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FORMULATION AND EVALUATION OF CIPROFLOXACIN GASTRORETENTIVE FLOATING TABLETS

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ABSTRACT

Gastro retentive drug delivery system is novel method to enhancing bioavailability of narrow absorption window drugs. This technique is applied in many of the compounds like antibiotics and drugs treating helicobacter infection. Ciprofloxacin is a broad-spectrum antibiotic, it active against both Gram-positive and Gramnegative bacteria. Ciprofloxacin have more absorption in stomach, so this drug will get more benefit to make as floating tablet. This present study describes formulation and evaluation of gastrorentive ciprofloxacin floating tablet, it was fabricate with different concentration of two polymers of different grades. The formulated tablets were evaluated in different parameters like hardness, friability, weight uniformity, buoyancy, swelling index and dissolution release profile. The best formulation is selected on the basis of buoyancy, gastro retardation and uniform drug release profile. In this research work formulation F 3 fulfills all the testing parameters in terms of pre and post compression.

KEYWORDS

Bioavailability, Buoyancy, Dissolution, Helicobacter infection and Swelling index.

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INTRODUCTION

Drug administration by oral route is most convenient and preferable method. In oral tablets can modify drug release and design to site specific drug release. In normal physiology the orally ingested drugs are push off to intestine after a specific period of 3-4 hours. The drug retardation technology the oral drug release possible up to 24 hours for many drugs, but if the drug should have to well absorb in entire gastrointestinal tract. A significant obstacle may arise if there is a narrow

window drug absorption in the gastrointestinal tract[1]. In gastro retentive floating drug delivery system is most beneficial for narrow absorption window drugs and make the drug candidate to prosperous and beneficial to patients. Prolongation of drug release in gastric part which improves bioavailability, reduce drug waste and improves solubility for the drug that are less soluble in a high pH environment[2].

Gastric retention is achieved by making the drug release in controlled manner within gastro intestinal tract (stomach). Several approaches are currently used in the prolongation of the gastric residence times (GRT) by one of the method is floating drug delivery systems (FDDS) with low- density polymer systems[3]. The bulk density of floating drug delivery system is lower than the gastric fluids, so it buoyant in upper part of stomach in longer period irrespective of gastric emptying rate influence. While the system is floating on gastric contents, drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This result is increase in GRT and a better control of fluctuations in plasma drug concentrations[4]. On the basis of buoyancy mechanism, two different technologies applied, i.e., non-effervescent and effervescent systems. Non-effervescent systems of floating use gel-forming or highly swell-able cellulose type hydrocolloids, polysaccharides and matrix forming polymers (polycarbonate, polyacrylate, polymethacrylate, and polystyrene) used. Effervescent systems matrices prepared with swell-able polymers such as methocel or chitosan and effervescent compounds, such as sodium bicarbonate and citric or tartaric acid[1].

Ciprofloxacin is a broad-spectrum antibiotic active against both Gram-positive and Gram-negative bacteria. The dosage is equivalent of 250 to 750 mg of ciprofloxacin twice daily. The objective of the present investigation is to prepare and evaluate gastro retentive Ciprofloxacin floating tablet which will help to retain the dosage form in the stomach and to increase gastric residence time, resulting in prolonged drug delivery in stomach using gel-forming polymers such as hydroxyl propylmethyl cellulose (HPMC K4M, HPMC K 100M) in different ratio with microcrystalline cellulose, sodium bicarbonate and magnesium stearate by direct compression techniques.

MATERIAL AND METHODS

The following chemicals were used. Ciprofloxacin hydrochloride, Low density powder polymers HPMC K 4M and HPMC K 100 M (Gift samples from Pharma fabrikon, Madurai, India.), Microcrystalline cellulose (Nice chemicals Pvt. Ltd), Magnesium stearate (High Purity Laboratory Chemicals) Sodium bicarbonate (Vikash Pharma, Mumbai) are used.

EXPERIMENT METHODS

Determination of λ max for Ciprofloxacin in 0.1N hydrochloric acid buffer pH 1.2

Ciprofloxacin solution 10 µg/ml in acid buffer pH 1.2 solution is prepared, then scanned by a UV spectrophotometer at wavelengths ranging from 400nm to 200nm, the λ max for solution was determined[5].

Fourier Transform-Infra Red (FT-IR) Studies[6,7]

Samples are prepared using KBr disc method and spectra are recorded over the range 600-4500 per cm. Spectra are analyzed for drug-carrier interaction and functional groups involved in the compellation process.

