THEOPHYLLINE LOADED GASTRORETENTIVE FLOATING TABLETS BASED ON HYDROPHILIC POLYMERS: PREPARATION AND *IN VITRO* EVALUATION

FERDOUS KHAN, MD. SHAIKHUL MILLAT IBN RAZZAK, MD. ZIAUR RAHMAN KHAN, MOHAMMAD ABUL KALAM AZAD, JAKIR AHMED CHOWDHURY AND MD. SELIM REZA*

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh

ABSTRACT

This investigation describes the preparation and *in vitro* evaluation of gastroretentive floating tablet of theophylline. Two hydrophilic cellulose derivatives, Methocel K100M and Methocel K15MCR were evaluated for their gel forming and release controlling properties. Sodium bicarbonate and citric acid were incorporated as gas generating agents. The effects of soluble components (sodium bicarbonate and citric acid), gel forming agents and amount variation of theophylline on drug release profile and floating properties were investigated. Tablets were prepared by direct compression technique. Formulations were evaluated for *in vitro* buoyancy and drug release study was evaluated for eight hours using USP XXII paddle-type dissolution apparatus using 0.1N HCl as dissolution medium. The release mechanisms were explored and explained with zero order, first order, Higuchi and Korsmeyer equations. The release rate, extent and mechanisms were found to be governed by polymer and floating agent content. The content of active ingredient was also a vital factor in controlling drug release pattern. It was found that polymer content and amount of floating agent significantly affected the mean dissolution time, percentage drug release after 8 hours, release rate constant and diffusion exponent.

Keywords: Gastroretentive dosage form, floating tablet, theophylline, absorption window, hydrophilic polymer.

INTRODUCTION

Rapid and unpredictable gastrointestinal transit could result in incomplete drug release from the device above the absorption zone leading to diminished efficacy of the administered dose (Iannuccelli *et al*., 1998). Gastroretentive systems can remain in the gastric region for several hours and hence can significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment of small intestine (Ponchel and Irache, 1998). It has applications also for local drug delivery to the stomach and proximal small intestine (Deshpande *et al.,* 1997). Therefore different approaches have been proposed to retain the dosage form in the stomach. Those approaches include synthesis of high density dosage form (Singh and Kim, 2000); concomitant administration of drugs or excipients, which slows the motility of stomach or small intestine (Moes, 1993); synthesis of bioadhesive or mucoadhesive dosage form (Akiyama *et al.,* 1998). But the simplest and possibly the most elegant way to improve drug absorption is to hold a drug delivery system above the absorption window. Because most absorption windows are located in the proximal small intestine (duodenum), the most effective strategy will be to hold the formulation in the stomach (Chen *et al.,* 2000).

When a drug is formulated with gel forming hydrocolloid such as HPMC, and carbon dioxide generating agents like citric acid and sodium hydrogen carbonate it swells in the gastric fluid as it gets contact with the aqueous medium. Formation of CO_2 and entrapment of that gas into the polymeric gel causes swelling of the dosage form resulting a bulk density less than 1. It then remains buoyant and floats in the gastric fluid, resulting a prolonged gastric residence time. This floating dosage form is well known as a Hydrodynamically Balanced System (HBS) (Uzdemir, *et al.*, 2000). It has been suggested that an active material should be formulated in the form of an HBS to enhance bioavailability of those drugs having a dissolution or stability problem in the small intestinal fluid, drugs which are being locally effective in the stomach and drugs with a narrow therapeutic window (Jobin, *et al*., 1985).

The aim of the present study was to prepare and characterize extended-release floating matrix tablets of theophylline using two hydrophilic cellulose derivatives; Methocel K100M and Methocel K15MCR. Investigations were performed whether there was any effect of floating agent content and theophylline content upon the floating lag time of the tablets. The impact of formulation variables upon the release rate, mean dissolution time and release mechanism were also evaluated with the help of various mathematical models.

