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Formulation and *in-vitro* evaluation of intra gastric delivery system for treatment of *H. Pylori* infection

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ABSTRACT

Objective: The purpose of our research was to formulate an intra gastric retentive targeted effervescent drug delivery form of Ofloxacin and Ornidazole for eradication of *H. Pylori* infection in stomach.

Materials and Methods: The HBS system was developed using polymers HPMC K4M and Carbopol 934P to circumvent the unregulated release of conventional formulation while overwhelming the short gastric retention time and the intra-mucosal colonization of *H. Pylori*. Effervescent tablets were manufactured by slugging and evaluated for content uniformity, friability, hardness and dissolution.

Results: The desirable buoyancy of the formulation was achieved by addition of citric acid and calcium carbonate. The tablets hence prepared exhibited floating capacity for a targeted period of above 12 hours and released 98% drug which was suitably analyzed by HPLC analysis.

Conclusion: The current research work was a successful attempt at formulating and characterizing intra gastric retentive targeted effervescent type of floating drug delivery system containing a combination of Ofloxacin and Ornidazole for treatment of *H. Pylori* infection

Keywords: effervescent, gastro retentive, floating, *H. Pylori*, Ofloxacin, Ornidazole.

INTRODUCTION

Helicobacter pylori is one of the most widespread bacterial infections affecting humans throughout the world. Approximately two-thirds of the world's population is infected with *H. pylori*. It is the causative agent for chronic gastric & duodenal ulcers, gastric reflux disease, erosive eosophagitis, gastric carcinoma, and mucosal-associated-lymphoid-type (MALT) lymphoma and atrophic gastritis in adults and children. Almost 90% of population suffering from duodenal or gastric ulcers has tested positive for this gram-negative bacterium (Cover and Blaser, 2012; Center for Disease Control and Prevention, 2005; Bardonnet et al., 2006).

H. pylori are spiral-shaped, gram-negative bacterium found in the gastric mucosal layer or adherent to the epithelial lining of the stomach. The unique structure of *H.pylori* suits the highly hostile environment of the gastro intestinal tract GIT. The bacterium drills into the mucus layer of the stomach with the help of its flagella and its helical body aids it in gaining entry. Hence, it takes advantage of the thick layer of mucus covering the stomach lining by getting ensconced in the mucus lining and generally dwells there for life. The bacteria secrete urease, which converts urea into bicarbonate and ammonia thereby maintaining a neutralizing microenvironment and promoting back diffusion of H^+ ions (Marshall-Warren, 1984; Kirsner, 1994; Konturek, 1996; Bardonnet et al., 2006).

Various antimicrobial therapies have emerged as important means to resolve *H pylori* infection. Antimicrobials like Amoxicillin, Ornidazole, Ofloxacin and acid suppressants like H_2 blockers or proton pump inhibitors are used in conjugation (Whitehead et al., 2000). The daily dosage regime for 2 weeks consists of administering anywhere from 6-12 tablets/capsules

per day (Heatly, 1992; Center for Disease Control and Prevention, 2005).

FDA-approved treatment options

Bismuth subsalicylate (Pepto Bismol®) 525 mg QID + metronidazole 250 mg QID + tetracycline 500 mg QID x 2 wks + H2 receptor antagonist therapy as directed x 4 wks.

The frequency of this regime is tedious but essential for the proper and complete eradication of the bacterium. A single antimicrobial is seldom given for treatment of *H.pylori* for fear of developing resistance; hence combination therapy is generally recommended. Also most antimicrobials degrade in the acidic environment of the stomach. Therefore an attempt was made to formulate and characterize intra gastric retentive targeted effervescent type of floating drug delivery system containing a combination of Ofloxacin and Ornidazole (Ichikawa et al., 1991). Fluoroquinolones like Ofloxacin along with the nitro imidazoles like Ornidazole produce a synergistic effect to eradicate *H.pylori* (Schwartz and Juener, 1976; Munoz et al., 1998; Lehman et al. 2000; Whitehead et al., 2000).

