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FORMULATION AND EVALUATION OF FLOATING TABLETS OF OFLOXACIN

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ABSTRACT

Ofloxacin is a synthetic chemotherapeutic antibiotic of the fluoroquinolone drug class considered to be a second-generation fluoroquinolone. 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. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. To overcome the problem of conventional dosageforms ofloxacin effervescent floating tablets were developed in six different formulations (F1 to F6) by employing different grades of polymers and effervescent agent sodium bicarbonate. The formulations were evaluated for various physical parameters, buoyancy studies, dissolution parameters and drug release mechanisms. F6 formulation showed good physical parameters and gave slow and maximum drug release of ofloxacin spread over 24 hours and showed maximum similarity with marketed product in dissolution profile. Different kinetic models were applied to drug release data in order to evaluate release mechanisms and kinetics.

INTRODUCTION: Ofloxacin is a new fluoroquinolone derivative with a broad spectrum of activity against a wide variety of bacteria.

Ofloxacin is a synthetic chemotherapeutic antibiotic of the fluoro-quinolone drug class considered to be a second-generation fluoroquinolone. Ofloxacin can be used for the treatment of acute exacerbations of chronic bronchitis, community-acquired pneumonia, skin and skin structure infections (uncomplicated), urethral and cervical gonorrhea (acute, uncomplicated), urethritis and cervicitis (non-gonococcal), mixed infections of the urethra and cervix, pelvic inflammatory disease (acute), cystitis (uncomplicated), urinary tract infections (complicated), prostatitis.

The bioavailability of ofloxacin in the tablet form is approximately 98% following oral administration reaching maximum serum concentrations within one to two hours. Between 65% and 80% of an administered oral dose of ofloxacin is excreted unchanged via the kidneys within 48 hours of dosing. Therefore, elimination is mainly by renal excretion. Plasma elimination half-life is approximately 4 to 5 hours in patients. 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, it is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa [1].

Several drug delivery systems with prolonged gastric retention time have been investigated [2-4]. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion [5, 6], flotation [7], sedimentation [8, 9], expansion [10, 11], modified shape systems [12, 13], or by the simultaneous administration of pharmacological agents [14, 15]. The floating system in particular has been extensively researched, mainly because the floating system does not adversely affect the motility of the GI tract. The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' ('HBS').

Since, they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3-4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents Small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves [16]. Many results have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved clinical situations.

MATERIALS AND METHODS:

Materials: Ofloxacin received as a gift sample from IPCA pharmaceutical limited, Mumbai. Hydroxy propyl methyl cellulose (HPMC) 100K (Yarrow chemicals, Mumbai), sodium bi carbonate, polyvinylpyrrolidine, talc and magnesium stearate (S.d fine chemicals, Mumbai) were obtained and used as received. Zanocin commercial product of ofloxacin was purchased from local market.

Methods:

Preparation of Ofloxacin floating tablets: Ofloxacin tablets were prepared using wet granulation technique. The composition of different formulations of ofloxacin floating tablets is shown in **table 1**. All the intragranular ingredients except PVP were passed through sieve no. 40#. After sieving, all the ingredients were weighed accurately and mixed thoroughly following geometric method. Granulation was done with a solution of PVP K-30 in sufficient iso propyl alcohol. The granules passed through 8# were dried in conventional hot air oven at 45^0c.Drying of granules was stopped when samples reached a loss on drying (LOD) value less than 2%.the granules were sized through sieve 20# and lubricated with magnesium stearate and talc.

TABLE 1: COMPOSITION OF FLOATING TABLETS OF OFLOXACIN

S. No.	Composition	Quantity					
		F1	F2	F3	F4	F5	F6
1	Micro crystalline cellulose	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
2	Hydroxy propyl methyl cellulose(100K)	200 mg	175 mg	150 mg	150 mg	125 mg	135 mg
3	Poly vinyl pyrollidine	40 mg	40 mg	40 mg	40 mg	40 mg	80 mg
4	Sodium bi carbonate	80mg	100 mg	120 mg	100 mg	100 mg	100 mg
5	Magnesium stearate	10.4mg	10.3mg	10.2mg	9.8mg	9.3mg	10.3mg
6	talc	10.4mg	10.3mg	10.2mg	9.8mg	9.3mg	10.3mg

The above blend was then compressed using 10mm punch under CADMAK tablet punching machine at 4kg/cm^2 force.

Evaluation of ofloxacin floating tablets:

1. **Weight variation, Hardness, Friability and Content uniformity:** Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. Hardness of the tablets was tested using a Monsanto hardness tester. Friability of tablets was determined in Roche friabilator.

   Ofloxacin content in the tablets was estimated by using UV spectrophotometer at λ_{max} 294 nm in phosphate buffer (pH 1.2). The results of characterization are shown in **table 2**.

