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Original Article

Formulation & Evaluation of Floatable *In-situ* Gel for Stomach-specific Drug Delivery of Ofloxacin

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ABSTRACT

Objective: The purpose of this study was to evaluate the potential for oral sustained delivery of ofloxacin. The plasma half-life of ofloxacin was 4 hrs and dose was 200-800mg twice/thrice a day depending on severity of infection. Dose >400mg was given in two divided dose. Hence ofloxacin was chosen as a model drug with an aim to develop a sustained release system for 16 hrs. **Experimental Method:** Oral administration of aqueous solution of sodium alginate (1% w/v) containing calcium ion (1.5% w/v) in complexed form resulted in formulation of gel. The effects of different concentration of sodium alginate and calcium carbonate on viscosity and drug release at 10 hrs (% Q10) were studied using 3^2 factorial designs. The prepared formulation were evaluated for various parameter like floating lag time, total floating time, pH, gelling time and gelling capacity, swelling index, drug content and in-vitro drug release. The optimized formulation was subjected to stability study for 1 month.

Keywords: *In-situ gel, sodium alginate,* sustained drug delivery.

INTRODUCTION

In situ gel forming systems have been widely investigated as vehicles for sustained drug. This interest has been sparked by the advantages shown by in situ forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. So, In situ gelling system via different route such as oral, nasal, ophthalmic etc can be formulated. Various natural and synthetic polymers such as gellan gum, alginic acid, xyloglucan, pectin,

chitosan, poly (DL lactic acid), poly (DL-lactide-co-glycolide) and poly-caprolactone are used for formulation development of in situ forming drug delivery systems. Gastroretentive in situ gelling system helps to increase bioavailability of drug compared to conventional liquid dosage form. The gel formed from in situ gelling system, being lighter than gastric fluids, floats over the stomach contents or adhere to gastric mucosa due to presence of bioadhesive nature of polymer and produce gastric retention of dosage form and increase gastric residence time resulting in prolonged drug delivery in gastrointestinal tract. This review attempts to discuss stomach specific in situ gelling system in detail including formulation factors to be considered in the development of in-situ drug delivery system.

In situ forming gels are formulations, applied as a solution, which undergoes gelation after instillation due to physicochemical changes inherent to the biological fluids. In this way, the polymers, which show sol-gel phase transition and thus trigger drug release in response to external stimuli, are the most investigated. In-situ hydrogels are providing such 'sensor' properties and can undergo reversible sol-gel phase transitions upon changes in the environmental condition. These "intelligent" or "smart" polymers play important role in drug delivery since they may dictate not only where a drug is delivered, but also when and with which interval it is released.

Ofloxacin is a synthetic fluorinated carboxyquinolone that has a broad spectrum of activity. It is highly soluble in acidic pH and has absorption window to upper part of GIT. 200-800mg dose administered twice or thrice a day for 5-7 days depending on severity of infection. Dose greater than 400 mg is given in two divided dose. In the present study, the potential for the sustained delivery of ofloxacin of a liquid formulation comprising a dilute aqueous solution of sodium alginate that is designed to form gels in situ in the acidic environment of the stomach. It requires multiple dosing to obtain the required therapeutic doses and to attain steady state plasma concentration. So, large dose of drug can be incorporated and ultimately frequency of administration is being reduced.

MATERIALS AND METHODS

Materials used in present investigation

Ofloxacin, Na-Alginate, HPMC K4M, HPMC K15M, Calcium Carbonate, Sodium Bicarbonate, Sodium Bicarbonate, Methyl Paraben, Propyl paraben, aspartame, 0.1 N HCl, HPMC K100M.

Equipments used

See table 1.

Method of preparation of in situ gelling solution

Sodium alginate solutions of concentrations 0.25, 0.5, 1.0, 1.5 and 2.0% (w/v) were prepared by adding the alginate to purified water containing 0.50% (w/v) Trisodium citrate with stirring and calcium carbonate (prescreened by 60 #) was dissolved in another beaker. Ofloxacin (2700 mg) was then dissolved in 10 ml of 0.1N HCl solution (pH 1.2) and added in the resulting solution. The HPMC K4M, HPMC K15M and HPMC K100M were also added in respective batch in different concentration. Methyl Paraben and Propyl Paraben were dissolved in 9:1 ratio in purified water in sufficient quantity along with aspartame. These solutions were mixed with above solution. The resulting alginate in situ gel solution containing Ofloxacin was checked for lag time, viscosity and gelling property. In the preliminary batches P1 to P15 the concentration of Aspartame, preservatives and Trisodium citrate were kept constant at 0.5, 0.2, and 0.5% respectively.

