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Research Article

Design and evaluation of bilayer floating tablets of amoxicillin trihydrate

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ABSTRACT

The present investigation concerns the development and evaluation of floating tablets of amoxicillin trihydrate which, after oral administration, are designed to prolong the gastric residence time and increase drug bioavailability. Bilayer floating tablets comprised two layers, immediate release and controlled release layers. The immediate release layer comprised sodium starch glycolate as a super disintegrant and the controlled release layer comprised HPMC K4M, K15M and SCMC as release retarding polymers. Sodium bicarbonate was used as a gas generating agent. The controlled layer was compressed and granules of the immediate release layer were added to it then both layers were compressed using a single station rotary press. Direct compression method was used for formulation of the bilayer tablets. The release of amoxicillin trihydrate was found to follow a mixed pattern of Korsmeyer-Peppas release model. The tablets were evaluated for hardness, friability, Drug content uniformity, swelling index, and in vitro drug release. Final formulation released approximately 87% drug in 12 h in vitro, while the floating lag time was 20 min, because of prompt disintegration of the fast releasing layer and the enhanced rate of dissolution of amoxicillin trihydrate from the system. Final formulation followed the Korsemeyer-Peppa's model and showed no significant change in physical appearance, drug content, floatability or in vitro dissolution pattern after storage at 40°C/75% RH for three months.

Keywords: Amoxicillin trihydrate; Bilayer-floating tablet (BFT); hydroxypropyl methyl cellulose (HPMC); relative humidity (RH).

INTRODUCTION

Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract. Controlled/sustained release preparations using alternating routes have also been formulated but oral route still remains preferable (Rahman, Z et al., 2006). The oral route of drug administration is the most convenient and commonly used method of drug delivery. However, this route has several physiological problems, including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (8–12 h), and the existence of an absorption window in the upper small intestine for several drugs (Agyilirah, GA et al., 1991; Hoffman, F et al., 1983). These difficulties have prompted researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period (Deshpande, AA et al., 1996; Hwang, SJ et al., 1998). Attempts are being made to develop a controlled drug delivery system, which can provide therapeutically effective plasma drug concentration for a longer period, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady-state by delivering the drug in a controlled and reproducible manner (Sood, RP 2003).

Amoxicillin trihydrate [2S-[2α,5α,6β(S*)]]-6-[[Amino(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3,2,0]heptane-2-carboxyllic acid trihydrate is (U.S. National Library of medicine, 2011) an moderate-spectrum, bacteriolytic, β-lactam antibiotic used to treat bacterial infections caused by susceptible microorganisms. It is usually the drug of choice within the class because it is better absorbed, following oral administration, than other β-lactam antibiotics. Amoxicillin is susceptible to degradation by β-lactamase-producing bacteria, about 20% is bound to plasma proteins in the circulation and plasma half-life of 1 to 1.5 hours has been reported (BP, 2001; Martindale, 1999). Since the half-life of amoxicillin trihydrate is 1-1.5 hours, multiple doses are needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance (Goodman, A. Gilman, A 2001).

Several methods have been reported which can be used to retain the dosage form in the stomach, which then results in the drug slowly release at the desired site with controlled release formulation. A gastroretentive dosage form will release the drug over an extended period in the stomach and upper gastrointes-

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tinal tract (GIT) thus enhancing the opportunity for absorption.

Various approaches have been proposed to control the gastric residence of drug delivery systems in the upper part of the GIT including floating drug delivery systems (FDDS) (Baumgartner, S et al., 2000). The influence of different grades of hydroxy methyl cellulose (HMC) and chitosan on the release kinetics was studied in floating tablets containing amoxicillin trihydrate as a model drug (Hilton, AK et al., 1992; Sahasathian, T et al., 2007). *In vitro* release showed that higher the amount of HPMC in tablet composition results in reduced drug release however addition of MCCP increases the drug release. Targeted retentive device for the treatment of periodontal infections with amoxicillin trihydrate from nylon fibers developed (Ahuja, A et al., 2006). It has also been reported that solubility parameter of amoxicillin trihydrate to influence the *in vitro* release (Karanth, H 2005).

