An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

FORMULATION AND EVALUATION OF OFLOXACIN GASTRO RETENTIVE FLOATING TABLETS

G. Saravanan*[1], S. Kiruthika[1], C. Aarthi priya[1]

[1]Faculty of Pharmacy, Karpagam Academy of Higher education, Coimbatore, Tamil nadu.

*Corresponding author E-mail: saravanan.nila@gmail.com

ARTICLE INFO

Key Words
Ofloxacin,
Floating tablets,
Gas generating agent,
direct compression,
floating capacity

ABSTRACT

The primary objective of the present study was to formulate and evaluate Ofloxacin gastro retentive floating tablets using different viscosity grades of HPMC polymer i.e. HPMC K15M and HPMC K100M in different ratios, along with gas generating agent such as sodium bicarbonate for the formulation of floating tablets. The final blend of the drug and excipients were evaluated for the powder flow properties, angle of repose, compressibility index and hausner's ratio. All the formulations were prepared by direct compression method. The prepared floating tablets were evaluated for floating capacity, influence of these polymers on *in vitro* release of ofloxacin and also an attempt was made to investigate the factors influencing the release kinetics.

INTRODUCTION

The primary aim of oral controlled drug delivery system is to deliver drugs for longer period of time to achieve better bioavailability, which should be predictable and reproducible. But this is difficult due to number of physiological problems such as fluctuation in the gastric emptying process, narrow absorption window and stability problem in the intestine.[1] To overcome these problems, different approaches have been proposed to retain dosage form in stomach. These include bioadhesive or mucoadhesives systems, swelling and expanding systems, floating systems and other delayed gastric emptying devices. The principle of floating preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.[2] Floating drug delivery system also known as hydrodynamically balanced system, have a bulk density lower Than gastric fluids and thus remain buoyant in the gastric fluids for a prolonged period of time without affecting the gastric emptying rate. While the system is floating on the gastric content, the drug is released slowly at desired rate from the system.[3] Hydrodynamically balanced drug delivery system, in either tablet or capsule form, is designed to prolong gastrointestinal (GI) residence time in an area of GI tract. It is prepared by incorporating a high level (20-70% w/w) of one or more gel forming hydrocolloids. On contact with gastric fluid hydrocolloid starts to become hydrate and build a gelled barrier around the device. This gel barrier controls the release of drug from the device.[4] Ofloxacin is a fluroquinolone antibacterial agent which is highly effective against gram positive and gram negative bacteria. It is widely used to treat infections of GI tract, respiratory tract and urinary tract. For mild or moderate infections, it is administered at a dose of

200mg twice a day. For uncomplicated urinary infections, administration of 400mg per day is normally adopted.[5] Ofloxacin exhibits pH dependent solubility. The solubility of ofloxacin in water is 60 mg/ml at pH value ranging from 2 to 5, falls to 4 mg/ml at pH 7 (near isoelectric pH).[6] Thus it is more soluble in acidic pH and slightly soluble at neutral or alkaline condition (intestinal environment). Hence an attempt will be made to develop gastro retentive delivery system of ofloxacin which would increase the bioavailability of ofloxacin and also to reduce frequency of administration, thereby improving patient compliance and therapeutic efficacy.

MATERIALS AND METHODS:

Materials: Ofloxacin was procured from AD Life Sciences Lab and HPMC K 15M, HPMC K 100M, Sodium bicarbonate, Micro crystalline cellulose, Magnesium stearate & Talc was provided from SD Fine Chemicals Ltd., Mumbai.

Methods:

Formulation and Preparation of Ofloxacin floating tablets:

All the formulations were prepared by direct compression method using different viscosity grades of HPMC polymers in various ratios as shown in Table-1. Ofloxacin and all other ingredients were individually passed through sieve ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method.

Evaluation of tablets[7]:

The formulated tablets were evaluated for the following physicochemical characteristics:

General appearance: The formulated tablets were assessed for its general appearance and observations were made for shape, color, texture and odor.

Bulk density:

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring pre sieved granules into a graduated cylinder via a large funnel and measure the volume and weight.

$$\textbf{Bulk density} = \frac{\textbf{weight of granules}}{\textbf{Bulk volume of granules}}$$

Bulk density was expressed in g/cc.

