ORIGINAL ARTICLE

Formulation and Evaluation of Gastro Retentive Floating Microspheres of Nimodipine

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Abstract

Introduction: 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. During the study, nimodipine encapsulated floating microspheres were formulated and characterized for enhancing residence time of drug in GIT. **Materials and Methods:** Floating microspheres of nimodipine with ethyl cellulose and Eudragit S100 were prepared by solvent evaporation method. Microspheres were characterized for their micromeritic properties, floating behavior, entrapment efficiency, scanning electron microscopy (SEM), X-ray diffraction, differential scanning calorimetry, and *in vitro* drug release. **Results and Discussion:** Floating microspheres were successfully prepared by solvent evaporation method. SEM images showed that microspheres prepared with different concentrations of polymer and emulsifier were spherical shaped with a smooth surface. The prepared microspheres also showed good flow properties. Size of microspheres was in the range of (90 ± 1.02)-(145 ± 1.34) µm. Microspheres were capable to float for 12 h. As the polymer concentration increases *in vitro* drug release was decreased. However, the release was controlled by polymer concentration for a longer period. **Conclusion:** The optimized formulation showed good results for all the evaluation parameters. Hence, it can be concluded that the developed formulation is a potential dosage form for nimodipine.

Key words: Eudragit S100, floating microspheres, nimodipine, solvent evaporation method

INTRODUCTION

Oral route of administration is most widely used due to its ease of administration. The main challenges with oral drug delivery systems are to deliver drugs at therapeutically effective rate to desirable site, modulate gastrointestinal transit time and to reduce first pass elimination. Rapid gastrointestinal transit can prevent the effective absorption of drug in the absorption zone and reduce the efficacy of administered dose.[1-6] To overcome this, many kinds of oral controlled drug delivery systems with prolonged gastric residence times have been reported such as; floating drug dosage systems (FDDS),[7-11] swelling or expanding system,[12] mucoadhesive systems,[13] modified shaped system, and other delayed gastric emptying devices.

Controlled release dosage form releases drug in a predetermined pattern for a fixed period. FDDS has lower density than gastric fluids and remain buoyant in the stomach fluid for a prolonged period. As the system floats in the gastric fluid, the drug is released slowly from the system at a desired rate.[14] Floating microspheres are the multiparticulate delivery system and are prepared to target drug to specific sites and to attain prolonged or controlled drug delivery to enhance bioavailability. Microspheres can also offer advantages such as reduced side effects, decreased dosing frequency, and improved patient compliance.

Nimodipine is a calcium channel blocker used for the treatment of high blood pressure and it can also prevent vasospasm. It stabilizes voltage-gated L-type calcium channels in their

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inactive conformation and thus acts on vascular smooth muscle cells. By inhibiting the influx of calcium in smooth muscle cells, the drug prevents calcium dependent smooth muscle contraction and thus vasoconstriction.[15,16] It has a half-life of 8-9 h with only 13% of bioavailability and is well absorbed in the upper part of gastrointestinal tract.[17-21] Hence, floating drug delivery system is preferred such that the dosage form can release drug in a controlled manner for a longer duration. By increasing the gastric residence time bioavailability of the drug can be enhanced.

This study aims at formulating and evaluating nimodipine floating microspheres with different ratios of polymers to control the release of the drug from microspheres and to increase the gastric residence time.

MATERIALS AND METHODS

Materials

Nimodipine was obtained from K. P. Labs, Hyderabad. Eudragit S100, ethyl cellulose, polyvinyl alcohol (PVA), and dichloromethane were procured from SD Fine Chemicals, Mumbai, India.

Methods

Preparation of floating microspheres

Nimodipine microspheres were prepared by solvent evaporation technique.[2,21,26] Drug and polymers were mixed in 1:1 mixture of dichloromethane and ethanol at room temperature. The slurry was slowly introduced into 200 ml of 0.25% w/v of polyvinyl alcohol as emulsifier. The system was stirred using mechanical stirrer for 2 h at room temperature to evaporate solvents and subsequently stored in desiccators. The formulations were shown in Table 1.

Characterization of floating microspheres

Micromeritic properties

The prepared nimodipine microspheres were characterized for their angle of repose, Hausner's ratio and compressibility index (Carr's index). Angle of repose of the microspheres measures the resistance to particle flow was measured by fixed funnel method using the following equation.[2,24,25]

$$\Theta = \tan^{-1} (h/r)$$

Where, h is the height of the pile, r is the radius of the base of the pile on the graph paper.

