



# IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH  
An official Publication of Human Journals

ISSN 2349-7203




Human Journals

**Research Article**

November 2021 Vol.:22, Issue:4

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## Formulation and Evaluation of Microsphere of Lercanidipine HCl



**IJPPR**  
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH  
An official Publication of Human Journals



ISSN 2349-7203

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**Submitted:** 24 October 2021  
**Accepted:** 30 October 2021  
**Published:** 30 November 2021



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**Keywords:** Delivery, oral, Microspheres, Lercanidipine, Sustain-Release

### ABSTRACT

The present research work is aimed to design sustained-release microspheres of Lercanidipine HCL as an anti-hypertension drug that is used in the treatment of hypertension and these are designed in such a way that release of the drug is for 24 hours. The Microspheres were prepared by the Ionic Gelation method using varying concentrations of sustained-release polymers Sodium alginate. The compatibility of the polymers was ruled out by FT-IR studies and found to be compatible. The Lercanidipine HCL microspheres were evaluated for their physical properties like the angle of repose, bulk density, and swelling index and found to have good flow properties. The prepared microspheres were evaluated for in-process and finished product quality control tests including Bulk density, Entrapment efficiency, and *in-vitro* drug release. The dissolution medium used was pH 6.8 phosphate buffer. The results of dissolution studies indicated all formulations released up to 24hours and formulations containing Sodium Alginate. e. F5 was the most successful formulation with 99.06% drug release with sustained release at the end of 24 hours.

## **INTRODUCTION:**

Microspheres can be defined as solid, approximately spherical particles with a diameter ranging from 1 to 1000 $\mu$ m, containing dispersed drug in either solution (or) microcrystalline form". The terms 'microcapsules' and 'microspheres' are often used interchangeably. If modified, the micro-particulate drug delivery systems are considered and approved as reliable means of delivering the drug to the target with precision and retaining the desired concentration at the site of interest without unfavorable side effects. Microspheres belong to Novel Drug Delivery System (NDDS) and it can help to improve the solubility of the drug and sustain release.<sup>1,2,3,4</sup>

Lercanidipine is a calcium channel blocker. It is a BCS class –II drug ie., it has low solubility and high permeability. As the solubility of the drug is less, it has low bioavailability. Thus, an attempt has been made to develop sustain release microspheres of lercanidipine to increase its bioavailability. Lercanidipine microspheres were prepared by Ionic Gelation method by employing polymers such as Sodium Alginate.<sup>5</sup>

## **MATERIALS AND METHODS:**

Materials: Lercanidipine HCL was obtained as a gift sample from CTX Life Sciences PVT.LTD. India. Sodium Alginate was purchased from Loba Chemie PVT.LTD. Calcium Chloride, Disodium Hydrogen Phosphate, and Potassium Dihydrogen Ortho Phosphate were purchased from Vishal Chem India.

### **Methods:**

#### **Preparation of Microspheres by Ionic Gelation Method:**

Polymer is dissolved in distilled water. Drug is dispersed in polymeric solution with continuous agitation. The resultant polymeric solution was then injected dropwise into calcium chloride solution. The resultant calcium alginate beads were then filtered and dried at room temperature.

**Process Flow Chart of microspheres**

Drug (Lercanidipine) + Polymer (Sodium alginate)



Dissolve in distilled water



Injected

Cacl + Methanol+ water containing solution



Stirred at 300 rpm for 1-2 hours



Formation of Microspheres

**Table 1: Formulation of Microspheres**

Ingredients	Formulation Ratios								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lercanidipine	10m g	10m g	10m g	10m g	10m g	10m g	10m g	10m g	10m g
Sodium Alginate	2%	2.5 %	3%	3.5 %	4%	4.5 %	5%	5.5 %	6%
Distilled Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Calcium chloride 5% Solutions	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

**Compatibility studies by FTIR:**

The compatibility between the drug and various polymers used was determined by using FTIR.

