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Formulation and Characterization of Sustained Release Gastroretentive Drug Delivery System for Ofloxacin

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ABSTRACT

The purpose of this work was to Formulate and Characterize a Sustained Release Gastroretentive Drug Delivery System for Ofloxacin. Six formulations were prepared with different combinations of polymers. All formulations were prepared by Dry Granulation Method and evaluated for various parameters like Hardness, Friability, weight variation, *in vitro* Buoyancy study, water uptake study and dissolution study. Formulations showed a sustained release. The physical parameters of tablets showed that the tablets of all batches had desirable physical characteristics. Granules and fines ratio of 80:20 was found to produce tablet with good characteristics. All batches of tablets except F2 were found to exhibit maximum floating time that is 26 hrs and the release of drug was a period of 12-14 hrs. Drug release was found to be very close to zero order kinetics and the mechanism of drug release was found to be erosion and diffusion. It was then concluded at last that the prepared formulations were having the required floating capacity and suitable as once day therapy.

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INTRODUCTION

Conventional oral controlled drug delivery system has not been suitable for a variety of important drugs, which is mainly due to the relatively short transit time of the dosage form in stomach and upper part of small intestine. The sustained release Gastroretentive drug delivery system offers numerous advantages as improved drug absorption, because of increased gastric retention time and more time spent by the dosage form at its absorption site, minimizing the mucosal irritation due to drugs, by drug releasing slowly at a controlled rate, protecting the drug from degradation in colon. It is evident from the recent scientific literature that one of the most feasible approaches for achieving prolonged and predictable drug delivery profile in the GI tract is to control Gastric Residence Time (GRT). Sustained release Gastroretentive dosage form enable prolonged and continuous input of the drug to the upper part of the GI tract and improve the bioavailability of medication that are characterized by a narrow absorption window.[1][2][3][4][5]

Floating tablet can be used for local action in the proximal GIT. Poorly soluble and unstable as well as poorly absorbable drugs are suitable candidates for floating dosage units. These systems are retained in the stomach for prolonged time due to their floating property. Floating dosage forms has been developed to float over GI fluid and to release the drug over a defined period of time. The exhausted system after drug delivery is emptied from the stomach. These systems are designed to have lesser specific gravity than the gastric content, thereby float on the gastric fluid for extended period.[6][7]

Ofloxacin is a Quinolone antibiotic used to treat Lungs, Skin, UTI caused by certain germs called bacteria. Tablets are indicated for the treatment of adults with mild to moderate infections. In this study, Ofloxacin was selected as a drug candidate because, it has a pH dependent solubility. Ofloxacin once daily formulation would require controlled drug release because it absorbed predominantly from the upper intestine. Formulation of Gastroretentive drug delivery system containing Ofloxacin, would remain in stomach and upper part of GIT for prolonged period of time in view to maximize the drug release in the upper part of GIT.[2]

The objective of the present study was to prepare sustained release Gastroretentive drug delivery system for Ofloxacin. To achieve this aim various formulation of Ofloxacin were prepared with different formulation of polymers like HPC, ethyl cellulose add incorporating sodium bicarbonate, crospovidone etc., by dry granulation method. So the presence of optimum amount

of HPC, ethyl cellulose, sodium bicarbonate and crospovidone important in achieving good floating time and minimum floating lag time. The incorporates of sodium bicarbonate help to improve floating properties by reacting with gastric fluids when dosage form comes in contact with media. These produce carbon dioxide gas which entraps inside the hydrophilic matrices leads to increase in volume of dosage form resulting in lowering of density and dosage form start to float. The one main reason for patient noncompliance is the dosing regimen complexity particularly during the multiple drug therapy, where each drug is prescribed for varied time intervals. But these prepared formulations were having the required floating capacity and sustained drug release as suitable as once a day therapy.[8]

MATERIALS AND METHODS

Ofloxacin which is obtained as gift sample from Ranbaxy Lab Ltd, industrial area-3 DEVAS and Hydroxypropyl cellulose ,Ethyl cellulose are also obtained from Ranbaxy Lab Ltd, industrial area-3 DEVAS.and all other chemicals used in this study are of Analytical grade.