Particle size

The size of microspheres was determined using optical microscope fitted with an ocular micrometer and stage micrometer (Magnus MLX-DX, Olympus, India). The mean particle size was calculated by measuring 200-300 particles.[2]

Drug entrapment efficiency

Microspheres equivalent to 60 mg of nimodipine were weighed accurately and crushed. These powdered microspheres were placed in 10 ml methanol and kept overnight for complete dissolution. Whattman filter paper No. 44 was used to filter the solution. Then, the solution was diluted with fresh solvent, and absorbance was measured at 255 nm using double beam ultraviolet (UV)-visible spectrophotometer (UV-3200, Labindia, Mumbai, India), and the percent drug entrapped was calculated.[2,21,23]

% Drug entrapment = (Calculated drug content/Theoretical drug content) × 100

Floating efficiency (% buoyancy)

Microspheres weighing 50 mg were placed in 100 ml of simulated gastric fluid (pH 1.2) containing Tween 20 (0.02% w/v) and stirred at 100 rpm using orbital shaker. After 12 h, the layer of floating microspheres was separated from settled microspheres. Both microspheres were dried and weighed. The % buoyancy of microspheres was calculated using the formula given below.[2,21-23]

$$\% \text{ Buoyancy} = W_f/(W_f+W_S)\times 100$$

Where W_f is the weight of the floating microspheres and W_S is the weight of the settled microspheres.

In vitro drug release

Release studies were conducted using USP-II (paddle apparatus). Floating microspheres equivalent to 60 mg of nimodipine were weighed accurately and placed in 900 ml of 0.1 N HCl having Tween 20 (0.02% w/v), maintained at 37 ± 0.5°C at a rotation speed of 100 rpm. Then at specified time intervals, 5 ml of samples were withdrawn, filtered, diluted with same medium and assayed at 255 nm for nimodipine using double beam UV-visible spectrophotometer (UV-3200, Labindia, Mumbai, India).[2,21]

Fourier transform infrared (FTIR) spectroscopy

Incompatibilities between drug and excipients of the formulation were evaluated using FTIR. The spectra were obtained using FTIR spectrophotometer (Bruker Alpha-T-1020, Ettlingen, Germany). The previously grounded samples of nimodipine, ethyl cellulose, Eudragit S100 and optimized formulation were mixed separately with KBr powder and were compressed into discs. The spectra were scanned over the range of 4000-400/cm.[27]

Table 1: Formulation of nimodipine floating microspheres

Formulation	Drug (mg)	Ethyl cellulose (mg)	Eudragit S100 (mg)	Ethanol (ml)	Dichloro methane (ml)	PVA (% w/v)	rpm
F_1	60	60	60	12.5	12.5	0.25	500
F_2	60	60	60	12.5	12.5	0.5	500
F_3	60	60	60	12.5	12.5	0.25	1000
F_4	60	60	60	12.5	12.5	0.5	1000
F_5	60	60	120	12.5	12.5	0.25	500
F_6	60	60	120	12.5	12.5	0.5	500
F_7	60	60	120	12.5	12.5	0.25	1000
F_8	60	60	120	12.5	12.5	0.5	1000
F_9	60	60	180	12.5	12.5	0.25	500
F_{10}	60	60	180	12.5	12.5	0.5	500
F_{11}	60	60	180	12.5	12.5	0.25	1000
F_{12}	60	60	180	12.5	12.5	0.5	1000

PVA: Polyvinyl alcohol

Surface morphology

The shape and surface characteristics of microparticles were determined using scanning electron microscope (SEM) (JSM 5610 LV SEM, JEOL, Datum Ltd., Japan). Samples of pellets were dusted onto a double-sided tape on an aluminum stub, and the stub was coated with gold to a thickness of 400 A° using cool sputter coater (Polaran E 5100). SEM images were taken at the accelerated voltage of 15 KV and chamber pressure of 0.6 mm Hg.[21,28]

X-ray diffraction (XRD) studies

X-ray diffractograms of nimodipine and optimized formulation were recorded with D8 advance X-ray diffractometer (Bruker AXS D8 Advance®, Germany). The sample was irradiated with Nickel filtered 2.2 KW Cu Anode, Dermic X-ray tube with a sample holder, with zero background and PMMA & Lynux eye detector. The samples were scanned at 0-70° at 2θ scale.[28]

Differential scanning calorimetry (DSC)

