Journal of Applied Pharmaceutical Science Vol. 3 (8 Suppl 1), pp. S37-S41, September, 2013
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2013.38.S7
ISSN 2231-3354

Development and evaluation of Methocel K15M based Theophylline floating tablets

Sayeeda Tasneem Chowdhury[1], A H M Mohidul Kabir[1], Nashid Karim[1], Md. Shahid Sarwar[2], Md. Delowar Hossain[2], Md. Shohel Hossain[2], Mohammad Safiqul Islam[2*]
[1]Department of Pharmacy, University of Asia Pacific, Dhaka-1207, Bangladesh.
[2]Department of Pharmacy, Noakhali Science and Technology University, Sonapur, Noakhali-3814, Bangladesh.

ARTICLE INFO

Article history:
Received on: 12/06/2013
Revised on: 15/07/2013
Accepted on: 05/08/2013
Available online: 18/09/2013

Key words:
Sustained release dosage form, floating tablet, theophylline, hydrophilic polymer.

ABSTRACT

The purpose of the investigation highlights the formulation and optimization of floating tablets containing theophylline as a model drug. Formulations were optimized for different concentrations of cetyl alcohol, citrc acid and methocel K15M by direct compression method. The dissolution study of the tablet matrices of 9 different formulations were carried out in 0.1N HCl as the medium (pH 1.3) for 8 hours using USP type II dissolution apparatus. It was observed the floating lag time for the tablet was 30 seconds and the total floating time was more than 8 hours. The drug release pattern was simulated in different kinetic orders such as Zero Order, First Order, Higuchi, and Korsmeyer release kinetic model. From the study, we observed that Higuchi release kinetics was predominant over other release kinetics and diffusion was the drug release mechanism from the matrices. Korsmeyer-Peppas release kinetics suggests that formulation F3, F4 and F9 followed Fickian type release mechanism whereas formulation F1, F2, F5, F6, F7 and F8 followed Non-Fickian type release mechanism. Thus, it is possible to design theophylline loaded Methocel K15M sustained release matrix tablets with desirable release characteristics by judicious and critical combination of Methocel K15M with other hydrophilic materials.

INTRODUCTION

Theophylline is a methyl xanthine derivative which is effectively used for the treatment of bronchial asthma and bronchospastic reactions. The therapeutic concentration of this drug range from 10 to 20 µg/ml while toxic effect appear at concentration above 20 µg/ml and the fluctuations of its serum concentrations may leads to variable clinical responses (Sarojini *et al.*,2010; Sundaran *et al.*,2013). In order to control this problem, short biological half life of drug (8.7 hours) favours development of sustained release formulation (Bosewell-Smith *et al.*,2006). Sustained release dosage forms are generally used to deliver adequate amount of drug for an extended period to achieve the optimum therapeutic activity of the drug (Sarwar and Hossain, 2012). Such dosage form with prolonged residence times in the stomach are desirable for drugs that are locally active in the stomach, have an absorption window in the stomach or in the upper small intestine, unstable in the intestinal or colonic environment, and/or have low solubility at high pH values. In addition, as the total gastrointestinal transit time of dosage forms is increased by prolonging the gastric residence time (Rathor and Ram 2013), these systems can also be used as sustained release devices with a reduced frequency of administration and therefore, improved patient compliance. Recent approaches to increase the gastric residence time of drug delivery systems include (i) bioadhesive devices (ii) systems that rapidly increase in size upon swallowing and (iii) low density devices that float on the gastric contents (Deshpande *et al.*, 1996; Ingani *et al.*, 1987; Singh and Kim, 2000). But the simplest and possibly the most elegant way to improve drug absorption is to hold a drug delivery system above the absorption window. The properties and type of polymer play very crucial role in release rate, mechanism and floating behaviors in the floating system (Hascicek *et al.*, 2000). The polymers considered as the first category are those which form insoluble or skeleton matrices while the second category represents hydrophobic and water-insoluble materials, which are potentially erodable and the third group

** Corresponding Author*
Dr. Mohammad Safiqul Islam, Associate Professor, Department of Pharmac, Noakhali Science and Technology University Sonapur, Noakhali-3814, Bangladesh. Tel: +88-0321-71483 (Office); + 88-01714165107(Mobile), Fax: +88-0321-62755

exhibits hydrophilic properties (Islam *et al.,* 2009). Methocel K15M is a hydrophilic polymer that become hydrated, swollen and facilitates to diffuse the drug (Bidah and Vernaud, 1991). Drugs that are formulated with such gel forming hydro-colloidal along with carbon dioxide generating agents like citric acid and sodium bicarbonate may swell in the gastric fluid as it gets contact with the aqueous medium.

