



Formulation and evaluation of intragastric buoyant tablets of amoxicillin trihydrate

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Abstract

Intragastric buoyant tablets, i.e., gastro retentive drug delivery systems of Amoxicillin trihydrate were prepared with the objective to obtain site-specific drug delivery for the stomach and to extend its duration of action. The sustained release of amoxicillin is desired because of its short biological half-life. Particularly to treat *Helicobacter pylori* infections, the sustained release is desired to be confined to the stomach. The intragastric buoyant tablets of amoxicillin will provide site-specific drug delivery and thereby extend its duration of action. The dosage form was designed by using HPMC K15M and HPMC K100 polymers as gelling agents, sodium bicarbonate as gas-generating agent and other excipients. Initially granules were prepared by wet granulation technique and compressed into tablets. The pharmaceutical properties of formulations, their buoyancy lag time and total floatation time and *in vitro* drug release were evaluated. It is found that the hardness of the tablet will affect the buoyancy characteristics of the dosage form. The *in vitro* release studies indicated that the floating dosage forms containing higher concentration of HPMC K100 showed slower release. The % drug release profile was in the order of F6 > F5 > F4 > F3 > F2 > F1. The *in vitro* release data was treated with mathematical equations, and it was concluded that Amoxicillin released from the tablet followed Peppas model with non-Fickian diffusion. Hence gastro retentive drug delivery system of Amoxicillin trihydrate is a promising approach as it can lead to decrease in the frequency of administration and ultimately lead to better patient compliance.

Key-Words: Gastro retentive, amoxicillin, *Helicobacter pylori*, *in vitro* drug release.

Introduction

Amoxicillin (α -amino-hydroxybenzylpenicillin) is a semisynthetic antibiotic, belonging to the β -lactam family (penicillin), which is effective for bacterial infection treatment, especially for *Helicobacter pylori* infection. It is an extended spectrum penicillin¹. Gastric *Helicobacter pylori* infection is associated with chronic gastritis and peptic ulcer². *H. pylori* are often observed to adhere to the anteral epithelium of the human stomach and gastric metaplasia in the duodenum. Gastric and duodenal ulcers are believed to develop as the result of damage to the gastric mucosa by cytotoxic substances (ammonia, cytotoxin, etc.) produced by *H. pylori*³. In Japan, amoxicillin is used for the eradication of *H. pylori* (as a part of triple therapy) as conventional tablets or capsules. These conventional preparations do not remain in the stomach for long, and therefore high doses of antibiotics must be administered to patients.

These high doses are considered to bring about adverse effects. To solve this problem, a novel drug delivery system that localizes the antibiotics at the site of infection to achieve desirable concentrations would be desirable. When a gastroretentive drug delivery system is achieved, the dose of amoxicillin can be reduced. As a result, the frequency of adverse effects will decrease. This system can be retained in the stomach and assists in improving the oral sustained delivery of the drugs that have an absorption window in a particular region of the gastrointestinal tract⁴. Sustained release is a kind of controlled release system that provides medication over an extended period of time. In other words, a sustained release system controls the drug concentration in the target tissue. Therefore, we studied an intragastric buoyant sustained-release tablet containing amoxicillin. Amoxicillin was selected because (a) Amoxicillin is usually used for the eradication of *H. pylori* as a component of triple therapy in Japan, (b) Amoxicillin has strong activity for *H. pylori*, (c) the oral bioavailability of Amoxicillin is poor, and unabsorbed Amoxicillin affects intestinal bacteria, which is considered to be one reason for the

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side effects, (d) Due to short half-life (1-2 hrs), amoxicillin is a suitable candidate for sustained release formulations.

To achieve the eradication therapy, a desired amoxicillin preparation must have three characteristics: (a) the ability of raising concentration of amoxicillin in stomach filled with meal above MIC as soon as possible, (b) showing the prolonged retention time in the stomach, (c) a sustained-release property to maintain the drug concentration in the stomach. The commercially available preparations of amoxicillin have only the first characteristics. Therefore, we have tried to prepare an intragastric sustained-release tablet with (b) and (c) characteristics described above. These tablets were prepared using HPMC K15M and HPMC K100. The effect of the gel-forming polymer HPMC on the floating properties and release characteristics of the intragastric tablets was evaluated.

Material and Methods

Amoxicillin trihydrate was obtained as gift sample from Surya Pharmaceuticals Ltd., Jammu, India. HPMC K15M (nominal viscosity of 2% aqueous solution 15,000cP) and HPMC K100 (nominal viscosity of 2% aqueous solution 100cP) were obtained as gift sample from M/s Ratanchand & Co., West Mumbai, India. All other chemicals were of analytical reagent grade.