The DSC analysis of pure drug and optimized microspheres was carried out using Perkin Elmer, USA (Diamond DSC) to evaluate any possible drug-polymer interaction. The optimized formulation (5 mg) was triturated to get finely divided powder. The powder was passed through sieve No. 100. Each sample was placed in an aluminum pan separately with heating and cooling rates of 10°C/min and 250°C/min, respectively. Measurements were performed over 50-300°C under nitrogen purge at 50 ml/min.[31]

Stability studies

Stability studies were conducted according to ICH guidelines by storing the formulation at 40°C/75%±5% RH for 3 months. After 3 months, microspheres were evaluated for drug entrapment efficiency, floating efficiency, and *in vitro* drug release.[27]

RESULTS AND DISCUSSION

FTIR

FTIR spectra and characteristic peaks of nimodipine, ethyl cellulose, Eudragit S100 and optimized microsphere formulation were obtained and were shown in Figure 1 and Table 2, respectively. FTIR spectrum of Nimodipine showed characteristic peaks at 3126.76/cm, 2963.47/cm, 2934.11/cm, 1698.44/cm. All the characteristic peaks of nimodipine were found in the FTIR spectrum of the optimized microsphere formulation. With this, it is revealed that there was no considerable interaction between the drug and the excipients in floating microsphere formulation.

Micromeritic properties

The angle of repose was found to be in the range of (20.45 ± 0.89)-(26.21 ± 0.82). All the formulations showed good flow properties. Carr's index, Hausner's ratio were found to be in the range of (16.54 ± 0.08)-(23.76 ± 0.36) and (1.05 ± 0.06)-(1.31 ± 0.07), respectively. Micromeritic properties were summarized in Table 3.

Particle size

Size of the particles was determined by using optical microscopy. Size of the microspheres was found to be in the range of (90 ± 1.02 µm) to (145 ± 1.34 µm). Size was increased with increased polymer concentration [Table 4].

