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Original Article

DEVELOPMENT AND EVALUATION OF OFLOXACIN FLOATING TABLETS USING NATURAL POLYMER: *STERCULIA FOETIDA* LINN. GUM

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ABSTRACT

Objective: The aim of the present work was to develop a gastro retentive drug delivery system of Ofloxacin with the objective of retarding the drug release when the dosage form is exposed to gastrointestinal fluid.

Methods: Floating tablets of Ofloxacin were developed using a natural gum like *Sterculia foetida.* The prepared tablets were evaluated in terms of their precompression parameters, physical characteristics, *in vitro* buoyancy, *in vitro* drug release and release order kinetics. The formulations were optimized for different concentrations of *Sterculia foetida*.

Results: The results of *in vitro* release studies showed that optimized formulation (F4) could sustain drug release (97.86%) for 24 h and remain buoyant for 24 h. The optimized formulation was subjected to various release kinetic investigations and it was found that the mechanism of drug release was predominantly diffusion with a minor contribution from polymeric relaxation.

Conclusion: Floating tablets of Ofloxacin were successfully formulated with the ability of providing controlled release and non-Fickian transport of the drug from tablets was confirmed.

Keywords: Ofloxacin, Floating drug delivery system, *Sterculia foetida*, Buoyancy

INTRODUCTION

Oral delivery of the drug is the most preferable route of drug delivery due to the ease of administration, patient compliance, and flexibility in the formulations [1]. To prolong the residence time of dosage forms within gastrointestinal tract until all drug is released at desired rate is one of the real challenges for oral controlled-release drug delivery system [2]. In the present era, gastro-retentive dosage forms (GRDF) receive great attention because they can improve the performance of controlled release systems. An optimum GRDF system can be defined as a system which remains in the stomach for a sufficient time interval against all the physiological barriers, releases active moiety in a controlled manner, and finally is easily metabolized in the body. Physiological barriers like gastric motility and gastric retention time (GRT) act as obstacles in developing an efficient GRDF [3]. Several technical approaches are currently utilized in the prolongation of gastric residence time, including high density, swelling and expanding, polymeric mucoadhesive, ion-exchange, raft forming, magnetic and floating drug delivery systems (FDDS), as well as other delayed gastric emptying devices [4]. Since decade or two, the development of floating drug delivery systems becomes a significant and novel tool as having low density than gastric content [5].

Ofloxacin (9-fluoro-2, 3-dihydro-3-methyl-10 (4-methyl-1-piperazinyl)-7-oxo-7H pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic-acid) is a synthetic fluoroquinolone derivative, which acts by inhibiting the topoisomerase enzyme which is essential in the reproduction of the bacterial DNA [6]. Ofloxacin has a short biological half-life (8-9 h) and it has been reported that its bioavailability is strongly dependent on the local physiology of the gastrointestinal tract [7]. It is highly soluble in acidic media and precipitates in alkaline media thereby losing its solubility [8]. Hence, gastro retentive floating systems of ofloxacin should enhance the bioavailability by retaining it in the acidic environment of the stomach.

Natural polysaccharides are widely used in the pharmaceutical and food industries as excipients and additives due to their low toxicity, biodegradability, bio-competitiveness, availability, and low cost. In the current investigations, the suitability of *Sterculia foetida* gum which has been reported as a controlled release matrix polymer was evaluated in the development of gastro retentive floating drug delivery systems (GRFDDS) [9].

MATERIALS AND METHODS

Ofloxacin was obtained as a gift sample from Zim Laboratories Ltd., Kalmeshwar, Maharashtra. The Gum of *Sterculia foetida* (Sterculiaceae) was procured from the vendor M/s Mr. Wagh Brothers, Nagpur. The gum was authenticated and approved after macroscopical and microscopical evaluation by Dr. Vinayak R. Naik, Senior Research Scientist, Nicholas Piramal Life Sciences Ltd., Mumbai. The said gum was used for the research work. All other chemicals used in the study were of analytical grade.