2. ***In Vitro* Buoyancy Studies**: The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing pH 1.2 buffers. The time required for the tablet to rise to the surface and float was determined as floating lag time. This test was performed on 3 tablets from each batch.

3. ***In-Vitro* Dissolution Studies:** The release rate of ofloxacin from floating tablets was determined using dissolution testing Apparatus USP II (paddle method). The dissolution test was performed using 900 mL of pH 1.2 buffer, at 37 ± 0.5°C and 50 rpm. A sample of 10ml was withdrawn from the dissolution apparatus at regular time intervals up to 24 hrs. These were filtered and diluted to a suitable concentration with pH 1.2 buffer. The samples were replaced with the same volume of fresh dissolution medium in basket. Absorbance of these solutions was measured at 294 nm using a UV/VIS spectrophotometer (JASCO). Cumulative percentage drug release was calculated using an equation obtained from a standard curve. y = 0.094x + 0.017.

4. **Analysis of Release Mechanism:** In order to examine the release mechanism of Ofloxacin from the prepared floating tablets of the optimized formulation (F6), the results of the dissolution study was examined in accordance to the kinetic models. The regression coefficient R^2 value nearer to 1 indicates the model fitting of the release mechanism. The results are shown in Table 3 and **Figure 2 to 5**.

5. **Comparison with Marketed Product**: The formulation (F6) *In-vitro* dissolution profiles were compared with marketed product Zanocin (Ofloxacin). The values of comparative *in-vitro* dissolution study of optimized formulation (F6) and marketed product were recorded in **figure 6**.

RESULTS AND DISCUSSION: The floating tablets of ofloxacin were formulated in six different batches F1 toF6. All formulations were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (1.2 pH buffer). It was observed that the gas generated is trapped and protected with gel, formed by hydration of polymer thus decreasing density of tablet below 1 and tablet becomes buoyant. The tablet swelled radially and axially during *in vitro* buoyancy studies. The prepared tablets of all the formulations were evaluated for physical characters like tablet hardness, friability, weight variation, buoyancy lag time, total floating time, assay and *In-vitro* drug release. The results were shown in **table 2**.

The weight variation was within range of ±5 % complying with pharmaceutical specifications. The hardness for formulations was found to be between 4.20-4.25 kg/cm^2 indicating satisfactory mechanical strength. The friability was below 1% for formulations 1, 2, 4, 5 & 6 but it exceeds 1% for formulation 3, which is an indication of less mechanical resistance for formulation 3, may be due to more amount of gas generating agent.

The content varied between 197.74 mg-199.01 mg in different formulations with coefficient of variation less than 2% indicating content uniformity in prepared batches. Floating lag time for F 1, F2, F3, F4, F5 & F6 was 75 sec, 45 sec, 15 sec, 37 sec, 32 sec and43 sec respectively. Total floating time for F1, F2, F4, F5 & F6 was 24hr, but it was 6 hr for F3 (as it disintegrated after 6 hrs). Increased amount of sodium bicarbonate was found to decrease floating lag time.

TABLE 2: PHYSICAL CHARACTERIZATION OF DIFFERENT FORMULATIONS

Code	Uniformity of weight (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (mg)	Floating lag time (sec)	Total floating time (hr)
F1	543.4	4.25	0.57	198.26	75	24
F2	533.9	4.20	0.54	197.92	45	24
F3	529.9	4.25	1.25	198.61	15	6
F4	511.2	4.23	0.46	197.74	43	24
F5	482.9	4.27	0.62	199.01	37	24
F6	534.7	4.25	0.51	198.87	52	24

It is evident from the *in vitro* dissolution data that increase in sodium bicarbonate increased the release rate but reduced the floating lag time, probably due to excess of carbon dioxide, disturbing monolithic tablet and as the amount of polymer decreasing the amount of drug release increasing. We can attribute release rate change to amount of polymer change and decrease in lag time to change in amount of sodium bicarbonate. The drug release from floating tablet was found to be 62% for formulation1, 84% for formulation 2, 92.8% for formulation4 and 97.9% for formulation6 at the end of 24 hr.

Formulation 5 showed 98.9% drug release at the end of 18 hrs itself, may be due to less amount of polymer whereas formulation 3 was disintegrated after 6 hrs may be due to increased porosity cause of decrease in polymer amount and increase in gas generating agent. This batch friability was also found out of IP specification. Maximum drug release of Ofloxacin spread over 24 hr was found in F6, Thus F6 formulation was said to be optimized formulation. The data obtained from *in vitro* dissolution studies of optimized formulation 6 and marketed formulation (MF) were fitted in different models viz. Zero order, First order, Higuchi model and Peppas model (**table 3**).

