AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Formulation and Evaluation of Gastroretentive Floating Tablets of Cefixime trihydrate and Ofloxacin

Jyoti Tiwari*
Saraswati institute of pharmaceutical sciences, Dhanap, Gandhinagar, 382355, India

ABSTRACT

Cefixime Trihydrate is an antibiotic third generation cephalosporin. Cefixime Trihydrate is highly stable in the presence of β-lactamase enzymes. Cefixime Trihydrate is an effective treatment to stop the spread of several bacterial infections. Ofloxacin belongs to fluoroquinolones group of antimicrobials. Ofloxacin used to treat pneumonia and bronchitis caused by *H.influenza*. It is also used in treatment of skin infections caused by *staphylococcus aureu*s and *streptococcus pyrogens* bacteria. It is mainly absorbed in stomach. Its PK_a is 2.5 and 5.45 individually; therefore it remains unionized in stomach and maximum absorption take place from stomach only. Gastroretentive Floating tablets were formulated using HPMC K100M as polymer, Citric acid and Sodium Bicarbonate as Gas generating agent, Lactose as diluent and Magnesium stearate as Lubricant. The prepared tablets were evaluated for number of parameters like Weight Variation, Hardness, Friability, Drug Content, *in vitro* buoyancy studies, Swelling index, % Drug release Drug release kinetic, Anti bacterial study, Stability study. The best release for Gastroretentive floating tablet was shown by F19exhibited less floating lag time, highest floating time. Also Formulation F19 was given above 96% drug release after 12hr and above 97% drug content. In FTIR, drug to polymer interaction was not found and formulation F19 was found to be stable.

Keywords: Cefixime Trihydrate, Ofloxacin, Gastro retentive floating tablets, Hydroxyl Propyl MethylCellulose.

*Corresponding Author Email: jyotitiwari0007@gmail.com
Received 14 November 2017, Accepted 03 December 2017

Please cite this article as: Tiwari J *et al*., Formulation and Evaluation of Gastroretentive Floating Tablets of Cefixime trihydrate and Ofloxacin. American Journal of PharmTech Research 2017.

INTRODUCTION

Gastro retentive medication conveyance framework fits in with oral sustained drug delivery framework that are capable to hold the drug into the stomach by passing the gastric transit time. These measurements structures are likewise characterized as floating medication conveyance framework, in that dose of drug can float into the substance of the stomach and discharge the medication in maintained way for the sustained drug delivery. The genuine test in the improvement of a gastroretentive medication conveyance framework is to maintain the dose structure discharge as well as to prolong the effect of drug into the stomach until all the medication is totally discharged. This can be expert by the floating medication conveyance framework, which holds measurement structure into the stomach and discharges the medication in sustained way for longer period of time [1]. Cefixime Trihydrate is a cephalosporin class of drug which is used for treatment of infections caused by susceptible strains of the designated microorganism (UTI, otitis media, pharyngitis and tonsillitis etc.[2,3] Ofloxacin is the class of natural mixes known as quinoline carboxylic acids. It is used in infection (RTI, kidney, UTI) cervical and urethral gonorrhea [4,5]

This combination of Cefixime trihydrate and Ofloxacin has unique dual mode of action i.e. in the combination ofloxacin prevents nucleic acid synthesis of bacteria and Cefixime inhibits bacterial cell wall synthesis. Both works instantly and synergistically and gives better patient compliance. The recommended adult oral dose of Cefixime Trihydrate and Ofloxacin are 200 mg two to three times in day. It is mainly absorbed in stomach. Its PK_a is 2.5 and 5.45 individually; therefore it remains unionized in stomach and maximum absorption take place from stomach only. But the drawback of conventional dosage form is the frequency of administration. Hence, the focus of present work is to prepare and evaluate Gastroretentive Floating tablets to increase residence time in stomach and they're by gives prolong action. Traditionally, Gastric retention is achieved with approaches like Floating drug delivery system, Bioadhesive drug delivery system, swelling and expanding system, High density system, Modified shape system, Raft forming system [6]. For the gastric retention floating approach is a simple approach when compared to other approaches. Here HPMC is release retardant polymer and which is widely used as an extended release agents in the pharmaceutical industry. Thus this study aimed to formulate the Gastroretentive floating tablets of cefixime trihydrate and ofloxacin using HPMC K100M as a polymer and evaluated the pre and post compression parameters of tablets.

MATERIALS AND METHOD

Materials

Cefixime trihydrate and Ofloxacin was gift sample from Montage lab, Himatnagar, Gujarat, India. HPMC were gifts samples from ACS chemical, Ahmedabad, India. All other Chemicals were used were of analytical grade.

Preparation of Gastroretentive Floating tablets of Cefixime trihydrate and Ofloxacin

Composition of preliminary trials for selection of polymer was shown in Table 1. Tablets containing different matrix forming agent were prepared by direct compression technique. All the powders were passed through 80 # sieve. Required quantity of drug and various ingredients like matrix forming agent, gas generating agent and diluent were mixed thoroughly. Talc and magnesium stearate were finally added as glidant and lubricant respectively. The blend was compressed using Remiek mini press tablet machine. Each tablet contained 100 mg of Cefixime Trihydrate and 100mg of Ofloxacin and other pharmaceutical ingredients as listed in table in each section. Different Polymers like HPMC K4M, HPMV K15M, HPMC K100M Gellan gum, Xanthan gum, Guar gum, PEO 301 and PEO 303 are used in 5%, 10%, 15% w/w along with drug and other excipients. In this formula two different gas generating agents like sodium bicarbonate and Citric acid were selected in same concentration. Selection of diluents using the release profile of Cefixime Trihydrate and Ofloxacin floating matrix tablet from different formulation batches containing lactose (water soluble) and dicalcium phosphate (DCP) (water insoluble) were formulated.

Table 1 Preparation of Gastroretentive Floating tablets of Cefixime trihydrate and Ofloxacin

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
ofloxacin	100	100	100	100	100	100	100	100	100	100	100	100
C.T	100	100	100	100	100	100	100	100	100	100	100	100
HPMCK4M	25	_	_	_	_	_	_	_	50	_	_	_
HPMCK15M	_	25	_	_	_	_	_	_	_	50	_	_
HPMCK100M	_	_	25	_	_	_	_	_	_	_	70	_
Gellan gum	_	_	_	25	_	_	_	_	_	_	_	50
Xanthan gum	_	_	_	_	25	_	_	_	_	_	_	_
guar gum	_	_	_	_	_	25	_	_	_	_	_	_
PEO301	_	_	_	_	_	_	25	_	_	_	_	_
PEO 303	_	_	_	_	_	_	_	25	_	_	_	_
citric acid	20	20	20	20	20	20	20	20	20	20	20	20
NAHCO3	20	20	20	20	20	20	20	20	20	20	20	20
sodium CMC	_	_	_	_	_	_	_	_	_	_	_	_
MCC	_	_	_	_	_	_	_	_	_	_	_	_
Lactose	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
DCP	_	_	_	_	_	_	_	_	_	_	_	_
Mannitol	_	_	_	_	_	_	_	_	_	_	_	_
Mg. stearate	10	10	10	10	10	10	10	10	10	10	10	10

