

To Prepare and Evaluate Floating, Gastroretentive Tablet of Ofloxacin

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Abstract – The aim of the present investigation was to develop and evaluate gastro retentive drug delivery tablets (GRDDTs) of Ofloxacin. Ofloxacin (OFX) is a synthetic broad spectrum analog of second generation fluoroquinolone antibiotic. It is used for the treatment of urinary tract, prostate, skin, urinary and respiratory tract infections. Gastro retentive dosage forms (GRDF) enable prolonged and continuous input of the drug to parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. A new strategy is proposed for the development of gastro retentive dosage forms for ofloxacin preferably once daily. The design of the delivery system was based on the sustained release formulation, with floating and swelling features in order to prolong the gastric retention time of the drug delivery systems. The optimized Tablet showed better sustained drug release and which also had good floating properties and fitted best to be Higuchi model with R^2 value of 0.955. FT-IR result showed that there is no drug excipient interaction. In vivo studies were conducted of loaded tablets to examine the increased gastric residence time of the prepared tablets. Floating tablets of Ofloxacin have shown controlled release thereby proper duration of action at a particular site and are designed to prolong the gastric residence time after oral administration. The study revealed that the tablet remained in the stomach for 310 ± 10 min which indicates the increase in the gastric residence time for the effective localized action of the ofloxacin in the treatment of *Helicobacter pylori* caused peptic ulcer.

Keywords – Gastro Retentive Drug Delivery, Ofloxacin, Gastro Retentive Tablet Evaluation.

I. INTRODUCTION

Gastroretentive drug delivery systems:

The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance. Therefore, extended release DDS possessing gastric retention properties may be potentially useful.

Need for gastro retention:

- Drugs that are absorbed from the proximal part of the GIT.
- Drugs that are less soluble or are degraded by alkaline pH they encounter at lower part of GIT.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained delivery to the stomach to treat certain conditions.

Advantages of gastroretentive drug delivery systems:

- ❖ **Enhanced bioavailability:** Enhanced bioavailability of the drug by gastroretentive drug delivery system.

- ❖ **Enhanced first-pass biotransformation:** The pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes in a sustained manner.
- ❖ **Sustained drug delivery/reduced frequency of dosing:** Drugs with relatively short biological half-life, sustained and slow input from sustained may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.
- ❖ **Reduced counter-activity of the body:** In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.
- ❖ **Extended time over critical (effective) concentration:** For certain drugs that have non-concentration dependent pharmacodynamics, such as betalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic

concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

- ❖ **Minimized adverse activity at the colon:** This Pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

Site specific drug delivery: The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. Reduces side effects that are caused by the drug in the blood circulation.

The present study concerns the development of floating tablets of ofloxacin which were designed to prolong the gastric residence time after oral administration. Ofloxacin is a fluoroquinolone antibacterial agent which is highly effective against gram positive and gram negative bacteria. Ofloxacin floating tablets were prepared by wet granulation method incorporating natural polymer guar gum with sodium bicarbonate as gas generating agent and were evaluated for parameters such as Weight variation, Hardness, Friability, Drug content, Swelling index, in vitro buoyancy study, in vitro drug release study.

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. To overcome these problems, different approaches have been proposed to retain dosage form in stomach. These include bioadhesive or mucoadhesive 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. 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. 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.

II. MATERIAL AND METHOD

Ofloxacin was obtain as gift sample from Zyduscadila. Guar gum, Sodium bicarbonate, PVP K-30, Ethanol,

Talcum, Magnesium stearate These entire chemicals used were of analytical grade.

III. PROCEDURE

Identification of drug:

Fourier Transform Infra Red Spectroscopy (FT-IR): FT-IR stands for Fourier Transform Infrared, the preferred method of infrared spectroscopy. In infrared spectroscopy, IR radiation is passed through a sample. Some of the infrared radiation is absorbed by the sample and some of it is passed through (transmitted). The resulting spectrum represents the molecular absorption and transmission, creating a molecular fingerprint of the sample. Like a fingerprint no two unique molecular structures produce the same infrared spectrum. This makes infrared spectroscopy useful for several types of analysis. Fourier Transform Infrared (FT-IR) spectrometry was developed in order to overcome the limitations encountered with dispersive instruments. The samples were scanned in 400-4000 wave number range, using KBr pellet technique.

