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FORMULATION AND EVALUATION OF GATIFLOXACIN FLOATING TABLETS BY DIRECT COMPRESSION METHOD

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ABSTRACT

Floating Drug delivery system is used to target the drug release in the stomach or to the upper parts of the intestine. The eradication of *Helicobacter pylori* requires the administration of various medicaments several times a day, which often results in poor patient compliance. More reliable therapy can be achieved by using FDDS which can be expected that the topical delivery of antibiotic through a FDDS may result in complete removal of the organisms in the fundal area due to bactericidal drug levels being reached in this area, and might lead to better treatment of peptic ulcer. Since gatifloxacin is a potential drug for eradication of H. Pylori infection responsible for gastric and duodenal ulcers, the oral delivery of antibiotic gatifloxacin was facilated by preparing a non-disintegrating floating dosage form which can increase its local availability in the stomach by increasing the drug's gastric residence time. The tablets were prepared in six batches F1 to F6 by the direct compression technique using polymers such as hydroxyl propylmethylcellulose (HPMC K4M, HPMCK 15M M, and HPMC K100M, along with sodium bicarbonate as the gas –generating agents. The prepared tablets were evaluated for their physicochemical properties and drug release. In-vitro release studies indicated that the gatifloxacin release form the floating dosage form was uniform F2 and F6 and followed Higuchi drug release. Sodium bicarbonate was used as the gas-generating agents which cause the tablets to float on the G.I fluids. Formulation showed a floating lag time less than 60 seconds and floating time above 12 hrs.

Keywords:- Floating drug delivery system, Gatifloxacin, HPMC, Direct compression technique.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms (S.S. Patel *et al*., 2006). Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa (M.D. Chavanpatil *et al*., 2006). Thus; small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the gastric emptying are summarized. Gastro retentive systems can remain in the gastric region for several hours

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and hence significantly prolong the gastric residence time of drugs due to buoyancy of the drug (Lannucelli V *et al*., 1998; M.N. Gambhire *et al*., 2007). Both effervescent and non effervescent systems of floating approach have been reported in literatures. (Hilton AK *et al*., 1992; Reddy LH *et al*., 2002; Bardonnet PL *et al*., 2006).

Recently Gatifloxacin is proved to be one of the potential drugs against H.pylori infection, responsible for duodenal ulcers and various cytotoxic complications. H.pylori resides mainly in stomach region, specifically in the sub-region of the mucous layer in stomach (Forman D *et al*., 1994; Megraud F *et al*., 1992) and produces gastric and duodenal ulcers and adeno carcinoma. So it demands prolonged and constant drug concentration at that particular site to eradicate the infection by the oral delivery of antibiotic gatifloxacin was facilated by preparing a non-disintegrating floating (Garg S *et al*., 2003; Harrigan RM. *et al*., 1997; Hamid AM *et al*., 2006) dosage form. This leads to the formulation of acceptable sustained-release dosage forms of Gatifloxacin. The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract (Singh BN *et al*., 2000). The local delivery of Gatifloxacin by this approach will also promote a fast and effective eradication of H.pylori rather than a conventional tablet containing Gatifloxacin. In the present study an attempt is made to develop effervescent floating drug delivery system of Gatifloxacin. The Gatifloxacin floating tablets were prepared by direct compression method by using polymer like HPMC of different grade along with sodium bicarbonate as the gas –generating agents. (Bomma R *et al*., 2009).

MATERIALS AND METHOD

Materials

Gatifloxacin was gifted from Dr. Reddy's Laboratory, India HPMC (HPMC K4M, HPMCK 15M M, and HPMC K100M, l were purchased from C.D.H Ltd, India. Sodium carbonate, citric acid, talc and magnesium stearate were purchased from S.D fine chemicals Ltd. All chemicals and drugs were analytical grade.

Method

Direct compression

Optimization of gas generating agent concentration

Preliminary formulations were studied to optimize the drug polymer ratio and effervescent composition. The formulation were prepared with varying proportions of 4:1,3:1 and 1:1 of gas generating agent composition in order to determine the effect of gas generating agent concentration on the buoyancy behavior of the formulations.

Preparation of gatifloxacin floating tablets

Floating tablet were prepared by direct compression method using HPMC as a rate controlling polymer, $NAHCO_3$ as a gas generating agent, methyl cellulose, magnesium stearate as glidant and carbapol as a floating agent. Preliminary formulations were optimized for the effervescent composition. The powder mixture containing drug, polymers and other excipients were weighed and thoroughly blended in mortar and pestle and then passed through sieve no 40and directly compressed using 8mm flat punches on a rotary punching machine. The compression force was adjusted to obtain tablets with crushing strength in the range of 5to 6Kg/cm·Six batches of tablets were prepared by this technique given in Table.no.1.