Ingredients	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24	F25	F26
ofloxacin	100	100	100	100	100	100	100	100	100	100	100	100	100	100
C.T	100	100	100	100	100	100	100	100	100	100	100	100	100	100
HPMCK4M	_	_	_	_	75	_	_	_	_	_	_	_	_	_
HPMCK15M	_	-	_	_	_	75	_	_	_	_	-	-	-	-
HPMCK100M	_	_	-	_	_	_	75	_	_	_	75	75	75	75
Gellan gum	_	_	_	-	_	_	_	_	_	_	-	-	-	-
Xanthan gum	50	_	_	_	-	_	_	_	-	_	-	-	-	-
guar gum	_	50	_	_	_	-	_	75	_		-	-	-	-
PEO301	_	_	50	_	_	_	_	_	75		-	-	-	-
PEO 303	_	_	_	50	_	_	_	_	_	75	-	-	-	-
citric acid	20	20	20	20	20	20	20	20	20	20	20	40	20	20
NAHCO3	20	20	20	20	20	20	20	20	20	20	40	20	20	20
sodium CMC	_	_	_	_	_	_	_	_	_	_	-	-	-	q.s
MCC	_	_	_	_	_	_	_	_	_	_	-	-	-	-
Lactose	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	-	-	-
DCP	_	_	_	_	_	_	_	_	_	_	-	-	q.s	-
Mannitol	_	_	_	_	_	_	_	_	_	_	-	-	-	-
Mg. stearate	10	10	10	10	10	10	10	10	10	10	10	10	10	10

Pre and post compression parameters of Gastroretentive floating tablets [7, 8]

The compressed tablets were assessed for angle of repose, Bulk and tapped density, Carr's Index, Hausner's ratio, weight variation, hardness, friability and drug content. To compute the weight variation, 20 tablets of each formulation were weighed using an electronic weighing balance (Shimadzu, Japan) and determined the average weight and deviation. Tablet hardness (n=6) was determined using Monsanto tablet hardness tester. Friability was calculated using ten tablets with the help of Roche friabilator (Electrolab, India).

Determination of drug content uniformity

10 tablets were randomly chosen from the batches, weighed and powdered. Powder proportional to 100 mg of Cefixime Trihydrate and 100mg of Ofloxacin was weighed and was diluted with a suitable volume of 0.1M Hydrochloric acid (HCL). The absorbance of the subsequent arrangement was measured spectrophotometrically at the most extreme wavelength of around 264.9 and 284.1 nm, utilizing the arrangement as a clear which is readied in the same way excluding the substance being analyzed**.**

Determination of Floating Parameters

The *in vitro* floating was dictated by watching floating lag time. The tablets were set in a 100 ml measuring beaker containing 0.1N HCl. The time required for the tablet to ascend to the surface and float was considered as the floating lag time. Swelling of hydrophilic polymer relies on the substance of the stomach and the osmolality of the medium. These in the long run impact the discharge, slowing activity and the residence time. For every plan, one tablet was weighed and put

in a measuring beaker containing 200 ml of refined water. After every hour the tablet was expelled from measuring beaker and weighed again up to 12 hrs. The % weight gain by the tablet was calculated by using the formula.

Swelling record (S.I) = {(Wt-W0)/W0} x 100

Where, S.I. = swelling Index, Wt = Weight of tablet at time t, W0 = Weight of tablet before submersion.

FTIR and DSC study

In order to check the compatibility of Cefixime Trihydrate and Ofloxacin with their Excipients, FT-IR spectra of the formulations along with Excipients were obtained. Potassium bromide (KBr) pellet method was employed. The samples were thoroughly blended with dry powdered KBr crystals. The mixtures were compressed to form a disc. The spectra of both the drug indicated that drugs have not any incompatibility with their Excipients. IR spectra of pure drug Cefixime Trihydrate and Ofloxacin, Excipient HPMC K100M, Different Combinations of Drugs and Excipients and Gastroretentive Floating Tablets were recorded in a Fourier transform infrared (FTIR) spectrophotometer with KBr pellets. 5 mg of pure drug Cefixime Trihydrate, Ofloxacin, HPMC K100M, different Combinations of drugs and excipient and Formulated Gastroretentive floating tablets were sealed in perforated aluminum pans for DSC scanning using an autoclave thermal analyzer system. Temperature calibration wee performed using indium as standard. An empty pan sealed in the same way as the sample was used as a reference. The entire samples were run at a scanning rate of 10◌C/min from 50-300 C.

In vitro dissolution study

The *in-vitro dissolution* tests were performed using USP apparatus (Paddle method).Total no. of tablets used for each test was six (6) units. The Dissolution medium was 900 ml of 0.1N HCl maintained at 37 ± 0.5°C as mentioned in monograph. The Paddle rotation speed was kept at 50 rpm. In all experiments, an aliquot of 5 ml dissolution samples was withdrawn at predetermined time intervals, and replaced with an equal volume of the fresh medium to maintain total volume constant (sink condition). Samples were filtered through filter and analyzed. Cumulative fractions of drug released from the tablets were calculated and plotted as function of time.

Drug release kinetics

The Data acquired from *in vitro* drug discharge studies were fitted into the Disso Software. The Different Kinetic models are used.

In order to understand the mechanism and kinetic of drug release, the drug release data of the in-vitro dissolution studies were analyzed with various kinetic model like, Zero order, First order,

Higuchi's, Korsmeyer peppa's and Hixon crowel

Comparison of Dissolution profile of Cefixime Trihydrate and Ofloxacin Gastroretentive floating tablet with Marketed Cefixime and Ofloxacin Combination

Both the formulations were subjected for in vitro dissolution test USP type II apparatus (Paddle method). The Dissolution medium was 900 ml of 0.1N HCl maintained at 37 ± 0.5°C as mentioned in monograph. The Paddle rotation speed was kept at 50 rpm. In all experiments, an aliquot of 5 ml dissolution samples was withdrawn at predetermined time intervals, and replaced with an equal volume of the fresh medium to maintain total volume constant (sink condition). Samples were filtered through filter and analyzed. Cumulative fractions of drug released from the tablets were calculated and plotted as function of time.

Antibacterial Assay

The antibacterial movement of Formulation was performed by Agar glass Method. It is one of the non computerized in vitro bacterial susceptibility tests. This exemplary technique yields a inhibition zone in mm result for the measure of antimicrobial agents that is expected to inhibit development of particular microorganisms. It is done in Petri plates.

Stability study:

The motivation of stability testing is to give proof of how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental elements. To assess the drug and formulation stability, stability studies were done as per ICH guidelines. Films were placed in a glass beaker lined with aluminum foil and kept in a humidity chamber maintained at 40 ± 2^{o} C and 75 ± 5% relative humidity for 1 month. Changes in the appearance, in-vitro release and unfolding behavior of the stored films were investigated.

RESULTS AND DISCUSSION

FTIR and DSC Study

FTIR spectra and characteristic peaks for pure drugs (Cefixime Trihydrate and Ofloxacin), polymer, and physical mixture of optimized batch were represented in figure 1 to 6 respectively. Pure drug characteristic peaks were observed in pure drug and physical mixture of optimized batch but not in pure polymer. Polymer chrematistic peaks were observed in polymer, physical mixture of optimized batch. Therefore, from this FTIR study can be concluding that the pure drug has no interaction with excipients.