Preformulation studies

Drug excipient compatibility studies

The compatibility studies provide the basis for selecting the right combination of drug and the excipients. Thus, the pure drug and physical mixture of drug and polymers were subjected to IR spectroscopic study using FT-IR spectrophotometer (IR Affinity-1, Shimadzu). The spectra were scanned over the wave number range from 4000–400 cm^{-1}. Additionally, the DSC thermograms of the pure drug, polymer and physical mixture of the drug and the polymer were recorded using differential scanning calorimeter (Perkin Elmer, USA). The samples were heated in an open aluminum pan from 40 to 300 °C at a scanning rate of 10 °C/min under the stream of nitrogen.

Formulation of ofloxacin floating tablets

Ofloxacin floating tablets were prepared as per the composition is shown in table 1. The ingredients were weighed accurately and mixed thoroughly. Granulation was done with the help of water. The granules were dried in conventional hot air oven at 50°C. Drying of the granules was stopped when the sample taken from the oven reached a loss on drying (LOD) value of 1 to 3%, as measured by a moisture balance at 105 °C. The dried granules were sized through 16 mesh, lubricated with magnesium stearate and purified talc and then compressed.

Table 1: **Composition of floating tablet formulation of ofloxacin**

S. No.	Ingredients (mg/tablet)	F1 10 %w/w	F2 20 %w/w	F3 30 %w/w	F4 40 %w/w
1	Ofloxacin	100	100	100	100
2	*Sterculia foetida* Gum	50	100	150	200
3	Lactose	290	240	190	140
4	Sodium bicarbonate	50	50	50	50
6	Magnesium stearate	5	5	5	5
7	Talc	5	5	5	5
8	Water	q. s.	q. s.	q. s.	q. s.
9	Total	500	500	500	500

Evaluation of floating tablets

Determination of precompression parameters

The flow properties of granules (before compression) were characterized for micrometric properties in terms of angle of repose, tapped density, bulk density, Carr's index and Hausner ratio [10, 11].

Determination of post compression parameters of floating tablets

Ofloxacin floating tablets were subjected to determination of post-compression parameters like hardness, weight variation and friability [12-14]. Ten tablets were selected at random, and the hardness of each tablet was measured on Monsanto hardness tester. Thickness and diameter of ten tablets were measured using Vernier callipers. Twenty tablets were selected at random, weighed together and individually to check for weight variation. The friability of the tablets was determined using Roche's friabilator. Twenty tablets were accurately weighed and placed in the friabilator and operated for 100 revolutions. The tablets were deducted and reweighed. The tablets that loose less than 1% weight were considered to be compliant.

$$\% \text{ friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Drug content estimation

The drug content in each formulation was determined by triturating 20 tablets, and powder equivalent to average weight was added in 100 ml of 0.1M hydrochloric acid, followed by stirring. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of the resultant solution was measured spectrophotometrically at 297 nm using 0.1 M hydrochloric acid as blank [15].

***In vitro* buoyancy studies**

The *in vitro* buoyancy was determined by the floating lag time. The tablets were placed in 100-mL beaker containing 0.1M HCL. The time required for the tablet to rise to the surface for floating was determined as the floating lag time and further floating duration of all tablets was determined by visual observations [16, 17].

***In vitro* dissolution studies**

The release rate of Ofloxacin from floating tablets was determined using USP Type II apparatus (TDT-08L, Electrolab, India) [18]. The dissolution test was performed using 900 ml of 0.1M hydrochloric acid, at 37±0.5 °C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and during each withdrawal, the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. The absorbance of these solutions was measured at 297 nm using a UV-Visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile.

Drug release kinetics

The kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, the *in vitro* drug release data was analyzed according to zero order, first order, Higuchi square root, Korsmeyer-Peppas model [19-21]. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test. The data were processed for regression analysis using graph pad prism.