**Evaluation of Microsphere:**

**Particle Size and shape:**

About 100 Microsphere were randomly picked up thrice and their sized of dried microspheres were measured by using a Stage Micrometer. The shape of the Microsphere was observed by visual observation.

**% Entrapment Efficiency:**

An accurately weighed quantity of 10 mg microspheres was taken and crushed in a mortar with a pestle and dissolved in 10 ml of phosphate buffer. The resultant suspension was centrifuged at 3600 rpm for 30 min. The solution was sonicated for 2 - 3 h using a sonicator (Citizen). The resultant dispersion was filtered through Whatman's filter paper (no. 041) and analyzed at 234 nm using UV spectrophotometry (Shimadzu, 1800). The experiments were done in triplicate and results were calculated.

The Encapsulation Efficiency was calculated by formula,

$$\% \text{Entrapment efficiency} = \frac{AQ}{TQ} * 100$$

Where, AQ- the actual amount of drug found in the microspheres, TQ-Theoretical amount of drug found in microspheres.

**Table 2: Mean particle size, shape, and Drug entrapment efficiency of different batches**

Sr. No.	Formulation code	Mean particle size (µm)	Shape	% Drug entrapment efficiency
1.	F1	954.4	Oval	29.07
2.	F2	750.4	Oval	31.4
3.	F3	450.02	Irregular	40.3
4.	F4	480.1	Irregular	57.1
5.	F5	542.9	Oval	70.04
6.	F6	806.9	Oval,round	85.3
7.	F7	890.6	Round	93.7
8.	F8	750.6	Irregular	87.3
9.	F9	658.6	Irregular	88.9

### Shape and surface morphology:

The morphology of microspheres was investigated by using optical Leica microscopy. The photographs of the optimized formulation taken by Leica microscope are shown in Fig. The results of the Leica microscope revealed that the microscope of Lercanidipine using sodium alginate as polymer was spherical and their surface was smooth and devoid of crack giving them a good appearance.

### Flow Properties of Microspheres:

#### • Bulk density:

Bulk density is determined by pouring microspheres into a graduated cylinder via a large funnel and measuring the volume and weight.

$$\text{Bulk density} = \frac{\text{Weight of microspheres}}{\text{Bulk volume of microspheres}}$$

#### •Tapped density:

Tapped density is determined by placing a graduated cylinder containing a known mass of microspheres and mechanical tapper apparatus, which is operated for a fixed number of taps using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.

$$\text{Tapped density} = \frac{\text{Weight of microspheres}}{\text{Tapped volume of microspheres}}$$

#### •Hausner's Ratio:

Hausner's ratio is measured by using the values of tapped density and bulk density.

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

#### Angle of Repose:

The Angle of repose of each microsphere blend was determined by the fixed funnel method. The microsphere was weighed accurately and passed freely through the funnel to form a heap. The height of the funnel was so adjusted that the tip of the funnel just touched the apex

of the heap. The diameter of the Microspheres cone so formed was measured and the angle of repose was calculated using the following equation,

$$\tan\theta = h/r$$

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

Where,  $\theta$  = angle of repose

h = height of the pile and,

r = radius of Microspheres cone respectively.

### Carr's Index:

The compressibility index is determined by measuring both bulk density and tapped density of microspheres. The percentage compressibility of microspheres was calculated according to the equation below,

$$\% \text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

### Differential Scanning Calorimetry:

The physical state of the drug, Drug polymer mixture, and formulation was analyzed by DSC. The thermograms of sodium alginate, Microspheres with polymer were obtained at a scanning rate of 10°C/min conducted over a temperature range of 25 350°C, respectively.

