ejpmr, 2023, 10(12), 372-382

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

DEVELOPMENT AND CHARACTERIZATION OF FELODIPINE HOLLOW MICROSPHERES

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Article Received on 11/10/2023 **Article Revised on 31/10/2023** **Article Accepted on 21/11/2023**

ABSTRACT

The objective of the present work was to formulate floating hollow microspheres of Felodipine which is soluble and shows better absorption in gastric pH. Microspheres were prepared by emulsion solvent diffusion technique. Using various such as ethylcellulose, carbopol 934, eudragit and sodium alginate polymers. The formulations were evaluated for micromeritic properties, buoyancy, % yield, entrapment efficiency and in vitro studies. They were characterized by FT-IR. FT-IR and studies indicated that there was no interaction between the drug and polymers. SEM photographs showed the outer surface of microspheres was smooth and dense whereas internal surface was porous which helped to prolong floating to increase residence time in stomach. The results showed that floating microspheres could be successfully prepared with better yield. Results showed larger the particle size, longer was the floating time. In vitro drug release studies showed controlled release of Felodipine for over 8 h. From the results it can be concluded that gastric floating hollow microspheres can be successfully used for the delivery of Felodipine to control the blood pressure.

KEYWORDS: Felodipine, Polymers, emulsion solvent diffusion technique, FTIR Studies, floating time, in vitro drug release studies.

INTRODUCTION

The constraints associated with conventional dosage forms and classical oral drug delivery systems is leading the pharmaceutical community towards a new era of drug delivery systems i.e., Novel Drug Delivery Systems (NDDS). The concept of targeted drug delivery, indeed, as a subset of NDDS is being investigated substantially nowadays. However, the concept of targeting is not new to the drug delivery domain. It dates back to 1906, when sir Paul Ehrlich, postulated the concept of 'magic bullet' and laid down the foundation of a new paradigm in the field of drug delivery.[1] Thenceforth, the concept has been evolving continuously, with newer and innovative approaches adding on to the existing knowledge.

Targeting refers to the selective accumulation of cargo in organs, tissues, cells or intracellular structures by systemic or local drug delivery.[2] The preferential accumulation of the drugs at the targeted site spares the rest of the healthy tissues of the body and increases the therapeutic index of the drug, thus improving the overall treatment outcome.[3] Targeting a drug delivery system, either passively or by specific means requires the use of carriers such as nanoparticles, liposomes, micellar systems, microspheres etc.[4]

The growing number of studies in the recent years, illustrating the potential use of microspheres as drug delivery carriers for targeted delivery has attracted the attention of researchers across the globe. Microspheres are free-flowing particles ranging between 1 µm and 1000µm and are capable of delivering the therapeutics with a satisfactory sustained release/controlled release profile.[5] They are matrix particles in which the actives are homogeneously distributed in the polymeric network. They are capable of encapsulating small molecules, proteins/peptides and nucleic acids.[6] The high translational efficiency and clinical success rate compared to nanoparticles give them an upper-hand over nanoparticulate drug delivery systems.[7] They provide several advantages over conventional dosage forms like enhanced solubility of poorly soluble drugs, protection of drugs from enzymatic and photolytic degradation, decreased dosing frequency, improved bioavailability, providing controlled release profile, reduction in dose and drug toxicities, etc.[8] They can be manufactured by various techniques including solvent evaporation[9,10], spray drying[11,12], phase separation[13] and polymerization.[14]

The currently marketed microsphere formulations are available as long-acting injectable depots which provide

controlled release of the encapsulated drug over a specific period of time. Most of these formulations contain hormonal analogues as the encapsulated drugs.[15] Apart from hormones, several other drugs acting on central nervous system and some opioid antagonists are also available as microsphere formulations for several applications.[16] Unfortunately, microspheres for targeted delivery of the drugs are not available in the market till date. However, a lot of research is currently in progress where these carriers are being explored for their applications in Targeted Drug Delivery System (TDDS). Indeed, several ongoing clinical trials on microspheres encapsulating anticancer drugs like doxorubicin (DOX) and irinotecan for colon cancer, rectal cancer and hepatocellular carcinoma are the proofs which showcase the potential of microspheres to be used in targeting drugs to desired locations.[17,18]

Microspheres can be targeted to the desired location by active or passive targeting strategies. Passive targeting is based upon the size and general surface properties of the microspheres such as degree of hydrophobicity, surface charge, and non-specific adhesion, which directs them towards the particular organ. Additionally, the approach confers special properties to the carriers which aid them to cross physiological barriers like the specialized epithelia and Blood Brain Barrier (BBB).[19] On the other hand, active targeting is mostly associated with ligand-receptor recognition, referred to as secondary active targeting. Apart from this, targeting to cell organelles i.e. tertiary targeting, and to different organs of the body i.e. primary targeting is also accomplished by microspheres.[20,21] Indeed, microspheres can be tailored to target a specific site by a combination of more than one targeting approaches to.[22] The choice of the targeting approach depends upon the intended area of human body, since each human body part has a different physiology. Size based targeting is mainly a cornerstone approach for lung targeting and liver targeting, as the drug cargo has to reach and get retained in the smallest capillary network of the lungs and in the arteries surrounding the tumours in the liver.[23,24] Surface modifications either by linking the microspheres with targeting moieties or by coating them with materials with special properties like acid resistant or mucoadhesive polymers can be used for targeting almost all the organs including lungs, brain, colon, eyes, tumours, etc.[19,25], [26], [27], [28] Apart from the normally explored targeting strategies, very specific approach lies in bone targeting, where inorganic materials are used to deliver the drugs to the bony tissues.[29]

The aim of present study was to develop a hollow microsphere of Felodipine in order to achieve an extended retention in upper GIT, which may result in enhanced absorption and there by improves bioavailability.