Method of preparation of floating tablets

The tablets were prepared by wet granulation method using varying concentrations of different grades of polymers with sodium bicarbonate. The composition of different formulations is given in Table no. 1. Amoxicillin concentration was kept fixed at 750mg. Amoxicillin, HPMC K100 and HPMC K15M were mixed homogeneously using a pestle and mortar and granulated using ethanol (sieve #16). The granules were dried for 30min at 60°C and sieved (sieve #40). The granules and sodium bicarbonate were mixed and talc and magnesium stearate added as lubricant and glidant, respectively, 4-5 mins before punching. 1gm of the mixture was compressed to form a tablet using single station compression machine (Company-Jyoti).

Table 1: Composition of Gastro-retentive Tablets of Amoxicillin Trihydrate (in mg)

Ingredients	F1	F2	F3	F4	F5	F6
HPMC K15M	30	50	70	125	145	165
HPMC K100	165	145	125	70	50	30
Sodium Bicarbonate	50	50	50	50	50	50
Purified Talc	2	2	2	2	2	2
Magnesium Stearate	4	4	4	4	4	4

Pre-compressional Evaluation⁵

Angle of repose: It is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. Angle repose of granules was determined by the funnel method. A glass funnel was held in place with clamp on a ring support over a glass plate. 20 g of granules were transferred into the funnel keeping the orifice of the funnel blocked by the thumb. The thumb was removed and when the granules were emptied from the funnel, the diameter and the height of the pile of the granules was measured and the angle of repose (θ) was calculated by using following equation.

$$\tan(\theta) = \text{height of the pile} / \text{radius of the pile}$$

Bulk density: The loose bulk density (LBD) and tapped bulk density (TBD) were determined calculated using the following formula:

$$\text{LBD} = \text{weight of the powder} / \text{volume of the packing (a)}$$

$$\text{TBD} = \text{weight of the powder} / \text{tapped volume of the packing (b)}$$

10 g of the granules were accurately weighed and transferred into the 100 mL graduated cylinder. The volume occupied by granules was measured "as it is" and loose bulk density is determined by equation (a). Tapped bulk density was determined by tapping the same graduated cylinder for 100 times onto a hard wooden surface and calculated by using equation (b).

Carr's compressibility index (CI): It is simple, fast and popular method of predicting powder flow characteristics.

$$\text{Carr's C.I.} = \frac{\text{Tapped bulk density} - \text{Loose bulk density}}{\text{Tapped bulk density}}$$

Hausner's ratio: It is the number that is correlated to the flowability of a powder. It is calculated by the formula:

$$H = \text{Tapped Bulk Density} / \text{Loose Bulk Density}$$

Post-compressional Evaluation

Hardness: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester⁶.

Friability test: The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_{initial}) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The % friability was then calculated by –

$$\%F = 100 (1 - W_0/W)$$

% Friability of tablets less than 1% are considered acceptable.

Weight Variation Test: Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation⁷.

Tablet Density: Tablet density (d) is an important parameter for floating tablets. The tablet will only float when its density is less than that of gastric fluid (1.004). The density was determined using following relationship.

$$V = \pi r^2 h$$

$$d = m/v$$

v = volume of tablet (cc), r = radius of tablet (cm), h = crown thickness of tablet (g/cc), m = mass of tablet

Buoyancy / Floating Test: The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT). The tablets were placed in a 100mL beaker containing 0.1N HCl⁸.

In-vitro Dissolution Study: In-vitro release studies were carried out using USP type II (paddle) dissolution test apparatus. 900ml of 0.1N HCl was filled in dissolution vessel and the temperature of the medium was set at 37°C±0.5°C. Sink condition was maintained for the whole experiment. The speed was set at 50 rpm. 5ml of sample was withdrawn at predetermined time intervals for 10 hours and same volume of fresh medium was replaced. The samples were analyzed for drug content against 0.1N HCl as a blank at λ_{max} 272nm using U.V. spectrophotometer.

Curve fitting analysis: The mechanism of Amoxicillin released from the matrix system was studied by fitting the dissolution data obtained to following equations.

- Korsmeyer – Peppas equation.
- Zero order equation.
- First order equation.
- Higuchi square root equation.

Results and Conclusion

Pre-compressional Evaluation

The values obtained for angle of repose for all formulations are tabulated in Table no. 2. The values were found to be in the range from 24^o.30' to 29.88'. This indicates good flow property of the powder blend. Compressibility index value ranges between 12.30% to 16.34% indicating that the powder blend have the required flow property for direct compression.

