Preparation and *In vitro* Evaluation of Theophylline Loaded Gastroretentive Floating Tablets of METHOCEL K4M

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ABSTRACT: This investigation describes the preparation and *in vitro* evaluation of gastroretentive floating tablets of theophylline. Hydrophilic polymer METHOCEL K4M was used for its 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 agent (METHOCEL K4M) and dose variation on drug release profile and floating properties were investigated. It has been observed that in all cases increase of the amount of floating agent caused a decrease of the floating lag time. Increase of theophylline load showed an increase of the floating lag time, which was independent of floating agent content. The release mechanisms were explored and explained with zero order, first order, Higuchi, Korsmeyer and Hixon-Crowell equations. The release rate, extent and mechanisms were found to be governed by the content of polymer and floating agent. 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 time required for 50% of drug release ($T_{50\%}$), percentage drug release after 8 hours, release rate constant, and diffusion exponent (n). Kinetic modeling of dissolution profiles revealed that the drug release mechanism could range from diffusion controlled to case II transport, which was mainly dependent on presence of relative amount of theophylline, polymer and floating agent.

Key words: Gastroretention, Floating tablet, Theophylline

INTRODUCTION

Rapid gastrointestinal transit could result in incomplete drug release from the device above the absorption zone leading to diminished efficacy of the administered dose.[1] Therefore different approaches have been proposed to retain the dosage form in the stomach. These include bioadhesive systems,[2] swelling and expanding systems,[3] and floating systems.[4] In some cases gastroretention is achieved by concomitant administration of drugs or excipients which slows the motility of GIT.[5] Perhaps the most promising approach to achieving gastroretention is that of creating a swelling or expanding system *in situ*. When the drug is formulated with a gel forming polymer such as semisynthetic derivative of cellulose, it swells in the gastric fluid with a bulk density less than one. It then remains buoyant and floats in the gastric fluid, affecting a prolonged gastric residence time (GRT). This floating dosage form is known as a hydrodynamically balanced system (HBS).[6] Hydrodynamically balanced systems can remain in the gastric region for several hours and

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hence 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. It has applications also for local drug delivery to the stomach and proximal small intestines.[7] In spite of having a lot of potential benefits floating drug delivery is associated with certain limitations. Drugs that irritate the gastric mucosa, those that have multiple absorption sites in the gastrointestinal tract, which undergo significant first pass metabolism and those that are not soluble and stable at gastric pH are not suitable candidates to be formulated as floating dosage forms.[8]

The aim of the present study was to prepare and characterize extended-release floating matrix tablets of theophylline using a hydrophilic cellulose derivative i.e. METHOCEL K4M. Citric acid and sodium hydrogen carbonate were incorporated as gas generating agents. Investigations were performed whether there was any effect of floating agent upon the floating lag time of the tablets. The impact of theophylline content upon the floating lag time was also investigated. The impact of formulation variables that means polymer content, floating agent content and theophylline content upon release rate, extent and mechanism were also investigated.

MATERIALS AND METHODS

Theophylline anhydrous was a kind gift from Square Pharmaceuticals Limited. METHOCEL K4M and ludipress were obtained from Colorcon, USA and BASF, Germany, respectively. Two gas generating agents citric acid and sodium hydrogen carbonate were obtained from Loba Cheme Pvt. Ltd., India. Aerosil 200 and magnesium stearate were collected 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. Theophylline loaded floating tablets were prepared by direct compression using METHCEL K4M as matrix former and sodium bicarbonate and citric acid as floating agents. Amounts of various ingredients (in mg) used in different formulations of gastroretentive tablets are presented in the Table 1. Appropriate amounts of the mixture were accurately weighted in an electronic balance for the preparation of each tablet and finally those amounts were 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 studies.

***In vitro* buoyancy study.** The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa *et al.*[9] The tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Study of release profile. The release of theophylline from floating tablets was determined by using Dissolution Tester USP XXII. The dissolution test was performed using 900 ml 0.1N HCl solution at 37 ± 0.5^{o}C and the paddles were rotated at 50 rpm. At every 1 hour interval, 10 ml of aliquot was withdrawn from the dissolution medium and it was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to suitable concentrations with 0.1 N HCl solution. The absorbances of the solutions were measured at 271 nm for theophylline with a Shimadzu 1201 UV-Visible double beam spectrophotometer (Shimadzu, Japan). Cumulative percentage drug release was calculated using an equation obtained from standard curve. The times for 50% and 80% drug release were calculated based on the Korsmeyer and Peppas model.[10]

Kinetic modeling of drug release. The dissolution profile of all the batches was fitted to zero order, first order,[11] Higuchi,[12] Hixon-Crowell,[13] Korsmeyer and Peppas,[14,15] equations to ascertain the kinetic modeling of drug release.