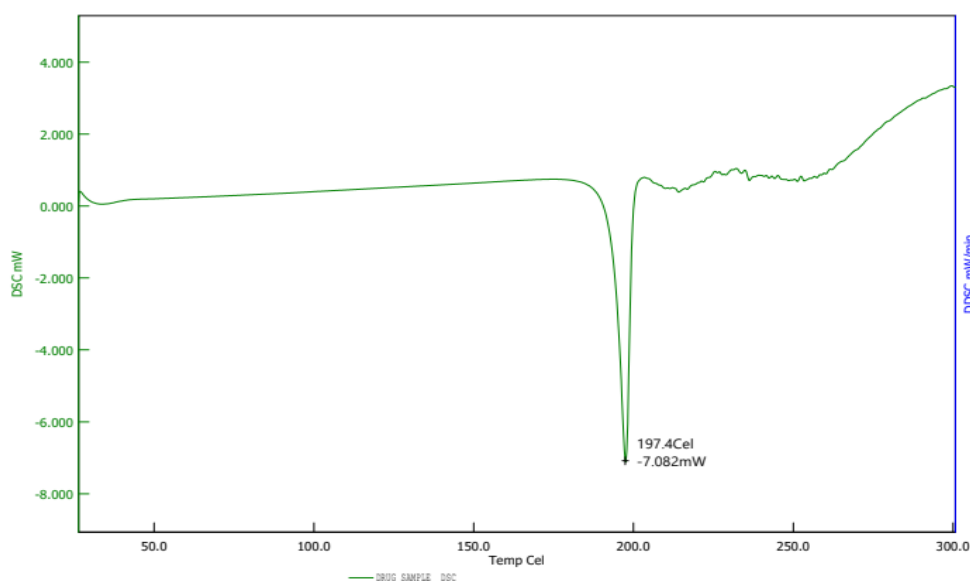


Figure No. 1: DSC of pure drug Lercanidipine HCL

**In-vitro dissolution studies**

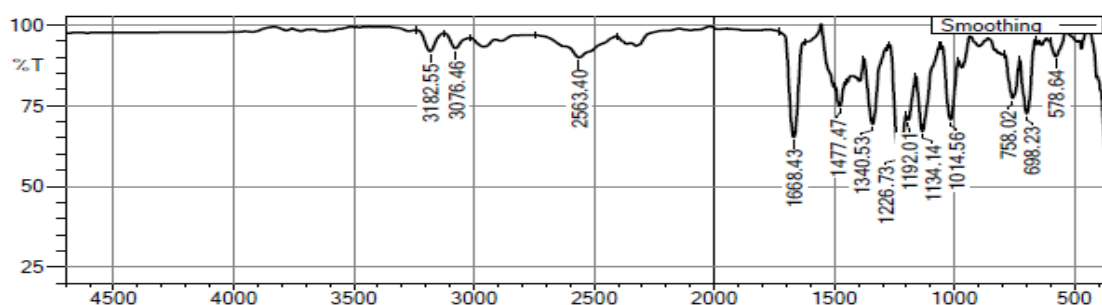
The release rate of Lercanidipine Microsphere was determined by employing USP type-2 apparatus by rotating paddle method. The desolation test was performed using 900 ml phosphate buffer 6.8 in  $37 \pm 0.5$  °C at 50 rpm. Lercanidipine microspheres equivalent to 500mg were placed in a basket. A sample (5ml) of the solution was withdrawn from the dissolution apparatus every 30 minutes for 12 hours. And samples were replaced with 5ml of fresh dissolution medium. The sample observance of the solutions was measured at 234 nm. Dissolution profiles of the formulation were analyzed by plotting drug release vs time plot. Data obtained was also subjected to kinetic treatment to understand the release mechanism.

**Table No. 3: Dissolution Test Details For Dissolution of Microspheres**

Sr. No	Specification	Standard Values
1	Apparatus	USP Dissolution apparatus II
2	Speed	50 rmp
3	Volume of Media	900 ml
4	Dissolution Media	Phosphate buffer 6.8pH
5	Stirrer	Paddle type.
6	Aliquot was taken it each time interval of 1 h	5 ml
7	Temperature	$37 \pm 0.5$ °C
8	$\lambda$ Max	234nm

**RESULT AND DISCUSSION:**

**Compatibility Studies:** IR spectra of pure Lercanidipine and the physical mixture of drug and polymers were shown in fig 2-5. As the identical principle peaks were observed in all the cases, It was confirmed that there is no interaction between the drug and polymers.