TABLE 3: KINETIC RELEASE DATA OF DIFFERENT MODEL FOR OPTIMIZED FORMULATION (F6) AND MARKETED FORMULATION (MF)

Zero Order (R^2)		First order (R^2)		Higuchi (R^2)		Korsmeyer-Peppas (R^2)		Korsemeyer-Peppas model (n value)	
F6	MF	F6	MF	F6	MF	F6	MF	F6	MF
0.892	0.936	0.976	0.975	0.974	0.982	0.977	0.978	0.617	0.504

For Marketed product and optimized formulation closer R^2 values were obtained in all models (i.e. Zero order, First order, Higuchi model and Korsemeyer-peppas model) whereas marketed formulation fitted well in higuchi model compared to optimized formulation. The value of exponent 'n' obtained is more than 0.5 in marketed formulation as well as in optimized formulation, hence as per n value of Korsmeyer & Peppas can be predicted that drug release mechanism follows non-Fickian law of diffusion. Slope values and R^2 values of different kinetic models of marketed formulation and optimized formulation were mentioned in table 3:

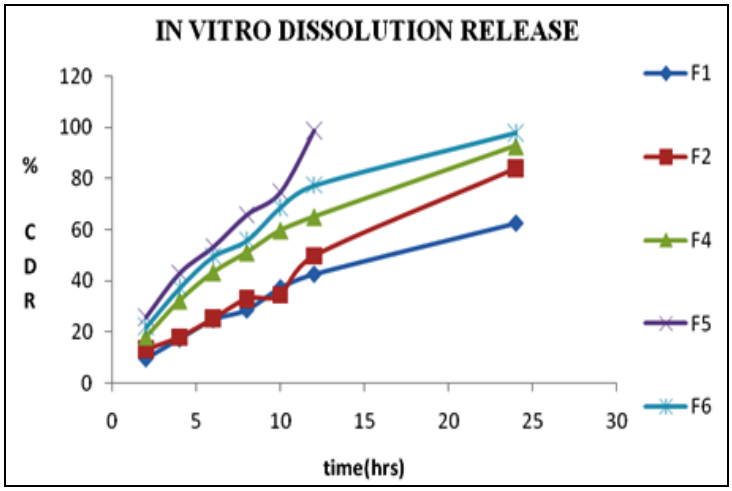

FIGURE 1: *IN-VITRO* DISSOLUTION PROFILE OF FORMULATIONS F 1 TO F 6 (% CDR = % cumulative drug release)

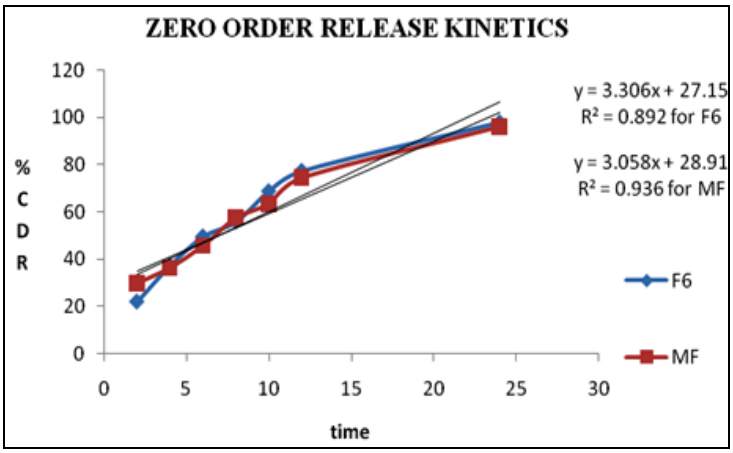

FIGURE 2: PLOT OF CUMULATIVE PERCENTAGE DRUG RELEASED VS. TIME OF OPTIMIZED FORMULATION AND MARKETED FORMULATION

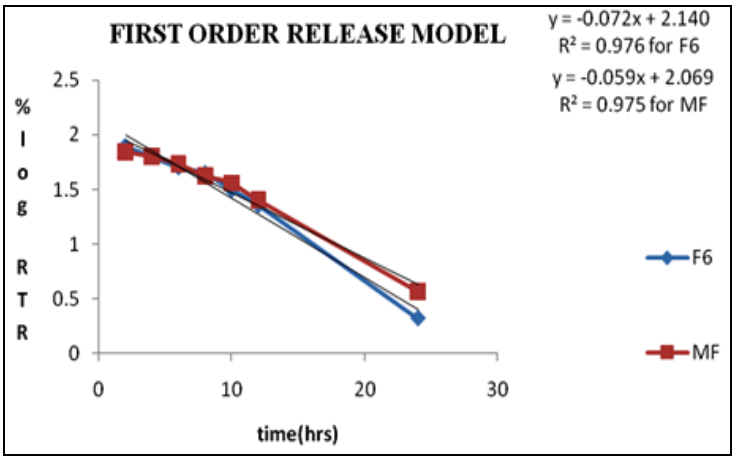

FIGURE 3: PLOT OF LOG CUMULATIVE PERCENTAGE DRUG RETAINED VS. TIME OF OPTIMIZED FORMULATION AND MARKETED FORMULATION (RTR= drug remaining to be released)