Dose calculation

Total dose = loading dose (immediate) + maintenance dose (sustained) = 170mg + 640mg = 810mg

Now, 810mg dose is given in 1 table spoonful (i.e. 15ml). So, for 50ml solution 50*810/15 = 2700mg ofloxacin required. [loading dose was calculated by IR = Css× Vd / F formula while maintenance dose was calculated by MD = IR (1+0.693× t/t1/2) formula.]

Determination of drug & its compatibility with excipients

1) IR Spectroscopy

The Infra red spectroscopy of the sample was carried out to ascertain identity of the drug. A pellet of approximately 1mm diameter of each drug was prepared by compressing 3-5mg of the drug with 100-150mg of potassium bromide in KBr press (Model M-15, Techno Search Instruments). The pellet was mounted in IR compartment and scanned between wave number 4000–600cm^{-1} using a Shimadzu Model 8400 FTIR.

2) Drug-Excipients Compatibility Study

FTIR absorption spectra of pure drug and physical mixture were recorded in range of 4000 – 400 cm^{-1} by KBr disc method using FTIR spectrophotometer.

EVALUATION PARAMETER OF IN SITU FLOATIG GEL pH

The pH was measured of in situ solutions of ofloxacin using a calibrated digital pH meter at 25°C. All measurements of pH were made in triplicate.

In-vitro floating study

Floating study was carried out in 500 ml of 0.1 N HCl (pH 1.2) in a beaker. Accurately measured 10 ml of solution was added to HCl. Time requires for immersed on surface after adding solution (floating lag time) and total floating time were measured.

Viscosity measurement of in situ gels

Viscosity of the *in situ* gelling solution was determined with a Brookfield viscometer (Model no RVT 6513476) using a 20 ml aliquot of the sample. Measurements were performed using spindle number 2 and the temperature was maintained at 25±1^{0}C. All measurements were made in triplicate.

In vitro gelation study

To evaluate formulation for their gelling capacity by visual method, coloured solution of *in situ* gel was prepared. The gelling capacity was measured by placing 5 ml of gelation solution (0.1 N HCl, pH 1.2) in test tube and maintained at 37±1^{0}C. One ml of coloured solution was added with pipette. The formulation was transferred in such a way that places pipette at surface of fluid in test tube and formulation was slowly released from pipette. As solution comes in contact with gelation solution, it was immediately converted into stiff gel like structure. The gelling capacity was evaluated on basis of stiffness of formed gel and time period for which formed gel remained as such. The gelling capacity was graded in 3 categories on basis of gelation time and time period for which formed gel remain as such.

\+ = gels after few minutes, dispersed rapidly
++ = gelation immediate remains for few hour
+++ = gelation immediate remains for an extended period.

Determination of drug content

Accurately, 1ml of *in situ* gelling solution (equivalent to 54mg of ofloxacin) was added to 53ml of purified water to yield solution containing strength of 1000µg/ml. From that 5µg/ml solution was prepared by diluting stock solution. The UV absorbance of the sample was determined at a wavelength of 294nm.

Swelling Index

A gel of 100mg was weighed accurately (W1). It was kept in a petri dish and 50ml of 0.1 N HCl was added. The petri dish was kept aside for 16 hrs. The weight of swollen matrix gel (W2) was measured and swelling index was calculated using following formulae:

$$\text{Swelling Index} = \frac{W2 - W1}{W1} \times 100$$

Where, W1 = initial weight of gel (100mg)
W2 = weight of swollen matrix after 16 hrs.