Oral controlled release dosage forms encounter several physiological constraints like inability to retain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variation in gastric emptying. This leads to non - uniform absorption profile, insufficient drug release and shorter residence time of the dosage form in the stomach. As the fallout of this event, there is incomplete absorption of the drug having absorption window especially, in the upper part of GIT. These considerations have led to the development of oral controlled release dosage forms with gastroretentive properties. Hollow microspheres hold promise as one of the potential approaches for gastric retention. Hollow microspheres are spherical empty particles without core and can remain in the gastric region for prolonged periods. They significantly extend the gastric residence time of drugs, thereby improving bioavailability, reduced the drug waste and improved solubility for drugs that are less soluble at a higher pH environment. This review attempts to bring more insight into recent advances in methods of fabrication techniques and applications of hollow microspheres.

Drugs that have narrow absorption window in upper part of GI tract i.e. stomach and small intestine, which is due to short transit time of dosage form. Formulation of these drug leave upper part of GI tract and reaches to non-absorbing distal regiment, resulting lesser bioavailability. Floating drug delivery systems are prolong the drug release rate from formulation in stomach and upper part of small intestine until all the drug is released for the desired period of time.

METHODOLOGY

Active pharmaceutical ingredient characterization

Physical properties

The color odour, taste of the drug were recorded using descriptive terminology.

Solubility studies

Solubility study of Felodipine was performed in dimethyl sulphoxide, methanol, ethanol, chloroform and insoluble in water.

Determination of melting point

Melting point of Felodipine was determined by capillary method.

Analytical Method Development For Felodipine

Before preparation of sustained release microspheres of Felodipine, standard curve of Felodipine sodium in different media was obtained to quantify the samples. All solutions were freshly prepared before use.

Preparation of Phosphate Buffer pH 1.2

8.5ml of HCL dissolved in 1000ml of water.

Preparation of standard solution of Felodipine

Stock solution – I

Accurately weighed 10 mg of Felodipine was placed in a 100 ml volumetric flask. The volume was made up to 10 ml using water to give 1000 mcg/ml solution.

Stock solution -II

From stock solution I 1ml aliquote was taken and placed in a 10 ml volumetric flask and diluted with water to 10ml to get 100mcg/ml.

Stock solution-III

From *stock solution -II*, a 1ml of aliquote was made up to 10ml to get 10mcg/ml.

Preparation of standard curve for Felodipine

Standard curves for Felodipine were obtained in 1.2 pH buffers. Aliquotes of 2,4,6,8 and 10ml of Felodipine standard solution of 100mcg/ml (*stock solution-II*) was taken and diluted to obtain concentrations from 10 mcg/ml with appropriate media. The absorbances of solutions were determined at 239 nm against respective media as blank.

Drug excipient compatibility studies

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in high density polyethylene bags and low density poly ethylene bags. Glass vials were exposed to 60^0C and 40^0C/75 % relative humidity for 4 weeks and low density polyethylene bags were exposed to 40^0C±75 % relative humidity for 4 weeks. Samples were observed periodically for any physical change.

Preparation and evaluation of Felodipine hollow microspheres

Formulation table.

Table 1: Formulation development of Felodipine hollow microspheres.

F. no	Polymer	Drug and polymer ratio	Stirring speed
F1	Eudragit	1:1	1000
F2	Eudragit	1:2	1000
F3	Ethycellulose	1:1	1000
F4	Ethycellulose	1:2	1000
F5	Carbopol 934	1:1	1000
F6	Carbopol 934	1:2	1000
F7	Sodium alginate	1:1	1000
F8	Sodium alginate	1:2	1000

METHOD

Emulsion-solvent-evaporation technique with some modifications was used to prepare Eudragit, carbopol 934, ethyl cellulose and sodium alginate microspheres containing Felodipine. Briefly Felodipine was dissolved in 5 ml distilled water. Polymers was dissolved in Dichloromethane at various drug - polymer ratios (1:1, 1:2 and 1:3). Then these drug and polymer solutions were mixed and emulsified using a Remi Lab Magnetic stirrer at 500 rpm for about 10 min to form stable w/o emulsion. This stable w/o emulsion was slowly added to 200 ml aqueous solution containing 1 % PVA and stirred at 1000 rpm by a mechanical stirrer equipped with a three bladed propeller (Remi motors, India) at room temperature for 2 h to allow the solvent to evaporate completely. Microspheres were isolated by filtration and washed with distilled water several time to remove PVA. The produced microspheres were dried at ambient temperature for 24 h and dried in vacuum chamber at 25 ^{0}C for 2 h to remove any residual solvent.

