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DESIGN AND DEVELOPMENT OF SUSTAINED RELEASE GASTRO RETENTIVE DRUG DELIVERY SYSTEM FOR OFLOXACIN.

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ABSTRACT

Sustained release (SR)-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. Different polymers, such as HPMC K4M, HPMC 5cps, sodium carboxymethyl cellulose, and its combinations were tried in order to get the desired sustained release profile over a period of 24 h. Various formulations were evaluated for buoyancy lag time, duration of buoyancy,. It was also found that in vitro drug release rate increased with increasing amount of Sodium carboxymethyl cellulose due to the increased water uptake, and hence increased driving force for drug release. The optimized formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines. There is no available marketed floating formulation of ofloxacin. Hence, the marketed extended release formulation (Zanocin-OD) was taken for comparison of the dissolution profile. Dissolution in 0.1N HCl showed a release of 63.5% at the end of 8 hours where as dissolution in pH 6.8 phosphate buffer showed a release of only 13.39% which clearly shows that Ofloxacin is poorly soluble in higher pH conditions. After conducting the drug release studies, formulation F5 was optimized as the best formulation because it released about 89.27% of the drug at the end of 8 hours while other formulations released not more than 80%.

1. INTRODUCTION

Oral sustained release (SR)-dosage forms (DFs) have been developed for the past three decades due to their considerable therapeutic advantages. However, this approach has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the gastrointestinal tract, i.e. stomach and small intestine [1]. This is due to the relatively short transit time of the DF in these anatomical segments. Thus, after only a short period of less than 6 h, the SR-DF has already left the upper gastrointestinal tract and the drug is released in non-absorbing distal segments of the gastrointestinal tract. This results in a short absorption phase that is often accompanied by lesser bioavailability [2]. It was suggested that compounding narrow absorption window drugs in a unique pharmaceutical DF with gastro retentive properties would enable an extended absorption phase of these drugs. After oral administration, such a DF would be retained in

the stomach and release the drug there in a sustained manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of SR-DFs for these drugs [3-4].

The need for gastro retentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. These efforts resulted in GRDFs that were designed in large part based on the following approaches: (a) low density form of the DF that causes buoyancy above gastric fluid; (b) high density DF that is retained in the bottom of the stomach; (c) bioadhesion to the stomach mucosa ; (d) slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients ; (e) expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter [5-9].

The objective of present work was to develop gastro retentive formulation, which releases drug in the stomach and upper gastrointestinal (GI) tract, and form an enhanced opportunity of absorption in the stomach and upper GI tract rather than the lower portions of the GI tract. Example of substance whose bioavailability is strongly dependent on the local physiology in the GI tract and which preferably is absorbed in the higher sections of the intestine is ofloxacin. Ofloxacin is readily soluble in the acidic environment of the stomach. In the intestine, where neutral to slightly alkaline pH conditions prevail; however, precipitation of the active compound occurs, which adversely affects absorption in the lower sections of the intestine. There is a need for systems that reside in the stomach over a relatively long time and release the active compound there in a sustained manner [10-12]. This necessitated the design and development of sustained release gastroretentive drug delivery system for ofloxacin using suitable polymers

MATERIALS AND METHODS

MATERIALS

Ofloxacin , HPMC K4M , HPMC 5cps were gifted by Macleoid Pharmaceuticals, India.,PVP K30 and Na CMC were obtained as gift samples from M/s Rohm Pharma, Germany. and were of analytical grade.

METHODS

General description of the manufacturing process for sustained release formulation of ofloxacin

Typical sustained release formulations of ofloxacin are listed in Table 1. Tablets were made by using sodium carboxy methyl cellulose (gelling agent, channeling agent and swelling agent), HPMC K4M was used as the rate retarding polymer while HPMC 5cps was used because its low density helps in floating of the tablet due to its swelling property which decreases the tablet density in solution and gives a buoy, sodium bicarbonate and citric acid (gas-generating agent) Tablets were made by using wet granulation process with PVP K30 (5%, w/v, isopropyl alcohol). Compression was done on a Cad mach single station tablet press using caplet shaped punches.

Table 1 Composition of ofloxacin floating tablets

Name of Excipients (Mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ofloxacin	200	200	200	200	200	200	200	200	200	200
HPMC K4M	100	50	50	65	65	65	65	65	65	65
HPMC 5cps	150	200	125	90	90	86	100	80	90	90
Na CMC	-	-	-	-	8	10	8	8	8	8
NaHCO3	25	25	25	27.5	27.5	27.5	22.5	32.5	27.5	27.5
Citric acid anhydrous	19	19	19	22.5	22.5	22.5	22.5	22.5	22.5	22.5
PVP K-30	40	40	20	25	25	25	25	25	25	25
Iso Propyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Na CMC	12	12	12	16	8	10	8	8	8	8
$NaHCO_3$	25	25	25	27.5	27.5	27.5	22.5	32.5	27.5	27.5
Citric acid anhydrous	19	19	19	22.5	22.5	22.5	22.5	22.5	22.5	22.5
Magnesium stearate	6	6	5	4	4	4	4	4	4	4
Tablet Weight	596	596	500	500	500	500	500	500	500	500

