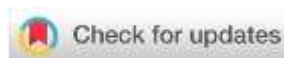
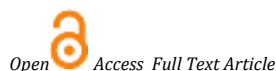


Available online on 15.06.2023 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Copyright © 2023 The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited



Research Article

Formulation and Evaluation of New Sustained Release Floating Microspheres of Cilnidipine by Solvent-Diffusion Evaporation Technique

Kritika Sharma, Priya Thakur, Shweta Agarwal*

Department of Pharmacy L.R. Institute of Pharmacy Jabli Kyar, Oachghat Solan 173223(H.P.), India

Article Info:

Abstract



Article History:

Received 07 April 2023

Reviewed 16 May 2023

Accepted 03 June 2023

Published 15 June 2023

Cite this article as:

Sharma K, Thakur P, Agarwal S, Formulation and Evaluation of New Sustained Release Floating Microspheres of Cilnidipine by Solvent-Diffusion Evaporation Technique, Journal of Drug Delivery and Therapeutics. 2023; 13(6):102-111

DOI: <http://dx.doi.org/10.22270/jddt.v13i6.5861>

*Address for Correspondence:

Dr. Shweta Agarwal, Department of Pharmacy L.R. Institute of Pharmacy Jabli Kyar, Oachghat Solan 173223(H.P.), India

The purpose of the present investigation was to develop a gastro-retentive cilnidipine loaded floating microspheres. The floating microspheres of cilnidipine were prepared by the solvent evaporation method for oral drug delivery using HPMCK4M and ethyl cellulose as polymers. The drug loaded microspheres were evaluated for particle size, drug content, entrapment efficiency and floating time. The in-vitro study was performed in pH 1.2 to determine the amount of drug released. Field emission scanning electron microscopy (SEM) was performed to check the surface morphology of microspheres. The mean particle size of the microspheres was in the range of 226.85 – 339.42µm. The drug content of the floating microspheres was more than 70% and drug entrapment efficiency of microspheres obtained between 64.64 – 83.0%. The in-vitro buoyancy was more than 70%. Cumulative % of drug release obtained between 73.12 – 89.68%. Field emission scanning microscopy results showed that the prepared microspheres were smooth and spherical. The study reveals that more the particle size extended the floating time, this methods reveals that the drug content of the microspheres enhanced as the amount of polymer increased or increased in ethyl cellulose concentration also leads to increase in entrapment efficiency and particle size. Cumulative % drug release decreased as ethyl cellulose concentration increased.

Keywords: cilnidipine, microspheres, floating drug delivery system, entrapment efficiency, cumulative drug release, ethyl cellulose, Field emission scanning electron microscopy, polymer, concentration

INTRODUCTION

The rates of high blood pressure control in several of these nations have, however, actually slowed during the past few years. Globally, 1.2 billion individuals are predicted to have hypertension by the year 2010¹. Among the various routes of drug delivery, oral route is the most convenient, easily preferred and patient compliance one. However, drugs administered orally undergoes hepatic first-pass metabolism and enzymatic degradation in the gastrointestinal tract (GI) or both². A type of gastro-retentive medication delivery system known as floating microspheres is composed of solid, roughly spherical particles with a size between 1 and 1000 µm³. These have a bulk density lower than the gastric content. They remain floating in the stomach for a prolonged period of time, with the possibility of a continuous release of the drug. Eventually, the residual system empties from the stomach. Gastric emptying is much faster in the fasting state, and floating systems rely heavily on the presence of food to delay emptying and provide sufficient fluid for effective buoyancy⁴⁻⁵. SRDDS is employed to give patients their medications. SRDDS is made to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with maximum therapeutic efficacy and minimal side effects. Its goal is to maintain consistent levels of medication over an extended period without allowing for fluctuations in absorption or metabolism⁶.

The gastric retention system can stay in the stomach for several hours, greatly extending the amount of time that

medications are present there, increasing their bioavailability, and minimizing drug loss. Gastro-retentive systems can also be used to administer medications locally to the stomach and proximal small intestine. Better access to novel products with novel therapeutic potential and significant patient benefits may result from this⁷.

Cilnidipine is a dual blocker of L-type voltage-gated calcium channels in vascular smooth muscle and N-type calcium channels in sympathetic nerve terminals that supply blood vessels. The inhibition of N-type calcium channels may provide a new strategy for the treatment of cardiovascular diseases. L-type calcium channels are the main targets of the CCB. N-type calcium is distributed along the nerve and in the brain. Cilnidipine is anticipated to exert specific action on nerve activity, such as inhibition of the sympathetic nervous system. It inhibits the calcium influx in both in a vessel & the nerve. So causes vasodilation & inhibits the release of norepinephrine, which causes the vasodilation and decreases the heart rate & also decreases cardiac contraction in the heart. So, used in the treatment of hypertension. Cilnidipine comes under BCS class II i.e., low solubility high permeability⁸. Cilnidipine has a half-life of 30.4 minutes, the bioavailability of 13%. Thus, it is decided to prolong the gastric residence time in terms of making a floating gastro retentive drug delivery system to increase drug absorption and hence bioavailability⁹.

MATERIAL AND METHOD:

Cilnidipine was obtained from gift sample from nest health care limited, HPMC K4M was obtained from gift sample from meridian medicare pharmaceutical solan, india, ethyl cellulose was obtained from yarrow chem. pvt. ltd. mumbai, india, dichloromethane was purchased from fisher scientific, methanol, HCL and Tween 80 was obtained from Yarrow chem. pvt. ltd. Mumbai, India.

Method:

Formulation of Sustained release floating microsphere

The cilnidipine loaded floating microspheres were prepared by the solvent-diffusion evaporation method. Briefly, the drug

was dissolved in the organic solvent (dichloromethane: Methanol 1:1). Further, add the specified amount of Ethyl Cellulose, and HPMC K4M to the above mixture at room temperature to get homogenous dispersion. Then the resultant mixture was slowly added (drop by drop) to 100 ml of distilled water containing 0.01% tween 80 at 800 rotation per minute by maintaining temperature 30 °C to 40 °C. Further, the mixture was continuously stirred by propellant agitator at 800 rotation per minute for 45 minutes. During this period the volatile solvent gets evaporated and the microspheres were finally obtained. Microspheres were then filtered, washed and dried overnight at room temperature ¹⁰⁻¹³.

Table 1: Composition of cilnidipine floating formulation

Formulation code	Methanol: Dichloromethane ratio	Cilnidipine: Ethyl cellulose (mg)	HPMC K4M (mg)
FM1	1:1	200:600(1:3)	40
FM2	1:1	200:800(1:4)	40
FM3	1:1	200:1000(1:5)	40
FM4	1:1	200:600(1:3)	80
FM5	1:1	200:800(1:4)	80
FM6	1:1	200:1000(1:5)	80
FM7	1:1	200:600(1:3)	120
FM8	1:1	200:800(1:4)	120
FM9	1:1	200:1000(1:5)	120

RESULTS AND DISCUSSION

FTIR spectroscopy

The FTIR spectra of cilnidipine, polymers are shown in the figure (1-4). Our experimental results were assessed on the basis of physical data obtained for drug and polymers.