Generation of carbon-di-oxide and entrapment of this gas into the polymeric gel causes swelling of the dosage form which results in a bulk density of 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 objective of the present study was to formulate and characterize sutained release floating matrix tablets of theophylline using the hydrophilic cellulose derivatives—Methocel K15. Studies were conducted to determine whether there was any effect of floating agent and rate-retarding agent upon the floating lag time of the tablets. The impact of formulation variables upon the release rate and the mechanism of release were also evaluated with various kinetic model studies.

MATERIALS AND METHODS

Materials

Theophylline was used as a model drug which was obtained as a gift sample from Square Pharmaceuticals Limited, Bangladesh. Methocel K15M was purchased from BASF, Germany while citric acid anhydrous and sodium bi-carbonate was obtained from Loba Cheme Pvt. Ltd., India. Avicel, magnesium stearate, cetyl alcohol and talc were sourced from BASF, Germany. All other chemicals and reagents used were of analytical and pharmaceutical grade.

Methods

Preparation of floating tablets of theophylline

Tablets containing theophyline as a pure drug were prepared by direct compression method. The active ingredient (theophylline) and other excipients were accurately weighted for twenty seven tablets according to the formulations (table 1). The respective powders (drug, polymers, and fillers) and optional additives were blended thoroughly with a mortar and pestle. Particular attention was given to ensure thorough mixing and phase homogenization. Finally powder blends were compressed using a Perkin-Elmer laboratory hydraulic press. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate to minimize friction during ejection. All the preparations were stored in airtight containers at room temperature for further study.

Floating behavior (buoyancy) of the tablets

The tablets were immersed in 900 ml of 0.1N HCl buffer in USP type II apparatus at 37 ± 0.5º C for 8 hours. The *in vitro* buoyancy was determined by floating lag time which is the time that is required to reach the tablet from the bottom to the top surface of the dissolution apparatus. The time for which the tablet constantly floats on the surface of the medium (Total floating time) was also measured (Rosa *et al.,* 1994; Abubkar and Jun 2000; Ali *et al.,* 2004)).

In vitro drug release studies

The *in vitro* drug release studies were carried in USP type II apparatus at 75 rpm maintained 37 ± 0.5º C containing 0.1N HCl (pH 1.3). Then 10 ml of aliquots was withdrawn from the dissolution medium at specific time intervals and replaced with equivalent volume of fresh medium to maintain the volume constant. Collected dissolution samples were filtered and diluted to a suitable concentration with 0.1 N HCl solution. The absorbances of the solutions were measured at 271 nm for theophylline by using UV spectrophotometer (Shimadzu UV 1201, Japan).

Kinetic analysis of the dissolution data

In order to study the exact mechanism of drug release from the matrix floating tablets, the *in vitro* dissolution data were fitted to various mathematical models like zero order, first order, Higuchi, and Korsmeyer-Peppas models (Varelas *et al.,* 1995; Mulye and Turco, 1996; Higuchi, 1961; Korsmeyer *et al.,* 1983).

Zero-order Model: $F = K_0 t$, where F represents the fraction of drug released in time t, and K_0 is the apparent release rate constant or zero-order release constant.

First-order Model: $\ln (F) = - K_1 t$, where F represents the fraction of drug released in time t, and K_1 is the first order release constant.

Higuchi Model: $F = K_H t$, where F represents the fraction of drug released in time t, and K_H is the Higuchi dissolution constant.

Korsmeyer-Peppas Model: $F = K_P t_n$, where F represents the fraction of drug released in time t, K_P is the rate constant and n is the release exponent, this indicates the drug release mechanism.

For cylindrical shaped tablets, n value below 0.45 indicates Fickian diffusion whereas n value between 0.45 and 0.89 indicate non-fickian or anomalous transport. When the n values are 0.89 or above, the release can be characterized by case II and super case II transport (Ritger and Peppas, 1987).