PREFORMULATION STUDY

Physical characterization of drug

The preformulation study like bulk density, tapped density and compressibility index were performed for drug.

Identification test[9]

Scanning of Ofloxacin in 0.1N HCl: The solution containing 20 µg/ml of ofloxacin in 0.1 N HCl was prepared and scanned over the wavelength range of 200nm to 400nm against 0.1N HCl as blank using double beam UV spectrophotometer.

Physical properties[10]: Powder flow, compressibility, dissolution and other properties may dependent on density. The following tests were performed for drug substance.

Bulk Density: The powder sample under test was screened through sieve no. 22 and the sample equivalent to 10g was accurately weighed and filled in a 50ml graduated cylinder and the powder was leveled and unsettled volume, V_0 was noted.

The bulk density was calculated in g/cm^3 by the formula,

$$\text{Bulk density}(\rho_0)=M/V_0$$

Where M=Weight of sample powder taken

V_0= Apparent unstirred volume

Tapped density: The powder sample under test was screened through sieve no. 22 and the weight of sample equivalent to 10g was filled in 50ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a constant rate for 100 times. Volume was considered as a tapped volume V_f

The tapped density was calculated in g/cm^3 by the formula,

$$\text{Tapped density } (\rho_t) = M/V_f$$

Where

M=weight of sample powder taken

V_f=Tapped volume

Hausner ratio: Tapped density and bulk density were determined and the Hausner ratio was calculated using the formula,

$$\text{Hausner ratio} = \rho_t/\rho_0$$

Where ,

ρ_t=tapped density

ρ_0=bulk density

Table 1: Standards for Hausner's ratio

1.2-1.3	Excellent
1.3-1.4	Good
1.4-1.5	Fair
1.5-1.6	Poor

Compressibility index: The bulk density and tapped density was determined and compressibility index was calculated using the formula,

$$\text{Compressibility Index} = \{(\rho_t - \rho_0)/\rho_t\} \times 100$$

Where ρ_t=tapped density

ρ_0=bulk density

Table 2: Standards for Carr's index

5-15	Excellent
12-16	Good
18-21	Fair
20-35	Poor
33-38	Very poor
>40	Extremely poor

Compatibility studies: To determine the physicochemical compatibility of ofloxacin with used excipients. Ofloxacin was mixed with an excipient in the ratio 1:1 and examined for any change in the physical appearance of mixture at room temperature for 4 weeks.

Standard curve of ofloxacin[11],[12]

Preparation of Standard curve in 0.1N HCl:

An accurately weighed quantity of ofloxacin (100mg) was dissolved in 100ml of 0.1N HCl to generate a stock solution having concentration of 1mg/ml. 1ml of stock solution was further diluted to 100ml to produce standard solution having concentration of 10µg/ml. The standard solution was serially diluted with 0.1N HCl to get working standard solution having concentrations of 2,4,6,8,10µg/ml. The absorbance of the solution was measured at 299.0nm using double beam UV visible spectrophotometer against 0.1N HCl as a blank. The plot of absorbance v/s concentration µg/ml was plotted and data was subjected to linear regression analysis.

FORMULATION DEVELOPMENT

All the formulations were prepared using dry granulation method.

Dry granulation method: In this method all the ingredients were weighed in required quantity, sieved and mixed together. The powdered blend was compacted in a roller compactor. The compacts were milled to obtain granules of varying sizes. The granules obtained were evaluated for their flow properties which showed that they can be made into tablet having good characteristics.

Result: Due to the advantage of having good flow property, increase in bulk density and uniform mixing of the blend obtained from dry granulation method, it was selected as the appropriate method for the formulation of ofloxacin tablets.