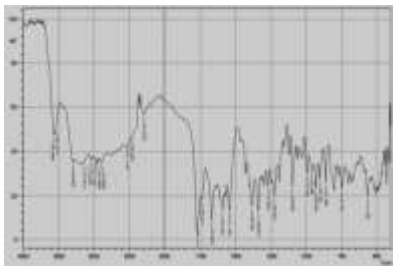

Figure 1:- FT-IR of Cefixime Trihydrate

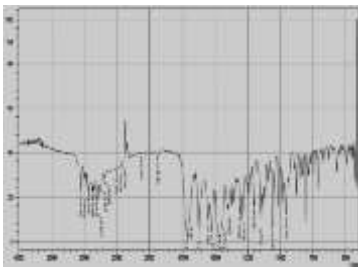

Figure 2:- FT-IR of Ofloxacin

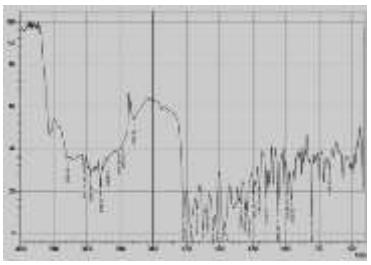

Figure 3:- FT-IR of Cefixime Trihydrate + Ofloxacin

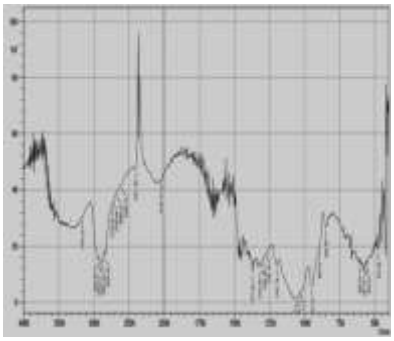

Figure 4:- FT-IR of HPMC K100M

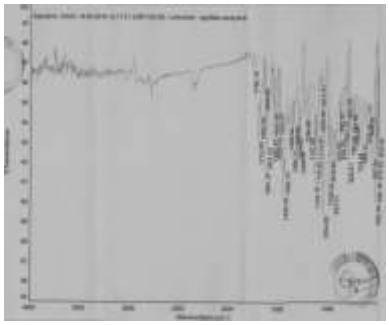

Figure 5:- FT-IR of Cefixime Trihydrate + Ofloxacin + HPMC K100M

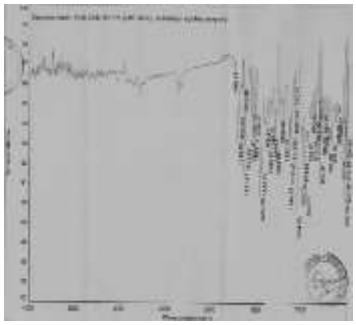

Figure 6:- FT-IR of Optimized Batch

DSC

DSC curve of pure Cefixime Trihydrate, Ofloxacin, Combination of both drug, HPMC K100M and Optimized batch are shown in Figure

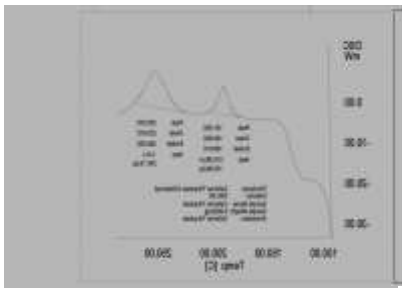

Figure 7 DSC of Cefixime Trihydrate

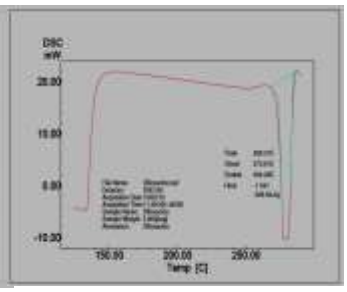

Figure 8 DSC of Ofloxacine

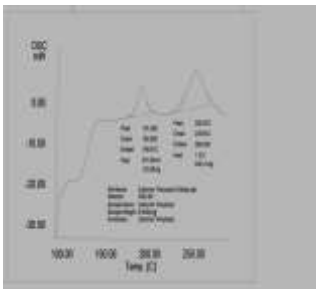

Figure 9 DSC of HPMC K100M

Figure 10 DSC of Cefixime trihydrate + Ofloxacine +HPMC K 100M

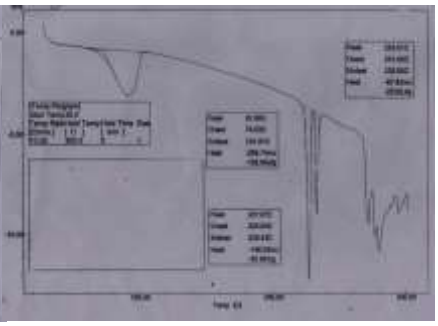

Figure 11 DSC of Optimized Batch

DSC curve of pure Cefixime Trihydrate, Ofloxacin, Combination of both drug, HPMC K100M and Optimized batch are shown in Fig 6 to 12. An endothermic sharp peak measured at 191 ̊C and 280 ̊C in the spectra of pure Cefixime Trihydrate and Ofloxacin correspondence to melting point. A broad endothermic peak observed at 121.98 ̊C correspondence to dehydration of HPMC K100M. In the spectra of Optimized Batch Broad endothermic peak observed at 227.07 ̊C and sharp endothermic peak observed at ̊C respectively for Cefixime Trihydrate and Ofloxacin correspondence to melting point of drug.

Evaluation of Pre-Compression parameters

Results of the pre-compression parameters performed for the powder formulations F1 to F26 are tabulated in Table 2. The bulk density and tapped density for all the formulations varied from 0.28±0.06 to 0.49±0.06 g/ml. The % compressibility was determined using Carr's index. The Hausner's ratio found to be in the range of 1.11±0.05 to 1.21±0.01. Angle of repose of all the formulations shows good flow property of the powder.

Table 2 Evaluation of Pre compression parameters

Batch	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
Cefixime Powder	0.35±0.04	0.39±0.03	12.4±1.8	1.20±0.03	24.52±0.03
Ofloxacin Powder	0.38±0.05	0.41±0.05	13.6±2.0	1.18±0.05	26.35±0.04
F1	0.36±0.06	0.41±.04	14.2±2.8	1.21±0.01	26.85±0.07
F2	0.35±0.04	0.40±.025	14.9±2.1	1.19±0.02	27.65±0.05
F3	0.34±0.05	0.39±0.06	14.7±0.86	1.19±0.05	29.23±0.08
F4	0.36±0.04	0.43±0.02	13.4±3.2	1.18±0.02	27.87±0.04
F5	0.34±0.06	0.41±0.01	13.7±0.66	1.20±0.01	26.43±0.02
F6	0.40±0.05	0.45±0.03	14.2±3.8	1.12±0.01	25.67±0.09
F7	0.39±0.05	0.41±0.03	15.2±4.31	1.18±0.01	26.56±0.0
F8	0.37±0.06	0.41±0.05	14.6±1.4	1.13±0.03	27.92±0.08
F9	0.38±0.05	0.41±0.03	15.4±3.32	1.14±0.02	25.85±0.07
F10	0.34±0.04	0.41±0.05	14.1±1.6	1.16±0.04	26.49±0.06
F11	O.34±0.05	0.42±0.08	14.5±0.51	1.19±0.04	26.67±0.08
F12	0.37±0.04	0.49±0.06	16.2±3.38	1.15±0.01	27.65±0.05
F13	0.34±0.06	0.46±0.09	14.42±1.8	1.17±0.05	27.86±0.01
F14	0.28±0.06	0.35±0.04	14.2±2.31	1.2±0.02	26.45±0.01
F15	0.31±0.05	0.43±0.06	14.3±4.9	1.18±0.04	25.42±0.01
F16	0.28±0.04	0.35±0.03	13.4±3.2	1.16±0.05	28.99±0.01
F17	0.34±0.06	0.45±0.05	11.1±4.3	1.11±0.02	23.88±0.04
F18	0.36±0.05	0.40±0.08	15.4±2.56	1.13±0.04	25.77±0.03
F19	0.35±0.04	0.41±0.05	10.3±0.80	1.17±0.03	22.66±0.06
F20	0.36±0.04	0.41±0.07	12.5±4.3	1.19±0.01	26.55±0.08
F21	0.40±0.06	0.45±0.09	14.03±3.6	1.16±004	26.44±0.06
F22	0.37±0.05	0.48±0.04	14.7±2.75	1.11±0.05	25.33±0.05
F23	0.31±0.05	0.42±0.06	12.5±3.15	1.18±0.01	27.72±0.08
F24	0.40±0.04	0.44±0.08	15.3±4.64	1.21±0.01	26.48±0.01
F25	0.28±0.06	0.40±0.05	13.8±3.6	1.15±0.02	27.63±0.09
F26	0.37±0.04	0.42±0.09	14.1±5.2	1.13±0.03	28.64±0.04

Evaluation of Post-Compression Parameters of Tablets

All the formulations were tested for physical parameters like Hardness, Friability, Weight Variation, and Drug Content. The results of the physical tests of many of the formulations were within the limits and it is comply with the standards.