Tapped density: Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

$$\textbf{Tapped density} = \frac{\textbf{weight of granules}}{\textbf{Tapped volume of granules}}$$

Carr's Index (CI): Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

$$\textbf{CI} = \frac{\textbf{(TD-BD) x100}}{\textbf{TD}}$$

Where TD = Tapped density
BD = Bulk density

Hausner's Ratio: It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

Hausner's Ratio = Tapped density / Bulk density

Angle of repose: The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The method used to find the angle of repose is to pour the powder ion a conical heat on a level, flat surface and measure the included angle with the horizontal.

$$\textbf{Tan}\theta = \textbf{h/r}$$

Where, h= height of the heap, r= Radius of the heap

Drug content: The 20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of Ofloxacin was transferred in to a 100 ml volumetric flask and the volume adjusted to 100ml with 0.1N HCl. Further 1ml of the above solution was diluted to 100 ml with 0.1N HCl and the absorbance of the resulting solution was observed at 221 nm.

***In vitro* Buoyancy studies[8]:**

The in *vitro* buoyancy was determined by floating lag time, and total floating time. The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the tablet constantly floats on the dissolution medium was noted as the Total Floating Time respectively (TFT).

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 as 0.1N HCl at 37±0.5°C. After 0.5, 1, 2, 3, 4, 5, and 6h, each dissolution basket containing tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed on the analytical balance (Schimdzu, AX 120). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula

$$\text{Swelling index} = \frac{\text{(Wet weight of tablet – Dry weight of tablet)}}{\text{Dry weight of tablet.}}$$

Dissolution Study[9]: The 900ml 0f 0.1 HCl was placed in the vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37 $\pm$ 0.5°C. Tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 8 hours at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fluid was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically at 221 nm.

Release Kinetics:

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, diffusion and Peppa's- Korsemeyer equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppa's-Korsemeyer equation.

RESULTS AND DISCUSSION:

The objective of the present study was to prepare Floating tablets of Ofloxacin. These were developed to prolong the gastric residence time and to increase the drug bioavailability. Ofloxacin was chosen as a model drug because it is better absorbed in the stomach than the lower gastro intestinal tract. The tablets were prepared by direct compression technique, using polymers such as HPMCK15M, HPMC K100M and other standard excipients.

Tablets were evaluated for physical characteristics such as hardness, floating capacity and weight variation. The in *vitro* release characteristics were evaluated for 12hrs. Totally 8 different formulations of Ofloxacin were prepared by using two different polymers like HPMC K15M, HPMC K100M and diluent microcrystalline cellulose in different concentrations. The amount of drug released from all the formulations depends upon the concentration of the polymer used. Finally, the retardant effect of the polymer on the drug release can be indicated as HPMC K100M > HPMC K15M. Swelling is crucial in determining the release rate. A direct correlation between swelling and drug release was observed and the swelling indices were increased with increase in polymer concentration. Among all the formulations the F8 formulation containing HPMC K100M shows the best result of swelling index. Among all the formulations the F8 formulation containing HPMC K100M shows the best result. The result was satisfactory (Tables 14,15,16,17 figure-16, 17, 18, 19) to examine the release mechanism of Ofloxacin floating tablets, the results were analyzed according to Higuchis equation. Release rate of Ofloxacin from the optimized formulation (F8) was found to follow Zero order kinetics (correlation coefficient, r^2 value 0.8783).

Table 1: Composition of different formulations

Formulation No.	F1	F2	F3	F4	F5	F6	F7	F8
Ofloxacin(mg)	200	200	200	200	200	200	200	200
HPMC K15M (mg)	50	100	150	200	---	---	---	---
HPMC K100M (mg)	---	---	---	---	50	100	150	200
$NaHCO_3$ (mg)	45	45	45	45	45	45	45	45
Mag. Stearate(mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc(mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Microcrystalline cellulose (mg)	150	100	50	--	150	100	50	--
Total (mg)	450	450	450	450	450	450	450	450

Table 2: Pre Formulation parameters of ofloxacin tablets blend.