RESULTS AND DISCUSSION

Tablets from formulations were evaluated for *in vitro* buoyancy study where they exhibited floating lag times below 1 minute (Table 2). The tablets were constantly floated on dissolution medium for more than 8 hours. It was observed that citric acid content significantly controls the floating lag times. Floating lag time was reduced due to increase of amount of floating agent. 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 (Khan *et al.,* 2009). The three formulations (F1, F4, and

F7) in the experiment contain no citric acid. The observation showed that after 8 hours of dissolution formulation F7 containing highest amount of cetyl alcohol (51 mg) released only 51.5% of drug while formulations F1 and F4 which contains no cetyl alcohol 0% and 6% cetyl alcohol respectively; showed a drug release of 48.2% and 47.8% respectively. Similarly, percent drug release from formulations F2, F5, F8 after 8 hours of dissolution is 47.1, 49 and 53% respectively as the amount of cetyl alcohol decreases. Percent drug release from F3, F6, F9 formulations after 8 hours of dissolution is 53.1, 51.5 and 55.8 % respectively. On the other hand, formulations F1, F6 and F8 contain 0% cetyl alcohol whereas 0, 4 and 2% of citric acid. After 8 hour of dissolution drug release from these formulations is 48.2, 51.5 and 53.0% respectively. After 8 hour of dissolution, drug release from formulations F2, F4, F9 is 47.1, 47.8 and 55.8% respectively. While, after 8 hour of dissolution drug release from formulations F3, F5, F7 is 53.1, 49 and 51.5% respectively. Increased drug release from latter formulation may be attributed to decreased amount of cetyl alcohol. It was observed that at low level of cetyl alcohol content (0%), increment of citric acid significantly increased drug release. On the other hand at higher level of cetyl alcohol content (3-6%), the effect of citric acid was reduced to some extent. In the experiment major determinant is found to be polymer concentration. In all cases, it was found that higher polymer concentration retarded the drug release.

The regression co-efficient (R^2) values of all the formulations for different kinetic model are indicated in Table 2. From the R^2 values, it was clearly found that all the formulations followed Higuchi release kinetics (Figure 1) other than the zero order or other release kinetics. On the other hand, analysis of release mechanism explored that formulation F3, F4 and F9 followed Fickian type release mechanism whereas formulation F1, F2, F5, F6, F7 and F8 followed Non-Fickian type release mechanism (Table 3). The rate and extent of drug release increased from the matrices with increasing the amount of citric acid in the formulation which is similar findings to previous study (Khan *et al.*, 2009).

From the data, it is clear that $T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ values were changed due to the change of amount of citric acid and cetyl alcohol in the matrix tablets (Table 4). In all these formulations the values of $T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ are larger for those formulations which contain higher quantities of citric acid and lowest quantities of cetyl alcohol. If we consider formulation F-1, F-6 and F-8 which contains 0% of cetyl alcohol and 0, 4 and 2% of citric acid, it is seen that highest values correspond to F6 which contains highest citric acid and no cetyl alcohol. Second highest values go to F1 which contains neither citric acid nor cetyl alcohol. Lowest values correspond to F8 possessing intermediate amount of citric acid and no cetyl alcohol. The similar observation is true for the F3-F6-F9, F2-F5-F8, F1-F4-F7, F2-F4-F9, and F3-F5-F7 groups.

