International Journal of Applied Pharmaceutics
Vol 2 Issue 1, 2010

Research Article

FORMULATION AND IN VITRO EVALUATION OF FLOATING MICROSPHERES OF KETOPROFEN PREPARED BY EMULSION SOLVENT DIFFUSION METHOD

M. NAJMUDDIN[1]*, SACHIN SHELAR, ASGAR ALI, V. PATEL, T. KHAN

[1]Department of pharmaceutics, Luqman College of Pharmacy, Gulbarga-585102. E mail- mmnnaj@gmail.com

ABSTRACT

The aim of present work is to prepare floating microspheres of ketoprofen using Eudragit S 100 and Eudragit L 100 as polymer. Floating drug delivery system have a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. Ketoprofen is nonsteroidal antiinflammatory drug with short elimination half life 1-3 hours. The short half life of ketoprofen and multiple administration dose make ketoprofen a very good candidate for formulation of floating drug delivery system. Floating microspheres of ketoprofen were prepared by emulsion solvent diffusion method using Eudragit S 100 and Eudragit L 100 as polymer. The floating microspheres was evaluated such as micromeritic properties, particle size, percentage yield, in vitro buoyancy, incorporation efficiency, drug polymer compatibility (IR study), scanning electron microscopy and drug release of microspheres. The micromeritic properties was found to be good and scanning electron microscopy confirmed their hollow structure with smooth surface. Formulation EU_2 prepared with Eudragit S 100 drug:polymer ratio (1:2) which exhibited excellent micromeritic properties, percentage yield, in vitro buoyancy, incorporation efficiency and percentage drug release 92.26 % for a period of 12 hrs. Results show that as increase in drug:polymer ratio affects the particle size, percentage yield, in vitro buoyancy and drug release of microspheres.

The data obtained in this study thus suggest that a floating microspheres of ketoprofen are promising for sustained drug delivery which can reduce dosing frequency.

Keywords: Ketoprofen, Eudragit S 100, Eudragit L 100, Floating microspheres.

INTRODUCTION

To develop oral drug delivery systems, it is necessary to optimize both the residence time of system within the gastrointestinal tract and release of drug from the system[1]. Drugs that are easily absorbed from the gastrointestinal tract and have a short half life are eliminated quickly from the blood circulation and require frequent dosing. To avoid this problems, the oral controlled release formulations have been developed in an attempt to release the drug slowly into the gastrointestinal tract and maintain a constant drug concentration in the serum for a longer period of time. Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation. Therefore prolonged gastric retention is important in acheiving control over the GRT because this helps to retain the controlled release system in the stomach for a longer time in a predictable manner. Various attempts have been made to prolong the residence time of the dosage forms within the stomach. The prolongatoion of the GRT of delivery devices could be acheived by adhesion to the mucous membranes, by preventing their passage through the pylorus or by maintaining them in buoyant fashion in gastric juice. Unfortunately floating devices administered in a single unit form (tablet) such as hydrodynamically balanced systems are unreliable in prolonging the GRT owing to their "all or none" emptying process and thus, they may cause high variability in bioavailibility and local irritation due to a large amount of drug delivered at a particular site of GIT. In contrast, multiple unit particulate dosage form (e.g.microspheres) have the advantages that they pass uniformly through the git to avoid the vagaries of gastric emptying and provide an adjustable release, thereby reducing intersubject variability in absorption and risk of local irritation[2,3]. Ketoprofen (2-aryl propionic acid derivative) is an important analgesic and nonsteroidal anti inflammatory drug, also with antipyretic properties, whose mechanism of action is the inhibition of prostaglandin synthetase. This drug is used in therapy of rheumatic disorder and its plasma elimination half life is 1 to 3 hours, and in order to maintain therapeutic plasma level drug must be administered at least thrice a day[4,5].

On the other hand, eudragit (methacrylate copolymers) have been recently received increased attention for preparing modified dosage forms because of their inertness, solubility, in relatively non toxic solvents of resins with different properties.

