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Development and *in vitro* evaluation of ciprofloxacin gastric floating tablets

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Abstract

Objective: The aim of present investigation was to formulate, evaluate and optimize process of gastroretentive tablets of ciprofloxacin hydrochloride. Ciprofloxacin hydrochloride has a short elimination half-life of about 4 hrs and oral bioavailability of about 70%. Ciprofloxacin hydrochloride has a narrow absorption window and is mainly absorbed in the proximal areas of GIT. Development of gastroretentive dosage form can be advantageous, that can provide prolong gastric retention and increase efficacy of the dosage form.

Methods: Gastroretentive floating tablets (GRFT) were prepared by using a hydrophilic polymer polyethylene oxide of different grades such as PEO WSR N-12 K, PEO 18 NF and olibanum gum as release retarding polymers and sodium bicarbonate as gas generating agent. The GRFT were compressed by wet granulation method.

Results: The tablets were evaluated for physicochemical properties, in vitro buoyancy, swelling studies, in vitro dissolution studies and release mechanism studies. From the dissolution and buoyancy studies, F 4 was selected as an optimized formulation.

Conclusion: Optimized formulation (F 4) when characterized with FTIR studies showed no interactions between drug and polymer. The gastroretentive floating drug delivery is a promising approach to achieve *in vitro* buoyancy by using hydrophilic polymers of polyethylene oxide grades such as PEO WSR N 12 K, PEO 18 NF

Keywords: Gastroretentive floating tablets, PEO 18 NF, wet granulation method, *in vitro* buoyancy

Introduction

After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT) [1]. These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose [2]. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment [3]. 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. Over the last few decades, several gastro retentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach [4], low density (floating) systems that causes buoyancy in gastric fluid [5, 6, 7] mucoadhesive systems that causes bioadhesion to stomach mucosa [8], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach [9, 10], superporous hydrogel systems [11], magnetic systems [12] etc.

Ciprofloxacin hydrochloride, a broad – spectrum fluoroquinolone antibacterial agent is more absorbed from the stomach and the proximal part of the small intestine [13] Oral bioavailability is about 70% and reaches the peak plasma concentration to 2.5 µg/ml in 1 to 2 h after administration of 500 mg. As the tablet passes down the GIT, the decrease absorption is the draw back with sustained release dosage form of ciprofloxacin hydrochloride. The aim of this study was to get better drug release with less fluctuation of plasma drug concentration of ciprofloxacin hydrochloride to the stomach, and the proximal parts of the small intestine floating tablet were prepared as compared to available dosage form and the drug release up to 12 hours with less fluctuation. This gastro retentive floating tablet increases the mean residence time (MRT) in the stomach and prolong the gastric emptying that provides the maximum drug at the site of absorption.

Material and Methods

Material

Ciprofloxacin HCL was provided by Lincoln Pharma Laboratories Ltd. PEO grades, Sodium bicarbonate, PVPK30, IPA and magnesium stearate were obtained as gift samples from Unichem Laboratories Ltd. All other reagents and chemicals were of analytical grade.

Preparation of Tablets

Ciprofloxacin HCl tablets are prepared by wet granulation method using hydrophilic polymer, gas generating agent, and swelling agents in each formulation.The composition different excipients in formulations are listed in Table I. All the ingredients are passed through sieve no. 60 and mixed in a polybag and granulated by using PVP K30 (5% *w*/*v* in

isopropyl alcohol). The wet mass is passed through sieve no. 14 and dried at 50°C. Dried granules are passed through sieve no. 16 and mixed with magnesium stearate, and talc. Granules are compressed by using caplet-shaped punches on cadmach 16-station rotary tablet press.