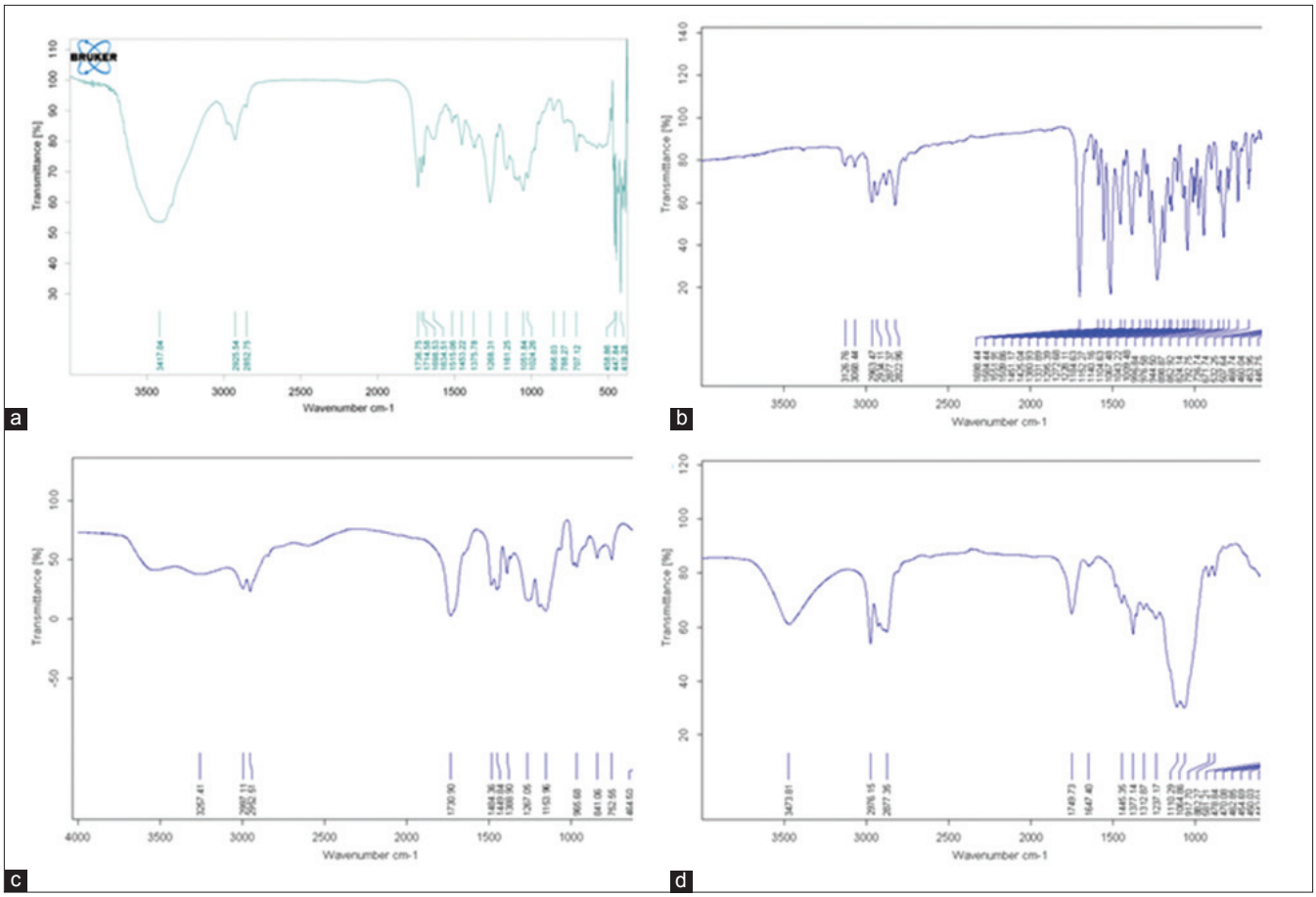

Figure 1: Fourier transform infrared spectra of, (a) Optimized formulation, (b) nimodipine, (c) Eudragit S 100, (d) ethyl cellulose

Table 2: Characteristic peaks of nimodipine, ethyl cellulose, Eudragit S100 and nimodipine loaded floating microspheres in FTIR spectrum

Sample	Characteristic functional groups	Type of vibration	Wave number range (cm^{-1})	Characteristic wave number (cm^{-1})
Nimodipine	NH	N-H stretching	3297	3126.76
	C=O	C=O stretching	1699	1698.44
Ethyl cellulose	OH	O-H stretching	3480	3473.81
	CH_2	C-H stretching	2974	2976.15
Eudragit S100	OH	O-H stretching	3438	3257.41
	C=O	C=O stretching	1730	1730.90
Nimodipine microspheres	NH	N-H stretching	3297	2925.54
	C=O	C=O stretching	1699	1698.53
	OH	O-H stretching	3480	3417.04
	CH_2	C-H stretching	2974	2924.54
	C=O	C=O stretching	1730	1736.75

FTIR: Fourier transform infrared spectroscopy

This may be due to increase in viscosity in a fixed volume of solvent, thus causing increase in emulsion drop size and finally increase in size of particle.[2] By increasing PVA concentration, particle size was decreased because more PVA molecules overlay the surface of droplets which will reduce the protection of droplets against coalescence leading to formation of smaller particles.[21] It was found that particle size was decreased with increasing stirring speed. This is because of the shearing forces developed at a higher speed which leads to the breaking of particles.

Table 3: Flow properties of nimodipine floating microspheres

Formulation	Carr's index	Hausner's ratio	Angle of repose(°)
F1	23.76±1.23	1.27±0.067	21.94±2.23
F2	18.96±4.65	1.05±0.087	20.45±2.76
F3	19.64±4.01	1.16±0.035	26.21±0.67
F4	17.85±2.25	1.22±0.454	25.75±0.85
F5	21.42±0.36	1.25±0.060	24.04±1.67
F6	19.35±1.45	1.14±0.090	23.51±0.42
F7	20.63±2.64	1.24±0.136	22.68±0.94
F8	17.62±3.12	1.24±0.360	21.82±0.71
F9	18.18±0.08	1.23±0.278	25.75±1.48
F10	22.32±1.34	1.15±0.056	26.06±0.58
F11	16.54±2.56	1.31±0.695	24.74±0.89
F12	18.43±3.65	1.23±0.453	23.52±2.34

Table 4: Particle size, entrapment efficiency and floating efficiency of nimodipine floating microspheres

Formulation	Particle size (μm)	Percentage entrapment efficiency	Percentage floating efficiency
F1	115±1.12	65.57±1.72	62.23±0.71
F2	98±1.02	60.69±0.91	55.45±0.88
F3	102±1.17	57.16±1.65	49.72±1.55
F4	90±0.77	53.29±1.25	43.34±1.24
F5	128±1.85	78.69±0.95	70.36±0.16
F6	115±1.99	70.82±1.58	64.65±0.85
F7	113±0.85	65.38±0.85	61.12±1.22
F8	105±1.52	60.85±1.10	54.25±1.00
F9	145±1.34	86.18±1.25	78.34±0.95
F10	130±1.43	77.39±1.00	71.38±1.27
F11	132±1.64	72.35±1.05	66.47±0.54
F12	125±1.52	67.9±1.60	61.62±1.22

