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Formulation and Evaluation of GRDDS of Gatifloxacin

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ABSTRACT

In the present study, an attempt was made to formulate and evaluate Gastro Retentive Drug Delivery Systems of Gatifloxacin which inhibits the bacterial enzymes DNA gyrase and topoisomerase IV. Estimation of Gatifloxacin carried out spectrophotometrically at 292nm. The floating tablets of Gatifloxacin, with different polymers release a therapeutic amount of Gatifloxacin to achieve and maintain the desired concentration. Direct compression method was used for formulation of floating tablets. Different types of polymers like HPMC K100M, Sodium CMC, Chitosan and Guar gum were studied for effervescent tablets. The release rate could effectively be modified by varying the "polymer" concentration. The optimized F3 formulation a prepared with HPMC K100M (90mg conc) passed all evaluation tests and showed best results like weight variation 448.54 (mg), Hardness (kg/cm²), thickness (4.41nm), Friability (0.42%), Drug content uniformity (99.93%), Floating lag time 94 sec, Swelling Index (49%) and the % drug release is 99.53% in 12 hrs. The drug release kinetics indicates that the formulation follows zero order release and diffusion mechanism.

Keywords: Gatifloxacin, floating tablets, HPMC K100M, Sodium CMC, Chitosan and Guar gum.

1. INTRODUCTION

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs [1-4]. Over the last few decades, several Gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid mucoadhesive systems that causes bioadhesion to stomach mucosa unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach super porous hydrogel systems, magnetic systems etc [6-10].

The present study is an attempt to develop floating tablets of Gatifloxacin, with different polymers which releases a therapeutic amount of Gatifloxacin to achieve and maintain the desired concentration.Gatifloxacin is an antibiotic of the fourth-generation Fluoroquinolone family that like other members of that family, inhibits the bacterial enzymes DNA gyrase and topoisomerase IV.

2. MATERIALS AND METHODS

Gatifloxacin obtained as a gift sample from Dr Reddy's, Different types of polymers like HPMC K100M, Sodium CMC, Chitosan and Guar gum were used from Rankem, Mumbai.

2.1 PREPARATION OF GATIFLOXACIN FLOATING TABLET

By direct compression method:

Gatifloxacin floating was prepared by direct compression technique using drug and variable concentration of polymers (HPMC K100M, HPC, Guar gum, Sodium cmc, Sodium Bicarbonate, MCC, Mg-stearate and Talc).

The respective powders & optional additives were blended thoroughly with a mortar and pestle. The powder blended was then lubricated with Mg-stearate and purified talc and then compressed on a tablet punching machine.

2.2 Evaluation parameters of Gatifloxacin floating tablets:

PRE-COMPRESSION EVALUATION:

a) Angle of Repose:

It is defined as the maximum angle possible between the surface pile of the powder and the horizontal plane.

$$\emptyset = \tan^{-1}\frac{h}{r}$$

Where, θ = angle of repose,
h = height of pile
r = radius of the base of pile.

Angle of Repose (ɵ)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

b) Bulk Density:

It is the ratio of powder to bulk volume. Bulk density is expressed in gm/cc and is given by,

$D_b = M/V_0$

Where, D_b = Bulk density (gm/cc)
M = Mass of the powder
V_0 = Bulk volume of powder (cc)

c) Tapped Density:

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight (M) of the blend was measured. The tapped density (D_t) was calculated using the following formula

$D_t = M / V_t$

Where, D_t = Tapped Density (gm/cc)
M = Mass of powder (g)
V_t = Tapped volume of powder (cc)

d) Carr's compressibility index:

The simplest way to measure free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index. The compressibility index of the granules was determined by Carr's compressibility index, which is calculated by using the following formula

$$I = \frac{Vo - Vt}{Vo} \times 100$$

e) Hausner's ratio:

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula

Hausner's ratio = Tapped density / Bulk density
Where D_t = tapped density
D_b = bulk density.

2.3 POST-COMPRESSION EVALUATION

a) Weight variation:

Twenty tablets were individually weighed and average weight was calculated. The individual weight was compared to the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage.

Percent deviation = [(Individual weight- average weight)/average weight] x 100

b) Hardness:

Take ten tablets individually. The hardness of the tablet from each formulation was determined using Monsanto hardness tester.

c) Friability:

Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution.

