World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 4.223

FORMULATION DEVELOPMENT AND EVALUATION OF FLOATING TABLETS CONTAINING NIZATIDINE

Mander Harmeet Kaur*, Rajesh Kumari Patil, Hanumant Rao Patil and Sunita Rani

Department of Pharmaceutical Sciences, Adesh Institute of Pharmaceutical and Biomedical Sciences, Bathinda (Pb.), India.

***Corresponding Author: Mander Harmeet Kaur**
Department of Pharmaceutical Sciences, Adesh Institute of Pharmaceutical and Biomedical Sciences, Bathinda (Pb.).

Article Received on 12/05/2017 **Article Revised on 02/06/2017** **Article Accepted on 23/06/2017**

ABSTRACT

The main aim of this investigation was to develop a controlled release floating drug delivery system (tablet) of Nizatidine. Floating tablets of nizatidine were prepared to extend gastric residence time and hence to enhance its bioavailability. The floating matrix tablets were prepared by direct compression technique using a combination of hydroxyl propyl methyl cellulose K15M (HPMC K15M) and Karaya gum as polymers and sodium bicarbonate as generating agent. The prepared floating tablets were evaluated for weight variation test, hardness, thickness, swelling index, *in vitro* floating capabilities, floating lag time, compatibility studies, and *in vitro* drug release. The swellable hydrophilic natural karaya gum was used to control the release of drug. The results showed that the optimized formulation F5, F6, F7 & F8 had good floating capability, shorter floating lag time, and sustained drug release for the period of ≥24 h. In the current study, it was also found that overall rate of drug release tends to decrease with increase in concentration of polymer. These observations are in agreement with the results reported in literature i.e. with the increase in polymer concentration or viscosity grade, the viscosity of gel layer around the tablet also increases leading to enhanced diffusion path length for the drug to follow and thus limits the release of active ingredient.

KEYWORDS: Nizatidine, gastro retentive, floating drug delivery, sustained release.

INTRODUCTION

Oral formulations have earned a significant place among the various dosage forms due to the ease of administration, patient compliance, and flexibility in formulation. In most of the cases, the conventional oral delivery systems show limited bioavailability because of fast gastric emptying time among many other reasons involved. However, the recent technological development has resulted in too many novel pharmaceutical products, mainly the controlled release drug delivery systems to help overcome this problem. Controlled-release systems aim to maintain the steady plasma level of the drug over a prolonged time period, reduce the adverse side effects, and improve patient convenience and compliance. Gastroretentive drug delivery system (GRDDS) is one such example where attributes like gastric retention time coupled with the drug release for extended time have significantly improved patient compliance.[1] Gastroretentive systems are able to increase residence time of dosage forms in the stomach thereby increase the bioavailability of drugs with narrow absorption window, drugs with less water solubility in alkaline pH of small intestine or drugs with poor stability in the intestinal or colonic environment.[2] The degree of absorption of a drug in the gastrointestinal tract is based on certain events which include drug release, drug in solution at absorptive sites, drug absorption into systemic circulation, liver and gut metabolism, decomposition, and transit.[3] Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms that retain in the stomach for a longer duration than conventional dosage forms.[4]

Nizatidine is an H_2-receptor antagonist mainly used for treatment of conditions where a controlled reduction of gastric acid is required such as acute duodenal ulcer, acute benign gastric ulcer, and gastroesophageal reflux (GERD) and prophylactic use in duodenal ulcer. The drug has very short elimination half-life of 1-2 h and low absolute oral bioavailability. The drug is prescribed as 150 mg twice daily for acute duodenal ulcer, acute benign gastric ulcer and GERD duration of 8-12 weeks. These attributes like stomach as site of action, short half life and low oral bioavailability make it a suitable candidate for FDDS.[5,6] Therefore, an attempt has been

made to develop stomach-specific FDDS of nizatidine to achieve local action of drug in the stomach by increasing its gastric residence time and also releasing it at a controlled rate to ensure 'once a day' administration and optimum bioavailability, thereby, minimizing its side effects and hence enhanced patient compliance.[7]

MATERIALS AND METHODS

Nizatidine was received as a gift sample by Shasun chemicals and Drugs Ltd, Cuddalore, India. Karaya gum was received as a gift sample from Girijan cooperative corporation, Visakhapatnam. Microcrystalline cellulose, Magnesium stearate, sodium bicarbonate, and lactose were purchased from SD Fine Chemicals Ltd. (Ahmedabad, India). All other excipients were of analytical reagent (AR) grade.