Table 3 Evaluation of Post-Compression Parameters of Tablets

Powder Blend	Wt Variation	Hardness	Friability	Dg content(C.T)	Dg Content(OFL) (Ofl)
F1	498±2.0	6.45±0.28	0.84 ± 0.26	98.8 ± 0.05	99.8 ± 0.03
F2	499±1.56	7.40±0.25	0.81±0.20	98.91± 0.07	98.99 ± 0.04
F3	500±2.63	6.30±0.29	0.65±0.18	97.52 ± 0.07	97.55 ± 0.02
F4	501±1.63	7.10±0.27	0.63 ± 0.21	97.74±0.0 9	98.76 ±0.0 4
F5	498±1.68	6.13±0.10	0.65 ± 0.24	96.73 ± 0.02	98.78 ± 0.04
F6	499±2.80	7.46±0.29	0.75 ± 0.16	95.51 ± 0.05	99.56 ± 0.02

F7	498±2.69	6.4±0.3	0.86 ± 0.14	95.94± 0.07	99.23± 0.06
F8	501±2.80	7.40±0.6	0.87 ± 0.23	98.25 ± 0.07	98.40 ± 0.03
F9	498±1.90	6.48±0.9	1.02 ± 0.26	96.25 ± 0.05	99.73 ± 0.01
F10	499±2.72	7.40±0.29	0.74 ± 0.17	98.32 ± 0.04	97.92 ± 0.03
F11	501±2.78	6.8±0.13	0.61 ± 0.27	95.60 ± 0.06	98.70 ± 0.02
F12	501±2.95	7.67±0.19	0.69 ± 0.18	98.39 ± 0.04	98.48 ± 0.06
F13	498±1.75	6.90±0.15	0.62 ± 0.15	98.24± 0.06	98.36± 0.03
F14	499±1.88	7.40±0.27	0.51 ± 0.27	93.58 ± 0.04	98.70 ± 0.04
F15	498±2.77	6.80±0.29	0.88 ± 0.13	96.28± 0.05	99.26± 0.02
F16	499±1.98	7.49±0.22	0.68 ± 0.12	99.26± 0.07	98.49 ± 0.02
F17	**501±2.90**	**6.40±0.15**	**0.71 ± 0.15**	**98.72 ± 0.06**	**97.80 ± 0.03**
F18	**500±1.60**	**7.90±0.18**	**0.83 ± 0.09**	**98.14 ± 0.12**	**99.55 ± 0.15**
F19	**498±2.81**	**6.40±0.29**	**0.77 ± 0.03**	**97.47± 0.04**	**98.55 ± 0.02**
F20	499±1.72	7.38±0.26	0.65 ± 0.09	99.63 ± 0.05	98.97 ± 0.03
F21	501±2.99	7.70±0.24	0.79 ± 0.05	94.17 ± 0.06	99.17 ± 0.01
F22	498±1.86	6.90±0.29	0.74 ± 0.27	98.22 ± 0.05	99.73 ± 0.01
F23	499±2.34	7.80±0.25	0.75±0.02	97.64± 0.07	99.26± 0.02
F24	500±1.90	6.88±0.14	0.53±0.25	97.83 ±0.0 5	98.76 ±0.0 4
F25	501±2.23	7.30±0.19	0.88±0.22	98.92 ± 0.04	98.55 ± 0.02
F26	502±0.08	7.35±0.24	0.68±0.32	96.56±0.07	95.64±0.07

Evaluation of In vitro Buoyancy studies:

In vitro buoyancy of the tablet formulations (F1 to F26) was evaluated and the results are mentioned in Table 4 Where, the lowest floating lag time (FLT) and highest total floating time (TFT) was observed with the formulation F17 and F19. The concentration of polymer as increases, floating lag time also increases and total floating time observed for all the formulations was >12 hours.

Figure 12 In vitro Buoyancy study

Table 4 *in vitro* Buoyancy studies

Formulation	Floating lag time (sec)	Total floating time (hr)
F1	uneven floating	5
F2	No floating	No
F3	uneven floating	6
F4	No floating	No
F5	No floating	No

F6	uneven floating	5
F7	No floating	7
F8	No floating	6
F9	201	8
F10	>300	8
F11	180	8
F12	No floating	No
F13	No floating	No
F14	180	8
F15	>300	7
F16	>300	6
F17	90	>12
F18	180	8
F19	51	>12
F20	180	>12
F21	240	8
F22	240	8
F23	120	8
F24	180	8
F25	60	>12
F26	90	>12

Swelling index:

The swelling index of the formulations (F19) was evaluated and the results are mentioned in Table 6.4 and plot of % swelling index vs. time (hrs) is depicted in Fig.13

Table 5 Swelling index

Time (hr)	% swelling index
0	0
1	35.4
2	73
3	111
4	124.6
5	145.4
6	133.8
7	114
8	103
12	96

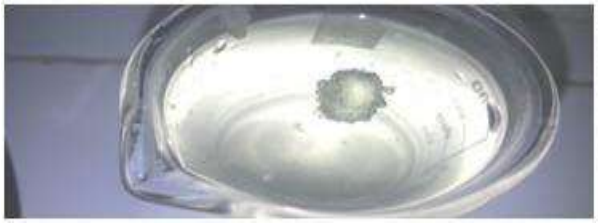

Figure 13: Swelling index

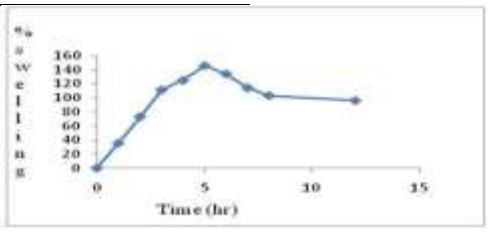

Figure 14: Graph of Swelling index (F19)

Evaluation of In vitro drug release study

Drug release parameter is a very important parameter in a sustained release drug delivery system. It helps to selection of optimized batch from all the formulated batches. Here formulation F1 to F8 taken for the drug release study. These batches (F1 to F8) release the drug within 7hr or less than it. These batches were not fulfilling the criteria as per the theoretical release profile.

