MIT International Journal of Pharmaceutical Sciences, Vol. 3, No. 1, January 2017, pp. 34–39
ISSN 2394-5338 (Print); 2394-5346 (Online) © MIT Publications

Original Article

Optimization and evaluation of Prazosin hydrochloride floating tablets

Virendra P. Omre*, Neelima Goswami, A.K. Pathak

Department of Pharmacy, Barkatullah University, Bhopal, Madhya Pradesh, India

Corresponding Author. Tel: +91 9752529694; *E-Mail address:* prasad11@gmail.com

ARTICLE INFO
Received 20 Jan 2017
Revised 27 Feb 2017
Accepted 28 Feb 2017

Keywords:
- Floating tablet
- Dissolution studies
- HPMC
- Floating lag time
- Diffusion
- Buoyancy
- Bioavailability

ABSTRACT

Prazosin HCl is an antihypertensive agent with short elimination half-life, pH-dependent solubility and narrow absorption window. So, the present study aimed to prolong its gastric residence time that entailed a development of an optimized gastro retentive floating tablets (GRFTs) using. The tablets were fabricated by direct compression using hydroxyl propyl methylcellulose and carbopol 934 as release retarding polymers. The quality attributes of the tablets were evaluated. The buoyancy lag time, total floating time, swelling ability and *in-vitro* release studies were also carried out in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C. Statistical data analysis revealed that the optimized formulation containing 21.91% HPMC and 15% carbopol 934 had acceptable hardness, optimum floating behavior and 24h controlled-release pattern. The design succeeded to develop CVD-GRFTs with floating ability and controlled release behavior that could improve its solubility, and improve its availability at the best absorptive site.

1. INTRODUCTION

Prazosin hydrochloride, a selective alpha-adrenergic receptor blocking agent, was loaded in the hollow floating tablet to improve bioavailability and patient compliance by prolonging the residence time in the gastrointestinal tract. The present study involves preparation and evaluation of floating tablet with Prazosin hydrochloride as model drug for prolongation of gastric residence time [1]. The sustain release gastro retentive dosage form offer many advantages for Prazosin hydrochloride drug. gastroretentive dosage form improves the bioavailability and reduces the side effect of Prazosin hydrochloride. The oral route is the most common and preferable route for the delivery of drugs. This may be due to ease of administration, patient compliance and flexibility in formulation [2-5]. The concept of floating tablet can also be utilized to minimize the irritant effect of weakly acidic drugs in the stomach by avoiding direct contact with stomach mucosa and providing a means of getting a low dosage for a prolonged period. Prazosin hydrochloride exhibit half-life of 2 to 3hrs which are neither very slow nor very fast rates of absorption and excretion. Drugs with very short half-life, $t_{1/2}$< 2 hrs are poor candidates for extended release dosage form because of the large quantities of drug required for such a formulation whereas those drugs with a very slow rate of excretion also do not need to be formulated as an extended release product. Prazosin hydrochloride is uniformly absorbed from the gastro intestinal tract. Prazosin hydrochloride possess a good margin of safety, the most widely used as a measure drug's safety is its therapeutic index, i.e., the median toxic dose divided by the median effective dose for very potent drugs the therapeutic index may be narrow or very small. The larger the therapeutic index the safer the drug. Drugs which are administered in very small doses or possess very narrow therapeutic index are consider as poor candidates for formulation into extended release formulations because of technological limitations, as precise control over release rate and risk of dose "dumping" due to a product defect [6]. They are used in the treatment of chronic rather than acute conditions of hypertension. The purpose of the present study was to develop an optimized gastric floating drug delivery system (GFDDS) to prolong the gastric residence time after oral administration, at a particular time and controlling the

ISSN 2394-5338 (Print); 2394-5346 (Online) © MIT Publications

release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Floating dosage form containing Prazosin hydrochloride as drug was designed for the treatment of hypertension. The dosage form was formulated by using polymers of different viscosity as gelling agents, sodium bicarbonate as gas generating agent and other excipients. Incorporation of gas generating agent together with polymer improved drug release. Effect on varying the concentration of ingredients was seen on hardness, *in-vitro* buoyancy, *in-vitro* drug release [7-9].

