FORMULATION AND EVALUATION OF FELODIPINE HOLLOW MICROSPHERES

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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 where as 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.

I.INTRODUCTION

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. [1,2] Hollow microspheres are gastroretentive drug delivery systems based on non-effervescent approach. They are spherical empty particles without core. They possess the unique advantages of multiple unit systems and their center hollow space imparts good floating properties making them promising buoyant systems. These microspheres are free flowing low density powders, having a size less than 200 µm, comprising of either proteins or synthetic polymers.[3]Felodipine is cardiovascular drug. It is used in various antianginal, antihypertension and Hepatic Dysfunction. Normal dosage regimen varies from 10-20 mg administered twice in a day. In severe cases, long-term therapy may also be required. Biological half-life of drug is from 11-16 hrs. As it requires frequent dosing to maintain the therapeutic effect, it was chosen as a model drug for the present study. Felodipine has poor and variable bioavailability which leads to the multiple daily dosing. The multiple daily dosing sometimes exhibits fluctuation of plasma drug concentration and also lead to poor patients' adherence. [4,5] In present study an attempt has been made to develop felodipine loaded hollow microspheres keeping in the view to get more effective delivery of felodipine. So, felodipine loaded microspheres were prepared and characterized with the aim to achieve the slow release of felodipine.[6]

II.MATERIALS AND METHODS

Felodipine was collected as a gift sample from Hetero labs, Hyderabad and various excipients like natural and synthetic polymers were purchased from AR chemicals, Hyderabad.

Methodology

Drug excipient compatibility studies[7]

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	500
F2	Eudragit	1:2	500
F3	Ethycellulose	1:1	500
F4	Ethycellulose	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

Method: [8,9]

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:[10]

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:[11]

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:[12]

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:[13]

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:[15]

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:[16]

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.

Stability Study:[17]

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.

III.RESULTS & DISCUSSION

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.

