International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 9, Issue 1, 2017

Original Article

VARIOUS FORMULATION VARIABLES EFFECTING FLOATATION BEHAVIOUR OF SINGLE UNIT GASTRORETENTIVE CAPSULES OF OFLOXACIN

SYED NAIEM RAZA, NISAR AHMAD KHAN

Department of Pharmaceutical Sciences, University of Kashmir
Email: syednaiem369@gmail.com

Received: 08 Jun 2016 Revised and Accepted: 23 Nov 2016

ABSTRACT

Objective: Objective of the present study was to prepare simple single unit gastro-retentive capsules of ofloxacin with the aim to have the gastric retention of the system for longer periods of time (12h) and to study the effect of various polymers on floating behaviour of such single unit gastro-retentive capsules of ofloxacin.

Methods: The method used for the preparation of gastro-retentive capsules was a simple physical blending of various low-density hydrophilic polymers alone and in combination with hydrophobic polymers and filling into capsules. These capsules were then subjected to *in vitro* floatation and matrix integrity study in 0.1N HCl using static volume beaker method and the United States pharmacopoeia (USP) type II dissolution apparatus method at 100rpm.

Results: Two grades of hydroxypropyl methylcellulose (HPMC) K4M and K15M used were found suitable for the purpose. Results showed that increase in HPMC level increased colloidal gel barrier strength along with matrix integrity with consequently improved buoyancy. Lactose which was added as release rate modifier decreased matrix integrity and buoyancy. Eudragit a hydrophobic polymer was added so as to have intact, the buoyant formulation for 12 h with desired drug release characteristics. The addition of eudragit enhanced matrix integrity and floatation time to certain levels but higher levels showed negative results. Floatation time of more than 16 h was observed in the formulations containing 2:1 ratio of HPMC K15M and eudragit respectively. 3^2 factorial design was used to study the effect of various formulation variables on buoyancy and matrix integrity. Formulations containing zero level of HPMC were found buoyant for more than 12 h with all levels of eudragit S100 (i.e.,-1, 0,+1 level). It was also observed that matrix integrity consequently buoyancy increased with increase in eudragit with all levels of HPMC.

Conclusion: The study concludes that eudragit S100 a hydrophobic polymer increased floatation time of the formulated capsules with all the three levels of HPMC K15M, but at the same time eudragit level should not exceed HPMC, while lactose a release rate enhancer decreased matrix integrity/floatation time of the formulated capsules.

Keywords: Gastro-retentive, Matrix integrity, Floating time, Ofloxacin, HPMC, Eudragit

DOI: http://dx.doi.org/10.22159/ijpps.2017v9i1.13962

INTRODUCTION

Among the various drug delivery routes, oral route has remained the most convenient route due to ease of administration of the dosage forms, patient acceptance and flexibility in formulation [1]. The success of an oral delivery depends on a number of factors like gastric emptying process, the gastrointestinal transit time of the dosage form, drug release from the dosage form and the site of absorption of drugs [2]. There are many limitations of most of the orally administered dosage forms such as rapid and inconsistent gastrointestinal transit time [3], incomplete drug release from the devices and too short residence time in the absorption region of the gastrointestinal tract, which may lead to lower bioavailability of the dosage form [4, 5]. Even if sustained release of the drug is attained, the drug may be released after the dosage form has passed the absorption site, thus lowering the efficacy of the drug. To solve these problems, oral controlled release gastro-retentive drug delivery system (GRDDS) has been developed. GRDDS prolongs the retention time of dosage forms in the stomach so that there is improved solubility, bioavailability and reduces drug waste [6]; thereby increases the therapeutic efficacy of the drugs.

In the last few decades various techniques have been developed for gastric retention which is based on the mechanisms of sedimentation [7, 8], expansion [9, 10] mucoadhesion [11], modified shape systems [12, 13], flotation [14], or simultaneous administration of pharmacological agents that delay gastric emptying [15]. These mechanisms are nowadays applied for the preparation of various single and multiple unit dosage forms for large scale manufacture.

