GASTRORETENTIVE DRUG DELIVERY SYSTEM OF AMOXYCILLIN: FORMULATION AND IN VITRO EVALUATION

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ABSTRACT

Gastro retentive drug delivery systems of Amoxycillin trihydrate as floating tablets were prepared with the objective to obtain site-specific drug delivery and to extend its duration of action. More over the floating system of amoxicillin will provide increased local and systemic action in stomach. The formulations were prepared as matrix tablets in the form non effervescent tablets. Various grades of hydroxy propyl methyl cellulose (HPMC) were used to achieve controlled release of the drug. The drug and polymers were found to be compatible as seen by IR studies. Initially granules were prepared by wet granulation technique and compressed into tablets. The prepared tablets were evaluated for weight variation, hardness, friability, drug content, buoyancy and *in-vitro* dissolution studies. Optimized formulation of amoxicillin was found to have increased gastric residence prolonging the release of drug with 85% of drug release in 6 hours by diffusion. The mechanism of drug release was found to be diffusion and followed combination of zero order and first order kinetics. Hence gastro retentive drug delivery system of Amoxycillin 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; amoxycillin; buoyancy; zero order

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INTRODUCTION

Amoxicillin (α-amino-hydroxybenzylpenicillin) is a semisynthetic antibiotic, belonging to the β-Lactam family, which is effective for bacterial infection treatment, especially for Helicobacter pylori infection. Helicobacter pylori is a major causative agent of diseases[1] such as Tonsillitis, Pneumonia, Bronchitis, Gonorrhea, ear infections, urinary tract infection and skin infection. In general, it exists in the gastric mucous layer or epithelial cell surfaces. Thus, the concentration and resident time of amoxicillin in stomach should be effective for complete eradication of Helicobacter pylori. Because the conventional amoxicillin has a short resident time in stomach and may be degraded in gastric acid resulting in lesser concentration in gastric blood, the extended resident time of the antimicrobial agent is desirable to provide more effective Helicobacter pylori eradication. In order to extend the residence period, a gastroretentive system of amoxicillin based on non effervescent mechanism has been developed.

Sustained release is a kind of controlled release system that provides medication over an extended period. In other words, a sustained release system controls the drug concentration in the target tissue[2]. Due to rapid degradation of amoxicillin, a sustained release dosage form that maintains therapeutic concentration in the blood for a longer period of time is desirable.

Hydroxypropylmethylcellulose (HPMC) is propylene glycol ether cellulose that is highly mucoadhesive, biocompatible, biodegradable, easily formed, pH insensitive and soluble in water and some organic solvents. HPMC has gained popularity in the formulation of sustained release dosage form as a swellable and hydrophilic polymer because of its non-toxic property; ease of handling minor influence on processing parameters and relatively simple manufacturing technology. Prolonged release from HPMC matrices are presumably derived from a gelatinous layer form when the polymer is hydrated upon contact with water. While poorly soluble drugs are released solely by erosion of HPMC matrics[2], water soluble drugs can also be released by diffusing out of the gelatinous layer of HPMC.

A variety of amoxicillin formulations such as mucoadhesive microspheres have recently gained considerable attention due to their ability to adhere to the mucous layer, as well as to release the drug in sustained manner[3]. The controlled release formulation of amoxicillin could be prepared in various forms, e.g. beads, microspheres and microcapsules. However, the use of tablet has hardly been reported, so it is interesting to study the release pattern of amoxicillin in the tablet formulations. The purpose of this work was to prepare new controlled release tablets of amoxicillin by using combination of polymers as a rate-controlling polymers.

MATERIALS AND METHODS

Amoxycillin trihydrate was obtained as gift sample from Sandoz Pharma Ltd. Mumbai, India and Dr. Reddy's Lab, Hyderabad, India respectively. Hydroxy propyl cellulose (HPC LF), hydroxy propyl methyl cellulose (HPMCK4M), HPMC 15 cps, and carboxy methyl cellulose (CMC) were obtained as gift sample from Zydus Recon, Bangalore, India. All other chemicals were of analytical grade.

Method

Study of hydrocolloids for buoyancy and matrix integrity

Hydrophilic polymers including HPMC, SCMC, ethyl cellulose, methyl cellulose, carboxy methyl cellulose etc. were evaluated for buoyancy and

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matrix integrity. 100 mg of each hydrocolloid was filled into hard gelatin capsules (No.1) and placed in beaker containing 100 ml of stimulated gastric fluid (pH 1.2) at room temperature. Periodic observations were made for buoyancy and matrix integrity.

Method of preparation of floating mini tablets

The tablets were prepared by wet granulation method (Table 1) by using 8mm punches on multistation tablet punching machine (Cadmach, India). The tablets were then coated by dip coating method[4] using 5 % PVP solution to decrease the friability of tablets. Prepared tablets were then evaluated for various parameters including swelling index and buoyancy studies.