The objective of present study was an approach to develop and evaluate bilayer matrix tablets of Amoxicillin trihydrate using hydroxypropyl methylcellulose K4M, hydroxypropyl methylcellulose K15 M and SCMC, to retain the tablets in the stomach by using sodium bicarbonate as gas-forming agent to achieve enhanced gastric residence time. As well as study the various effects of additives on developed formulation.

MATERIALS AND METHODS

Materials

Amoxicillin trihydrate was a gift from Maxheal pharmaceutical, (Nasik, India). HPMC K4M, HPMC K15M and SCMC were received as gift sample from Torrent pharmaceutical, Ahmadabad. Tartarzine, sodium starch glycolate, starch, magnesium stearate and ferric chloride were purchased from SD Fine Chemicals, Mumbai, India. All solvents used were of analytical grade.

Methods

Preparation of bilayer tablets

Bilayer floating tablets were prepared by direct compression involving two steps, immediate release and controlled release layer. The immediate releasing layer mixture was prepared by coating the drug with lactose, starch and color tartarzine using warm water as a wetting agent. The granules were dried at 45 to 50°C for 30 minutes in an oven (IP, 1996; Streubel, A et al., 2003; Patel, VF 2007). All ingredients were passed through a sieve (30#) and mixed well in a mortar then mixed with sodium starch glycolate as a super disintegrant and magnesium stearate as shown in Table No.1.

Second, controlled release layer prepared by uniform mixture of amoxicillin trihydrate along with the HPMC K4M, K15M and SCMC as release retarding polymers. Sodium bicarbonate was used as a gas generating agent. An optimized formulation was taken in a mortar with other excipients. Homogenous mixture was obtained by blending and sieving processes. Then the blend of powder was compressed by direct compression technique to get the controlled release layer as shown in Table No.2.

Finally the floating tablets containing amoxicillin were prepared by combining immediate release layer and various formulations of controlled release layer. After the compression upper punch was lifted and the blend of powder for immediate release layer was poured into the die, containing initially compressed matrix tablet on (Rimek multi station punching machine) using 12.5 mm flat punches, with the hardness of 4.5 kg/cm^2.

Table 1: Formulation of immediate release layer

Ingredients	A1	A2	A3
Amoxicillin trihydrate	50	50	50
Sodium starch glycolate	6	8	10
Starch	5	5	5
Tartarzine	0.625	0.625	0.625
Lactose	60.875	58.875	56.875
MgS	2.5	2.5	2.5

All the amounts are shown as milligrams.

Table 2: Formulations of controlled release layer

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Amoxicillin trihydrate	200	200	200	200	200	200	200	200
HPMC K4M	100	150	200	134	-	-	-	-
HPMC K15M	-	-	-	-	200	100	134	150
Sodium CMC	100	150	100	66	100	100	66	150
Lactose	141	41	41	141	141	41	41	141
$NaHCO_3$	72	72	72	72	72	72	72	72
MgS	12	12	12	12	12	12	12	12

All the amounts are shown as milligrams.