Evaluation of of hollow microspheres

Particle size analysis

Particle size analysis plays an important role in determining the release characteristics and floating property. The sizes of hollow microspheres were measured by using a set of standard sieves ranging from 14, 16, 18, 22, 30 and pan. The sieves were arranged in increasing order from top to bottom. The hollow microspheres were passed through the set of sieves and amount retained on each sieve was weighed and calculate the % weight of hollow microspheres retained by each sieve. Mean particle size for all formulation was determined by dividing the total weight size of formulation to % total weight of hollow microspheres.

Floating Property of Hollow microsphere

100 mg of the hollow microsphere were placed in 0.1 N HCI (300 ml) containing 0.02% Tween 20. The mixture was stirred with paddle at 100rpm. The layer of buoyant microballoons was pipetted and separated by filtration at 1, 2, 4 and 6 hours. The collected microballoons were dried in a desiccator over night.

The percentage of microballoons was calculated by the following equation.

$$\% \text{ hollow microsphere} = \frac{\text{Weight of hollow microsphere}}{\text{Initial weight of hollow microsphere}} \times 100$$

Drug Entrapment

The various formulations of the hollow microspheres were subjected for drug content. 50 mg of hollow microspheres from all batches were accurately weighed and crushed. The powdered of microspheres were dissolved with 10ml ethanol in 100ml volumetric flask and makeup the volume with 0.1 N HCl. This resulting solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 10 ml was taken out and diluted up to 100 ml with 0.1 N HCl. Again from this solution 2 ml was taken out and diluted

up to 10 m1 with 0.1 N HCI and the absorbance was measured at 239 nm against 0.1 N HCI as a blank.

The percentage drug entrapment was calculated as follows.

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Percentage Yield

The percentage yield of different formulations was determined by weighing the hollow microspheres after drying. The percentage yield was calculated as follows.

$$\% \text{ Yield} = \frac{\text{Total weight of hollow microspheres}}{\text{Total weight of drug and polymer}} \times 100$$

Shape and Surface Characterization by Scanning Electron Microscopy

From the formulated batches of hollow microspheres, formulation which showed an appropriate balance between the buoyancy and the percentage release were examined for surface morphology and shape using scanning electron microscope Hitachi, Japan. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 20KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

In vitro drug release study

In vitro drug release studies were carried out for all formulations in Franz diffusion cell. Microspheres equivalent to 10 mg of Felodipine were poured into 1 ml aliquots were withdrawn at a predetermined intervals and equal volume of dissolution medium was replaced to maintain sink conditions. The necessary dilutions were made with 1.2 pH buffer and the solution was analysed for the drug content spectrophotometrically using UV-Visible spectrophotometer.

Kinetic Modeling of Drug Release Profiles

The rate and mechanism of release of Paliperidone from the prepared sustained release tablets were analyzed by fitting the dissolution data into the zero-order equation,

$Q = k_0 t$

Where Q is the amount of drug released at time t, and k_0 is the zero order release rate constant.

The dissolution data was fitted to the first order equation:

$\ln (100–Q) = \ln 100 – k1t$

Where k1 is the first order release rate constant.

The dissolution data was fitted to the Higuchi's equation.

$Q = k2t1/2$

Where k2 is the diffusion rate constant.

The dissolution data was also fitted to the well known equation (Korsmeyer equation), which is often used to describe the drug release behaviour from polymeric systems

$Mt/ M = k3tn$ (5.13) $\log (Mt/ M\infty) = \log k3 + n \log t$

Where Mt is the amount of drug released at time t, $M\infty$ is the amount of drug release after infinite time, k is a release rate constant incorporating structural and geometric characteristics of the tablet and n is the diffusional exponent indicative of the mechanism of drug release. For a matrix tablet, when 'n' takes the value of (In case of cylindrical shape), 0.45 - Fickian diffusion-controlled drug release.

Stability Study

From the prepared hollow microspheres which showed appropriate balance between the buoyancy and the percentage release was selected for stability studies. The prepared formulation were placed in borosilicate screw capped glass containers and stored at room temperature (27 ± 2° C), oven temperature (42±2° C) and in refrigerator (5-8° C) for a period of 30 days. The samples were assayed for drug content at regular intervals of two week.

RESULT AND DISCUSSION

In the present study 8 formulations with variable concentration of polymer were prepared and evaluated for physic-chemical parameters, in vitro drug release studies and stability studies.

Preformulation studies

a) Organoleptic evaluation

Table-7: Organoleptic properties of Felodipine.

Properties	Results
Description	Powder
Taste	tasteless
Odour	Odourless
Colour	Colour White to off white

b) Determination of melting point

Melting point of Felodipine was found in the range of 142-145^{0}c, which complied with the standard, indicating purity of the drug sample.

c) Solubility

Soluble in water, Sparingly soluble in ethanol, acetone, slightly soluble in ethyl acetate.