Determination of flow properties of lubricated blend

Angle of repose method Angle of repose was determined by fixed funnel and free standing cone method. A funnel with the end of the stem cut perpendicular to its axis of symmetry was fixed at a given height (h) above the graph paper placed on a flat horizontal surface. The gum powder was carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. The radius of the base (r) of the pile was determined and the tangent angle of the repose (θ) was calculated by following equation [14]

$$\tan \theta = h/r$$

Determination of compressibility index, Hausner´s ratio: Compressibility index (C.I) and Hausner's ratio of the lubricated blend was determined by measuring the Bulk density (BD) and Tapped density (TD) of a powder. The BD was determined by three tap method. An amount of powder equivalent to 10 g was accurately weighed, placed in a 100 mL measuring cylinder without compaction. The volume occupied was measured and the initial bulk density was calculated by the following equation [15].

$$\text{Bulk volume of the powder} = \frac{\text{Mass of the powder}}{\text{Bulk volume of the powder}}$$

Tapped density (TD) of a powder is the ratio of the mass of the powder to the volume occupied by the powder after a fixed number of taps. The tapped density of the powder represents its random dense packing

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of the powder}}$$

Hausner's ratio was determined by dividing the tapped density (TD) by bulk density (BD), and Carr's compressibility index (CI) was determined using following equation

$$CI(\%) = \frac{TD - BD}{TD} \times 100$$

Evaluation of the tablets

Weight variation test

To study weight variation twenty tablets of the formulation were weighed using a Sartorius electronic balance and the test was performed according to the official method. Determinations were made in triplicate.

Hardness

The hardness of five tablets was determined using the monsanto Hardness Tester tester and the average values were calculated. Determinations were made in triplicate.

Thickness

The thickness of the tables was determined by using vernier calipers. Five tablets were used, and average values were calculated. Determinations were made in triplicate.

Friability

The friability of the tablets was measured in a Roche friabilator Tablets of a known weight (W0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determinations were made in triplicate. [16]

$$\%Friability = \frac{W_0 - W}{W_0} 100$$

Drug Content

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (950 mg) was extracted in 100 mL of 0.1N HCl. The solution was filtered through 0.45 membrane. The drug content was determined by Shimadzu UV-1800 at a wavelength of 276 nm after a suitable dilution with 0.1 N HCl. [17]

***In vitro* buoyancy study**

The in vitro buoyancy was determined by floating lag time method described by Rosa *et al*. [18]. The tablets were placed in 100 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time.

Swelling studies the swelling ability of the GRFT was determined in 900 mL of acidic medium (0.1 N HCl) at room temperature. Weighed tablet was immersed in the medium and it was removed periodically from the medium. After draining the free water, the tablets were measured for weight gain. Swelling index (% SI) was expressed by the following equation [19]

$$\%SI = \frac{\text{Weight of swollen tablet} - \text{initial weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

***In vitro* dissolution studies**

The release rate of ciprofloxacin hydrochloride from floating tablets (n=3) was determined using *The United States Pharmacopoeia* (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37±0.5 ^{0}C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at an interval of 1, 2, 3, 4, 6, 8, 10, 12, 14 and the samples were replaced with fresh dissolution medium maintained at 37 0.5 C. The samples were filtered through a 0.45 membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 276 nm using a Shimadzu UV1800 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Table 1: Formula of Ciprofloxacin HCl gastro retentive floating tablets.

Composition (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ciprofloxacin Hcl	500	500	500	500	500	500	500	500	500	500
PEO WSR N-12 K	135	180	225	-	-	-	-	-	-	-
PEO 18 NF	-	-	-	135	180	225	-	-	-	-
Olibanum gum	-	-	-	-	-	-	135	180	225	180
Sodium bi carbonate	90	90	90	90	90	90	90	90	90	90
PVP-k-30	18	18	18	18	18	18	18	18	18	18
MCC	139	94	49	139	94	49	139	94	49	49
Talc	9	9	9	9	9	9	9	9	9	9
Magnesium stearate	9	9	9	9	9	9	9	9	9	9
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
EC	-	--	-	-	-	-	-	-	-	45

Release kinetics

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, Peppas and Hixson-Crowell cube root law. Based on the r-value, the best-fitted model was selected.

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation,

$$Q_t = Q_o + K_o t$$

Q t = amount of drug dissolved in time t.
Q o = initial amount of the drug in the solution and
K o = zero order release constant.

First order kinetics

To study the first order release rate kinetics, the release rate data were fitted to the following equation,

$$\text{Log } Q_t = \log Q_o + K_1 t/2.303$$

Where,
Qt =the amount of drug released in time t
Qo=the initial amount of drug in the solution
K1 is the first order release constant.