**Figure No. 2: FT – IR spectra of pure drug**

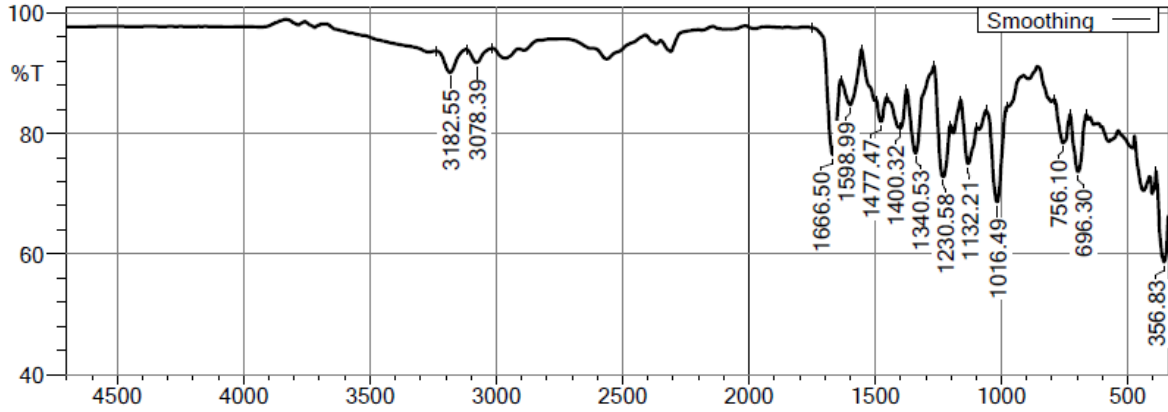


Figure No. 3: FT-IR spectra of physical mixture of sodium alginate

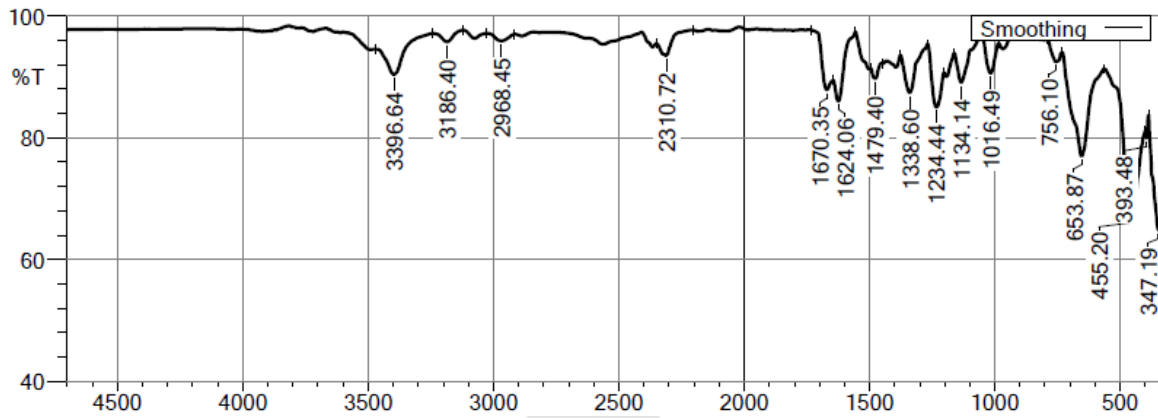


Figure No. 4: FT-IR spectra of physical mixture of calcium chloride

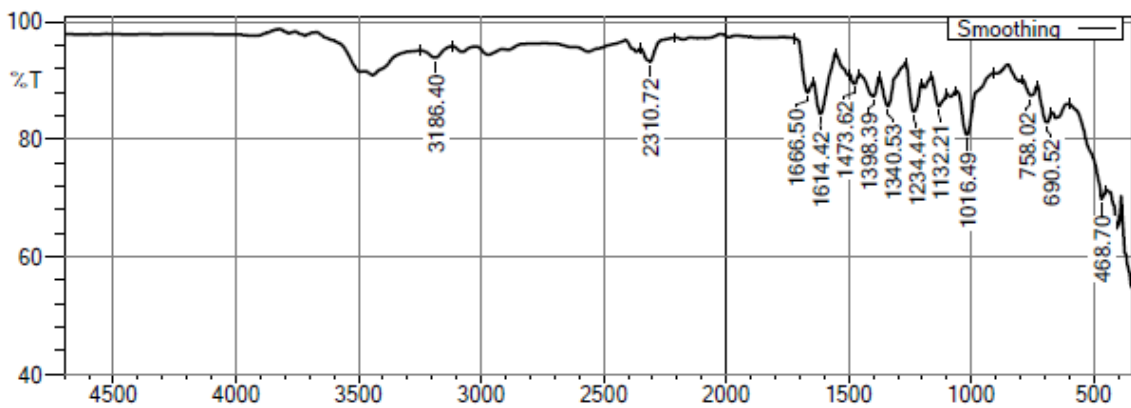


Figure No. 5: FT-IR of physical mixture of drug + Calcium chloride + Sodium alginate

**Particle size analysis:** Particle size was determined by the Optical microscopy method. It plays important role in the release of drugs from microspheres. The means size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to increased droplet size and finally a large microsphere size.



Uniform average particle size was obtained for formulation F7. Microspheres obtained with batch F7 showed a uniform average particle size of 890.6 $\mu$ m.

**Drug Entrapment Efficiency (DEE %):** The concentration of sodium alginate had a significant impact on drug entrapment efficiency and particle size.

As the concentration increases of polymer, the drug entrapment increases from 70.04 % - 85.3%. but at the same time, the drug entrapment efficiency of microspheres increases the drug: polymer ratio. The best drug entrapment efficiency was (F7 93.7%).

**Shape and surface morphology:**



**Figure No. 6: Morphology of microspheres**

The morphology of microspheres was investigated by using Leica microscopy. The results of Leica microscope revealed that the microspheres of Lercanidipine combination with sodium alginate as a polymer (F7) were spherical and their surface was smooth and devoid of cracks giving them a good appearance.