Rationale of the study

Ofloxacin, a second-generation fluoroquinolone, is a synthetic chemotherapeutic broad spectrum antibiotic which acts by inhibiting DNA gyrase; an enzyme necessary to separate replicated DNA, thereby inhibiting bacterial cell division. Ofloxacin is a drug with its absorption window in the upper region of GIT. Ofloxacin is soluble in aqueous solutions with pH between 2 and 5 i.e., at gastric pH. In the intestine due to the prevalence of neutral to slightly alkaline pH conditions, precipitation of ofloxacin occurs; this adversely affects its absorption in the lower sections of the intestine [16]. Thus acidic environment of the stomach provides a suitable site for the retention of ofloxacin as it is readily soluble in an acidic environment.

The objective of the present study was to study the effect of various polymers on matrix integrity and floating behaviour of the single unit gastro-retentive capsules of ofloxacin. Low-density single unit gastro-retentive systems remain buoyant above the gastric secretions for sufficient time to ensure sustained release of the drug[3]. Matrix integrity refers to a condition in which the dosage form remains intact without losing its physical integrity i.e. there is no disintegration of the dosage form. If the dosage form does not maintain its physical integrity, it may be split into smaller fragments and will escape from the stomach to the lower parts of the gastrointestinal tract (GIT).

MATERIALS AND METHODS

Materials

Ofloxacin was obtained as a gift sample from Ranbaxy Laboratories Ltd., Sirmour, India; hydroxypropyl methylcellulose (HPMC) K_4 M and K_{15} M, ethyl cellulose, carbopol, sodium carboxy-methylcellulose (Sod. CMC), eudragit S100 and eudragit L 100 were all obtained as gift from Medley Pharmaceuticals Ltd., Mumbai, India; lactose, sodium were purchased from Central Drug House (P) Ltd., New

Delhi, India; Clear capsules were kindly sent by SKIMS, Srinagar and Eaton laboratories ltd., Srinagar, India.

Methods

Preparation of single unit gastro-retentive capsules

Different formulation variables were used to prepare gastro-retentive capsules of ofloxacin. Each ingredient was carefully weighed using an electronic balance (AXIS-LCGC). The ingredients were homogeneously blended and filled in gelatin capsules in accordance with the method used by "Ali *et al.*" for the preparation of single unit HBS capsules of metformin [17] (table 1).

***In vitro* buoyancy studies**

Static volume beaker method

Static volume beaker method was initially used to have an idea of the floatation behaviour of the proposed dosage forms. In this method, capsules filled with different polymer blends and drug were taken and placed individually in separate beakers containing 900 ml of 0.1 N HCl[18]. The physical condition of the capsules was observed at regular time intervals. This method lacked simulation, so, it was decided to study the floatation capabilities in *USP apparatus type II*.

USP dissolution apparatus type II

In this method, the formulation was placed in 900 ml of 0.1N HCl as a dissolution medium maintained at 37±0.5 °C using USP *dissolution apparatus type II* (Bells India; PLC dissolution rate test apparatus USP/BP/IPStd.)[19,20]. Amid constant stirring of 100 rpm, the formulations were evaluated for matrix integrity, buoyancy/ floatation time.

RESULTS AND DISCUSSION

Preformulation study for right selection of polymers

During this study different low-density hydrophilic polymers like carbopol, ethyl cellulose, hydroxypropyl methyl cellulose (HPMC) K_4M and $K_{15}M$, methylcellulose, sodium carboxymethyl cellulose (Sod. CMC) in different combinations and ratios along with the drug were blended and subjected to buoyancy and matrix integrity study using static volume beaker method. These results showed the suitability of HPMC K_4M and HPMC $K_{15}M$ for the study. The initial combinations (ratios) of HPMC $K_{15}M$ and the drug used in pre-formulation study are shown in table 1a. Matrix integrity and floatation behaviour is shown in table 1b. It was observed that buoyancy of the formulations containing lower quantities of HPMC (P 1 and P 2) was lost due to disruption of the capsules. If HPMC is not present in sufficient amounts, a complete gel layer may not form[21].

As there was stepped up HPMC ratio, there was an increase in matrix integrity and consequently buoyancy. This may be explained by an increase in thickness and strength of the colloidal gel barrier formed around the surface. Further studies were performed on combinations containing both hydrophilic polymers mentioned above and hydrophobic polymers. Eudragit S100 and eudragit L100 were used as hydrophobic polymers. Eudragit S100 gave better results compared to eudragit L100 and was used for the study.