Formulation and evaluation of ciprofloxacin floating tablet

The floating tablet of ciprofloxacin was prepared by direct compression method using different grade of polymers and excipients like HPMC K-4 M, HPMC K-100, Sodium bicarbonate and microcrystalline cellulose. Three formulations were prepared as per formula designed.

Preformulation study for Ciprofloxacin floating tablets

Angle of Repose[7,8]

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the

surface of the pile of powder and the horizontal plane.

$\tan(\theta) = \tan^{-1}(h / r)$

Where, θ is the angle of repose, h is the height in centimeters, r is the radius in centimeters.

Bulk Density[9]

It is the ratio of total mass of powder to the bulk volume of powder. Bulk density is calculated by pre weighted powder was poured in to measuring cylinder and then the intial volume was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M / V_b$$

Where, M is the mass (weight) of powder V_b is the bulk volume of the powder.

Tapped Density[4,10]

Tapped volume was measured by, pre weighted powder was poured in measuring cylinder and noted the volume, start tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is greater than 2%, tapping is continued for 1250 times and tapped volume was noted.

$Dt = M / Vt$

Where, M is the mass of powder, V_t is the tapped volume of the powder.

Percentage of compressibility (or) Carr's index[7,9]

It indicates powder flow properties. It is expressed in percentage and is give

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where, Dt is the tapped density, D_b is the bulk density

Hausner ratio[11]

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

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post compression evaluation of floating tablet

Thickness and Diameter[12]

Tablet thickness and diameter measured by varnier calipers. 5 tablets were taken and their thickness and diameter was measured.

Hardness[10]

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of floating tablets because excessive crushing strength significantly reduces the disintegration time.

Weight variation test[7,13]

20 tablets were selected randomly from the all formulation and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in the table.

Friability test[9,14]

Friability of the tablet determined using friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre weighted tablets samples was placed in to the friabilator and allowed rotate 100 times. Tablets were dusted by using a soft muslin cloth and reweighed. The friability (F) is calculated by the formula.

$$\text{Friability} = \frac{\text{W initial} - \text{W final}}{\text{W initial}}$$

Uniformity of Drug Content[15]

Twenty tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 10mg of Ciprofloxacin was weighed and dissolved in acid buffer pH 1.2, the volume was made up to 100ml with pH 1.2 acid buffer. From the stock solution 1ml sample was withdrawn and diluted to 10ml with acid buffer pH 1.2, the absorbance was measured at wavelength 277nm using UV-Visible spectrophotometer. Content uniformity was calculated using formula.

$$\%\ DC = \frac{Absorbance\ of\ unknown\ (Au)}{\text{Absorbance of Standard (As)}}$$

Swelling index[8,10,16]

The floating tablets were weighed individually (W_0) and placed separately in glass beaker containing

200 ml of 0.1N hydrochloric acid buffer at 37^0 ± 1^0C at regular 2 hour intervals tablets were removed from beaker and weighed (W_t) and the percentage of swelling index was calculate

Swelling index $= \frac{(Wt-Wo)}{Wo}$ X 100

Where, W_t - weight of the tablet at time t, W_0 - weight of the tablet before immence.

***In vitro* drug release studies**[16-18]

Dissolution studies of all tablets were performed using dissolution tester. Tablets were added to the 900 ml of 0.1N hydrochloric acid buffer pH 1.2 at 37°C ± 0.5°C, which was stirred with a rotating paddle at 50 rpm. 5ml samples were withdrawn from the dissolution apparatus at the specified time intervals, equal volume of fresh medium was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test.

Floating / buoyancy test[19-21]

The tablets were placed in 100ml beaker containing 0.1N hydrochloric acid buffer. The time taken for the dosage from to reach (float) on upper surface of the medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time the dosage form remains buoyant is called Total Floating Time.

Best formulation selection

Among three formulations, best was selected on the basis of Drug content, Buoyancy, drug release profile, swelling index, stability and minimum chemicals composition.

RESULTS AND DISCUSSION

The absorption maximum (λ_{max}) of Ciprofloxacin was estimated by scanning the drug solution (1µg/ml) between 200-400 nm regions on UV spectrophotometer. The obtained spectrum showed that the absorption maximum (λ_{max}) was 277nm in 0.1 N hydrochloric acid buffer pH 1.2.

