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FORMULATION AND EVALUATION OF GASTRORETENTIVE CEFUROXIME AXETIL FLOATING MICROSPHERES

Laukik S. Chorghe* and Madhuri T. Deshmukh

Department of Pharmaceutics, Rajgad Dnyanpeeth College of Pharmacy, Bhor, Pune, Maharashtra.

***Corresponding Author: Laukik S. Chorghe**

Department of Pharmaceutics, Rajgad Dnyanpeeth College of Pharmacy, Bhor, Pune, Maharashtra.

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ABSTRACT

Objective: The objective of this research was to formulate and evaluate Cefuroxime axetil floating microsphere prepared using sodium alginate and carbopol 934. Cefuroxime axetil having extensive hepatic first pass metabolism and low bioavailability problem, determined the need for the development of sustained release formulation. **Methods:** Cefuroxime axetil floating microspheres were prepared by ionic gelation method Cefuroxime axetil floating microspheres were prepared by ionic gelation method by using carbopol as crosslinking agent. The Cefuroxime axetil floating microsphere was characterized by particle size measurement, process yield, morphology of microsphere, drug entrapment efficiency, differential scanning calorimetry, Fourier transforms infrared (FTIR) study and in-vitro drug release. **Results:** The Cefuroxime axetil floating microsphere having mean particle size ranged from 493 µm to 660 µm, and the entrapment efficiencies ranged from 94% to 95%. All the cefuroxime axetil microsphere batches showed good in-vitro mucoadhesive property ranging from 74.40% to 97.97. FTIR studies indicated the no drug-polymer interactions in the ideal formulation F2. There were no compatibility issues. and the crystallinity of Cefuroxime was found to be reduced shoeing less intense peak in prepared floating microspheres, which were confirmed by differential scanning calorimeter. Among different formulations, the Cefuroxime microspheres of batch F2 had shown the optimum percent drug entrapment of microspheres. Release pattern of Cefuroxime from F2 microspheres batch followed Higuchi kinetic model. Stability studies were carried out for F2 formulation at 4°C/ambient, 95.611±0.256°% relative humidity revealed that the drug entrapment, floating behavior, and drug release were within permissible limits. **Conclusion:** The results obtained in this work demonstrate the use of carbopol and sodium alginate polymer for preparation of floating microsphere.

KEYWORDS: Ionic gelation method, Gastroretentive delivery, floating microsphere, Sodium alginate, Carbopol.

INTRODUCTION

Oral controlled drug delivery system such as floating microsphere drug delivery systems used to prolong the residence time at the site of application or absorption. Microsphere is useful to maintain therapeutically effective plasma drug concentration levels for a longer duration there by reducing the dosing frequency and to minimize fluctuations in the plasma drug concentration at the steady state by delivering the drug in a controlled and reproducible manner. floating microspheres become adhesive on hydration and hence can be used for localizing the drugs to a particular target site of gastrointestinal tract (GIT) for prolong periods of time. Moreover, it is easy for administration, no patient compliances, and flexibility in the formulation. floating microspheres have advantages such as efficient absorption, enhanced bioavailability of the drugs, maximum utilization of drugs, much more intimate contact with intestinal cells, better patience compliance, and targeting to specific absorption site.[1-3]

Cefuroxime axetil is an antibacteriall used in the treatment of upper and lower respiratory tract infection. Cefuroxime is slightly soluble in water in alcohol and having only 75% oral bioavailability. Cefuroxime axetil undergoes extensive first pass metabolism. In this regard, our main focus of this research is to prepare sustain microspheres of Cefuroxime axetil which provides slow release in GIT and also assures the presence of dosage form at the site of absorption.

MATERIALS AND METHODS

Materials

Cefuroxime axetil was obtained from Orchid health care Private Ltd, Mumbai, India. Sodium alginate gift sample from S.D. Fine Chemical Mumbai, carbopol from Colorcon Asia Pvt. Ltd., Goa, and Sod CMC was purchased from S.B. Fine chemicals Ltd, Mumbai.