Drug entrapment efficiency

Effect of polymer concentration, stirring speed and emulsifier concentration on entrapment efficiency was studied. It was observed that entrapment efficiency was increased with increase in the polymer concentration. This may be due to increase in viscosity of internal phase which reduces migration of drug molecules without getting entrapped in oil globules.[26] However, drug loading was found to be decreased with increase in stirring speed and emulsifier concentration.

This may be due to the formation of microspheres of smaller size at higher speed of rotation and higher concentration of PVA. Loss of drug from surface of smaller particles is more when compared to the larger particles during washing of microspheres.[21]

Floating efficiency

Microspheres showed lower densities which influence buoyancy and they were to be retained for a longer period in the stomach. By increasing the polymer concentration, floating efficiency was also increased because of the increased particle size at higher concentration of polymer.[2] It was observed that the floating efficiency was decreased by increasing PVA concentration and stirring speed as the particle size was decreased at higher speed and higher concentration of PVA. Results of entrapment efficiency and floating efficiency were summarized in Table 4.

In vitro drug release

A dissolution study was done in 900 ml of 0.1 N HCl for 12 h. Release of the drug shows no burst effect in any of the formulation indicating homogeneous drug distribution. The microspheres retained their integrity during *in vitro* dissolution studies as the acrylic polymers are insoluble in acidic medium. It was observed that increase in polymer concentration leads to the formation of high density polymer matrix into the microspheres, which result in an increased diffusion path length and consequent retardation in drug release. However, the release was best controlled by polymer concentration for a prolonged period. The rate of drug release was highly influenced by the initial drug loading. It was observed that by increasing the drug loading the rate of drug release from microspheres was increased. This is in good agreement with the results reported by Filipovic-Grcic *et al*.[29] in their work on the nifedipine loaded Chitosan microspheres and Tefft and Friend from herbicide-loaded microspheres.[30] The release rate of nimodipine from smaller microspheres is higher than from larger microspheres which may be due to the greater surface area of smaller microspheres. *In vitro* release profiles of all the formulations were shown in Figure 2.

Formulation F9 was optimized as it showed good entrapment efficiency and good floating on simulated gastric fluid for a longer period. It also showed good controlled release for a prolonged period.

SEM

SEM photographs confirmed the spherical shape of the prepared microspheres with smooth perforated surface [Figure 3]. The formation of pores was attributed to evaporation of alcohol from microspheres.[2] It was also observed that formation of irregular particles occurred with increased stirring rate. High drug loaded microspheres were not as smooth as low drug loaded microspheres as their surface was covered with drug crystals.[16]

