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Intragastric Floating Drug Delivery System of Levofloxacin: Formulation and Evaluation

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Abstract

The present study was aimed to develop new intra-gastric floating microspheres for controlled delivery of levofloxacin for the treatment of peptic ulcer caused by *Helicobacter pylori* (*H. pylori)*. Floating microspheres of levofloxacin were prepared by emulsion solvent evaporation technique. The drug was encapsulated with HPMC and Eudragit S 100 in different polymers ratios. i.e. 1**:**1,1**:**2,1**:**3.prepared microspheres were evaluated for % entrapment, particle size, Buoyancy, dissolution study and drug release kinetics.

The % Yield of microspheres was high in HPMC batches over Eudragit S 100 batches. The particle sizes of microspheres was increased by increasing the polymer concentration. Percentage Buoyancy of microspheres was found to be in the range of 63.38%-75.58% indicated that most of the microspheres were still floatable after 12hours because of their low density and internal voids. Microspheres of levofloxacin with HPMC showed enhanced release rate when compared to levofloxacin with Eudragit S 100. From the results it was concluded that, the prolonged GI residence time of the formulation & its controlled release in the gastric environment makes complete eradication of H.pylori from GIT more effectively than conventional tablets.

Keywords: *Floating microspheres, Levofloxacin, HPMC 15 cps, Eudragit S 100,*

INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most common pathogenic bacterial infections, colonizing an estimated half of all humans[1]. It is associated with the development of serious gastro duodenal disease including peptic ulcers, gastric lymphoma and acute chronic gastritis[2]. *H. pylori* reside mainly in the gastric mucosa or at the interface between the mucous layer and the epithelial cells of the antral region of the stomach[3] . The discovery of this microorganism has revolutionized the diagnosis and treatment of peptic ulcer. Most antibacterial agents have low minimum inhibitory concentrations (MIC) against *H. pylori* in culture. And also single antibiotic therapy is not effective for the eradication of *H. pylori* infection in vivo. This is because the low concentration of the antibiotic reaching the bacteria under the mucosa, instability of the drug in the low pH of gastric fluid and short residence time of the antibiotic in the stomach[4] . Combination of more than one antibiotic and anti-secretory agent are required for complete eradication of *H. pylori* but these regimens are not fully effective. Patient compliance, side effects and bacterial resistance are the other problems. Other than the multi-antibiotic therapy, different therapeutic strategies have been examined to completely eradicate *H. pylori* from the stomach. One way to improve the efficacy in eradicating the infection is to deliver the antibiotic locally in the stomach[5]. Better stability and longer residence time will allow more of the antibiotic to penetrate through the gastric mucus layer to act on *H. pylori* [6] . The reason for the incomplete eradication of *H. pylori* is probably due to short residence time of antimicrobial agents in the stomach so that effective antimicrobial concentration cannot be achieved in the gastric mucous layer or epithelial cell surfaces where *H. pylori* exists[7].

Therefore, some researchers had prepared and reported new formulations, such as floating tablets, mucoadhesive tablets, pH sensitive excipients composition mucoadhesive microspheres, etc., which were able to reside in stomach for an extended period for more effective *H. pylori* eradication [8].

Levofloxacin, a synthetic fluorinated quinolone derivative, is effective for the treatment of *H. pylori*. The failure of the antibiotic therapy can be avoided by providing the effective concentration of drug at the site of action[9]**.** With this view in the present study, an attempt has been made to formulate levofloxacin floating microspheres for the eradication of *H. pylori* infection.

MATERIALS

Levofloxacin was purchased from yarrow chem. product. Mumbai, Eudragit S-100 and HPMC 15 cps were purchased from Sd-fine chemical. Ltd. All the chemicals and reagents used were of analytical grade.