2. EXPERIMENTAL

Prazosin hydrochloride was obtained as a gift sample by Sun Pharmaceutical Pvt. Ltd. India, HPMC K15, K4M, Carbopol 934P, PVP, sodium bicarbonate, microcrystalline cellulose were obtained from Central Drug House (P) Ltd, India; Mg. stearate were supplied by Effective enterprises, Bhopal. All other reagents used were of analytical and pharmaceutical grade.

2.1 Preparation of floating tablet

Prazosin hydrochloride floating tablet were prepared by direct compression technique using varying concentrations of different grades of polymers with sodium bicarbonate and citric acid. All the ingredients were accurately weighted and pass through different mesh sieves. Then except magnesium stearate all other ingredients were blended uniformly in glass mortar after sufficient mixing of drug as well as other components, magnesium stearate was added, as post lubricant, and further mixed for additional 2-3 minutes. The tablets were compressed using rotary tablet machine. The weights of tablets were kept constant for all formulation [10].

Table 1. Different tablet compositions

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	10	10	10	10	10	10	10	10	10	10
HPMC K15M	100	-	75	50	50	75	50	75	100	100
HPMC K4M	-	-	25	50	-	25	25	-	-	50
CARBOPOL - 934 P	-	100	-	-	50	25	25	25	50	-
MCC	100	100	100	100	100	75	100	100	50	50
Sodium Bicarbonate	30	30	30	30	30	60	60	60	60	60
Citric Acid	15	15	15	15	15	30	30	30	30	30
PVP	5	5	5	5	5	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10	10	10	10	10
Total	260	260	260	260	260	310	310	310	310	310

NOTE: All the weights are in milligrams.

3. EVALUATION PARAMETERS [11, 12]

3.1 Evaluation of flow property of granules *(*Pre-compression parameters)[13-16]

(*a*) *Angle of Repose*

Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a white paper is placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. These studies were carried out before and after incorporating lubricant/glidant. The angle of repose (θ) was then calculated.

$$\tan\theta \frac{h}{r} \text{ And } \tan^{-1}\frac{h}{r}$$

(Where, θ = Angle of repose, h = Height of the cone base, r = Radius of the cone base)

(b) Bulk Density

Bulk density was determined using bulk density apparatus by placing a stack of powder into a measuring cylinder.

$$\text{Bulkiness} = \frac{1}{\text{Db}}$$

(Where, Db = Bulk density)

$$\text{Db} = \frac{\text{M}}{\text{Vb}}$$

(Where, Db =Bulk density, M = Weight of sample (gm), Vb = Bulk volume (untapped volume)

(*c*) *Tapped Density*

Tapped density was determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapping apparatus, which is operated for a fixed number of taps (100) or until the powder bed volume has reached a minimum. The tapped density is computed by taking the weight of drug in cylinder and final tapped volume of powder/granules

Tapped density is expressed in g/ml and is given by formula:

$$\text{Dt} = \frac{\text{M}}{\text{Vt}}$$

(Where, M = Mass of powder, Vt = Tapped volume of the powder)

(*d*) Carr's index (or) % compressibility

It is also known as compressibility index as it is used to determine compressibility of a powder. If powder particles are more compressible that means they have less flowing property. Carr's index also expressed as percentage and can be given as:

$$\text{I} = \frac{\text{Dt} - \text{Db}}{\text{Dt}} \times 100$$

(Where, Dt = Tapped density of the powder, Db = Bulk density of the powder)

(*e*) Hausner's ratio

Hausner's has given an index to explain flow property of powder. This ration is known as Hausner's ratio and can be given as:

$$\text{Hausner's Ratio} = \frac{\text{Dt}}{\text{Db}}$$

(Where, Dt = Tapped density, Db = Bulk density)

Hausner's ratio <1.25 – Good flow which means 20% compressibility index

Hausner's ratio >1.25 – Poor flow which means 33% compressibility index

ISSN 2394-5338 (Print); 2394-5346 (Online) © MIT Publications

4.1 Evaluation of Formulation [17-20]

4.1.1 Weight variation

20 Tablets were selected randomly from the batch and weighted individually to check for weight variation. Weight variation specifications were as per I.P.