The entire tablets contain 250 mg of Gatifloxacin, 5 mg Magnesium stearate and 5 mg talc. The average weight of each tablet was 500 mg.

EVALUATION

Evaluation of final blend

The flow properties of granules were characterized in terms of angle of repose, tapped density, bulk density and the Carr's index and hausner ratio.

Evaluation of physicochemical properties

The formulated tablets were evaluated for weight variation, thickness, crushing strength, friability, content uniformity, invitro buoyancy properties, invitro release studies and invivo residence time.

PHYSICAL CHARACTERIZATION

The prepared tablets were characterized for weight variation (n=20), hardness (n=6), %, thickness using screw gauge micrometer (n=10), % friability (n=10).

Weight variation test

Twenty tablets were selected at random and the average weight of the tablets was determined. The weight of individual tablets was compared with the average weight.

Hardness test

Hardness of the prepared formulations was determined using Monsanto hardness tester.

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.

Swelling index

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium 0.1N HCl at 37 ± 0.5C. After 0.5, one, two, three, four, five, six, seven and eight hours, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, AX 120). Swelling index was calculated by using the following formula.

$$\textbf{Swelling index} = \frac{\text{wet weight of tablet- Dry weight of tablet}}{\text{Dry weight of tablet}}$$

Floating capacity

The in vitro buoyancy was determined by floating lag times as per method described by Rosa *et. al.* The tablet was placed in 100 ml beaker containing 0.1 N HCl. The time required for tablets to rise to the surface was determined as floating lag time and duration of the tablet remaining buoyant was observed.

Content uniformity test

Prepared tablets were accurately weighed and finally crushed in a mortar and pestle. A weighed powder portion of each powder and the powder equivalent to dose (mg) of the prepared tablet was transferred to 100 ml standard volumetric flask. The powder was dissolved in suitable quantity of 0.1N HCL. The sample was mixed thoroughly and filtered through 0.45µ membrane filter. The filtered solution was diluted suitably diluted and the diluted solution was analyzed for drug content by using UV- spectrophotometer (Systronics) UV-1700 at wavelength of 292nm.

***In vitro* dissolution studies**

The release rate of Gatifloxacin from floating tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml 0.1 N HCl solution at 37 ± 0.5°C and50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hrs and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filters and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 292nm using a UV-spectrophotometer (Systronics). The percentage drug release was plotted against time to determine the release profile.

RESULTS AND DISCUSSION

Physical Characterization

Requirement of low pH for optimum absorption and better availability of gatifloxacin at G.I. Tract reflects its ideal candidature for development of floating drug delivery system. In the present study an attempt is made to develop effervescent floating drug delivery system of Gatifloxacin. Six batches (F1 to F6) of floating dosage forms are developed in this study. Tablets are prepared by using HPMC, methyl cellulose, sodium bi carbonate as a gas generating agent and Mg stearate and talc as glidants and lubricants. The data of physical parameters like thickness, content uniformity, weight variation, hardness of the tablet and floating lag time, of all the formulations is enclosed in Table-2, which were observed to be within the range. The average weight of tablets was 500 mg and the weight variation for every batch was less than $\pm$ 5.

The hardness was maintained as 5-6 kg/cm^2 in all the formulations. The friability of all the formulations are in the acceptable limit and the content uniformity was found to be in the range of 95.16 –98.43%. Floating capacity of fabricated tablets was determined in 0.1 N HCl and all the tablets exhibited desired floating lag time an average value of less than 60 sec with floating time greater than 12 hrs for all the batches. The results of floating studies are included in table 2. This is mainly due to evaluation of CO2 entrapped inside the hydrated polymeric matrices resulting from interaction between gas generating agent(NaHCO3) and dissolution media(0.1N HCl, pH 1.2) of matrices enabling the matrices to float.