METHOD

Preparation of Microspheres

Six batches of microspheres were prepared by taking drug: polymer ratio as 1:1, 1:2 and 1:3 with same drug and two different polymers. The formulation batches were designated as A, B, C for HPMC (1:1,1:2 and 1:3 respectively) and D, E, F for Eudragit (1:1,1:2 and 1:3 respectively). Drug and polymer in different proportions were weighed and co-dissolved at room temperature into a mixture of ethanol and dichloromethane (1:1) with vigorous agitation to form uniform drug polymer dispersion. This was slowly poured into the dispersion medium consisting of heavy liquid

paraffin (50ml) containing 1.5% span 80. The system was stirred using REMI over head propeller agitator at a speed of 700-800 rpm at room temperature over a period of 4-5 hrs, to ensure complete evaporation of the solvent. Liquid paraffin was decanted and the microspheres were separated by filtration through a whatmann filter paper, washed thrice with n-Hexane and air dried for 24 hrs [10]. (Table 1)

Table 1: Formulation batches of floating microspheres of Levofloxacin

Ingredients	*A*	*B*	*C*	*D*	*E*	*F*
Levofloxacin(g)	1	1	1	1	1	1
Hpmc(g)	1	2	3	-	-	-
Eudragit S 100(g)	-	-	-	1	2	3
Heavy liquid paraffin(ml)	50	50	50	50	50	50
Dichloromethane(ml)	5	5	5	5	5	5
Ethanol(ml)	5	5	5	5	5	5
Span 80(%)	1.5	1.5	1.5	1.5	1.5	1.5
n-Hexane(ml)	180	180	180	180	180	180

IR spectroscopy:

FT-IR spectroscopy was found to be the most reliable technique for predicting the possible interaction between the drug and polymers. The IR spectra of drug, polymer and microsphere were studied using KBr disc method [11].

Particle size analysis:

The particle size of floating microspheres in all samples was analyzed using optical microscopy method [12].

Drug Entrapment Efficiency (DEE):

Microspheres equivalent to 50 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance was measured after suitable dilution using spectrophotometrically (UV 1700, Shimadzu, Japan) at 293 nm against appropriate blank . The amount of drug entrapped in the microspheres was calculated by the following formula[13]:

DEE = (Amount of drug actually present) / (Theoretical drug load expected) × 100

Buoyancy:

Microspheres (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1 N hydrochloric acid containing 0.02% tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres [14].

% floating microspheres=(initial weight of floating microspheres/weight of floating microspheres)×100

Scanning Electron Microscopy:

The surface morphology and particle size was confirmed by Scanning Electron Microscopy and the picture of microspheres was taken by random scanning of the substance [15].

Dissolution study:

Dissolution studies were carried out by using dissolution apparatus USP XXII (Electrolab). Drug loaded microspheres equivalent to 100 mg of drug was introduced into the 900 ml of 0.1N HCl. The medium was maintained at 37±0.5ºC at 100 rpm. Aliquots of 5ml were withdrawn at regular intervals for 12 hours and analyzed spectrophotometrically (UV 1700, Shimadzu, Japan) at 293nm. Three trials were carried out for all formulations in 0.1N Hcl (pH 1.2). Sink condition was maintained throughout the study by replacing equal volume of fresh dissolution medium[16].

Data Analysis of Release Studies:

The *in vitro* release data obtained was treated to First order, Higuchi and Korsemeyer – Peppas to know precisely the mechanism of drug release of the floating microspheres.

RESULT & DISCUSSION

Floating Microspheres of levofloxacin were prepared by solvent evaporation method using HPMC and Eudragit S 100 as polymers with various proportions. The parameters which were evaluated for microspheres are given in the Table 2.

Drug-polymer compatibility:

FT-IR spectra of Levofloxacin alone and its combination with polymers are shown in Figure 1. FTIR spectra of the pure Levofloxacin and the drug polymer mixture indicate that Levofloxacin is not involved in any chemical reactions with the polymer used.

Drug entrapment efficiency:

All batches show percent entrapment more than 45% and it was found that entrapment of drug increases with an increase in the amount of the polymer. Formulation C shows maximum entrapment whereas formulation A shows minimum entrapment in HPMC polymer and Formulation F shows maximum entrapment whereas formulation D shows minimum entrapment in Eudragit S 100 polymer and as shown in table 2.