Determination of λ_{max} :

First stock solution of ofloxacin (100mg/100ml=1000 μ g/ml) prepared by using 0.1N HCl. For the determination of λ_{max} of ofloxacin, 10 μ g/ml solution of ofloxacin drug was prepared from the stock solution by dilution with 0.1N HCl. With the help of UV spectrophotometer (Shimadzu-1800, Japan) the maximum absorption of ofloxacin drug solution was determined at 200-400 nm by wavelength scanning. The maximum absorption at particular wavelength taken as λ_{max} (294nm) value for a given ofloxacin drug.

Preparation of standard curve:

The prepared stock solution was further diluted with 0.1N HCl to get different concentrations (2,4,6,8,10 μ g/ml) to construct standard curve for ofloxacin. The absorbance of each solution was measured at 294nm for ofloxacin against 0.1N HCl as blank. The standard curve for ofloxacin was plotted by taking concentration of drug on X-axis and absorbance on Y-axis. Such drug concentrations are obeying Beer's Lambert law.

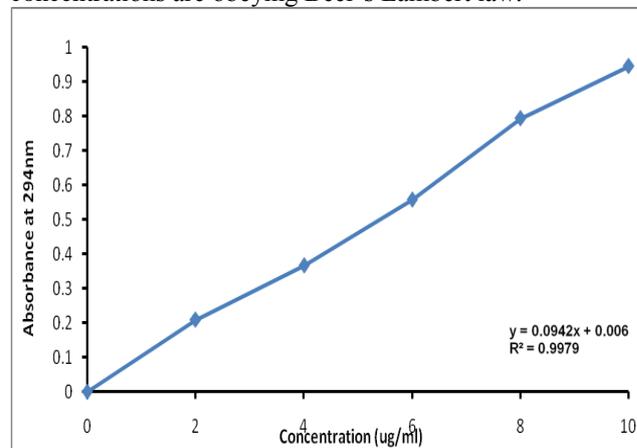


Fig.1. Standerd curve of Ofloxacin in 0.1 N HCl

IV. METHOD OF PREPARATION: (WET GRANULATION)

Floating tablets containing ofloxacin were prepared by wet granulation technique. The desired quantities of ofloxacin, guar gum and sodium bicarbonate are weighed as per the working formula. The powders are thoroughly mixed in mortar with pestle to obtain uniform mix of the material. A small quantity of granulating medium (5% solution of PVP k-30 in Ethanol) is taken and transferred to the mortar containing powders and triturated. This procedure is continued until smooth dough is formed. The wet mass pass through 16 mesh sieve and granules dried in hot air oven at 60°C for 1 hr. Dried granules pass through 22 mesh sieve. Now add talc, magnesium stearate and remaining starch in granules and mix in polythin bag for 3 min.

V. EVALUATION OF GRANULES

1. Angle of repose:

It was measured by fixed funnel method. The fixed funnel method employ a funnel that was secured with its tip at a given height, above graph paper that was placed on a flat horizontal surface. Granules were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. Thus, with r being the radius of the base of the conical pile.

$$\theta = \tan^{-1} \left(\frac{h}{r} \right)$$

Where, θ = Angle of repose
 h = Height of pile
 r = Radius of pile

Table 1: Standards of Angle of repose

Flow Property Depending upon Angle of Repose (θ)	
Angle of repose	Type of Flow
25-30	Excellent
31-35	Good
36-40	Fair
41-45	Passable
46-55	Poor
56-65	Very poor
> 66	Very very poor

2. Bulk Density:

The bulk density of a powder is the weight of the powder divided by the volume it occupies, normally expressed as gm/ml or kg/l or gm/cm³.

3. Tapped Density:

The bulk density of a powder is the weight of the powder divided by the tapped volume it occupies, normally expressed as gm/ml or kg/l or gm/cm³.

4. Hausner's Ratio:

It is the ratio of tapped density to bulk density.

Table 2: Standards of Hausner's ratio

Flow Property Depending upon Hausner's ratio	
Hausner's ratio	Type of Flow
1.0 – 1.11	Excellent
1.12 – 1.18	Good
1.19 – 1.25	Fair
1.26 – 1.34	Passable
1.35 – 1.45	Poor
1.46 – 1.59	Very poor
> 1.60	Very very poor

5. Carr's Index:

The Carr index is frequently used in pharmaceuticals as an indication of the flow ability of a powder

Table 3: Standards of Carr's Index

Flow Property Depending upon % Carr's Index	
% Carr's Index	Type of Flow
< 10	Excellent
11 – 15	Good
16 – 20	Fair
21 – 25	Passable
26 – 31	Poor
32 – 37	Very poor
> 38	Extremely poor

6. Percentage Compressibility:

It is an important measure that can be obtained from bulk density measurements. The following formula was used to compute the percent compressibility.