Swelling index

In vitro dissolution studies

The invitro drug release studies revealed that formulation F1 and F2 released 93.5 % and 98.6 % in 10 hrs and 12 hrs respectively. This could be due to different polymer concentration. Both formulations floated for 12 hrs having floating lag time 45 and 52 sec respectively. Formulation F3 and F4 is made up of HPMC K100 M and showed drug release 93.8 and 96.5 %.These variation in drug release were due to change in polymer concentrations of the tablet. Formulation F5 and F6 are made up of HPMC K4M,in these F6 formulation shows the desired drug release profile in 12 hrs and floated with a lag time 60 seconds. It was, therefore considered the best formulations in all series. The results are shown in table-

3.The drug release from the floating tablet was sustained for a prolonged period of time due to the viscous nature of the HPMC matrix through which the drug diffuses. HPMC K4M helped to increase the drug release with in 12 hrs and maintain the integrity and buoyancy of the tablets showing floating time 53 and 55 sec for F5 and F6 formulation. The increased drug release from the floating matrix tablets containing smaller amount may be due to matrix erosion in the former and swelling diffusion and a slight erosion mechanism in the latter. However the matrix containing high viscosity grade of polymer with large molecular mass results in swelling properties with little erosion and vice versa. Integrity and floating properties of floating tablets were thus maintained (Fig-2). The drug release showed 98.25 % for F6 formulation in 12 hrs as in Table. no. 3 and fig-1. Both F2 and F6 formulation shows prominent results in floating lag time, floating time (Figure-F2) and in vitro drug release. The invitro drug release was fit to kinetic models to explain the release kinetics from the floating tablets. The kinetic models used were zero order equation; first order equation, Higuchi and korsemeyer peppas models (Kosemeyer RV et al 1983). The cumulative amount of the drug released from the tablets were best fit to the Higuchi model with correlation coefficient (r^2=0.98 to 0.99) compared with zero order (r^2=0.93 to 0.96) and first order (r^2=0.57 to 0.62).

Table 1. Composition of gatifloxacin floating tablets

Formulation	HPMC 4M	HPMC 15M	HPMC 100M	Sodium bicarbonate	Citric acid	MCC
F1	--	50	--	50	12.5	127.5
F2	--	75	--	50	12.5	102.5
F3	--	--	25	50	12.5	152.5
F4	--	--	50	50	12.5	127.5
F5	75	--	--	50	12.5	85.5
F6	100	--	--	50	12.5	60.5

Table 2. Evaluation Parameter of Gatifloxacin Floating tablets

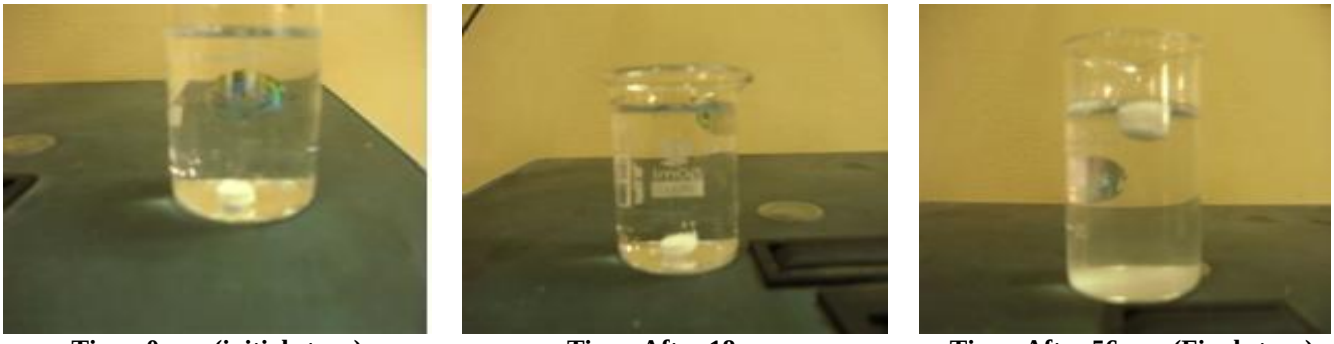
Parameters	F1	F2	F3	F4	F5	F6
Thickness (mm)	6.48±0.04	6.75±0.03	6.66±0.02	6.65±0.01	6.62±0.04	6.55±0.03
Weight variation(mg)[a]	500±1.1	501±1.4	499±1.6	503±1.2	498±1.9	502±1.2
Hardness(kg/cm^2)[b]	5.7±0.5	5.9±0.5	5.2±0.3	5.4±0.2	5.8±0.1	6.1±0.1
Friability%	0.51	0.48	0.42	0.44	0.42	0.48
Swelling index	0.012	0.017	0.018	0.016	0.019	0.018
Floating lag time(sec)	45	52	54	60	55	53
Floating time(h)	>12	>12	>12	>12	>12	>12
Drug conten(t%)[c]	95.43±1.5	98.25±1.6	99.24±1.2	82.30±1.5	98.90±1.2	98.25±1.4