**Corresponding author:* Ph: +880-2-8612069; Fax: +880-2-8615583, e-mail: selimreza_04@yahoo.com

MATERIALS AND METHODS

Materials

Theophylline was a kind gift from Square Pharmaceuticals Limited. The source of Methocel K15MCR, Methocel K100M and ludipress were Colorcon, USA and BASF, Germany respectively. Two gas generating agents citric acid anhydrous and sodium hydrogen carbonate were obtained from Loba Cheme Pvt. Ltd., India. Aerosil 200 and magnesium stearate were sourced respectively from Degussa, Germany and Wilfrid Smith Ltd. UK. All other chemicals and reagents used were of analytical and pharmaceutical grade.

Preparation of floating tablets of theophylline

The active ingredient and other excipients were accurately weighted for thirty tablets according to the formulations (table 1). Particular attention has been given to ensure thorough mixing and phase homogenization. The appropriate amounts of the mixture were accurately weighted in an electronic balance for the preparation of each tablet and finally compressed using a Perkin-Elmer laboratory hydraulic press. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate. All the preparations were stored in airtight containers at room temperature for further study.

Determination of in vitro floating lag time

The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa and his co-workers. The tablets were placed in a 100 mL beaker containing 0.1N HCl. The media was kept in stagnant condition and the temperature was maintained at 37°C. The time required for the tablet to rise to the surface and float was determined as floating lag time (Rosa *et al.*, 1994).

Dissolution study

The release of theophylline from floating tablets was determined by using Dissolution Tester USP XXII in paddle method. The dissolution test was performed using 900ml 0.1N HCl solution at 37°C ± 0.5°C temperature and at 50 rpm. At every 1 hour interval samples of 10ml were withdrawn from the dissolution medium and that amount was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to a suitable concentration with 0.1 N HCl solution. The absorbances of the solutions were measured at 271nm for theophylline by using a Shimadzu 1201 UV-Visible double beam spectrophotometer (Shimadzu, Japan). Cumulative percentage drug release was calculated using an equation obtained from standard curve.

Kinetic modeling of drug release

The dissolution profiles of all the batches were fitted to zero order, first order (Wagner, 1969) and Higuchi equations (Higuchi, 1961) (equation 1-3 respectively).

$$M_t = M_0 + k_0 t \quad (1)$$

$$\ln M_t = \ln M_0 + k_1 t \quad (2)$$

$$M_t = M_0 - k_H t^{1/2} \quad (3)$$

In these equations, M_t is the cumulative amount of drug released at any specified time (t) and M_0 is the dose of the drug incorporated in the delivery system. k_0, k_1 and k_H are rate constants for zero order, first order and Higuchi model respectively. These models fail to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore the dissolution data were also fitted to well-known Korsmeyer and Peppas semi-empirical model (Peppas, 1985; Korsmeyer *et al.*, 1983) to ascertain the mechanism of drug release.

Table 1: Composition of different formulations of floating tablets

Formula	Theophylline (mg)	Methocel K100M (mg)	Methocel K15MCR (mg)	Citric acid anhydrous (mg)	Sodium bicarbonate (mg)	Total (mg)
F-1	100	100	-	25	50	306
F-2	100	100	-	50	75	356
F-3	200	100	-	25	50	406
F-4	200	100	-	50	75	456
F-5	300	100	-	25	50	506
F-6	300	100	-	50	75	556
F-7	100	-	100	25	50	306
F-8	100	-	100	50	75	356
F-9	200	-	100	25	50	406
F-10	200	-	100	50	75	456
F-11	300	-	100	25	50	506
F-12	300	-	100	50	75	556

Besides these ingredients each tablet contains 25 mg ludipress, 4 mg aerosil and 2 mg magnesium stearate.

$$\log (M_t/M_\infty) = \log k + n \log t \quad (4)$$

Where, M_∞ is the amount of drug release after infinite time; k is the release rate constant which considers structural and geometric characteristics of the tablet; and n is the diffusional exponent; indicative of the mechanism of drug release. For a tablet having cylindrical shape n value below 0.45 indicate Fickian diffusion and n value between 0.45 and 0.89 indicate anomalous transport, often termed as first-order release. If the n value reaches 0.89 or above, the release can be characterized by case II and super case II transport, which means the drug release rate does not change over time and the drug is released by zero-order mechanism. In this case, the drug release is dominated by the erosion and swelling of the polymer (Ritger and Peppas, 1987). Mean dissolution time (MDT) was calculated from dissolution data using the following equation (Mockel and Lippold, 1993):

$$MDT = (\frac{n}{n+1})k^{-1/n}$$

Table 2: Floating lag time and release parameters of folating tablets of theophylline