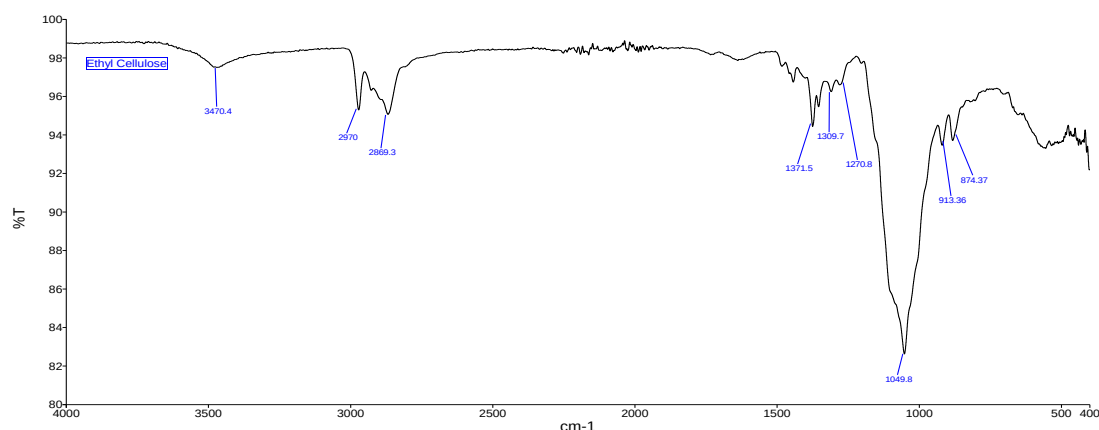


Figure 1: FTIR spectra of Ethyl cellulose

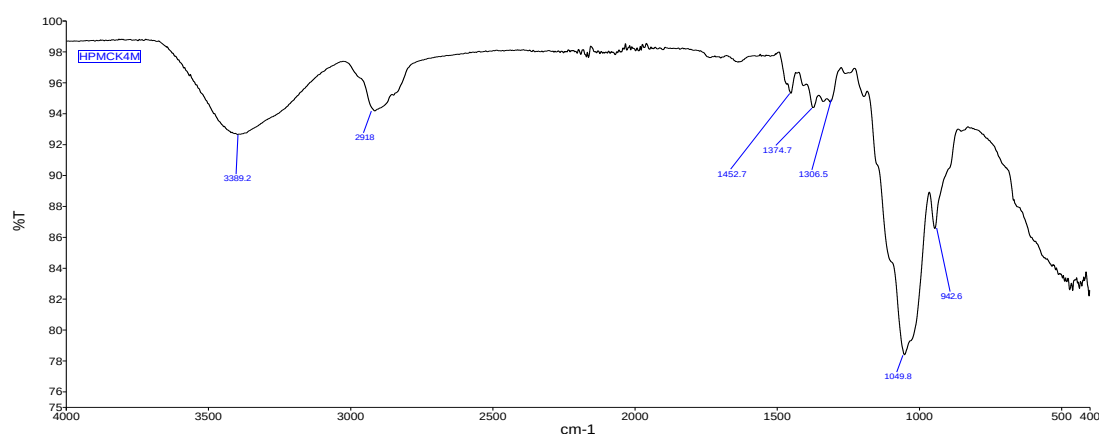


Figure 2: FTIR spectra of HPMC K4M

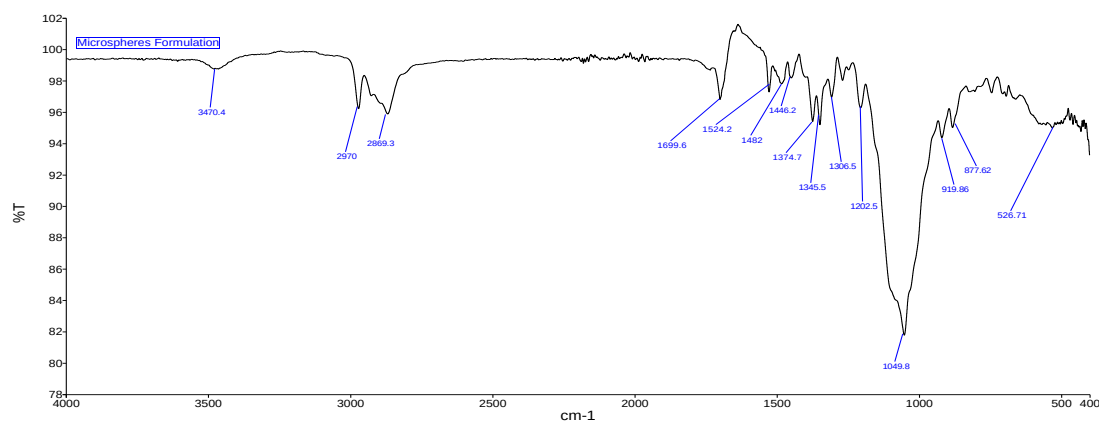


Figure 3: FTIR spectra of microsphere formulation

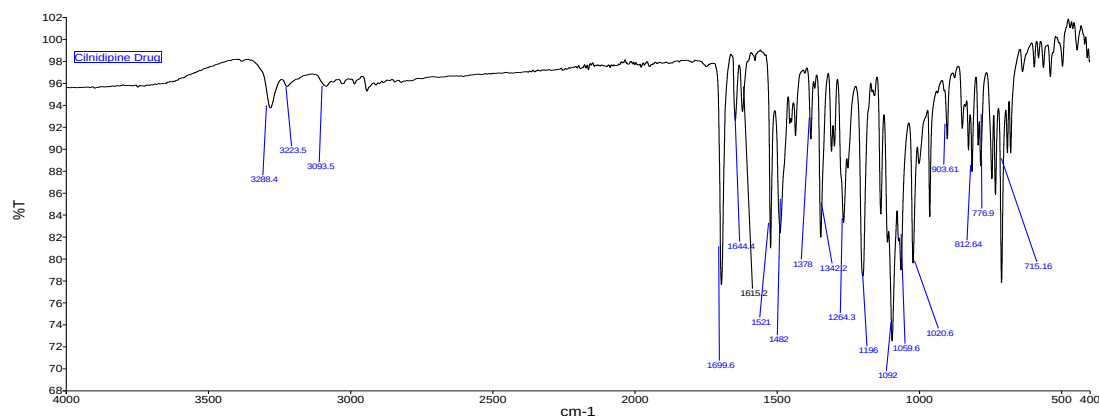


Figure 4: FTIR spectra of pure drug Cilnidipine

FTIR interpretation of cilnidipine

The absorption spectrum consists of few bonds and the substance. The presence of aromatic amine and methoxy group is indicated absorption at 3288.4cm^{-1} and 3093.5cm^{-1} as highly intense peak. The absorption spectrum group of alkenes indicated absorption at 1644cm^{-1} due to C=C stretching, 1264cm^{-1} due to N=O stretching, 1342cm^{-1} due to N-O stretching, 1699.6cm^{-1} due to C=O stretching as high and medium intensity peak. (Fig 4)