Formulation code	Bulk density(g/cc)	Tapped density(g/cc)	Carr'index (%)	Hausners ratio	Angle of repose(θ)	Flow properties
F1	0.214	0.251	14.74	1.17	25.49	Good
F2	0.308	0.364	15.38	1.18	26.24	Good
F3	0.276	0.322	14.28	1.16	29.05	Good
F4	0.521	0.629	17.17	1.20	33.65	Fair
F5	0.324	0.376	13.82	1.16	29.25	Good
F6	0.320	0.397	19.39	1.24	32.27	Fair
F7	0.518	0.627	17.38	1.21	33.21	Fair
F8	0.341	0.388	12.11	1.13	26.97	Free flowing

Table 3: Quality Control Parameters of Ofloxacin floating Tablets

Formulation No.	Avg. Weight (Mean± S.D) (n=20)	Hardness (kg/cm^2) (n=3)	Thickness (mm)	Friability (Mean±S.D) (n=20)	% Drug content (mg)	Buoyancy Lag time (min)	Total floating Time(hrs)
F1	453±0.6	7.2±0.2	3.4	0.546	97±0.7	3min 36sec	4.2
F2	450±0.9	7.5±0.2	3.35	0.612	99±0.5	4min 43sec	5.1
F3	447±0.3	8.0	3.21	0.827	100±0.6	5min 56sec	4.9
F4	451±0.4	7.6±0.2	3.36	0.611	99±0.6	4min 21sec	5.8
F5	456±0.8	7.6±0.2	3.3	0.625	99±0.6	4min 21sec	5.3
F6	446±0.8	7.3±0.4	3.33	0.655	98±0.5	3min 56sec	8.2
F7	443±0.4	8	3.2	0.711	100±0.3	5min	9.8
F8	449±0.9	7.7±0.5	3.25	0.702	99±0.4	2min 32sec	12

Table 4: Swelling index profile of Ofloxacin floating tablet formulations

S.NO	Formulation code	Swelling index
1	F1	65.65
2	F2	70.21
3	F3	74.21
4	F4	81.03
5	F5	78.23
6	F6	85.48
7	F7	92.87
8	F8	107.14

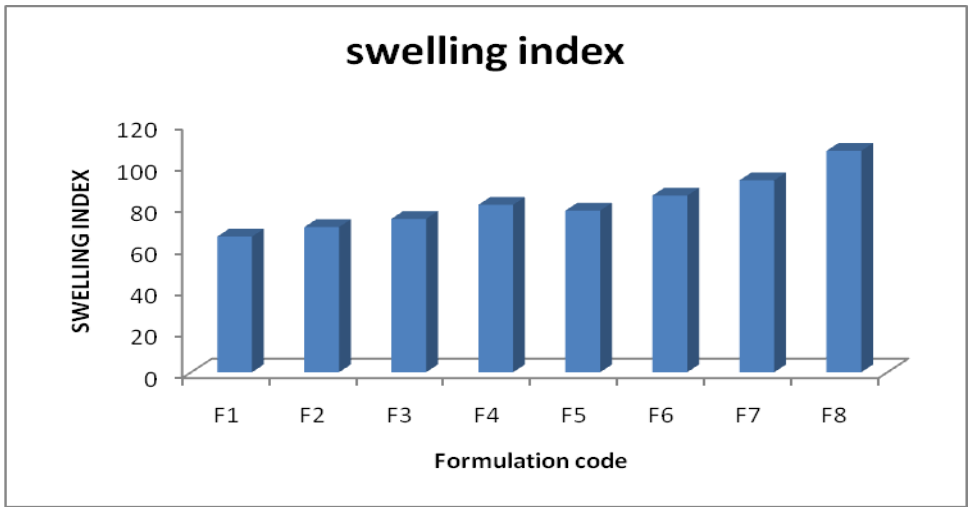

Fig 1: Swelling index of the floating tablets

Table 5: Dissolution data of Ofloxacin tablets prepared with HPMC K15M in different concentrations

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	62.45	58.32	45.56	42.67	50.65	48.34	42.34	37.34
2	76.56	74.12	68.34	63.76	68.54	61.54	55.47	46.23
3	83.21	79.45	76.32	73.54	76.54	68.45	62.56	52.04
4	98.21	90.21	86.32	82.65	81.25	75.56	68.24	57.54
5		97.56	98.45	89.32	98.21	82.34	75.56	62.42
6				97.76		89.21	82.54	69.32
8						97.69	91.24	79.53
10							98.67	89.61
12								98.87