Table 2. Weight variation specification as per IP

Average Weight of Tablet	% Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

4.1.2 Friability

Preweighed tablets are placed in the friability test apparatus. Friability test apparatus consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friability test apparatus for at least 4 minutes. At the end of test tablets were dusted and reweighed; the loss in the weight of tablet was measured of friability and is expressed in percentage as:

$$\% \text{ Friability} = \frac{[W_0 - Wf]}{W_0} \times 100$$

(W_0 = Initial weight of tablets, W_f= Final weight of tablets), Limit- less than 1%.

4.1.3 Hardness (Crushing strength)

A tablet is placed was kept in b/w jaws of Monsanto hardness tester and load required to crush the tablet was measured. The hardness of floating tablets is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tablet. The force is measured in kg and the hardness of about 3-5 kg/cm^2 is considered to be satisfactory for uncoated tablets.

4.1.4 Drug content uniformity

Twenty tablets were powdered, and 100 mg equivalent weight of Prazosin was weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of phosphate buffer (pH 6.8) was added and shaken for 10 min. Then, the volume was made up to 100 ml with same phosphate buffer. The solution in the volumetric flask was filtered, diluted suitably and analyzed by UV visible spectrophotometer at 246 nm.

4.1.5 *In-vitro* buoyancy studies

In-vitro buoyancy studies were performed for all formulations as per the method described by Rosa et al [21]. The randomly selected tablets from each formulation were kept in a 100 ml beaker containing simulated gastric fluid, pH 1.2 as per IP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of the medium was determined as the total floating time (TFT).

4.1.6 *In-vitro* dissolution study

The *in-vitro* dissolution study (n = 3) were carried out using USP dissolution test apparatus (type-2). The release studies were performed at 50 rpm in 900 ml, 1.2 pH HCl at 37±0.5°C. Aliquots of 5ml were withdrawn at 1 hr interval for 12 hrs. Dissolution study and the volume of dissolution medium were maintained by adding the 5ml of fresh dissolution medium. The test sample was filtered through Whatman filter paper and the concentration of Prazosin hydrochloride was measured by UV-Visible spectrophotometer at 246 nm and the percentage of drug release was plotted against time to determine the release profile. The % of the drug release and release kinetics is given in table: (8.2) and (8.3) respectively.

5. RESULTS AND DISCUSSION

5.1 Flow properties

The prepared granules were determined for following flow properties as presented in table 3 and their characteristics were also made on the basis of standard [21].

Table 3. Flow properties of the granules

Parameters	F7	F8	F9	Characteristics
Angle of repose	36	26	25	Good flow properties
Bulk Density	0.42	0.47	0.57	Lighter in density
Tapped density	0.58	0.57	0.59	Lighter in density
Carr's index	12.1	13.20	14.03	Good flow properties
Hausner's ratio	1.380	1.212	1.035	Good flow properties

5.2 Weight Variation

The weight of the tablet varied between 260 mg to 310 mg for different formulations with indicating uniformity of weight. The variation in weight was within the range of ±5% complying with pharmacopoeia specifications (Indian Pharmacopoeia 1996). Tablets prepared by direct compression were under the limits.

Table 4. Weight variation of the tablets

Batch no.	Weight variation
F7	Passed
F8	Passed
F9	Passed

5.3 Friability

The friability of tablets comes under the limit of less than 1 as presented in Table 5.

Table 5. Friability of the tablets

Batch no.	Friability (%)
F7	0.3
F8	0.36
F9	0.5

ISSN 2394-5338 (Print); 2394-5346 (Online) © MIT Publications

5.4 Hardness

The hardness of tablet was presented in table 6 and the values showed the good crushing strength that can bear wear and tear losses.

Table 6. Hardness of the tablets

Batch no.	Hardness (kg/cm^2)
F7	2.5
F8	3.8
F9	2.8

5.5 Drug content uniformity

The drug content uniformity was found to be around 92%, 90% and 88.9% respectively of batch F7, F8, F9.

