of all the formulations was shown in table No: 18

SURFACE MORPHOLOGY

SEM was performed on the prepared Lercanidipine Hydrochloride microspheres to access their surface and morphological characteristics as shown in fig: 24 Scanning Electron Microphotographs indicate that microsphere were spherical and discrete.





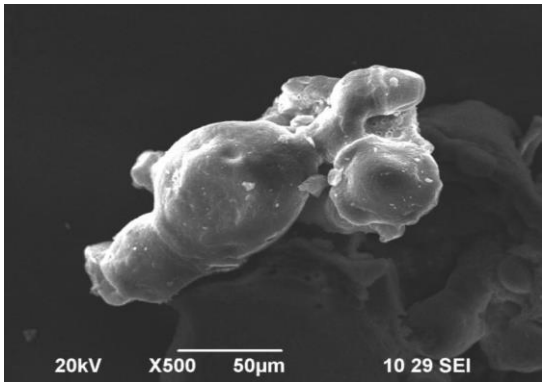


Figure 27: SEM analysis for formulation F9 Swelling Index (%).

The swelling index for all F1 to F9 formulations are ranges from 190 to 186%.

DRUG CONTENT (%)

Loading efficiency of drug loaded batches was found to be 80% to 96 %. The drug loading efficiency of all formulations were shown in table No.20 which indicates that the highest drug loading was found to be F9 as 96%.

DRUG ENTRAPMENT

The microspheres exhibited an increase in drug entrapment with an increase in the proper ratio up to a particular concentration. A decrease in drug entrapment was observed after that point due to saturation capacity of the polymer. The entrapment efficiency of drug loaded batches, ranges from 25 to 95. The results were shown in table No.21.

The maximum drug entrapped in the F9 formulation, 96%. The results are shown in table no.21

BUOYANCY STUDIES

In this study the values ranges from 87.5 to 97.00.

***IN-VITRO* DISSOLUTION STUDY**

Cumulative percentage release of Lercanidipine Hydrochloride loaded microsphere carried out in 1.2 pH HCl buffer for two hours and then 7.4 pH phosphate buffer upto 8, hours. The release rate was decreased by increasing the polymer concentration and particle size. The rapid release was obtained in formulation F9 due to low concentration of polymer and size of the particle results in higher contact of dissolution medium due to increased surface area.

Drug release from all the formulations was slow and sustained over 8 hours. By the end of 8 hours, F1, F2, F3, F4, F5, F6,F7, F8,F9 released 96.89 of loaded drug respectively. The polymer/drug F9 showed better sustained release pattern and drug entrapment and found to be most suitable among all the other formulations. *In-vitro* profiles of all the formulations have been shown in fig no.23

STABILITY STUDIES

The stability studies indicates the significant difference between the release patterns of microsphere at 40°C and RH and at room temperature for one month.

The stability studies were carried out at and optimized formulation, i.e, from F9 forumulation. The formulation was store at (40°C±2°C at 75% RH ± 5 %) for 1 months. Sample were withdrawn and retested for drug release and was compare with the formulation diffusion profile.

Table 27: Stability studies for formulated floating microparticles of Lercanidipine Hydrochloride.

Characters	**Initial month**	**After 1 month**
Appearance	Spherical	Spherical
Solubility	Soluble in phosphate buffer	Solubile in phosphate buffer
Colour	Half white	Half white
Particle size	482	489
Swelling index	196	196
***In-vitro* drug release in hours**	**Mean cumulative release in percentage (%)**	
1	11.82	11.93
2	30.12	30.45
3	43.15	43.95
4	57.89	58.12
5	69.12	68.95
6	78.95	79.01
7	89.01	89.25
8	96.89	96.45

SUMMARY AND CONCLUSION

Floating Lercanidipine Hydrochloride microparticles using polymer ethylcellulose, HPMC, Poly vinyl pyrrolidine and Eudragit RS 100 was developed by solvent evaporation method and it was found to be a suitable floating oral drug delivery system in terms of particle size distribution, drug loading capacity and Sustained release Lercanidipine Hydrochloride microparticles obtained was spherical in shape, discrete and free flow in nature. It can be concluded that.

Polymer-drug ratio influence the particle size as well as

drug release pattern of microsphere.

Entrapment efficiency of drug loaded batches F1 to F9 were determined and it was found that F2 and F9 had a better drug entrapment efficiency of 95% and 96%.

Drug loading efficiency was better with F9 showed 96%.

Percentage yield from all the formulation were high and F9 showed good percentage yield of 96%.

Flow properties were determined for all the formulations F1 to F9. The result of Carr's index and angle of repose values indicated that all the formulations showed good flow properties.

In-vitro drug release from all the formulations was found to be slow and sustained over the period of 8 hours was found to be 96.89%.

Stability studies of formulated Lercanidipine microparticles was done at 40° C± 2°C and 75%±5 RH. Evaluating initial month and after one month founded that there is no significant changes in appearance, solubility, colour, particle size, swelling index, *in-vitro* drug release.

Decided to do *in-vivo* studies in future.

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