Preparation of microsphere

Ionic gelation method

Microspheres were prepared by orifice ionic gelation method with polymer combinations of sodium alginate, carbopol and Sodium CMC (carboxy methyl cellulose). Cefuroxime Axetil loaded microsphere were prepared by ionic gelation method. Accurately weighed quantities of polymers and weighed quantities of Cefuroxime Axetil were dispersed in 10 ml distilled water with a constant stirring at 300 rpm for 30 min. The resultant dispersion was added dropwise through a syringe (17 guage) into the Ca.chloride solution (10 % w/v). Thus so formed microspheres were kept for 30 min for complete reaction and afterwards, microspheres were recovered by filtration through a sintered glass filter, under vacuum, dried in hot air oven at 60°C for 1 hour.

Experimental design

The formula optimization was done by 32 factorial design using design expert (Version 9.2; Stat-Ease Inc., Minneapolis, Minnesota, USA) for mathematical modeling and analysis of responses. The optimal level of variables was determined by 32 factorial design including center point. The significant factors selected were concentration of carbopol and cross-linker concentration examining 9 runs.

Variables for experimental designs

Independent variable

1 X = concentration of polymer
X = cross-linking agent.

2 Dependent variable
1 Y = Particle size
2 Y = Entrapment efficiency
3 Y = t% release

Particle size measurement

The size of the prepared microcapsules was measured by the optical microscopy method using a calibrated stage micrometer. Particle size was calculated using equation, $X = 10 \times ([n \times \log X]/N)$, Where, X is geometric mean diameter, n is number of particle in range, X is the midpoint of range and N is the total number of particles.[8]

Process yield

1 1
1 2

Dried microspheres were accurately weighed, and considering the total amount of drug and polymers used for preparing the feed solution, the process yield was calculated, a using following formula.[10]

Entrapment efficiency= Estimated % drug content □ 100
Theorotical % drug content

In-vitro dissolution

The release rate of Cefuroxime from Cefuroxime microspheres was determined using USP Type II (paddle) dissolution test apparatus. The dissolution test was performed using 900 ml of dissolution medium of 0.1 N hydrochloric acids, at 37±0.5°C and a rotation speed of 50 rpm. In specified time intervals, an aliquot of 5 ml samples of the solution were withdrawn

Release kinetic studies

The rate and the mechanism of release of Cefuroxime from the prepared Floating microspheres were analyzed by fitting the dissolution data into various kinetic models such as zero order; first order, Higuchi's model, and coefficient of correlation (r) values were calculated for the linear curves by regression analysis of the above plots.[9]

Fourier transforms infrared spectroscopy (FTIR) studies

Infrared spectra for pure Cefuroxime and for the physical mixture of Cefuroxime and polymer was determined to check the intactness of the drug in the polymer mixture using FTIR - spectrophotometer. The samples were analyzed between wave numbers 4000 and 400/cm resolution.[15]

Differential scanning calorimeter (DSC) studies

The thermal behavior of pure Cefuroxime and Cefuroxime microspheres were studied using a DSC Perkin Elmer DSC at a heating rate of 10°C/minutes. Samples were accurately weighed into aluminum pans and then sealed. The measurements were performed at a heating range of 25-300°C under nitrogen atmospheres.[16,17]

Morphology of microsphere

The external and internal morphology of the microspheres were studied using scanning electron microscopy in Pune University (Physics Department). The sample was loaded on copper sample holder and sputter coated with platinum.

Drug entrapment efficiency

Microspheres (50 mg) were powdered and suspended in 50 ml of 0.1 N HCl followed by 30 minutes sonication. The solution was kept undisturbed for 24 hrs; and filtered. The filtrate recovered was examined spectrophotometrically at 227 nm, and entrapment efficiency was calculated by the following formula

Table 1: Formulation of microsphere.