As *H.pylori* populate the GIT membrane, it would be prudent enough to make antimicrobials available at higher concentrations within in this region ensuring total elimination of the micro biota. Amongst the various approaches mentioned in literature (Yang et al., 1994; Wei et al. 2004; Basak et al., 2004; Bardonnet, 2006) formulations remaining buoyant while delivering the drug in the GIT has attracted widespread attention. Literature reports have mentioned different approaches for gastro retentive systems including altered density formulation based on the principle that greater weight would sink and lesser would float (Erni and Held, 1987; Streubel et al., 2003; Talukdar and Fassihi, 2004; Bardonnet, 2006). Swelling/expanding systems or size based system and bioadhesives, which adhere to the stomach wall, and deliver their contents in a controlled release fashion, are also used (Moes, 1993; Bardonnet, 2006).

Besides these, systems based on effervescent mixtures were also formulated. Such systems initiate the formation of gases while being in the gastric milieu and impart added buoyancy, alongside providing an initial alkaline microenvironment for polymers to form a gel (Deshpande et al., 1999; Ichikawa et al., 1991). The liberated carbon dioxide could also facilitate hydration of polymers that is characteristic to the hydrogel with a promise of better gastro retention. Taking into cognizance the habitat of *H.pylori*, which is in the luminal surface and under the mucus gel of the GIT, it seems pertinent to provide for an efficacious delivery of therapeutic agents capable of disrupting the mechanism of colonization by targeting drug delivery within the stomach. Therefore an attempt was made to formulate a targeted intra gastric effervescent type of FDDS containing a combination of Ofloxacin and Ornidazole which releases most of the drug in the stomach thereby circumventing the problem of unregulated drug release from conventional dosage forms (Hou et al., 2003; Talukdar and Fassihi, 2004).

Table 1. Optimization of polymer, effervescent agent and citric acid quantities.

Code. No*	Carbopol 934 P (mg)	HPMC K4M (mg)	Sod CMC (mg)	Citric acid (mg)	Ca. Carbonate (mg)	Floating time (hrs)
A_1	200	-	-	-	-	+
A_2	-	200	-	-	-	+
A_3	-	-	200	-	-	+
B_1	400	-	-	-	-	++
B_2	-	400		-	-	++
B_3	-	-	400	-	-	+
C_1	400	-	-	40	10	+++
C_2	-	400	-	40	10	+++
D_1	400	-	-	40	20	+++
D_2	-	400	-	40	20	+++
E_1	400	-	-	80	20	++++
E_2	-	400	-	80	20	++++
F_1	100	300	-	80	20	++++
F_2	130	270	-	80	20	++++
F_3	**140**	**260**	**-**	**80**	**20**	**+++++**

*All formulations contain the Drug Mix (200mg Ofloxacin + 500mg Ornidazole); Floating time parameter: += 1-2.5 hr, ++ =3-4.2 hr, +++= 4.8-6.3 hrs, ++++= 6.5-8.5 hrs, +++++= 8.6-12 hrs; 1% Magnesium stearate was added according to final weight of formulation.

Such a system would also fulfill the basic target of this gastro retentive system by increasing residence time for enhanced local action on *H.pylori*. The reduced dosing frequency would augment patient compliance and would also be economically viable. More importantly this therapy ensures complete and efficient eradication of *H. pylori* infection.

MATERIALS AND METHODS

Hydroxy Propyl Methyl Cellulose K4M (HPMC K4M), Sodium Carboxy Methyl Cellulose (NaCMC) and Carbopol 934P were obtained from Continental Enterprises, Delhi. Citric Acid Monohydrate and Calcium Carbonate were obtained from CDH, India. Ornidazole and Ofloxacin were obtained as gift samples from Panacea Biotec Ltd. New Delhi. Other excipients and solvents were Analytical grade and were used as received.

Formulation development

Various low-density polymers were screened and selected on the basis of literature reports and were then subjected to drug-polymer compatibility studies on the basis of visual observation.

Formulation of HBS tablets

After selecting polymers on the basis of compatibility studies, tablets were prepared by slugging method. Single/combination of different polymers with varying concentrations with or without effervescent mixture were used to get the desired floating time (Talwar et al., 2001). The two drugs were mixed with magnesium stearate in a mortar and slugged using a rotary press. These slugs were granulated in an oscillating granulator and sieved using BSS sieve no.20. The resultant granules that passed through the sieve were mixed with the polymers, effervescent agents and lubricant and compressed using a rotary press into tablets of 1200mg (Table 1).