The aim of present study was to develop and evaluate floating microspheres of Ketoprofen using Eudragit S-100 & Eudragit L-100 as polymer and emulsion solvent diffusion as a method of preparation. Ketoprofen whose physicochemical properties and short half life make it suitable candidate for floating drug delivery system.

MATERIALS AND METHODS

Materials

Ketoprofen was received as gift sample from Ciron Drugs and Pharmaceutical Pvt. Ltd. Mumbai (India), Eudragit S 100 and Eudragit L 100 was received as gift sample from Deggusa india pvt. Ltd., Mumbai. ethanol, methanol, dichloromethane, tween 20 was obtained from SD fine chemicals Ltd., Mumbai (India). All other chemical and reagent used in this study were of analytical grade.

Method of preparation[6]

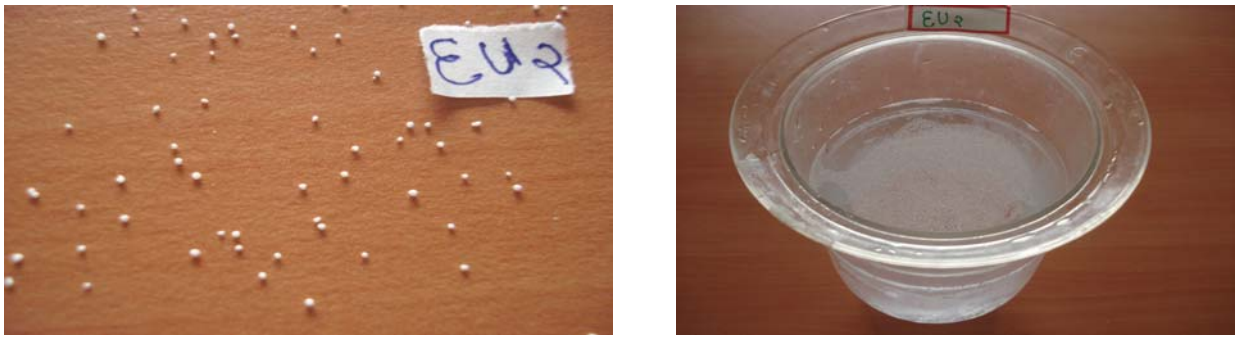
Floating micropsheres were prepared by emulsion solvent diffusion method. Weighed amount (as shown in table 1) of ketoprofen was mixed with Eudragit S 100 and Eudragit L 100 drug:polymer ratio (1:1, 1:2, 1:3) in a solution of ethanol :dichloromethane (1:1) at room temperature. The resulting drug polymer solution was poured slowly using glass tube into 200 ml of water containing 0.75 % w/v polyvinyl alcohol, maintained at constant temperature of 40^0 c and preparation was stirred at 300 rpm for 1 hr. The finely developed floating microspheres were then filtered, washed with water and seived between 50 and 30 mesh size and dried overnight at 40^0 C.

Evaluation of floating microspheres

Yield of Floating microspheres[7,8]:

The prepared floating microspheres with a size range of 102 - 192 µm were collected and weighed. The measured weight was divided by total amount of all non-volatile components which were used for the preparation of microspheres.

% yield = (Actual weight of product / Total weight of excipient and drug) x 100



(A) **(B)**

Fig. 1: Image showing floating microspheres of ketoprefen formulations: (A)In vitro buoyancy of EU_2 (b) Particle of EU_2

In vitro Buoyancy[1,9,2]

Floating microspheres (equivalent to 100 mg) were dispersed in 900ml of 0.1 N hydrochloric acid solution (pH 1.2) containing tween 20 (0.02 W/V%) to simulate gastric fluid at 37°. The mixture was stirred with a paddle at 100 rpm and after 12 hr, the layer of buoyant microspheres (W_f) was pipetted and separated by filtration simultaneously sinking microspheres (W_s) was also separated. Both microspheres type were dried at 40°C overneight. Each weight was measured and buoyancy was determined by the weight ratio of the floating microsphers to the sum of floating and sinking microsphers.