FTIR spectra of cilnidipine loaded floating microspheres

The FTIR spectroscopy was done to find out any chemical interaction between cilnidipine and polymer used. The spectra

obtained showed that the principal peaks of the drug were not overlapping with the peaks of the excipient indicated by the required wave number of the pure drug and the excipients. (Fig 3)

Differential scanning calorimetry

The differential scanning calorimetry thermogram of the cilnidipine & polymers depicted. DSC is an important technique used to characterize the solubility and physical state of the drug in the polymeric matrix. Melting point of cilnidipine was detected 109.49°C (Figure 5-8).

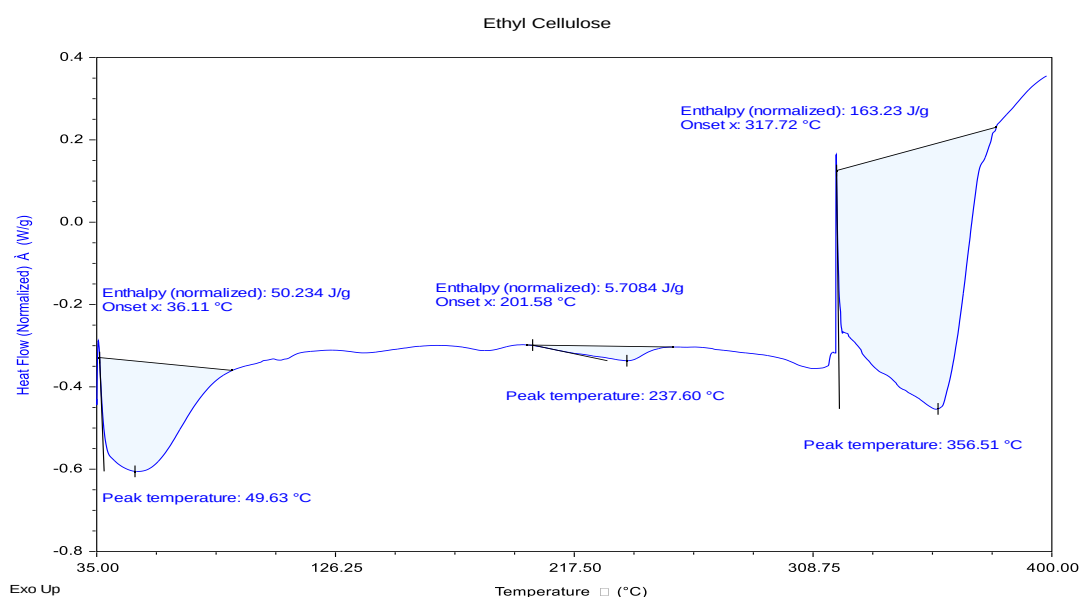


Figure 5: DSC of ethyl cellulose