IN VITRO RELEASE STUDY

The release of ofloxacin from the tablets was stud-ied using USP dissolution Apparatus I. The dissolution medium was phosphate buffer pH 1.2 for first 2 h, phosphate buffer pH 4.5 for next 2 h and pH 7.4 for remain-ing hours, the volume being 900 ml. The temperature was maintained at 37 ± 0.5◦C. The rotation speed was 100 rpm. Five milliliters of aliquot were withdrawn at predetermined time intervals of 1, 2, 3, 4, 6, 8, 10, 12, 14, 16 and 24 h. The medium was replenished with 5 ml of fresh buffer each time. Sample was analyzed by using UV spectrophotometry at 291 nm. [13-14]

Buoyancy lag time and the duration of buoyancy

The buoyancy lag time and the duration of buoyancy were determined in the USP dissolution Apparatus II in an acid environment.[15] The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as buoyancy lag time and the duration of buoyancy was observed visually.[20]

Evaluation of Ofloxacin Floating Tablets

The prepared tablets were evaluated for the following parameters.

Weight variation:

20 tablets were randomly selected from each formulation trial batch and the average weights were calculated on an analytical balance. The individual weights were also calculated and the percentage deviation was calculated. Limits were set as per USP 31.[21]

Acceptance limits: ± 5% of the weight of the tablet.

Hardness:

The tablets were tested for their hardness using Dr. Schleuniger hardness tester. The average hardness and the standard deviation were reported.

Thickness:

Randomly 10 tablets were taken from each formulation trial batch and their thickness was measured using Digital vernier calipers. The individual tablet was placed between the anvils and the sliding knob was rotated until the tablet was tightly fitted. The digital reading displayed was noted.

Acceptance limits: ± 4%

Friability:

Tablets equivalent to a minimum of 6.5g were weighed and placed in a Roche friabilator where the tablets were exposed to repeated rolling shocks due to free fall within the apparatus. After 100 revolutions, the tablets were removed, dedusted and weighed. The percentage loss in weight was determined.[22]

Acceptance limits: ± 1%

Floating lag time:

Around 150ml of 0.1N HCl was taken in a 250ml beaker and a tablet was dropped in to the solution. The stop watch was started and the time taken for the tablet to reach the surface was reported.

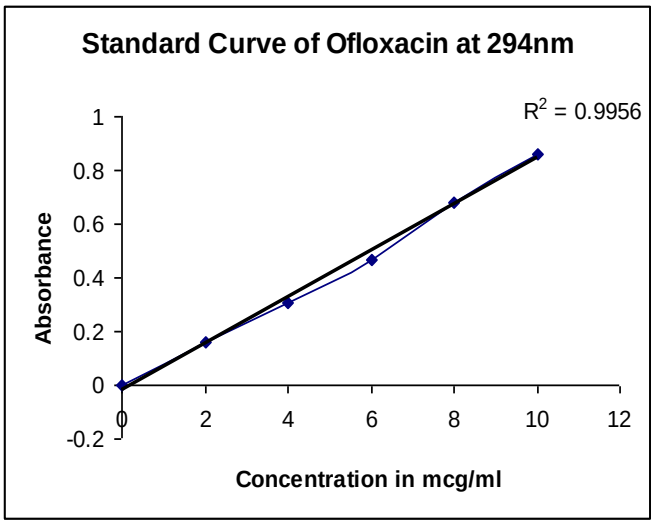
Floating duration:

The tablet was dropped in the beaker as in the test for the floating lag time. The same tablet is tested for the time duration it remains floating on the surface of the solution.

Assay:

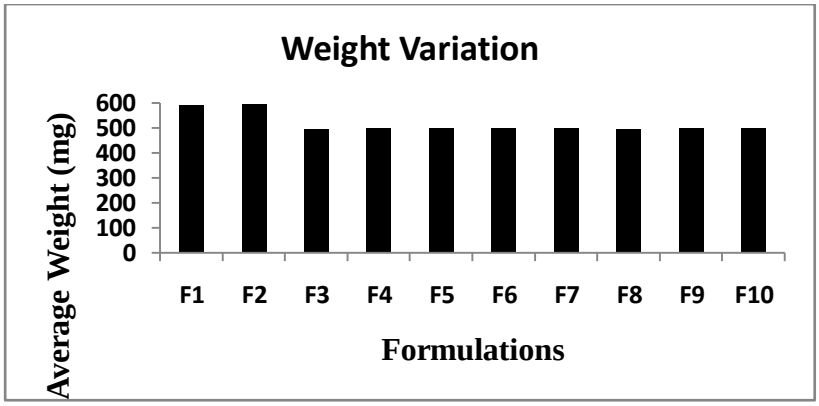
From each batch of the formulation, 10 tablets were collected randomly and powered using a mortar and pestle. A quantity of the powder equivalent to the weight of one tablet (200mg drug) was transferred to a 100ml volumetric flask. To this, about 50ml of 0.1N HCl was added and subjected to sonication for 15 minutes. The volume was then made up to 100ml with the same solution. This solution was suitably diluted using 0.1N HCl to get a concentration between 2mcg/ml to 10 mcg/ml. These solutions are then analyzed by UV spectrometer as per the calibration graph method by recording the absorbance at 294nm.Acceptance limits: 90 – 110%.[24]