Incorporation efficiency[10,11]

Floating microspheres were dissolved in a minimum amount of methanol and drug was extracted into suitable aqueous media (0.1 N hydrochloric acid) by evaporating methanol. The solution was filtered through whatman filter paper, diluted suitably and analyzed for drug content spectrophotometrically at 254 nm using 0.1N hydrochloric acid as blank

Micromeritic properties[11]

The floating microspheres were characterized by their micromeritic properties such as particle size, bulk density,tapped density, hausners ratio, carr's index and angle of repose.

Drug release[13]

Drug release from Floating microspheres having a size range between 102 - 192 μm and floating microspheres equivalent to 150 mg of drug was carried out using paddle method at 100 rpm, for the first 2 hrs in pH 1.2 with tween 20 (0.02 W/V%) to simulate gastric fluid and 10 hrs in phosphate buffer pH 7.4. with tween 20 (0.02 W/V%) to simulate gastric fluid. Each time 5 ml of samples were withdrawn at different time intervals and replaced with fresh phosphate buffer, the amount of drug release was analyzed at 254 nm using shimadzu UV visible spectrophotometer.

Table 1: Formulation table of floating microspheres of ketoprofen

Ingredients	Formulation code					
	EU_1	EU_2	EU_3	EU_4	EU_5	EU_6
Eudragit S 100	0.500	1.000	1.500	-	-	-
Eudragit L 100	-	-	-	0.500	1.000	1.500
Ketoprofen	0.500	0.500	0.500	0.500	0.500	0.500
Ethanol	8	8	8	8	8	8
Dichloromethane	8	8	8	8	8	8

Table 2: Percentage yield, in vitro buoyancy and incorporation efficiency of floating microspheres of ketoprofen

Formulation code	Percentage yield	In vitro buoyancy	Incorporation efficiency
EU_1	62.40 ± 0.72	80.66 ± 2.08	61.59 ± 1.58
EU_2	86.13 ± 2.00	87.00 ± 1.00	81.70 ± 2.02
EU_3	89.45 ± 1.50	91.66 ± 1.52	79.94 ± 2.28
EU_4	65.26 ± 2.05	71.66 ± 4.04	61.07 ± 0.98
EU_5	77.73 ± 1.51	90.33 ± 1.52	71.78 ± 2.34
EU_6	81.08 ± 1.97	91.33 ± 3.05	79.03 ± 2.00

All values are represented as mean ± standard deviation (n=3)

RESULTS AND DISCUSSION

Method of introducing polymer solution

The high surface tension of water caused the solidification and aggregation of Eudragit S100 and Eudragit L 100 on the surface of aqueous phase. To minimize the contact of polymer solution with the air - water interface and to develop a continuous process for preparing microspheres, a new method of introducing the polymer solution into aqueous phase was developed. The method involves the use of a glass tube immersed in an aqueous phase and the introduction of the polymer solution through the glass tube without contacting the surface of water. This method improved the yield of microspheres and reduced the extent of aggregate formation and made it possible to make microspheres continuously. As the polymer solution is continuously introduced into the main vessel, it will overflow from the top of the vessel together with the prepared microspheres, since most of the formed microspheres will float on the top of the aqueous phase.

Yield of microspheres

The percentage yield of microspheres was in range of 62.40± 0.72 to 89.45 ± 1.50 (as shown in table 2). To observe the effect of polymer concentration on the percentage yield of the resulting microspheres formulation were prepared using varying drug: polymer ratio of Eudragit S 100 and Eudragit L 100. The percentage yield of the microspheres was found to be increased with increasing Eudragit S100 and Eudragit L 100 concentration.

In vitro buoyancy

The in vitro buoyancy test was carried out to investigate buoyancy of prepared microspheres. The microspheres formulations $EU_1$to EU_6 showed good floating ability range from 80.66 ± 2.08 to 91.66 ± 1.52.(as shown in table 2). The results also showed a tendency that, larger the particle size longer the floating time.