RESULTS AND DISCUSSION

Drug-polymer compatibility studies

The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, easy to administer and safe. The major FT-IR peaks observed in Ofloxacin were-OH stretch (3100 cm^{-1}), N-CH_3 (2750 cm^{-1}), C=O (1725 cm^{-1}),-F (1175 cm^{-1}),-CN stretch (850 cm^{-1}), FT-IR peaks observed in physical mixture of Ofloxacin and *Sterculia foetida* gum were-OH stretch (3150 cm^{-1}), N-CH_3 (2800 cm^{-1}),-C=O (1700 cm^{-1}),-F (1175 cm^{-1}),-CN stretch (850 cm^{-1}), as shown in fig. 1 and 2 respectively. No extra peaks were observed in the spectrum which inferred that the chosen natural gum was compatible with Ofloxacin. Compatibility studies were also carried out using DSC, which allows determination of thermotropic phase transition behavior in a quantitative manner. The thermograms recorded during analysis display pronounced melting peaks. The narrow peak at 268.75 °C for Ofloxacin (fig. 3A) infers the presence of a crystalline form of the drug. The thermogram of *Sterculia foetida* displayed a slight peak at 288.23 ºC (fig. 3B). The physical mixture of the drug and the carrier retained the crystalline peak of the drug (fig. 3C) demonstrating clearly the compatibility of Ofloxacin with the said gum.

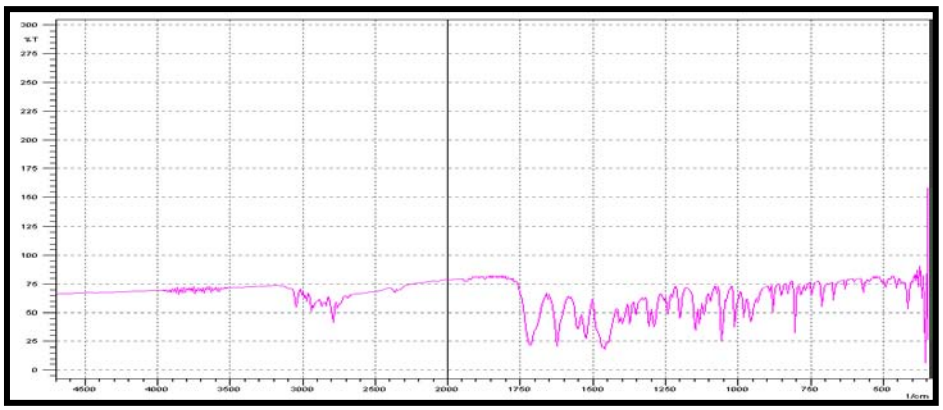

Fig. 1: FT-IR spectrum of Ofloxacin

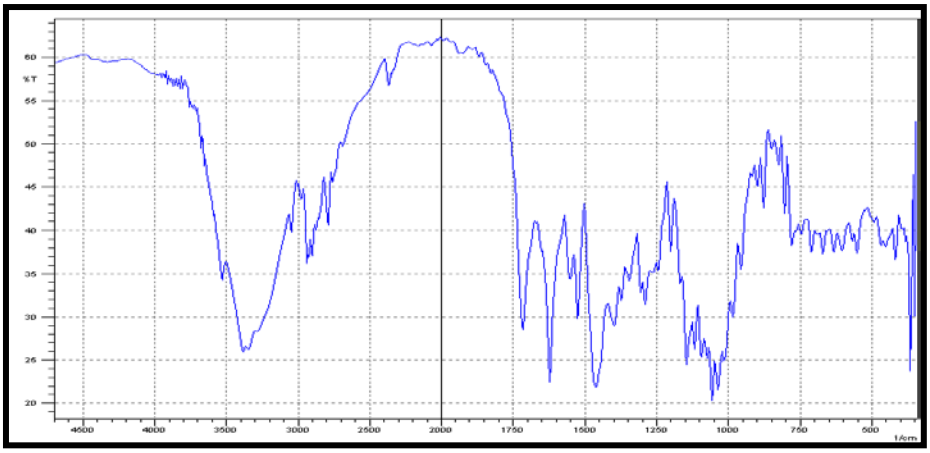

Fig. 2: FT-IR spectrum of physical mixture of Ofloxacin and *Sterculia foetida* gum