Higuchi model

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is,

$$Q_t = K_H \cdot t_{1/2}$$

Where,
Q_t = amount of drug released in time t,
K_H = Higuchi dissolution constant.

Peppas release model

To study this model the release rate data are fitted to the following equation,

$$Mt / M\infty = K \cdot t_n$$

Where,
Mt / M ∞ =the fraction of drug release
K =the release constant
t = the release time
n = the diffusion coefficient for the drug release that is dependent on the shape of the matrix dosage form.
In this model, the value of *n* characterizes the release mechanism of drug as described in the following table.

Table 2: Drug transport mechanisms suggested based on 'n' value.

S. No	Release exponent	Drug transport mechanism	Rate as a function of time
1	0.5	Fickian diffusion	$t^{-0.5}$
2	0.45 < n = 0.89	Non -Fickian transport	t^{n-1}
3	0.89	Case II transport	Zero order release
4	Higher than 0.89	Super case II transport	t^{n-1}

Characterization of the optimized formulation: Formulations were optimized based on the 12 h drug retarding property, minimal polymer quantity and well buoyancy properties. Optimized formulation was further characterized with Fourier transformation-infrared spectroscopy (FTIR) for interaction studies.

Fourier transformation-infrared spectroscopy (FTIR)

FTIR was used to identify if there is any drug excipient interaction. FTIR studies were performed on drug, polymer and optimized formulation. Samples were analyzed by potassium bromide pellet method in an IR spectrophotometer (Shimadzu, FTIR 8700) in the region between 3500-500 cm-1.

Results and Discussion

Pre-compression studies

The values of angle of repose were found to be in the range of 26.4 to 30.2 which indicates that the powder blends have good flow and compressible properties. This was further supported by Carr's index values which were in the range of 10 to 15% and Hausner's ratio values which were in between 1.11 to 1.18.

It was concluded that all the formulations have good flow properties and the values were in the acceptable limits, which indicates that the powder blends have required flow property for direct compression.

Table 3: Flow properties of various formulations

Powder Blend	Angle of Repose (θ)	Carr's Index (%)	Hausner's Ratio
F1	28.3	13.10	1.151
F2	27.5	11.46	1.129
F3	28.0	10.00	1.111
F4	28.5	12.31	1.140
F5	29.3	12.93	1.148
F6	30.2	11.25	1.127
F7	25.2	14.77	1.173
F8	24.5	15.68	1.186
F9	24.2	13.95	1.162
F10	24.3	14.67	1.171

Tableting properties

Thickness of the tablets was found to be in the range of 5.75 mm to 6.30mm. The average weights of the tablets of various batches were in between 896 mg to 903 mg. According to IP, the percentage deviation for the tablets with average weight of 900 mg is ± 5%. The percentage deviation for all the batches was found to be within compendial (IP) limits. The hardness of all the formulations ranged from 4.7 to 5.4 Kg/cm^2. The percentage friability values of the all batches were in between 0.33 % to 0.88 % which indicates that the formulations have sufficient mechanical strength and are with in the acceptable limits i.e less than 1%. All the formulations passed the drug content uniformity test, which indicates that there is a uniform dose distribution among all formulations.

***In vitro* buoyancy studies**

Floating lag time was determined by using 0.1 N HCl.. The formulations containing PEO WSR N-12k have less floating lag time and the total floating duration is >12 hrs. Formulations containing PEO 18 NF have total floating duration of >12. Formulations containing Olibanum gum shown more floating lag time but they have total floating duration upto 12 hrs.

Total floating time is higher for the formulations containing olibanum gum when compared to formulations containing PEO WSR N-12k and PEO 18 NF. This was due to high viscosity of poly ethylene oxide, which requires more time to hydrate and to float on the surface, hence it has more floating lag time and longer floating duration.

