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FORMULATION AND EVALUATION OF FELODIPINE HOLLOW MICROSPHERES

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ABSTRACT
Felodipine is a calcium channel blocker which is used for the treatment of high blood pressure to prevent heart stroke. In the current research work hollow microspheres of Felodipine with better absorption in gastric pH was formulated by using various polymers. Drug polymer compatibility was characterized by FT-IR. Microspheres were prepared by emulsion solvent diffusion technique by using different polymers such as ethyl cellulose, carbopol 934, eudragit and sodium alginate at varying concentrations. The formulations were evaluated for micromeritic properties, buoyancy, percentage yield, entrapment efficiency, *in vitro* studies and stability stuides. SEM photographs showed outer surface of microspheres was smooth and dense where as internal surface was porous which helped to prolong floating. Optimized F2 formulation exhibited higher release rate 95.55%. *In vitro* drug release studies showed controlled release of Felodipine for over 8h. Stability studies indicated the F2 formulation was stable with respect to its drug release.

KEYWORDS: Felodipine hollow microspheres, polymers, emulsion solvent diffusion technique, FTIR Studies, floating time, *in vitro* drug release studies.

INTRODUCTION
Oral drug delivery has been known for decades as the most widely used route of administration among all the routes. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief. Pharmaceutical product designed for oral delivery which are currently available in the market mostly immediate-release or conventional release, which maintains the drug concentration within the therapeutically effective range only, when administered several times a day. This results in a significant fluctuation in the drug level.[1,2] An effective drug therapy not only depends on the inherent therapeutic activity of the drug molecule but also the efficiency of its delivery at the site of action. Drug absorption at the desired rate means, first, to reach the effective plasma level within an acceptable short time period; second, to avoid an overshoot in the case of rapidly absorbed drugs and third, to maintain effective plasma levels over the desired time period. To develop a drug delivery system for oral administration, it is necessary to optimize not only the release rate of an active ingredient from the system but also the residence time of the system in the gastrointestinal tract.[3] One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), by using gastro-retentive dosage forms (GRDFs).[4,5] Floating systems were first described by Davis in 1968. FDDS is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. FDDS are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. Floating systems can be classified as follows. The various buoyant preparation include hollow microsphere (micro balloons), granules powder, capsule, tablet (pills) laminated films. Hollow microspheres float immediately upon contact with gastric fluid and gives promising approaches for increasing the bioavailability of drugs with absorption windows in upper small intestine and stomach. However, immediate floating can only be achieved, when the density of the device is lower than gastric fluid 1.004 gm/cm^3.[6,7] Hollow microspheres of non-steroidal anti-inflammatory drugs are very effective for controlled release, and reduce the major side effect of gastric irritation. For example, floating microspheres of indomethacin are quite beneficial for rheumatic patients.[8,9] Hollow microspheres can greatly improve the pharmacotherapy of the stomach through local drug release, leading to

high drug concentrations at the gastric mucosa, thus eradicating *Helicobacter pylori* from the sub-mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis.[10,11,12]

MATERIALS AND METHODS

Materials

Felodipine, Eudragit, Carbopol 934, Ethyl cellulose, Sodium alginate, Methanol and Dichloromethane were procured from A. R. Chemicals, Hyderabad, India.

Methods

Active pharmaceutical ingredient characterization

Physical properties

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

Solubility studies

Solubility study of Felodipine was performed in dimethyl sulphoxide, methanol, ethanol, chloroform and 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 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 aliquot 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 aliquot was made up to 10ml to get 10mcg/ml.

Preparation of standard curve for Felodipine

Standard curve for Felodipine was obtained in 1.2 pH buffer. Aliquots 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 absorbance of solutions was determined at 239 nm against respective media as blank.

Drug Excipient compatibility studies

Drug excipient compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipient 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 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 were dissolved in dichloromethane at various drugs - polymer ratios (1:1, 1:2 and 1:3). Then these drug and polymer solutions were mixed and emulsified using a 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 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.

Table 1: Formulation development of Felodipine hollow microspheres.