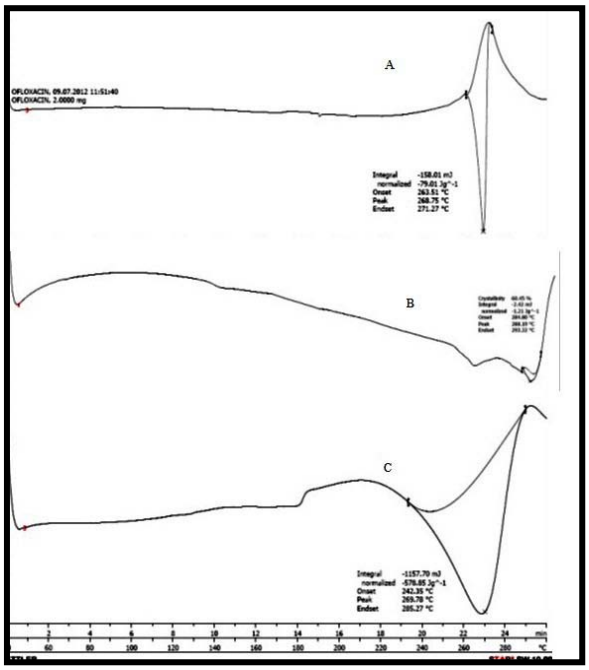

Fig. 3: DSC thermogram of (A) Ofloxacin (B) *Sterculia foetida* gum and (C) Physical mixture of Ofloxacin and *Sterculia foetida* gum

Determination of precompression parameters

Table 2 depicts the precompression parameters of Ofloxacin granules. The granules showed good flow property. The angle of repose ranged from 21 °±0.8 to 24 °±0.7 and the compressibility index ranged from 9.91±0.32 to 14.58±0.74. The bulk density and tapped density of the prepared granules ranged from 0.322±0.011 to 0.333±0.113 and 0.363±0.038 to 0.377±0.041 respectively. The results of the angle of repose indicated good flow property of the granules and the value of compressibility index and Hausner's ratio further showed support for the good flow property.

Determination of post compression parameters of floating tablets

The results of post compression parameters of Ofloxacin floating tablets are as shown in the table 3. The thickness of tablets was measured by Vernier calipers and ranged between 4.80±0.01 to 4.85±0.01 mm, respectively. The hardness of the tablets was measured by Monsanto hardness tester and ranged in between 4.2±0.27 to 5.0±0.35 kg/cm^2. The friability was found to be 0.59±0.05 to 0.95±0.06 %, which is an indication of the satisfactory mechanical resistance of the tablets as shown in the table 3. All the formulations showed values within the prescribed limits for tests like hardness, friability, and weight variation which indicate that the prepared tablets are of standard quality.

Drug content estimation

The drug content estimations showed values in the range of 96.4±0.006 to 99.4±0.002 % (Table4) which reflects good uniformity in drug content among different formulations.

Table 2: Precompression parameters of ofloxacin granules

Formulation code	Evaluation parameters				
	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (θ)	Carr's index	Hausner's ratio
F1	0.322±0.011	0.377±0.041	24 °±0.7	14.58±0.74	1.17±0.32
F2	0.327±0.005	0.370±0.096	23 °±1.0	11.62±0.52	1.13±0.27
F3	0.333±0.113	0.370±0.013	23 °±0.4	10.0±0.79	1.11±0.15
F4	0.327±0.035	0.363±0.038	21 °±0.8	9.91±0.32	1.11±0.54

Data expressed as mean±SD; n=3

Table 3: Evaluation of post-compression properties of floating tablets

Formulation Code	Evaluation parameters (mean±SD)			
	Thickness (mm), n=10	Hardness (Kg/cm^2), n=10	Friability (%) n=20	Weight variation(g), n=20
F1	4.84±0.01	4.2±0.27	0.95±0.06	0.493±1.78
F2	4.82±0.35	4.5±0.35	0.80±0.08	0.496±0.57
F3	4.80±0.01	4.6±0.22	0.72±0.03	0.496±0.67
F4	4.85±0.01	5.0±0.35	0.59±0.05	0.496±1.92

Table 4: Estimation of drug content

Formulation code	Calculated value (mg)	Estimated value (mg)	% Drug content
F1	100	96.4±0.003	96.4±0.006
F2	100	97.9±0.005	97.9±0.004
F3	100	98.4±0.006	98.4±0.005
F4	100	99.4±0.004	99.4±0.002

Data expressed as mean±SD; n=3

In vitro buoyancy studies

All the tablets were prepared by the effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in the presence of dissolution medium (0.1 M hydrochloric acid). It was observed that the gas generated was trapped and protected within the gel, thus decreasing the density of the tablet below 1 and as a result, the tablet became buoyant. The tablet swelled radially and axially during *in vitro* buoyancy studies. In this study it was observed, an increase in the concentration of *Sterculia foetida* gum decreased the floating lag time (table 5). Thus, the results indicated that as the concentration of polymer increased, floating lag time decreased due to the hydrophilic nature of polymer which allowed the penetration of media through the pores formed on the surface of the tablet and total floating time increased due to the swelling nature of the tablet which kept it intact for a longer duration. Similar observations have been reported earlier [22].