EVALUATION OF FLOATING TABLETS

Pre-compressional Evaluation[4]

a) Bulk Density

It was expressed in gm/ ml and given by

$$\text{Bulk Density} = \frac{\text{Weight of granules}}{\text{Bulk volume of granules}}$$

b) Carr's Consolidation Index

Carr's Index explains flow properties of the granules. It was expressed in percentage and given by

$$\text{Consolidation Index} = \frac{\text{Tapped Density - Untapped Density}}{\text{Tapped Density}} X100$$

c) Angle of Repose

Angle of repose for prepared granules were determined by fixed funnel method. A funnel was fixed with its tip at a given height h above a flat horizontal surface to which a graph paper was placed. The granules were carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using the formula

$$\text{Angle of Repose } (\theta) = \text{Tan}^{-1} (\text{ Height of Pile/ Radius of the base of the pile})$$

d) Flow rate

The flow rate of the granules was determined by hopper flow rate method, in which time taken for a weighed quantity of granules to flow through an orifice was calculated. It was expressed as gm/sec.

Post-Compressional Evaluation

a) Thickness and diameter

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The thickness and diameter of the tablets were determined by using screw gauze. Thickness of ten tablets was determined randomly. It was expressed in mm.

b) Crushing strength

The monsanto hardness tester was used to determine the tablet crushing strength. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gave a measure of the hardness of tablet. Hardness was expressed in Kg/ cm^2.

c) Friability

Friability was determined using Roche Friabilator. Twenty tablets were weighed and placed in the friabilator and then operated at 25 rpm for four minutes. The tablets were then dedusted and weighed. It was expressed in percentage. The difference in the two weights is used to calculate friability.

$$Friability = 100X(1 - \frac{W}{W_0})$$

where W_0 = Initial weight ,W = Final weight

d) Weight Variation Test

Twenty tablets were weighed individually and average weight was calculated. The individual weights were then compared with average weight. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of tablet differ by more than double percentage limit.

$$PD = \frac{W_{avg} - W_{ind}}{W_{avg}} X100$$

where,

PD= Percentage Deviation

W_{avg} = Average Weight of Tablet

W_{ind} = Individual Weight of Tablet

e) Drug Content

Drug content was performed to check dose uniformity in the formulation. Randomly ten tablets were weighed and powdered. A quantity equivalent to 250 mg of amoxycillin was added in to a 100 ml volumetric flask and dissolved in methanol, shaken for 10 minutes and made up the volume up to the mark and filtered. After suitable dilutions the drug content was determined by UV spectrophotometer at 272 nm against blank.

Swelling index of floating tablets

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The studies were carried out gravimetrically. Swelling media used for these studies were distilled water and simulated gastric fluid (pH 1.2). The prepared tablets were introduced into the swelling media. At predetermined time intervals the tablets were removed from medium, excess water was blotted with tissue paper and immediately weighed. This procedure was repeated until the tablet reached constant weight. The swelling index was calculated using following formula

$$\text{Swelling Index} = \frac{W_i - W_0}{W_0} X100$$

Where,

W_1=Weight of dry tablet, W_0= Weight of swollen tablet

Buoyancy studies

Buoyancy studies[5] were carried out in disintegration apparatus (Electrolab ED2L). About 900 ml of simulated gastric fluid was transferred in to 1000 ml flask. Six tablets were placed in the apparatus and studies were carried out.

Fourier Transform infrared spectrum (FTIR) studies

Infrared spectra were recorded on a Shimadzu FTIR-8700 spectrophotometer. Pellets were prepared from a finely ground mixture of test sample (1–2 mg) and dried KBr (200–300 mg) using a Quick Press and a 7 mm die set (Perkin-Elmer, USA). The various samples analyzed were: (a) Amoxycillin (b) crushed and powdered tablets. The samples were scanned between 4000 and 450 cm^{-1} at an interval of 1.0 cm^{-1}.

In vitro Release studies for floating tablets

The drug release rate was determined using USP dissolution apparatus II. Dissolution media was 900 ml of simulated gastric fluid (pH 1.2) maintained at 37 ± 0.1°C and stirred at 100 rpm. Samples were withdrawn at suitable time intervals and compensated with fresh dissolution medium and assayed spectrophotometrically[9] at 272 nm in Shimadzu U.V. spectrophotometer. Samples were assayed in triplicate.

RESULTS AND DISCUSSIONS

Formulation of floating tablet

Hydrocolloids having maximum buoyancy were selected for formulation of mini floating tablets. Maximum buoyancy was observed in formulations containing HPMC K4M and HPMC(15cps) used alone or in combination with other tablet ingredients as shown in Table 2.