Characterization of tablets

Physical evaluation of amoxicillin trihydrate floating tablets

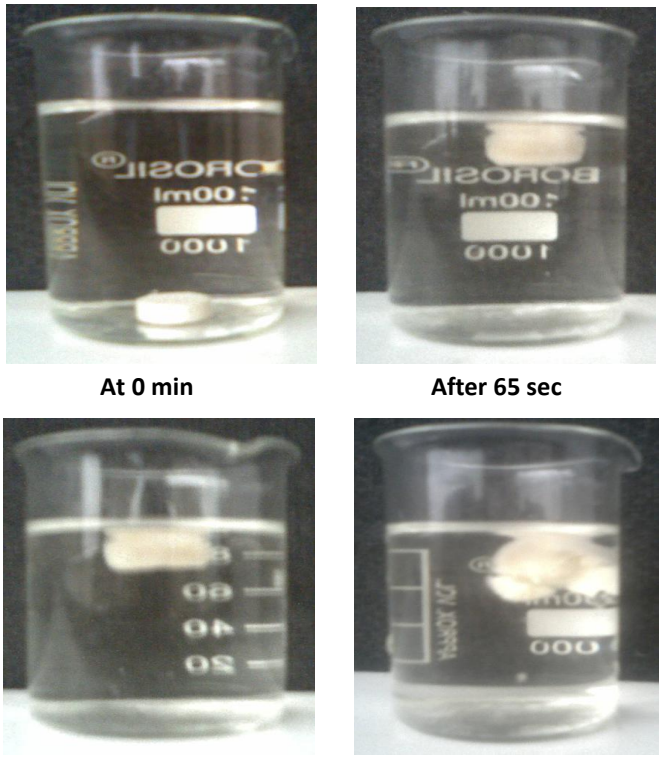
Two tablets from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. The prepared floating tablets were evaluated for weight variation using 10 tablets, hardness using three tablets from each batch (Monsanto tester), friability using 20 tablets (Roche friabilator) (IP, 1996)

Drug content uniformity

Twenty tablets were weighed and triturated to get fine powder. Weight equivalent to 100 mg of Amoxicillin trihydrate was dissolved in 50 ml of pH 1.2 buffer and sonicated for 15 min, the volume was adjusted to 100 ml using 1.2 pH buffer and filtered. 2 ml of this solution (withdrawn from supernatant aqueous part) was diluted to 10 ml with pH 1.2 buffer and volume adjusted up to mark. Filtered through 0.45 µm whatman filter paper, and analyzed at 230 nm using UV spectrophotometer (Labindia, Mumbai) after suitable dilution (Streubel, A et al., 2003).

Buoyancy lag-time studies

This test was characterized by floating lag time and total floating time. The test was performed using USP XXIII type II paddle dissolution apparatus (Labindia, Disso 2000, Mumbai) using 900 ml of pH 1.2 buffer at paddle rotation of 50 rpm at 37 ± 0.5^{o} C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium was noted as floating lag time and total floating time (Patel, VF 2007; Patel, VF et al., 2005).



At 0 min **After 65 sec**

After 1 h **After 12 h**

Figure 1: Bilayer floating tablet buoyancy time study

Table 3: Evaluation parameters of optimized formulations

Formulation code	Evaluation parameters			
	Hardness ± S.D. (kg/cm^2) (n = 5)	Friability (%)	Average weight variation (n=10)	Drug content (%)
F1	4.4± 0.4	0.389	0.753 ± 0.011	98.88
F2	4.2 ± 0.2	0.133	0.751 ± 0.010	101.53
F3	4.2 ± 0.5	0.135	0.742 ± 0.010	101.16
F4	4.4 ± 0.1	0.460	0.753 ± 0.022	98.45
F5	4.2 ± 0.3	0.133	0.751 ± 0.010	98.24
F6	4.2 ± 0.2	0.298	0.752 ± 0.008	99.95
F7	4.5 ± 0.3	0.436	0.749 ± 0.008	99.33
F8	4.2 ± 0.4	0.467	0.752 ± 0.008	98.56

Dissolution studies

The release rate of amoxicillin trihydrate from floating tablets was determined using USP XXIII dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml pH 1.2 buffer, at 37 ± 0.5°C and 50 rpm. Samples of 5 ml were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through whatman filter paper and the absorbance of these solutions was measured at 230 nm. The cumulative percentage drug release was calculated using 'PCP Disso v2.08' Software (Poona College of Pharmacy, Pune, India) (Patel, VF 2007; Paulo, C 2001).