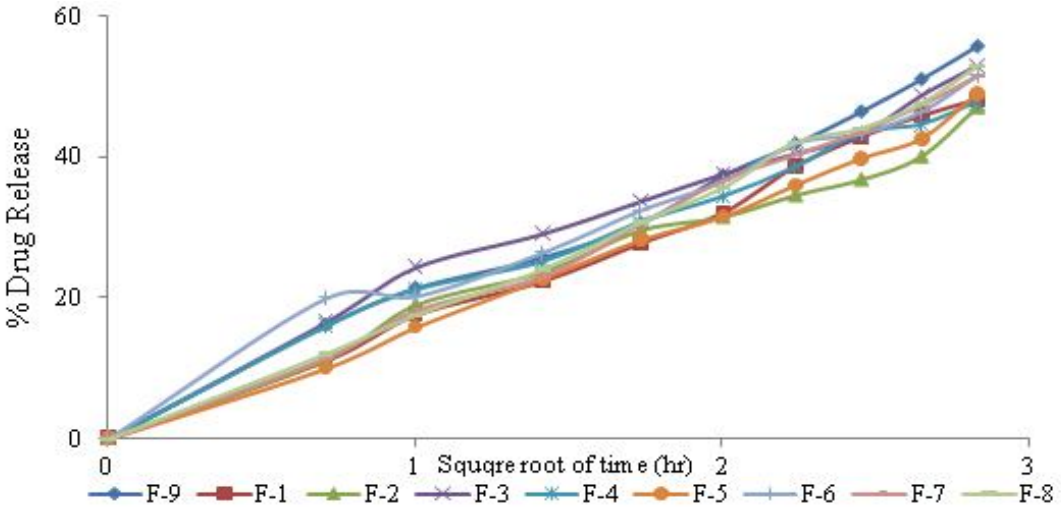

Fig. 1: Higuchi release kinetics of theophylline floating tablets.

Table. 1: Formulation of the sustained release matrix tablet of theophylline.

Code	Theophylline	Methocel K15M	$NaHCO_3$	Citric Acid	Cetyl Alcohol	Avicel	Mg Stearate	Talc
F1	0.975	0.341	0.171	0	0	0.219	0.017	0.017
F2	0.975	0.341	0.171	0.034	0.051	0.134	0.017	0.017
F3	0.975	0.341	0.171	0.068	0.102	0.049	0.017	0.017
F4	0.975	0.341	0.171	0	0.051	0.168	0.017	0.017
F5	0.975	0.341	0.171	0.034	0.102	0.083	0.017	0.017
F6	0.975	0.341	0.171	0.068	0	0.151	0.017	0.017
F7	0.975	0.341	0.171	0	0.102	0.117	0.017	0.017
F8	0.975	0.341	0.171	0.034	0	0.185	0.017	0.017
F9	0.975	0.341	0.171	0.068	0.051	0.1	0.017	0.017

*All the amounts are expressed in gm.

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

Code	Floating Lag time	% Drug Release	Zero Order		First Order		Higuchi		Korsmeyer	
			K_o	R^2	K_1	R^2	K_H	R^2	K_p	R^2
F1	25.3±3.27	48.2	5.506	0.941	0.033	0.975	17.35	0.995	0.789	0.993
F2	20.5±3.02	47.1	4.775	0.897	0.028	0.937	15.34	0.985	0.768	0.979
F3	18.5±4.46	53.1	5.312	0.875	0.034	0.936	17.26	0.983	0.647	0.986
F4	30.2±5.04	47.8	5.004	0.889	0.03	0.942	16.19	0.99	0.688	0.991
F5	26.5±6.83	49.0	5.348	0.943	0.032	0.974	16.84	0.995	0.819	0.996
F6	22.7±6.19	51.5	5.47	0.904	0.034	0.954	17.6	0.996	0.709	0.997
F7	25.0±3.85	51.5	5.77	0.935	0.036	0.975	18.26	0.997	0.769	0.994
F8	20.5±3.25	53.0	5.9	0.941	0.037	0.978	18.61	0.997	0.761	0.998
F9	18.5±4.46	55.8	5.948	0.934	0.039	0.975	18.78	0.991	0.683	0.979

Table. 3: In-vitro drug release mechanism of floating tablets of theophylline.

Code	Release exponent (n)	Release mechanism
F1	0.523	Non-Fickian
F2	0.460	Non-Fickian
F3	0.387	Fickian
F4	0.394	Fickian
F5	0.546	Non-Fickian
F6	0.457	Non-Fickian
F7	0.530	Non-Fickian
F8	0.528	Non-Fickian
F9	0.443	Fickian

Table. 4: Successive fractional dissolution time of theophylline released from Methocel K15M based matrix tablets.

Code	$T_{25\%}$	$T_{50\%}$	$T_{80\%}$
F1	2.3	8.5	20.9
F2	2.3	10.4	29
F3	1.3	7.8	26.4
F4	1.7	9.5	31.4
F5	2.3	8.3	19.7
F6	1.7	7.8	22
F7	2.1	7.6	18.5
F8	2	7.4	18.1
F9	1.5	7.3	21.2

CONCLUSION

The approach of the present study was to develop a sustained release theophylline matrix tablet with Methocel K15M. The study reveals that, it is possible to design theophylline loaded Methocel K15M sustained release matrix tablets with desirable release characteristics by judicious and critical combination of Methocel K15M with other hydrophilic materials. Commercial availability of Methocel K15M and its direct compression characteristics will reduce the unit cost of product by decreasing processing steps; the presence of citric acid in the matrix will modulate the drug release to an acceptable pharmacokinetic profile. The Korsmeyer release rate along with Higuchi release rate and T_{50}% data clearly manifests the necessity of combining a hydrophilic matrix system with Methocel K15M. However, further studies in this context should be carried out to evaluate stability and reproducibility of this dosage form. *In vitro-In vivo* correlation should also be performed to assess the efficacy of Methocel K15M based matrix tablets in *in vivo* environment.