Preparation of Nizatidine floating tablets (Preliminary Trials)

The floating tablets of Nizatidine were prepared by direct compression technique. For each tablet formulation, drug, HPMC-K15M, karaya gum, sodium bicarbonate, and diluents were blended homogeneously for 10 min followed by addition of magnesium stearate. The total weight of each tablet was 330 mg. The amount of karaya gum used was 50–90 mg, whereas concentration of HPMC was 20–40 mg (table 1). The concentration of sodium bicarbonate was 10-40 mg in all tablets. The powder mixture was further mixed for 5 min in a mortar. The resultant mixture was compressed into tablets using a single punch rotary tablet machine at the compression force of 8 KN. The compositions of floating tablets are given in table 1.

Table 1: Composition of Floating tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Nizatidine	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**
Karaya Gum	50	50	50	50	70	70	70	70
HPMC K15M	20	40	30	30	20	40	30	40
$NaHCO_3$	20	20	10	30	10	10	20	30
PVPK30	15	15	15	15	15	15	15	15
Magnesium Stearate	5	5	5	5	5	5	5	5
Lactose	70	50	70	50	60	40	40	20
Total (mg)	**330**	**330**	**330**	**330**	**330**	**330**	**330**	**330**

Physical Evaluation of floating matrix tablets

Weight Variation

20 tablets of each batch were weighed individually using digital weighing balance and their average weight was calculated. Then individual tablet weight was compared with average weight.

Hardness

The tablet hardness was measured using Monsanto tablet hardness tester. The force required to crush the tablet was recorded as hardness in Kg/cm^2.

Friability

10 tablets were weighed accurately and then placed in Roche-type friabilator which was rotated at 25 rpm for 4 min (i.e. 100 revolutions). Then tablets were taken out of the friabilator and again weighed after dusting. The percent friability was calculated as follow:

$$\% \text{ Friability} = (W_i - W_f / W_i) \times 100$$

Where, W_i – initial weight of tablets, W_f – final weight of tablets

Drug Content

From each formulation, ten tablets were weighed and powdered. A quantity of powder equivalent to 150 mg of nizatidine was accurately weighed and dissolved in 100 ml of 0.1 N HCl and stirred for 30 minutes. The solution was filtered, diluted appropriately and analyzed spectrophotometrically at 314 nm using 0.1 N HCl as blank. The drug content was determined from absorbance values using calibration curve.[8]

Floating Lag Time (FLT) and Total Floating Time (TFT)

The floating behavior of the tablets was evaluated by placing them in beaker containing 200 ml of 0.1N HCl (pH 1.2). The beaker was kept over a magnetic stirrer. The time taken by the tablets to emerge on the surface of medium was noted as floating lag time and the total time duration for which tablets remained buoyant was noted as total floating time.[9]

Dissolution study

The *in vitro* drug release rate (dissolution rate) of Nizatidine from the formulated floating tablets was determined USP type-I dissolution tester (basket type). The dissolution test was performed using 900 ml of 0.1 N HCl buffer (pH 1.2), at 37 ± 0.5°C and 75 rpm speed. The samples (5 ml) of the solution were withdrawn from the dissolution apparatus at pre-determined time intervals of 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 h, and the samples were replaced with fresh dissolution medium at each time interval in order to maintain sink conditions.[10] The samples were filtered through 0.45 µm membrane filter and diluted suitably with 0.1 N HCl buffer. Absorbance of these solutions was measured at the wavelength of 314 nm using a UV-Visible double-beam spectrophotometer. Release profiles of different formulations of floating tablets were compared with release profile of marketed formulation (obtained as gift sample from Dr. Reddy's Laboratories).