In-vitro characterization

Compressed tablets were evaluated for physical appearance by visual observation, friability, hardness, uniformity of content, stability, in-vitro floatation behavior and dissolution studies.

Weight variation, Hardness and Friability test

Weight variation, hardness and friability test were done according to IP 1996.

In-vitro floating behavior

Floating behavior was studied using both static beaker method (Rosa et al., 1994) as well as USP 24 dissolution apparatus II. In the static beaker method, a beaker containing 500 mL 0.1 N HCl at 37±0.5°C was used in which individual tablets were introduced and their subsequent floatation and buoyancy was observed visually. The time interval between introduction of tablet to the medium and its gaining buoyancy to the surface was seen as the floating lag time. The duration for which the tablet remained buoyant was observed visually.

In vitro dissolution using HPLC analysis

In – vitro release studies were conducted in USP apparatus II with the mentioned method (Chavanpatil et., 2005) (paddle method) using 900mL of 0.1 N HCl. The paddle speed was maintained at 50 rotations per minute at 37±0.5°C. The concomitant release of Ornidazole and Ofloxacin was determined by using an HPLC method (Shimadzu, Model L-ECD-6A) specifically developed for the present study. Samples of dissolution media (5ml) were withdrawn at predetermined intervals of 0.5 hrs and hourly up to 12 hours. Each sample was replaced by an equal amount of fresh medium to maintain a constant volume 20 µl of aliquot was directly injected for HPLC analysis. The sampling was done in triplicate and averages were taken to minimize errors.The simultaneous release of Ornidazole and Ofloxacin was determined by using an HPLC method (Shimadzu, Model L-ECD-6A) specifically developed for the present study. The liquid chromatograph equipped with 294 nm detector and a 3.9 mm x 30 cm, C-18 column was used. The flow rate of 1 ml/min in an isocratic mode was used. The mobile phase constituted of 800 ml of 0.025 M Phosphoric acid and 200 ml of acetonitrile and pH was adjusted to 3 with triethylamine. Ornidazole and Ofloxacin showed a retention time of 8.43 minutes and 3.8 minutes respectively.

Stability studies

Optimized HBS tablets were stored in a stability chamber at 40±5°C and 75% RH for 0, 30, 60, 90 days and evaluated for general appearance and drug content using HPLC method as per ICH guidelines for stability testing (Singh and Kim,2000).

RESULTS

Table 2. Weight Variation, Hardness and Friability Test for HBS Tablets.

S. No.	Formulation code	Floating (hr)	Tablet weight (mg)	% Friability	Hardness (kps)
1	E_1	6.5	1212.92	<0.8	4.8
2	E_2	7	1217.8	<0.8	5.0
3	F_1	8	1220	<0.8	5.2
4	F_2	8.5	1219.98	<0.8	5.6
5	F_3	12	1216.9	<0.8	5.5

In-vitro characterization

The in-vitro characterization parameters as discussed are given in the following sections:

Weight variation, Hardness and Friability test:
These tests were done according to the IPC 1996.The results are shown in Table 2.

In-vitro floating behavior:

Table 3: Drug Release for the optimized Formulation.

S.No	Formulation code	Floating (hr)	Drug release	
			Ofloxacin	Ornidazole
1	E_1	6.5	86.5%	88.5%
2	E_2	7	87.2%	89%
3	F_1	8	93%	95%
4	F_2	8.5	95%	96%
5	F_3	12	97.2%	98.6%

In vitro dissolution analysis using HPLC

The floatation and swelling behavior of the tablets was observed and found to be satisfactory. The tablets were then subjected to in-vitro dissolution studies using USP dissolution apparatus II (0.1N HCl, 50c rpm). Each dissolution flask contained 800ml 0.1N HCl and 100 ml methanol. 5ml of sample was withdrawn from each flask every hour and fresh dissolution media was added to keep volume constant. The samples were analyzed by HPLC method and results obtained are mentioned in Table 1, Figure 1.