Calibration of Ciprofloxacin in 0.1N hydrochloric acid buffer pH 1.2

The Standard Calibration curves of Ciprofloxacin hydrochloride were prepared using 0.1N Hydrochloric acid buffer pH 1.2 at drug concentration of 1 to 8µg. The absorbance were measured at λ_{max} of 277nm. The correlation coefficient was found to be 0.9997.Ciprofloxacin hydrochloride obeys the beer's law within the concentration range of (1-8µg/ml). Calibration plot of ciprofloxacin in 0.1N hydrochloride buffer pH 1.2 was shown in Table No.4 and Figure No.1.

Fourier Transform Infrared Spectroscopic studies

FT-IR spectrum of the pure drug, HPMC K-4M, HPMC-K-100M, Microcrystalline cellulose, Polymer and drug mixtures of F-1, F-2 and F-3 formulations. Pure Ciprofloxacin hydrochloride spectra showed sharp characteristic peaks at 3370.37 (NH stretch), 1623.95 (NH bending), 1707.85 (C=0 stretch), 1270.04 (CF stretch), 1850 (cyclic - 3 membered ring) and1309.58cm-1 (CN stretch). All the above characteristic peaks appear in FT-IR spectrum of all formulation which indicates that there is no modification or interaction between drug and excipients.

Pre formulation study for floating tablets:

The angle of repose was used to determine the flow properties of powder blend. The angle of repose of all the formulations ranged from 23˚.17' to 27˚.29'. The results indicated that all the formulations exhibited excellent flow properties. The results of angle of repose for all the formulations were shown in Table No.5.

Bulk density

The bulk density of all the formulations was in the range of 0.45 to 0.56 g/cm^3.The values of bulk density showed that the blend was not tightly packed and indicated good flow properties. The results of bulk density for all the formulations were shown in Table No.5.

Tapped Density

The tapped density of all the formulations were in the range of 0.47 to 0.58g/cm^3.The results indicated that the blends of all the formulation had good flow properties. The results of tapped density for all the formulations were shown in Table No.5.

Carr's Compressibility Index

The compressibility index of all the formulations ranged from 2.55 to 4.26 %. This value below 10%

indicates a powder having excellent flow property and good propensity of compression. The results of compressibility for all formulations were shown in Table No.5.

Hausner's Ratio

The Hausner's ratio of all the formulations ranged from 1.03 to 1.05. It was less than 1.11 indicated better flow property of blend. The results of Hausner's ratio were shown in Table No.5.

Formulation of ciprofloxacin floating tablets

The floating tablet of ciprofloxacin was prepared by direct compression method using excipients of Sodium bicarbonate, microcrystalline cellulose and different grade polymers of HPMC K-4 M, HPMC K-100. Three formulations (F1, F2 and F3) were prepared as per formula designed. All the tablets were white colour and round in shape having 12 mm diameter.

Post compression evaluation

The prepared tablets were evaluated on various parameters such as thickness and diameter, hardness, weight variation, friability, buoyancy, uniformity of drug content, swelling index and *In-vitro* dissolution test. The results were summarized in Table No.6 and No.7.

Thickness and Diameter

The thickness of the tablet in all formulation was 4.83 - 5.1 mm and the diameter of the tablet in all formulation was 12mm.The results indicating all the formulations had uniform size and shape. The results were shown in Table No.6.

Hardness

The hardness of the tablets of all the formulations was found to be 4.73 - 5.76 kg/cm^2. The result indicated that all the tablets had a good mechanical strength. The results of the hardness for all the formulations were shown in Table No.6.

Weight Variation Test

The weight of all the tablets from each formulation was in the range from 484.6 mg to 492.6 mg. It was found all the tablets passed weight variation test, as the percentage weight variation was within the acceptable limits of ± 5%. The results were shown in Table No.6.

Friability test

The results showed that the friability of all the formulation was ranged from 0.57 % to 0.71%. Friability of all the formulation was lesser than 1 % which indicated the tablets had a good mechanical resistance. The results were shown in Table No.6.

Uniformity of drug Content

The drug content in the tablet of all the formulations was found to be in the range of 93.56 - 96.76 %. The results indicated all the formulations were within the acceptable limits as per USP limits. The results were shown in Table No.6.

***In vitro* buoyancy studies**

The formulated tablets were dropped in to 100 ml of 0.1N hydrochloric acid buffer in 250 ml beaker. The tablets were observed for the floating time of both floating lag time and total floating time. All the formulation shows floating lag time of 2 seconds to 11 seconds total floating time of more than 9 hours. The results are shown in Table No.6 and Figure No.3.

Swelling index

The results of swelling index of all the formulation was 98 -325 %, which reflects in retardation and release of drug. It is shown in Table No.7 and Figure No.4.