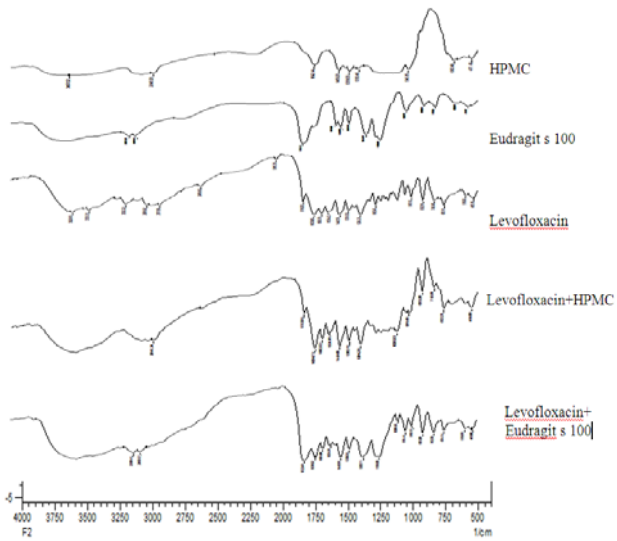

Fig. 1: FTIR spectra of levofloxacin, HPMC, Eudragit E 100, Levofloxacin HPMC Microspheres and Levofloxacin Eudragit Microspheres.

Table 2: Characterization of floating microsphere

Batches	*DEE*	*Particle Size (µm)*	*% Buoyancy*
A	51.03 ± 1.15	63.87 ± 1.56	72.74 ± 0.95
B	59.03 ± 0.75	94.44 ± 2.03	73.95 ± 0.88
C	74.93 ± 0.78	103.11 ± 1.34	75.59 ± 0.79
D	45.62 ± 0.89	50.32 ± 1.43	63.38 ± 1.14
E	65.67 ± 1.11	78.32 ± 1.83	67.45 ± 0.87
F	69.78 ± 0.98	85.43 ± 2.01	70.35 ± 1.12

Particle size analysis:

Microspheres were prepared using a gradually increasing HPMC and Eudragit S 100 for formulations A, B, C and D, E, F respectively, to assess the effect of polymer concentration on the size of microspheres. The mean particle size of the microspheres significantly increased with increasing polymer concentration and was in the range of 50.32 ± 1.43µm to 103.11 ± 1.34. Table 2

SEM study:

Results showed that HPMC and Eudragit S 100 floating microspheres of levofloxacin were predominantly spherical in shape with smooth surface. The porous nature and characteristics internal structure of the microspheres, a hollow cavity inside enclosed with the rigid shell constructed with drug and polymer was clearly evident. HPMC K4M based floating microspheres were found to be much more elongated in nature than microspheres prepared by using Eudragit S100. The porous nature and cavity formed in the microspheres would dictate the floating behaviour of microspheres of levofloxacin as shown in figure 2.

The Percentage Buoyancy:

The Percentage Buoyancy for all batches was almost above 60%, which was studied for 12 h. Average buoyancy in percentage was found to be 63.38 ± 1.14 to 75.59 ± 0.79. The highest percentage was obtained with formulation C. In general with increase in the amount of polymer (HPMC), there was an increase in the buoyancy percentage. From the table 2, it was concluded that on increasing polymers concentration, incorporation efficiency and % buoyancy increase continuously.