RESULTS AND DISCUSSION



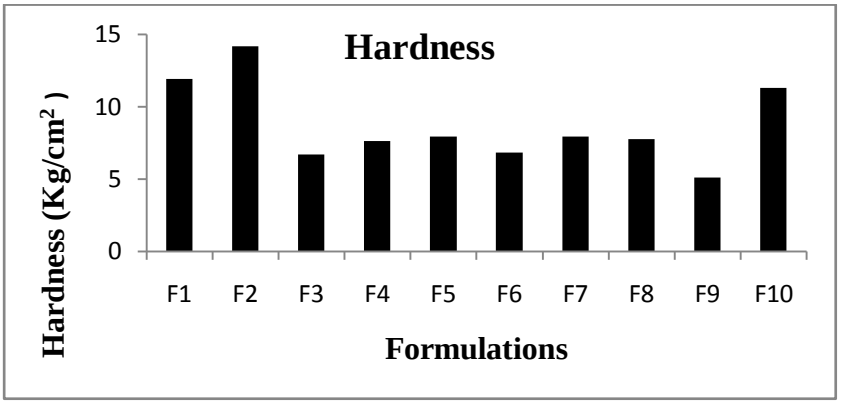
Weight variation:

The hardness of the tablets of all the batches were tested and the tablets were found to have Uniform weights with an RSD of not more than 5% as per the limits set.[27]



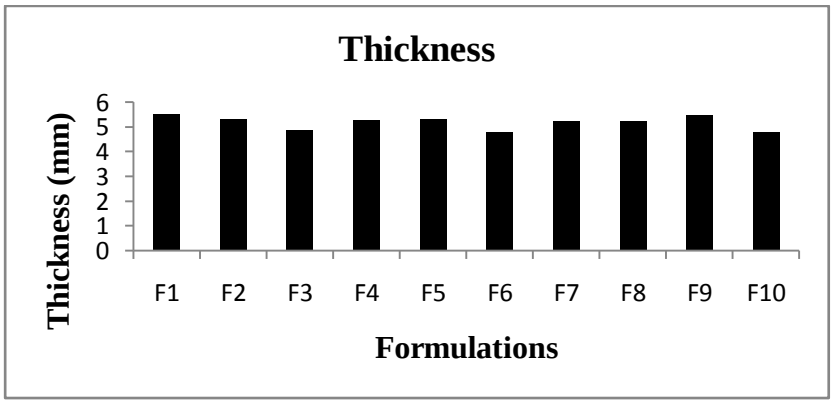
Hardness:

The hardness of the tablets was tested and was found to be within the specified preset limits. Each formulation was given a range based on the requirement for optimizing the floating and drug release properties of the formulations.



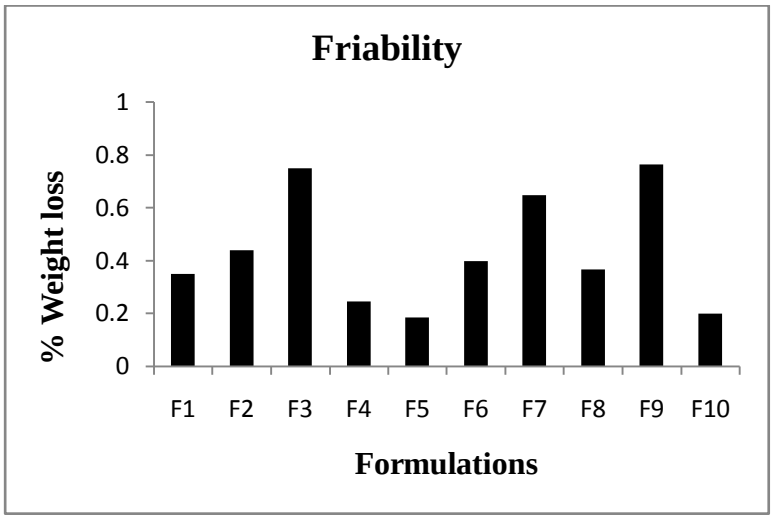
Thickness:

The thickness of the tablets was recorded and was found that all the batches were having the thickness within the specified limit i.e. not more than 1% RSD.[28]