Incorporation efficiency

The incorporation efficiency of formulation F1 to F6 was carried out and found to be in a range 61.07 ± 0.98 to 81.70 ± 2.02 (as shown in table 2.)

Micromeritic properties

The mean particle size of floating microspheres formulation EU_1 to EU_6 was found to be 102.33 ± 15.27 to 192.33 ± 27.50 (as shown in table 3). The effect of polymer concentration on the particle size of floating microspheres was determined. The mean particle size of the microspheres was found to be increase with increasing Eudragit concentration (as shown in table 1). The viscosity of medium increases at a higher Eudragit concentration resulting in enhanced

interfacial tension. Shearing effieincy is also diminished at higher viscosities. This results in the formation of larger particles. The bulk density, tapped density, hausners ratio of formulation EU_1 TO EU_6 ranges from 0.591 ± 0.04 to 0.722 ± 0.02gm/cm^3, 0.652 ± 0.05 to 0.773 ± 0.016 gm/cm^3, 1.04 ± 0.02 to 1.10 ±0.03 respectively. The carr's index ranges between 5.00 ± 2.34 to 10.01± 1.05 %. The angle of repose of microspheres ranges from 13.25 ± 2.40 to 20.07 ± 1.68 (as shown in table 3). The values of carr's index and angle of repose indicate excellent flow properties.

Infrared spectroscopy

The FT-IR spectra study showed no change in the finger print of pure drug spectra, thus confirming absence of drug and polymer interaction.

Table 3: Micromeritic properties of floating microspheres of ketoprofen

Formulation code	Mean particle size	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausners ratio	Carr's index	Angle of repose
EU_1	123.33±15.27	0.622±0.05	0.692±0.07	1.10±0.01	10.1±1.05	16.77±1.43
EU_2	161.33±11.01	0.632±0.02	0.684±0.03	1.07±0.03	7.63±2.66	19.11±2.42
EU_3	192.33±27.50	0.674±0.03	0.725±0.05	1.04±0.02	5.00±2.34	20.07±1.68
EU_4	102.33±21.12	0.591±0.04	0.652±0.05	1.10±0.01	9.16±0.80	16.79±1.59
EU_5	122.66±19.60	0.658±0.03	0.707±0.05	1.07±0.03	6.80±3.29	20.07±1.68
EU_6	156.66±27.53	0.722±0.02	0.773±0.01	1.06±0.02	4.73±2.73	13.25±2.40

All values are represented as mean ± standard deviation (n=3)

(A) **(B)**

Fig. 2: *in vitro* buoyancy of floating microspheres of ketoprofen: (A) formulation EU_1 To EU_3 (B) EU_4 to EU_6