F. No	Polymer	Drug and polymer ratio	Stirring speed
F1	Eudragit	1:1	500
F2	Eudragit	1:2	500
F3	Ethyl Cellulose	1:1	500
F4	Ethyl Cellulose	1:2	500
F5	Carbopol 934	1:1	500
F6	Carbopol 934	1:2	500
F7	Sodium alginate	1:1	500
F8	Sodium alginate	1:2	500

Evaluation 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 the % weight of hollow microspheres retained by each sieve was calculated. 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 HCl (300 ml) containing 0.02% tween 20. The mixture was stirred with paddle at 100rpm. The layer of buoyant microspheres was pipetted and separated by filtration at 1, 2, 4 and 6 hours. The collected microspheres were dried in a desiccator over night.

The percentage of microspheres 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 microspheres were dissolved with 10ml ethanol in 100ml volumetric flask and the volume was made up 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 HCl 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.

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

Surface Characterization by SEM / Photomicrography

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. 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 for all formulations were carried out using the USP type –II dissolution basket assembly. Microspheres equivalent to 100 mg of Felodipine were taken. The dissolution media of 900 ml of stimulated gastric fluid (pH1.2) was maintained at 37±0.5 ºC and stirred at 100 rpm. 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 analyzed for the drug content spectrophotometrically using UV-Visible spectrophotometer.

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 for two weeks.

RESULTS AND DISSCUSSION

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

Preformulation studies

a) Organoleptic evaluation

Table 2: 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. It followed the Beer's law in the concentration range of 2-10 mcg/ml. 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 3: 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

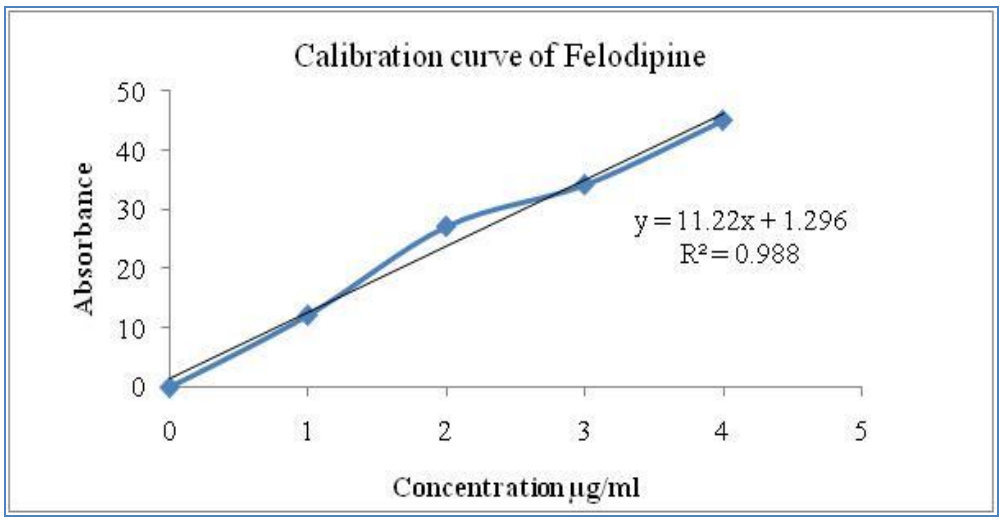

Fig 1: Calibration curve of Felodipine.

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.