Table 6 % Drug release in F1-F8 (Cefixime Trihydrate)

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	7.76±0.01	8.40±0.04	9.70±0.03	8.40±0.02	7.76±0.04	7.76±0.02	10.15±0.01	8.73±0.03
1	16.27±0.03	15.50±0.05	15.05±0.05	23.38±0.03	22.73±0.06	16.27±0.03	15.31±0.03	13.62±0.05
2	30.97±0.02	31.81±0.01	31.17±0.05	42.00±0.03	42.64±0.02	30.97±0.01	30.33±0.06	29.67±0.04
3	48.07±0.03	47.50±0.07	48.21±0.02	64.98±0.04	64.27±0.02	48.07±0.04	48.53±0.07	49.93±0.01
4	73.87±0.05	6±0.045.28	64.44±0.03	97.34±0.05	98.63±0.04	73.87±0.02	63.79±0.04	64.69±0.05
5	96.90±0.03	83.93±0.03	89.10±0.04	-	-	96.86±0.06	83.28±0.06	86.50±0.07
6	-	99.90±0.05	96.70±0.03	-	-	-	91.49±0.05	97.32±0.06
7	-	-	-	-	-	-	99.10±0.05	-

Table 7 % Drug release in F1-F8 (Ofloxacin)

Time(hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	22.20±0.03	19.28±0.01	22.20±0.04	26.00±0.06	31.54±0.03	30.23±0.05	20.16±0.02	17.24±0.02
1	33.42±0.03	34.72±0.03	33.42±0.06	47.16±0.04	49.82±0.04	46.75±0.02	36.33±0.06	39.67±0.07
2	41.78±0.05	47.75±0.05	41.78±0.02	66.25±0.02	75.20±0.05	69.19±0.05	43.82±0.01	53.61±0.04
3	55.43±0.05	59.98±0.02	55.43±0.04	84.57±0.01	90.79±0.01	87.23±0.02	56.18±0.03	70.10±
4	76.61±0.02	78.27±0.04	76.61±0.01	99.19±0.06	99.90±0.06	99.09±0.01	69.48±0.02	77.49±0.02
5	98.34±0.01	94.60±0.03	98.34±0.06	-	-	99.32±0.01	78.62±0.03	87.70±0.03
6	-	98.77±0.01	99.32±0.03	-	-	-	87.07±0.04	99.41±0.04
7	-	-	-	-	-	-	99.07±0.06	-

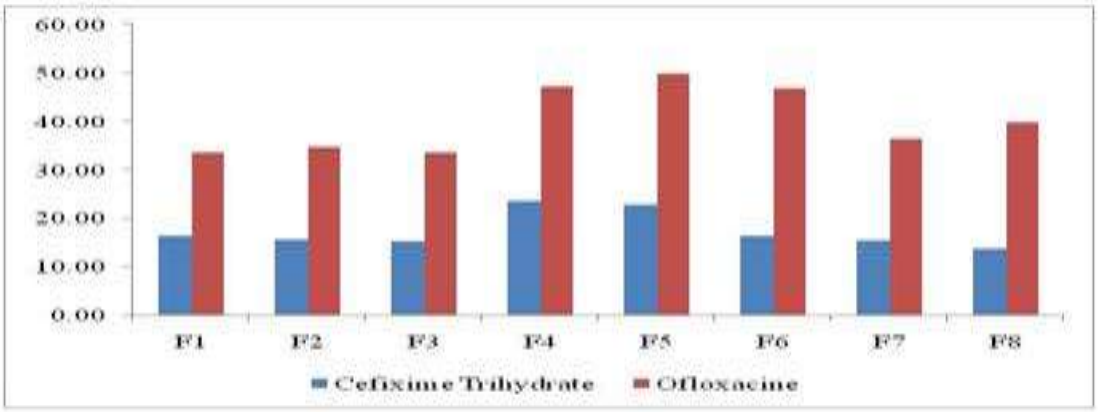

Figure 14: % Drug release of Cefixime Trihydrate and Ofloxacin into F1-F8

Here formulation F9 to F16 taken for the drug release study. These batches (F9 to F16) release the drug within 8hr or less than it. These batches were not fulfilling the criteria as per the Theoretical release profile.

Table 8 % Drug release in F9-F16 (Cefixime Trihydrate)

Time (hr)	F9	F10	F11	F12	F13	F14	F15	F16
0	0	0	0	0	0	0	0	0
0.5	10.15±0.02	9.44±0.03	8.73±0.05	16.94±0.02	16.23±0.03	13.06±0.02	16.16±0.02	16.419±0.03
1	16.41±0.03	15.76±0.01	16.79±0.01	28.92±0.03	30.60±0.02	18.75±0.03	25.3±0.03	24.914±0.04
2	26.13±0.01	24.90±0.04	25.48±0.03	50.55±0.01	50.87±0.05	29.39±0.01	30.41±0.04	41.211±0.04
3	35.97±0.04	35.31±0.01	39.26±0.07	64.53±0.05	73.20±0.07	39.12±0.05	41.89±0.05	62.124±0.03
4	48.45±0.06	48.76±0.01	51.69±0.01	78.07±0.02	83.29±0.05	52.20±0.01	61.32±0.06	73.454±0.01
5	63.59±0.02	64.02±0.06	64.97±0.05	93.36±0.05	96.03±0.02	63.15±0.03	71.03±0.07	84.198±0.03
6	81.52±0.06	89.91±0.06	75.09±0.03	-	-	75.78±0.05	83.70±0.01	94.353±0.06
7	87.13±0.04	96.86±0.01	84.54±0.01	-	-	83.30±0.01	93.85±0.02	-
8	96.65±0.05	99.97±0.03	97.28±0.02	-	-	99.27±0.05	-	-

Table 9 % Drug release in F9-F16 (Ofloxacin)

Time (hr)	F9	F10	F11	F12	F13	F14	F15	F16
0	0	0	0	0	0	0	0	0
0.5	18.70±0.01	16.65±0.01	19.28±0.01	23.81±0.01	24.98±0.04	18.11±0.01	20.74±0.03	26.58±0.02
1	38.65±0.02	28.13±0.02	26.69±0.02	35.47±0.02	37.08±0.02	26	31.07±0.01	35.92±0.03
2	49.08±0.06	38.07±0.03	37.64±0.03	48.95±0.03	50.42±0.02	37.63±0.02	41.90±0.04	50.57±0.01
3	64.10±0.05	46.16±0.04	47.91±0.04	62.21±0.04	63.40±0.01	470.06±0.03	52.06±0.02	63.84±0.04
4	71.75±0.01	56.92±0.05	57.66±0.05	83.42±0.05	84.18±0.06	57.51±0.04	62.71±0.01	72.80±0.02
5	80.60±0.05	64.38±0.06	65.86±0.06	97.60±0.06	99.24±0.01	66.58±0.01	68.89±0.04	83.71±0.05
6	88.63±0.06	74.22±0.07	77.90±0.07	-	-	76.14±0.05	84.59±0.04	99.78±0.03
7	91.45±0.02	88.20±0.01	86.35±0.01	-	-	86.62±0.07	99.93±0.05	-
8	99.82±0.06	97.87±0.02	98.49±0.02	-	-	99.21±0.04	-	-

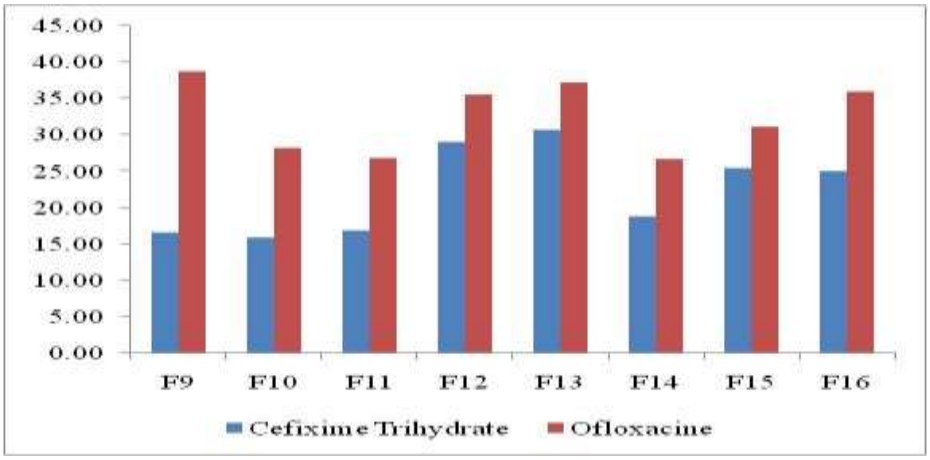

Figure 15 % Drug release of Cefixime Trihydrate and Ofloxacin into F9-F16

Here formulation F17 to F22 were taken for the drug release study. These batches (F17 to F22) release the drug up to 12hrs. Formulations F17, F19 and F20 show the optimum drug release and fulfill the criteria of Theoretical drug release profile. Other batches were not fulfill the criteria as per the Theoretical release profile so left for further evaluation and further study.