Preparation of standard curve of Felodipine

Standard curve of Felodipine was determined by plotting absorbance V/s concentration at 239 nm. Using solution prepared in pH 1.2 at 239 nm. And it follows the Beer's law. The R^2 value is 0.997.

Determination of absorption maxima (λ_{max}) for Felodipine

A 10mcg/ml standard solution of Felodipine was scanned on a double beam spectrophotometer against respective media blanks. An absorption maximum (λ_{max}) of 239 nm was obtained for all solutions and was selected to prepare standard curve.

Table 2: Calibration curve of Felodipine.

S. no	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.136
3	4	0.241
4	6	0.330
5	8	0.426
6	10	0.531

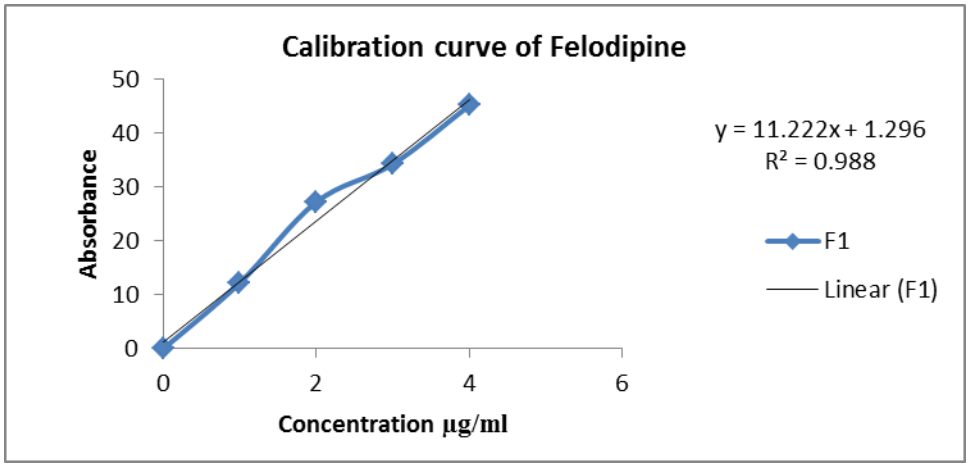

Fig-1: Calibration curve of Felodipine.

FT-IR Spectrum of Felodipine

FT-IR Spectra of Felodipine and F2 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Felodipine and polymer. It also confirmed that the stability of drug during microencapsulation process.

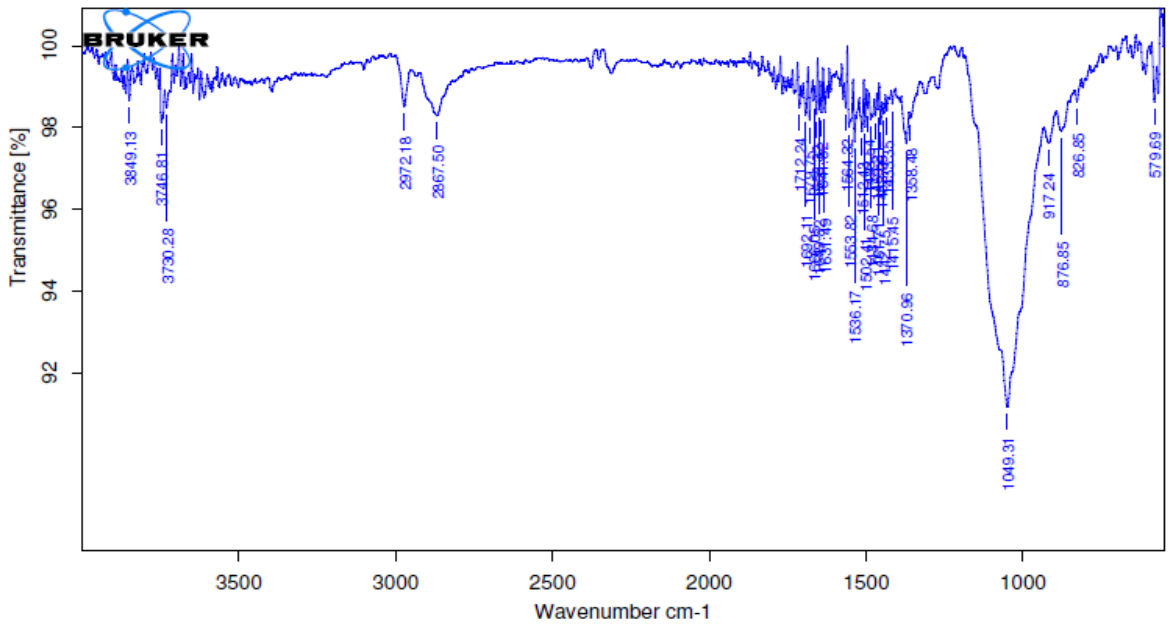

Fig-2: FTIR Studies of Felodipine.

Table-3: Characteristic Peaks for Felodipine.