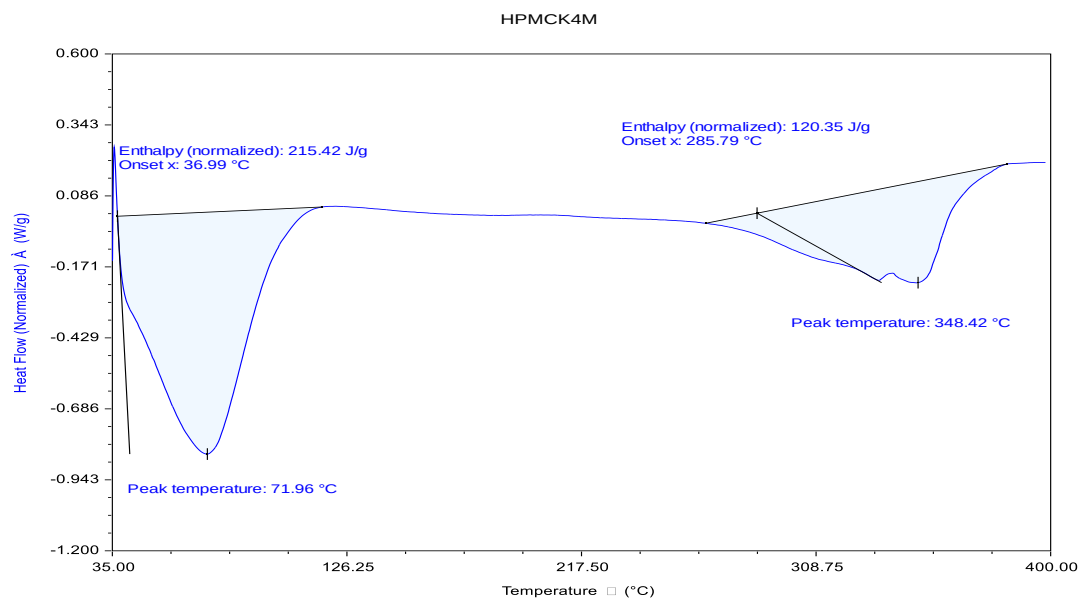


Figure 6: DSC of HPMC K4M

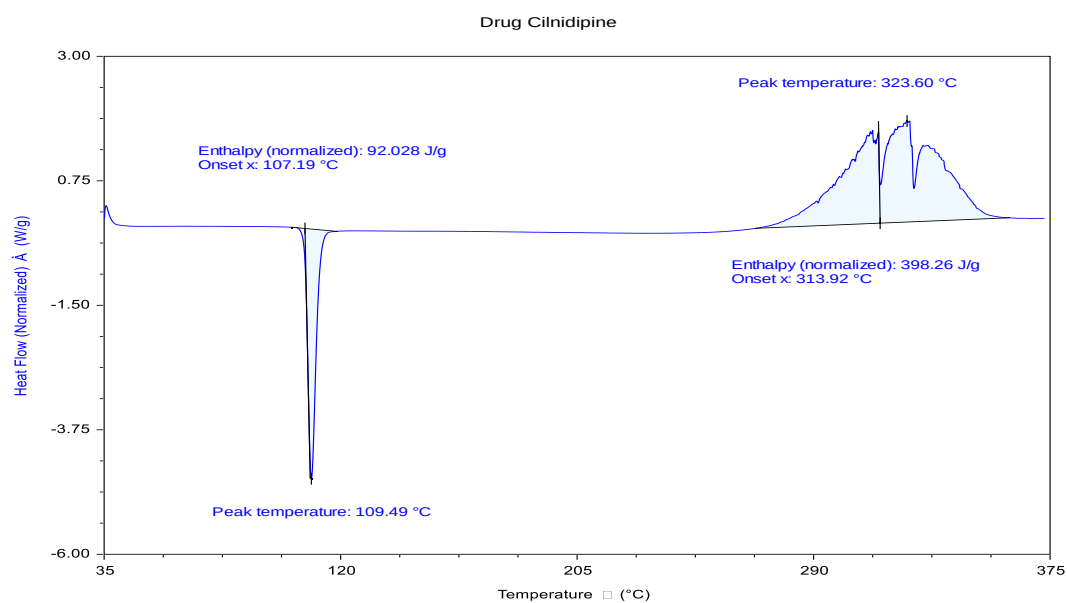


Figure 7: DSC of Drug cilnidipine

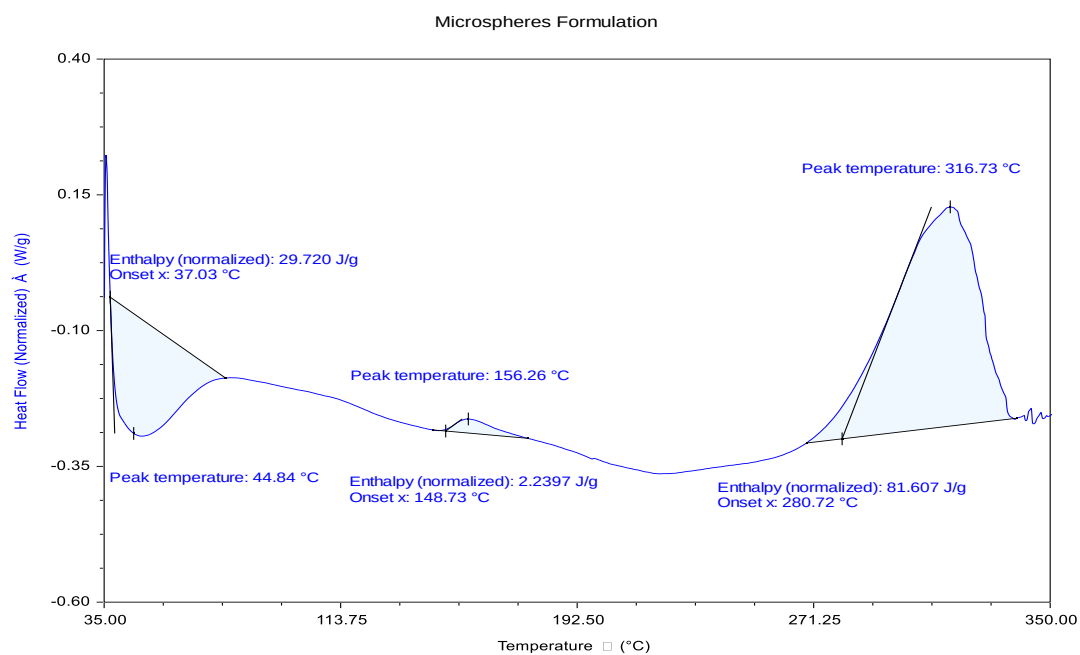
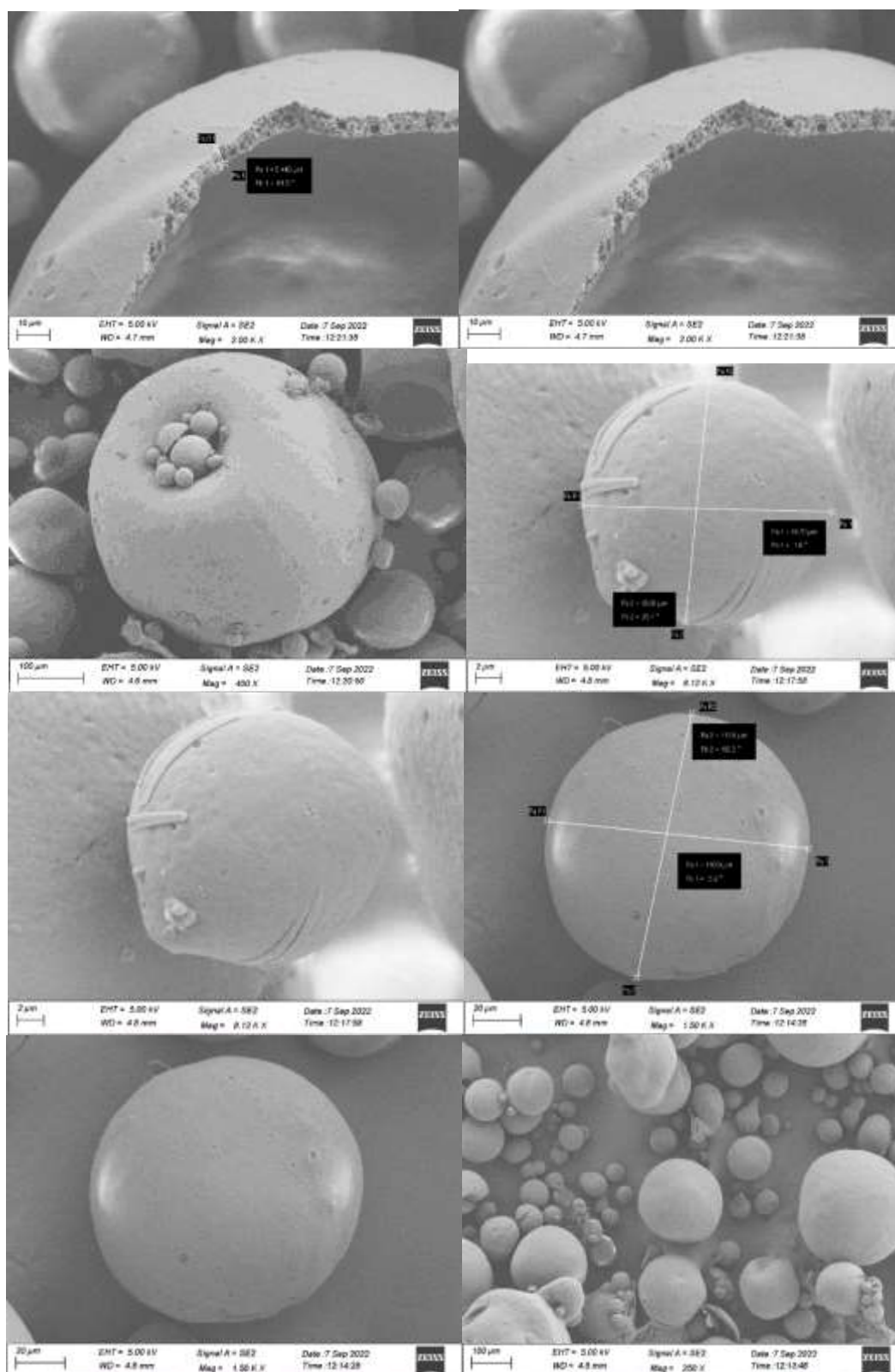


Figure 8: DSC of Microsphere formulation

FESM

Morphology of microspheres was examined by scanning electron microscopy. The view of the microspheres showed a hollow spherical structure with a smooth surface some of the microspheres showed a dented surface structure but they

showed good floating ability on the surface of the medium, indicating intact surface. The outer surface of the microspheres was smooth and dense, while the internal surface was porous. The shell of the microspheres also showed some porous structure (Figure 9).