In vitro drug release study

The release rate of ofloxacin was determined using USP apparatus 1 (basket covered with muslin cloth/cellophane paper) at 50 rpm. This speed slow enough to avoid breaking of gelled formulation and was maintaining mild agitation condition exist *in vivo*. The dissolution medium used was 900ml of 0.1 N HCl and temperature was maintained at 37^0C. A sample was withdrawn at 0.5,1,2,3,4,6,8,10,12,14 and 16 hrs of dissolution. The sample was analysed and % cumulative release was calculated.

Stability study

Accelerated stability testing of promising formulation was performed as per International Conference on Harmonization (ICH) guidelines. The optimized formulation (F5) was stored at 40 ± 2^0C/75±5% RH in Temperature/ Humidity Control Chamber for a period of 1 months. The chemical stability was analyzed by percentage drug release. The samples were withdrawn after 1 month and the was analyzed spectrophotometrically at 294nm.

RESULT & DISCUSSION

Justification for selection of promising batch (p13)

Sodium alginate at 1% concentration, it formed stiff gel. Below 1%, gel was formed but rupture. HPMC-K_{15}M formed viscous solution at 0.5% concentration. HPMC-K_{100}M formed non-pourable solution at 0.5% concentration. HPMC-K_4M at low concentration (0.5%) gave moderately viscous solution along with enough gel strength. Sodium bicarbonate showed dosage form dumping & gel shows fragmentation within 4-5 hr. Calcium carbonate at low concentration (<1%) showed poor cross-linking due to insufficient concentration of Calcium ions.

Here, in batches P1, P2 and P3 gel was formed but it was rupture and showed fragmentation in 2-3 hrs due to poor cross linking of sodium ion due to low concentration of sodium bicarbonate. While in case of batches P4, P5 and P6 solution were highly viscous due to HPMC K_{15}M. At the same time batches P7 and P8 were non-pourable due to HPMC K_{100}M. Dissolution studies were performed only for P6, P7 and P8 batches. In case of batches from P9 to P12, gel were formed and remained intake for 7-8 hrs with floating lag time ranges from 30-90 seconds. Batch P13 was taken as a promising batch. The reason was that it remained intake for >16 hrs and it had optimum viscosity along with sufficient gel capacity. Concentration of sodium alginate was optimized at 1% and HPMC K $_4$M was optimized at 0.5%. Among all these batches (from P1 to P15), batch 13 had optimum viscosity and it has enough gel capacity. P13 showed maximum drug release in 16 hrs among selected batches. So, on bases of these evaluation parameters and release profile, **P13** had been selected as promising batch.

Comparison of dissolution of preliminary batches

See fig. 3 & Table 7.

Comparison of dissolution of factorial Design batches

Here, batch F1, F2 and F3 formed gel and it remained intake upto 8 hrs due to slightly low concentration of sodium alginate. Hence, dissolution of these batches was not taken. Batch F5 gives maximum % release of drug in 16 hrs. F4 releases more than 90% of drug but only for 10-11 hrs. F9 showed 85% release in 16 hrs due to slightly higher amount of Sodium alginate and calcium carbonate. So, F5 considered as optimized batch in suitable time period.

Statistical analysis of data

- A full factorial 3^2 design was used for optimization procedure. This study investigated utility of a 2-factor, 3-level design and optimization process. The studied factors (independent variables) were concentration of sodium alginate (X1) and concentration of calcium carbonate (X2). Preliminary studies provided a setting of the levels for each formulation variable. The response (Y) (dependent variables) studied were viscosity and % drug release at 10 hrs (Q10). The factorial formulations were coded as F1 to F9.
- A statistical model incorporating interactive and polynomial term was used to evaluate the response
- $Y = \beta0 + \beta1X1 + \beta2X2 + \beta12X1X2 + \beta11X12 + \beta22X22$
- Where, Y is the dependent variables, β0 is the arithmetic mean response of the nine runs, and β1 is the estimated coefficient for the factor β1. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1X2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X12and X22) are included to investigate non-linearity.