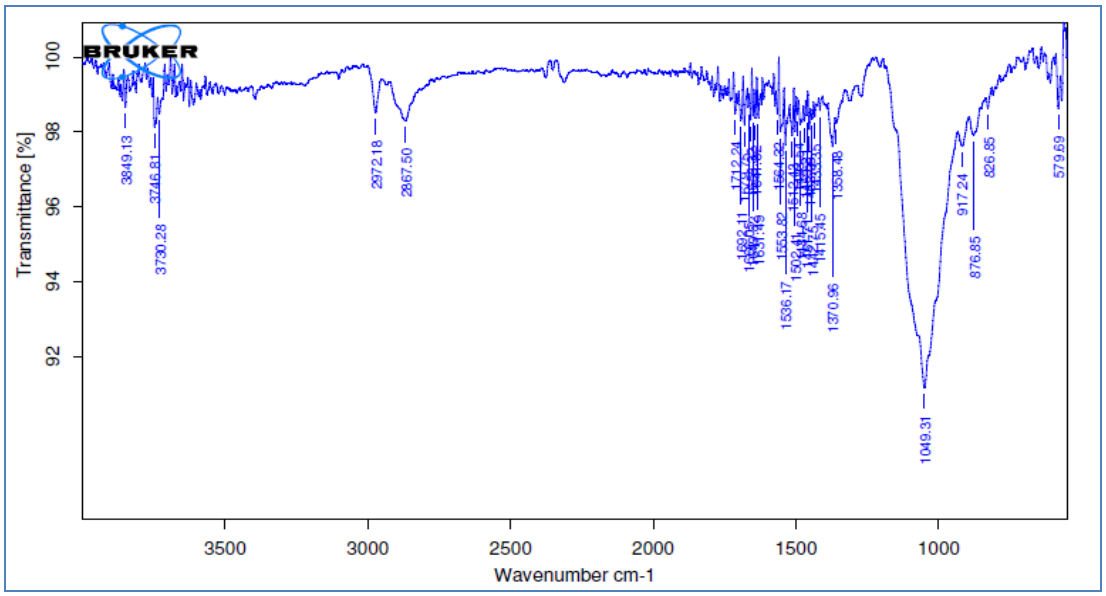

Fig 2: FTIR Studies of Felodipine.

Table 4: FTIR 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

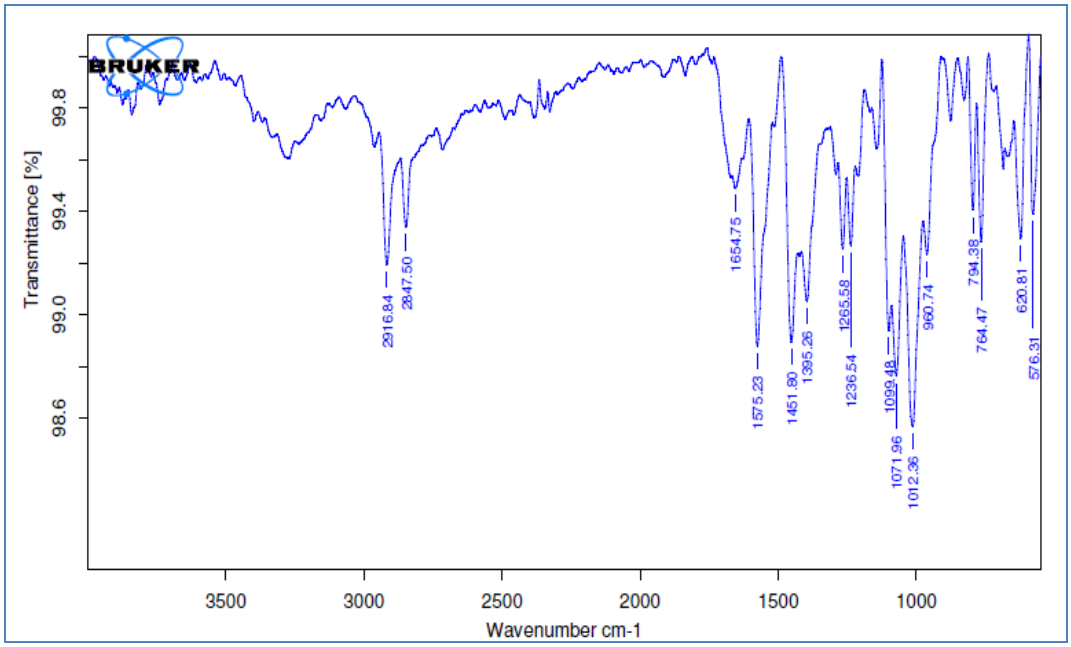

Fig 3: FTIR Studies of physical mixture.

Table 5: 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 an 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 microspheres range between 500mm - 1000mm, floating ability will be more and release rate will be in sustained manner. The mean particle size of hollow microsphere was in range 799-841mm.

Table 6: Particle size of Different Batches of Hollow microsphere.

S. No	Formulation code	Mean particle size (μm)
1	F1	815
2	F2	799
3	F3	838
4	F4	812
5	F5	799
6	F6	816
7	F7	822
8	F8	829

Floating Property of hollow microsphere

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

Table 7: Floating property of Hollow microsphere.