RESULTS AND DISCUSSION

After performing dissolution study drug release profiles were analyzed on the basis of various mathematical models. The values of release exponent (n) were calculated from Korsmeyer and Peppas equation. For those tablets having cylindrical shape n value below 0.45 indicated Fickian diffusion and n value between 0.45 and 0.89 indicated anomalous transport, often termed as first-order release. If the n value reaches 0.89 and 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.[16]

***In vitro* buoyancy study.** Formulations were evaluated for *in vitro* buoyancy and all formulations had floating lag times below 2 minutes 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. It was reduced due to increase of amount of floating agent which caused rapid formation and entrapment of CO_2 gas into the hydrophilic polymeric gel.

Effect of amount variation of floating agent on dissolution behavior. To evaluate the effect of amount variation of floating agent F-1a which contained 100 mg theophylline and 75 mg floating agent was compared with formulation F-1b which contained 100 mg theophylline and 125 mg floating agent (Table 1). Similarly F-2a was compared with F-2b and F-3a with F-3b. R^2 values obtained from zero order equation for F-1a, F-1b, F-2a, F-2b, F-3a and F-3b were 0.976, 0.778, 0.985, 0.988, 0.981 and 0.978, respectively. On the other hand, R^2 values obtained from Korsmeyer and Peppas model for F-1a, F-1b, F-2a, F-2b, F-3a and F-3b were 0.999, 0.992, 0.995, 0.985, 0.995 and 0.981, respectively (Table 2). Only F-2b showed better fitting with zero order kinetics than Korsmeyer and Peppas mathematical model. The value of release exponent (n) for F-1a and F-1b, 0.712 and 0.335, indicated that release pattern of drug from these two formulations were anomalous and perfectly Fickian diffusion controlled, respectively. The n values obtained from Korsmeyer kinetic model were 0.912 for F-2a, 0.723 for F-2b, 0.813 for F-3a and 0.640 for F-3b. The n values indicated that from F-2a drug release followed case II transport mechanism and from F-2b the drug release mechanism was anomalous which was co-dominated

Table 1. Composition of different formulations (mg) of floating tablets

Ingredients	Formulations					
	F-1a	F-1b	F-2a	F-2b	F-3a	F-3b
Theophylline	100	100	200	200	300	300
Ludipress	25	25	25	25	25	25
METHOCEL K4M	100	100	100	100	100	100
Citric acid anhydrous	25	50	25	50	25	50
Na bicarbonate	50	75	50	75	50	75
Aerosil 200	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2
Total weight/Tablet	**306**	**356**	**406**	**456**	**506**	**556**

Table 2. Floating lag time and various release parameters for floating tablets of METHOCEL K4M

Formulation code	Floating lag time (sec)	% Release after 8 hour	$T_{50\%}$ (hrs)	$T_{80\%}$ (hrs)	Zero order		Higuchi		Korsmeyer	
					K_o	R^2	K_h	R^2	n	R^2
F-1a	21.3±3.61	65.0±4.60	6.2	10.2	7.88	0.976	24.02	0.977	0.712	0.999
F-1b	13.5±2.43	86.2±1.64	4.1	10.0	8.67	0.778	29.40	0.962	0.335	0.992
F-2a	28.7±3.01	52.6±3.51	9.9	16.6	5.72	0.985	17.08	0.946	0.912	0.995
F-2b	24.5±2.59	55.6±2.34	5.5	16.5	7.77	0.988	23.25	0.952	0.723	0.985
F-3a	60.3±8.36	49.4±3.79	9.5	15.7	6.06	0.981	18.32	0.964	0.813	0.995
F-3b	45.7±6.19	66.0±3.35	9.1	18.4	6.49	0.978	19.67	0.967	0.640	0.981

by both diffusion and erosion. On the other hand, n values of F-3a and F-3b indicated that the drug release mechanisms were anomalous for both of these formulations but in case of F-3b the release mechanism was slightly dominated by Fickian diffusion pattern. The magnitudes of n were reduced as more soluble components were incorporated into the tablet matrix. The lowering of the values of diffusional exponent (n) establishes the fact that drug release mechanism shifts from zero order to diffusion controlled mechanism due to an increase in the amount of soluble component of the tablet matrix.

The increase of floating agent content always displayed a common phenomenon that the drug release rate and extent were increased in all cases, which were supported by zero order release rate and $t_{50\%}$ values (Table 2). But interestingly, it was observed that $t_{80\%}$ values were not affected significantly in case of first two pairs. From the dissolution data, it is clear that if the amount of floating agent is increased, it causes an abrupt rise in the release of the drug at the initial level, but in course of time the release rates become similar, which is demonstrated by $T_{50\%}$, and $T_{80\%}$ values in Table 2. Increase of soluble component of the formulation resulted in the increase of drug release rate and extent possibly due to the formation of channels which stimulates water penetration into the inner part of the matrix and thus exposure of new surfaces of tablet matrix to the dissolution medium. Another reason may be enhanced erosion of polymer, which results in faster diffusion of drug from the matrix of polymer into the dissolution media. Similar observations were found by Sung and co-workers[17] while they were evaluating the effect of formulation variables on drug and polymer release from HPMC-based matrix tablets.[17] 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 Figure 1 it is clearly observed that increase in the amount of floating agent caused the increase of release rate and extent which was particularly significant at the initial stages of the dissolution study.