Procedure

All the required ingredients were taken and weighed.ofloxacin was sifted and collected in a polybag. Sifted remaining ingredients all together except magnesium stearate and collected in a polybag. Sifted magnesium stearate separately collected in a polybag. Loaded materials of step 3 to a blender and blending done. Added half the materials of step 2 to above material and blending done for few minutes. The remaining material of step 2 was then added and further blending done till the premix is homogeneous. Added magnesium stearate as an intragranular material to the blender and blending done for few minutes. Unloaded the material in a polybag. The above step material was then compacted and compacts collected in suitable container. The compacted material sieved through mesh#18 to remove fines, which was again compacted. The compacted material was then milled. The milled material was then sifted to separate granules and fines which were collected separately and packed in a polybag. The granules and fines in the required ratio were taken in blender and blending done for few minutes. Added remaining quantity of magnesium stearate to above blend and blending done for few minutes. Unload the blend in a polybag. Loaded the blend prepared for compression into the hopper of the tablet compression machine and compression was done.

Table 3: Formula for F1,F2,F3.

Sl. no	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)
1	Ofloxacin	800	800	800
2	Crospovidone	112	-	54
3	Starch	-	112	-
4	Sodium alginate	8	8	8
5	Xantham gum	12	12	12
6	Sodium bicarbonate	80	80	80
7	Colloidal anhydrous silica (Aerosil)	1	1	1
8	Ethyl cellulose	88	88	88
9	Hydroxypropyl cellulose	-	-	146
10	Magnesium stearate	9	9	9
Total weight (mg)		1110	1110	1110

Objective: To take a batch of ofloxacin 800mg tablet with a varying ratio of granules:fines.

It was done to overcome the flow problems observed during compression of trial 1,2,3 formulations. The ratio of granules:fines was taken as 70:30 in formulations F1, F2, F3. Formulation F3 showed better results during *in vitro* drug release studies than F1, F2, so F3 was selected as a base for further studying.

Table 4: Basic Formula for F4, F5, F6

Sl. no	Ingredients	Proposed quantity (mg per tablet)
1	Ofloxacin	800
2	Crospovidone	54
3	Hydroxypropyl cellulose	146
4	Sodium alginate	8
5	Xanthan gum	12
6	Sodium bicarbonate	80
7	Colloidal anhydrous silica	1
8	Magnesium stearate	9
Total weight	1110	1110

Table 5 : Granules : Fines Ratio for F4, F5, F6

Formulation code	Granules:fines ratio
Trial 4 (F4)	90:10
Trial 5 (F5)	80:20
Trial 6 (F6)	60:40

Compression: It was carried out using 20×9 mm capsule shaped punches, adjusting the die fill weight to 1110mg.

Table 6: Compression parameters

Parameters	Limits
Average weight	1110±15mg
Uniformity of weight	±5% of average weight
Hardness	10-25kp
Thickness	6.0±.5mm
Friability	NMT1.0%W/W

Blend characteristics[11]

The flow properties of granules (before compression) were characterization in terms of angle of repose, Carr's index, Hausner ratio.

Angle of repose: It is the tan inverse of angle between height of pile of powder and radius of the base of conical pile. It can be obtained between the free standing surface of powder heap and the horizontal plane. The fixed funnel that is secured with its tip at a given height h, above graph paper, placed on the flat horizontal surface. Powder is carefully poured through until the apex of conical pile just touches the tip of funnel.

Density: Granules were poured gently through a glass funnel into a granulated cylinder exactly to 10ml mark and the weight was taken off the filled granules. The cylinder was then tapped 100 times from a height of 2.0cm. Bulk density and tapped density were calculated. Hausner ratio (Hr) and Carr's index (Ic) were also calculated.

Evaluation of floating tablets

Hardness: The hardness of ten tablets were measured using Hardness tester. Mean and standard deviation were computed and reported. It is expressed in kilopascal(kp).