S. No	Formulation code	% of floating
1	F1	79.86
2	F2	89.58
3	F3	82.40
4	F4	79.99
5	F5	78.15
6	F6	85.09
7	F7	75.15
8	F8	83.64

Drug Entrapment efficiency

The drug entrapment efficiency of different formulations was in range of 75.15-89.58%. Drug entrapment efficacy increases with increase in eudragit content in micro balloons.

Table 8: Drug entrapment for different formulations.

Formulation	Drug Entrapment
F1	89.95
F2	96.60
F3	85.23
F4	90.66
F5	93.15
F6	89.99
F7	92.15
F8	93.28

Percentage Yield

Percentage yield of different formulation was determined by weighing the hollow microspheres after drying. The percentage yield of different formulation was in range of 79.60 – 80.55%.

Table 9: Percentage yield for different formulation.

Formulation	Percent Yield (%)
F1	79.90
F2	79.60
F3	80.55
F4	72.85
F5	85.61
F6	78.05
F7	90.12
F8	83.20

Scanning Electronic Microscopy

Shape and surface characteristic of hollow microspheres examined by Scanning Electronic Microscopy analysis are shown in Fig. 4 and 5. Surface morphology of F2 formulation examined at different magnification 40X and 200X, which illustrate the smooth surface of floating microspheres and small hollow cavity present in microsphere which is responsible for floating property.

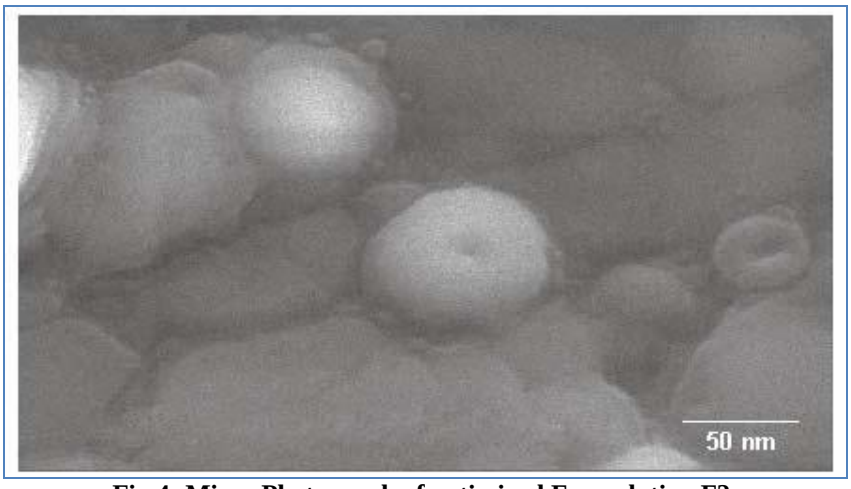

Fig 4: Micro Photograph of optimized Formulation F2.

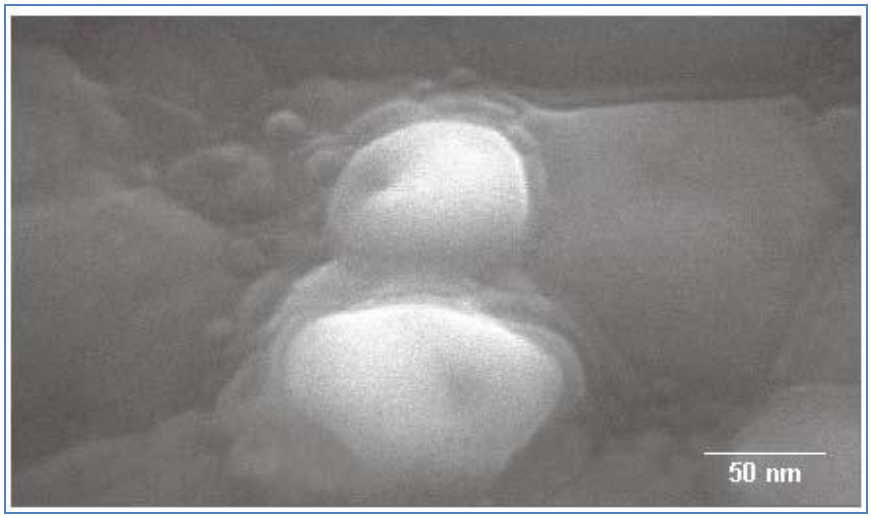

Fig 5: Cross Section Micro Photograph of optimized Formulation F2.