Swelling study

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of 1.2 pH buffer at 37 ± 0.5°C. The tablets were removed periodically from the dissolution medium and, after removing free water, the weight gain was measured. The swelling characteristics were expressed in terms of the percentage water uptake (WU%) according to the equation (Patel, VM et al., 2007; Deshpande, AA et al., 1997).

$$\% WU = (Wt\text{-}Wo/Wo) \times 100$$

WU – Water uptake, Wt – Weight of tablet at time t,

Wo – Weight of tablet before immersion

Stability studies of the optimized formulation

The stability studies were carried out according to ICH and WHO guidelines to assess the drug and formulation stability. Optimized F3 and F5 formulations were sealed in aluminum packaging having a polyethylene coating on the inside. Samples were kept in a humidity chamber maintained at 40°C and 75% RH for 3 months (Yorco Scientific Industries, India). At the end of the study period, samples were analyzed for drug content, buoyancy lag-time, *in vitro* dissolution and other physicochemical parameters (Jain, SK et al., 2005).

RESULT AND DISCUSSION

All formulations were prepared as bilayered tablets. First, the immediate release layer was prepared and evaluated on the basis of floating behavior studies. The first layer contains a mixture of amoxicillin trihydrate, Sodium starch glycolate lactose, starch, color tartarzine using warm water as a wetting agent. The tablets thus obtained were subjected to *in vitro* dissolution study and the batch having good percentage cumulative release of amoxicillin trihydrate is used for the preparation of bilayer tablet. The second controlled release layer contains the drug, in which sodium bicarbonate was added as a gas-generating agent with SCMC, HPMC K4M and HPMC K14M grade polymer as release retarding polymers. Hence, the unique combination of floating and bioadhesion is highly likely to prolong the gastric retention time of amoxicillin trihydrate. From the dissolution profile of the three formulations it was observed that high concentration of sodium starch glycolate releases more drug with respect to time. Almost half amount of drug was found to be released within 40 to 50 min. The batch with 10 mg concentration of sodium starch glycolate having 99% cumulative

Table 4: Floating lag time of prepared bilayer floating tablet

Formulation code	Floating lag time (sec)	Total floating time
F1	62	More than 12 h
F2	76	More than 12 h
F3	98	More than 12 h
F4	70	More than 12 h
F5	95	More than 12 h
F6	74	More than 12 h
F7	86	More than 12 h
F8	82	More than 12 h

Table 5: Water uptake of formulated batches

Time (h)	Formulations							
	F1	F2	F3	F4	F5	F6	F7	F8
1	75.9	78.7	76.3	67.9	77.4	80	78.4	81.2
2	86.8	93.6	98.6	83.8	93.55	90.7	84.7	92.8
3	89.9	100.2	101.5	89.9	100.88	97.3	88.8	99.2
4	103.1	104.6	115.4	101.1	108.7	106.6	94.4	102.6
5	108	114.6	123.6	112	114	110.6	102.6	109.6
6	118.3	119.7	127.2	118.3	121.9	116.6	111	114.7
7	108.5	112.1	120.3	112.5	115.8	111.9	104.2	111.1
8	101.5	102.7	117.7	106.5	109.6	106.1	101.5	106.7
9	96.2	98	110.1	104.2	104.4	100.8	98.4	102.8
10	94.2	96.5	102.7	102.2	98.8	97.8	96.2	97.5

drug release in 1 h was then used to combine with controlled release layer for the formulation of bilayer floating tablet.

The ideal amount of both, effervescent mixture and polymer, for the floating layer was estimated by determining the onset time of floating. From the results of floating behavior studies, it was found that as the concentration of effervescent mixture increased, the floating lag time, floating duration and matrix integrity decreased and *vice versa*. A reverse trend was observed on increasing the polymer concentration. Therefore the concentration of the effervescent mixture was chosen so as not to compromise the matrix integrity with the possible shortest lag time and floating duration of up to 12 h. The optimized floating layer formulation had the floating lag time of 3 min, good matrix integrity and floating duration of more than 12 h. as shown in Fig 1.