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	3500-3000	2972.18
2	OH Bending	1000-1500	1049.31
3	C-H stretching	3000-2500	2867.50
4	C=O stretching	2000-1500	1692.11

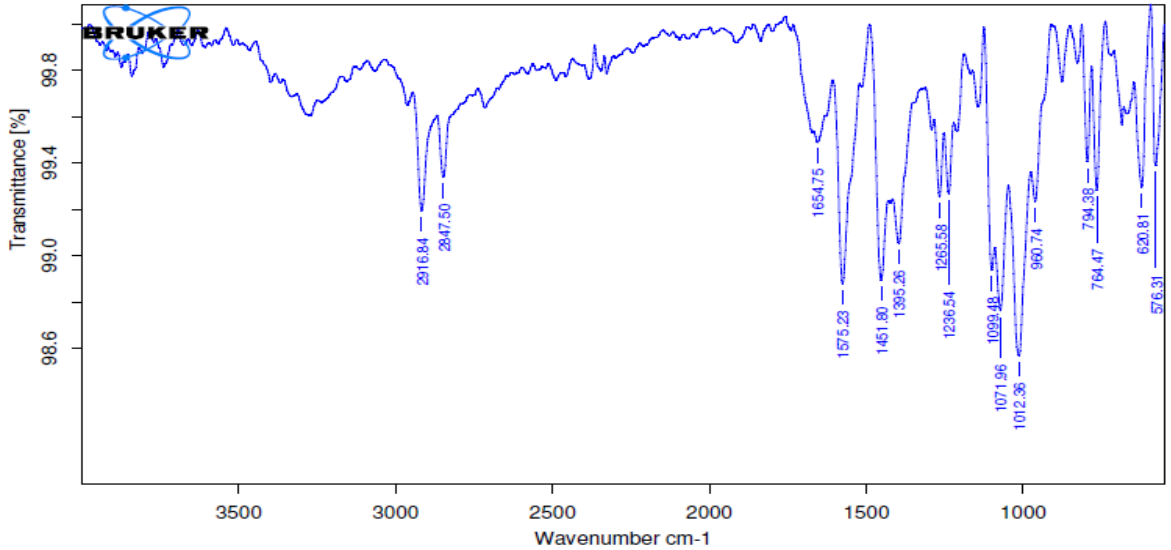

Fig-3: FTIR Studies of physical mixture.

Table-4: Characteristic Peaks for physical mixture.

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	3000-2500	2916.84
2	OH Bending	1100-1070	1071.96
3	C=O stretching	2000-1500	1575.23

Evaluations of hollow microspheres

Particle size analysis

Particle size was determined by sieving method it plays important role in floating ability and release corrected of drug from hollow microspheres. If size of hollow microspheres less than 500 mm so release rate of drug will be high and floating ability will reduce, while microballoons range between 500µm - 1000µm, floating ability will be more and release rate will be in sustained manner. The mean particle size of hollow microsphere was in range 788-832µm.

Table-5: Particle size of Different Batches of Hollow microsphere.

S. No	Formulation code	Mean particle size (µm)
1	F1	788
2	F2	810
3	F3	822
4	F4	798
5	F5	825
6	F6	793
7	F7	832
8	F8	828

Floating Property of hollow microsphere

Floating ability of different formulation were found to be differed according to polymer ratio.

Table-6: Floating property of Hollow microsphere.

S. No	Formulation code	% of floating
1	F1	81.56
2	F2	85.92
3	F3	80.81
4	F4	83.96
5	F5	90.55
6	F6	83.15
7	F7	89.36
8	F8	85.93

Drug Entrapment efficiency

The drug entrapment efficiency of different formulations were in range of 88.21 – 95.93%. Drug entrapment efficacy increases with increases eudragit content in microballoons. This is due to the permeation characteristics of eudragit, that could facilitate the diffusion of part of entrapped drug to surrounding medium during preparation of hollow microspheres.

Table-7: Drug entrapment for different formulation.

Formulation	Drug Entrapment
F1	87.89
F2	93.25
F3	90.74
F4	88.21
F5	95.93
F6	91.36
F7	92.28
F8	95.23

Table 8: Percentage yield for different formulation.

Formulation	Percent Yield(%)
F1	80.12
F2	79.35
F3	82.16
F4	83.55
F5	85.10
F6	80.22
F7	79.31
F8	81.15

Percentage Yield

Percentage yield of different formulation was determined by weighing the hollow microspheres after drying. The percentage yield of different formulation were in range of 79.60 – 85.10% as shown in Table.

Scanning Electronic Microscopy

Shape and surface characteristic of hollow microspheres examine by Scanning Electronic Microscopy analysis as shown in Fig. Surface morphology of F5 formulation examine at different magnification 40X and 200X, which illustrate the smooth surface of floating microballoons and small hollow cavity present in microsphere which is responsible for floating property.