Water Uptake Study

The swelling of the tablets takes place due to the ability of polymers to hydrate and swell. The swelling characteristics of the tablet was determined by immersing the tablet in a beaker containing 200 ml of 0.1 N HCl (pH 1.2) and stirred at 37°C. After the predetermined time intervals, tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed. Swelling index (SI), expressed as percentage, was calculated using following equation.[11,12]

$$SI = \frac{\text{weight of swollen tablet - initial weight of tablet}}{\text{initial weight of tablet}} \text{ X } 100$$

Mechanism of drug release (drug release kinetics)

The different mathematical models may be applied for describing the kinetics of the drug release process from tablets; the most suited being the one which best fits to the experimental results. These models best describe drug release from pharmaceutical systems resulting from a simple phenomenon, or when this phenomenon, by being the rate-limiting step, conditions all the process occurring in the system.[13]

The kinetics of nizatidine release from tablets formulations were determined by finding the best fit of the release data to zero order, first order, matrix, Hixson-Crowell, Higuchi, and Korsmeyer- Peppas plots.[14]

Higuchi developed several theoretical models to study release of high and low water soluble drugs incorporated in the semi-solid and/or solid matrices. According to this model, drug release was described as a square root of time-dependent diffusion process based on Fick's law. This relation can be used to describe drug dissolution from several types of modified release pharmaceutical dosage forms.

$$Q_t = K_H \sqrt{t}$$

Where K_H is Higuchi's rate constant, and Q_t is the amount of drug released at time t. If a plot of square root of time vs cumulative amount of drug released yields a straight line, and the slope is 1 or more than 1, then the particular dosage form is considered to follow Higuchi kinetics of drug release. Under some experimental situations the release mechanism deviates from the Fick's equation, following an anomalous behavior (Non-Fickian release). In these cases a more generic equation can be used. Korsmeyer et al. developed a simple, semi-empirical, relating exponentially the drug release to the lapsed time.[15]

$$Q_t/Q_\alpha = Kt^n$$

Where Q_t/Q_α is the fraction of drug released at time t; K is the constant comprising a structural and geometric characteristics of the tablets; and n, the release exponent, is a parameter that depends on the release mechanism and is thus used to characterize it. Peppas used this n value in order to characterize different release mechanisms.[16] If the n value is 0.5 or less, the release mechanism follows Fickian diffusion, and higher values ($0.5 < n < 1$) for mass transfer follow a non-Fickian model (anomalous transport). Hixson-Crowell[17] recognized that particle regular area is proportional to the cubic root of its volume, derived an equation that can be describe in the following manner.

$$W_0^{1/3} - W_t^{1/3} = K_S\, t$$

Where W_0 is the initial amount of drug, W_t is the remaining amount of drug in dosage form at time t, and K_S is a constant incorporating the surface volume relation (table 5).

RESULTS AND DISCUSSION

All the batches of prepared tablets were evaluated for various physical parameters like weight variation, hardness, friability and drug content uniformity. The results are shown in Table 2. The hardness of all the formulations was kept between 4-6 Kg/cm^2. The tablets must have an optimum hardness in order to have less floating lag time and longer total floating time. The reason is that a high degree of hardness may reduce the porosity of tablets and the compacted polymer particles on the surface of tablets cannot hydrate rapidly on contact with gastric fluid. Consequently, the ability of tablet to float can be significantly reduced. On the other hand, very low hardness results in tablets which are friable and therefore not acceptable. Hence, there must be an optimum hardness for tablets to remain buoyant and to meet pharmacopoeial requirements of stability. The friability values for all the prepared batches were less than 1. Weight variation and drug content were within the USP limits (Table 2).

Table 2: Values of various physical parameters of Nizatidine floating tablets.

Formulation	Weight Variation (n=20)	Hardness (n=3)	% age Friability (n=6)	Assay (n=10)
F1	Passed	5.17±0.24	0.69	99.67
F2	Passed	6.0±0.16	0.58	97.32
F3	Passed	4.67±0.15	0.38	98.51
F4	Passed	5.9±0.15	0.51	98.84
F5	Passed	5.9±0.12	0.78	99.02
F6	Passed	5.03±0.03	0.71	99.26
F7	Passed	5.87±0.12	0.58	98.68
F8	Passed	5.97±0.06	0.39	99.45

Hardness (Kg/cm^2); All values are given as Mean±S.D

Floating Lag time and Total Floating Time

On placing the tablets in the beaker containing 0.1 N HCl, all the tablets first sank to the bottom and then they came up to the surface. The beakers were kept over magnetic stirrer to simulate the peristaltic movements of the GIT and FLT and TFT were recorded by visual inspection. All the formulations had FLT of ≤ 2 minutes and remained buoyant for more than 20 h (except F1, F2 & F3) on the medium without disintegration. F1-F3 had total floating time of 13 h, 15 h and 18h respectively whereas F4 and F8 had ≥20 h.