Table 4: Standards of % compressibility

Flow Property Depending upon % Compressibility	
% Compressibility	Type of Flow
< 10	Excellent
11 – 15	Good
16 – 20	Fair
21 – 25	Passable
26 – 31	Poor
32 – 37	Very poor
> 38	Extremely poor

7. Percentage Yield:

The obtained Beads of each formulation were collected and weighed to determine production yield (PY) using following equation (Thomas M. et. al., 2010).

$$\text{Practical yield/Theoretical yield} \times 100$$

8. Buoyancy study:

Floating properties of beads were evaluated using USP dissolution apparatus containing SGF (pH 1.2). Beads (one hundred) of each batch were placed in 100 ml of 0.1 N HCl agitated at 100 rpm, temperature was maintained at

$37 \pm 0.5^{\circ}\text{C}$. The number of sinking beads was observed visually. The percentage of floating beads was calculated according to the following equation:

$$F (\%) = \frac{NF}{NT} \times 100$$

F: floating percent; NF: number of floating beads; NT: total number of the beads. (Yao Huimin et. al., 2011).

9. Drug entrapment and entrapment efficiency:

Accurately weighed quantities of approximately 50 mg beads were dissolved in 5 ml 0.1 N HCL (simulated gastric fluid, pH 1.2) and then boil for 20 minute. The solution was centrifuged at 5000 rpm for 30 min and drug concentration was assayed at 289 nm using a spectrophotometer. The drug concentration in the sample was used to calculate the percentage drug loading by dividing the weight of beads initially dissolved and the encapsulation efficiency was calculated:

$$DL (\%) = \frac{WD}{WT} \times 100$$

DL: drug loading; WD: the weight of the drug loaded in the beads; WT: the total weight of the beads.

$$EE (\%) = \frac{WA}{WT} \times 100$$

EE: encapsulation efficiency; WA: actual drug content; WT: theoretical drug content (Yao Huimin et. al., 2011).

10. Swelling study:

Swelling studies of the beads were carried out by taking Known weight of the Beads and immersed in excess of 0.1NHCL for definite time interval and then beads were removed and weighed immediately at regular time interval. The percentage swelling (P_s) of the beads was calculated as:

$$P_s = \frac{W_s - W_d}{W_d} \times 100$$

Where W_s is the weight of swollen beads and W_d is the weight of dried beads. (Pasparakis George et. al., 2006)

VI. Evaluation of Tablets:

1. Thickness:

The thickness of the tablets was determined by using vernier calipers. Randomly 10 ofloxacin tablets were used for determination of thickness that expressed in Mean \pm SD.

2. Hardness:

Randomly 10 tablets form conventional ofloxacin tablets were tested for the diametrical crushing strength using the Monsanto hardness tester. The crushing strengths (hardness values) were determined and reported.

3. Weight variation:

Weigh individually 20 tablets selected at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table and none deviates by more than twice that percentage.

4. Friability:

The friability of the tablets was tested by an Electrolab EF-2 Roche-type friabilator at a speed of 25 rpm for 4 minutes. The acceptable formulations from these tests were then promoted towards the dissolution tests.

5. Drug content:

For drug content 10 tab of average weight 546.75mg are taken and crushed to get powder form. Therefore, 100mg ofloxacin equivalent tablet powder = $(546.75 \times 100)/200 = 273.37\text{mg}$ tablet powder dissolved in 100ml of 0.1N HCl diluted up to 100 times. Solution should be filtered before taking absorbance. Then take the absorbance of this solution at 294nm.

6. Disintegration Test:

The assembly to be attached to the device for raising and lowering it smoothly at a constant frequency of between 28 and 32 cycles per minute through a distance of 50 to 60 mm. The assembly is suspended in 1-litre of 0.1N HCl in a beaker maintaining the temperature at $37^{\circ} \pm 2^{\circ}$. Place 6 tablets into six tubes. Suspend the assembly in the beaker containing the 0.1N HCl and operate the apparatus for the specified time (2hrs.). Replace the 0.1N HCl to the mixed phosphate buffer pH 6.8 and run the assembly for 60 mins. The tablets pass the test if all of them have disintegrated. If 1 or 2 tablets fail to disintegrate, repeat the test on 12 additional tablets; not less than 16 of the total of 18 tablets tested disintegrate. If the tablets adhere to the disc and the preparation under examination fails to comply, repeat the test omitting the disc. The preparation complies with the test if all the tablets in the repeat test disintegrate.