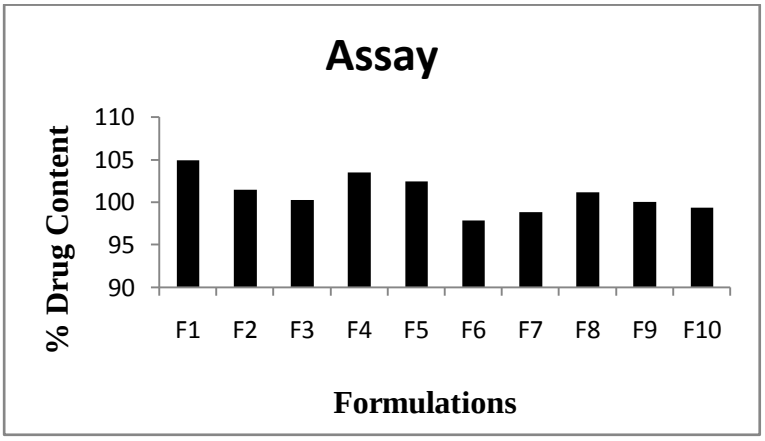
Friability:

The friability results for all the formulations were found to be <1%



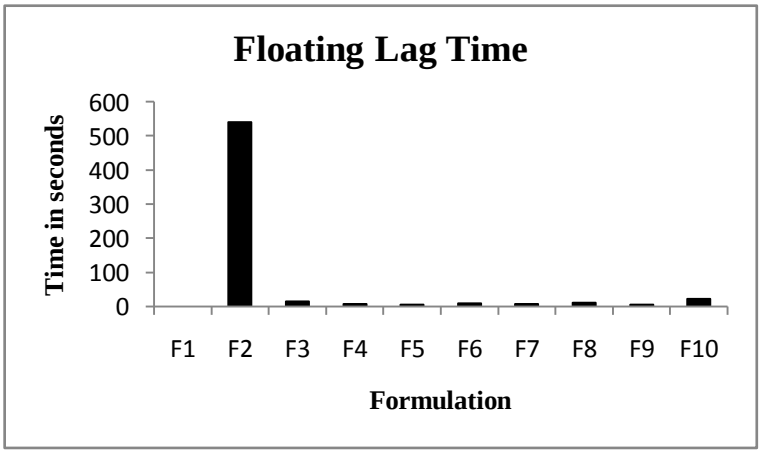
Assay:

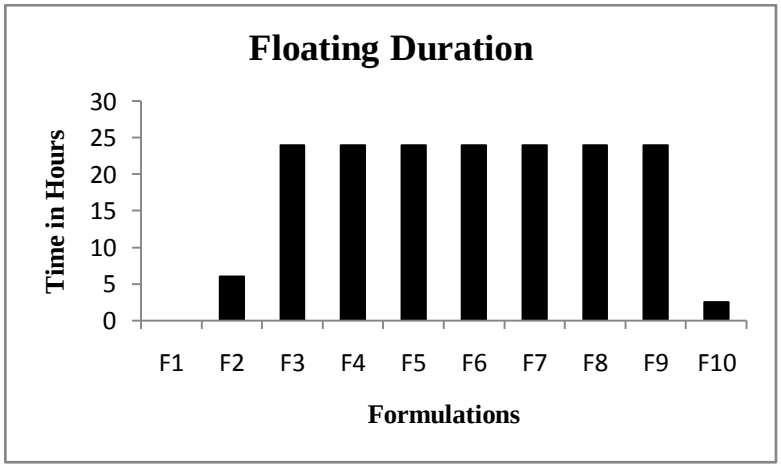
Each batch of the tablets were analyzed for the drug content and all the batches were found to be within the limits i.e. 90 to 110%.



Floating parameters

The floating lag time and the floating duration were reported. The formulations which did not float or which did not have a long floating duration were exempted from further drug release studies.



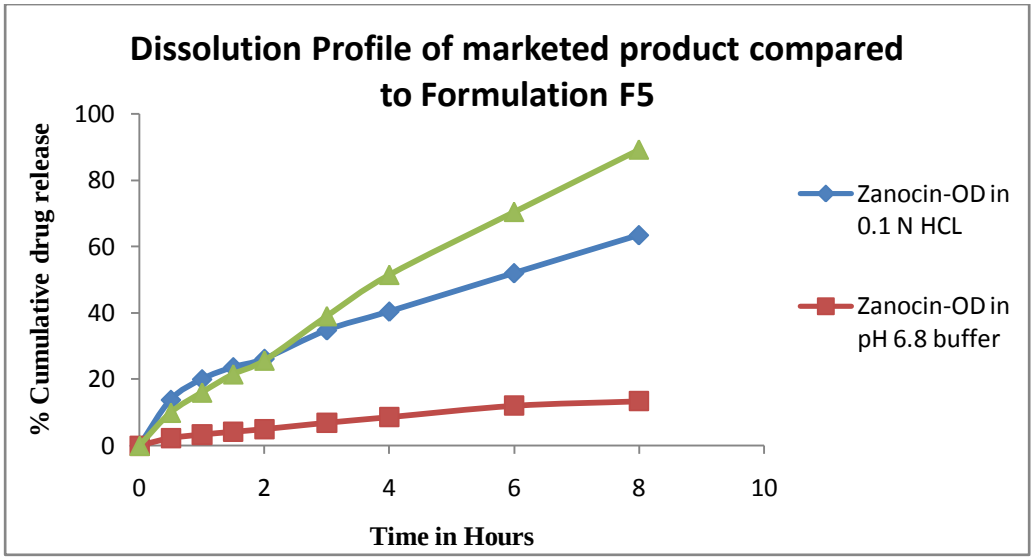


Dissolution Study of the Marketed Product (Zanocin – OD)

In vitro dissolution study of the marketed product (Zanocin – OD 400mg) was carried out to compare the drug release profile with that of the formulated ofloxacin floating tablets. The same dissolution method used for the formulations was used for the marketed formulation. In addition dissolution was also carried out in pH 6.8 phosphate buffer to study the release of the drug.