From the data of viscosity, a polynomial equation for full model was derived as shown below:

$Y1 = 233.7756 + 48.11X1 + 31.22167X2 – 1.335X1X2 – 0.3333X12 + 6.331667X22$

Equation gives positive value of X1 and X2 which indicates X1 and X2 have positive effect on viscosity. From regression analysis for viscosity, it was shown that only effect of X1 and X2 are significant. So polynomial equation has reduced form as shown in equation below:

$Y1 = 233.7756 + 48.11X1 + 31.22167X2$

From the data of Q10, a polynomial equation for full model was derived as shown below:

$Y2 = 78.27778 + 33.00833X1 – 5.15333X2 – 3.5325X1X2 – 47.6917X12 + 3.63333X22$

Equation gives positive value of X1 which indicates X1 have positive effect on Q10 i.e. drug release in 10 hrs. From regression analysis for Q10, it was shown that only effect of X1 and X12 are significant. So polynomial equation has reduced form as shown in equation below:

$Y2 = 78.27778 + 33.00833X1 - 47.6917X12$

Photoes of In-situ gel

See fig. 5,6.

Conclusion

Ofloxacin was successfully formulated as a floatable in-situ gel for delivery of drug into gastric region for 16 hrs. The floating lag time decreases as concentration of calcium carbonate increases and viscosity increases with increases in concentration of sodium alginate and HPMC K_4M. The optimized formulation (**F5** of factorial batch i.e. 1.0 % sodium alginate, 0.5% HPMC K_4M and 1.5% calcium

carbonate) showed moderate viscosity along with sufficient gel strength. >95.0% drug release achieved at the end of 16.0 hrs. Drug release and viscosity could be adjusted by varying concentration of sodium alginate, HPMC K_4M and calcium carbonate. The optimized formulation **F5** was seen to be stable after 1 month of stability study. The result suggested that developed floating in-situ gel could perform better than conventional dosage form leading to improve efficacy and better patient compliance.

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Table 1. List of equipments used in present investigation

EQUIPMENTS	MODEL/COMPANY
Digital weighing balance	Shimadzu-AUX220
UV-spectrophotometer	Shimadzu-1800
Mechanical stirrer	DBK- instruments
IR spectrophotometer	Shimadzu 8400
Dissolution test apparatus	Electrolab TDT-081
Brookfield viscometer	RVT-6513476

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Table 2. Composition of preliminary batches (P1 to P8)

Ingredients (mg)	P1	P2	P3	P4	P5	P6	P7	P8
OFLOXACIN	2700	2700	2700	2700	2700	2700	2700	2700
Sodium alginate	250	500	1000	500	750	1000	250	500
HPMC-K_4M	500	500	500	-	-	-	-	-
HPMC-$K_{15}M$	-	-	-	250	250	250	-	-
HPMC-$K_{100}M$	-	-	-	-	-	-	250	250
$CaCO_3$	-	-	-	500	500	500	500	500
$NaHCO_3$	500	500	500	-	-	-	-	-
Trisodium-citrate	250	250	250	250	250	250	250	250
Methyl Paraben	90	90	90	90	90	90	90	90
Propyl Paraben	10	10	10	10	10	10	10	10
Aspartame	250	250	250	250	250	250	250	250
Purified H_2O Upto (ml)	50	50	50	50	50	50	50	50

Table 3. Composition of preliminary batches (P9 to P15)

Ingredients (mg)	P9	P10	P11	P12	P13	P14	P15
OFLOXACIN	2700	2700	2700	2700	**2700**	2700	2700
Sodium alginate	500	750	1000	250	**500**	750	500
HPMC-K_4M	250	250	250	250	**250**	250	250
HPMC-$K_{15}M$	-	-	-	-	**-**	-	-
HPMC-$K_{100}M$	-	-	-	-	**-**	-	-
$CaCO_3$	400	400	400	750	**750**	750	1000
$NaHCO_3$	-	-	-	-	**-**	-	-
Trisodium-citrate	250	250	250	250	**250**	250	250
Methyl Paraben	90	90	90	90	**90**	90	90
Propyl Paraben	10	10	10	10	**10**	10	10
Aspartame	250	250	250	250	**250**	250	250
Purified H_2O Upto (ml)	50	50	50	50	**50**	50	50