Physical evaluation

The weight variation, friability, hardness and content uniformity were found to be within acceptable limits (Table No. 3).

Thus, all the physical properties of these tablets were satisfactory as specified in the Indian Pharmacopoeia (IP, 1996).

Buoyancy lag-time studies

All tablet formulations exhibited satisfactory floatation ability and remained buoyant for more than 24 h in dissolution medium subjected to rotation. The buoyancy lag-time of tablets depends on the amount of sodium bicarbonate involved in CO_2 formation. For a floating system, the ideal matrix or coating material should be highly permeable to dissolution media in order to initiate rapid generation of CO_2 and allow release of CO_2 to promote floating. The floating lag time for all the formulations was found to be less than five minutes. The floating time for the 8 formulation was found to be increasing with the increasing amount of HPMC as per the polymer-drug concentration (Table No. 4).

Swelling study

From the study it was found that maximum liquid uptake and swelling of polymer was achieved up to 6 h and then gradually decreased. In the formulation F3 maximum swelling index was 127.2 at 6 h (Table No. 5).

The percentage water uptake was found to be increased on increasing the concentration of HPMC K4M and K15M in the formulations and hence the water uptake capacity increases. Drug diffusion depends significantly on the water content of the tablet. This may be because the mobility of the polymer chains is very dependent on the water content of the system. In the case of high water content, polymer chain relaxation takes place with volume expansion resulting in marked swelling of the system. Also, higher water content could lead to greater penetration of the gastric fluid into the tablet leading to faster carbon dioxide gas generation, thereby reducing the floating lag-time. Consequently, faster and greater swelling of the tablet would lead to an increase in the dimensions of the tablet leading to an increasing in the diffusion pathways and thus a reduction in diffusion rate. So, the drug release was found to be high initially and then gradually decreased.

In vitro dissolution studies

The release data were evaluated by the model dependent (Curve fitting) method using 'PCP Disso v2.08' software. The release rate kinetic data for all formulations are shown in Table No. 6.

The data obtained from *in vitro* dissolution studies were fitted in different models like zero order, first order, Higuchi and Korsemeyer-Peppa's model. The zero order plots were found to be fairly linear as indicated by their high regression values (r^2= 0.976-0.994). To confirm the exact mechanism of drug release from these bilayer floating tablets the data was fitted according to Korsemeyer's equation. Linear regression analysis and model fitting showed that all these formulations follows Korsemeyer-Peppa's model.

$$\log \%R = \log K + n \log t.$$

Where %R is the percentage drug release, K is release rate constant, n is diffusional release exponent that could be used to characterize the diffusional release mechanisms as n = o.1 to 0.5 (Fickian diffusion), 0.5< n <1 (anomalous transport), n = 1 (case II transport; ie, zero-order release), and n >1(super case II transport). Regression values r^2 were found 0.939 to 0.979 for different formulations. The mean diffusional exponent values (n) was found to be ranged between 0.438 to 0.503 indicates that all these formulations presented a dissolution behavior controlled by Fickian-diffusion mechanism. Thus it was found that the drug release from the amoxicillin trihydrate bilyered floating tablets follows Korsemeyer-Peppa's model. The results of the *in vitro* release studies are shown in Fig.2 and 3.

The concentration of HPMC K15M and K4M in the release layer was the key factor governing drug release. In the bilayer tablet, the drug release layer included the gelling agent forming a gelatinous barrier which controls the drug release without interference from gas bubbles generated in the floating layer.