Formulation No.	Drug Quantity	Sodium Alginate	Carbopol	Sodium CMC
F1	100 mg	200 mg	50 mg	50 mg
F2	100 mg	100 mg	75 mg	25 mg
F3	100 mg	200 mg	25 mg	75 mg
F4	100 mg	150 mg	50 mg	100 mg
F5	100 mg	150 mg	100 mg	50 mg
F6	100 mg	50 mg	75 mg	25 mg
F7	100 mg	175 mg	25 mg	75 mg
F8	100 mg	100 mg	50 mg	100 mg
F9	100 mg	150 mg	100 mg	50 mg

Stability study

Stability studies were carried out for Cefuroxime microsphere as per ICH guidelines. The best Floating microspheres formulation (F2) was sealed in high-density polyethylene bottles and stored at 25±2°C/60±5%, 40±2°C/75±5% relative humidity (RH) for 90 days. The samples (F2) were evaluated for entrapment efficiency and percentage mucoadhesion

RESULT AND DISCUSSION

The Cefuroxime microsphere was prepared by ionic gelation method. The formula optimization was done by 32 factorial design. The significant factors selected were concentration of sodium alginate and cross-linking agent. The dependant variables selected were entrapment efficiency, % mucoadhesion, and % drug release. Two factors affecting the experimental responses and three factors were selected as independent variables at three levels (−1, 0, +1) as shown in (Table 1). Polynomial equations for individual response reflect the relationship between dependent and independent factors The model was analyzed for fitting into appropriate mathematical model and evaluated statistically for analysis of variance. The response surface analysis was carried out employing the 3D response surfaces.

Percentage yield

The percentage yield of microspheres was calculated using the weight of final product after drying with respect to initial total weight. The maximum percentage yield was found of F2 batch and was noted to be 96.48% among all the batches. The production yields of microspheres prepared by ionotropic gelation method were found to be between 93% and 96% as shown in Table 2.

Particle size

The average particle size of Cefuroxime microspheres ranged from 589 µm.The mean particle size was significantly increased with increasing mucoadhesive polymer concentration this may be attributed to high viscosity of mucoadhesive polymer concentration (Table 2).

Table 2: Percentage yield, particle size, percentage mucoadhesion, in-vitro release ((%)±S.D (n=3)) data of all batches.

Formulation code	Percentage yield	Particle size	Percentage mucoadhesion	In-vitro release
F1	90.64±0.602	660±3.46	68.12±0.75	96.47±0.16
F2	96.48±0.617	589.2±2.68	72.39±1.11	90.2±0.36
F3	95.91±0.779	620±2.19	80.12±1.66	87.35±0.26
F4	96.65±0.56	493±3.65	71.1±1.26	88.37±0.36
F5	95.17±1.84	560.4±1.54	79±1.46	82.58±0.41
F6	93.7±8.80	589.1±3.89	85±1.06	78.19±0.04
F7	92.88±0.24	620.1±1.36	75.5±0.96	80.17±0.36
F8	96.72±0.71	493.2±1.27	81.3±1.46	78.64±0.29
F9	93.70±0.80	560.3±1.94	80.31±1.56	75.89±0.26

Morphology of microspheres

The morphology of the mucoadhesive microspheres of best formulation F2 was examined by scanning electron microscopy (SEM). The SEM Photographs revealed that ritonavir microspheres were discrete and irregular shape with a rough surface morphology (Fig. 1).

Entrapment efficiency

The maximum percentage yield was found of F2 batch and was noted to be 95.27% among all the batches. This may be attributed to increase in concentration of the sodium alginate polymer increased the entrapment efficiency of the microspheres due to the formation of more intact matrix network.