Table 1: (a): Showing composition (in milligrams) of preformulation gastro-retentive single unit capsules (b): flotation behaviour of the capsules using static volume beaker method

(a)

Formulation code	P 1	P 2	P 3	P 4
Drug	200	200	200	200
HPMC $K_{15}M$	250	300	350	400

(b)

Formulation code	Matrix integrity; n=3	Floating/buoyancy time (h); n=3
P 1	++	++
P 2	++	++
P 3	++++	++++
P 4	++++	++++

'++++' ≥ 12 h; '+++'= 10-12h; '++'= 7-10h and '+' = 4-7 h (n=3; means all experiments were carried out three times)

Effect of hydrophobic polymers on matrix integrity, buoyancy/ floating time

Effect of hydrophobic polymers (eudragit S100) on floatation behaviour was observed by blending them along with hydrophilic polymer (HPMC $K_{15}M$) in the ratios 1:1, 1:2, 1:3, 2:1 and 3:1, and 200 mg of drug, keeping weight of contents of gastro-retentive capsules equal to 550 mg (table 2a). Initially, buoyancy studies were performed as per static volume beaker method followed by USP type II dissolution apparatus method. During the pre-formulation study, eudragit S 100 gave better results than eudragit L 100, so only eudragit S100 was used for the study. It was observed that as the amount of HPMC was decreased (ratio of hydrophobic polymers exceeded the hydrophilic), matrix integrity, consequently buoyancy was lost. Disruption in such cases (formulations F 4 and F 5) could be due to less quantity of HPMC K_{15} which was unable to form stable outer colloidal gel layer, consequently unable to hold the contents intact. If insoluble excipients are present in large amount, homogenous gel layer may not form.

Formulations F 1, F 2 and F 3 exhibited good matrix integrity and also buoyancy time of more than 12 h. F 2 and F 3 contained 2:1 and 3:1 ratio of HPMC K_{15}: eudragit S100 respectively showed buoyancy for more than 16 h (table 2b, 2c). Thus it may be concluded that incorporation of eudragit S100 has increased matrix integrity which may be because eudragit forms insoluble mass with HPMC, longer residence of eudragit in gel layer and insoluble nature of eudragit S100 [22] but there might be sufficient amounts of hydrophilic polymer and also ratio of hydrophobic polymer (eudragit) should not exceed hydrophilic (HPMC), i.e., an appropriate ratio of the hydrophilic and hydrophobic polymers are required for such type of systems to show floatation behaviour for longer periods of time without losing their integrity.

Effect of release modifiers on matrix integrity, buoyancy/ floating time

Lactose was used as a release rate modifier (table 3a) which caused a decrease in matrix integrity and consequently buoyancy. A decrease of more than 3-6 h in floatation time was observed due to the addition of lactose to formulation F 1 and F 2 (table 3b) which may be attributed to high solubility of lactose which forms channels within dosage form, develops osmotic pressure inside the dosage due to hydration [23]; weakens the integrity of matrix[24],thus causing disruption of the dosage form.

Effect of formulation variables

To evaluate the effect of various levels of HPMC K_{15} and eudragit S100 on matrix integrity, floating time and drug release, 3^2 factorial design was applied to F 3_L. In this design two factors were evaluated, each at three levels, and experimental trials

were performed at all 9 possible combinations. Table 4a summarises independent and dependent variables along with their levels. Various formulations were prepared as per the compositions mentioned in table 4b. Total weight of the gastro-retentive capsules was 605 mg, results of responses are given in table 4c.

Table 2: (a): Composition of gastro-retentive capsules containing both hydrophilic and hydrophobic polymers (b): Floatation behaviour of the capsules using static volume beaker method (c): Floatation behaviour of the capsules using USP paddle type apparatus

(a)

Formulation code	HPMC K_{15}	Eudragit S100	Drug
F 1	175.0 mg	175.0 mg	200.0 mg
F 2	233.4 mg	116.6 mg	200.0 mg
F 3	262.5 mg	87.5 mg	200.0 mg
F 4	116.6 mg	233.4 mg	200.0 mg
F 5	87.5 mg	262.5 mg	200.0 mg

(b)

Formulation code	Matrix integrity n=3	Floating/buoyancy time (h) n=3
F 1	++++	++++
F 2	++++	++++
F 3	++++	++++
F 4	++	++
F 5	+	+

'++++' ≥ 12 h; '+++' = 10-12h; '++' = 7-10h and '+' = 4-7 h

(c)

Formulation code	Matrix integrity, n=3	Floating/buoyancy time (h), n=3
F 1	++++	++++
F 2	++++	++++
F 3	++++	++++