Friability: The friability of the tablets were determined using thermonik friabilator. It is expressed in percentage (%). 10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated using 25 rpm for four minutes. After four minutes, the tablets were weighed again. The percentage friability was then calculated using the formula.

$$\% \text{ friability} = \text{Initial weight-final weight/initial weight} \times 100$$

Weight variation:[12] Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets were calculated. The batch passes the test for weight variation if not more than two of the individual tablets weights deviate from the average weight by more than the percentage.

Table 7: The weight variation tolerance for uncoated tablets

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	10
130-324	7.5
More than 324	5

***In vitro* Buoyancy study:** All the batches of tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas generating agent. It was determined by floating lag time, per the method described by Rosa *et al*. the tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time (FLT). The duration of time the dosage form constantly remained on surface of medium was determined as the total floating time (TFLT).

Water uptake study[12]

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by various techniques. The water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was distilled water, 900ml rotated at 50 rpm. The tablets were removed periodically from the dissolution medium and after removing free water, the weight gain was measured. The medium was maintained at 37±0.5˚C throughout the study. Swelling characteristics of the tablets were expressed in terms of water uptake(WU) as

WU(%) =Weight of the swollen tablet- Initial weight of the tablet/Initial weight of the tablet×100

Dissolution study:[12] The release of ofloxacin from tablets was studied using USP dissolution apparatus I. The dissolution medium was 0.1N HCl 900ml. The temperature was maintained at 37±0.5˚C. The rotation speed was 100 rpm. Five milliliters of aliquot was withdrawn at predetermined time intervals of 1, 2, 3, 4, 6, 8, 10, 12, 14 hrs. The medium was replenished with 5ml of fresh 0.1N HCl as a blank using double beam UV-visible spectrophotometer at a wavelength of 299.0nm.[13]

RESULTS AND DISCUSSION

PRE-FORMULATION STUDY OF DRUG

Physical properties:

Identification test: Scanning of ofloxacin in 0.1N HCl: UV spectrum of ofloxacin in 0.1N HCl showed that the drug had λ_{max} of 299.0nm.

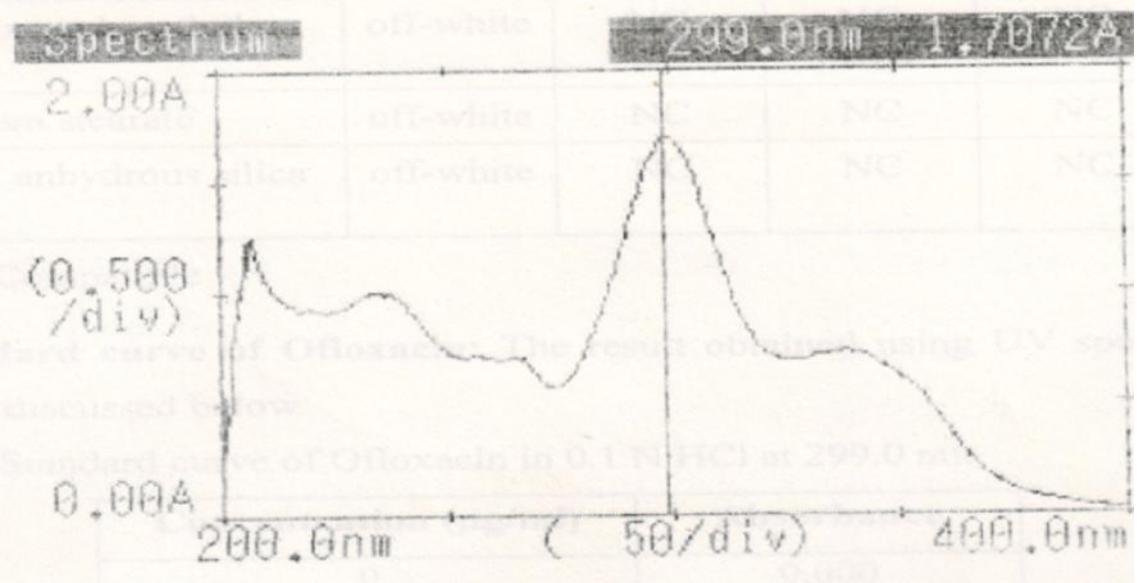

Figure 1: UV Spectrum of Ofloxacin in 0.1N HCl.