Mean±SD: a n=20, b n=6, c n=3

Table 3. Cumulative percent drug releases for gatifloxacin floating tablets

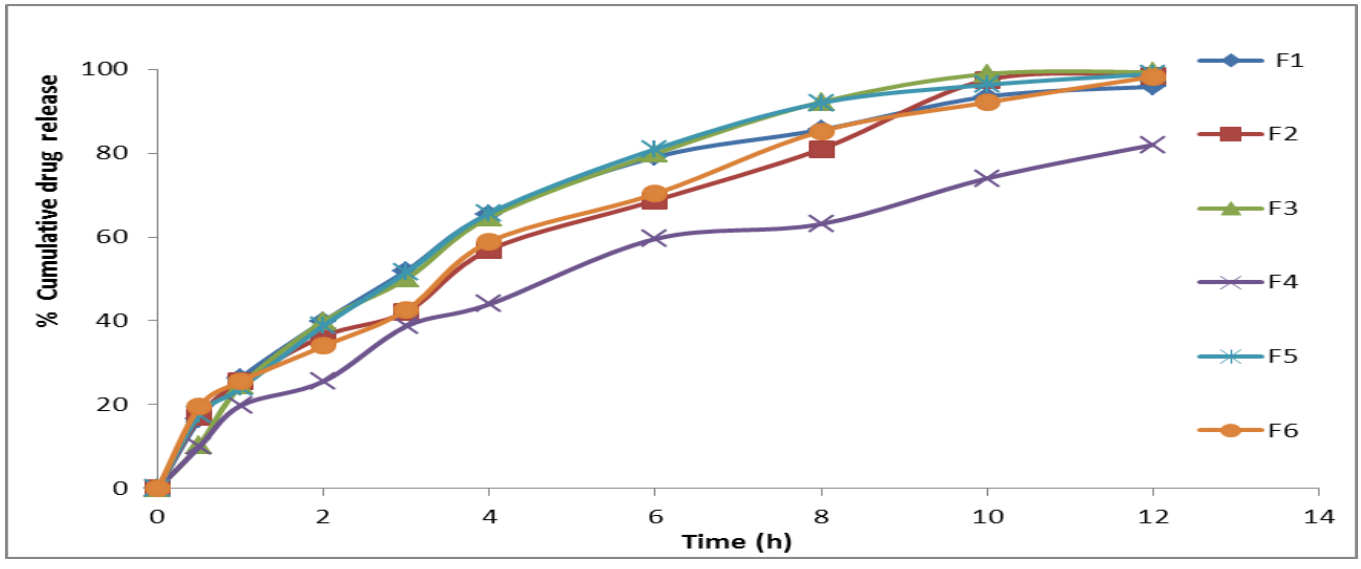
S.No	Time (hrs)	Cumulative percent drug release for different gatifloxacin floating tablets (%)					
		F1	F2	F3	F4	F5	F6
1	0	0.00	0.00	0.00	0.00	0.00	0.00
2	0.5	16.50	17.12	10.45	10.00	17.60	19.50
3	1	26.40	25.5	24.5	19.80	23.99	25.60
4	2	39.90	36.40	39.88	25.6	38.88	34.00
5	3	52.00	42.23	50.10	38.76	51.56	42.66
6	4	65.50	56.99	64.76	44.10	65.67	58.90
7	6	79.10	68.75	79.90	59.5	81.00	70.33
8	8	85.60	81.00	92.20	65.11	92.00	85.23
9	10	93.50	97.50	98.90	74.50	96.30	92.12
10	12	95.87	98.50	99.32	82.00	98.90	98.25

Fig 1. Swelling index floating tablet (F6)



Time: 0 sec. (initial stage) **Time: After 18 sec.** **Time: After 56 sec. (Final stage)**

Fig 2. In vitro dissolution studies of floating tablet



CONCLUSION

The Gatifloxacin floating tablets were prepared by effervescent system using direct compression method. The effervescent based drug deliver shows promising results in in-vitro buoyancy. The gel forming polymer HPMC and gas generating agent such as sodium bicarbonate are essential to achieve optimum buoyancy. The invitro release kinetics is best fit with Higuchi model. And it was suggested that gastric retention of gatifloxacin can be achieved by floating drug delivery to eradicate H.Pylori infection by increasing local concentration of the drug.

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