Fig 2: Dissolution graph for F1-F4

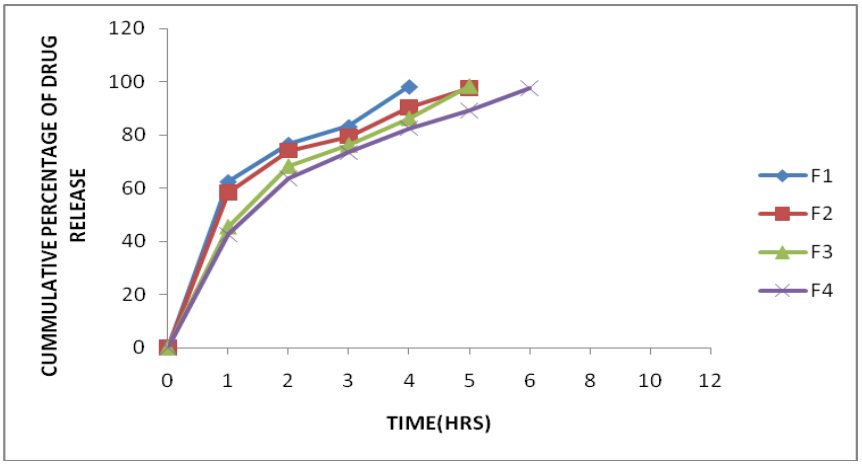

Fig 3: Dissolution graph for F5-F8

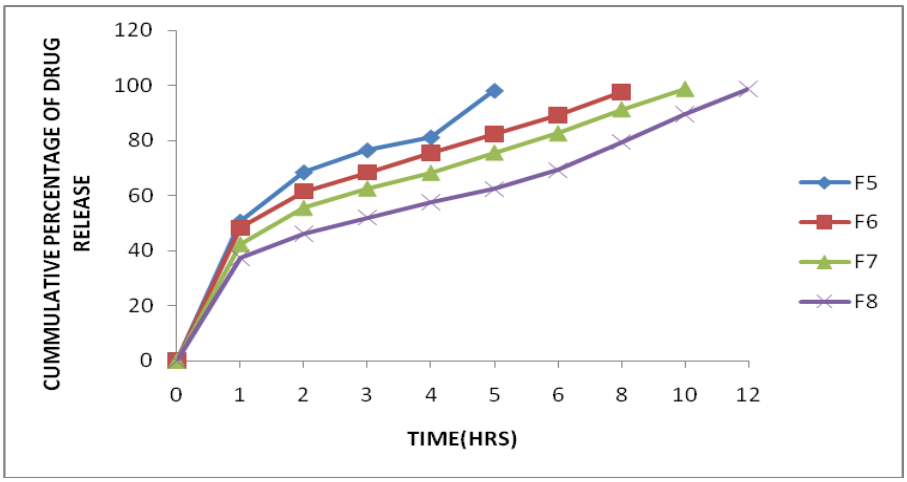

Table 6: Release kinetics: Coefficient of correlation (r) values of different batches of Ofloxacin floating tablets

Release Kineitcs				
	Zero	**Higuchi**	**Peppas**	**First**
	Q Vs T	Q Vs √T	Log C Vs Log T	Log % Remain Vs T
Slope	0.1127	3.2243	0.3924	-0.0237
Intercept	24.8094	9.5815	0.8473	2.9237
Correlation	0.9372	0.9948	0.9899	-0.9047
R 2	0.8783	0.9896	0.9800	0.8186

Higuchi plot showed an r^2 valve of 0.9896 for formulation F8 suggesting that the diffusion plays an important role in the controlled release. The data was fitted to Korsemeyer equation; and the value of diffusion exponent 'n' (0.39) indicated that the drug release shows fickian diffusion.

CONCLUSION:

The Ofloxacin is a quinolone/fluoroquinolone antibiotic. Ofloxacin is bactericidal and its mode of action depends on blocking of bacterial DNA replication by binding itself to an enzyme called DNA gyrase, which allows the untwisting required to replicate one DNA double helix into two.. In this study Ofloxacin tablets were prepared by using different polymers like HPMC K15M and K100M. Eight formulations of floating tablets of Ofloxacin were developed by direct compression technique. The F8 formulation was found to be best of all the trials showing the sustainity in drug release up to 12hrs. The best formulation F8 can successfully be employed as a controlled release floating drug delivery system. The floating tablets can control the fluctuations in the plasma drug concentration, increase the gastric residence time and eventually improve the bioavailability of the drug. The FTIR study ruled out the drug-polymer interaction.