In-vitro drug release studies

The in-vitro drug release studies were carried out for all batches of microspheres shown in Fig. 4. Drug release from these floating microspheres were slow, controlled release, and dependent on the nature and concentration of

polymers used. Among all the formulations F2 showed good dissolution profile with 97.97%. It was found that drug release rate decreased as the concentration of polymer increased and also with increased concentration of cross-linking. Hence, it is considered as the best microsphere formulation, which seems to be a good candidate for controlled release of Cefuroxime axetil.

DSC studies

The thermal behavior of prepared Cefuroxime microsphere was studied in comparison with thermograms of pure Cefuroxime as shown in (FIg 7) the thermogram of pure Cefuroxime showed sharp endothermic peak at 195 c whereas formulation containing Cefuroxime showed 2 melting endothermal at 126.95°C and 190.14°C which correspond to melting platinum of polymer and drug indicating that there is no interaction between drug and polymer as shown in Fig. 7

FTIR studies

FTIR spectrum of pure drug and Floating microsphere of drug and polymers were studied (Fig. 5). It was observed that Cefuroxime showed Characteristic peak at 3337/cm for –NH group whereas sodium alginate showed –CO group at 1670/cm –OH group at3100/cm and NH group at 3563. While carbopol showed –CO group at 1653/cm however shift in –CO group peak of polymer (alginate) and –NH group of OLE to 1696/cm and 3563/cm suggested possibility of H-bonding between drug and polymer

Stability studies

Stability studies for the optimized microsphere were carried out at a temperature of 40±2°C/RH 75±5% for a period of 90 days. Formulation good stability during their shelf life any significant change in physical appearance and drug content during stability studies. Hence, it was concluded that the F2 batch of microsphere has was evaluated for physical appearance and drug content. There was no any significant change in physical appearance and drug content during stability studies. Hence, it was concluded that the F2 batch of Cefuroxime has good stability during their shelf life.

CONCLUSION

This study has been attempted to formulate a Floating microsphere of Cefuroxime for oral administration for increasing bioavailability of the drug. The results of 3^2 full factorial design revealed that the concentration of sodium alginate significantly affected the dependent variables percentage mucoadhesion, drug entrapment efficiency, and drug release property. Microsphere formulation of Cefuroxime was prepared using ionic gelation method using sodium alginate as polymer and calcium chloride as a cross-linking agent. From the results, it can be concluded that the IR and DSC spectra revealed that there was no interaction between polymer and drug Cefuroxime. The particle size analysis revealed that all formulations having particles in the range of 546.0-553.3 µm. Among all the formulation F2 was selected as best formulation which showed the good entrapment efficiency (96.12%), good mucoadhesion in 8 hrs (80.31%) and good drug release profile (75.89%). In-vitro drug release data followed Higuchi model with regression values ranging from 0.9439 to 0.9971. SEM analysis of the F2 microspheres revealed that the formulation was spherical and rough surface morphology. The prepared Floating microspheres of Cefuroxime showed sustained release action with increased therapeutic efficacy and increased patient compliance.