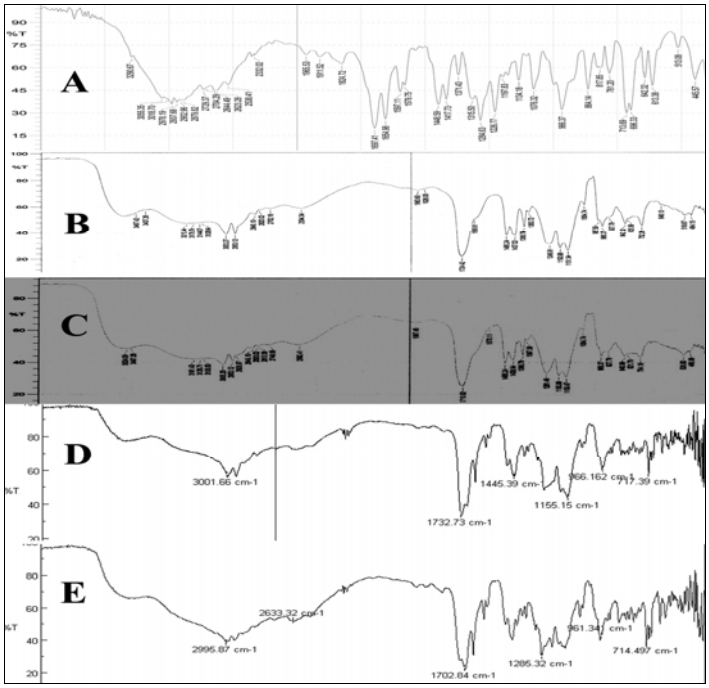


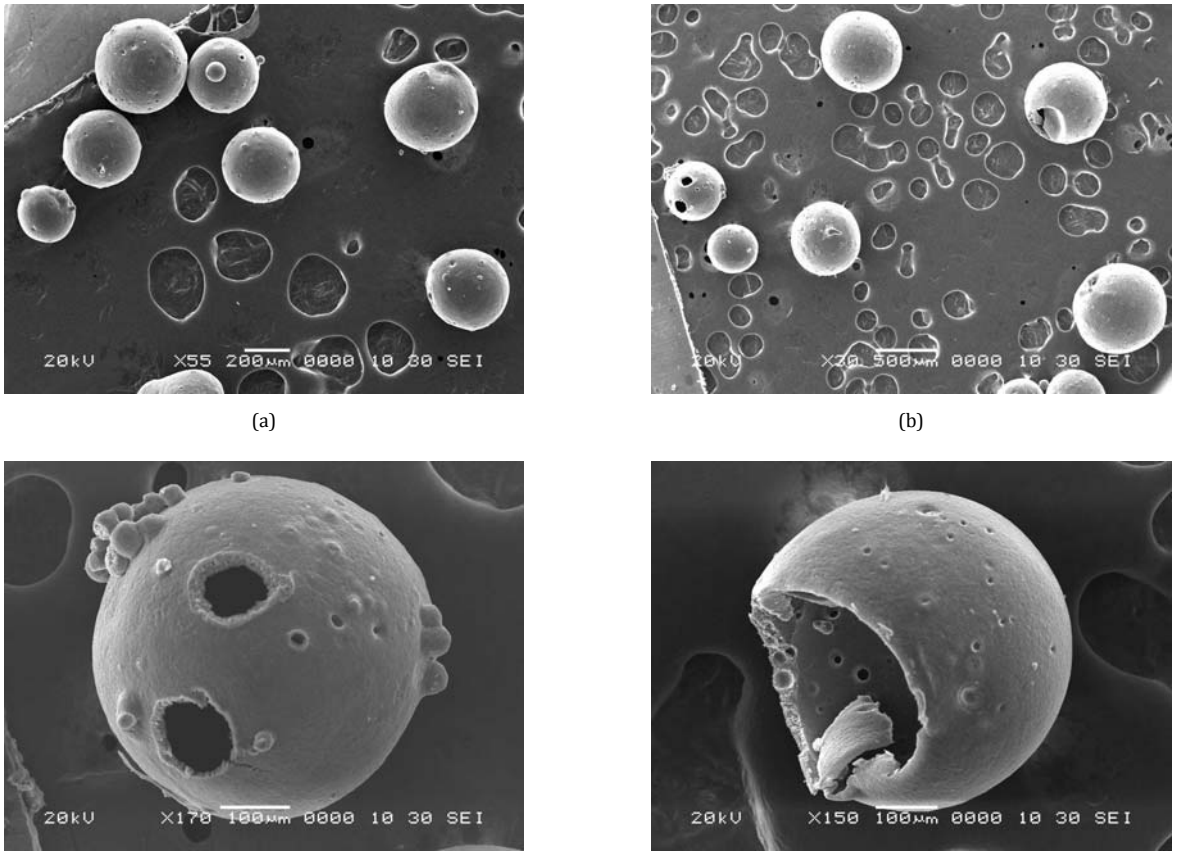
Fig. 3: Image showing drug polymer interaction study by FT-IR: (A) Ketoprofen (B) Eudragit S 100 (C) Eudragit S 100 (D) EU_2 (E) EU_4

Scanning electron microscopy (SEM)

Morphology of floating microspheres was examined by scanning electron microscopy. The view of the microspheres showed hollow structure with a smooth surface morphology (fig. 3 a, b, c) exhibited range of sizes within each batch. The outer surface of microspheres was smooth and dense, while the internal surface was porous. The shell of microspheres also showed some porous structure (fig. 3d) it may be caused by evaporation of solvent entrapped within the shell of microsphere after forming smooth and dense layer.