5.6 *In-vitro* buoyancy study

The tablet floating lag time (FLT) was found to be less than 30s and total floating time more than 12 h. The floating lag time may be explained as a result of the time required for dissolution medium to penetrate the tablet matrix and develop the swollen layer for entrapment of CO_2 generated *in-situ*. The tablet mass decreased progressively due to liberation of CO_2 and release of drug from the matrix. On the other hand as solvent front penetrated the glassy polymer layer, the swelling of Carbopol 934P and HPMC K15M caused an increase in volume of the tablet. The combined effect is a net reduction in density of the tablets, which prolongs the duration of floatation beyond 12 h. Both the swelling polymers (Carbopol 934P and HPMC K15M) appeared to prolong the lag time while sodium bicarbonate appeared to reduce the lag time as expected. This is in perfect agreement with release rate and mechanism observed, since the polymers did not swell initially, but helped in keeping the tablet a float during the late hours of dissolution.

5.7 *In-vitro* drug release study

The *in-vitro* drug release study was performed for best optimized formulation F8. The release was determined using 0.1 N HCl buffer solution (pH 1.2). (The release data of formulation F8 shows that 89.87 of drug release for 12 hours (Figure 1).The release kinetics was studies by using various kinetics models such as zero order, first order, Higuchi model, Korsmeyer Peppas model release kinetics (Fig. 2,3,4,5). As per data of regression coefficient, it was inferred that release kinetics of drug from formulation F8 was according to Higuchi kinetic model (Table 9).

Table 7. % drug release formulation code F8.

S. No.	Time (hrs.)	% drug release
1.	1	17.09
2.	2	29.87
3.	3	34.27
4.	4	48.52
5.	5	54.82
6.	6	61.72
7.	7	67.82
8.	8	73.45
9.	9	78.21
10.	10	82.52
11.	11	86.01
12.	12	89.87

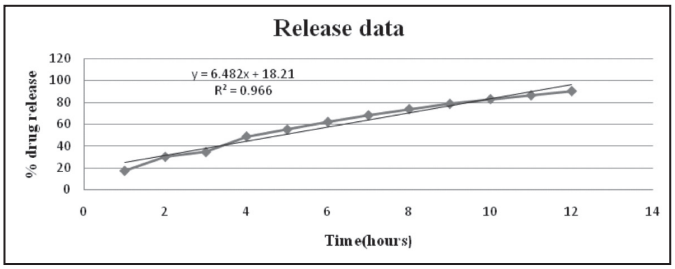

Fig. 1. % Drug release of formulation F8, Where Y= Absorbance, X= Concentration, R^2= Regression.

Table 8. *In-vitro* drug release studies of Formulation F8

Time (hrs.)	Log Time	Square root of Time	% CD Release	% CD Retained	Log % CD Release	Log % CD Retained
1.	0	1	17.09	82.91	1.23	1.91
2.	0.30	1.41	29.87	70.13	1.47	1.84
3.	0.47	1.73	34.27	65.73	1.53	1.81
4.	0.60	2	48.52	51.48	1.68	1.71
5.	0.69	2.23	54.82	45.18	1.73	1.65
6.	0.77	2.44	61.72	38.28	1.79	1.58
7.	0.84	2.64	67.82	33.18	1.83	1.52
8.	0.90	2.82	73.45	26.55	1.86	1.42
9.	0.95	3	78.21	21.79	1.89	1.33
10.	1	3.16	82.52	17.48	1.91	1.24
11.	1.01	3.31	86.01	13.99	1.93	1.14
12.	1.07	3.46	89.87	10.13	1.95	1.00

