Formulation and evaluation of gastroretentive floating microspheres of nimodipine

Maimuna Khathun [1*], P Raghupathi [2], K Aniketh Reddy [3], Shamin Akhtar [4], Md Zishan Hossain [5]
[1] Asst Professor, Department of Pharmacology, Sree Dattha Institute of Pharmacy Sheriguda (V), Ibrahimpatnam (M) Ranga Reddy, Telangana, India
[2-5] Department of Pharmaceutics, Sree Dattha Institute of Pharmacy, Sagar Road, Sheriguda, Ibrahimpatnam, Telangana, India

* Corresponding Author: **Haranath Chinthaginjala**

Article Info

ISSN (online): 2582-8940
Volume: 05
Issue: 02
April-June 2024
Received: 08-03-2024;
Accepted: 10-04-2024
Page No: 26-30

Abstract
The objective of the present work was to formulate floating hollow microspheres of Nimodipine which is soluble and shows better absorption in gastric pH. Microspheres were prepared by emulsion solvent diffusion technique. Using various such as ethyl cellulose, 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 Nimodipine for over 8 h. From the results it can be concluded that gastric floating hollow microspheres can be successfully used for the delivery of Nimodipine to control the blood pressure.

Keywords: Nimodipine, Polymers, emulsion solvent diffusion technique, FTIR Studies, floating time, *in vitro* drug release studies

Introduction
Majority of drugs are preferentially absorbed in the upper part of the small intestine. So, Gastro retentive drug delivery systems are preferred. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with GI mucosa leading to higher bioavailability and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance [1]. FDDS are preferred as they are economic and has improved patient compliance and they are advantageous for drugs absorbed from the stomach EG: ferrous salts and for drugs meant for local action in the stomach [2]. The floating systems are low-density systems that have sufficient buoyancy to float over the gastric content and remain buoyant the stomach without affecting the gastric emptying rate for a prolonged period of time which causes the inadequate release of drug at the absorption site [3]. Here we are developing lower density system that's floating microsphere, is prepared by solvent evaporation method incorporating Nimodipineas a model drug [4].
Nimodipine is a dihydropyridine calcium channel blocker developed for the treatment of high blood pressure. Nimodipine has a half-life of 8-9 h the bioavailability of 13% and it has narrow absorption window in upper part of the gastrointestinal tract (GIT), hence floating drug delivery system (FDDS) is preferred [5]

Materials
Nimodipine was obtained from Micro lab, HYD. Eudragit and ethyl cellulose were procured from Synpharma Research Labs, Hyderabad, and other chemicals the reagents used were of analytical grade.

Methodology

Drug excipient compatibility studies [6]

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 Nimodipine Floating microspheres

Formulation table

Table 1: Formulation development of Nimodipine Floating 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

Method: [7]

Emulsion-solvent-evaporation technique with some modifications was used to prepare Eudragit, and ethyl cellulose microspheres containing Nimodipine. Briefly Nimodipine was dissolved in 5 ml distilled water. Polymers was dissolved in Dichloromethane at various drug - polymer ratios (1:1, 1: 2). 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 Floating microspheres

Particle size analysis

Particle size analysis plays an important role in determining the release characteristics and floating property. The sizes of Floating 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 Floating microspheres were passed through the set of sieves and amount retained on each sieve was weighed and calculate the % weight of Floating 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 Floating microspheres.

Floating Property of Floating microsphere: [9]

100 mg of the Floating 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 overnight.

The percentage of microballoons was calculated by the following equation:

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

Drug Entrapment Efficiency: [10]

The various formulations of the Floating microspheres were subjected for drug content. 50 mg of Floating 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: [11]

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

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

Shape and Surface Characterization by Scanning Electron Microscopy: [12]

From the formulated batches of Floating 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 [13]

In vitro drug release studies were carried out for all formulations in Franz diffusion cell. Microspheres equivalent to 10 mg of Nimodipine 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: [14]

From the prepared Floating 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.

Results and Discussion

FT-IR Spectrum of Nimodipine

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

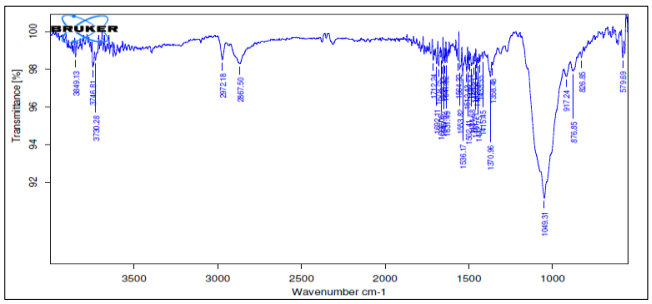

Fig 1: FTIR Studies of Nimodipine

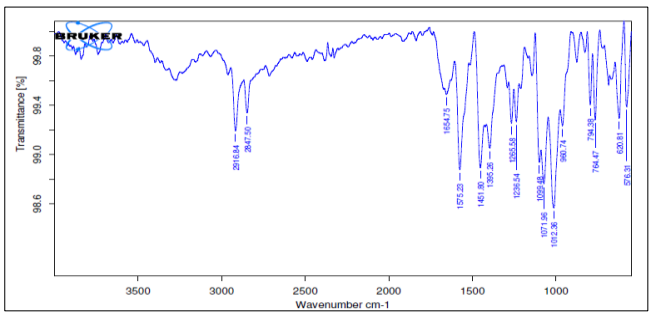

Fig 2: FTIR Studies of physical mixture

Evaluations of Floating microspheres

Particle size analysis

Particle size was determined by sieving method it plays important role in floating ability and release corrected of drug from Floating microspheres. If size of Floating 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 Floating microsphere was in range 788-822µm.