7. In-vitro Dissolution study:

Dissolution test was performed on two tablets from the each formulations accepted by friability and hardness (crushing strength) tests. The USP apparatus 2 (ElectrolabTDT-06P Dissolution Tester) at a speed of 50rpm, with 900 ml 0.1N HCl as the dissolution medium was used, and samples were taken after 1, 2, 3.....20 hrs. The amounts of dissolved ofloxacin were then determined by spectrophotometer at 294 nm, using filtered portions of the samples. The release in any time was obtained by calculating the mean cumulative percent release of the two tablets tested. These test conditions were according to test 2 in the monograph of ofloxacin conventional tablet in USP XXIV. The percent drug release was then graphed against time and the release profiles studied.

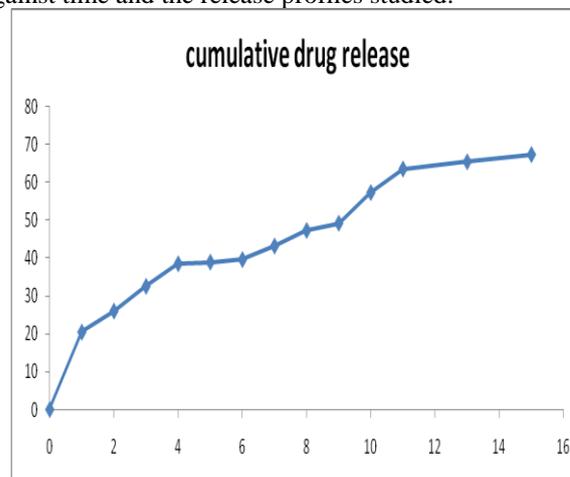


Fig.2. Cumulative drug release of Ofloxacin

8. Drug release kinetics:

The release kinetic was studied by various kinetic models as zero order plot, first order plot, Higuchi plot and Korsmeyer-peppas. In order to identify a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model. It is therefore clear that only a combination of accurate and precise data with models accurately depicting the physical situation will provide an insight into the actual mechanism of release. To analyse the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted into Zero order, First order, Higuchi matrix, Korsmeyer-Peppas. By comparing the R^2 -values obtained from the above equations, the best-fit model was selected