REFERENCES:

1. Overington JP, Al-Lazikani B, Hopkins AL: How many drug targets are there? Nat Rev Drug Discov. 2006, 5(12): P.993-996.
2. Imming P, Sinning C, Meyer A: Drugs, their targets and the nature and number of drug targets. Nat Rev Drug Discov. 2006, 5(10): P. 821-834.
3. Turner AK, Nair S, Wain J: The acquisition of full fluoroquinolone resistance in Salmonella Typhi by accumulation of point mutations in the topoisomerase targets. J Antimicrob Chemother. 2006, 58(4): P.733-740.
4. Ishiguro F, Toho M, Yamazaki M, Matsuyuki S, Moriya K, Tanaka D, Isobe J, Kyota Y, Muraoka M: [Mutations of gyrA gene and parC gene in fluoroquinolone-resistant Escherichia coli isolates from sporadic diarrheal cases] Kansenshogaku Zasshi. 2006, 80(5): P.507- 512.

5. Drlica K, Zhao X: DNA gyrase, topoisomerase IV, and the 4-quinolones. Microbiol Mol Biol Rev. 1997, 61(3): P. 377- 392.
6. Robinson Jr, Lee V.H.L, Controlled drug delivery: Fundamentals and Applications, 2nd ed. Marcel Dekker, New York: 1978 P.24-36.
7. Sheth, P.R., Tossounian, J., The hydro dynamically balanced system (HBSTM): a novel drug delivery system for oral use, Drug Dev. Ind. Pharm., 1984: 10: P.313-339.
8. Gutierrez-rocca, J., Omidian, H., Shah, K., Progress in Gastro retentive drug delivery systems, Business Briefing,Pharmatech, 2003: P.152-156.
9. Hou, S.Y., Cowles, V.E., Berner, B., Gastric retentive dosageforms: a review, Crit. Rev. Ther. Drug Carrier Syst., 2003: 20(6): P.459-497.
10. Brunton Laurence L., Lazo John S., Parker Keith L, Goodman & Gilman's the pharmacological basis of therapeutics. Eleventh Edition: Mc Graw Hill Medical publication divison; 1866: P. 971-972,
11. Chein Y.W, Novel Drug Delivery Systems, 2nd ed.: Marcel Dekker; New York: 1992, P.4-56.
12. Banker G.S, Rhodes C.T, Modern Pharmaceutics. 3rd ed. Marcel Dekker, New York: 1996: P.678-721.
13. Vyas S.P, Khar R.K, and Controlled Drug Delivery: Concepts and Advances, 1st ed. Vallabh prakashan, New Delhi: 2002: P.345-376.
14. P.G.Yeole, Floating Drug Delivery System: Need and Development, Ind. J. Pharm. Sci., 2005: 67(3); P. 265-272.
15. Shweta Aurora, Floating Drug Delivery: A Review, AAPS Pharmscitech. 2005: 47(11); P.268-272.
16. Desai S, Bolton S. A Floating Controlled Release System: In-vitro and In-vivo evaluation, J. Pharm. Res., 1993: 10; P.1321-1325.
17. Narendra C, Srinath MS, Babu G. Optimization of Bilayer Floating Tablet Containing Nevirapineas a Model Drug for Gastric Retention. AAPS Pharm Sci Tech 2006; P.7.
18. Srivastava AK, Wadhwa S, Ridhurkar D, Mishra B. Oral sustained delivery of atenolol from floating matrix tablets-formulation and in vitro evaluation. Drug Dev. Ind. Pharm 2005; 31: P.367-74.
19. Dave BS, Amin AF, Patel MM. Gastro retentive Drug Delivery System of Ranitidine Hydrochloride: Formulation and In Vitro Evaluation. AAPS Pharm. Sci. Tech 2004; P.5.
20. Dalavi V.V. and Patel J. S. Gastro retentive drug delivery system of an antiretroviral agent/Int. J. Pharm Tech Res.2009, 1(4) , P 1678-1684.
21. M. Sivabalan, T Punitha Vani, Phaneendhar Reddy, Vasudevaiah, Anup Jose and G Nigila. Formulation and evaluation of gastro retentive Glipizide floating tablets. Int. j. compre. Pharmacy 2011, 1 (03).
22. Sunil K. Jain Govind P. Agrawal and Narendra K. Jain, Evaluation of Porous Carrier-based Floating Orlistat Microspheres for Gastric Delivery AAPS Pharm. SciTech. 2006; 7(4).