ACKNOWLEDGEMENT

The authors are thankful to Square Pharmaceuticals Ltd. for their generous donation of Theophylline. The authors are also thankful to all the teachers and staffs of The University of the Asia Pacific for their support and co-operation.

REFERENCES

Abubkar ON, Jun SZ. Captopril floating and/or bioadhesive tablets: Design and release kinetics. Drug Dev Ind Pharm, 2000; 26(9):965-969.

Ali J, Arora S, Ahuja A, Khar RK. Development and evaluation of floating drug delivery system for Celecoxib. Ind J Pharm Sci, 2004; 66(4):475.

Bidah D, Vernaud JM. Dosage forms with a polymer matrix and swelling polymer. Int J Pharmaceutics, 1991; 77:81-87.

Bosewell-Smith V, Cazzola M, Page CP. Are Phosphodiesterase 4 inhibitors just more theophylline. J Allergy Clin Immunol, 2006; 117:1237-1243.

Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled release drug delivery system for prolonged gastric residence: A Review. Drug Dev Ind Pharm, 1996; 22(6):531-539.

Hascicek C, YukseL-Tilkan G, Turkmen B, Ozdemir N. Effect of formulation parameters on the drug release and floating properties of gastric floating two-layer tablets with acetylsalicylic acid. Acta Pharm, 2011; 61:303–312.

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

Ingani HM, Timmermans J, Moes AJ. Conception and *in vivo* investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. Int J Pharm, 1987; 35:157-164.

Islam MS, Haque T, Jahangir R, Fatema K, Vhuiyan MI, Biva IJ. In Vitro Release Kinetic Study of Ciprofloxacin HCl from Methocel K15M CR, Methocel K4M CR and Methocel K4M Premium Matrix Tablets. S J Pharm Sci, 2009; 2(1):37-43.

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

Khan F, Razzak MSM, Khan MZR, Azad MAK, Chowdhury JA, Reza MS. Theophylline loaded gastro-retentive floating tablets based on hydrophilic polymers: Preparation and *in vitro* evaluation. Pak J Pharm Sci, 2009; 22(2):155-161.

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

Mulye NV, Turco ST. An examination of assumptions underlying the first order kinetic model for release of water soluble drugs from dicalcium phosphate dehydrate matrices. Drug Dev Ind Pharm, 1996; 22:673-679.

Rathor S, Ram A. Floating drug delivery system as an approach to increase the gastric retention of methotrexate: formulation and evaluation. Asian Journal of Pharmaceutical and Clinical Research, 2013; 6(1):42-47.

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

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

Sarojini S, Arivazagan D, Manavalan R, Jayanthi V. Buoyant sustained release tablets based on polyethylene oxide. International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2(1):144-149.

Sarwar MS, Hossain MS. Development and evaluation of sustained release losartan potassium matrix tablet using kollidon SR as release retardant. Brazilian Journal of Pharmaceutical Sciences, 2012; 48(4):621-628.

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

Sundaran S, Buvaneswari, Muralidharan S, Saji M, Rajendran S, Sankar S. A reliable reverse phase high performance liquid chromatography method for a frequently prescribed bronchodilator – theophylline. Asian Journal of Pharmaceutical and Clinical Research, 2013; 6(2):30-32.

Varelas CG, Dixon DG, Steiner C. Zero-order release from biphasic polymer hydrogels. J Control Release, 1995; 34:185-192.

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

How to cite this article:

Sayeeda Tasneem Chowdhury, AHM Mohidul Kabir, Nashid Karim, Md. Shahid Sarwar, Md. Delowar Hossain, Md. Shohel Hossain, Mohammad Safiqul Islam., Development and evaluation of Methocel K15M based Theophylline floating tablets. J App Pharm Sci, 2013; 3 (8 Suppl 1): S37-S41.