Table 19: Drug release of Marketed formulation

Time (Hrs)	% Cumulative Drug Release		
	0.1N HCl	pH 6.8 buffer	F5
0.5	13.814	2.252	9.958
1	20.017	3.331	16.046
1.5	23.663	4.163	21.539
2	26.188	4.972	25.671
3	34.807	6.896	39.062
4	40.444	8.595	51.509
6	52.034	12.035	70.492
8	63.5	13.392	89.275
R^2	**0.951**	**0.969**	**0.993**

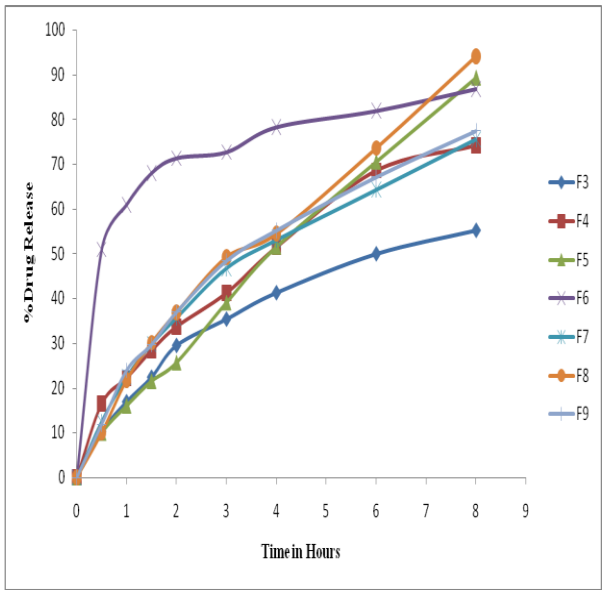


Dissolution Study of Ofloxacin Floating Tablets

The dissolution studies were carried out as per dissolution method mentioned previously in 3.4.3.8. Out of the 10 formulations, seven formulations were taken for the dissolution studies. Dissolution for F1, F2 and F10 was not done since they were not meeting the specific characteristics for floating tablets. The following table shows the drug release profiles of the formulations for a period of 8 hours.

Table 20: % Cumulative Drug release from the Formulations

Time (Hrs)	F3	F4	F5	F6	F7	F8	F9
0.5	10.32	16.499	9.958	50.93	12.523	10.023	11.894
1	16.939	22.213	16.046	60.935	22.493	21.809	23.988
1.5	22.43	28.382	21.539	67.986	29.78	30.103	29.718
2	29.52	33.678	25.671	71.302	35.713	36.864	36.988
3	35.39	41.206	39.062	72.647	46.774	49.242	48.413
4	41.283	51.415	51.509	78.218	53.081	54.436	55.208
6	49.97	68.518	70.492	81.853	64.297	73.59	67.142
8	55.221	74.141	89.275	86.755	75.61	94.117	77.455

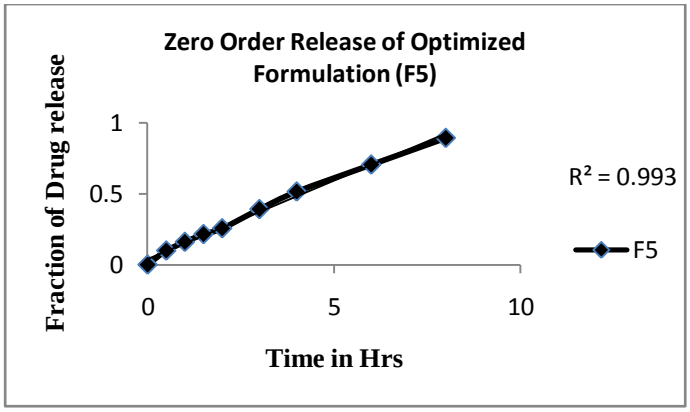


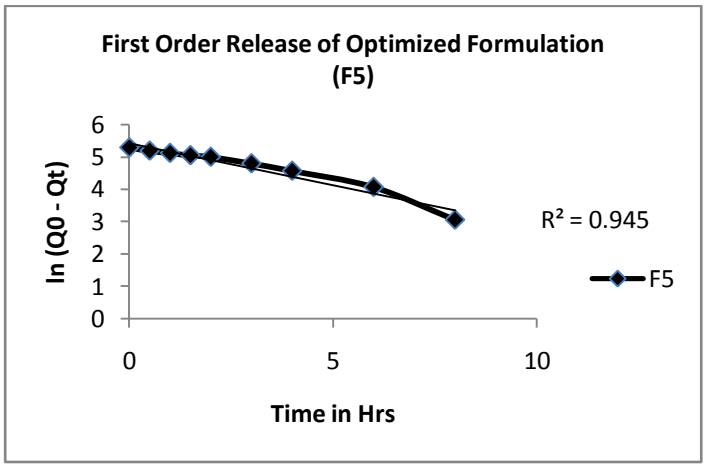
Drug Release Kinetics -Model fitting of the dissolution data