The floating tablets composed of polymeric matrices will build up a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release from the matrix tablet. The formulations containing PEO have exhibited good swelling and tablet integrity. As, the amount of polymer concentration is increased the water uptake ratio is also found to be increasing. Floating lag time formulations were found to be in the range of 45 to 600 sec respectively. Total floating times of same based formulations were in the range of 10-14 h respectively. From the buoyancy properties, it was observed that sodium bi carbonate is essential for the floating. Sodium bi carbonate liberates carbon dioxide, when it contact with acidic medium. The gas generated is trapped and protected within the gel formed by hydration of the PEO, thus decreasing the density of the tablet below 1 g/mL, and the tablet becomes buoyant Both grades of PEO are readily swellable polymers; this made the tablets buoyant in less time. PEO WSR 18 NF based formulations floated rapidly than PEO WSR N- 12 K. And Olibanum gum. Formulations done by using olibanum gum shows poor floating character so to improve the floating character tried with channelling agent Ethyl cellulose. And floating character of olibanum gum was improved with ethyl cellulose.

Fig 1: F4 At initial time

Fig 2: F4 after 72 sec

Fig 3: F4 after 12

Swelling Studies

Swelling is also a vital factor to ensure buoyancy and drug dissolution of the matrix tablet. The swelling studies of the floating tablets were conducted for 12 h. swelling index of the all formulations was exhibited in the range of 62.7-99.3 %**.** From the swelling results, it is confirmed that swelling index is depended upon the quantity of the polymer and exposure time of the tablet to the medium. The swelling of

the floating tablet has been increased gradually along with the time and it reached to saturation at particular time depends upon the quantity of the polymer it has. Results showed that the swelling index increases with increased in concentration of PEO. But in case of olibanum gum formulations swelling character was not good.

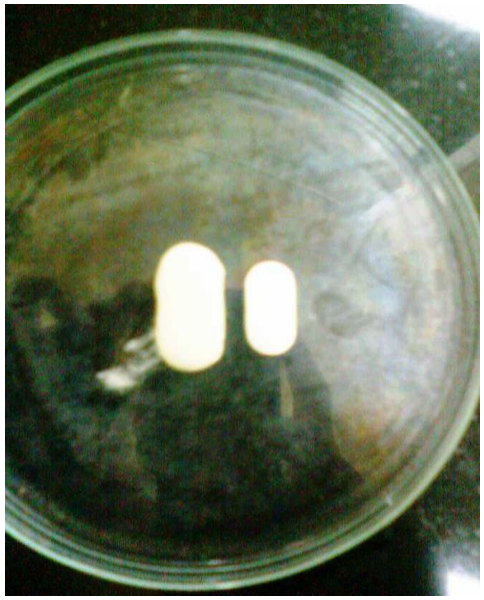

Fig 4: F4 tablet swelling index

Table 4: Floating Characteristics of formulations

Formulation Code	Floating Lag Time (Sec)	Total Floating Duration (hrs)	Swelling Index
F1	120±0.42	>12	64.8
F2	100 ±0.65	>12	76.2
F3	70±0.23	>12	84.5
F4	72±0.34	>12	90.5
F5	60±0.51	>12	92.2
F6	45±0.23	>12	99.3
F7	300±0.34	>12	68.8
F8	420±0.65	>12	64.6
F9	600±0.56	>12	62.7
F10	120±0.34	>12	70.6

In vitro dissolution studies

The In vitro drug release study of Ciprofloxacin tablets was carried out in 1.2pH Hydrochloric acid buffer for12 hours and the values were shown as in the tables. The plot of time vs percentage cumulative drug release were plotted and depicted as shown in the figures. From the in vitro release data it was found that the drug release from the formulations containing PEO WSR N-12 K, F1 to F3 was 99.45%, 99.37% and 99.23% respectively after 10 hrs. Formulations containing PEO 18 NF (F4-F6) showed 99.56%, 99.31% and 98.10% drug release respectively. Formulations containing Olibanum gum resin (F7-F10) showed 99.36%, 98.43%, 96.53% and 99.94% respectively. It was observed from the results, that the formulations containing PEO WSR N-12k shown maximum drug release rate after 10 hrs, 12hrs and 14 hrs where as the formulations containing PEO 18 NF and Olibanum gum were shown maximum drug release after 12 hrs and 14 hrs. The sustaining action of the polymers was in the order such as Olibanum gum > PEO 18 NF> PEO WSR N-12k. F 4 formulated with PEO 18 NF was selected as an optimized formulation as the same desired results were obtained with less quantity of the polymer besides its good buoyancy properties.