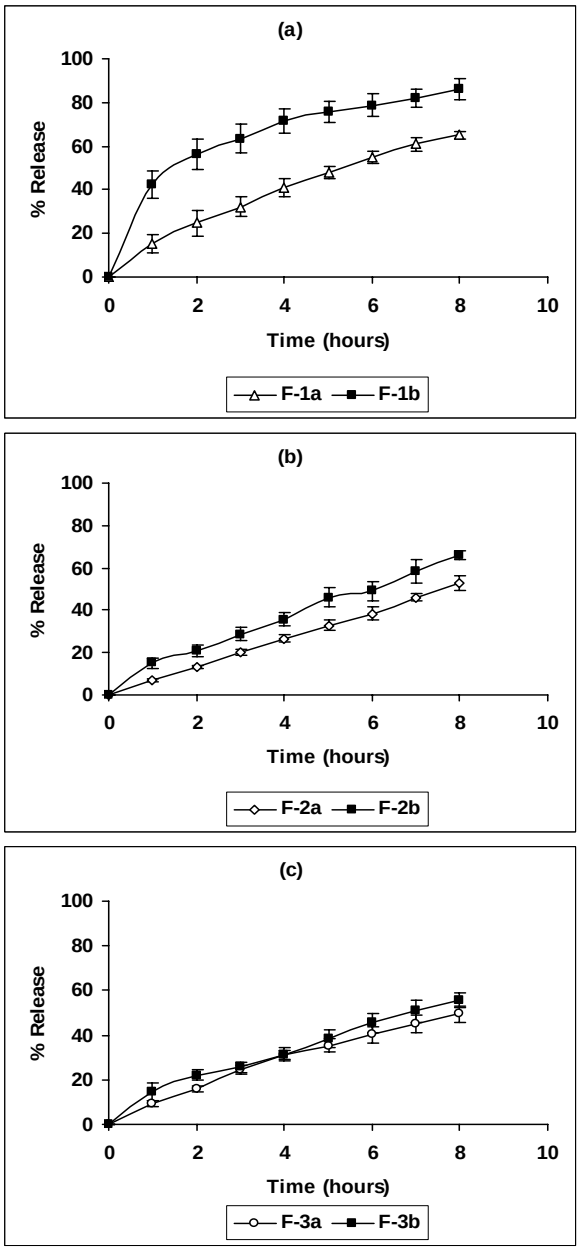

Figure 1. Release profile of Theophylline from (a) Theophylline 100 mg (b) Theophylline 200 mg (c) Theophylline 300 mg

Impact of increasing the amount of theophyloline on dissolution behavior. From the zero order release profile it is observed that the total percent release of theophylline from F-1a, F-2a and F-3a were 65.0, 52.6 and 49.4%, respectively at the

end of eight hour (Table 2). Similar pattern of changes were also observed in case of F-1b, F-2b and F-3b. Due to the increase of amount of theophylline, the extent of drug release had been reduced relatively (Figure 2). The values of diffusion exponents (n) for F-2a and F-3a were higher than that for F-1a (Table 2). Similar trends were also observed in case of comparison of F-2b and F-3b with F-1b. 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.[18]

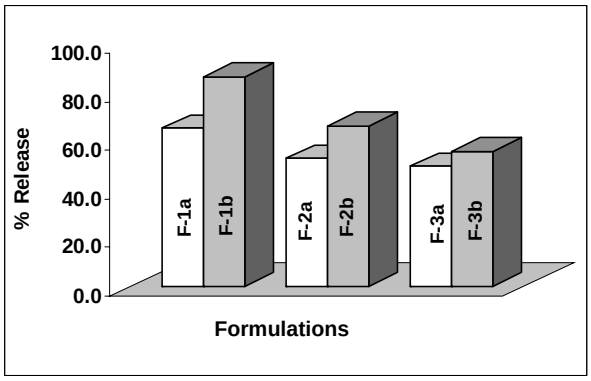

Figure 2. Bar diagram showing the release of Theophylline at the end of eight hour from various Gastroretentive floating talets

CONCLUSION

It was observed that in all cases the increase in 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. Similarly, it can be concluded that decrease of polymer content is the reason which is responsible for the shifting of erosion and swelling dominated mechanism towards a mechanism which is dominated by diffusion of the drug from the polymer matrix. It was also observed that at relatively higher polymer contents the drug release pattern becomes slow but steady. The drug load, amount of soluble component and the polymer content of the matrix affected the release profile of theophylline from hydrated METHOCEL K4M matrix significantly. These results indicated that a low amount of floating agent and a high amount of METHOCEL K4M favors sustained release of theophylline from the gastroretentive tablet formulations.

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