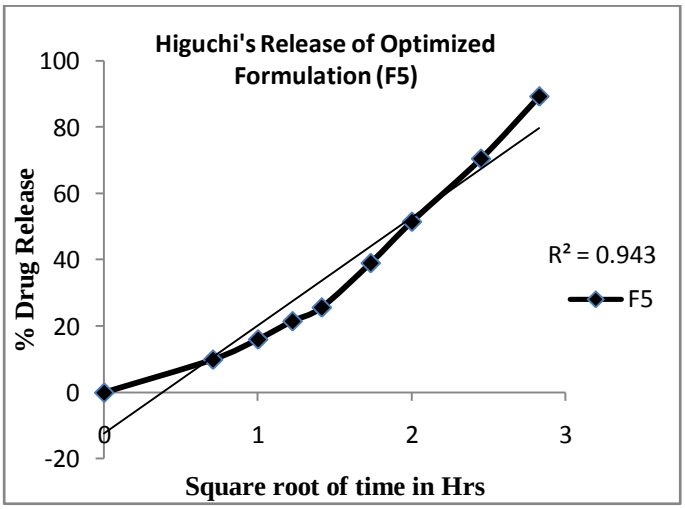
The dissolution data obtained was fitted into various models and the formulation best followed which type of model was decided based on the regression value.

Drug Release Kinetics of Ofloxacin Floating Tablets

S. No	Formulation	Regression Coefficient (r^2)		
		Zero order	First order	Higuchi's
1	**F3**	0.901	0.960	0.782
2	**F4**	0.940	0.989	0.989
3	**F5**	0.993	0.945	0.943
4	**F6**	0.507	0.799	0.782
5	**F7**	0.923	0.992	0.993
6	**F8**	0.961	0.911	0.973
7	**F9**	0.925	0.991	0.990

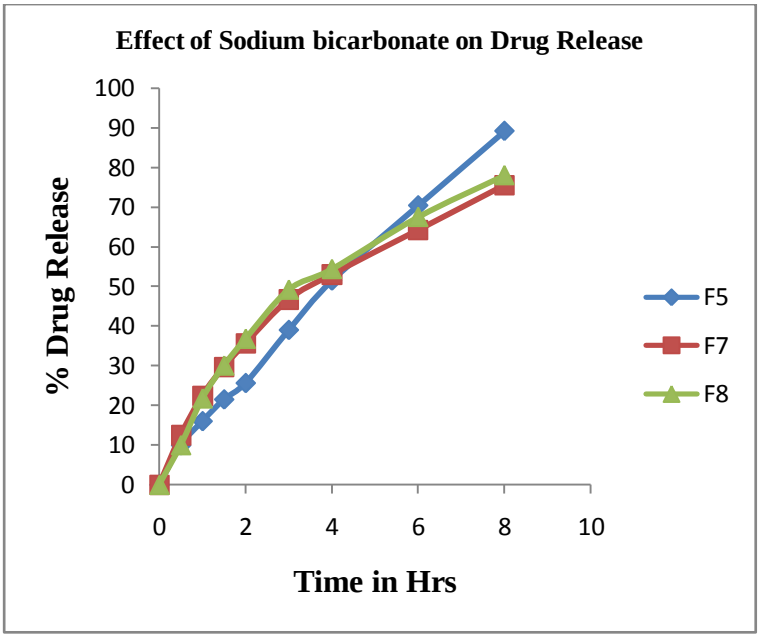






Study of Effect of Sodium bicarbonate on Drug Release

Formulations F7 and F8 were prepared with a 2% decrease and increase of sodium bicarbonate levels respectively in the two formulations to study its effect on the dissolution with comparision to the optimized formulation F5.