It was found that the formulation (F1) having low concentration of HPMC K15M floated for small duration of time (13 h) as compared to other formulations (Table.3). Also, formulations F6 & F8 containing higher concentration of same polymer showed floatation for longer duration of time than formulations with lower concentration. This may be due to the ability of higher concentration of HPMC to hold the generated carbon dioxide for longer period of time.

Table 3: Floating Lag time (FLT) and Total Floating Time (TFT) of different formulations.

Formulation	FLT (sec)	TFT
F1	13	13 h
F2	15	15 h
F3	22	18 h
F4	24	20 h
F5	59	>20 h
F6	30	>20 h
F7	44	>20 h
F8	60	>20 h

In Vitro Dissolution Studies

In vitro dissolution studies were carried out as per USP procedure using 0.1 N HCl (pH 1.2) as dissolution medium at 75 rpm. The *in-vitro* release profiles of Nizatidine from various formulations are shown in figure 1. Under fasting conditions, housekeeper waves clear the undigested material from the stomach every 1.5-2 h. So when the tablet is taken orally, it remains in the stomach for 2 h and then expelled in the intestine. It can be seen from the table that marketed tablet releases 100 % of the drug within 2 h. But in case of floating matrix tablets, release of the drug was controlled significantly over a broad period of time. These studies were carried out for 24 h. In all the formulations, the amount of drug was kept constant i.e. 150 mg which is the dose of the drug. In case of formulations F1-F2 (containing karaya gum & PVP K_{30} in varying concentrations), a complete drug release was achieved within 12 h. However, the release data showed that as the level of polymer increases, release rate decreases. A higher concentration of polymer karaya gum was used for formulations F5-F8 in varying concentrations. In case of F6, 97% drug release was achieved in 24h whereas in F7 & F8 almost 83% & 78% drug release was achieved in 24h whereas in case of F5, a complete 100% drug was released after 24 h.

It has been reported that floating drug delivery systems can prolong the gastric retention time and thus increase the overall drug bioavailability of drugs like Nizatidine that shows better absorption at the proximal part of the intestine. The concentration of gum, polymer, and diluent had a remarkable influence on the drug release. Increase in the concentration of gum with decrease in lactose concentration decreases the drug release this may be due to the formation of thick gel barrier. Formulation F8 showed the least drug release among other formulations; this may be due to formation of a thick gel barrier on the tablet. As the thickness of the gel barrier increases, the drug takes more time to diffuse through it. However, this was not true in F1 because of increases in the concentration of lactose. The controlled release of drug from the formulations may be because of the release medium being diffused into the matrix, whereby drug may have diffused out of the tablets. Thus the results suggested that the karaya gum could be used for the preparation of gastric floating controlled delivery systems.

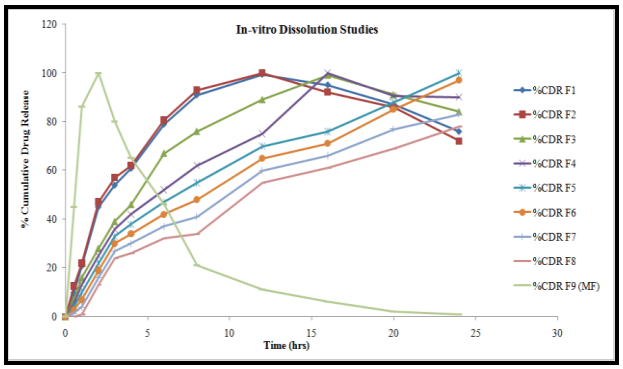

Figure 1: *In-vitro* drug release profile of marketed product and prepared formulations F1-F8.

Swelling Studies

Maximum swelling was achieved at the end of 12 h for formulations F5 - F7, and 16 h for F8 as shown in Table.4.

Table 4: Comparison of swelling index of optimized formulations.