Table 4. Composition of 3^2 factorial design batches

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ofloxacin	2700	2700	2700	2700	2700	2700	2700	2700	2700
Sodium alginate	350	350	350	500	500	500	650	650	650
HPMC-K_4M	250	250	250	250	250	250	250	250	250
$CaCO_3$	600	750	900	600	750	900	600	750	900
Trisodium-citrate	250	250	250	250	250	250	250	250	250
Methyl Paraben	90	90	90	90	90	90	90	90	90
Propyl Paraben	10	10	10	10	10	10	10	10	10
Aspartame	250	250	250	250	250	250	250	250	250
Purified H_2O Upto (ml)	50	50	50	50	50	50	50	50	50

Table 5. Evaluation parameter of preliminary batches P1 to P8

Evaluation Parameter	P1	P2	P3	P4	P5	P6	P7	P8
Lag time (sec)	55.66± 2.51	78.33 ± 2.516	112.3± 2.516	65.66 ± 2.309	87.33 ± 2.081	107.6 ± 6.658	79.0 ± 1.732	102.3± 6.027
pH	7.13± 0.057	7.03 ± 0.057	6.86 ± 0.057	6.96 ± 0.057	7.13 ± 0.057	7.16 ± 0.057	7.23 ± 0.057	7.26± 0.057
Gelling time (min)	3.33± 0.152	2.33± 0.208	2.43± 0.208	9.66± 0.057	7.46± 0.208	6.70± 0.173	7.63 ± 0.152	6.26 ± 0.057
Gel capacity	+	+	+ +	+ +	+ +	+ + +	+ + +	+ + +
Viscosity (cp)	78.0± 2.00	92.66 ± 1.154	134.6 ± 3.055	253.3 ± 3.055	284.6 ± 3.055	324.0 ± 3.464	421.6±2. 886	470.0 ± 5.00
Total Floating Time (hr)	<3	<3	<5	<8	<8	>16	>16	> 16
Swelling index (% at 16 hr)	34.69± 3.11	47.98 ± 2.647	62.80 ± 3.601	42.02 ± 2.245	55.22 ± 2.557	65.51 ± 1.992	59.77±1. 651	77.5 ± 3.330
Drug content (%)	83.59± 4.36	83.42± 4.348	93.3± 1.773	89.56 ± 0.807	103.1 ± 4.497	93.13 ± 2.127	95.96 ±2.543	108.7±3. 820
Dissolution (%CR upto)	-	-	-	-	-	79.87 (16 hr)	64.64 (16 hr)	61.36 (16 hr)

Table 6. Evaluation parameter of preliminary batches P9 to P15

Evaluation Parameter	P9	P10	P11	P12	P13	P14	P15
Lag time (sec)	65.66 ± 2.081	80.66 ± 2.56	86.66 ± 4.59	35.33 ± 1.57	**56.0 ± 2.65**	72.66 ± 3.24	48.66 ± 2.309
pH	7.13± 0.057	7.00± 0.07	6.93 ± 0.07	7.23 ± 0.07	**7.36 ± 0.07**	7.40 ± 0.07	7.46 ± 0.057
Gelling time (min)	9.73 ± 0.152	8.56 ± 0.28	7.93 ± 0.12	12.46 ± 0.28	**10.26 ± 0.12**	8.96 ± 0.28	9.96 ± 0.152
Gel capacity	++	++	++	++	**+++**	+++	+++
Viscosity (cp)	106.0 ± 3.464	122.6 ± 1.14	134.6 ± 3.05	201.3 ± 2.39	**241.3 ± 3.05**	272.0 ± 2.00	265.3 ± 1.154
TFT (hr)	<8	<8	<8	<8	**>16**	>16	>16
Swelling index (% at 16 hr)	43.09 ± 1.842	58.72 ± 1.94	71.79 ± 3.25	28.41 ± 2.73	**43.54 ± 2.51**	61.44 ± 1.73	48.58 ± 1.887
Drug content (%)	96.32 ± 2.607	83.58 ± 2.81	87.74 ± 1.78	92.93 ± 0.55	**98.62 ± 2.17**	93.01 ± 1.92	85.28 ± 1.392
Dissolution (%CR upto)	-	-	-	-	**94.72 (16 hr)**	88.82 (16 hr)	90.62 (16 hr)