In vitro dissolution studies

In vitro dissolution studies of all the formulations of floating tablets of Ofloxacin were carried out in 0.1N HCl. The study was performed for 24h and cumulative drug release was calculated at every one hour time interval. *In vitro* dissolution studies of all the formulations are shown in fig. 4. A natural gum was used to prepare floating tablets. It was observed that the type of natural gum influences the drug release pattern. All the formulations contained gas generating agent (sodium bicarbonate). A significantly higher rate and extent of drug release were observed from the batches based on *Sterculia foetida* gum. Varying the amount of *Sterculia foetida* gum affected the drug release. Moreover, tablets formulated using *Sterculia foetida* gum (formulation F1) could not bear their matrix shapes until 24 h and the released the drug before 24 h. Among the tablets F2-F4, an increasing concentration of *Sterculia foetida* gum was present, and it was found that the formulation F4 sustained the drug release up to 24 h. Thus, formulation F4 was considered as the optimized formulation based on drug release and *in vitro* buoyancy studies.

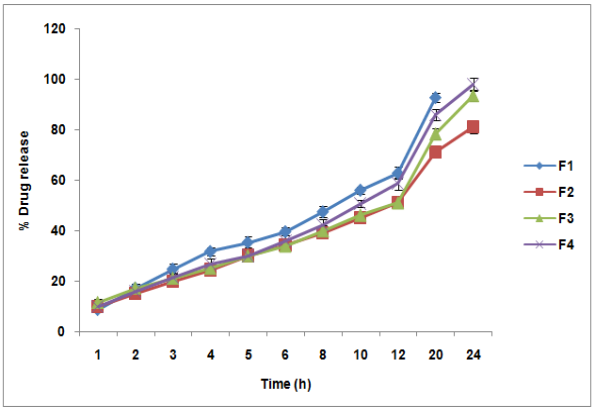

Fig. 4: Comparative *in vitro* dissolution profiles of floating tablets (formulation F1-F4)

Table 5: *In vitro* buoyancy studies of floating tablets

Formulation code	Floating lag time (sec)	Total floating time (hr)
F1	255±2.06	>23
F2	110±1.0	>24
F3	65±0.57	*> 24*
F4	35±1.52	*> 24*

Data expressed as mean±SD; n=3

Table 6: Kinetic release data of different model for optimized formulation (F4)

Model	Slope	R^2
Zero order	0.663	0.9984
First order	0.713	0.8744
Higuchi	0.567	0.9319
Korsmeyer-Peppas	0.659	0.9876

Drug release kinetics

The drug release data of optimized formulation (F4) were fitted to models representing Higuchi's, zero order, first order and Korsmeyer's equation kinetics to know the release mechanisms. The data were processed for regression analysis using Graph pad prism statistical function. The results are shown in table 6. In the present study, *in vitro* release profiles could be best expressed by zero-order equation, as optimized formulation (F4) showed good linearity (R2= 0.9984) indicating diffusion as the dominant mechanism of drug release from the formulations. The values of slope for the korsemeyer-Peppas model indicated that the drug release from the tablets was non fickian diffusion.

CONCLUSION

In the present study, Ofloxacin floating tablets were formulated by wet granulation method using a natural gum like *Sterculia foetida.* Formulation (F4) containing *Sterculia foetida* showed controlled drug release for 24 h, emerging as best formulation. Mechanism of drug release of optimized formulation (F4) was found to be Zero order with non Fickian diffusion.

The present study, in conclusion, highlights the potential application of a plant-based polymer as a viable replacement for synthetic polymers in the development of controlled release dosage forms. Formulations prepared by such economical, renewable and eco-friendly plant resources can be considered to contain promising

controlled release polymer substances with the ability to bring about desired drug release supported by more elaborated research in this aspect.

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CONFLICT OF INTERESTS

Declared none

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