Time (hr)	F5	F6	F7	F8
0	0	0	0	0
1	47.40±1.13	59.71±1.56	53.99±1.72	69.99±1.75
2	58.01±1.01	82.36±2.13	72.98±2.09	90.69±2.27
3	82.04±1.97	107.63±1.53	95.96±2.06	117.03±2.61
4	101.97±3.55	132.32±2.11	107.29±2.58	128.99±1.67
5	132.69±2.09	153.73±2.60	141.33±3.21	160.32±2.12
6	142.26±2.09	161.13±1.55	150.49±1.53	173.97±1.03
8	155.74±2.08	166.34±2.07	158.71±1.58	185.29±1.17
12	164.60±2.87	180.99±1.67	173.96±2.08	189.34±2.08
16	146.42±1.67	176.29±1.12	169.99±1.98	211.67±1.57
24	129.38±2.70	173.77±2.41	161.28±4.21	193.46±4.39

All values are expressed as mean ± S.D, n=3.

The plot of swelling index versus time is given in Fig.6. Swelling is generally essential to ensure floating. It was observed that HPMC grade also affects the swelling. The values of swelling index start decreasing when polymer erosion starts in the medium. A direct correlation between swelling and drug release was observed. It was found that with an increase in polymer concentration, swelling increases but the rate of drug release slows down. It may be due to the reason that increase in polymer concentration results in formation of thicker gel network that retards the drug release. The swelling of the tablet in release media ensures that it will have high gastric residence time and will not pass through the pyloric sphincter.

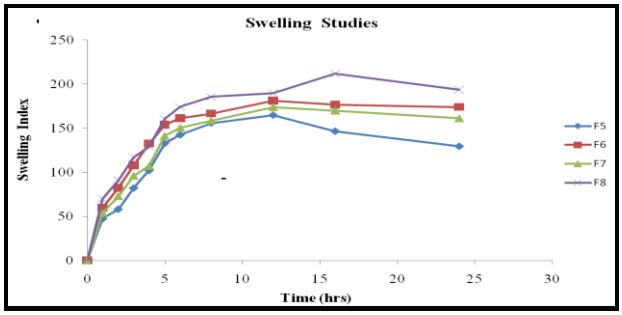

Figure 2: Plot of swelling index of optimized formulations versus time.

Analysis of Drug Release Mechanism

The *in vitro* drug dissolution profiles of optimized formulations were fitted to various models and release data were analyzed on the basis of Korsmeyer-Peppas equation and Higuchi kinetics. The diffusion exponent ranges from 0.375 to 0.682. Coefficients of correlation (r^2) were used to evaluate the accuracy of the model fitting. On calculating and comparing r^2 values for Huguchi, Korsmeyer-Peppas, 1st order and zero order models, F5, F6 and F8 gave a good fit to Korsmeyer-Peppas model, whereas F7 fitted to Higuchi model. According to the Higuchi model the drug release from the tablet (F7) may be controlled by micropore diffusion. F5, F6, and F8 showed Fickian release and F7 showed non-Fickian or anomalous release. If the value of 'n' in Korsmeyer-Peppas is 0.5 or less the release mechanism follows a Fickian diffusion, and for anomalous or non-Fickian release the release is mainly by diffusion with n values between 0.5-1. This model is used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomenon could be involved. The fundamental of diffusion is based on Fick's laws, which describes the macroscopic transport of molecules by a concentration gradient.

Table 5: Kinetic Treatment of Optimized Formulations.

Formulation	Zero-order plot	First-order plot	Korsmeyer-Peppas plot	Higuchi plot	Mechanism of drug release	Release Kinetics
	R^2	R^2	R^2	R^2		
F5	0.906	0.449	0.998	0.996	Fickian	Peppas
F6	0.930	0.435	0.993	0.992	Fickian	Peppas
F7	0.920	0.456	0.994	0.997	Non-Fickian	Higuchi
F8	0.923	0.469	0.998	0.997	Fickian	Peppas

CONCLUSION

This study discusses the preparation of floating tablets using Karaya gum and HPMC. The effervescent gastric floating drug delivery system was a promising approach to achieve *in vitro* buoyancy and to improve the absorption of nizatidine. All the formulations were evaluated for different parameters like floating lag time, floating duration, physical tests, *in vitro* dissolution study, release mechanism and swelling characteristics. Weight variation, hardness, friability and drug content of all the formulations were within the pharmacopoeial limits. All the formulations had floating lag time below 2 minutes. In order to prolong the gastric residence time, a gas generator was used to keep the tablets floating over the medium, and addition of gel forming polymer and gum was essential to achieve *in vitro* buoyancy. Total floating time of formulations F_1-F_4 were ≤ 20 h whereas all other formulations floated for more than 20 h. Formulations F_5-F_8 sufficiently sustained the drug release for 24 h or even more. Optimized formulations were subjected to drug release kinetics and it was observed that formulations F5, F6 and F8 were following Korsmeyer-Peppas model (n = 0.375-0.458; fickian release) whereas F7 was found following Higuchi model (n = 0.682; non-fickian). From the results of present study, it may be suggested that maintaining local concentration of nizatidine in the stomach for prolonged period of time by formulating stomach-specific FDDS, may be a better therapeutic approach to treat gastric ulcers and GERD.