Drug release

The drug release from formulation EU_1 TO EU_6 (as shown in fig 5) was as follows. EU_1, EU_3, EU_4, EU_6 show percentage drug release 82.66 ± 0.95 to 90.31 ± 2.11 at end of 12 hour and formulation EU_2 and EU_5 show percent drug release 92.26 ± 1.96 and 90.31 ± 2.11 at end of 12 hr. Among all formulation EU_2 was found to be the best formulation as it release ketoprofen in a sustained manner with constant fashion over extended period of time (after 12 hr). it was observed as the concentration of Eudragit S 100 and Eudragit L 100 was increased percent release of ketoprofen decreases. The increase in Eudragit S 100 and Eudragit L 100 concentration leads to the increased density of polymer matrix into the microspheres which result in an increased diffusional path length. This may decrease the overall drug release from polymer matrix. Furthermore smaller microspheres are formed at lower polymer concentration and have larger surface area exposed to dissolution medium.



(a) (b)

(c) (d)

Fig. 4: Scanning electron microphotographs of floating microsphere of ketoprofen: (a) & (b) smoothness of the surface of spherical shaped microsphere (c) & (d) internal view of the shell having porous structure.

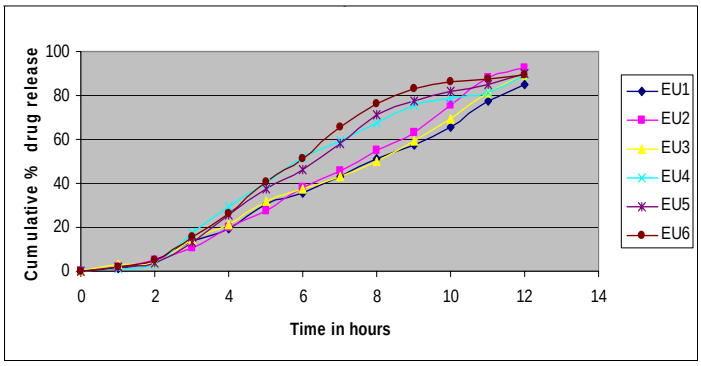


Fig. 5: *In vitro* drug release profile of floating microspheres of ketoprofen formulation EU_1 to EU_6

CONCLUSION

Floating microspheres of ketoprofen with enteric acrylic polymers such as Eudragit S 100 and Eudragit L 100 were successfully prepared by the emulsion solvent diffusion method. The formulation EU_2 with drug:polymer ratio (1:2) was found to be satisfactory in terms of excellent micromeritic properties, yield of microspheres (86.13 %), incorporation efficiency (81.70 %), in vitro buoyancy (87.00 %) and highest in vitro drug release of 92.26 % in sustained manner with constant fashion over extended period of time for 12 hrs. From the results it was observed that Drug: Polymer ratio influences the particle size, in vitro buoyancy, as well as drug release pattern of floating microspheres.

ACKNOWLEDGEMENTS

Author's are thankful to Principal Luqman College of Pharmacy, Gulbarga (India) for providing research laboratory to carry out this project work and also extend thanks to Ciron Drugs and Pharmaceutical Pvt. Ltd., Mumbai for providing gift sample of ketoprofen and thanks to Deggusa india pvt. Ltd., Mumbai for providing gift sample of Eudragit S 100 and Eudragit L 100.