Formula	Floating Lag Time (sec)	% Release	MDT (Hour)	Zero Order		Higuchi		Korsemeyer	
				Ko	R^2	K_h	R^2	n	R^2
F-1	25.3±3.27	60.4±1.41	6.2±0.45	7.73	0.995	22.84	0.935	0.949	0.998
F-2	20.5±3.02	71.8±3.33	4.1±0.74	8.05	0.933	25.39	0.998	0.533	0.998
F-3	38.5±4.46	41.9±2.11	9.8±0.62	5.21	0.995	15.31	0.925	0.909	0.991
F-4	30.2±5.04	58.4±3.82	5.4±0.67	6.28	0.870	20.46	0.994	0.426	0.995
F-5	56.5±6.83	39.7±2.42	9.5±0.77	4.99	0.988	14.91	0.949	0.937	0.991
F-6	45.7±6.19	47.5±5.53	9.1±0.93	5.56	0.980	16.87	0.973	0.668	0.994
F-7	25.0±3.85	61.1±2.76	6.1±0.32	7.68	0.991	22.90	0.949	0.897	0.997
F-8	20.5±3.25	89.1±5.17	1.2±0.36	8.66	0.705	30.24	0.924	0.283	0.970
F-9	38.5±4.46	54.6±3.43	8.9±0.45	5.45	0.983	16.51	0.970	0.774	0.998
F-10	30.2±5.04	69.8±4.52	3.7±0.77	7.54	0.888	24.31	0.994	0.419	0.984
F-11	56.5±6.83	51.4±4.15	8.5±0.88	5.77	0.974	17.55	0.970	0.644	0.992
F-12	45.7±6.19	69.1±3.10	3.6±0.95	7.49	0.864	24.43	0.991	0.428	0.993

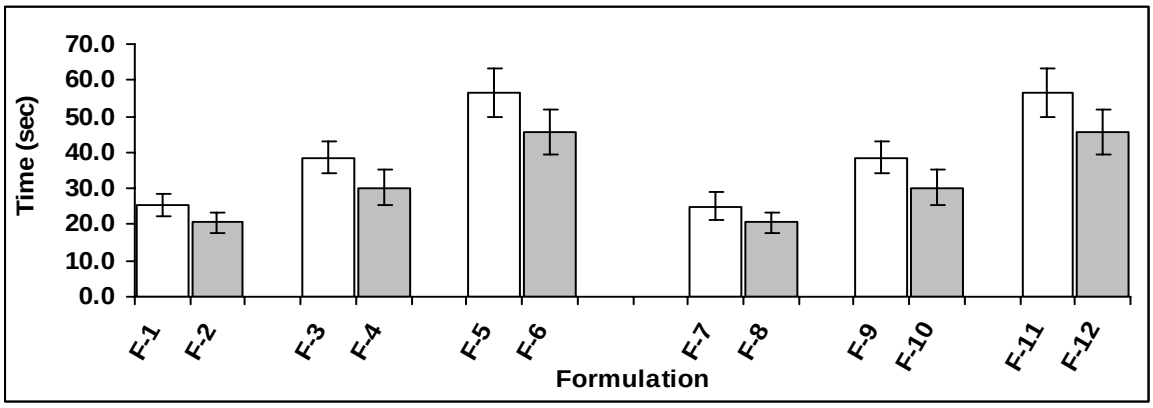

Fig. 1: *In vitro* floating lag time of gastroretentive floating tablets of Methocel K100M (F1~F-6) and K15MCR (F-7~F-12).

At initial time. After 24 seconds After 25 seconds

Fig. 2: Pictorial presentation of *in vitro* floating behavior of a representative tablet of Methocel K100M.