ACKNOWLEDGMENTS

Authors are very thankful to Department of Pharmaceutical Sciences, Adesh Institute of Pharmaceutical and Biomedical Sciences, Bathinda (Pb) for providing us the facilities to carry out the work. Authors are also very grateful to Mr Ashish Garg for his technical guidance, analytical skills and continuous motivational support.

REFERENCES

1. Mohamed A El Nabarawi, Mahmoud HT, Rehab A El-M, Nagla A El N, Dalia AG. Formulation, release

characteristics, and bioavailability study of gastroretentive floating matrix tablet and floating raft system of Mebeverine HCl. Drug Design, Development and Therapy, 2017; 11: 1081-93.
2. Bahri-Najafi R, Mostafavi A, Tavakoli N, Taymouri S, Shahraki M-M. Preparation and *in-vitro in-vivo* evaluation of acyclovir floating tablets. Research in Pharmaceutical Sciences, 2017; 12(2): 128-36.
3. Ndidi CN, Yahya EC, Girish M, Lisa CT, Pradeep K, Leith M *et al*. *Ex-vivo* and *in-vivo* Characterization of Interpolymeric Blend/Nanoenabled Gastroretentive Levodopa Delivery Systems. Parkinson's Disease, 2017; 2017: 1-14.
4. Bhandari N, Bali T, Tangum, Simran, Sumeena, Choudhary S. Gastro Retentive Drug Delivery System: A Review. World Journal of Pharmacy and Pharmaceutical Sciences, 2017; 6(4): 346-63.
5. Akash J, Vikas P, Aditya G, Nazneen D, Divya B. Formulation and characterization of floating microballoons of Nizatidine for effective treatment of gastric ulcers in murine model. Drug Delivery, 2015; 22(3): 306-11.
6. Bandameedi R, Pandiyan S. Formulation and Evaluation of Floating Osmotic Tablets of Nizatidine. Journal of Applied Pharmacy, 2015; 8(1): 1-7.
7. Prasanthi CH, Prasanthi NL, Deepika K. Formulation and Evaluation of Nizatidine Floating Tablets by using Natural, Semisynthetic and Synthetic Polymers. Research Journal of Pharmacy and Technology, 2013; 6(9): 1032-36.
8. Gangadharappa HV, Rahamath-Ulla M, Pramod-Kumar TM, Shakeel F. Floating drug delivery system of verapamil hydrochloride using karaya gum and HPMC. Clinical Research and Regulatory Affairs, 2010; 27(1): 13-20.
9. Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. European Journal of Pharmaceutical Sciences, 2003; 18(1): 37-45.
10. Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavia PR. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. International Journal of Pharmaceutics, 2006; 316(1-2): 86-92.
11. Siahi MR, Barzegar-Jalai M, Monajjemzadeh M, Ghaffari F, Azarmi S. Design and evaluation of 1- and 3- layer matrices of verapamil hydrochloride for sustaining its release. AAPS PharmSciTech, 2005; 6(4): E626-32.
12. Havaldar VD, Kulkarni AS, Dias RJ, Mali KK. Optimization and *in-vitro* evaluation of floating tablets of atenolol. Journal of Pharmaceutical Research, 2008; 1: 73-78.
13. Hina KS, Kshirsagar RV, Patil SG. Mathematical Models for Drug Release Characterization: A Review. World Journal of Pharmaceutical Research, 2015; 4(4): 324-38.
14. Grassi M and Grassi G. Application of mathematical modeling in sustained release delivery systems. Expert Opinion on Drug Delivery, 2014; 11(8): 1299-1321.
15. Korsmeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics, 1983; 15(1): 25-35.
16. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharmaceutica Acta Helvetiae, 1985; 60(4): 110-1.