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Table 2
Selection of hydrocolloids

Sl. No.	Polymer	Floating Time (hrs)	Buoyancy Matrix Integrity
1.	MC	6 hours	+++
2.	S C M C	20 hours	+++
3.	HPMC (K4M)	30 hours	++++
4.	HPMC (15cps)	24 hours	++++
5.	EC	3 hours	++
6.	PVP	30 min.	+
7.	HEC	2 hours	+
8.	SMC	4 hours	+++
9.	Sodium Alginate	50 min.	+

++++ = ***Excellent*** +++ = ***Good*** ++ = ***Not good*** + = ***Poor***

Evaluation of floating tablets

The tapped bulk density of the granules ranged from 0.245 ± 0.003 to 0.581 ± 0.001 g/cc whereas the untapped bulk density was between 0.257 ± 0.009 to 0.402 ± 0.004 g/cc. The percentage compressibility ranged from 11.132 ± 0.7078 to 15.382 ± 0.9600 which indicated excellent flow properties. Angle of repose of the granules varied between 25°14' ± 0.4649 to 28°11' ± 0.2606 which also indicated excellent flow properties. Table 3 shows the granular properties of selected formulation i.e. F_4 and F_5.

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Table 3
Granular Properties of HBS formulations F_4

Sl. No.	Granule Property	Selected Formulation F_4
1.	Bulk density (Untapped) gm/ml	0.362 ± 0.03
2.	Bulk density (Tapped) gm/ml	0.310 ± 0.08
3.	Carr's Index %	12 ± 0.32
4.	Angle of Repose	26^0 24"
5.	Flow rate gm/sec	2.8 ± 0.25
6.	Percent fines %	14

The average weight variation deviation of the formulated tablets was found to be less than 5 % which are within the limits. The hardness ranged from 2.3100 ± 0.2000 kg/m^2 to 3.00 ± 0.0577 kg/cm^2 and it was observed that if hardness was increased buoyancy of the tablets were lost. All the formulations were found to have friability within the limits. The drug content of all the formulations varied from 90.12 to 97.76 %. Table 3 shows the post compressional properties of selected formulation. Swelling index of optimized formulations was carried out in distilled water and in simulated gastric fluid. It was found that the formulation showed rapid uptake of distilled water whereas there was gradual constant uptake of simulated gastric fluid . The buoyancy of the formulation was found to be more than 20 hours with good matrix integrity (Table 1).

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Table 1
Composition of Amoxycillin floating tablets

Ingredients/ Formulations* Codes	SCMC (mg)	HPMC (K4M)	HPMC (15 cps) (mg)	Methyl Cellulose (mg)	MCC (mg)	Sodium Alginate (mg)	Buoy ancy
F_1	25	50	-	-	-	-	+ +
F_2	25	50	-	-	-	-	++
F_3	15	50	5	5	-	-	++
F_4	15	30	5	-	-	-	++
F_5	20	30	5	5	-	-	+++
F_6	15	45	-	-	10	-	++
F_7	–	50	-	-	15	-	+
F_8	–	50	10	–	15	-	+
F_9	15	30	15	5	5	-	+++
F_{10}	15	35	-	-	-	10	++
F_{11}	–	40	15	5	–	5	+ +
F_{12}	–	40	-	-	5	15	+

* *250 mg of Amoxycillin trihydrate*

During FTIR studies it was found that floating tablets has shown almost similar peaks as that of pure drug, indicating compatibility of drug and polymers.

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Table 4
Evaluation parameters for Amoxycillin floating tablet

Sl.No.	Parameter	F_4^*
1.	Thickness (mm)	5.87 ± 0.25
2.	Diameter (mm)	8 ± 0.12
3.	Crushing strength(kg/cm^2)	2.8 ± 0.59
4.	Friability (%)	0.812 ± 0.48
5.	Average weight (mg)	309.9 ± 0.34
6.	Percent weight variation (%)	2.69 ± 0.75
7.	Drug content (%)	97.10 ± 0.5
8.	Cumulative percent release (%) In 6 hrs (pH 1.2 Buffer)	85.0 ± 0.85

In-vitro Release and Data Analysis of floating Tablets

In-vitro release studies were carried out in simulated gastric fluid. Release was observed after a lag period of 15 minutes after which steady and constant release of the drug was observed for a period of 6 h leaving behind the buoyant mass of tablet matrix. The data obtained was fit in to Higuchi's, Peppas and Wagner's model inorder to determine the mechanism of release[12]. Higuchi's model showed a regression coefficient of 0.9799 for selected formulation, indicating the release pattern may follow diffusion, further supported by Peppas model where regression coefficient was 0.855. In order to understand the order of release a

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logarithmic value of drug remaining in tablet against time was plotted as suggested by Wagner's plot which suggested that the release pattern did not completely follow first order kinetics as the regression analysis showed a lower coefficient value of 0.8770. Data plotted as cumulative percent drug release versus time, has shown regression coefficient of 0.9804, which suggest that release follows zero order kinetic.

CONCLUSION

Thus it can be concluded that gastro retentive drug delivery system of ciprofloxacin hydro chloride could be successfully prepared using different viscosity grades of hydroxy propyl methyl cellulose and alsoincombination of other cellulose derivative polymers. The tablet formulations of amoxicillin may be an advantageous alternative for oral sustained release formulation and be helpful for the treatment of peptic ulcer.

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