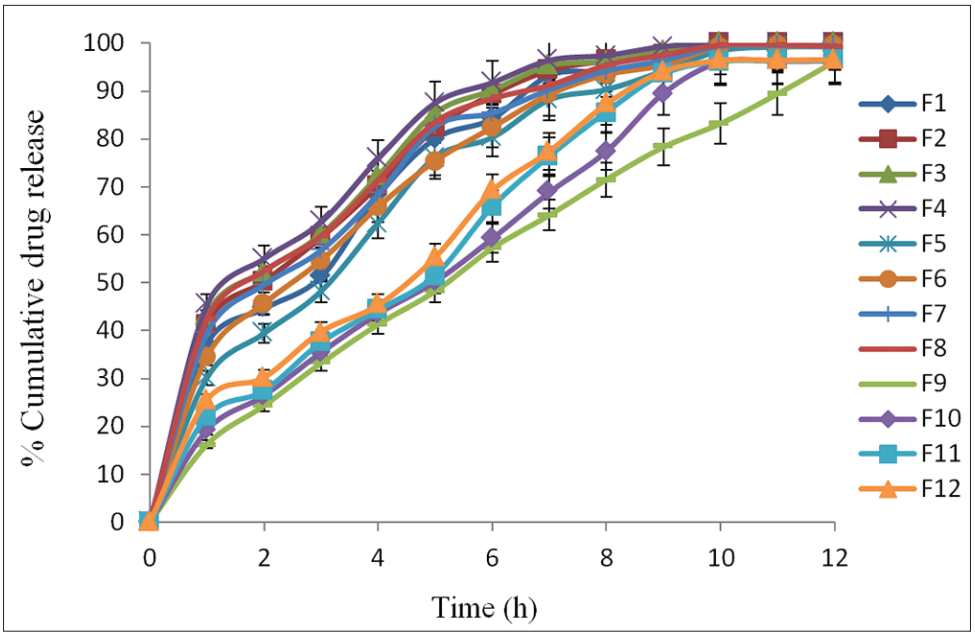

Figure 2: *In vitro* drug release

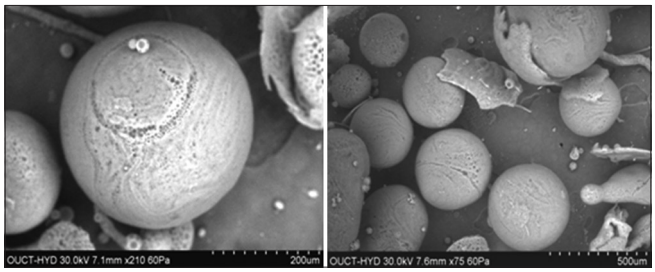

Figure 3: Scanning electron microscopy images of optimized formulation at two different magnifications

XRD studies

XRD analysis was used to assess the degree of crystallinity of the microsphere constituents. Nimodipine showed major peaks at 2 values of 15, 18, 22, 25, 26 which were found to be absent in the optimized formulation [Figures 4 and 5]. Analysis of powder XRD patterns of the optimized formulation indicated that the degree of crystallinity of microspheres was decreased by the addition of excipients to the formulation. A fall in degree of crystallinity means an improvement in amorphous nature of the formulation. Hence, from the above discussion it was concluded that the microspheres resulted in an amorphous form of Nimodipine, which led to improve *in vitro* release profile.

DSC

DSC curves of pure drug and optimized formulation were shown in Figure 5. Pure drug exhibited a sharp endothermic peak at around 170°C corresponding to its melting point and infers the presence of crystalline form of the drug. However, endothermic peaks were absent in the optimized formulation which indicates the transformation of crystalline structure of nimodipine into amorphous form in microspheres.

Table 5: Stability studies for optimized formulation

Time (h)	Percentage cummulative drug release	
	Initial	After storage at 40°C/75±5% RH for 3 months
1	16.23±2.33	15.35±3.44
2	24.34±3.51	24.12±3.12
3	33.23±2.44	32.46±4.38
4	41.32±4.21	40.23±3.26
5	48.23±3.32	47.34±5.11
6	57.86±1.82	56.43±4.25
7	64.12±2.25	64.11±5.12
8	71.56±3.34	70.54±2.27
9	78.34±2.11	77.58±2.78
10	83.24±2.55	83.21±1.32
11	89.45±4.26	88.45±2.32
12	96.23±4.44	95.93±4.61
Percentage floating ability	78.34±0.95	78.21±1.23
Percentage encapsulation efficiency	86.18±1.25	85.26±1.64

F2>50, **P*>0.05

Stability studies

Stability studies at accelerated conditions of 40°C/75% RH for 3 months were carried out for optimized formulation. No significant change was observed in drug release, floating ability and encapsulation efficiency before and after storage. The results were depicted in Table 5.