**Studies on flow properties:** The microspheres were evaluated for various derived properties such as bulk density, tapped density, and flow properties such as Angle of repose, Hausner's ratio, and Carr's index, all the results were shown in the table.

The results of the flowability studies indicated that the microspheres of all formulations were having well to excellent flowability. These studies combined indicated that the microspheres of all formulations were efficient for either compression or filling into a capsule.

**Table No. 4: Flow properties of Lercanidipine Microspheres**

Formulation code	Bulk Density	Tapped Density	Angle of repose	Carr's Index	Hausners'ratio (Avg. ± S.D.)
	(Avg. ± S.D.)	(Avg. ± S.D.)	(Avg. ± S.D.)	(Avg. ± S.D.)	
F1	0.769 ± 0.01	0.833 ± 0.01	26.93 ± 0.12	7.68 ± 0.01	1.083 ± 0.01
F2	0.666 ± 0.02	0.833 ± 0.02	25.74 ± 0.11	20.04 ± 0.02	1.250 ± 0.01
F3	0.625 ± 0.01	0.714 ± 0.01	32.94 ± 0.09	8.9 ± 0.01	1.142 ± 0.01
F4	0.714 ± 0.01	0.834 ± 0.01	33.81 ± 0.13	14.38 ± 0.02	1.680 ± 0.01
F5	0.834 ± 0.02	0.909 ± 0.02	28.67 ± 0.12	8.25 ± 0.02	1.089 ± 0.01
F6	0.625 ± 0.01	0.714 ± 0.01	27.08 ± 0.12	8.9 ± 0.01	1.142 ± 0.01
F7	0.714 ± 0.01	0.834 ± 0.01	33.61 ± 0.13	14.38 ± 0.02	1.680 ± 0.01
F8	0.588 ± 0.02	0.666 ± 0.02	34.54 ± 0.13	10.51 ± 0.01	1.132 ± 0.01
F9	0.555 ± 0.01	0.625 ± 0.01	37.12 ± 0.15	11.2 ± 0.02	1.261 ± 0.01

**Differential scanning calorimetry (DSC):** Thermal analysis of pure LER was performed by differential scanning calorimetry (DSC) as shown in fig. DSC curve of LER showed the endothermic peak at 197°C.