Table 8: Physical properties of drug

TEST	Result
Description	Pale yellow crystalline powder
Bulk density	0.455g/ml
Tapped density	0.510g/ml
Compressibility index	10.8
Hausner's ratio	1.121

Compatibility studies

Table 9: Compatibility studies of drug and excipients

Ingredients	Initial	1 week	2 week	3 week	4 week
Ofloxacin	Off-white	NC	NC	NC	NC
Sodium alginate	Off-white	NC	NC	NC	NC
Crospovidone	Off-white	NC	NC	NC	NC
Sodium bicarbonate	Off-white	NC	NC	NC	NC
Hydroxypropyl cellulose	Off-white	NC	NC	NC	NC
Ethyl cellulose	Off-white	NC	NC	NC	NC
Starch	Off-white	NC	NC	NC	NC
Hydroxypropyl methyl cellulose	Off-white	NC	NC	NC	NC
Magnesium stearate	Off-white	NC	NC	NC	NC
Colloidal anhydrous silica (Aerosil)	Off-white	NC	NC	NC	NC

NC: Non-compatibile

Standard curve of ofloxacin

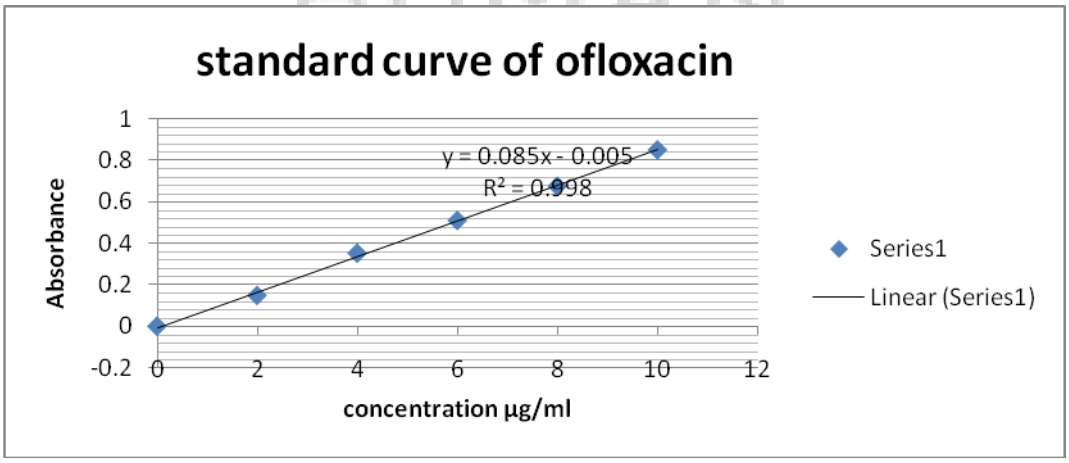

Figure 2: Standard curve of ofloxacin in 0.1N HCl at 299.0nm

EVALUATION OF FORMULATED BATCHES

Evaluation of blend:

The blends prepared for compression of floating tablet were evaluated for their flow properties and were found to be as follows.

Table 10: Flow properties of blends

Formulation code	Granules:fines	Granules flow property				
		Angle of repose Θ	Bulk density gm/cm^3	Tapped density gm/cm^3	Hausner's Ratio (H_R)	Carr's index ((I_C)
F1	70:30	29.653˚	0.518	0.628	1.212	17.5
F2	70:30	28.561˚	0.524	0.637	1.216	17.7
F3	70:30	28.840˚	0.544	0.651	1.197	16.3
F4	90:10	24.625˚	0.489	0.564	1.153	13.3
F5	80:20	26.210˚	0.500	0.579	1.158	12.7
F6	60:40	33.05˚	0.513	0.610	1.190	15.9

Improper filling of the die cavity was observed for the formulated trials F1, F2, F3 during compression. Dies are not filled properly when machine speed is in excess of the granulation flow capabilities. To overcome this problem, for formulations F1, F2, F3 machine speed during compression was varied, but the problem did not solve out indicating that flow need to be improved for the proper filling of the die cavity.