Table 2: Flow properties of granules prepared by different techniques

Batch	Angle of Repose (θ)	Bulk density (g/cm ³)	Tappe d densit y (g/cm ³)	Hausner's Ratio(H R)	Com pressi bility Index
F1	24°30'	0.401	0.457	1.139	12.3
F2	26°77'	0.575	0.680	1.182	15.4
F3	25°48'	0.560	0.652	1.164	14.2
F4	25°28'	0.447	0.524	1.172	14.8
F5	28°56'	0.473	0.565	1.194	16.3
F6	29°88'	0.569	0.672	1.181	15.4

Post-compressional Evaluation

The floating tablets were prepared by wet-granulation method using HPMC K100 and HPMC K15M to provide sufficient drug release retardation and sodium bicarbonate was used as gas generating agent to provide sufficient buoyancy to the tablets. The results of post-compressional evaluation are shown in Table no. 3.

The measured hardness of tablets of each batch ranged between 4.1 to 4.8kg/cm². This ensures good handling characteristics of all batches.

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric contents (1.004g/cm³). All the batches showed density below that of gastric fluid (1.004). When tablet contacts the test medium, tablet expanded (because of swellable polymers) and there was liberation of CO₂ gas (because of effervescent agent, sodium bicarbonate). The density decreased due to this expansion and upward force of CO₂ gas generation. This plays an important role in ensuring the floating capability of the dosage form.

All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The weight of all the tablets was found to be uniform with low standard deviation values.

The tablet density was found to be uniform among different batches of floating tablets and ranged from 0.93 to 0.98 g/cm³. The tablet density is less than gastric fluid both before and after ingestion so that the tablets float on the surface of the gastric fluid for as long as 10-12 hrs.

On immersion in 0.1N Hydrochloric acid solution at 37⁰C, the tablets floated, and remained buoyant without disintegration. Table no. 3 shows the results of Buoyancy study. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1N HCl). It was observed that the gas generated is entrapped and protected within the glassy polymer layer, formed by hydration of the polymer, causing an increase in the volume of the tablet and hence decreasing density of the tablet below 1 and tablet becomes buoyant. Both the swelling polymers (HPMC K15M and HPMC K 100) appeared to prolong the lag time, while sodium bicarbonate appeared to reduce the lag time as expected. This is in perfect agreement with release rate and mechanism observed, since the polymers did not swell initially, but helped in keeping the tablet afloat during the late hours of dissolution.

Table 3 : Physical Properties of Tablets of Batch F1 to F6

Batch es	Hardne ss (Kg/cm ²)	Friabili ty (%)	FLT (sec s)	TF T (hrs)	Weight Variati on (mg)
F1	4.5	0.96	40	>12	1000 ±28
F2	4.4	0.72	38	>12	1000±15
F3	4.1	0.91	36	>12	1000±26
F4	4.6	0.82	44	>12	1000±25
F5	4.8	0.86	48	>12	1000±18
F6	4.5	0.79	39	>12	1000±22

In-vitro Dissolution Study: The in-vitro drug release profiles of tablet from each batch (F1 to F6) are shown in Table no. 4. The plot of % cumulative drug release V/s time (hr) was plotted and depicted as shown in Fig.1 and Fig.2.

The primary objective of the study was to design a floating tablet of the high drug dose of amoxicillin trihydrate with a release profile sufficient to maintain adequately high local/systemic concentration. Preliminary formulations with various polymers, either alone or in combination, yielded a wide variety of release profiles to obtain an idea of the range and type of polymers to be used in the final formulation design. Based on such studies, HPMC K15M and HPMC K100 were selected as release modifier polymeric fillers and sodium bicarbonate as the float accelerator. The drug was kept fixed at its dose level.

Table No. 4: Cumulative % age Drug Released from Tablet Formulations F1 to F6.

Time (hrs)	F1	F2	F3	F4	F5	F6
0.5	11.9	12.1	12.4	12.3	12.4	13.1
1	20.7	21.6	21.7	22.4	22.5	22.6
2	31.5	33.3	30.8	31.9	32.4	30.9
3	46.8	47.7	46.9	48.6	49.5	47.6
4	53.1	56.7	54.4	56.8	58.5	55.8
5	62.1	64.8	65.9	66.6	70.2	68.4
6	68.4	69.3	72.5	74.7	75.6	73.6
8	73.8	76.5	76.4	78.9	80.1	81.9
10	78.3	79.2	80.1	81.9	83.7	85.2

A rigorous study of their dissolution profile yielded some insight into the effect of polymeric fillers and gas generating agent on release profile of the formulations. From figure, the effects of HPMC K15M and HPMC K100 could be observed at constant sodium bicarbonate level. The presence of HPMC K15M increased the release-rate and extent slightly compared to HPMC K100. Thus, in the formulations containing relatively higher % of HPMC K15M, the release was higher, viz., F6 > F5 > F4 > F3 > F2 > F1.