Friability (f) = $(1 - \frac{W_0}{W}) \times 100$

Where, W_0 = weight of the tablets before the test
W = weight of the tablet after the test

d) Thickness and diameter:

The thickness and diameter of tablet was carried out using Digital calliper. Five tablets were used for the above test from each batch and results were expressed in millimetre.

e) Drug content:

Powdered five tablets extraction was carried out using 0.1 N HCL. The concentration was determined spectrophotometrically against appropriate blank. Calculate the content of Gatifloxacin specific absorbance at 292 nm as given in IP.

f) Floating or Buoyancy Test:

The time taken for tablet to emerge on the surface of the medium is called the floating lag time (FLT) or buoyancy lag time (BLT) and duration of time the dosage form constantly remains on the surface of the medium is called the total floating time (TFT). The buoyancy of the tablets was studied in USP type II dissolution apparatus at 37 ± 0.5^0C in 900ml of simulated gastric fluid at 0.1N HCl. The time of duration of floatation was observed visually.

g) Swelling index:

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all the formulation was studied. One tablet from each formulation was kept in a Petridish containing 50 ml of 0.1N HCL. At the end of 1 hr, the tablet was withdrawn, soaked with tissue paper, and weighed and taken after 10 hrs. % weight gain by the tablet was calculated by formula;

S.I = {(Mt-Mo) / Mo} X 100,

Where, S.I = Swelling index,
Mt = Weight of tablet at time "t"
Mo = weight of tablet at time t = 0.

h) In-vitro buoyancy studies

The *in vitro* floating behaviour of the tablets was studied by placing them in 100 ml beaker containing 100 ml of 0.1 N HCL (pH 1.2, 37^{0}C). The time, tablet required for the drug to emerge on the surface is floating lag time (FLT) or buoyancy lag time (BLT).

i) *In-vitro* dissolution studies

The release rate of Gatifloxacin from floating tablet was determined using the United States Pharmacopoeia (USP) dissolution testing apparatus II. The dissolution test was performed using 900 ml of 0.1 N HCL, at 37 ± 0.5^{0}C and 50 rpm. The samples were taken at pre-selected time intervals with replacement of equal volume of dissolution medium.

Table 1: Composition of Gatifloxacin floating Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug(mg)	200	200	200	200	200	200	200	200	200	200	200	200
HPMCK100M (mg)	45	67.5	90	--	--	--	--	--	--	--	--	--
Sodium CMC (mg)	--	--	--	45	67.5	90	--	--	--	--	--	--
Guar Gum(Mg)	--	--	--	--	--	--	45	67.5	90	--	--	--
CHITOSAN(mg)	--	--	--	--	--	--	--	--	--	45	67.5	90
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
$NAHCO_3$(mg)	40	40	40	40	40	40	40	40	40	40	40	40
Mg –Stearate	9	9	9	9	9	9	9	9	9	9	9	9
TALC(mg)	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Total (mg)	450	450	450	450	450	450	450	450	450	450	450	450

3. RESULTS AND DISCUSSION

The solubility of Gatifloxacin was very poor in water (0.126mg/ml) when compared to 0.1N HCl & 6.8 pH (0.358 & 0.220mg/ml) From the Fig, it indicated that, as the pH of the buffer increased, the solubility decreased from 0.358 to 0.220 mg/ml. Hence the solubility of Gatifloxacin was pH independent. Determination of Gatifloxacin λ-max was done in 0.1N HCL medium for accurate quantitative assessment of drug dissolution rate. The λ-max was found to be 292 nm, i.e., at its absorption maxima.