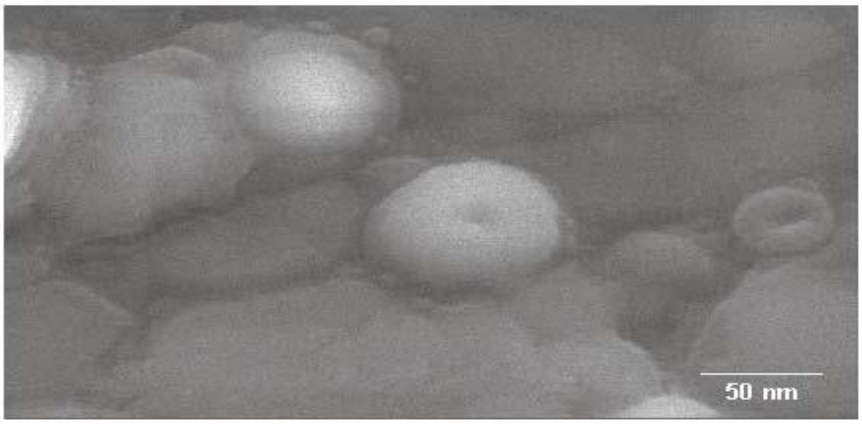

Fig-4: Micro Photographs Of Formulation F5.

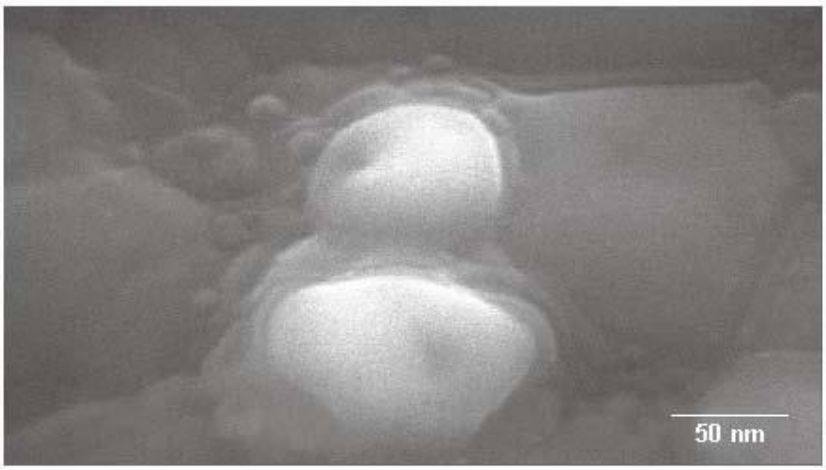

Fig-5: Cross Section.

***IN-VITRO* Drug release study**

In-vitro drug release study of hollow microspheres was evaluated in phosphate buffer pH 1.2. Eudragit RS100 which is present in all formulation, have low permeability in acid medium. F5 formulation showed best appropriate balance between buoyancy and drug release rate.

Table-9: *In-Vitro* Drug Release Profile for Formulation in pH 1.2.

TIME (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	13.20	14.85	15.89	17.18	17.93	16.32	13.85	15.90
2	20.16	25.81	24.21	25.75	28.85	25.94	24.62	23.57
3	31.02	32.18	35.15	34.84	37.78	32.86	33.56	30.41
4	42.18	45.21	48.93	45.55	48.12	45.21	44.12	43.86
5	51.35	53.93	54.28	52.18	55.22	54.55	50.21	51.21
6	71.20	72.85	62.18	61.84	69.18	65.32	63.85	60.98
7	75.16	81.24	78.75	83.64	84.32	79.11	82.22	78.85
8	85.91	90.25	91.23	93.86	95.85	93.23	91.84	92.12

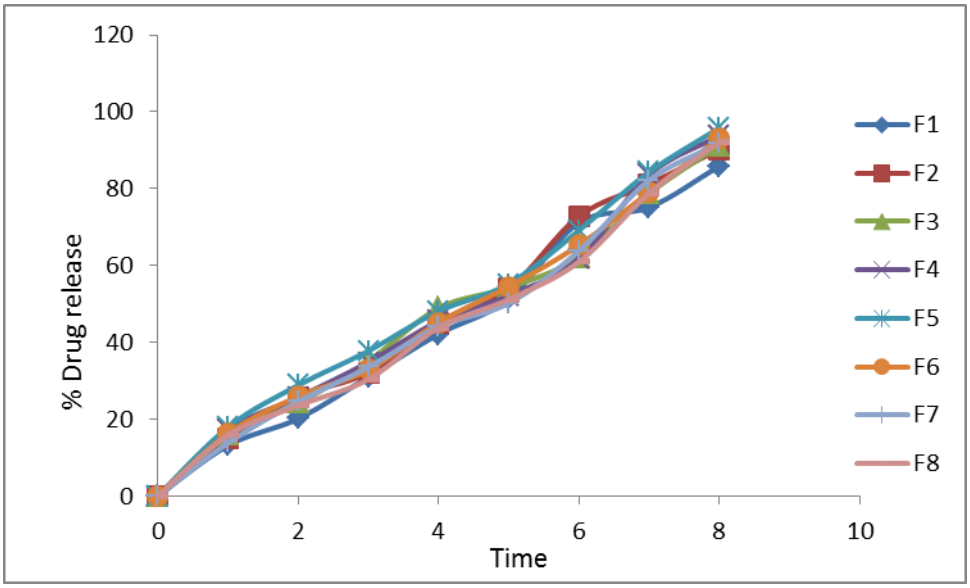

Fig-6: In-Vitro Drug Release Profile Of all formulations.