'++++' ≥ 12 h; '+++' = 10-12h; '++' = 7-10h and '+' = 4-7 h

Table 3: (a): Composition of Gastro-retentive capsules containing lactose (b): Floatation behaviour of the capsules using USP paddle type apparatus

(a)

Formulation code	HPMC K_{15}	Eudragit S100	Lactose	Drug
F 1_L	175 mg	175 mg	55 mg	200 mg
F 2_L	233.4 mg	116.6 mg	55 mg	200 mg
F 3_L	262.5 mg	87.5 mg	55 mg	200 mg

(b)

Formulation code	Matrix integrity, n=3	Floating/buoyancy time (h), n=3
F 1_L	+	+
F 2_L	+++	+++
F 3_L	++++	++++

'++++' ≥ 12 h; '+++' = 10-12h; '++' = 7-10h and '+' = 4-7 h

Out of nine formulations, F 3_L, F 3_{La}, F 3_{Lb} and F 3_{Lh} remained intact and floated for more than 12 h. F 3_{Lc}, F 3_{Ld}, F 3_{Le}, F 3_{Lf} and F 3_{Lg} were intact and buoyant up to 9.0, 5.5, 11.0, 10.0 and 6.5 h respectively. These results showed that gastro-retentive capsules which contained 0 level (262.5 mg) of HPMC K_{15} showed greater matrix integrity and buoyancy with all levels of Eudragit S100 (F 3_L, F 3_{La} and F 3_{Lb}) than the capsules containing-1 (236.25 mg) and+1 (288.25 mg) levels of HPMC K_{15}M.+1 level was stable only with one level (+1) of Eudragit S100 (F 3_{Lh}). When+1 level of HPMC K_{15}M is taken into consideration, an increase in floating time (from 6.5 to more than 12 h) was observed with increase in eudragit level from–1 to+1 level.–1 level of HPMC K_{15}M showed similar results, i.e., an increase in eudragit level increased matrix integrity but none was intact for 12 h. Almost one hour difference in floating times was observed between+1 and–1 levels of HPMC (containing the same level of eudragit S100). Thus it may be interpreted that matrix integrity and floating time increased with increase in HPMC K_{15}M from–1 to 0 level and then decreased with a further increase from 0 to+1 level. This may be due to the reason that with the increase in HPMC from-1 to 0 level there is an increase in matrix integrity and buoyancy time because of the formation of stable gel matrix layer which keeps the dosage form intact. In-1 HPMC level amount of HPMC may not be sufficient to form stable outer gel matrix layer; as a result, there is disruption of capsules into smaller fragments which may escape lower parts of GIT. If HPMC is not present in sufficient amounts, a complete gel layer may not form [21]. As there is an increase in HPMC content the gel matrix becomes stronger [25]. As the HPMC level increases (from 0 to+1 level), there is an increase in water imbibition, due to which there is an increase in density of the dosage form. At a point where density exceeds the density of the gastric fluid, the dosage form loses buoyancy (sinks). Increase in eudragit level has increased matrix integrity with all levels of HPMC (fig. 1). Eudragit S100 is an anionic methyl methacrylate copolymer insoluble in aqueous medium.

The combination of HPMC and polymethacrylates, most notably anionic polymers form an insoluble mass. Also, anionic polymers increase the gel strength and also show higher residence time within the matrix gel [22]. Because of these reasons, i.e. hydrophobic nature, the formation of solid mass with HPMC and higher residence time within matrix gel layer, there is enhanced matrix integrity/ buoyancy due to the addition of eudragit S100.

Table 4: (a): Factors (independent variables), factor levels and responses (dependent variables) used in 3^2 factorial experimental design (b) composition of the gastro-retentive capsules (c): Floatation behaviour of the capsules

(a)

Factors	Factor level			Response
	-1	0	+1	
X1= Amount of HPMC $K_{15}M$	236.25	262.50	288.25	Y1= Matrix integrity
X2= Amount of Eudragit S100	78.25	87.50	96.25	Y2= Floating time

(b)

Formulation code	F 3_L	F 3_{La}	F 3_{Lb}	F 3_{Lc}	F 3_{Ld}	F 3_{Le}	F 3_{Lf}	F 3_{Lg}	F 3_{Lh}
Drug	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00
HPMC $K_{15}M$	262.50	262.50	262.50	236.25	236.25	236.25	288.25	288.25	288.25
Eudragit S100	87.50	78.75	96.25	87.50	78.75	96.25	87.50	78.75	96.25
Lactose	55.00	63.75	46.25	81.25	90.00	72.50	29.25	38.00	20.50