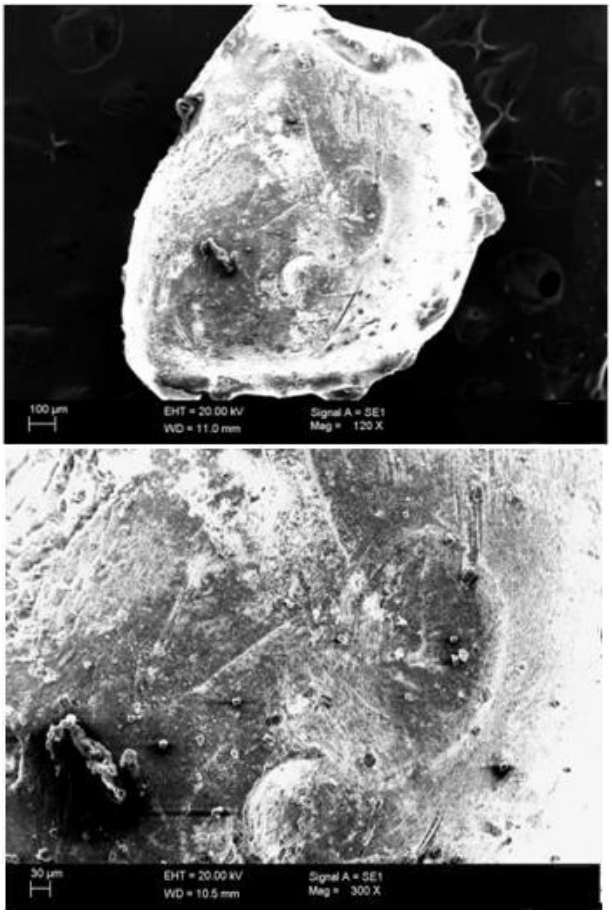

Fig. 1: Scanning electron photomicrographs of the formulation F2.

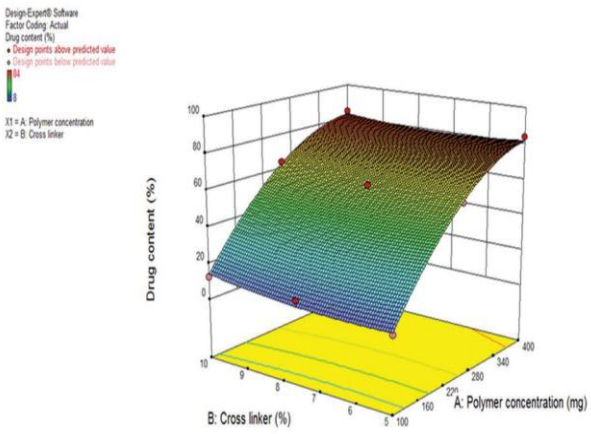

Fig. 2: Drug content 3 D graph.

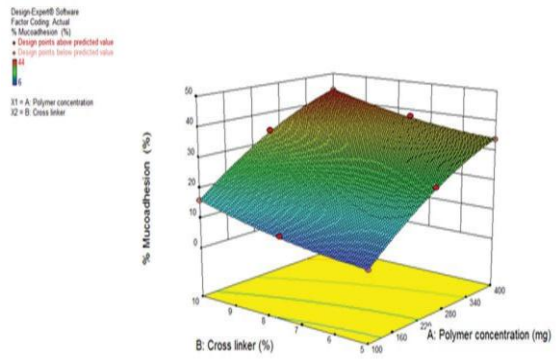

Fig. 3: Percent 3 D graph.

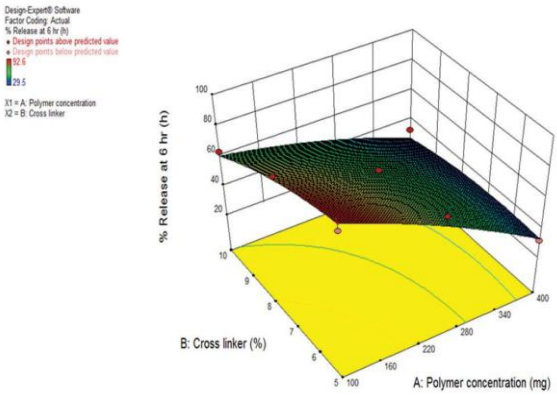

Fig. 4: Percent drug release 3 D graph.