Table 10 % Drug release in F17-F22 (Cefixime Trihydrate)

Time(hr)	F17	F18	F19	F20	F21	F22
0	0	0	0	0	0	0
0.5	13.51±0.03	11.89±0.02	11.57±0.02	16.87±0.02	7.69±0.02	7.43±0.02
1	28.00±0.03	24.24±0.04	27.99±0.01	31.06±0.04	10.51±0.02	10.06±0.03
2	36.42±0.02	31.80±0.02	34.80±0.05	36.72±0.04	18.01±0.01	17.68±0.01
3	42.96±0.05	43.29±0.01	39.71±0.02	45.97±0.03	28.77±0.03	28.38±0.03
4	48.43±0.01	55.81±0.05	45.49±0.04	49.46±0.04	44.90±0.05	44.50±0.05
5	52.51±0.02	65.62±0.01	53.49±0.03	56.19±0.03	61.88±0.02	59.55±0.03
6	60.94±0.04	75.87±0.04	60.90±0.05	62.31±0.01	69.08±0.02	66.47±0.02
7	67.09±0.04	89.21±0.02	65.75±0.01	70.41±0.02	77.21±0.05	73.94±0.02
8	72.62±0.06	91.63±0.03	73.22±0.04	77.90±0.05	91.85±0.03	94.38±0.04
12	94.34±0.01	-	96.88±0.03	98.36±0.05	-	-

Table 11 % Drug release in F17-F22 (Ofloxacin)

Time(hr)	F17	F18	F19	F20	F21	F22
0	0	0	0	0	0	0
0.5	15.78±0.01	6.44±0.01	15.05±0.01	7.75±0.02	19.14±0.01	16.51±0.02
1	27.40±0.03	13.63±0.03	28.42±0.03	17.14±0.07	24.06±0.03	24.63±0.01
2	32.80±0.01	22.02±0.04	33.10±0.05	21.76±0.04	39.52±0.05	37.46±0.06
3	43.79±0.03	33.67±0.04	41.89±0.06	31.22±0.05	46.30±0.06	45.99±0.02
4	49.86±0.05	43.49±0.03	48.10±0.03	36.20±0.06	56.34±0.01	55.44±0.03
5	53.78±0.02	53.80±0.06	53.04±0.06	45.01±0.04	68.18±0.05	64.21±0.05
6	60.50±0.05	64.02±0.05	60.77±0.04	50.37±0.01	77.74±0.04	77.69±0.07
7	69.58±0.05	75.75±0.02	67.96±0.03	64.51±0.01	85.17±0.02	84.83±0.06
8	74.05±0.01	88.72±0.01	73.87±0.05	77.56±0.02	98.33±0.05	98.42±0.02
12	98.09±0.04	-	97.04±0.03	91.55±0.02	-	-

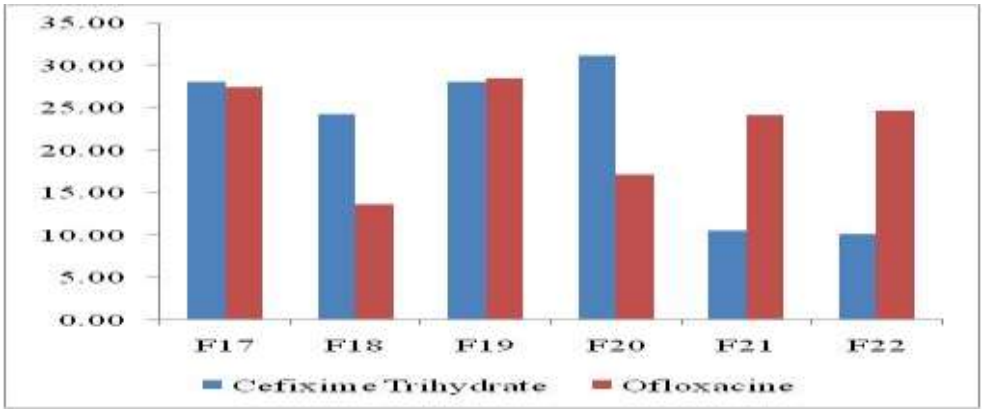

Figure 16 % Drug release of Cefixime Trihydrate and Ofloxacin into F17-F22

Table 12 % Drug release in F23-F26 (Cefixime Trihydrate)

Time(hr)	F23	F24	F25	F26
0	0	0	0	0
0.5	17.07±0.03	8.34±0.02	6.72±0.01	7.82±0.01
1	25.56±0.02	10.97±0.04	8.89±0.04	14.59±0.05
2	37.34±0.01	19.31±0.05	14.11±0.04	21.39±0.02
3	45.30±0.05	29.37±0.02	19.62±0.05	25.52±0.05

4	54.60±0.06	45.49±0.03	30.01±0.07	31.22±0.06
5	67.18±0.01	62.49±0.05	37.09±0.02	37.91±0.01
6	74.01±0.01	74.92±0.05	43.88±0.02	47.82±0.05
7	80.23±0.02	84.37±0.02	63.19±0.06	61.39±0.06
8	92.30±0.04	92.59±0.02	66.77±0.07	68.84±0.01
12			80.06±0.02	84.08±0.04

Here formulation F23 to F26 taken for the drug release study. These batches (F23 to F26) release the drug unevenly. These batches were not fulfilling the criteria as per the theoretical release profile.

Table 13 % Drug release in F23-F26 (Ofloxacin)

Time(hr)	F23	F24	F25	F26
0	0	0	0	0
0.5	7.90±0.02	17.38±0.02	12.86±0.01	13.30±0.04
1	14.51±0.01	23.47±0.05	26.36±0.04	24.90±0.05
2	23.49±0.05	36.73±0.02	33.07±0.05	31.61±0.03
3	35.15±0.06	47.44±0.04	40.41±0.04	38.93±0.02
4	47.90±0.02	59.82±0.05	47.49±0.02	46.01±0.01
5	55.31±0.02	68.90±0.06	58.26±0.01	56.77±0.01
6	69.34±0.03	78.47±0.02	60.91±0.05	59.41±0.06
7	83.14±0.05	89.12±0.02	66.20±0.02	64.70±0.03
8	93.23±0.01	98.80±0.04	76.19±0.07	77.60±0.04
12	-	-	91.20±0.04	92.62±0.05