(c)

Formulation code	Matrix integrity, n=3	Floating/buoyancy time (h), n=3
F 3_L	++++	++++
F 3_{La}	++++	++++
F 3_{Lb}	++++	++++
F 3_{Lc}	++	++
F 3_{Ld}	+	+
F 3_{Le}	+++	+++
F 3_{Lf}	+++	+++
F 3_{Lg}	+	+
F 3_{Lh}	++++	++++

'++++' ≥ 12 h; '+++' = 10-12h; '++' = 7-10h and '+' = 4-7 h

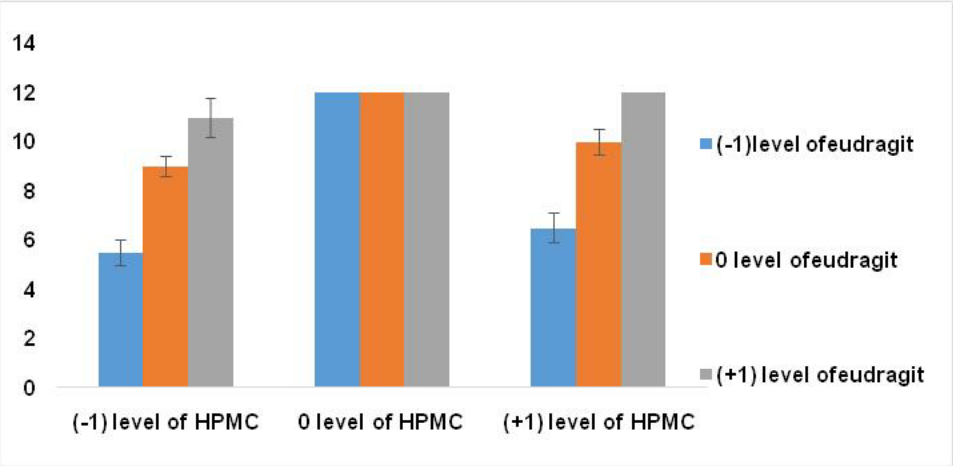

Fig. 1: Effect of various levels of HPMC $K_{15}M$ and eudragit S100 on floatation behaviour of single unit gastro-retentive capsules

CONCLUSION

Gastro-retentive capsules of ofloxacin were successfully formulated with the help of low-density polymers with desired floating time. Effect of various polymers including release rate modifier on matrix integrity and buoyancy were also studied; from which it was concluded that use of lower levels of HPMC $K_{15}M$ was unable to form stable outer colloidal gel layer thus unable to hold the contents intact. As the ratio of HPMC increased an increase in floating time was noted. Excessive amounts of HPMC decreased floating time because of increase in density of dosage forms. Eudragit L 100 and S 100 increased floating behaviour of gastro-retentive capsules, however, udragit S100 gave better results than eudragit L 100. 3^2 Factorial design was used to study effect of independent variables (X1= amount of HPMC $K_{15}M$, X2= amount of eudragit S100) on matrix integrity and floating time (dependent variables): from which it was concluded that increase in eudragit level from-1 to 0 to+1 level increased floating time with all levels of HPMC, which was attributed to water insolubility of eudragit S100, formation of insoluble mass with HPMC, longer residence time of eudragit S100 within gel matrix layer; however eudragit S 100 level should not surpass HPMC which causes a negative effect because of formation of incomplete and unstable gel matrix layer. Use of release rate modifier (lactose) caused a decrease in floating behaviour of the said formulations due to increase in osmotic pressure within dosage form.

Thus to have gastric retention of such capsules over extended periods of time, an appropriate ratio of the drug and such ingredients is a need.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Ummadi S, Shravani B, Rao NGR, Reddy MS, Sanjeev B. Overview on controlled release dosage form. Int J Pharma Sci 2013;3:258–69.
2. Chhetri HP, Thapa P. An overview on gastro retentive drug delivery system. Kathmandu Univ J Sci Eng Technol 2014;10:90–103.