RESULTS AND DISCUSSION

In vitro buoyancy study

Formulations were evaluated for *in vitro* buoyancy and all formulations had floating lag times below 1 minute and constantly floated on dissolution medium for more than 8 hours. Floating lag times were found to be significantly controlled by citric acid and sodium hydrogen carbonate content. Floating lag time was reduced due to increase of amount of floating agent (fig. 1). Increased amount of floating agent caused rapid formation as well as entrapment of CO_2 gas into the hydrophilic polymeric gel which eventually resulted in reduction of floating lag time.

Effect of floating agent content on release of theophylline

First of all the formulations of Methocel K100M were compared to explore the effect of changing amount of floating agent and changing amount of theophylline. To evaluate the effect of amount variation of floating agent F-1 which contained 100 mg theophylline and 75 mg floating agent was compared with F-2 which contained 100 mg theophylline and 125 mg floating agent (table 1). Similarly F-3 was compared with F-4 and F-5 with F-6. Percent release of drug at the end of eight hour for F-1 was 60.4% and for F-2 was 71.8%. These values clearly indicated the increase of drug release as a consequence of increase of floating agent content. Comparisons of F-3 with F-4 and F-5 with F-6 showed similar pattern of change. R^2 values obtained from zero order equation for F-1 and F-2 are 0.995 and 0.933 respectively (table 2). These values indicated that due to the increase of amount of floating agent the drug release mechanism had been deviated from zero order release profile. From the table 2 it is also clear that zero order release rates were increased due to the increase of floating agent content of the formulation. So it can be claimed that due to increase of amount of floating agent in a formulation, zero order release rate was increased but the fitting of formulation with zero order release pattern was lost significantly (in single factor ANOVA, p = 0.00000065). Similar results were found in case comparisons of F-3 with F-4 and F-5 with F-6 (in these cases p values were also less than 0.05). On the other hand R^2 values obtained from Korsmeyer and Peppas model for F-1, F-2, F-3, F-4, F-5 and F-6 were 0.998, 0.998, 0.991, 0.995, 0.991 and 0.994 respectively (table 2). The values of release exponent (n) for F-1 and F-2 were 0.949 and 0.533 which indicated that release of theophylline from these two formulations were controlled by case II transport mechanism and anomalous type of diffusion respectively. The n values obtained from Korsmeyer kinetic model were 0.909 for F-3, 0.426 for F-4 which also indicated that drug release mechanisms were shifted from non-Fickian to Fickian direction due to the increase of amount of floating agent. Similarly n values of F-5 and F-6 indicated that the drug release mechanism was shifted towards diffusion dominated mechanism from case II transport mechanism due to the increase of amount of floating agent. Being soluble excipients citric acid and sodium bicarbonate increased the tablet porosity and stimulated water penetration into the inner parts of the matrix, which resulted in a faster diffusion of drug and erosion of polymer, causing rapid release of drug from the tablets (Sako, *et al.,* 2002). Thus the rapid release of theophylline from F-2, F-4 and F-6 due to the increase of soluble component of the formulation could be explained by the increase of floating agent content in those formulations. These data are in accordance with some other studies (Huang and Tsai, 2004)

Similar pattern of changes were also observed among the formulations of Methocel K15MCR. In all cases the increases of floating agent content caused increase of zero order release (fig. 4) and also decrease of fitting with zero order release mechanisms. All three formulations of Methocel K15MCR containing 75 mg of floating agent were found to follow anomalous type of transport mechanism whereas three other formulations containing 125 mg floating agent were found to follow Fickian diffusion mechanism (table 2).