Drug release kinetics

The kinetic of drug release for formulation F5 was calculated and plotted. The formulation F5 follows first order release kinetics and the drug release mechanism was found to be non-Fickan anomalous diffusion.

In-vitro Dissolution Study and Kinetic modeling of drug release

The results obtaining in vitro release studies were plotted in different model.

1. Zero order rate kinetics
2. First Order rate Kinetics
3. Higuchi's models
4. Krosmayer peppas

Table-10: Drug Release Kinetics of Formulation F5.

TIME	%CDR	SQARE T	LOG T	LOG%CDR	ARA	LOG%ARA
0	0	0	0	0	0	0
1	17.93	1	0	1.25358029	82.07	1.91418443
2	28.85	1.41421356	0.30103	1.46014582	71.15	1.8521749
3	37.78	1.73205081	0.47712125	1.57726195	62.22	1.79393001
4	48.12	2	0.60205999	1.68232562	51.88	1.71499997
5	55.22	2.23606798	0.69897	1.7420964	44.78	1.65108409
6	69.18	2.44948974	0.77815125	1.83998056	30.87	1.48953663
7	84.32	2.64575131	0.84509804	1.9259306	15.68	1.19534606
8	95.85	2.82842712	0.90308999	1.98159212	4.15	0.6180481

Zero order kinetics

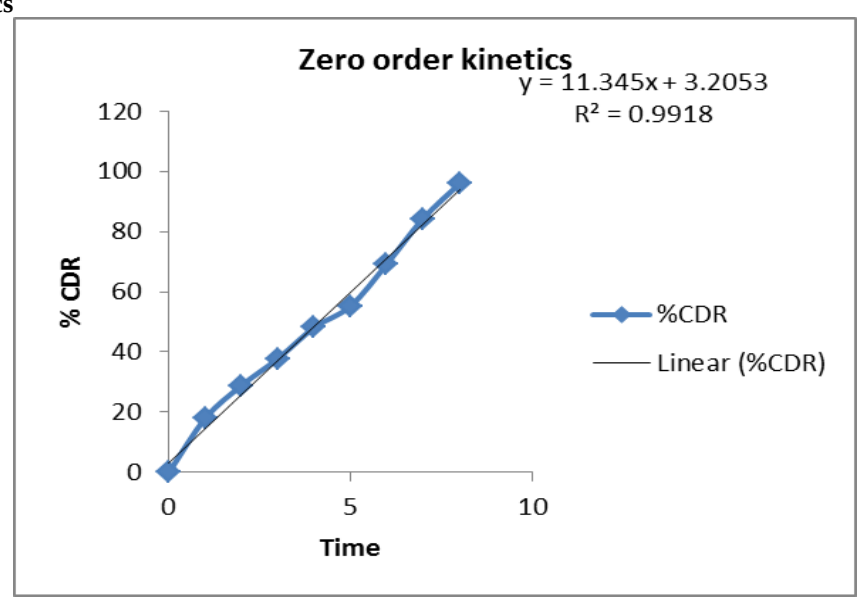

Fig-7: Zero order kinetics.

First order kinetics

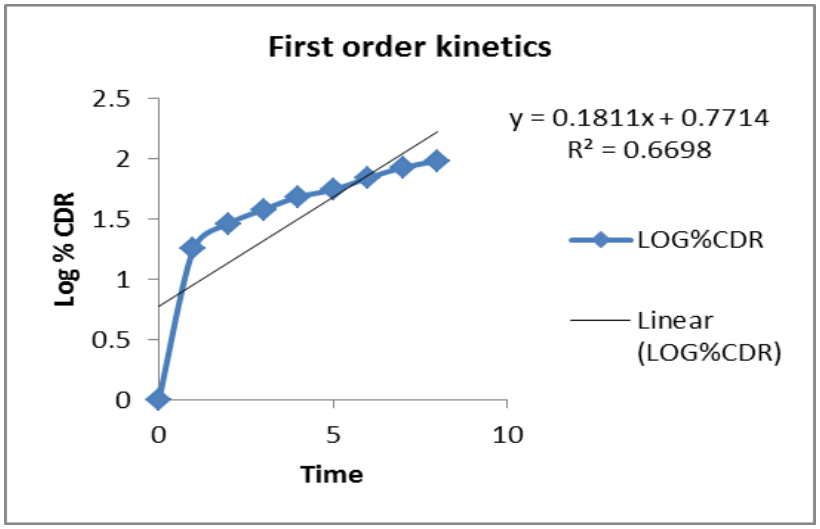

Fig-8: First order kinetics.