REFERENCES

1. Yasunori Sato, Yoshiaki Kawashima, Hirofumi takeuchi, hiromitsu yamamoto. In vitro evaluation of floating and drug releasing behaviour of hollow microsphers (microballoons) prepared by emulsion solvent diffusion method. European journal of pharmaceutics and biopharmaceutics 2004; 57: 235–243.
2. J.Varshosaz, M Tabbakhian, M.Zahrooni. Development and Characterization of floating microballoons for oral delivery of cinnarazine by a factorial design. Journal of microencapsulation 2007; 24 (3): 253–262.
3. Kumaresh S. Soppimath, Anandrao R Kulkarni, Tejraj M Aminabhavi. Development of Hollow Microspheres as Floating Controlled-Release Systems for Cardiovascular Drugs: Preparation and Release Characteristics. Drug Development and Industrial Pharmacy 2001; 27(6): 507-515.
4. Martindale,the complete drug refrence, 33 rd edition, edited by sean c.sweetman, published by pharmaceutical press, london, 2002:11:65: 47-48.
5. Klaus Florey. Analytical profiles of drug substances. Elsevier, New Delhi, 2006; 443-471.
6. Basavaraj BV, Deveswaran R, Bharath S, Sindhu Abraham, Sharon Furtado, Madvan V. Hollow microspheres of diclofenac sodium – A gastroretentive controlled drug delivery system. Pakistan journal of pharmaceutical sciences 2008; 21(4):451-454.
7. Yogesh S Gattani, Durgacharan A Bhagwat, Akhil P Maske. Formulation and evaluation of intragastric floating drug delivery system of dilitiazem hydrochloride. Asian journal of pharmaceutics 2008; oct-dec:228-231
8. Asha Patel, Subhabrata Ray, Ram Sharangat Thakur. In vitro evaluation and optimization of controlled release floating drug delivery system of metformin hydrochloride. DARU 2006; 14(2): 57–64.
9. Yuveraj Singh Tanwar, Pushpendra Singh Naruka, Garima Rani Ojha. Development and evaluation of floating microspheres of verpamil hydrochloride. Brazilian Journal of Pharmaceutical Sciences 2007; 43 (4): 529–534.
10. Shashikant P Bharate, Yogesh S rupnvar, Rupesh M Sonvane, Kapil R. Pawar, Rahulkumar P Rahane. Formulation and evaluation of floating microspheres of ketrolac trometamol. International journal of pharmaceutical research and development online 2009; 1(9): 1-8
11. Parul trivedi, AML verma, N garud. Preparation and characterization of aceclofenac microspheres . Asian journal of pharmaceutics 2008; APRIL: 110-115.
12. M.Saravanan, K.Bhaskar, G.Srinivasa Rao and M.D. Dhanaraju. Ibuprofen loaded ethylcellulose / polystyrene microsphers an approach to get prolonged drug release with reduced burst effect and low ethylcellulose content. J.Microencapsulation 2003; 20 (3): 289–302.
13. R D kale, P T Tayade. A multiple unit floating drug delivery system of piroxicam using eudragit as polymer. Indian journal of pharmaceutical sciences 2007:jan-feb: 120-123.
14. Ashishkumar jain, C P Jain, Y S Tanwar, P S Naruka. Formulation, characterization and in vitro evaluation of floating microspheres of famotidine as a gastroretentive dosage form. Asian journal of pharmaceutics 2009; jul-sep: 222-226
15. S Haznedar, B Portune. Preparation and in vitro evaluation of eudragit microspheres containing acetazolamide. International journal of pharmaceutics 2004;269: 131-140
16. Mostafa Safari, Malihe Shahbazi, Shafee ardestani. Formulation and in vitro evaluation of eudragit L 100 micropshere of piroxicam. Nature preceddings 2008:1-5.
17. Amol Pahuri, aweshik yadav, sunil k jain, shyam s Panholi, govind agrawal. Eudragit coated pectin microspheres of 5-flurouracil for colon targeting. AAPS pharscitech 2007;8(1): E87-E93.