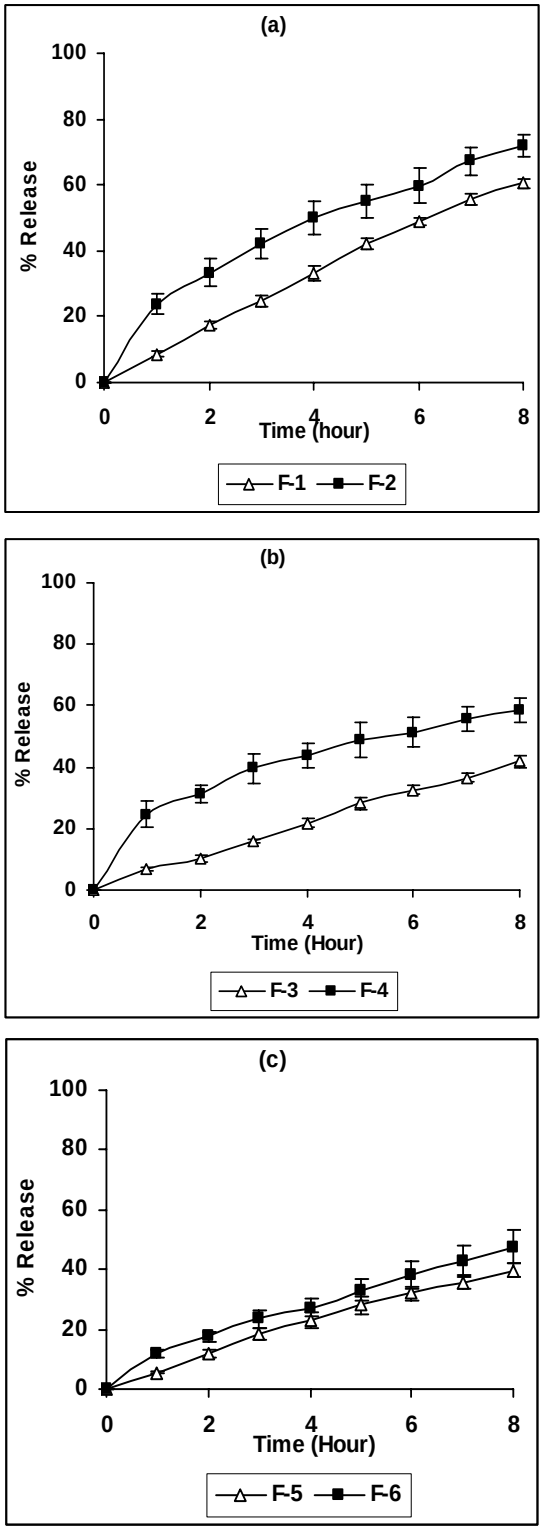

Fig. 3: Zero order plot of release kinetics of Theophylline showing the variation of drug release due to change of amount of floating agent from various formulations of Methocel K100M.

(a) Theophylline 100mg, (b) Theophylline 200mg
(c) Theophylline 300mg

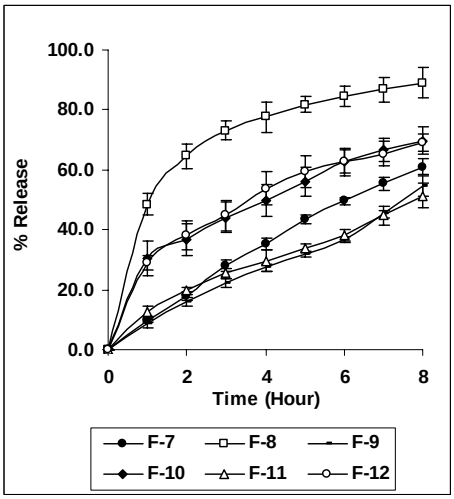

Fig. 4: Zero order release profile of Theophylline from six different formulations of floating tablet of Methocel K15MCR.

Increase of floating agent content always displayed a common phenomenon that the drug release rate and extent were increased in all cases which were also supported by MDT (mean dissolution time) values (table 2 and fig. 5). From the dissolution data, it is clear that as the amount of floating agents were increased; the percent release of theophylline was increased abruptly at the initial level. Increase of soluble component (citric acid and sodium hydrogen carbonate) of the formulations resulted in the increase of drug release rate and extent possibly due to the formation of channels which stimulated water penetration into the inner part of the matrix and thus exposure of new surfaces of tablet matrix to the dissolution medium. Similar observations were found by Sung and coworkers while they were evaluating the effect of formulation variables on drug and polymer release from HPMC-based matrix tablets (Sung *et al.,* 1996). When the amount of floating agent was increased the control of the polymer upon the drug release was to some extent lost which is demonstrated by the standard error bars parallel to Y-axis. From figs. 3 and 4 it is clearly observed that increasing amount of floating agent caused the increase of release rate and extent which was particularly significant at the initial stages of the dissolution study.