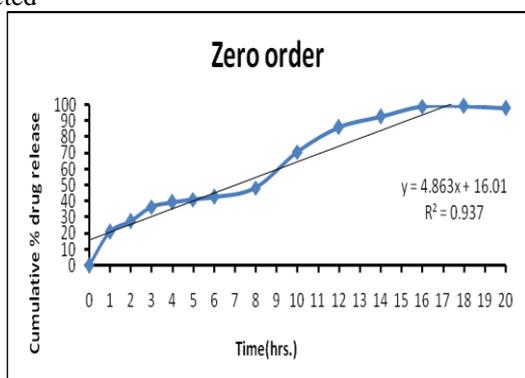


Fig.3. Zero order graph

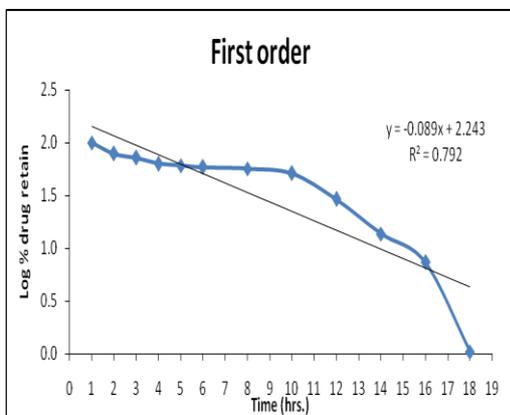


Fig.4. First order graph

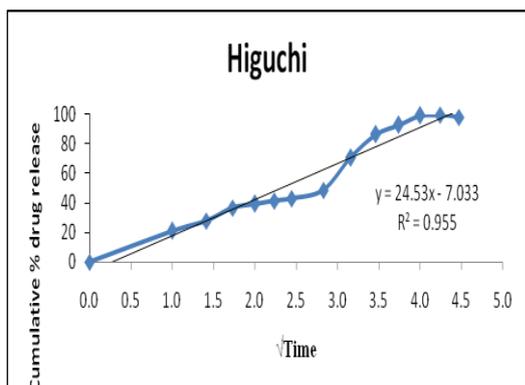


Fig.5. Higuchi graph

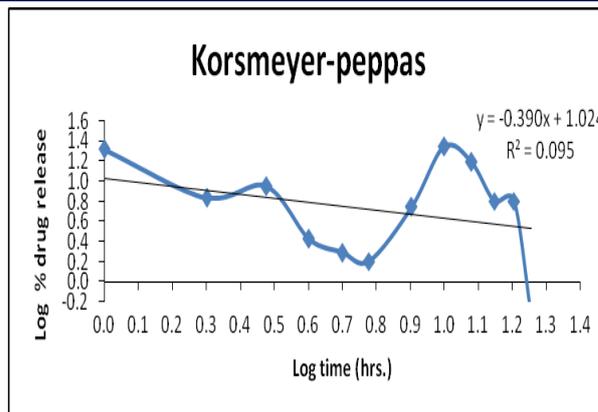


Fig.6. Korsmeyer-peppas graph

VII. RESULT AND DISCUSSION

The aim of the study was to develop and physically characterize the floating Tablet of Ofloxacin. Ofloxacin is a fluoroquinolone antibacterial agent which is highly effective against gram positive and gram negative bacteria. 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). Thus it is more soluble in acidic pH and slightly soluble at neutral or alkaline condition (intestinal environment). Hence, in the present study natural polymer guar gum would be used along with gasgenerating agent like sodium bicarbonate for the formulation of floating tablets of ofloxacin which would increase the bioavailability of Ofloxacin and also to reduce frequency of administration, thereby improving patient compliance and therapeutic efficacy. Drug and formulations were subjected for the compatibility study using FTIR. Result showed that All the important functional group frequencies for Ofloxacin were present in the spectral peaks of the formulations indicating the compatibility of the drug with the polymers. The standard calibration curve of ofloxacin in 0.1 N HCl (pH 1.2) was found to be linear in the Beer's range. Polymer Guar gum were used for the present study. Formulation were evaluated for production yield, particle size, swelling index, buoyancy, drug entrapment efficiency, morphology, *in vitro* release characteristics. Formulation were evaluated for entrapment efficiency. Results of entrapment efficiency showed that the entrapment efficacy of granules was dependent upon polymer concentration. Entrapment efficacy increased with increase in the concentration of the polymer. This may be because of increase in viscosity of polymeric solution, which in turn increases the crosslinking of polymer and prevents drug diffusion out of the system. The swelling behavior of alginate polymer was found to be an important factor in controlling the release of the drug from the bead system. Results showed that the swelling was related to the polymer concentration with swelling being more significant for granules containing high polymer content. Formulation showed satisfactory floating characteristics and subjected for *in vitro* release

study using pH 1.2 0.1N HCl in USP apparatus II (paddle type). The results indicated that formulation sustain the drug release better up to 12 hr. To analyze the mechanism of drug release from the tablets, the *in vitro* release data was fitted into various release models. It was observed that the release of the drug followed Higuchi model.

VIII. CONCLUSION

Recent scientific and patent literature shows increased interest in academics and industrial research groups regarding novel dosage forms that can be retained in the stomach for prolonged and predictable period of time and the most feasible approach for this is to control the gastric residence time using gastroretentive dosage forms which will provide new and important therapeutic option. But the problem can arise if there is a narrow window for drug absorption in the GIT or drug is unstable in the intestinal fluid. So the development of oral controlled dosage form is not just to prolong the drug release but also to ensure the presence of dosage form in the stomach or upper GIT so that drug is released and absorbed for the desired period of time. Controlling the residence of a drug delivery system in a particular region of the gastrointestinal tract, can utilize several approaches: intragastric floating systems, high density systems, mucoadhesive systems, magnetic systems, unfoldable, extended or expandable systems and superporous, biodegradable hydrogel systems. The formulated Ofloxacin tablet was found to have better floating efficacy and invitro release profile characteristics. Hence it may represent as a new alternative, natural and cheaper formulation of ofloxacin which may improve the patient compliance.

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