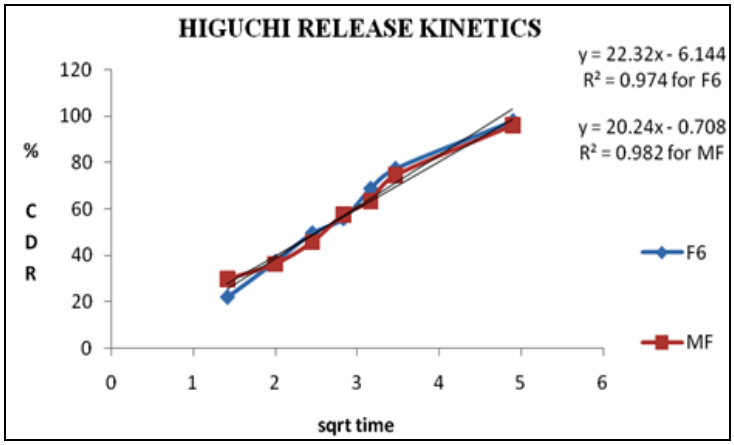

FIGURE 4: PLOT OF CUMULATIVE PERCENTAGE DRUG RELEASED VS. ROOT TIME OF OPTIMIZED FORMULATION AND MARKETED FORMULATION

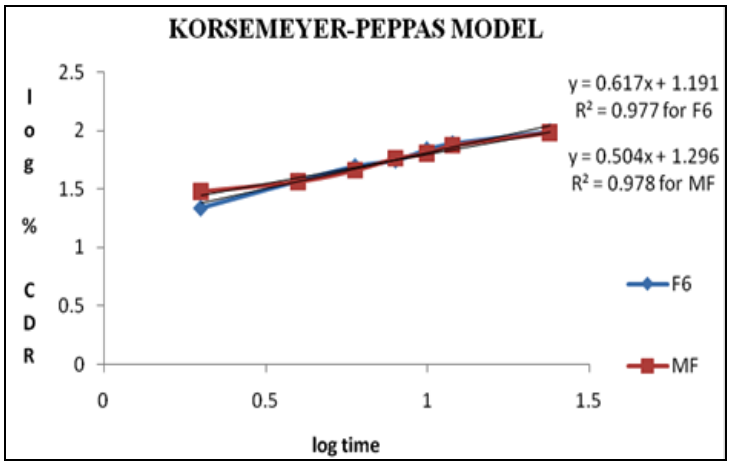

FIGURE 5: PLOT OF LOG CUMULATIVE PERCENTAGE DRUG RELEASED VS. LOG TIME OF OPTIMIZED FORMULATION AND MARKETED FORMULATION

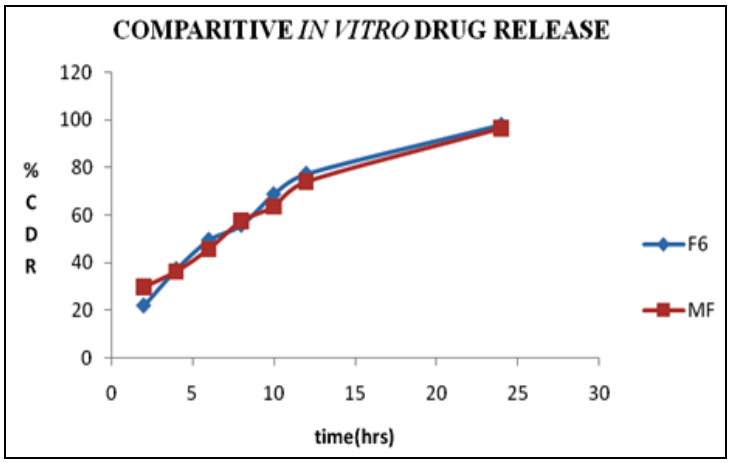

FIGURE 6: *IN-VITRO* DISSOLUTION PROFILE OF OPTIMIZED FORMULATION AND MARKETED FORMULATION

CONCLUSION: The effervescent based floating drug delivery was a promising approach to achieve in vitro buoyancy. The addition of gel forming polymer and gas generating agent sodium bicarbonate was essential to achieve in vitro buoyancy.

The drug release from the tablet was sufficiently sustained for 24 hr and non fickian transport of the drug from tablet was confirmed, so drug release appears to be a complex mechanism of swelling, diffusion and erosion.

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