Impact of Theophylline content on release profile

From the zero order release profile it was observed that the total percent release of theophylline from those three formulations which contained 75 mg of floating agent were decreased gradually due to the increase of amount of theophylline. The results resemble with the previous finding; the increase of amount of insoluble component (increase of theophylline which in an insoluble drug) caused the reduction in the percent release and reduction of zero order release rate (table 2). Similar pattern of changes were also observed in case of F-2, F-4 and F-6.

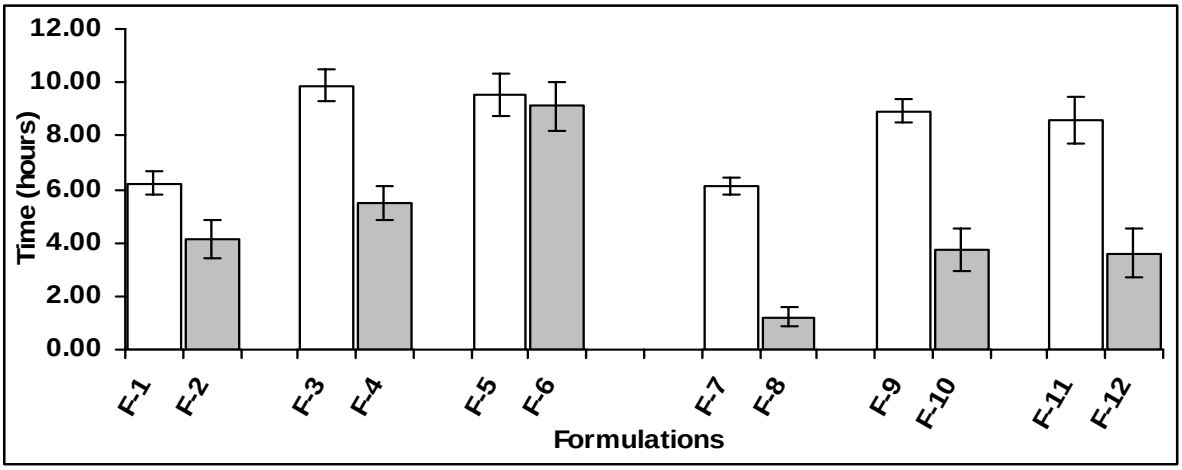

Fig. 5: Mean Dissolution Time (MDT) of gastroretentive floating tablets of Methocel K100M (F1~F-6) and K15MCR (F-7~F-12).

Due to the increase of amount of theophylline, the extent of drug release had been reduced relatively. Higher values of n for higher amounts of theophylline indicated that, due to the increase of the amount of theophylline the release mechanism shifts from diffusion dominated to erosion dominated direction. The possible reason may be the increase of the amount of theophylline resembles with the relative decrease in the amount of soluble component. Similar results were also observed by Vueba and co-workers while they were evaluating the influence of cellulose ether polymers on ketoprofen release from hydrophilic matrix tablets (Vueba *et al.,* 2004).

CONCLUSION

It was observed that in all cases the increase of amount of floating agent caused the decrease of floating lag time. At relatively higher polymer contents all formulations displayed better fitting with zero order release kinetics. In all cases the increase of the floating agent content caused a lowering of the magnitude of release exponent (n) indicating the shifting of release mechanism from non-Fickian to Fickian direction. All these results indicated that a low amount of foloating agent and high amount of hydrophilic polymer favoured the sustained release of theophylline from gastroretentive tablet formulations. It can be concluded that, drug load, amount of soluble component, polymer type and the polymer content of the matrix affected the release profile of theophylline from hydrated HPMC matrices significantly. These studies indicated that the proper balance between a hydrophilic matrix former and a soluble component can produce a drug dissolution profile similar to a theoretical dissolution profile.