Table 7. Evaluation parameter of Factorial Design Batches

Evaluation Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lag time (sec)	80.0 ± 3.605	58.3 ± 2.516	40.3 ± 4.725	86.0 ± 4.00	**53.0± 2.645**	44.3 ± 3.214	86.3 ± 4.932	57.3 ± 4.041	46.6 ± 4.725
pH	7.26 ± 0.057	7.43 ± 0.057	7.66 ± 0.057	7.16 ± 0.057	**7.43 ± 0.057**	7.56 ± 0.057	6.96 ± 0.057	7.10 ± 1.087	7.26 ± 0.057
Gelling time (min)	12.50± 0.26	11.86± 0.208	10.86± 0.208	11.16± 0.057	**10.2 ± 0.057**	9.90 ± 0.173	9.13 ± 0.115	8.66 ± 0.152	8.10± 0.200
Gel capacity	++	++	++	++	**+++**	+++	+++	+++	+++
Viscosity (cp)	161.3 ± 1.15	185.3 ± 3.05	222.0 ± 2.00	205.3 ± 3.05	**232.0± 2.00**	276.6 ± 1.15	259.3 ± 2.30	283.3± 1.15	314.6± 3.05
Total Floating Time (hr)	<8	<8	<8	<12	**>16**	>16	>16	>16	>16
Swelling index (% at 16 hr)	32.89± 1.60	37.56± 4.206	41.72± 0.620	44.38± 1.818	**48.2 ± 1.550**	53.9 ± 1.899	53.95± 2.767	58.3 ± 1.355	60.7 ± 1.831
Drug content (%)	86.82± 1.51	103.8± 3.825	95.11± 1.877	89.09± 2.123	**97.8 ± 0.767**	93.5± 2.078	105.5± 2.754	83.7 ± 2.154	95.5 ± 3.690
Dissolution (%CR of 16 hr)	-	-	-	93.72 (10 hr)	**97.84**	94.64	93.52	90.22	85.80

Table 8. Regression analysis of viscosity (Y1)

Regression statistics	
Multiple R	0.998272
R square	0.996546
Adjusted R square	0.990791
Standard error	4.785369
Coefficients	**P value**
β_0 = + 233.7756	7.83E – 06
β_1 = + 48.11	0.000147
β_2 = + 31.22167	0.000533
β_{12} = -1.335	0.61581
β_1^2 = -0.3333	0.927741
β_2^2 = +6.331667	0.158067

Table 9. Regression analysis of Q10 (Y2)

Regression statistics	
Multiple R	0.993902
R square	0.98784
Adjusted R square	0.967574
Standard error	6.815843
Coefficients	**P value**
β_0 = + 233.7756	0.000594
β_1 = + 48.11	0.001288
β_2 = + 31.22167	0.161102
β_{12} = -1.335	0.376161
β_1^2 = -0.3333	0.002195
β_2^2 = +6.331667	0.505697

Table 10. Summary of results of regression analysis

Viscosity						
Response	β_0	β_1	β_2	β_{12}	β_1^2	β_2^2
FM	233.7756	48.11 P=0.000147	31.221 P=0.000533	- 1.335	- 0.3333	6.3316
RM	233.7756	48.11	31.221	-	-	-
%Q10						
Response	β_0	β_1	β_2	β_{12}	β_1^2	β_2^2
FM	78.27778	33.00833 P=0.001288	- 5.1533	- 3.5325	- 47.6917 P=0.002195	3.63333
RM	78.27778	33.00833	-	-	- 47.6917	