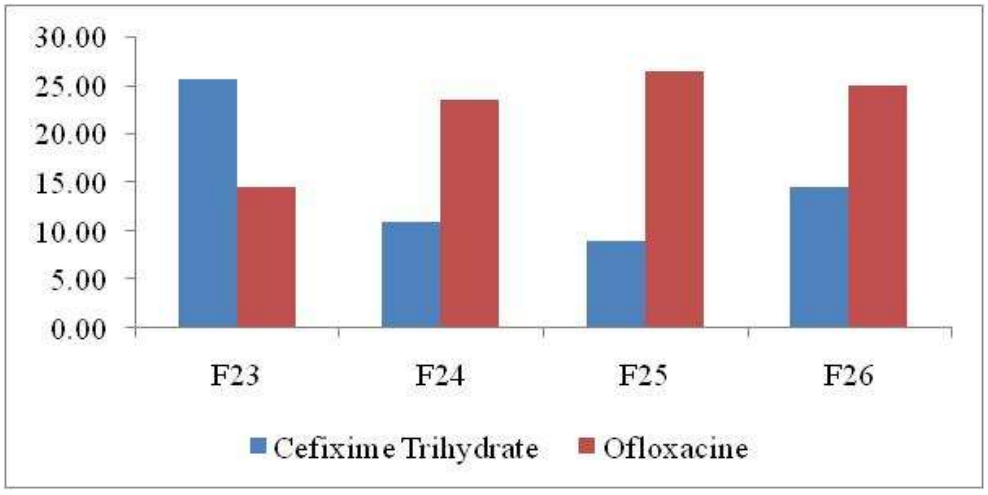

Figure 17 % Drug release of Cefixime Trihydrate and Ofloxacin into F23-F26

The Drug release rate parameters of Cefixime Trihydrate in all the formulations (F1 to F26) were evaluated and the results are mentioned in Table 13.Comparison of F17, F19 and F20 with Theoretical drug release profile is depicted in fig: 18

Table 13 Drug Release rate parameters of Cefixime Trihydrate

Batch	Q1	Q12	t80 (hr)	MDT	f2value
F1	16.27±0.03	-	4.5	1.60	48.46
F2	15.50±0.0.5	-	5	1.52	55.5
F3	15.05±0.05	-	5	1.69	53.35
F4	23.38±0.03	-	3.5	1.30	46.92
F5	22.73±0.0.6	-	3.5	1.32	46.52
F6	16.27±0.03	-	4.5	1.06	48.47
F7	15.31±0.03	-	5	1.79	46.55
F8	13.62±0.05	-	5	1.72	47.54
F9	16.41±0.03	-	6	2.11	54.05
F10	15.76±0.01	-	5.5	2.09	48.48
F11	16.79±0.01	-	6.5	2.13	55.85
BATCH					
F12	28.92±0.03	-	4.5	1.26	46.46
F13	30.60±0.02	-	4	1.21	43.45
F14	18.75±0.03	-	6.5	2.14	56.43
F15	25.3±0.03	-	6	1.78	53.54
F16	24.91±0.04	-	4.5	1.44	46.79
F17	28.00±0.03	94.34±0.01	9	2.29	88.11
F18	24.24±0.04	-	6.5	1.86	57.13
F19	27.99±0.01	96.88±0.03	9	2.76	92.03
F20	31.06±0.04	98.35±0.05	8.5	2.58	83.35
F21	10.51±0.02	-	7.5	2.28	56.06
F22	10.06±0.03	-	7.5	2.38	56.5
BATCH					
F23	25.56±0.02	-	7	1.87	60.12
F24	10.97±0.04	-	6.5	2.11	54.57
F25	8.89±0.04	80.059±0.02	12	2.95	48.94
F26	14.59±0.05	84.078±0.04	9	2.93	54.03

The Drug release rate parameters of Ofloxacin in all the formulations (F1 to F26) were evaluated and the results are mentioned in Table 14.Comparison of F17, F19 and F20 with Theoretical drug release profile is depicted in fig: 19

Table 14 Drug Release rate parameters of Ofloxacin

Batch	Q1	Q12	t80 (hr)	MDT	f2value
F1	33.42±0.03	-	4.5	1.38	46.92
F2	34.72±0.03	-	4.5	1.35	42.79
F3	33.42±0.06 3	-	4.5	1.40	42.78
F4	47.16±0.04	-	2.5	0.93	39.78
F5	49.82±0.01	-	2.5	0.84	37.28
F6	46.75±0.02	-	2.5	0.90	35.99
F7	36.33±0.06	-	5.5	1.57	46.81
F8	39.67±0.07	-	4.5	1.30	42.22
F9	38.65±0.01	-	5	1.52	43.91

F10	28.13±0.01	-	6.5	1.93	55.63
F11	26.69±0.01	-	6.5	1.92	54.51
BATCH					
F12	35.47±0.03	-	3.5	1.26	44.38
F13	37.08±0.02	-	3.5	1.25	43.48
F14	26.53±0.03	-	6.5	1.94	54.63
F15	31.07±0.03	-	5.5	1.74	50.37
F16	35.92±0.01	-	4.5	1.39	44.26
F17	27.40±0.03	94.34±0.04	9	2.72	91.75
F18	13.63±0.03	-	7.5	2.25	62.22
F19	28.42±0.03	96.88±0.03	9	2.72	94.71
F20	17.14±0.07	98.35±0.02	8.5	2.83	61.44
F21	24.06±0.03	-	6.5	1.93	54.61
F22	24.63±0.01	-	6.5	1.97	55.82
BATCH					
F23	14.51±0.01	-	6.5	2.21	58.93
F24	23.47±0.05	-	6.5	1.91	52.85
F25	26.36±0.04	80.06±0.04	8.5	2.46	81.84
F26	24.90±0.05	84.08±0.05	8.5	2.54	81.82

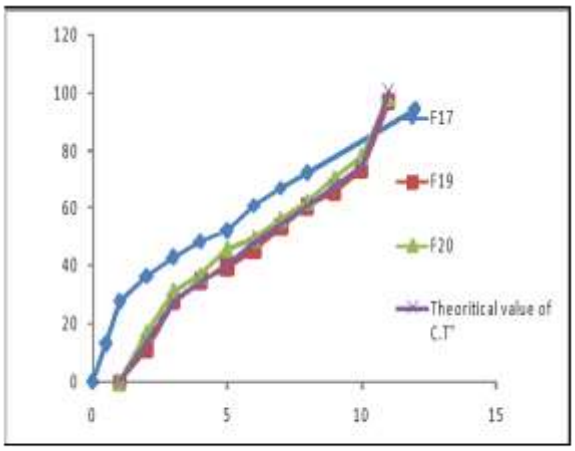

Figure 18 % Drug release of F17, F19, F20 and Theoritical value of Cefixime

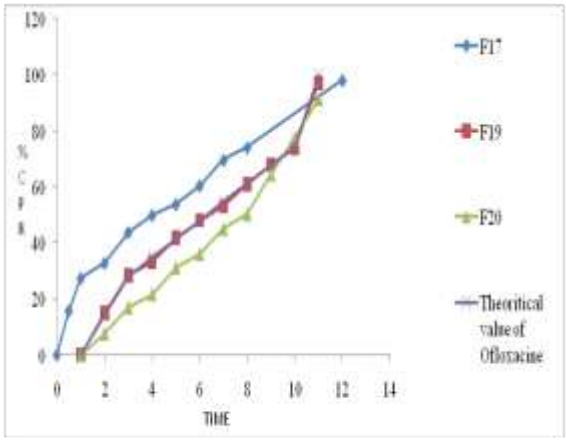

Figure 19 % Drug release of F17, F19, F20 and Theoritical value of Ofloxacine

Drug Release Kinetics

In order to understand the mechanism and kinetic of drug release, the drug release data of the in-vitro dissolution studies were analyzed with various kinetic model like, Zero order, First order, Higuchi's, Korsmeyer peppa's, Hixon crowel. The values of coefficient of correlation (R^2) of different kinetic models were calculated for formulation **F17, F19 and F20** by regression analysis. Results are in Table 15.

Table 15 Drug Release Kinetics

Formulation	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer-Peppas N	Korsmeyer-Peppas R^2	Hixon-crowel
F17	0.998909	0.97893	0.994507	0.487141	0.993794	-0.99891

F19	0.999448	0.987659	0.988237	0.502527	0.985152	-0.99945
F20	0.991413	0.984539	0.998164	0.477121	0.985108	-0.99816

From the above data of Table 6.16, coefficient of correlation (R^2) value of F19 formulation best fit was to the **zero order** model (R^2=09948). The release exponent n of 0.502527

Indicates release occurs by **anomalous (non-Fickian transport) diffusion** mechanism.