REFERENCES

Akiyama Y, Nagahara N, Nara E, Kitano M, Yamamoto I, Azuma J and Ogawa Y (1998). Evaluation of oral mucoadhesive microspheres in man on the basis of the pharmacokinetics of flurosemide and riboflavin, compounds with limited gastrointestinal absorption sites. *J. Pharm. Pharmacol.,* **50**: 159-166.

Chen J, Blevins WE, Park H and Park K (2000). Gastric retention properties of Superporous hydrogen composites. *J. Control. Release,* **64**: 39-51.

Deshpande AA, Rhodes CT, Shah NH and Malick AW (1996). Controlled-release drug delivery systems for prolonged gastric residence: an overview. *Drug Dev. Ind. Pharm*., **22**: 531-539.

Higuchi T (1961). Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci*., **50**: 874-875.

Huang YB, Tsai YH, Yang WC, Chang JS, Wu PC and Takayama K (2004). Once-daily propranolol extended-release tablet dosage form: formulation design and in vitro/in vivo investigation. *Eur. J. Pharm. Biopharm.,* **58**: 607-614.

Iannuccelli V, Coppi G, Bernabei MT and Cameroni R (1998). Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study. *Int. J. Pharm*., **174**: 47-54.

Jobin G, Cortot A and Godbillon J (1985). Investigation of drug absorption from the gastrointestinal tract of man, I: metoprolol in stomach, duodenum, and jejunum. *Br. J. Clin. Pharmacol*., **19**: 97S-105S.

Korsmeyer RW, Gurny R, Docler E, Buri P and Peppas NA (1983). Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm*., **15**: 25-35.

Moes AJ (1993). Gastroretentive dosage forms. *Crit. Rev. Ther. Drug Carrier Syst.,* **10**(2): 143-159.

Mockel JE and Lippold BC (1993). Zero order release from hydrocolloid matrices. *Pharm Res*., **10**: 1066-1070.

Peppas NA (1985). Analysis of Fickian and non-Fickian drug release from polymers. *Pharm Acta Helv*. **60**: 110-111.

Ponchel G and Irache JM (1998). Specific and non-specific bioadhesive particulate system for oral delivery to the gastrointestinal tract. *Adv. Drug Del. Rev.,* **34**: 191-219.

Ritger PL and Peppas NA (1987). A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. *J. Control. Release,* **5**: 37-42.

Rosa M, Zia H and Rhodes T (1994). Dosing and testing *in-vitro* of a bioadhesive and floating drug delivery system for oral application. *Int. J. Pharm*., **105**: 65-70.

Sako K, Sawada T, Nakashima H, Yokohama S and Sonobe T (2002). Influence of water soluble fillers in hydroxypropylmethylcellulose matrices on in vitro and in vivo drug release. *J. Controlled Release,* **81**: 165-172.

Singh BN and Kim KH (2000). Floating drug delivery system: An approach to oral controlled drug delivery via gastric retention. *J. Control. Release,* **63**: 235-259.

Sung KC, Nixon PR, Skoug JW, Ju TR, Gao P, Topp EM and Patel MV (1996). Effect of formulation variables on drug and polymer release from HPMC-based matrix tablets. *Int. J. Pharm.,* **142**: 53-60.

Uzdemir N, Ordu S and Ozkan Y (2000). Studies of floating dosage forms of furosemide: *in vitro* and *in vivo* evaluation of bilayer tablet formulations. *Drug Dev. Ind. Pharm.,* **26**: 857–866.

Vueba ML, Batista DC, Veiga F, Sousa JJ and Pina ME (2004). Influence of cellulose ether polymers on ketoprofen release from hydrophilic matrix tablets. *Eur. J. Pharm. Biopharm.,* **58**: 51-59.

Wagner JG (1969). Interpretation of percent dissolved-time plots derived from in vitro testing of conventional tablets and capsules. *J. Pharm. Sci*., **58**: 1253-1257.