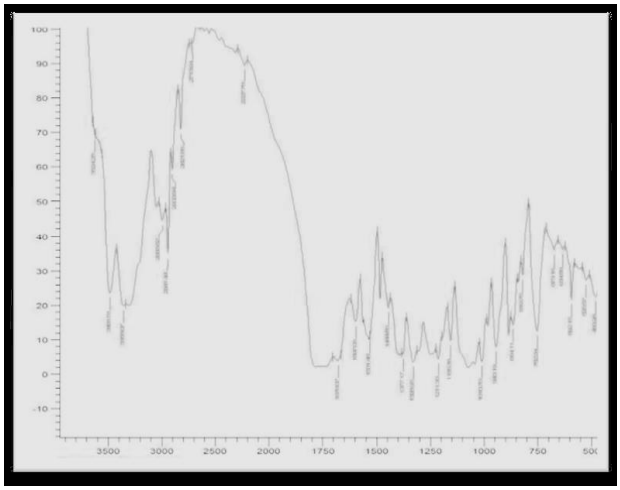

Fig. 5: Fourier transforms infrared of pure Cefuroxime axetil.

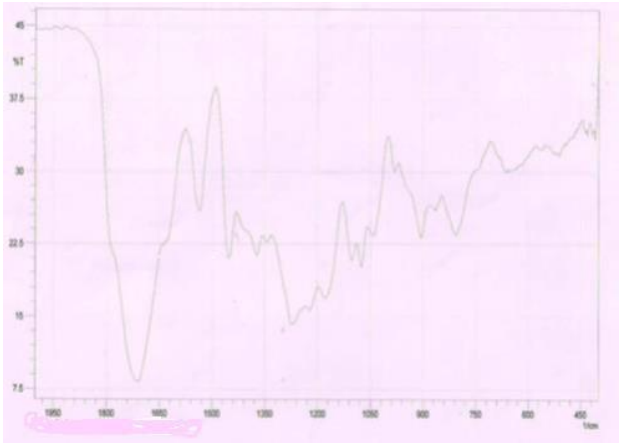

Fig. 6: Fourier transforms infrared of Cefuroxime axetil microsphere.

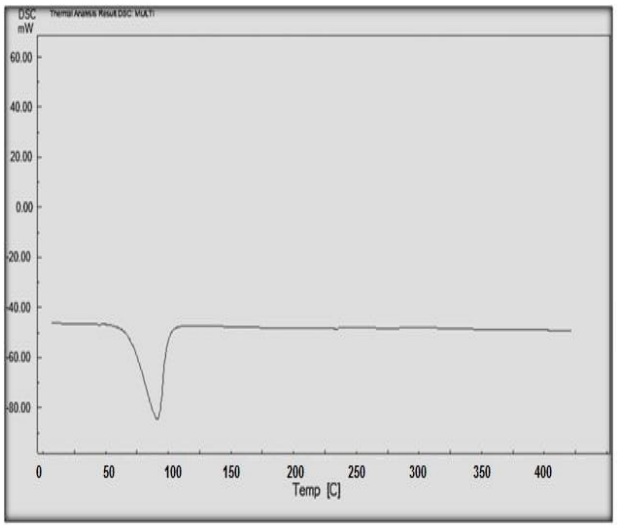

Fig. 7: Differential scanning calorimeter thermogram of Cefuroxime axetil.

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REFERENCES

1. Alexander Streubel. Drug Delivery to the upper small intestine window using Gastroretentive technologies, current option in pharmacology, 2006: 6:501 – 508.
2. Bardonn. PL, Faivre V, Pugh WJ,. Piffaretti JC, Falson. F. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. J. Control. Rel., 2006; 111: 1-18.
3. Bechgaard H, Ladefoged K. Distribution of pellets in the gastrointestinal tract. The influence on tramsit time exerted by the density or diameter of pellets, J. Pharm. Pharmacol, 1978; 30: 690-692.
4. Caldwell LJ, Gardner RC, Cargill RC. Drug delivery device which can be retained in the stomach for a controlled period of times, US patent4735804, April 5, 1988.