Comparison of Dissolution profile of Cefixime Trihydrate and Ofloxacin Gastroretentive floating tablet with Marketed Cefixime and Ofloxacin Combination.

Both the formulations were subjected for in the vitro dissolution test using USP type II apparatus. The Dissolution medium was 900 ml of 0.1N HCl maintained at 37 ± 0.5°C as mentioned in monograph. The Paddle rotation speed was kept at 50 rpm. The *in-vitro* drug release studies of F19 and Standard is shown in Figure. The *in-vitro* dissolution studies of formulation F19 was compared with conventional tablet formulation available in market. The study shows better dissolution profile of Gastroretentive floating tablets of Cefixime Trihydrate and Ofloxacin.

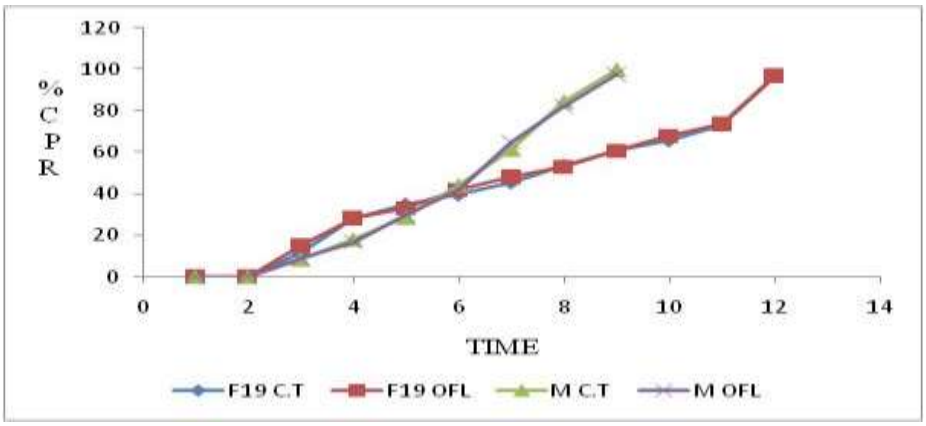

Figure 20 Comparison of F19 with Marketed Product

Antibacterial Assay

The antibacterial activity of Formulation 19 was performed by Agar cup Method. This is carried out with *Staphylococcus aureus* and *E.coli.* The results of anti bacterial assay which shows Zone of Inhibition in mm as shown in Table 16.

Table 16 Antibacterial Assay

SR. No	Treatment	*Staphylococcus aureus*	*E.coli*
1	F19	26.7 mm	28.31 mm

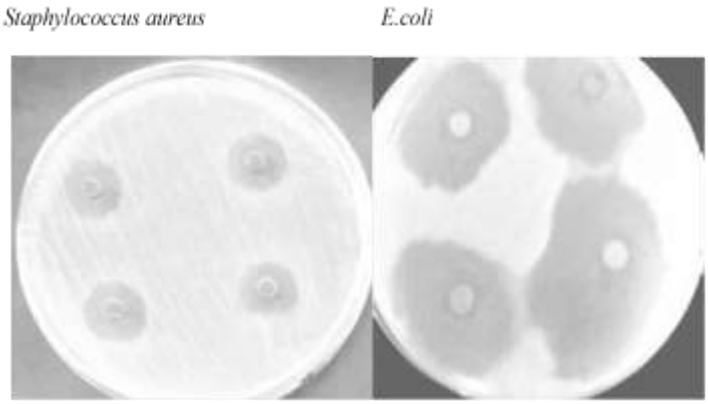

Figure 21 Antibacterial assay of Cefixime Trihydrate and Ofloxacin

Stability studies

The formulated films were stored in a glass beaker lined with aluminium foil and kept in a humidity chamber maintained at 40 ± 2°C and 75 ± 5% relative humidity for 1 month. The physical and chemical parameters were investigated at the end of every 2 week. The stability studies were carried out on the most satisfactory formulations F19. There was no significant difference in Drug content, folding endurance, flexibility, transparency and stickiness. Table 6.18 shows relevant details of stability studies.

Table 17 Results of Stability study of Formulation F19

Time (hrs)	Tablets at Day 1		Tablets after 1 month	
	C.T	OFL	C.T	OFL
0	0	0	0	0
1	27.99 ± 0.015	28.41 ±	26.95	28.12
2	34.80 ± 0.036	33.09	34.21	32.50
3	39.71 ± 0.024	41.89	39.31	41.59
4	45.49 ± 0.042	48.10	42.24	47.36
5	53.49 ± 0.021	53.03	52.81	52.58
6	60.90 ± 0.029	60.76	60.21	60.46
7	65.75 ± 0.014	67.95	64.41	66.77
8	73.22 ± 0.033	73.87	73.17	73.26
12	96.88 ± 0.044	97.04	95.54	96.72

CONCLUSION

Gastro retentive Tablets of Cefixime Trihydrate and Ofloxacin were prepared by direct compression method using HPMC K4M, HPMC K15M, HPMC K100M, Gellan Gum, Xanthan Gum, Guar Gum, PEO301 and PEO 303. The prepared tablets were evaluated for number of parameters like Hardness, Friability, Weight variation, Floating lag time, Total Floating time, Drug content, Swelling Index, antibacterial Test, stability Study and In vitro drug release studies. The best release for gastro retentive tablets was shown by formulation F19 (HPMC K100M).

Formulation F19 exhibited less Floating lag time and up to 12hrs total floating time. Formulation F19 was given 96.88±0.03% Cefixime trihydrate release and 97.04±0.03 % Ofloxacin drug released after 12 hr. In FTIR, drug to polymer interaction was not found. Considering all above mentioned facts it can be concluded that prepared gastro retentive floating tablets of cefixime trihydrate and Ofloxacin formulation **F19** shows desirable release profile, good floating property and adequate sustained release effect in stomach.

ACKNOWLEDGEMENT

The authors are thankful to staff of Saraswati institute of pharmaceutical sciences for providing necessary equipment facilities & chemicals to carry out research work

REFERENCES

1. Shaik T, Sundaram MA and Umasankar K, "Review on gastroretentive drug delivery system." Int. J. Res. Pharmceu. Nano Sci. 2014, 177 – 185.
2. Drug Bank, "Information of Cefixime", http://www.drugbank.ca/drugs/DB00671
3. Chemicalland21.com, "Information of Cefixime Trihydrate"
4. http://www.chemicalland21.com/lifescience/phar/CEFIXIME%20TRIHYDRATE.htm
5. Drugs.com, "Information of Ofloxacin", http://www.drugs.com/cdi/ofloxacin.html
6. Drug bank, "Information of Ofloxacin", http://www.drugbank.ca/drugs/DB01165
7. Badoni , A. Ojha, G. Gnanarajan, P. Kothiyal, Review on Gastro Retentive Drug Delivery System, The Pharma Innovation, 2012, 1 (8), 35-42.
8. B.V. Ramana, C. Pallavi, V. Suman Kumar, C.Triveni, G. Nagarajan, T.E.G.K. Murthy, "Formulation And In Vitro Evaluation Of Fast Dissolving Tablets Of Cefixime Trihydrate." Int. J Pharm Pharm. Sci. 2013, 559-563.
9. N. G. Raghavendra Rao, Harsh A Panchal and Pentewar Ram, "Formulation and in-vitro evaluation Gastroretentive drug delivery system of Cefixime for prolong release", Der Pharmacia Sinica, 2011, 2 (2): 236-248.