***In-vitro* drug release Studies**

The formulated floating tablet dissolution profile at 8th hour, the range from 32.76% - 94.04%. The dissolution drug release rate was found to be comparatively less in formulation F1. The maximum drug release rate was observed with F3 (The results shown in Table No.8 and Figure No.5). This study indicated that the increased amount of microcrystalline cellulose formulation (F-3) was produce better drug release rate than other formulations.

BEST FORMULATION SELECTION

Among three formulations, the best was selected on the basis of buoyancy, swelling index, drug retardation, uniform release profile, friability and stability. The formulation F-3 showed quick buoyancy lag time of 2 seconds, prolong total floating time of more than 9 hours, swelling index

325% and retardation of uniform drug release 94.04%. In all those parameter would drive the F-3 formulation as a best comparatively.

Table No.1: Formulation formulas

S.No	Ingredients	F 1	F 2	F 3
1	Ciprofloxacin	250	250	250
2	HPMC K4	100	-	-
3	HPMC K100	-	100	50
4	Sodium bicarbonate	50	50	50
5	Micro crystalline cellulose	90	90	140
6	Magnesium stearate	10	10	10
7	Total weight	500	500	500

Table No.2: Relationship between percentage of compressibility and flow ability

S.No	Percentage Compressibility	Flow ability
1	5 – 12	Excellent
2	12 – 16	Good
3	18 – 21	Fair Passable
4	23 – 35	Poor
5	33 – 38	Very Poor
6	< 40	Very Very Poor

Table No.3: Weight variation reference range

S.No	Average weight of tablet	% Deviation
1	80mg or Less	±10
2	More than 80mg but less than 250mg	±7.5
3	250mg or more	±5

Table No.4: Calibration values

S.No	Concentration in µg	Absorption
1	1	0.223 ± 0.005
2	2	0.451 ± 0.001
3	3	0.682 ± 0.005
4	4	0.885 ± 0.005
5	5	1.102 ± 0.002
6	6	1.342 ± 0.006
7	7	1.580 ± 0.009
8	8	1.79 ± 0.009
9	Regression	0.99983

Table No.5: Preformulation parameters

S.No	F-Code	Angle of repose	Bulk Density	Tapped Density	carr's index	Hausner ratio
1	F-1	23.17 ± 0.47	0.45 ± 0.12	0.47 ± 0.10	4.26 ± 0.15	1.05 ± 0.01
2	F-2	25.75 ± 0.76	0.56 ± 0.10	0.58 ± 0.01	3.63 ± 0.27	1.04 ± 0.01
3	F-3	27.92 ± 0.58	0.48 ± 0.10	0.49 ± 0.10	2.55 ± 0.46	1.03 ± 0.01

* SEM 3 trials

Table No.6: Post compression evaluation

S.No	F-Code	Weight uniformity (mg)	% Drug Content	Hardness [kg/cm2]	Thickness (mm)	Friability [%]	Floating lag time (Sec)
1	F -1	484 ± 1.52	96.19 ± 0.88	5.76 ± 0.05	4.96 ± 0.15	0.57 ± 0.01	11 ± 1
2	F -2	487 ± 1.15	93.56 ± 0.65	5.30 ± 0.10	4.83 ± 0.05	0.71 ± 0.03	4 ± 0.5
3	F -3	492 ± 1.52	96.76 ± 0.65	4.73 ± 0.11	5.10 ± 0.10	0.58 ± 0.03	2 ± 0.5