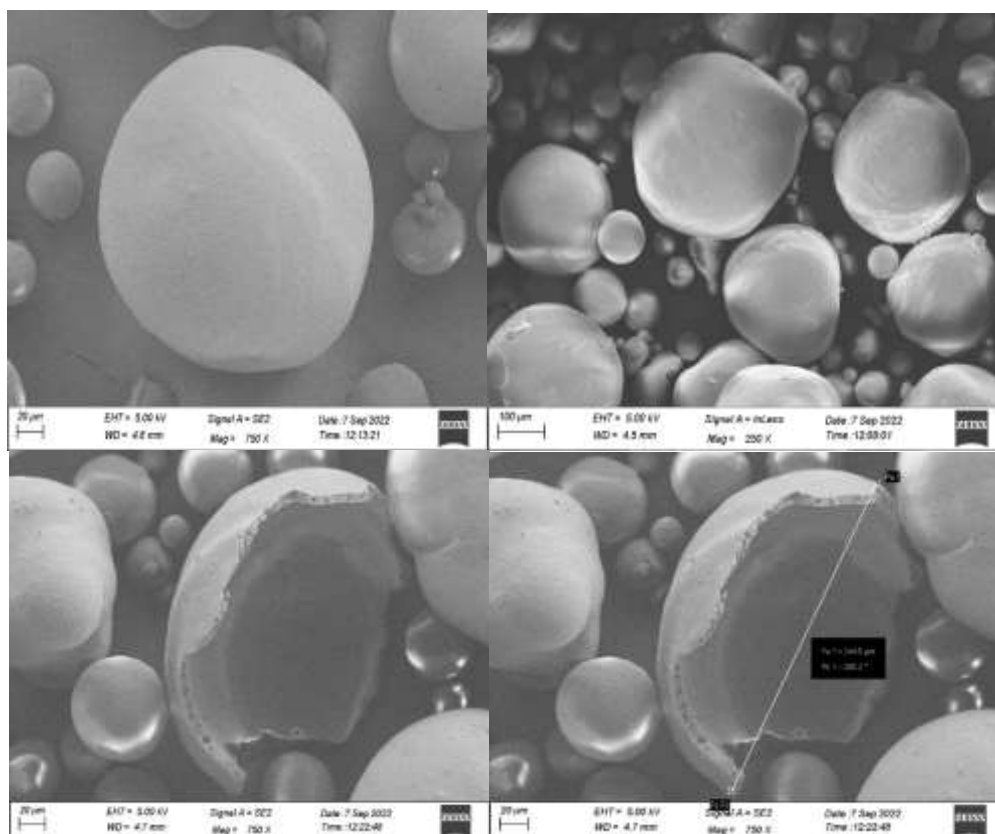


Figure 9: Field emission scanning microscopy

Characterization of floating microsphere

The method employed for preparation of floating microsphere was solvent diffusion-evaporation technique, for which the drug and polymer mixture should possess good flow properties.

Micromeritic properties

The angle of repose of all formulations was found to be in the range of 20.666 to 37.523. All formulation showed good angle of repose indicating satisfactory flow. The tapped density for all the formulations were found to be in the range of 0.192 to

0.278g/cm³ and the bulk density was found to be in the range of 0.238 to 0.279. The values obtained, were within the acceptable range and there was no significant difference found between the bulk density and tapped density values. The compressibility index (Carr's index) was found to be in the range of 11.03% to 20.16% and all formulation showed good carr's index. For all the formulation the Hausner's ratio was found to be in the range of 1.11 to 1.24. The above results for all the formulation are given in (Table2).

Table 2: Micromeritics properties of floating microsphere

Formulation Code	Bulk density	Tapped density	Hausner's ratio	Carr's index	Angle of repose
FM1	0.2411±0.006	0.2215±0.009	1.15±0.010	14.43±0.276	20.666±1.260
FM2	0.2714±0.005	0.2605±0.010	1.17±0.010	14.60±0.247	25.143±2.502
FM3	0.2561±0.011	0.2546±0.011	1.21±0.011	18.40±0.581	26.206±1.125
FM4	0.2391±0.010	0.2002±0.012	1.13±0.005	12.56±0.381	28.110±2.084
FM5	0.2381±0.007	0.1926±0.010	1.11±0.004	11.03±0.212	25.730±1.448
FM6	0.2588±0.010	0.2533±0.011	1.24±0.004	20.16±0.307	37.523±1.361
FM7	0.2781±0.009	0.2446±0.010	1.13±0.005	12.60±0.421	20.823±1.206
FM8	0.2761±0.007	0.2743±0.018	1.24±0.005	20.03±0.181	24.040±1.695
FM9	0.2795±0.011	0.2786±0.010	1.24±0.010	19.10±0.161	25.610±1.156

All values represented as mean ± standard deviation (n=3)

Particle size analysis

The mean particle size of the microsphere's formulation FM1 to FM9 containing HPMC & ethyl cellulose as in the range of 226.85 ± 1.42 to 339.42 ± 1.50 respectively. The effect of polymer concentration on the particle size of microspheres was determined. The mean particle size of the microspheres was found to increase with increasing ethyl cellulose concentration. The viscosity of the medium increases at a higher ethyl cellulose concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities which results in the formation of larger particles.

Drug content

The percentage yield of floating microsphere formulation FM1 to FM9 containing HPMC & ethyl-cellulose & formulation was in range of 68.49 ± 0.195 to $83.423 \pm 0.262\%$. To observe the effect of polymer concentration on the percentage yield of the floating microspheres, formulations were prepared at varying concentration of ethyl cellulose & HPMC K4M. The yield of the

floating microspheres increased with increasing polymer concentration. At low concentration of ethyl-cellulose part of the polymer solution aggregated in a fibrous structure, as it solidified prior to forming droplets or the transient droplets were broken before solidification was complete due to poor mechanical strength resulting into low yield.