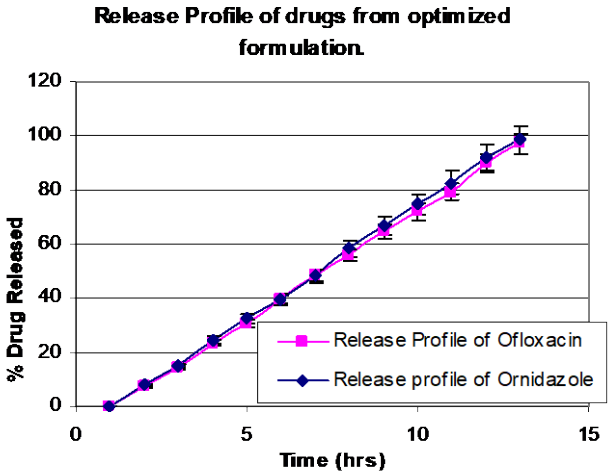

Figure1. Release profile of drugs from optimized formulation.

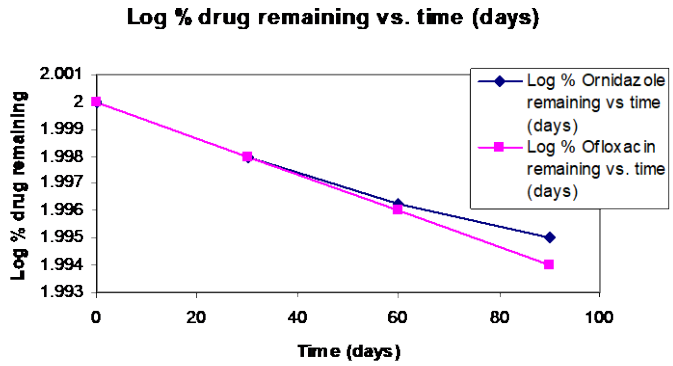

Figure 2: Log percent drug remained vs. time.

Stability studies

Graph was plotted for the stability studies between the log % drug remaining vs time (days).

DISCUSSIONS

H. pylori is a bacteria affecting more than two third of the world population. It enters the mucosal layer of the stomach and generally persists there for life. Single antimicrobial therapy is susceptible to resistance, thus a combination therapy has been proposed for the complete eradication of *H. pylori* (Rune, 1996; Bardonnet, 2006). The aim of the research was to circumvent the unregulated release of drugs from conventional dosage forms and to supply controlled delivery of Ofloxacin and Ornidazole simultaneously from a gastro retentive formulation for local effect as long as 12 hours in the stomach with use of polymers. These polymers are known to inherently possess low density and hydrocolloid gelling properties. On contact with the intra gastric fluid, they form a gelatinous mass thereby remaining buoyant in the GIT (Whitehead et al., 1998; Talwar et al., 2001).

An effervescent approach was chosen for this research, as effervescent agents have been proved to aid in buoyancy (Dave et al., 2004; Talwar et al., 2001) and hence tablets were manufactured using slugging method to eliminate use of fluids.

Selection of polymer was done on basis of literature survey, preformulation studies and data obtained during optimization of formulation. Compatibility of polymers with drug was studied and chosen polymers were found to be compatible with the drugs as no changes in color were observed. Polymers investigated were HPMC K4M, Carbopol 934P (Li et al. 2003) and Sodium Carboxy Methyl Cellulose. The floating and dissolution behavior studies showed that HPMC K4M was the most suitable polymer as it showed better matrix formation with the maximum buoyancy. Using

varied combinations of the polymer and effervescent agents and testing them for buoyancy and swelling derived the optimum amount to be used. Citric acid provides for an acidic medium for the calcium carbonate thus aiding generation of CO_2 when in contact with an aqueous media (Whitehead et al., 1998; Talwar et al., 2001).

In the initial three trials (A_1, A_2, A_3) the two drugs were mixed and compressed using 200mg of one of the polymer into three sets (Baumgartner et al., 2000). These tablets showed little or no swelling and floatation of 1-2.5 hours. Thus it was concluded that 200mg of polymer was inadequate for floatation of tablet. Another set of tablets (B_1, B_2, and B3) was formulated using the drug mixture and 400 mg of polymer. These tablets demonstrated little swelling and floated for about 3-4.2 hours. Throughout this period, it was observed that Sodium CMC showed swelling behavior but little or no floatation at all. Thus it was dropped from further studies (Table 1).