5. Chavanpatil, P. chaudari, vavia P, Development of Sustained release gastroretentive drug delivery system, Int. J. Pharm, 2005; 304(1-2): 178-184.
6. Chen GL, Hao WH. In Vitro performance of floating sustained-release capsule of Verapamil. Drug DevInd Pharm, 1998; 24(11): 1067-72.
7. Chen J, park k, Synthesis and characterization of superporous hydrogel composites. ,J. Contro. Release, 2000; 65(1-2): 73-82.
8. Chien Y. W., "Novel Drug Delivery system", (2nd ed.), Marcel Dekker, 1992; 139-196.
9. Dave BS, Amin AF, Patel MN. Gastroretentive drug delivery systems of Ranitidine HCl: Formulation &In vitro evaluation. AAPS Pharm Sci Tech, 2004; 5(2): Article 34.
10. Davis SS. "Formulation strategies for absorption, windows", Drug Discovery Today. 2005; 10: 249-256.
11. Dennis A, Timmins P, Lee K. Buoyant controlled release powder formulation.US patent, 8 Dec 1992; 5: 169-638.
12. Desai S, Bolton S. A floating controlled-release Drug Delivery system: In-vitro – in vivo Evaluation. Pharma Res., 1993; 10: 1321-5.
13. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention, Pharm.Res., 1997; 14: 815-819.
14. Drs Jose, Progresses in Gastroretentive Drug Delivery Systems.,Business Briefing Pharmatech, 2009.
15. Gerogiannis VS, Rekkas DM, Dallas PP, Choulis NH. Floating and swelling characteristics of various excipients used in controlled release technology. Drug DevInd Pharm, 1993; 19(9): 1061-81.
16. Groning R, Heum G, Dosage forms with controlled gastrointestinal passage-studies on the absorption of nitrofuranto, Int. J. Pharm, 1989; 56: 111-116.
17. Gutierrez-rocca J, Omidian H, Shah K. "Progress in Gastroretentive drug delivery systems", Business Briefing, Pharmatech, 2003; 152-156.
18. Hilton AK, Deasy PB. In vitro and In vivo evaluation of an oral sustained release floating dosage form of Amoxicillin trihydrate. Int J Pharm, 1992; 86: 79-88.
19. Hou, SY, Cowles VE, Berner B. "Gastric retentive dosage forms: a review", Crit. Rev. Ther. Drug Carrier Syst, 2003; 20(6): 459-97.
20. Iannuccelli V, Coppi G, Leo E, Fontana F, Bernabei MT. PVP Solid dispersions for the controlled release of furosemide from a floating multiple-unit system. Drug DevInd Pharm, 2000; 26(6): 595-603.
21. Ichikawa M, Watanabe S, Miyake Y.A New multiple-unit oral floating dosage system. Preparation and in-vitro evaluation of floating and sustained-release characteristics. J Pharma Sci, 1991; 80(11): 1062-066.
22. Inez Jimenezmartinez, Tomas Quirino-Berreda and Leopolda Villafuerte-Robles. Sustained delivery of captopril from gloating matrix microspheres. Int. J. Pharm, 2008; 362: 37-43.
23. Ingani HM, Timmermans J, Moes AJ. Conception and in vivo investigation of per oral sustained release floating dosage forms with enhanced gastrointestinal transit. Int J Pharm, 1987; 35: 157-64.
24. Jain NK. "Advance in Controlled and Novel drug delivery", CBS publisher and distributor, New Delhi, 76-95.
25. Jimenez-Castellanos MR, Zia H, Rhodes CT. Design and testing in vitro of a bioadhesive and floating drug delivery system for oral application. Int J Pharm, 1994; 105: 65-70.
26. Katayama H, Nishimura T, Ochi S, Tsuruta Y, Yamazaki Y. Sustained release Liquid preparation using sodium alginate for eradication of Helicobacter pylori. Biol Pharm Bull, 1999; 22: 55-60.
27. Kawashima Y, Niwa H, Takeuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug dlivery system in the stomach. J Pharm Sci, 1992; 81: 135-40.
28. Krogel I, Bodmeier R. Development of a multifunctional matrix drug delivery system surrounded by an impermeable cylinder. J ContrRel, 1999; 61: 43-50.