***In-vitro* drug release study:**

The results of the dissolution studies of microspheres of formulation F1 to F3 were shown in the table. The result indicated increasing the concentration of sodium alginate; the drug release rate was more controlled. The results of the dissolution studies of microspheres of formulation F4 to F6 were shown in the table. These results indicated that by increasing the

concentration of sodium alginate, the drug release rate was found to be increased. The Comparison of Formulation F6 to F9 was found more sustain release i.e the best sustain release was found in F7.

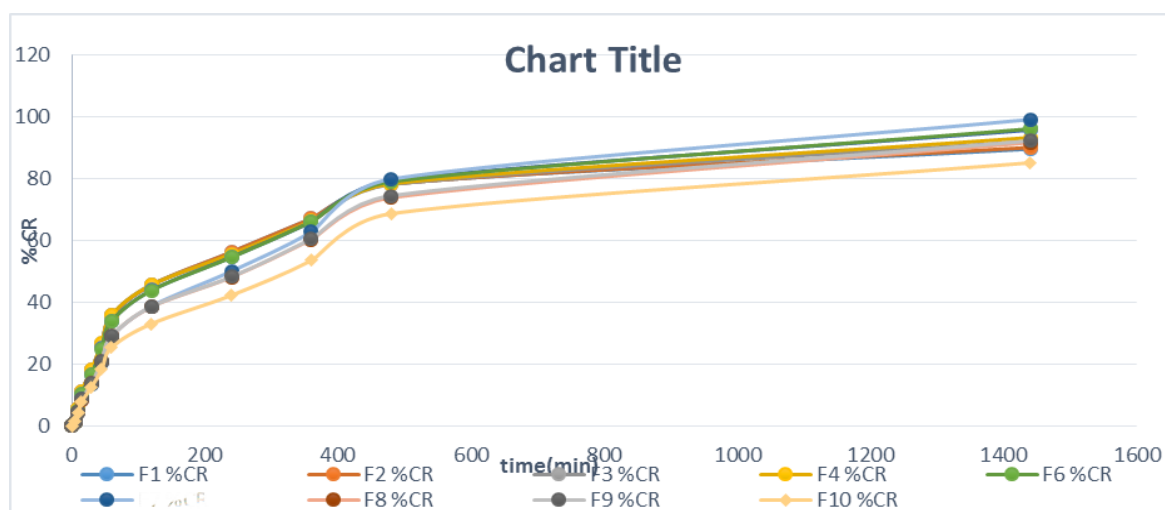


Figure No. 7: In-vitro Drug release study

## CONCLUSION:

Studies have been carried out on the study of the influence of formulation and process parameters on the drug sustained-release rate from Lercanidipine microsphere. The research was undertaken to study the influence of polymer phase and temperature as process parameters and the concentration of polymers as the formulation parameter. The drug was found to be compatible with the polymer-based on IR spectral studies. Another interesting finding was the Microspheres prepared from high viscosity polymer phase were smaller in size than those prepared from the lower viscosity polymer phase. The compressibility and flow properties like Bulk Density, Tapped Density, Hausner's ratio, and angle of Repose were found to be good. From *in-vitro* drug release study it was observed that the Ionic Gelation method was found to be more successful for the sustained release of microspheres of the Lercanidipine.

## ACKNOWLEDGEMENT:

Author would like to express my sincere gratitude to Dr. Sheela Yadav for her constant support and guidance throughout the research project.

## CONFLICT OF INTEREST:

Declared None.

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