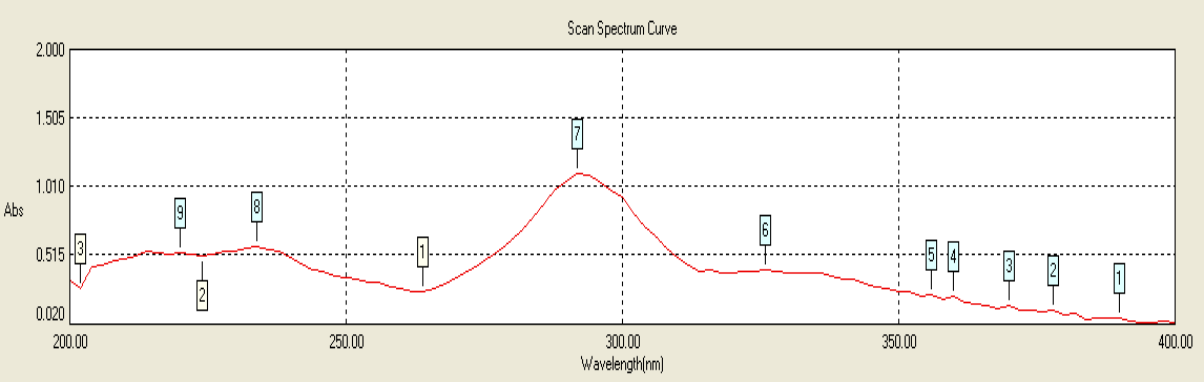

Figure 1: Scan Spectra of Gatifloxacin

Table 2: Standard graph of Gatifloxacin in 0.1N HCL (λmax 292 nm)

Concentration (µg/ml)	Absorbance
0	0
2	0.11
4	0.238
6	0.369
8	0.499
10	0.64
12	0.775