In-vitro evaluation of floating ability

The purpose of preparing floating microspheres was to extend the gastric residence time of a drug. The buoyancy test was carried out to investigate the floatability of the prepared microspheres. The microspheres were spread over the surface of a simulated gastric fluid and the fraction of microspheres buoyant and settled down as a function of time was quantitated. The *in-vitro* buoyancy of formulation FM1 to FM9 containing HPMC & ethyl-cellulose & formulation was in range from 73.47 ± 0.164 to $86.60 \pm 0.227\%$ respectively. Among all formulation FM6 was found to be highest in-vitro buoyancy $86.60 \pm 0.227\%$. The results also showed a tendency that the larger the particle size, the longer floating time.



Figure 10: in-vitro buoyancy of floating microspheres of cilnidipine formulation

Table 3: Particle size, percentage yield, in-vitro buoyancy and Entrapment efficiency

Formulation code	Mean particle size	Drug content (%)	In-vitro buoyancy(%)	Entrapment efficiency(%)
FM1	273.55 ± 3.04	74.69 ± 0.322	81.45 ± 0.385	71.30 ± 0.121
FM2	312.31 ± 1.10	77.33 ± 0.359	83.57 ± 0.790	81.75 ± 0.302
FM3	339.42 ± 1.50	81.526 ± 0.337	84.68 ± 0.410	83.04 ± 0.102
FM4	243.75 ± 1.10	72.27 ± 0.155	82.44 ± 0.480	64.62 ± 0.374
FM5	285.23 ± 2.25	78.40 ± 0.503	84.61 ± 0.528	75.05 ± 0.295
FM6	327.11 ± 1.63	83.423 ± 0.262	86.60 ± 0.227	81.88 ± 0.252
FM7	226.85 ± 1.42	68.49 ± 0.195	73.47 ± 0.264	62.34 ± 0.298
FM8	268.23 ± 2.03	74.02 ± 0.848	75.14 ± 0.418	64.64 ± 0.045
FM9	312.64 ± 3.41	76.51 ± 0.339	83.28 ± 0.382	72.30 ± 0.600

All values represented as mean $\pm$ standard deviation (n=3)

Percentage of drug entrapment efficiency

The incorporation efficiency of formulation FM1 to FM9 containing HPMC & ethyl-cellulose & formulation was in the range of 62.34 ± 0.198 to 83.04 ± 0.102 respectively. Among all

formulation FM3 83.04 ± 0.102 . Results demonstrated that increase in concentration of ethyl-cellulose increased the entrapment of the drug. The drug entrapment efficiency was found to be good in all the formulation.

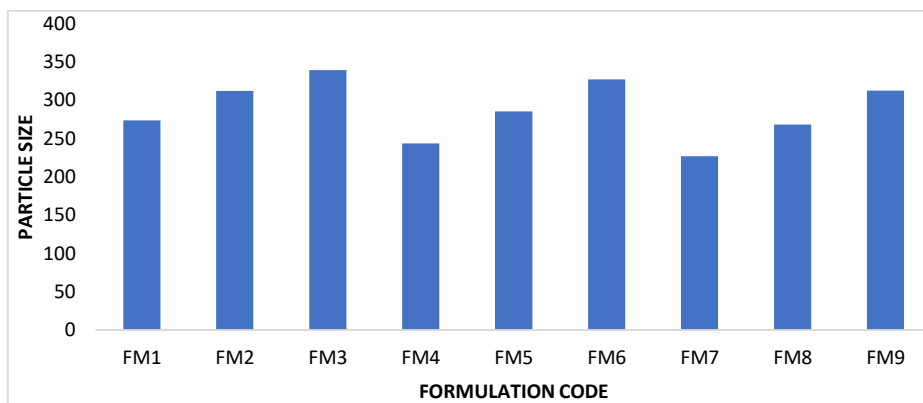


Figure 11: Comparison of average particle size of floating microsphere of cilnidipine

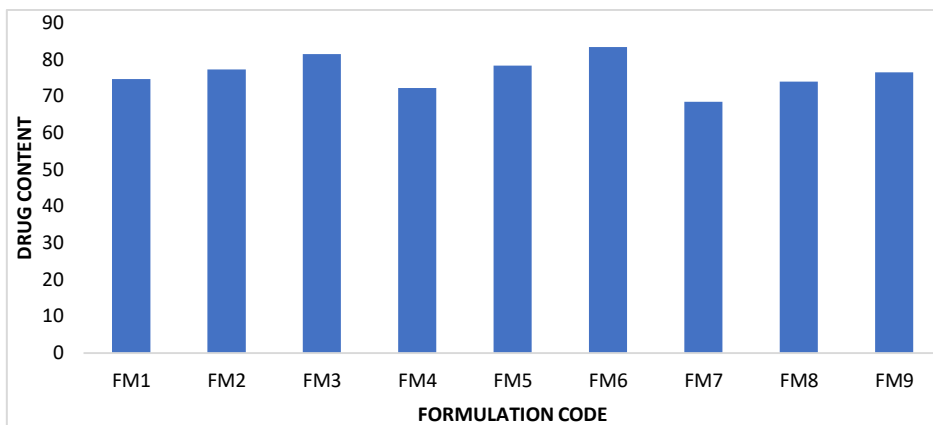


Figure 12: Comparison of drug content of floating microspheres of cilnidipine

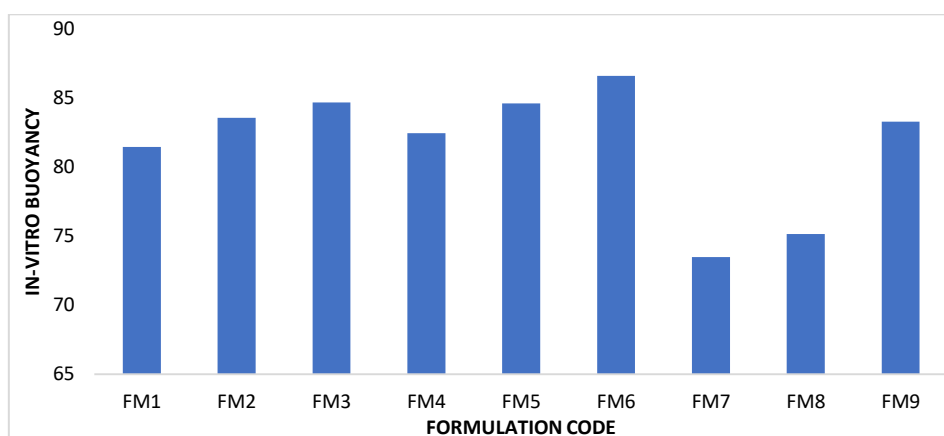


Figure 13: Comparison of percent *in-vitro* buoyancy of floating microspheres of cilnidipine