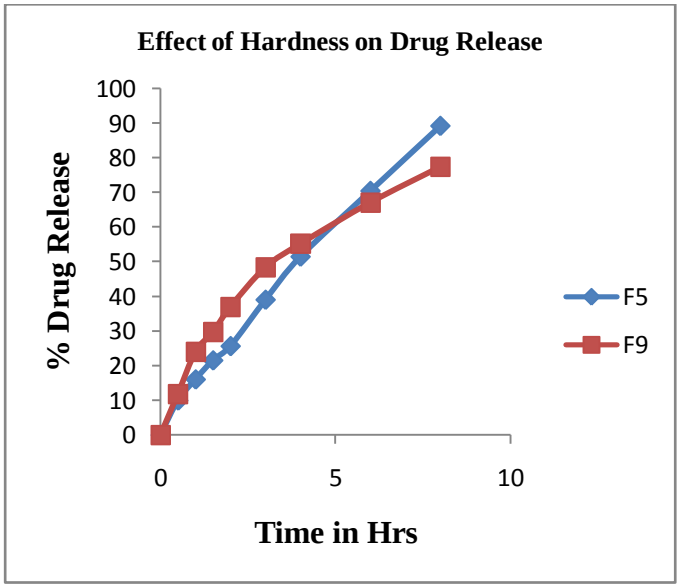


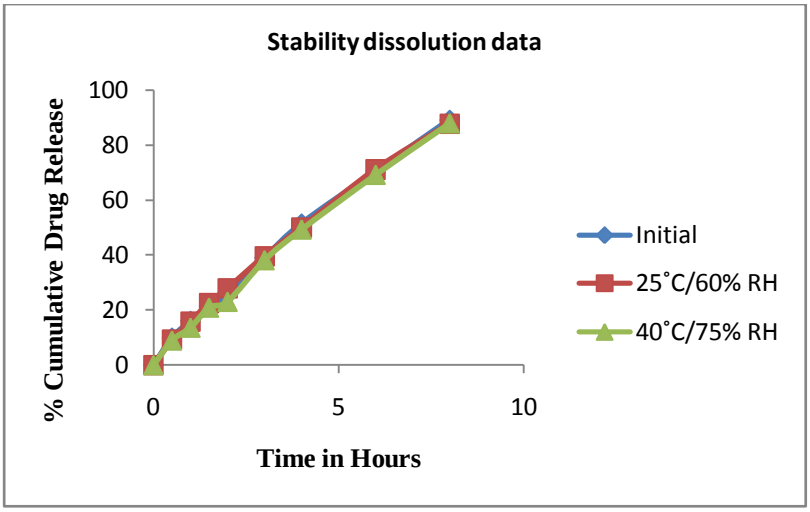
Study of the effect of Hardness on Drug Release

Formulations F9 and F10 were prepared with decreased and increased hardness respectively to study its effect on the dissolution with comparision to the hardness of the optimized formulation (F5). Formulation F10 failed to pass the Floating duration hence was exempted from the dissolution study.

Hardness specifications for the formulations F5, F9 and F10

S. No	Formulation	Hardness (Kg/cm^2)	Limits for Hardness (Kg/cm^2)
1	F5	7.94±0.20	6 – 8
2	F9	5.10±0.20	4 – 6
3	F10	11.29±0.18	10 - 12





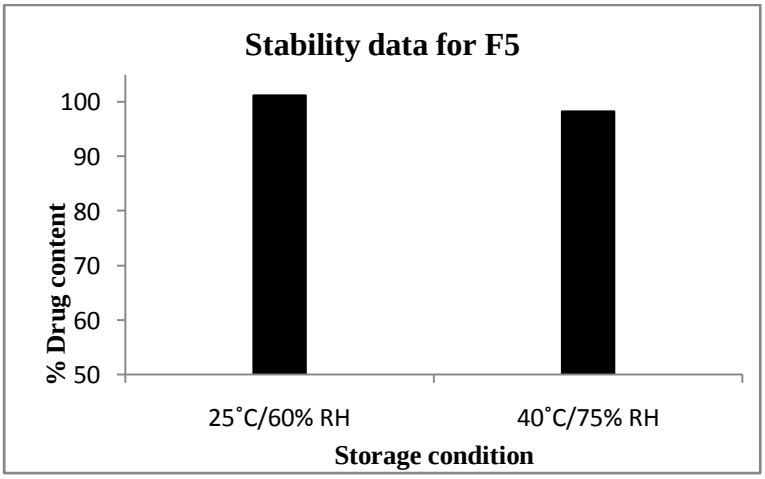
DISCUSSION

The formulations from F1 to F10 were formulated using wet granulation method using the excipients HPMC K4M, HPMC 5cps, sodium carboxymethyl cellulose, sodium bicarbonate, citric acid anhydrous, magnesium stearate, PVP K30 and IPA. HPMC K4M was used as the rate retarding polymer while HPMC 5cps was used because its low density helps in floating of the tablet due to its swelling property which decreases the tablet density in solution and gives a buoy. Sodium carboxymethyl cellulose is used as a channeling agent which guides water into the tablet by forming pores due to its swelling property. Sodium bicarbonate and citric acid anhydrous together are used as the effervescent agent which gives a quick thrust to the tablet to float immediately. Magnesium stearate was used as the lubricant while PVP K30 and IPA were used binder and vehicle respectively, for the binding solution.[29] The effervescent agent was added in equal amounts both in the intra granular and the extra granular parts so as to provide continuous thrust throughout the floating time of the tablet. Sodium carboxymethyl cellulose was used totally in the extra granular part up to F4 and then divided equally in to both phases from F5 to F10. Formulations from F1 to F6 were prepared for optimizing the formula. Further optimization was done by varying sodium bicarbonate levels (F7 and F8) and varying the hardness (F9 and F10).