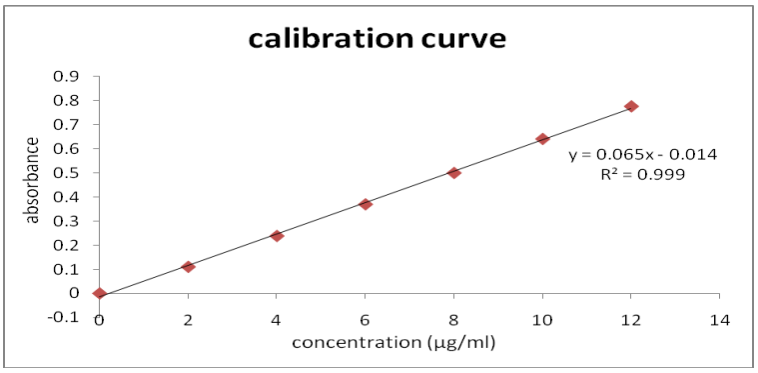

Figure 2: Standard calibration curve of Gatifloxacin in 0.1N HCL

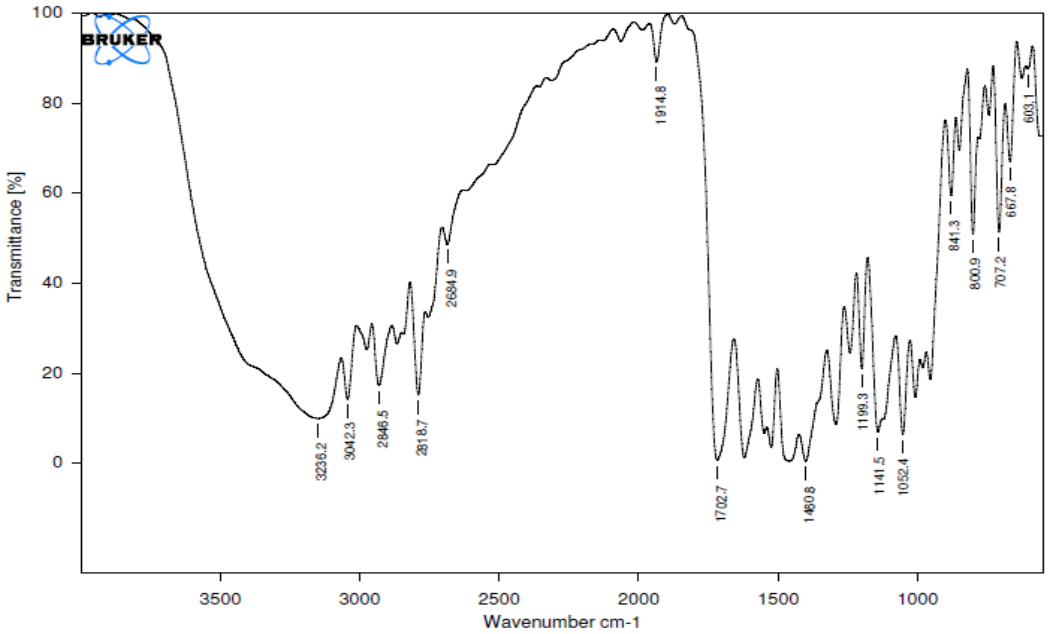

Figure 3: IR spectrum of Gatifloxacin pure

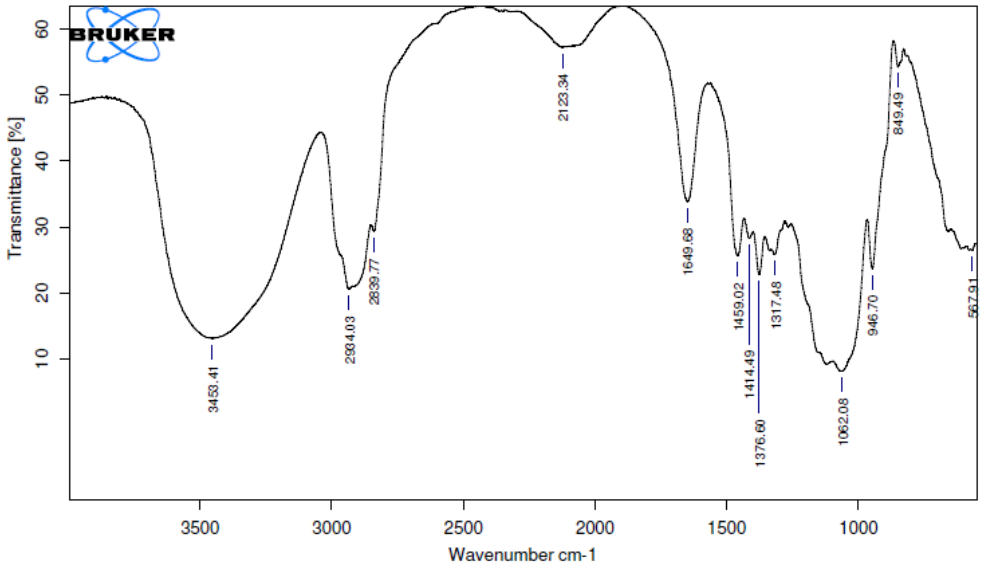

Figure 4: FT-IR Spectra of Gatifloxacin optimized

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied.

Pre-compression parameters of Gatifloxacin floating tablets

- Angle of repose was in the range of 21.30^0 – 25.31^0
- Bulk density was in range of 0.210 – 0.251 gm/ml
- Tapped density was in the range of 0.250 – 0.300 gm/ml
- Hausner's ratio was in the range of 1.124 - 1.209
- Carr's index was in the range of (11.423 – 17.676)

Post-compression evaluation of Gatifloxacin floating tablets

- Weight variation values -- within the limits,
- Hardness of the prepared formulations --3.02 – 3.75 Kg/cm^2
- Thickness of the prepared formulations ranges from4.11 – 4.42 mm
- Friability of all the prepared formulations was less than 1%
- Drug content uniformity of all the prepared formulations was between 96.37 – 99.43%.
- Floating lag time ranges from61-148 sec
- Total floating time more than 12 hrs
- Swelling index values ranges from 49-98% by the end of 10 hours.

Table 3: *In-vitro* drug release data of formulation F1 – F6

Time (hrs)	% Cumulative Drug Release					
	F1±SD	**F2±SD**	**F3±SD**	**F4±SD**	**F5±SD**	**F6±SD**
0	0	0	0	0	0	0
1	16.20±0.120	14.70±0.120	11.15±0.245	27.03.±0.150	24.98±0.101	20.44±0.154
2	23.04±0.112	20.23±0.100	19.37±0.119	36.14±0.089	35.74±0.074	33.23±0.069
3	31.48±0.145	28.77±0.242	26.10±0.098	45.25±0.231	45.69±0.087	40.96±0.250
4	44.31±0.210	39.35±0.254	37.41±0.021	57.93±0.175	53.26±0.112	49.78±0.189
5	55.08±0.147	47.07±0.174	44.18±0.144	68.74±0.100	64.01±0.207	57.55±0.050
6	67.66±0.162	56.56±0.058	54.64±0.112	77.60±0.098	75.78±0.348	68.01±0.147
7	78.33±0.152	67.91±0.156	63.11±0.054	85.56±0.114	82.17±0.307	76.34±0.215
8	85.78±0.158	75.84±0.132 84.03±0.007	72.03±0.214	92.24±0.123	89.03±0.309	81.13±0.121
9	91.23±0.089		80.82±0.033	98.06±0.245 ---	94.17±0.352	88.08±0.097
10	98.49±0.178 ---	90.15±0.102	88.36±0.102	---	100.77±0.396 ---	93.58±0.145
11	---	97.72±0.144	93.23±0.110	---	---	97.30±0.015
12		---	99.57±0.201			---