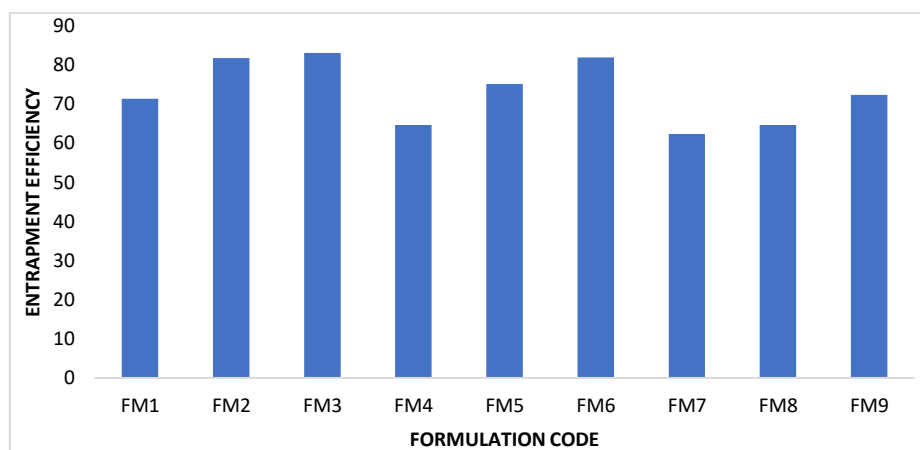


Figure 14: Comparison of entrapment efficiency of floating microsphere of Cilnidipine

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

In-vitro drug release studies of Cilnidipine floating microspheres were performed in pH 1.2 for 12 hrs in dissolution test apparatus. FM1- FM9 show percentage drug release 73.12 to 89.36% at end of 12 hour. Amongst the formulation FM7 was found to be the best formulation as it releases Cilnidipine 89.36% in a sustained manner with constant fashion over extended period of time (after 12 hrs).

It was observed as the concentration of ethyl-cellulose was increased percent release of cilnidipine decreases. The increase in ethyl-cellulose concentration leads to the increased density of polymer matrix into the microspheres which result in an increased diffusional path length. This may decrease the overall drug release from polymer matrix. Furthermore, smaller microspheres are formed at lower polymer concentration and have larger surface area exposed to dissolution medium. Graph is plotted between time in hours and percentage.

Table 4: *In-Vitro* Drug Release Profile

Time (hrs)	FM1	FM2	FM3	FM4	FM5	FM6	FM7	FM8	FM9
0	0	0	0	0	0	0	0	0	0
1	4.23	3.72	3.10	6.18	6.55	9.16	6.04	6.12	7.12
2	11.36	9.54	10.12	12.42	13.55	16.24	17.10	17.36	13.82
3	18.84	16.36	17.08	20.23	22.20	25.12	23.86	25.42	23.12
4	24.52	26.32	25.17	27.17	30.08	36.29	31.12	32.84	34.16
5	31.84	33.84	32.62	34.18	36.27	42.12	40.85	41.12	41.86
6	37.72	39.72	36.92	40.42	44.06	48.17	49.12	49.16	52.92
7	42.84	46.12	43.28	48.32	53.24	54.32	56.32	57.62	58.32
8	50.12	52.46	49.32	55.60	61.36	61.39	65.86	64.18	62.42
9	56.36	59.10	54.48	62.10	70.88	67.48	71.12	69.12	67.60
10	61.37	64.08	60.28	68.07	75.62	73.84	77.32	75.18	74.72
11	69.18	68.13	66.72	74.12	81.72	79.38	82.86	81.86	79.92
12	78.39	77.02	73.12	85.13	84.23	84.42	89.36	87.12	84.68

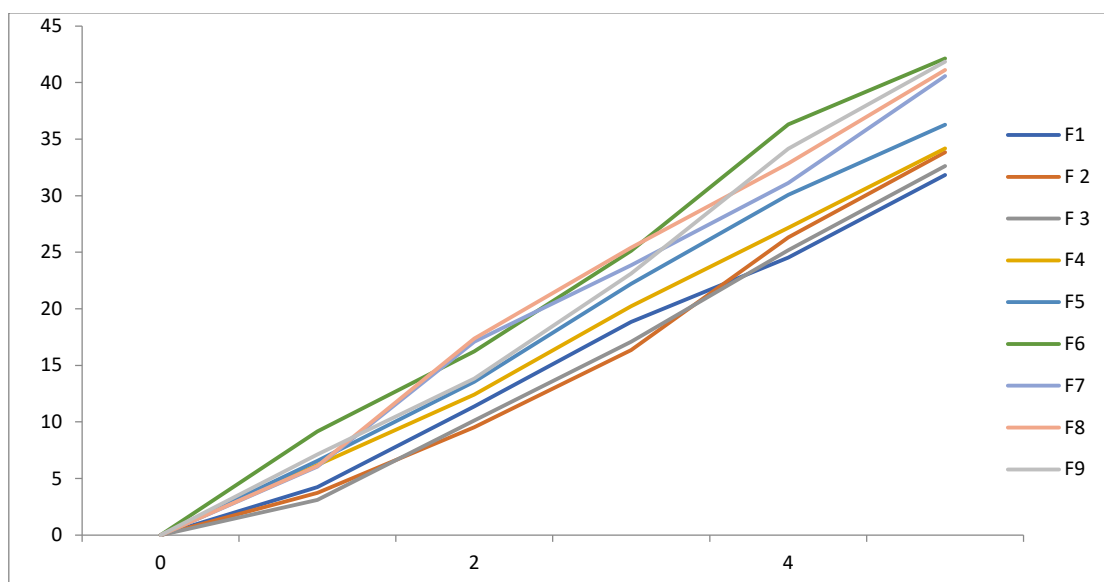


Figure 15: Cumulative % drug release of cilnidipine in different formulations

Kinetic modeling of selected batch FM6

Table No. 5 shows the R^2 and release constant for various kinetic models to release data of batch FM6. It can be seen that highest R^2 (0.994) has been obtained for first order making it

the best fit model for release kinetic and give evidence of sustained drug release of drug.