An effervescent approach was then adopted to aid the buoyancy of formulation. Batches C_1 and C_2 were formulated using the drug mixture and 400 mg of each polymer and 40 mg of citric acid and 10 mg of calcium carbonate. Calcium carbonate was used as an effervescence producing agent and citric acid was used to provide an acidic milieu and to aid in the buoyancy of the HBS. Calcium carbonate generates CO_2 gas on coming in contact with the acidic media produced by citric acid and dissolution media. The CO_2 thus produced remains trapped inside the gel formed by HPMC K4M and thereby decreases the density of the formulation thereby confers buoyancy. The floatation did not increase considerably for C_1 and C_2 (4.8-6.3 hours), although there was reasonable swelling observed. Thus, it could be deduced that amount of polymer as well as effervescent agent were to be increased. Nevertheless, it was established at this stage that the floatation/swelling of the tablets was aided on addition of effervescent agents (Dave et al., 2004). The floatability indicated that the amount of polymer used was satisfactory. However since none of the tablets so far showed desirable floatation for 12 hours, there was scope for further experimentation. As polymer weight already reached a point of no more addition, it was decided that the quantity of effervescent agent would be increased to improve on the duration of floatation.

Hence formulation D_1 and D_2 were prepared using drug mixture, 400mg of each polymer, 40 mg of citric acid and 20 mg of calcium carbonate. The amount of effervescent agent was doubled to increase the floatation time. These tablets showed inadequate swelling and floatation.

Additional set of tablets, E_1 and E_2 were now formulated using the drug mixture of Ofloxacin an Ornidazole and 400mg each of HPMC K4M and Carbopol. Citric acid and Calcium carbonate amounts were increased to 80 and 20 mg respectively. Citric acid concentration being doubled lead to a slight increase of floatation.

The preparation E_1 illustrated good extended release behavior with 86.5% of Ofloxacin and 88.5% of Ornidazole released over a period of 6.5-8.5 hours. However buoyancy of the tablets was questionable as the tablet sank at 8hrs. Thus Carbopol extended the release of drugs but couldn't impart extended floatation. Hence it was concluded that incorporation of Carbopol leads to the stabilization of tablet shape even till the end.

The formulation E_2 showed good floatation in flask however could control release of drug only up to 8.5 hrs releasing 87.2% Ofloxacin and 89% Ornidazole. Thus it was apparent that although HPMC K4M could impart good floatability it could not be used as a standalone polymer to reach the target of this research.

Tablets of F_1 showed extended release up to 10 hrs and floatation was also reasonably acceptable (6.5-8.5 hrs). However the release of Ofloxacin was 93% for 10 hrs and 95% for Ornidazole over 9 hrs. It was hence inferred that ratio of Carbopol: HPMC in 1:3 was not giving satisfactory results.

Batch F_2 released 95% Ofloxacin and 96% Ornidazole over a period of 11 hrs. It appeared that the quantity of HPMC K4M imparted good floatation, buoyancy and swelling. However to modify the release further, amount of Carbopol used would have to be increased further.

Batch F_3 showed excellent floatability of 12 hours and released 97.2% Ofloxacin and 98.6% Ornidazole in this period. The swelling was seen as satisfactory and the quantity of HPMC K4M sufficed buoyancy for 12 hours. Carbopol 934P provided for the structural integrity whereas HPMC K4M lent the prolonged floatation time aided with calcium carbonate and citric acid.

CONCLUSION

A gastro retentive system for Ofloxacin and Ornidazole was successfully developed to a satisfactory level in terms of floatability and release. The In-vitro release was found to be nearly 100% for the optimized formulation in 12 hours. The gastro retentive system thus developed can be used for the effective and complete treatment of *H. pylori*. The formulation neatly addresses the tedious problem of multiple dosage regimens by combining the various antibiotics into one tablet and reducing the frequency of administration. Thereby increasing patient compliance, reducing cost therapy and storage space required. There is scope for further in-vitro and in-vivo studies that would study the microbiological and pharmacokinetic parameters of the release in a more stringent study.

CONFLICT OF INTEREST

None declared.

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