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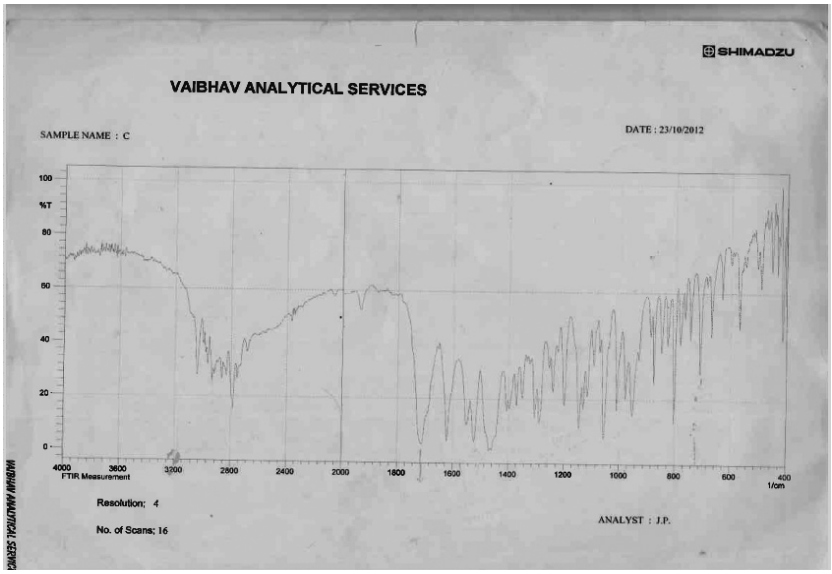
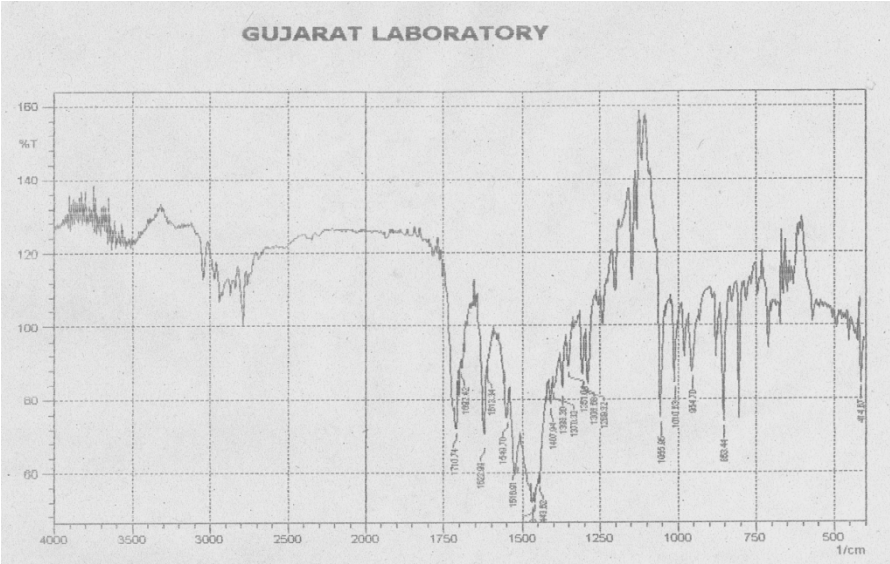


Ofloxacin gives the peak due to ketone (1750-1700 cm-1), quinolone (1650-1600 cm^{-1}), hydroxil (3000-2950 cm-1), C-F strtching (1050-1000 cm^{-1}) group , which are in the ranges that are mentioned in the literature which confirms the identification of drug with its functional groups.

Figure 1. FTIR spectra of Ofloxacin



All the peaks present in physical mixture confirming the presence of Ofloxacin peak in the physical mixture without any interaction. so, drug & polymer are compatible.