***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 has low permeability in acid medium. F2 formulation showed best appropriate balance between buoyancy and drug release rate.

Table 10: *In vitro* Drug Release Profile of Formulations in pH 1.2.

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	12.20	15.50	18.96	16.55	11.42	13.28	14.25	14.63
2	27.18	29.56	28.92	27.90	25.21	27.73	26.63	25.85
3	34.22	36.45	37.55	38.45	33.18	32.60	35.43	37.18
4	45.10	49.25	51.44	48.20	44.26	43.43	49.50	47.18
5	53.81	55.90	58.55	52.15	50.70	51.82	53.55	50.22
6	69.46	71.65	63.56	70.22	65.53	68.13	69.70	63.87
7	79.90	80.15	75.72	80.25	75.85	78.20	82.72	75.75
8	90.88	95.55	92.80	89.62	88.88	89.37	91.75	83.91

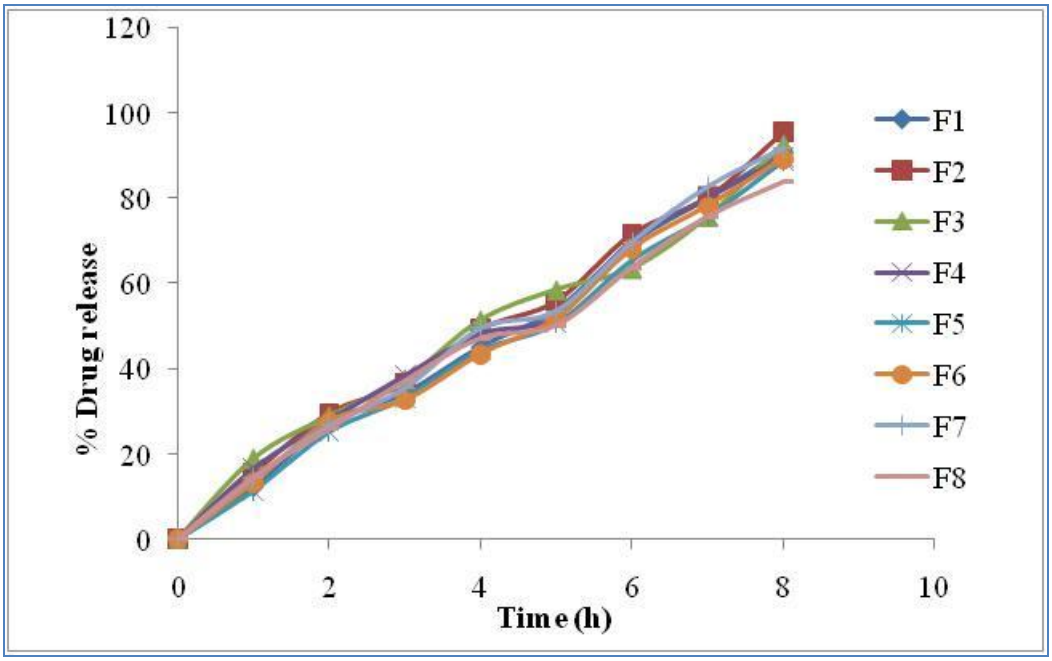

Fig 6: *In vitro* Drug Release Profile of all formulations.

Stability Study

Stability study was carried out for the F2 formulation by exposing it to different temperature for 30 days. The sample was analyzed for drug content at the regular intervals. It was found that no remarkable change in the drug content of F2 formulation. This indicates that F2 was stable for following temperature.

Table 11: Results of stability studies of optimized formulation F-2.

S. No	Time in days	Physical changes	% Drug release		
			Felodipine		
			25^0C/60%	30^0C/75%	40^0C/75%
1.	01	No Change	95.55	95.55	95.55
2.	30	No Change	95.50	95.48	95.32

CONCLUSION

The present study hollow microsphere of Felodipine was prepared by emulsion solvent diffusion technique by using various polymers. 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. 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. F2 formulation showed best appropriate balance between buoyancy and drug release rate, it considered as a best fit for drug release. The design system F2 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 of Felodipine.

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