Higuchi model

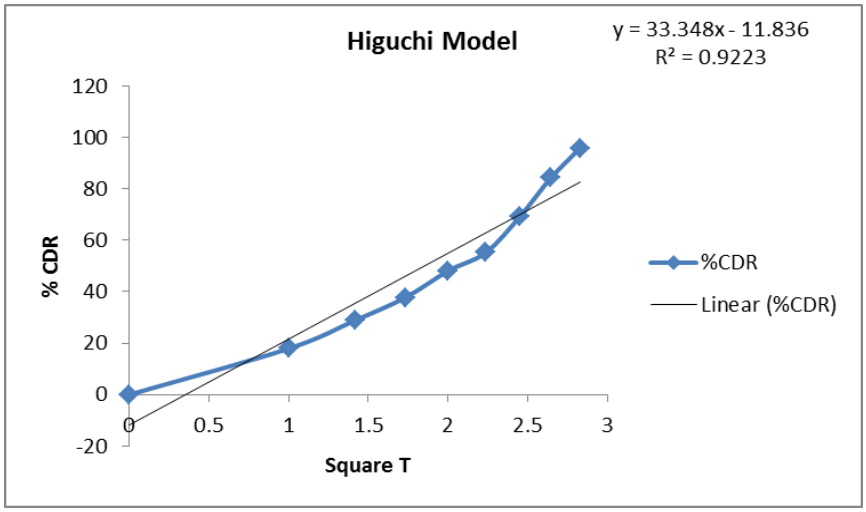

Fig-9: Higuchi model.

korsmeyer peppas

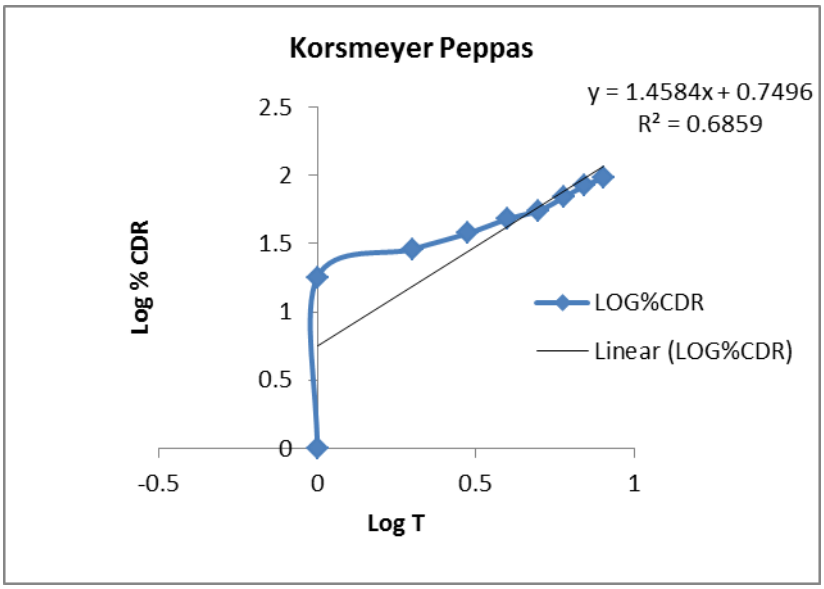

Fig-10: korsmeyer peppas.

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix, Peppas were respectively.

Stability Study

Stability study was carried out for the F5 formulation by exposing it to different temperature for 3 months. The sample was analyzed for drug content at the regular intervals. It was found that no remarkable change in the drug content of F5 formulation. This indicates that F5 was stable for following temperature.

Table-11: Results of stability studies of optimized formulation F-5.

S.NO	Time in days	Physical changes	% drug release		
			Felodipine		
			25^0C/60%	30^0C/75%	40^0C/75%
1.	01	No Change	95.85	95.85	95.85
2.	30	No Change	95.82	95.78	95.42
3	60	No Change	94.86	94.52	94.48
4	90	No Change	93.99	93.86	93.90

SUMMARY

The present study hollow microsphere of Felodipine was prepared by emulsion solvent diffusion technique by using various polymers. Mean particle size range for all formulation was varied from 788-832 µm, due to change in drug and polymer ratio. Drug entrapment of all formulation were found in range of 87.89-95.93% and its efficiency slightly decrease with increasing the Eudragit content. Shape of the hollow microsphere was found to be spherical by SEM study, small cavity was present on surface. It is responsible for floating property.

Drug release pattern was evaluated in pH 1.2. Release rate of F1-F8 formulations were found to be slow and incomplete in dissolution medium. In order to increase the release rate of drug the ratio of Eudragit increased respectively. Ideal property of hollow microsphere includes high buoyancy and sufficient release of drug in pH 1.2. It is necessary to select an appropriate balance between buoyancy and drug release rate from all developing hollow microsphere. F5 formulation showed best appropriate balance between buoyancy and drug release rate, it considered as a best fit for drug release.

CONCLUSION

Hollow microspheres of Felodipine were prepared by emulsion solvent diffusion technique and performances of this formulation were evaluated. It increases the bioavailability of dosage form with prolong effect hence improves the patients' compliances. Mean particle size for all formulations were varied, due to change in drug and polymer ratio. Drug entrapment efficiency slightly decreases with increasing the polymer content.

The design system F5 might be able to float in the stomach. This phenomenon could prolong the gastric residence time (GRT) consequently, it provides sustained action. In addition, hollow microspheres enabled increased drug absorption rate, as it gradually sank in the stomach and arrived at the absorption site. The developed formulation overcomes the drawbacks and limitations of sustained release preparations. Therefore,

multiple unit floating system, i.e., hollow microsphere will be possibly beneficial with subject to sustain action.

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