To improve the flow properties, formulation trials F4, F5, F6 were made by varying the granules to fines ratio. The fines amount in the compression blend was varied from 10-40%w/w. Appearance of the tablet becomes better with increasing fines amounts. Formulation F5 had a tablet surface smoother than the surface of formulations F3, F4, F6. The granules to fines ratio of 80:20 was found to produce tablet having satisfactory tablet attributes.

Evaluation of floating tablets

Physical characterization

Table 11: Physical characterization of ofloxacin floating tablets

Formulation code	Uniformity of weight (mg)		Hardness (Kp)		Thickness (mm)	Friability (%)
	Average weight	S.D	Mean	S.D		
F1	1108.2	4.319	16.97	0.525	6.3	Nil
F2	1107.8	3.855	17.04	0.326	6.3	Nil
F3	1107.7	4.042	16.94	0.334	6.3	Nil
F4	1109.6	2.404	17.08	0.245	6.3	Nil
F5	1109.3	2.274	17.05	0.323	6.3	Nil
F6	1105.1	6.157	16.92	0.298	6.3	Nil

The result in the table shows that the parameters achieved for the physical characterization of fabricated tablets were with the desired limits. The variation in weight was within the range of ±5% complying with USP specifications. The hardness achieved for the formulated tablets indicated strength. The friability for all formulations was found to be 0%, which is an indication of the good mechanical resistance of the tablets.

***In vitro* buoyancy studies :**

Table 12: Determination of floating capacity of formulated tablets

TERM	F1	F2	F3	F4	F5	F6
FLT (seconds)	38	6	23	22	22	21
TFT (hours)	26.10	5.35	22.13	22.05	22.10	21.55

All batches of tablets were found to exhibit short floating lag times due to presence of sodium bicarbonate. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium(0.1N HCl). It was observed that the gas generated is trapped and protected within the

gel, formed by hydration of polymer (methocel). Thus, decreasing the density of the tablet below 1.0 and the tablet becomes buoyant.

Floating lag time was observed and was found to be different for various batches of prepared tablets. The total floating time for the formulated tablets was found to be more than 14hrs except the formulation F2 which showed disintegration of tablet after 5:35hr of floating.