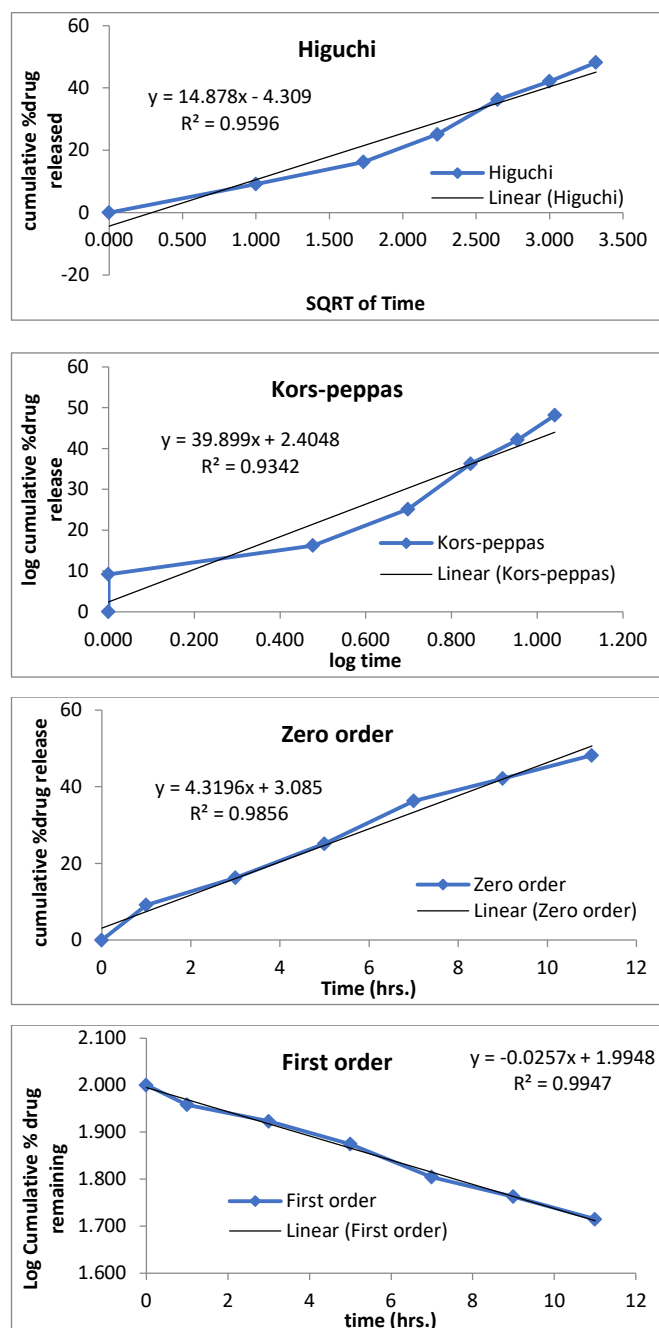


Figure 16: kinetic model of FM6

Table 5: kinetic model release data FM6

FM6	Zero order	First order	Higuchi	Kors-peppas
R ²	0.985	0.994	0.959	0.934

CONCLUSION

In this study, the floating microsphere of cilnidipine was prepared by the using solvent diffusion-evaporation technique. The floating microsphere of cilnidipine successfully prepared using HPMC K4M and ethyl cellulose as a polymer. The percentage yield of the floating microsphere was more than 70% proposing that the technique used for encapsulation was effective. The percentage yield was sensitively enhanced as the amount of polymer was increased in each preparation. The entrapment efficacy was worthy in all the cases. The *in-vitro* buoyancy was more than 70% shown the satisfactory result of projected formulations. The percent buoyancy

increased sensitively as the quantity of polymer was increased in each preparation. Between all formulation, the *In-vitro* release of formulation FM7 was institute to be the finest formulation as it releases cilnidipine 89.36% in a persistent routine over a prolonged period (after 12 hours). The mean particle size of microspheres was in the range 226.85 ± 1.42 to 339.42 ± 1.50 μm . The particle size enlarged as the amount of polymer increased. The micromeritics property of all prepared microspheres was decent. FM6 show good entrapment efficiency, drug content and cumulative drug release more than 80% so this formulation was institute finest formulation. Hence, finally, it was established that the prepared microspheres of cilnidipine may demonstrate to be an approaching aspirant for safe and effective persistent drug delivery over an extended period which can diminish the dosing rate.

REFERENCES

- Sixth Report of The Joint National Committee On Prevention. Detection, Evaluation, And Treatment Of High Blood Pressure. Archives of Internal Medicine, 1997; 157:2413-2446. <https://doi.org/10.1001/archinte.157.21.2413>
- Chien YW. Novel drug delivery systems. 2nd ed. Marcel Dekker, New York, Revised and expanded; 1982. p. 197-228.
- FmthCelvia Miranda, Krishnananda Kamath K. And A. R. Shabaraya Floating Microspheres: A Review World Journal of Pharmacy And Pharmaceutical Sciences 8(7):379-403.
- Bhalekar M, Avari J, Umalkar RA. Preparation and in vitro evaluation of sustained release drug delivery system for verapamil HCl. Ind J Pharm Sci. 2007; 69(1-3):418-22. <https://doi.org/10.4103/0250-474X.34553>
- Burn S.J, Attwood D, Barnwell S.G. Assessment of a dissolution vessel designed for use with floating and erodible dosage forms. Int. J. Pharmaceutics. 1998; 160:213-218. [https://doi.org/10.1016/S0378-5173\(97\)00312-8](https://doi.org/10.1016/S0378-5173(97)00312-8)
- Darandale As, GhulePj, Aher Aa, Narwate Bm. Sustained Release Dosage Form: A Concise Review. International Journal Of Pharmaceutics And Drug Analysis, 2017; 5:153-160.
- Arora S, Ali J, Ahuja A, Khar Rk, Baboota S. Floating Drug Delivery System. A Review. Aaps Pharm Sci Tech 2005; 6(3):372-390. <https://doi.org/10.1208/pt060347>
- Yoshimoto R, Dohmoto H, Yamada K, Goto. A Prolonged inhibition of vascular contraction and calcium influx by the novel 1,4-dihydropyridine calcium cilnidipine (FRC-8653). Jpn J Pharmacol. 1991 Jun; 56(2):225- 9. [https://doi.org/10.1016/S0021-5198\(19\)39885-3](https://doi.org/10.1016/S0021-5198(19)39885-3)
- Uneyama H, Uchida H, Konda T, Yoshimoto R, Akaike N: Selectivity of Dihydro pyridines for cardiac L- type and sympathetic N-type Ca²⁺ channels. Eur J 1999 May 28; 373(1):93-100. [https://doi.org/10.1016/S0014-2999\(99\)00237-X](https://doi.org/10.1016/S0014-2999(99)00237-X)
- Goyal P, Gill S, Gupta UD. Development and characterization of rifampicin loaded floating microspheres. Artif Cell Blood Substit Biotechnology. 2011; 39:330-4. <https://doi.org/10.3109/10731199.2011.573482>
- Ramachandran S, Shaheedha SM, Thirumurugan G, Dhanaraju MD. Floating controlled drug delivery system of famotidine loaded hollow microspheres (micro balloons) in the stomach. Current Drug Delivery. 2010; 7:93-7. <https://doi.org/10.2174/156720110790396436>
- Goyal P, Gill S, Gupta UD. Development and characterization of rifampicin loaded floating microspheres. Artif Cell Blood Substit Biotechnol. 2011; 39:330-4. <https://doi.org/10.3109/10731199.2011.573482>
- Ramachandran S, Shaheedha SM, Thirumurugan G, Dhanaraju MD. Floating controlled drug delivery system of famotidine loaded hollow microspheres (micro balloons) in the stomach. Curr Drug Deliv. 2010; 7:93-7. <https://doi.org/10.2174/156720110790396436>