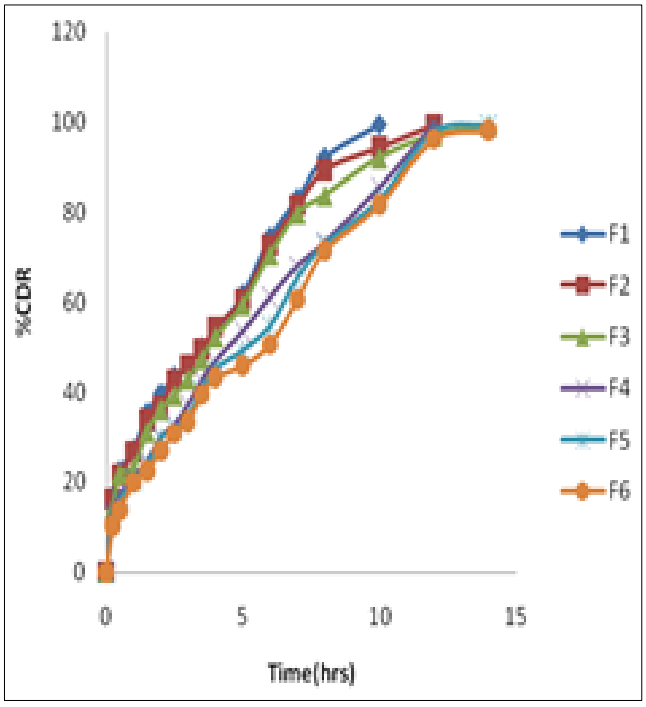

Fig 5: *In vitro* drug release profile (F1 to F6)

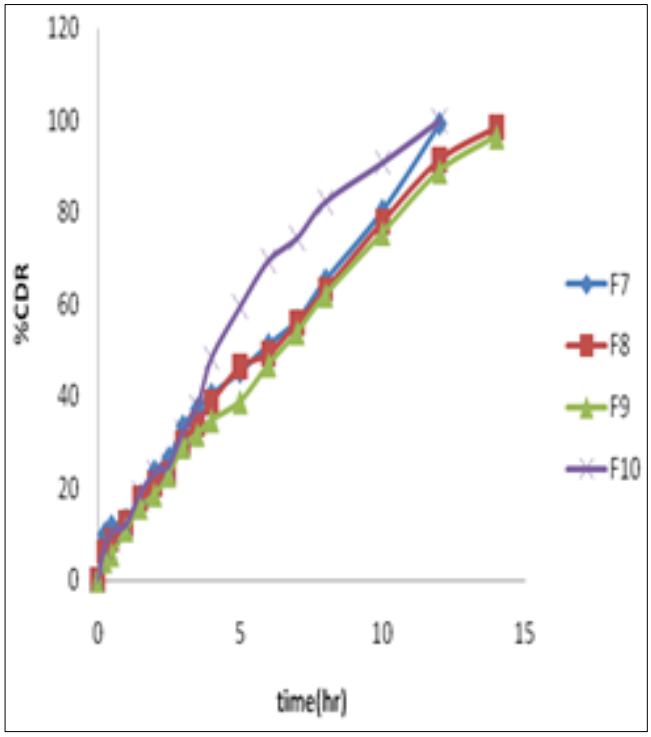

Fig 6: *In vitro* drug release profile for formulations (F7 to F10)

Release kinetics

All the formulations made with PEO WSR N-12 K, PEO WSR 18 NF and olibanum gum followed zero order kinetics. All PEO WSR 18 NF based formulations followed zero order rate kinetics with non Fickian diffusion mechanism.