Table 2: Particle size of Different Batches of Floating microsphere

S. No	Formulation code	Mean particle size (µm)
1	F1	788
2	F2	810
3	F3	822
4	F4	798

Floating Property of Floating microsphere

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

Table 3: Floating property of Floating microsphere

S. No	Formulation code	% of floating
1	F1	81.56
2	F2	85.92
3	F3	80.81
4	F4	83.96

Drug Entrapment efficiency

The drug entrapment efficiency of different formulations were in range of 88.21 – 93.25%. Drug entrapment efficacy increases with increases eudragitcontent inmicroballoons. 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 Floating microspheres.

Table 4: Drug entrapment for different formulation

Formulation	Drug Entrapment
F1	87.89
F2	93.25
F3	90.74
F4	88.21

Percentage Yield

Percentage yield of different formulation was determined by weighing the Floating microspheres after drying. The percentage yield of different formulation were in range of 79.35 – 83.55% as shown in Table.

Table 5: Percentage yield for different formulation

Formulation	Percent Yield (%)
F1	80.12
F2	79.35
F3	82.16
F4	83.55

Scanning Electronic Microscopy

Shape and surface characteristic of Floating 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 Floating cavity present in microsphere which is responsible for floating property.

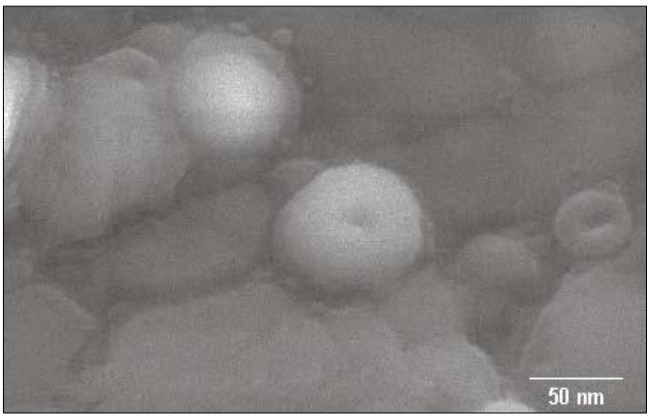

Fig 3: Micro Photographs of Formulation F2

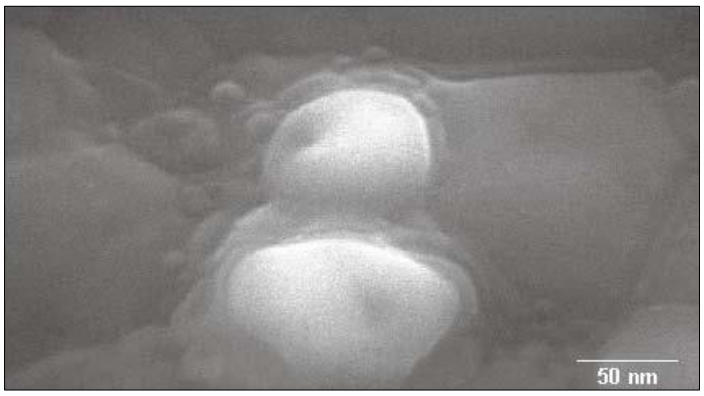

Fig 4: Cross Section

In-Vitro Drug release study

In-vitro drug release study of Floating 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
0	0	0	0	0
1	13.20	14.85	15.89	17.18
2	20.16	25.81	24.21	25.75
3	31.02	32.18	35.15	34.84
4	42.18	45.21	48.93	45.55
5	51.35	53.93	54.28	52.18
6	71.20	72.85	62.18	61.84
7	75.16	81.24	78.75	83.64
8	85.91	97.15	91.23	93.86

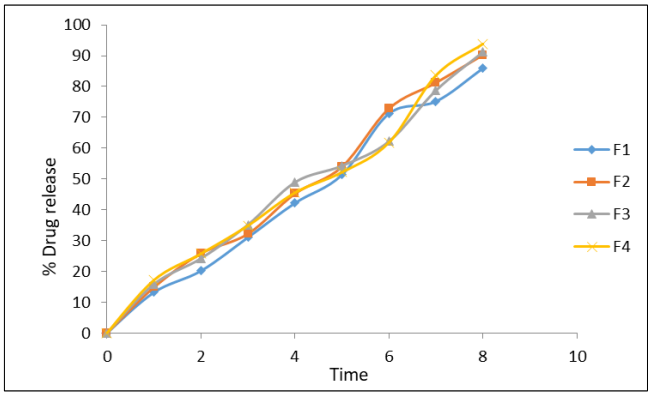

Fig 5: *In-Vitro* Drug Release Profile Of all formulations

Stability Study

Stability study was carried out for the F2 formulation by exposing it to different temperature for 3 months. The sample was analysed for drug content at the regular intervals. It was found that no remarkable change in the drug content of F2 formulation. This indicates that F2was stable for following temperature.

Table 7: Results of stability studies of optimized formulation F-2

S.NO	Time in Days	Physical Changes	% Drug Release		
			Nimodipine		
			25^0C/60%	30^0C/75%	40^0C/75%
1.	01	No Change	97.15	97.15	97.15
2.	30	No Change	96.89	96.75	96.55
3	60	No Change	95.99	95.33	95.89
4	90	No Change	94.52	94.31	94.22

Conclusion

Floating microspheres of Nimodipine 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 decreased 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 Floating microsphere includes high buoyancy and sufficient release of drug in pH 1.2. It is necessary to select inappropriate balance between buoyancy and drug release rate from all developing Floating 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. The developed formulation overcomes the drawbacks and limitations of sustained release preparations. Therefore multiple unit floating system, i.e., Floating microsphere will be possibly beneficial with subject to sustainaction.

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