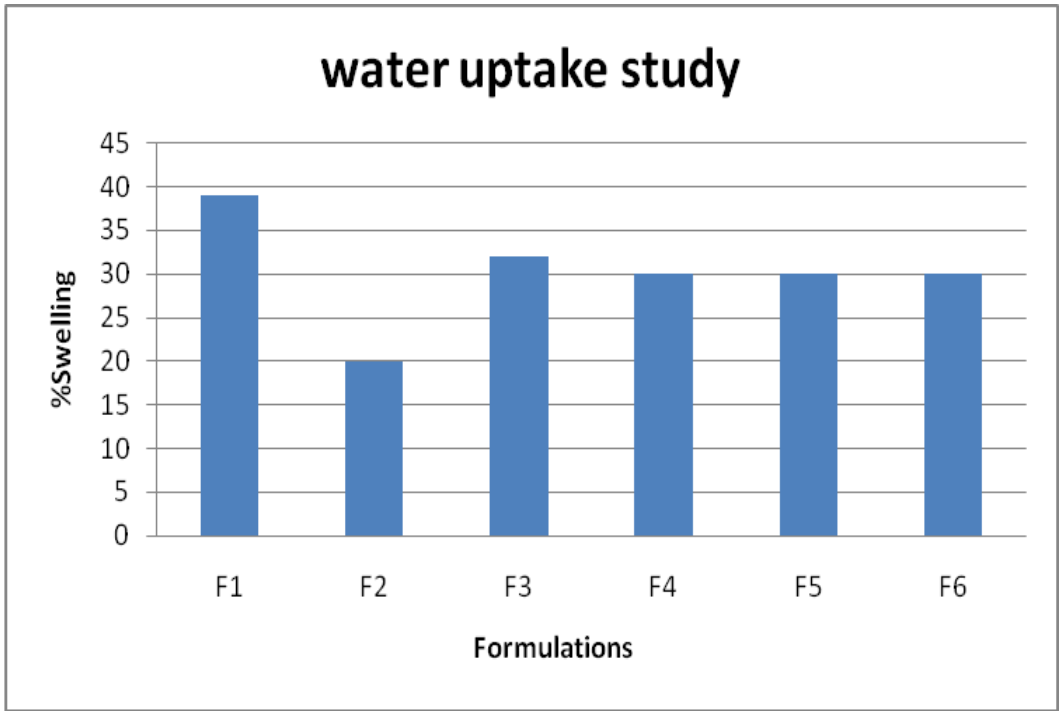

Figure 3 :Water uptake study

The percentage swelling of the tablets was determined at different time intervals. The complete swelling was achieved at the end of 2hrs. The percentage swelling of F1 was found to be higher than that of other formulations.

Drug release studies

Table 13: Percentage cumulative drug release from the formulations (F1, F3)

Time (hrs)	Formulation code			
	F1		F3	
	%CDR	SD	%CDR	SD
0	0	0.00	0	0.00
1	16.05	1.92	22.50	1.84
2	25.60	1.43	35.75	1.63
4	48.50	1.84	53.10	1.08
6	70.45	0.89	64.30	1.92
8	82.40	1.00	75.60	0.89
10	91.25	1.26	83.88	1.00
12	99.00	1.00	94.10	1.00
14	-	-	99.00	1.00

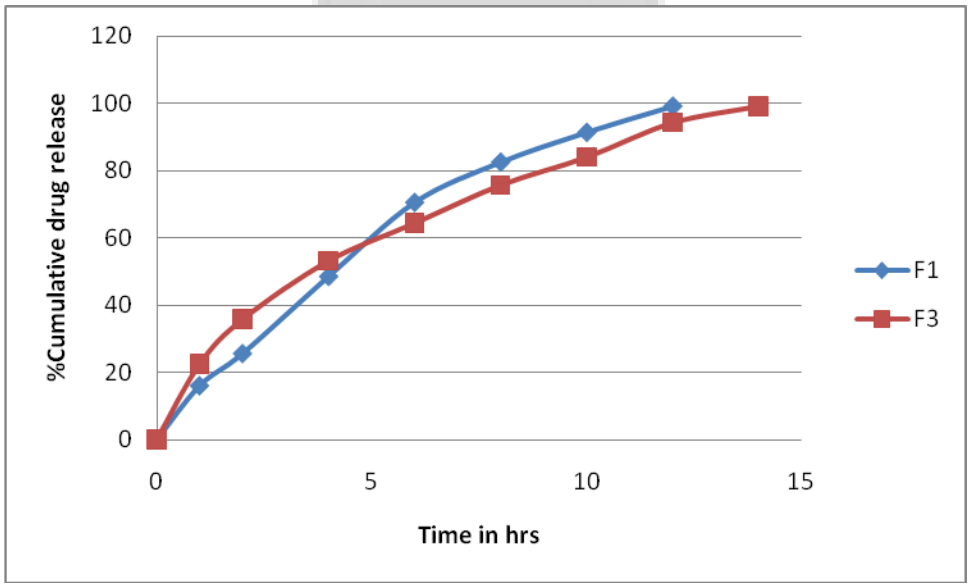

Figure 4: Comparative *in vitro* release of ofloxacin from developed formulations (n=6). Standard deviations was found to be less than 2% in all the *in vitro* release profiles.