Figure 2. FTIR spectra of Ofloxacin and physical mixture

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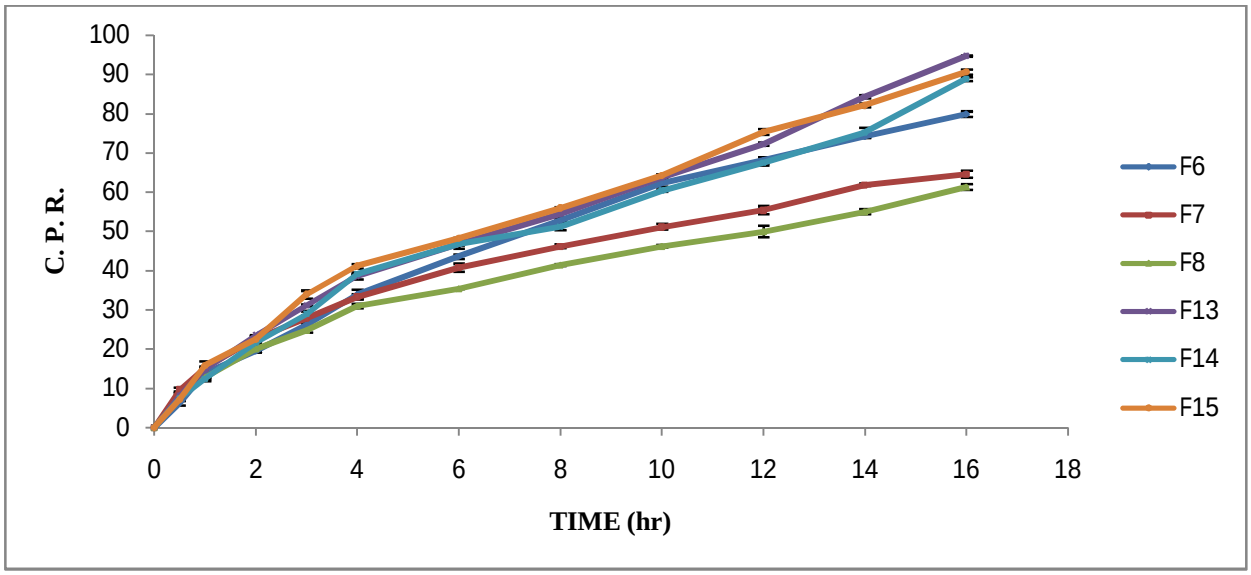

Figure 3. Comparison of release profile of selected batches

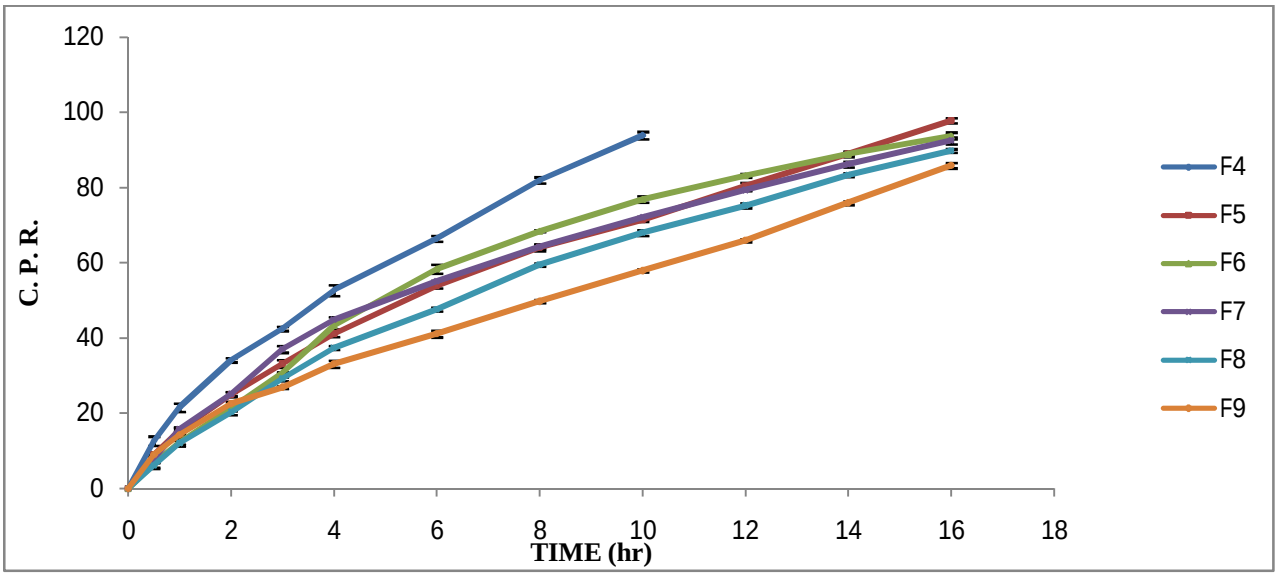

Figure 4. Comparison of release profile of factorial batches

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Figure 5. Immersion of floating *in-situ* gel towards interface

Figure 6. Top view of floating *in-situ* gel after 2 hrs