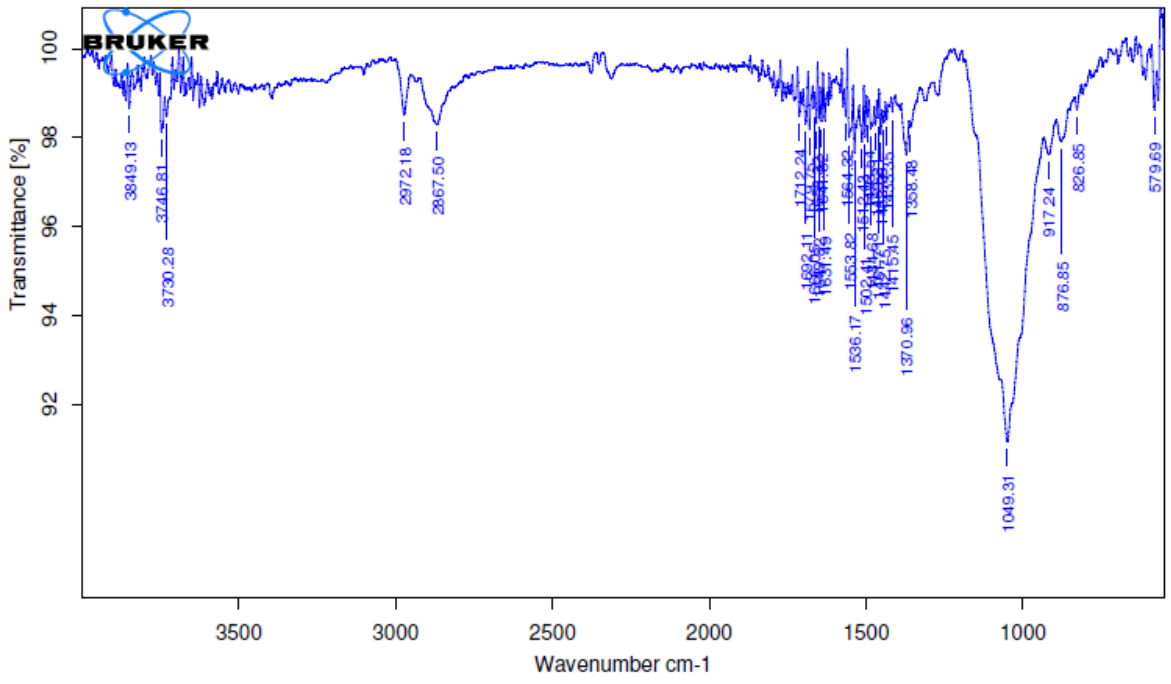

Fig-1: FTIR Studies of Felodipine

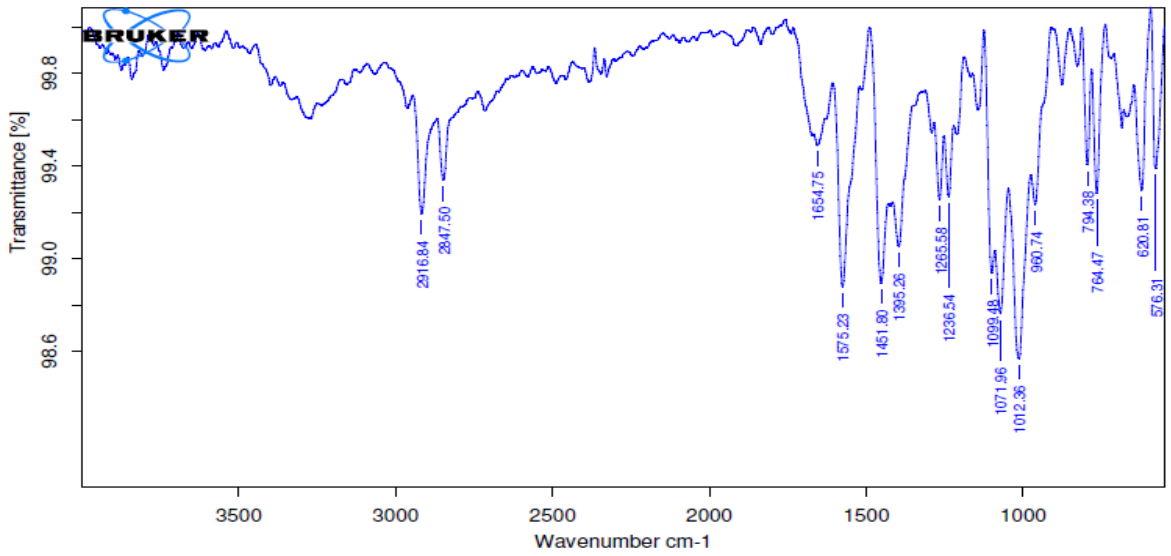

Fig-2: FTIR Studies of physical mixture

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 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-2: 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 were found to be differed according to polymer ratio.

Table-3: 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 were in range of 75.15-89.58%. 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-4: Drug entrapment for different formulation

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 were in range of 79.60 – 80.55% as shown in Table.

Table –5: 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 examine by Scanning Electronic Microscopy analysis as shown in Fig. Surface morphology of F2 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.

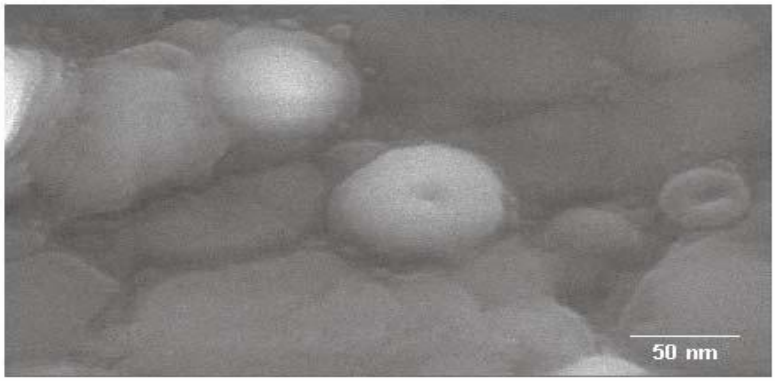

Fig-3: Micro Photographs Of Formulation F2

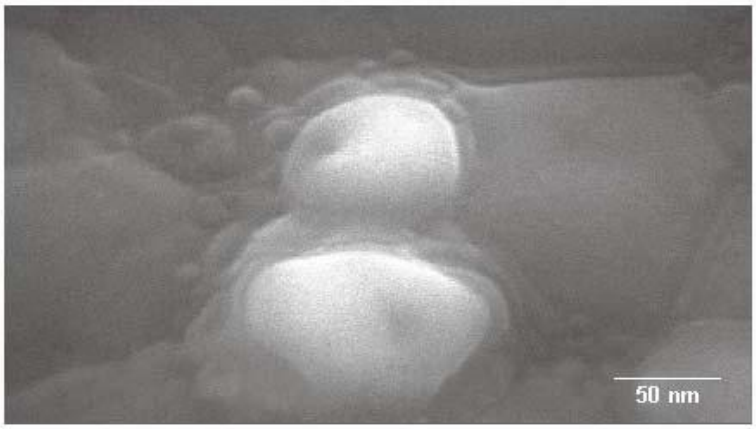

Fig-4: Cross Section

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. F2 formulation showed best appropriate balance between buoyancy and drug release rate.

Table-6: *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	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

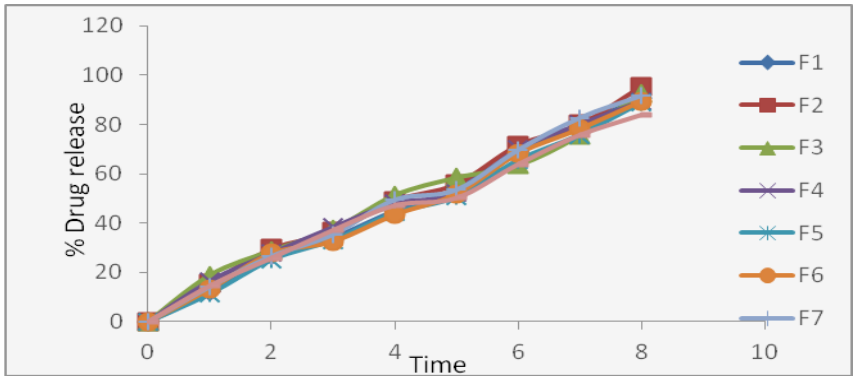

Fig-5: In-Vitro Drug Release Profile Of all formulations

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.

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. Drug release pattern was evaluated in pH 1.2. Release rate of F1-F4 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. 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.

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