***In-vitro* dissolution studies:**

The dissolution rate studies were performed to evaluate the dissolution character of Levofloxacin from the floating microspheres. Floating Microspheres of Levofloxacin with HPMC (Batches A, B, C) showed enhanced release rate when compared to Levofloxacin with Eudragit-E100 (batches D, E, F). The % Cr at 12th hrs for batch A was found to be 89.59 ± 0.90%, and 70.23 ± 0.58 in batch D. The rates of dissolution of HPMC batches were much better than Eudragit batches due to hydrophilic nature of polymer. With increase in polymer concentration there was a decrease in drug release rate in both the batches. (Table 3, Fig 3)

Mechanism of release:

The data obtained for *in-vitro* release were fitted into equations for the zero-order, first- order and higuchi and peppas model. The interpretation of data was based on the value of the resulting regression coefficients. The *in-vitro* drug release showed the highest regression coefficient values for peppas model, indicating swelling diffusion to be the predominant mechanism of drug release. (Table-3)

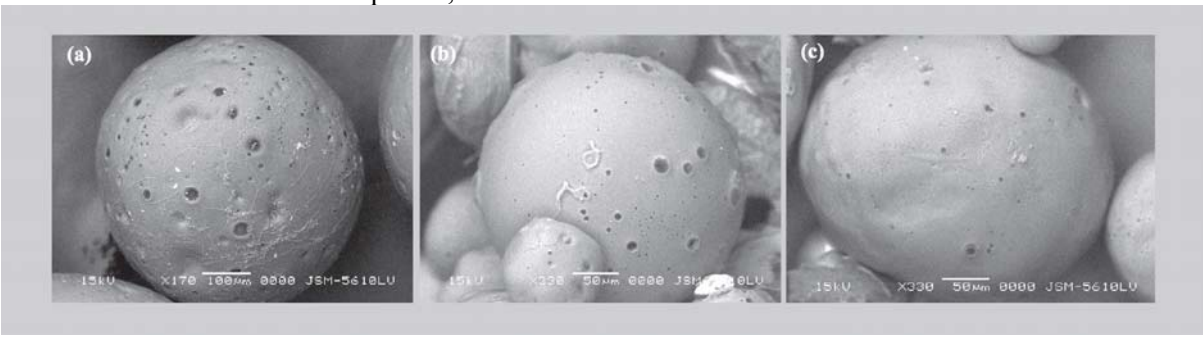

Fig. 2: SEM photograph of levofloxacin floating microsphere.

Table: 3 Release kinetic pattern of levofloxacin floating microspheres

Formulation Code	First-order model		Higuchi model		Korsenmeyer-peppas model	
	R^2	K_1	R^2	K_h	R^2	N
A	0.994	-7.815	0.906	28.77	0.991	1.140
B	0.973	-7.653	0.905	28.38	0.977	1.233
C	0.976	-7.047	0.913	26.30	0.976	1.140
D	0.973	-6.694	0.889	24.69	0.983	1.353
E	0.947	-6.379	0.892	23.92	0.956	1.452
F	0.961	-6.164	0.882	22.72	0.964	1.526

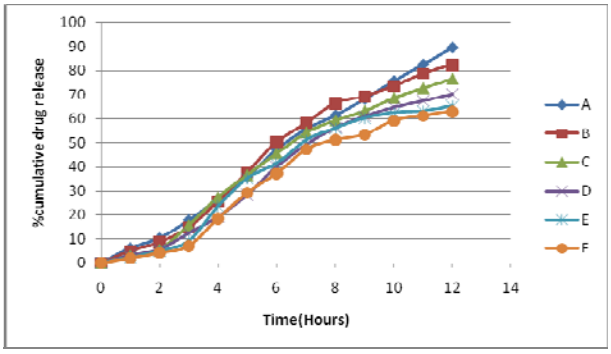

Fig 3: Percentage cumulative release of Levofloxacin floating microspheres

CONCLUSION

Floating microspheres of Levofloxacin were prepared by a solvent evaporation method. The nature of polymer influenced the physical characteristics as well as floating behaviour of the microspheres. *In vitro* buoyancy study confirmed the excellent floating properties of microspheres. The drug release was sufficiently sustained and non-Fickian transport of the drug from floating microspheres was confirmed. Hence the floating microspheres of Levofloxacin prepared with HPMC and Eudragit- S 100 may provide a convenient dosage form for achieving best performance regarding flow, release and floating properties. Further,

Extended resident time of the Levofloxacin in stomach is desirable for effective eradication of *H. Pylori*.

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