Time (Hrs)	% Cumulative Drug Release					
	F7±SD	**F8±SD**	**F9±SD**	**F10±SD**	**F11±SD**	**F12±SD**
0	**0**	0	0	0	0	0
1	8.42±0.150	13.45±0.120	12.06±0.088	15.05±0.112	14.08±0.207	12.44±0.116
2	16.08±0.059	20.60±0.116	18.37±0.222	27.23±0.021	25.51±0.198	20.23±0.148
3	27.11±0.101	25.23±0.232	26.10±0.129	36.41±0.214	32.42±0.041	28.96±0.155
4	36.36±0.203	40.80±0.250	35.41±0.079	47.55±0.147	44.34±0.212	36.78±0.212
5	47.57±0.254	53.47±0.148	46.18±0.120	58.36±0.104	53.09±0.100	47.55±0.236
6	55.78±0.039	59.70±0.211	57.64±0.236	67.09±0.254	62.43±0.098	59.01±0.125

7	63.90±0.100	67.03±0.140	64.11±0.244	74.04±0.198	71.17±0.203	67.34±0.200
8	72.86±0.187	74.36±0.254	75.03±0.123	81.45±0.168	79.22±0.174	78.13±0.215
9	81.66±0.123	83.69±0.258	84.82±0.036	90.22±0.152	85.84±0.078	87.08±0.198
10	88.06±0.241	87.45±0.098	89.36±0.147	98.78±0.187	91.65±0.169	92.58±0.008
11	97.27±0.098	91.47±0.102	93.23±0.115		97.74±0.202	98.30±0.140
12		96.78±0.075	97.57±0.216			

In vitro dissolution studies for all the formulations (F1-F12) were studied. All the formulations showed sustained release but the formulation which contained drug and HPMC K100M (90 mg) (F3) showed sustained release of 99.57% by the end of 12 hours was selected as optimized formulation. From the above In vitro drug release kinetics studies we can say that the optimized formulation (F3follows zero order release with R^2 value 0.996 and best fitted into higuchi plot with R^2 value 0.936 indicates diffusion mechanism of drug release.

Table 4: Release Kinetic data of Optimised Formulation (F3)

order of kinetics	Zero order	First Order	Higuchi	Korsmeyer peppas
Release Kinetics	0.996	0.722	0.936	0.809

Comparison with Marketed Product:

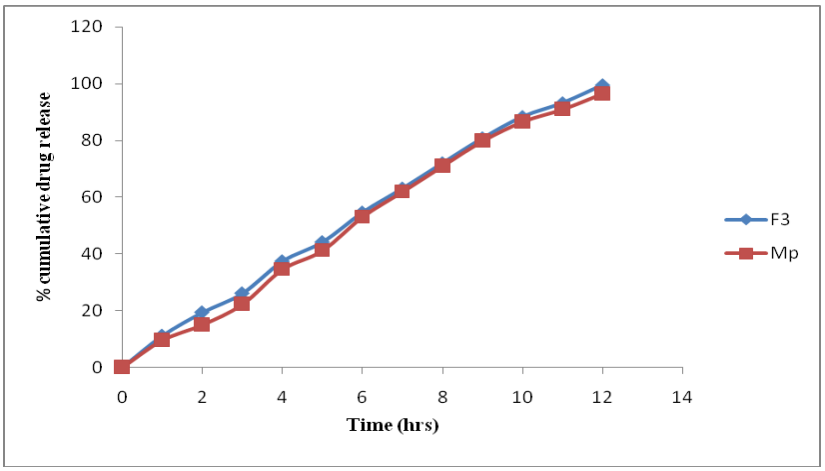

Figure 5: Comparison of *in vitro* drug release profile of F3 and Marketed product

4. CONCLUSION

Basing on the project results, it is concluded that, HPMCK100M, Guar gum, Chitosan, Sodium CMC were compatible with drug Gatifloxacin and thus suitable for the formulation of Gatifloxacin floating tablets. The concentration of the polymer is a major factor affecting the drug release and floating properties of FDDS. Gatifloxacin has been successfully formulated as floating drug delivery system meeting the objectives of the study.

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