3. Etman ME, Mahmoud EH, Galal S, Nada AH. Floating ranitidine micro particulates: development and *in vitro* evaluation. Int J Appl Pharm 2016;8:1–9.
4. Kale RD, Tayade PT. A multiple units floating drug delivery system of piroxicam using eudragit polymer. Indian J Pharm Sci 2007;69:120–3.
5. Raza S, Khan N. Gastric retention–an innovative approach to increasing bioavailability. Int J Biol Pharm Allied Sci 2014;3:113–33.
6. Nayak AK, Maji R, Das B. Gastroretentive drug delivery systems: a review. Asian J Pharm Clin Res 2010;3:2–10.
7. Rednick AB, Tucker SJ. Sustained release bolus for animal husbandry. United States Patent 3507952; 1970. p. 1–7.
8. Davis SS, Stockwell AF, Taylor MJ, Hardy JG, Whalley DR, Wilson CG, *et al.* The effect of density on the gastric emptying of single and multiple-unit dosage forms. Pharm Res 1986;3:208–13.
9. Mamajek R, Moyer ES. Drug dispensing device and method. United States Patent 4207890; 1980.
10. Urquhart J, Theeuwes F. Drug delivery system comprising a reservoir containing a plurality of tiny pills the United States Patent 4434153; 1984.
11. Ponchel G, Irachi J. Specific and non-specific bioadhesive particulate systems for oral delivery to the gastrointestinal tract. Adv Drug Delivery Rev 1998;1:191–219.
12. Fix J, Cargill R, Engle K. Controlled gastric emptying. III. The gastric residence time of a nondisintegrating geometric shape in human volunteers. Pharm Res 1993;10:1087–9.
13. Kedzierewicz F, Thouvenot P, Lemut J, Etienne A, Hoffman M, Maincent P. Evaluation of peroral silicone dosage forms in humans by gamma-scintigraphy. J Controlled Release 1999;58:195–205.
14. Deshpande A, Shah NH, Rhodes TC, Malick W. Development of a novel controlled release system for gastric retention. Pharm Res 1997;14:815–9.
15. Groning R, G Heun. Oral dosage forms with controlled gastrointestinal transit. Drug Dev Ind Pharm 1984;10:527–39.
16. Lahoti SR, Shinde RK, Ali SAy, Guleeha B. PH triggered sol-gel transition system of ofloxacin for prolonged gastric retention. Der Pharm Sin 2011;2:235–50.
17. Ali J, Arora S, Ahuja A, Babbar AK, Sharma RK, Khar RK, *et al.* Formulation and development of hydrodynamically balanced system for metformin: *in vitro* and *in vivo* evaluation. Eur J Pharm Biopharm 2007;67:196–201.
18. Sathiyaraj S, Devi RD, Hari VBN. Lornoxicam gastro retentive floating matrix tablets: design and *in-vitro* evaluation. J Adv Pharm Technol Res 2011;2:156–62.
19. Remya PN, Damodharan N, Priyadarsini SG, Prabaharan K. Effect of various surfactants on release behaviour of furosemide from floating tablets. Int J Pharm Pharm Sci 2010;2:2–5.
20. Yin L, Qin C, Chen K, Zhu C, Cao H, Zhou J, *et al.* Gastro-floating tablets of cephalexin: preparation and *in vitro*/*in vivo* evaluation. Int J Pharm 2013;452:241–8.
21. Cheong LWS, Heng PWS, Wong LF. The relationship between polymer viscosity and drug release from a matrix system. Pharm Res 1992;9:1510–4.
22. Tiwari S, Rajabi-Siahboomi AR. Modulation of drug releases from hydrophilic matrices. Pharm Technol Eur 2008;20:24–32.
23. Jamzad S, Fassihi R. Development of a controlled release low dose class II drug-Glipizide. Int J Pharm 2006;312:24–32.
24. Rahman M, Hasan S, Alam A, Roy S, Jha MK, Ahsan Q, *et al.* Formulation and evaluation of ranolazine sustained release matrix tablets using eudragit and HPMC. Int J Pharm Biomed Res 2011;2:7–12.
25. Lee BJ, Ryu SG, Cui JH. Formulation and release characteristics of hydroxypropyl methylcellulose matrix tablet containing melatonin. Drug Dev Ind Pharm 1999;25:493–501.

How to cite this article

- Syed Naiem Raza, Nisar Ahmad Khan. Various formulation variables effecting flotation behaviour of single unit Gastroretentive capsules of ofloxacin. Int J Pharm Pharm Sci 2017;9(1):213-217.