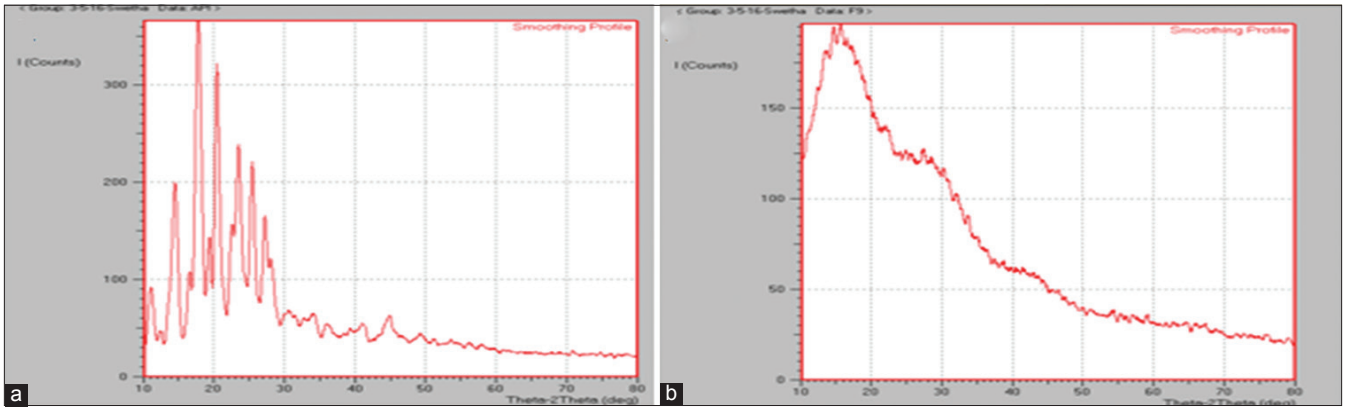

Figure 4: X-ray diffraction diffractograms of, (a) nimodipine (b) optimized formation

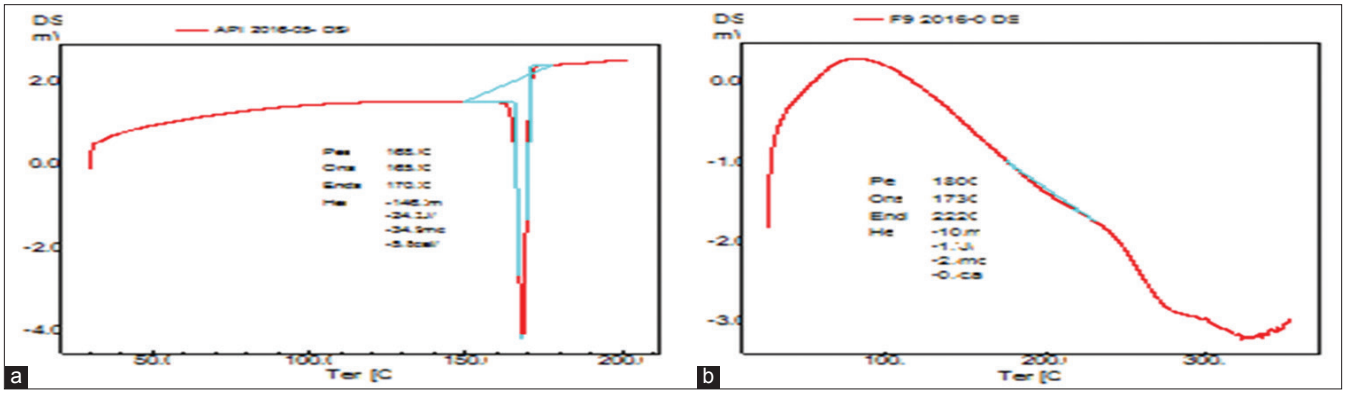

Figure 5: Differential scanning calorimetry thermogram of, (a) nimodipine (b) optimized formulation

CONCLUSION

Nimodipine loaded floating microspheres were successfully formulated with various concentrations of polymers and emulsifier. Various parameters like particle size, micromeritic properties, floating ability, drug entrapment ability, and *in vitro* drug release were carried out and performance of the formulation was evaluated. The optimized formulation shows good controlled release for 12 h. It also showed good entrapment efficiency and *in vitro* floating efficiency. Hence, it can be concluded that the developed formulation is a potential dosage form for nimodipine.

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REFERENCES

1. Garg R, Gupta G. Progress in controlled gastroretentive delivery systems. Trop J Pharm Res 2008;7:1055-66.
2. Gupta R, Prajapati SK, Pattnaik S, Bhardwaj P. Formulation and evaluation of novel stomach specific floating microspheres bearing famotidine for treatment of gastric ulcer and their radiographic study. Asian Pac J Trop Biomed 2014;4:729-35.
3. Kaushik K, Chaurasia D, Chaurasia H, Mishra SK, Bhardwaj P. Development and characterization of floating alginate beads for gastroretentive drug delivery system. Acta Pharma Sci 2011;53:551-62.
4. Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and *in vitro-in vivo* evaluation in healthy human volunteers. Eur J Pharm Biopharm 2010;74:332-9.
5. Moes AJ. Gastroretentive dosage forms. Crit Rev Ther Drug Carrier Syst 1993;10:143-95.
6. Chueh HR, Zia H, Rhodes CT. Optimization of sotalol floating and bioadhesive extended release tablet formulation. Drug Dev Ind Pharm 1995;21:1725-47.
7. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000;195:125-35.
8. Akiyama Y, Nagahara N, Kashihara T, Hirai S, Toguchi H. *In-vitro* and *in-vivo* evaluation of mucoadhesive microspheres prepared for gastrointestinal tract by polyglycerol ester of fatty acids and (acrylic acid) derivatives. Pharm Res 1995;12:397-405.