Table 14: Percentage cumulative drug release from the formulations (F4-F6)

Time (hrs)	Formulation code					
	F4		F5		F6	
	%CDR	SD	%CDR	SD	%CDR	SD
0	0	0.00	0	0.00	0	0.00
1	21.50	1.48	21.75	1.26	25.05	1.43
2	31.75	0.89	34.55	1.41	39.40	2.25
4	44.10	1.53	50.55	1.98	56.25	1.26
6	61.55	1.92	63.20	1.73	68.15	1.32
8	75.60	1.00	76.10	0.89	77.45	1.00
10	82.60	0.89	83.75	1.10	84.30	1.10
12	92.10	1.10	92.95	1.41	94.85	1.63
14	99	1.00	99	1.00	99	1.00

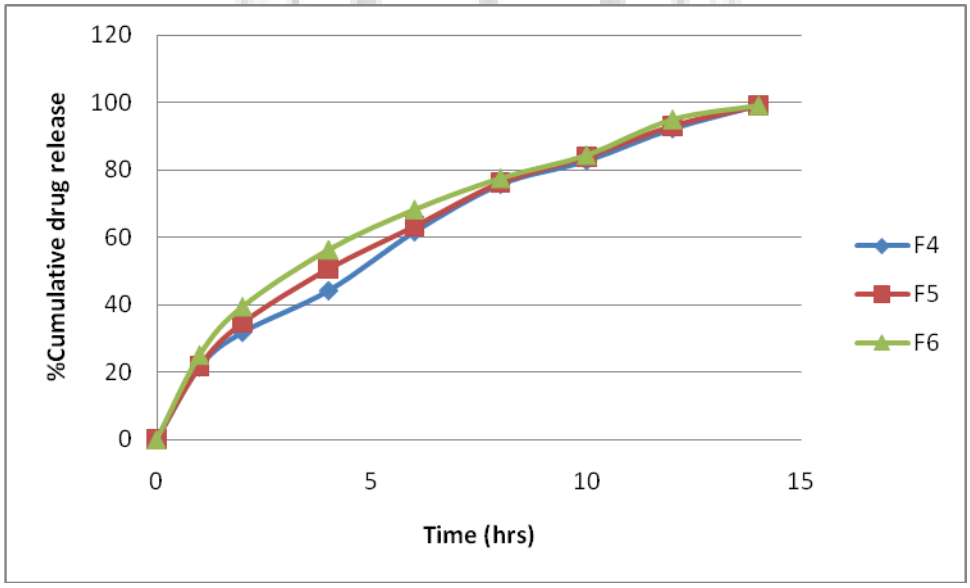

Figure 5: Comparative *in vitro* release of ofloxacin from developed formulations (n=6). Standard deviation was found to be less than 2% in all the *in vitro* drug release profiles.

During the early hrs of study, the % cumulative drug release after 4hrs for formulations F4, F5, F6 were 44.10±1.53, 50.55±1.98, 53.10±1.08, 56.25±1.26%, respectively. This showed that with

an increase in the amount of fines in the formulation percentage drug release was also increased. Formulations F3-F6 were found to be release the drug for a period up to 14 hrs.

CONCLUSION

It can be concluded that gastric retention time of ofloxacin can be increased by formulating it in a floating dosage form using optimum amount of HPC, $NaHCO_3$ and crospovidone. The produced tablet exhibited good floating time and controlled drug release over a period of 14 hours. It was concluded that the floating tablet released drug in stomach in view to have desired action in stomach. The tablets were prepared using dry granulation method and it was realized that the ratio of granules:fines needs to be optimized for achieving good flow property and a satisfactory tablet attributes. The ratio of 80:20 was found to produce tablets showing good results on evaluation. The mechanism of drug release from the tablet was found to be diffusion as well as swelling controlled drug release. As the drug release from optimized formulation was found up to 14 hours, thus, it can be concluded that the prepared formulation can be used as a once a day therapy.

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