Stability study

The stability studies were carried out on the optimized formulation F3 and F5. The formulations were stored at 40 ± 2°C/75 ± 5% RH for 3 months to assess their long term stability. The protocol of the stability studies conformed to WHO guidelines for stability testing of protocols intended for the global market. The results indicated that, irrespective of the concentration of

polymer, these formulations remained stable for three months (Table No.7).

nate as gas generating agent in polymers facilitating local action due to prolonged residence time in sto-

Table 6: Kinetics of *In vitro* amoxycillin trihydrate release from bilayer floating tablet

Code	Zero Order		First Order		Higuchi		Korsemeyer-Peppas	
	K	r^2	K	r^2	k	r^2	n	r^2
F1	0.109	0.980	-0.001	0.699	3.168	0.959	0.475	0.979
F2	0.119	0.984	-0.001	0.891	3.292	0.929	0.438	0.977
F3	0.098	0.978	-0.001	0.927	2.847	0.966	0.474	0.939
F4	0.115	0.976	-0.001	0.845	3.301	0.927	0.459	0.957
F5	0.108	0.980	-0.001	0.946	3.134	0.965	0.448	0.974
F6	0.128	0.993	-0.071	0.766	3.670	0.948	0.503	0.966
F7	0.123	0.991	-0.001	0.829	3.501	0.936	0.478	0.952
F8	0.115	0.994	-0.001	0.915	3.297	0.955	0.467	0.964

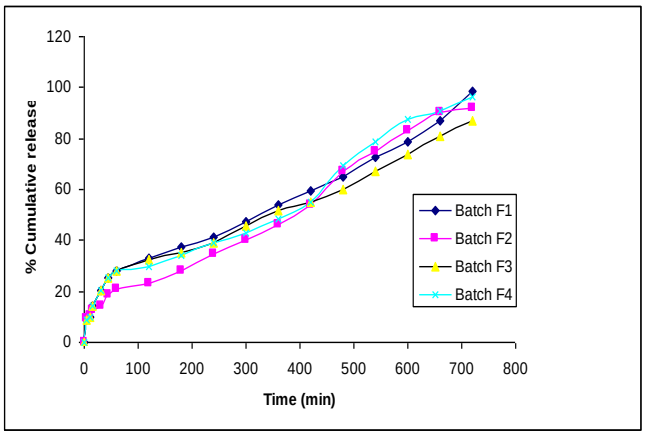


Figure 2: *In vitro* dissolution profile of Batch F1-F4

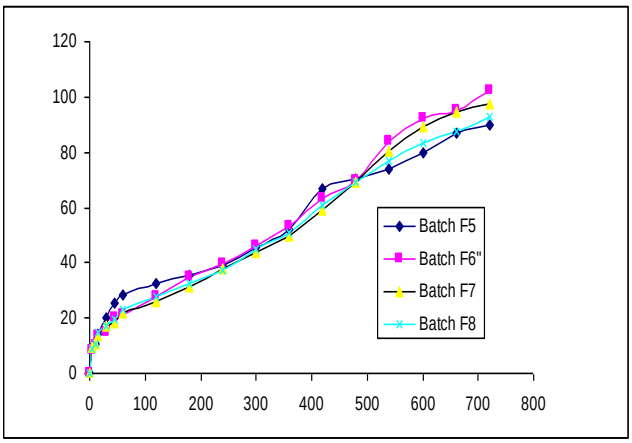


Figure 3: *In vitro* dissolution profile of Batch F5- F8

Table 7: Stability study of Batch F3 and F5 for % cumulative drug release

Time	% Cumulative Drug Release	
	F3	F5
After 1 month	89.54	89.46
After 2 month	92.43	87.83
After 3 month	91.65	92.45

CONCLUSION

It is evident from this study that controlled release bilayer tablets of amoxicillin trihydrate can be prepared successfully by incorporating sodium bicarbomach. *In vitro* dissolution studies showed controlled release for more than 12 h. Thus, results of the current study clearly indicate, a promising potential of the dosage form can control the release, avoid dose dumping, and extend the duration of action of a drug with pro-

longed floating time. This dosage form holds promise for further in vivo studies, which can be extrapolated for the development of other delivery systems.

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