Table 5: *In vitro* Drug Release kinetics for optimized formulations

Formulation	r^2 values				
	Zero order	First order	Higuchi matrix	Kosmeyers peppas	
				r^2	n
F1	0.957	0.847	0.913	0.983	0.517
F2	0.936	0.904	0.936	0.989	0.515
F3	0.922	0.914	0.942	0.979	0.512
F4	0.977	0.730	0.904	0.988	0.571
F5	0.971	0.853	0.902	0.990	0.579
F6	0.975	0.890	0.892	0.989	0.607
F7	0.992	0.704	0.866	0.980	0.696
F8	0.991	0.848	0.891	0.995	0.753
F9	0.994	0.894	0.8922	0.999	0.853
F10	0.966	0.717	0.916	0.965	0.799

Optimization

Based on the low polymer concentration, good buoyancy properties and drug retardation property up to 12 h, the formulation F 4 was selected as an optimized. PEO 18 NF was selected as a suitable polymer for the development of gastro retentive floating drug delivery system

Fourier transformation-infrared spectroscopy (FTIR)

Drug- excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between ciprofloxacin hydrochloride and the polymers used. Infrared absorption spectroscopy (IR) of ciprofloxacin hydrochloride showed sharp band at 3490, 3320, 2930, 1696, 1605 and 1480 due to O-H stretch, N-H stretch, aliphatic C-H stretch, C=O stretch of carboxyl group, C=O stretch of quinoline, C-N stretch. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.

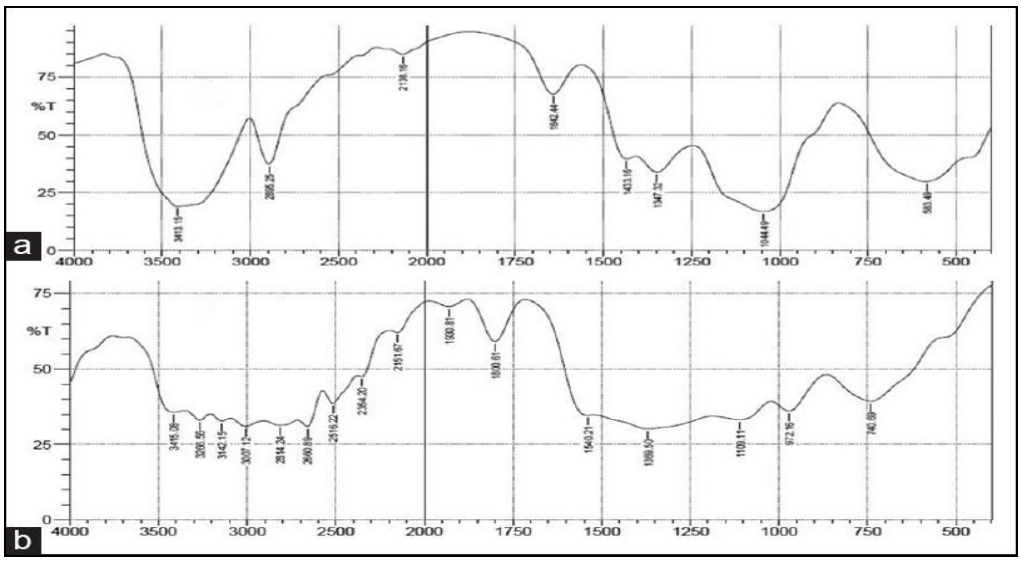

Fig 7: FTIR spectra of (A) Ciprofloxacin HCl (B) formulation F4.

Conclusion

The gastroretentive floating drug delivery is a promising approach to achieve *in vitro* buoyancy by using hydrophilic polymers of polyethylene oxide grades such as PEO WSR N 12 K, PEO 18 NF, olibanum gum and gas-generating agent Sodium bicarbonate. The results concluded that PEO WSR N-12 K, PEO 18 NF, olibanum gum based formulations at the 15%, 20% and 25% respectively retarded the drug release. High molecular weight PEO grade exhibited higher retarding property and good buoyancy properties but in case of olibanum gum formulations shows poor floating character. The optimized formulation gives the best result in terms of the required floating lag time and total floating time. Optimized formulation (F 4) when characterized with FTIR studies showed no interactions between drug and polymer. Hence, it can be concluded that, PEO is a suitable polymer for the development of gastro retentive floating drug delivery systems.

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