% CD = Cumulative drug release

ISSN 2394-5338 (Print); 2394-5346 (Online) © MIT Publications

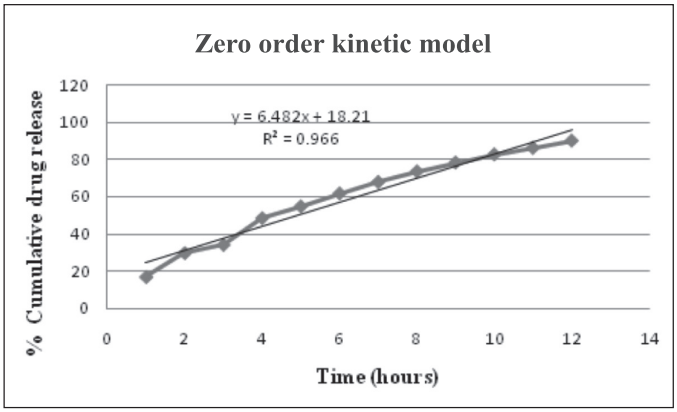

Fig. 2. Zero order kinetics model of drug release from formulation F8

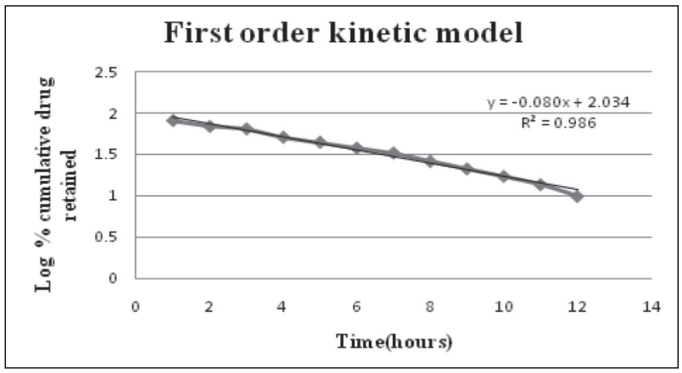

Fig. 3. First order kinetics model of drug release from formulation F8

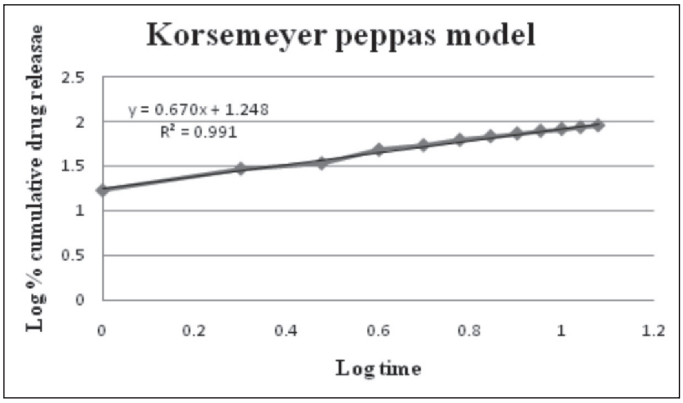

Fig. 4. Korsmeyer Peppas model of drug release from formulation F8

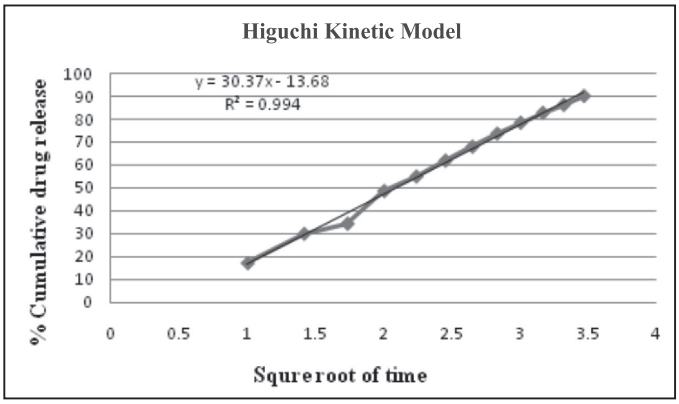

Fig. 5. Higuchi kinetics model of drug release from formulation F8

Table 9. Regression coefficient values of different release order kinetic model for F8

S. No.	Release order kinetic model	Regression coefficient (R^2)
1.	Zero order kinetics model	0.966
2.	First order kinetics model	0.986
3.	Korsmeyer Peppas model	0.991
4.	**Higuchi kinetic model**	**0.994**

6. CONCLUSION

Thus, from the above study it is concluded that floating tablet used as anti-hypertension drug Prazosin hydrochloride can be formulated as an approach to increase gastric residence time and there by improve its bioavailability. Formulated tablets gave satisfactory result for various physicochemical evaluations for tablet like, hardness, weight variation, floating time, lag time, and *in-vitro* drug release formulation F8 gave better controlled drug release in comparison to other prepared formulation. Further it is concluded that, gastric retentive formulation of Prazosin hydrochloride can be obtain with minimum expenditure of time and money. Thus, the objective of formulating floating drug delivery dosage form of Prazosin hydrochloride has been achieved. The various concentration of HPMC K15M and Carbopol 934P was used to formulation, which sustained the release of Prazosin hydrochloride for 12 hrs. The reason behind choosing the HPMC K15M and Carbopol 934P polymer was its low density hydrocolloid system. HPMC K15M and Carbopol 934P provide several advantages i.e. sustained release, good stability in varying pH values and moisture levels.