9. Bulgarelli E, Forni F, Bernabei MT. Effect of matrix composition and process conditions on casein-gelatin beads floating properties. Int J Pharm 2000;198:157-65.
10. Taghizadeh Davoudi E, Ibrahim Noordin M, Kadivar A, Kamalidehghan B, Farjam AS, Akbari Javar H. Preparation and characterization of a gastric floating dosage form of capecitabine. Biomed Res Int 2013;2013:495319.
11. Singh BN, Kim KH. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Control Release 2000;63:235-59.
12. Chen J, Park K. Synthesis of fast-swelling, superporous sucrose hydrogels. Carbohyd Polym 2000;41:259-68.
13. Shaikh R, Singh TR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci 2011;3:89-100.
14. Hwang SJ, Park H, Park K. Gastric retentive drug-delivery system. Crit Rev Ther Drug Carrier Syst 1998;15:243-84.
15. Patil AK, Majahar S, Irfani G. Floating tablets of nimodipine and its inclusion complex with β-Cyclodextrin for controlled release. Int J Pharm Tech Res 2011;3:619-25.
16. Atyabi F, Mohammadi A, Dinarvand R. Preparation of nimodipine loaded microspheres: Evaluation of parameters. IJPS Summer 2005;1:143-52.
17. Shah SH, Patel NV, Patel JK. An overview of gastro-retentive floating drug delivery system. Asian J Pharm Sci 2009;4:65-80.
18. Lee JH, Park TG, Choi HK. Development of oral drug delivery system using floating microspheres. J Microencapsul 1999;16:715-29.
19. Haznedar S, Dortunç B. Preparation and *in vitro* evaluation of Eudragit microspheres containing acetazolamide. Int J Pharm 2004;269:131-40.
20. Jain SK, Awasthi AM, Jain NK, Agrawal GP. Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: Preparation and *in-vitro* characterization. J Control Release 2005;107:300-9.
21. Sharma M, Kohli S, Dinda A. *In-vitro* and *in-vivo* evaluation of repaglinide loaded floating microspheres prepared from different viscosity grades of HPMC polymer. Saudi Pharm J 2015;23:675-82.
22. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci 1992;81:135-40.
23. Patel A, Ray S, Thakur RS. *In-vitro* evaluation and optimization of controlled release floating drug delivery system of metformin hydrochloride. DARU 2006;14:57-64.
24. Bhardwaj P, Singh R, Swarup A. Development and *in-vitro* evaluation of floating microspheres of 5-fluorouracil. Int J Pharm Sci Res 2012;3:934-41.
25. Soppimath KS, Kulkarni AR, Aminabhavi TM. Development of hollow microspheres as floating controlled-release systems for cardiovascular drugs: Preparation and and release characteristics. Drug Dev Ind Pharm 2001;27:507-15.
26. Yelugam M, Koteshwara KB, Reddy MS. Gastro retentive floating microspheres of carvedilol: Formulation characterization and *in-vitro* evaluation. Int J Pharm Pharm Sci 2013;5 Suppl 3:686-90.
27. Srimathkandala MH, Sanka K, Bakshi V, Ananthula MB, Diwan PV. Formulation and optimization of thermoresponsive gatifloxacin ocular *in situ* gel using 3^2 factorial design: *In vitro* and *in vivo* evaluation. Der Pharmacia Lett 2014;6:95-106.
28. Mishra SK, Khatri S. Formulation and evaluation of sustained release gastro-retentive drug delivery system of acyclovir leading to enhanced bioavailability. BJPR 2015;7:428-39.
29. Filipovic-Grcic J, Becirevic-Lacan M, Skalko N, Jalsenjak I. Chitosan microspheres of nifedipine and nifedipine-cyclodextrin inclusion complexes. Int J Pharm 1996;135:183-90.
30. Tefft J, Friend DR. Controlled release herbicide formulations based on polymeric microspheres. J Control Release 1993;27:27-35.
31. Sethi RK, Barik BB, Sahoo SK. Preparation and determination of drug-polymer interaction and *in-vitro* release of didanosine microspheres made of cellulose acetate phthalate or ethyl cellulose polymers. Int J Drug Dev Res 2013;5:341-53.

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