Further, no characteristic trend for dissolution can be mentioned upto 1 hour. This may be due to the time taken for both the polymers in tablet matrix to get hydrated before changing from glassy to rubbery state. Thus, during the first hour of dissolution, there was no significant polymer chain relaxation due to which a rate controlling gel barrier could not be formed. Most of the sodium bicarbonate present on the outer layer of the tablet was involved in reaction with acidic medium. Thus, during this period channels for later absorption of solvent were being formed along with liberation of CO₂ that imparted initial buoyancy to the tablets. This also explains the absence of any lag phase in the release profile. Had there been any immediate gel formation, there would have been a distinct lag-time in release.

Curve-fitting analysis: The kinetic values obtained for different formulations are tabulated in Table no. 5.

Table 5: Kinetics of in vitro Amoxicillin trihydrate release from floating tablets.

Code	Zero order	First order	Higuchi	Korsmeyer	
	R ²	R ²	R ²	N	R ²
F1	0.892	0.974	0.981	0.648	0.981
F2	0.881	0.970	0.978	0.645	0.979
F3	0.887	0.962	0.973	0.645	0.979
F4	0.885	0.964	0.973	0.653	0.978
F5	0.880	0.965	0.971	0.660	0.977
F6	0.907	0.985	0.978	0.651	0.985

In the present study 'n' value ranges between 0.645 to 0.660 for all six batches. It ranges between 0.5 to 1, so it was concluded that the drug release occurred via non-Fickian diffusion, which shows that the release from initially dry, hydrophilic glassy polymers that swell when added to water and become rubbery show anomalous diffusion as a result of the rearrangement of macromolecular chains. The most probable mechanism that the release patterns of all formulations followed was non-fickian diffusion or anomalous diffusion wherein the drug release mechanism is controlled by both diffusion as well as polymer relaxation process. The n value of Korsmeyer-Peppas model of all formulations was between 0.645 and 0.660. It may be said that the swellable polymers could not turn into gel immediately in contact with dissolution fluid, thereby giving an initial higher release rate from the tablets. However, once the gel barrier is established around the tablet, the rate of gel barrier progression became the rate limiting factor by modulating the drug diffusibility. The rate of drug permeation out of the matrix is supposed to be proportional to the rate of solvent entry and broadening of the diffusion path length due to swelling of the matrix as a result of polymer hydration and subsequent strand relaxation. That this mechanism was operative throughout the dissolution period for all the formulations is evident from the closeness of R^2 values to 1.

Fig. 1. In vitro release profile of F1-F3.

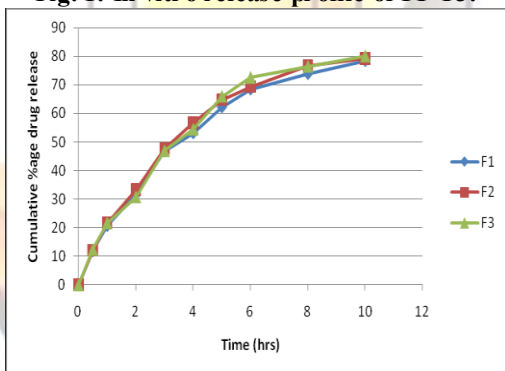
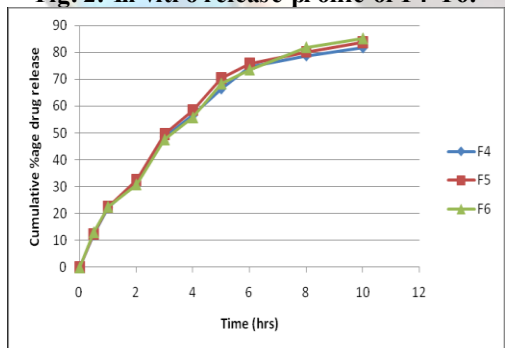


Fig. 2. In vitro release profile of F4-F6.



It can be concluded that gastro retentive drug delivery system of amoxicillin trihydrate could be successfully prepared using different viscosity grades of hydroxy propylmethyl cellulose polymers and gas generating agent, sodium bicarbonate. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed. The tablet formulations of amoxicillin may be an advantageous alternative for oral sustained release formulation and be helpful for the treatment of peptic ulcers.

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