The λmax of Ofloxacin in 0.1N HCl was scanned and was found to be 294nm. The standard graph was plotted and a good linearity was observed with an r^2 value of 0.9956 which obeys Beer's Lambert's Law.[30-31] The tablet parameters i.e. weight variation, hardness, thickness and friability and the assay values were all found to be within the specified limits. The floating lag time was good for all the formulations which was found to be less than 15 seconds, except F1 and F2. F1 did not float and F2 took 9 minutes to float. The floating duration in all the formulations was found to be more than 24 hours except F1, F2 and F10. F1 and F2 did not have the required thrust while F10 had high hardness. The hardness and thickness of the tablets influenced floating properties. Lower hardness and higher thickness decreased the floating lag time and increased floating duration.

There is no available marketed floating formulation of ofloxacin. Hence, the marketed extended release formulation (Zanocin-OD) was taken for comparison of the dissolution profile. Dissolution in 0.1N HCl showed a release of 63.5% at the end of 8 hours where as dissolution in pH 6.8 phosphate buffer showed a release of

only 13.39% which clearly shows that Ofloxacin is poorly soluble in higher pH conditions. After conducting the drug release studies, formulation F5 was optimized as the best formulation because it released about 89.27% of the drug at the end of 8 hours while other formulations released not more than 80%. All the formulations showed a good linearity except F6 which showed burst effect and released 50.93% within 0.5 hours. This may be due to high sodium carboxymethyl cellulose content which might have caused excessive channeling, thereby giving a burst release. Formulations F1 did not float and F2 and F10 had very small floating duration (6 and 2.5 hours). Hence, were exempted from drug release studies. Modeling of the drug release was done using the best-fit method. The release was plotted according to the Zero order, First order and Higuchi's equations graphically and the regression coefficient values were studied. Optimized formulation F5 was found to follow zero order kinetics with r^2 value of 0.993. Formulations F3, F4, F7 and F9 were found to follow first order kinetics as well as Higuchi's kinetics showing that drug release takes place through porous matrix systems with freely soluble drug since ofloxacin is freely soluble at low pH conditions. Formulation F6 failed to follow any release mechanism since there was burst release which might be due to excessive channeling and swelling because of higher NaCMC. F8 was close to following Higuchi's kinetics since the r^2 value was 0.973. The effect of sodium bicarbonate on the drug release was studied with low and high contents in F7 and F8 respectively. F7 showed slightly reduced drug release while F8 showed slightly higher release, both following Higuchi's release kinetics. This may be because F7 had lower sodium bicarbonate levels which provided lesser channeling for the drug to release and the opposite is the case for F8. The effect of hardness showed an impact. The formulation with higher hardness (11.29±0.18) i.e. F10 though having a short lag time (15 sec), floated only for 2.5 hours. The formulation with lower hardness F9 showed release similar to F5 up to 4 hours. Last two time points showed reduced release which might be due to excessive swelling of the polymer thereby retarding the drug release after 6 hours. The stability studies were carried out with the optimized formulation (F5) for one month at two conditions i.e. 25˚C/60% RH and 40˚C/75% RH as per ICH guidelines. The assay results and the dissolution data were found to be similar to that of the initial formulation. This demonstrated the stability of the formulation.



SUMMARY AND CONCLUSION

The floating lag time and the floating duration of the tablets are the most important parameters. All the formulations except F1, F2 and F10 had a floating lag time of less than 15 seconds and floated for a period of 24 hours.

Formulation F5 was found to release the maximum drug (89.27%) compared to other formulations. The formulations F4, F7 and F9 were found to follow first order release model followed by Higuchi's model indicating diffusion controlled release mechanism. F8 followed Higuchi's kinetics. The optimized formula F5followed zero order kinetics.

The marketed formulation (Zanocin-OD), an extended release tablet was taken for comparison of the drug profile due to the unavailability of a floating marketed formulation of ofloxacin. Zanocin-OD showed high drug release in 0.1N HCl and low release in pH6.8 buffer showing that the solubility of the drug decreases at higher pH conditions. This clearly showed that the drug is poorly soluble in higher pH conditions. Zanocin-OD being given as once daily tablet might not release the drug efficiently after entering small intestine due to high pH. This might lead to lower bioavailability of the drug.

Hence, diffusion controlled Ofloxacin gastro retentive tablets were formulated and evaluated and formulation F5 was concluded as the best formulation for the manufacture of Ofloxacin gastro retentive tablets which can assure 100% bioavailability. Further, imaging studies, pharmacokinetic and pharmacodynamic studies and clinical trials can be performed to develop a marketed formulation of ofloxacin for effective therapy.

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Hence the objective of the study was to formulate and evaluate Ofloxacin Gastro retentive tablets. The tablets were formulated using wet granulation method using varying quantities of the excipients. The formulated tablets were tested for the parameters such as weight variation, hardness, thickness, friability and drug content and were found to be within the limits.

REFERENCE:

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