REFERENCES

[1] Singh, S.; Tiwari, A.K. Floating microspheres of Prazosin Hydrochloride: Formulation, Characterization and *in-vitro* evaluation. *Der Pharmacia Lett* **2012**, 4, 1327-38.

[2] Banker, G.S.; Rhodes. C.T. Modern Pharmaceutics. Marcel Dekker, 2nd ed, **2002**, 575-77.

[3] Vyas, S.P.; Khar, R.K. Controlled drug delivery concepts and advances. Vallabh Prakashan, 1sted, **2002**, 196-213.

[4] Menon, A.; Ritschel, W.A.; Sakr, A. Development and Evaluation of monolithic floating dosage form for furosemide. *J Pharma Sci* **1994**, 83, 239-45.

[5] Kamble, S.; Ghorpade, P. Gastro-retentive floating drug delivery system containing antihypertensive drug-An overview. *W J Pharma Res*, **2014**, 3, 1076-92.

[6] Yie, W.; Chien. Novel Drug Delivery Systems, 2nd Edition, Revised and Expanded, Published by- Informa Healthcare USA, Inc. **1992**, (50); 2,17&33.

[7] Hamman, J.H.; Demana, P.H.; Olivier, E.I. Targeting receptors, transporters and site of absorption to improve oral drug delivery. *Drug Target Insights* **2007**, 2, 71.

[8] Garg. R.; Gupta, G.D. Progress in controlled gastro retentive delivery systems. *Tropical J Pharm Res* **2008**, 7(3), 1055-66.

[9] Rouge, N.; Buri, P.; Doelker, E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. *Int J Pharm* **1996**, 136(1-2), 117-39.

[10] Arora, S.; Ali, J.; Ahuja, A.; Khar, R.K.; Baboota, S. Floating drug delivery systems: a review. *Aaps Pharm Sci Tech* **2005**, 6(3), E372-90.

[11] Rocca, J.G.; Omidian, H.; Shah, K. Progresses in gastro retentive drug delivery systems. Business briefing. *Pharma Tech* **2003**, 5, 152-6.

[12] Patil, S.N.; Deshmukh, T.A. Gastro retentive drug delivery system: An Overview. *Indo Am J Pharm Res* **2013,** 3(9), 7562-72.

[13] Singh, B.N.; Kim, K.H. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *J Control Release* **2000**, 63(3):235-59.

[14] Garg, S.; Sharma, S. Gastro retentive drug delivery systems: Business Briefing, *Pharmatech* **2003**, 5, 160-6.

[15] Rocca, J.G.; Shah, K.U. Gastric retention of solid dosage forms: A review of the current climate, *AAPS News Magazine* **2004**, 22-23.

[16] Qureshi, M.J.; Ali, J.; Ahuja, A.; Baboota, S. Formulation strategy for low absorption window antihypertensive agent. *Indian J Pharm Sci* **2007**, 69(3):360.

[17] Streubel, A.; Siepmann, J.; Bodmeier, R. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. *Eur J Pharm Sci* **2003**, 18(1), 37-45.

[18] Jain, A.; Jain, P.; Jain, S.K.; Agrawal, R.K.; Agrawal, G.P. Calcium-silicate-based floating granular delivery system of ranitidine hydrochloride for effective management of peptic ulcer. *J Med Chem* **2008,** 17(2-7), 305-17.

[19] Jain, S.K.; Agrawal, G.P.; Jain, N.K. A novel calcium silicate based microspheres of repaglinide: in vivo investigations. *J Control Release* **2006**, 113(2), 111-6.

[20] Gupta, N.; Aggarwal, N. Stomach-specific drug delivery of 5-fluorouracil using floating alginate beads. *AAPS Pharm Sci Tech* **2007**, 8(2), E143-9.

[21] Murata, Y.N.; Sasaki, N.; Miyamoto, E.; Kawashima, S. Use of floating alginate gel beads for stomach-specific drug delivery. *Eur J Pharm Biopharm* **2000**, 50(2), 221-6.