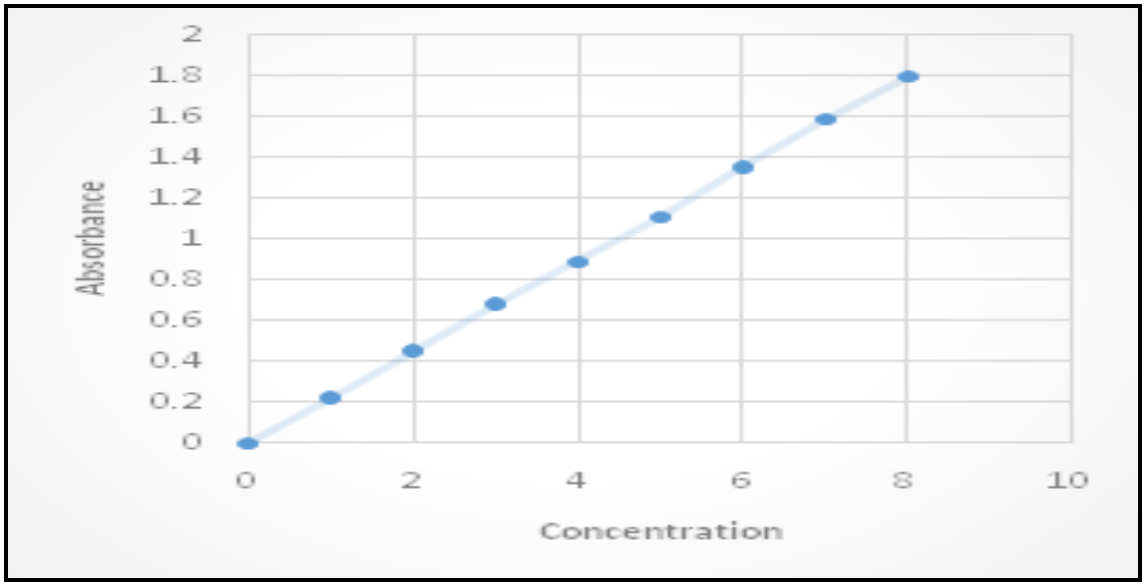
Table No.7: Swelling index

S.No	Time in hours	Percentage of swelling index		
		F1	F2	F3
1	0	0	0	0
2	2	68	240	260
3	4	89	260	280
4	6	96	280	310
5	8	98	290	325

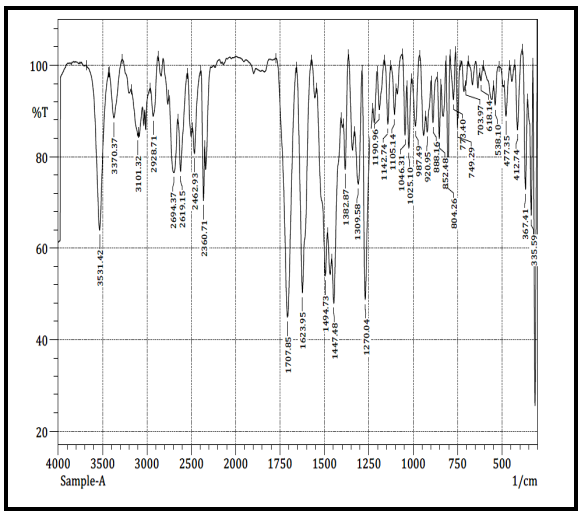
Table No.8: Dissolution profile of drug release

S.No	Time in Hours	Percentage of drug release		
		F 1	F 2	F 3
1	0	0	0	0
2	1	12.09 ± 0.8	8.42 ± 0.45	19.21 ± 0.19
3	2	20.04 ± 0.96	18.50 ± 0.59	30.78 ± 0.84
4	3	22.57 ± 1.01	27.78 ± 0.65	41.14 ± 0.79
5	4	24.51 ± .078	29.12 ± 0.89	55.01 ± 0.28
6	5	25.88 ± 0.65	32.65 ± 0.12	64.17 ± 0.85
7	6	28.15 ± 0.85	37.16 ± 0.82	77.075 ± 0.54
8	7	31.17 ± 0.94	42.41 ± 0.46	89.13 ± 0.98
9	8	32.76 ± 0.75	44.04 ± 0.96	94.04 ± 0.95

*SEM 3



***SEM 3 Figure No.1: Standard curve of Ciprofloxacin**



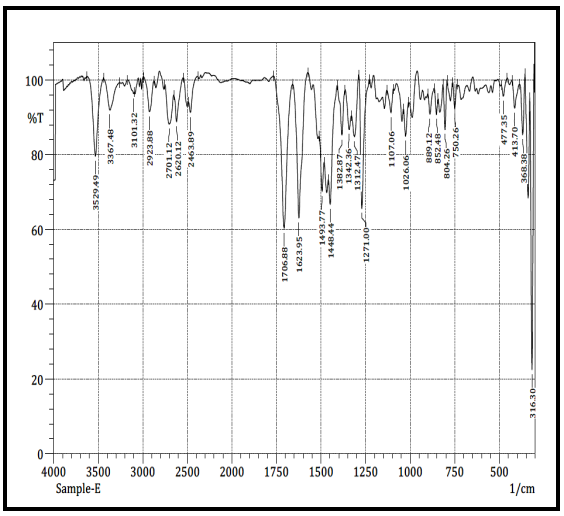


Figure No.2: FT IR of Pure drug Ciprofloxacin Figure No.2: FT-IR of Physical mixture of F3

Figure No.3: *In vitro* buoyancy study

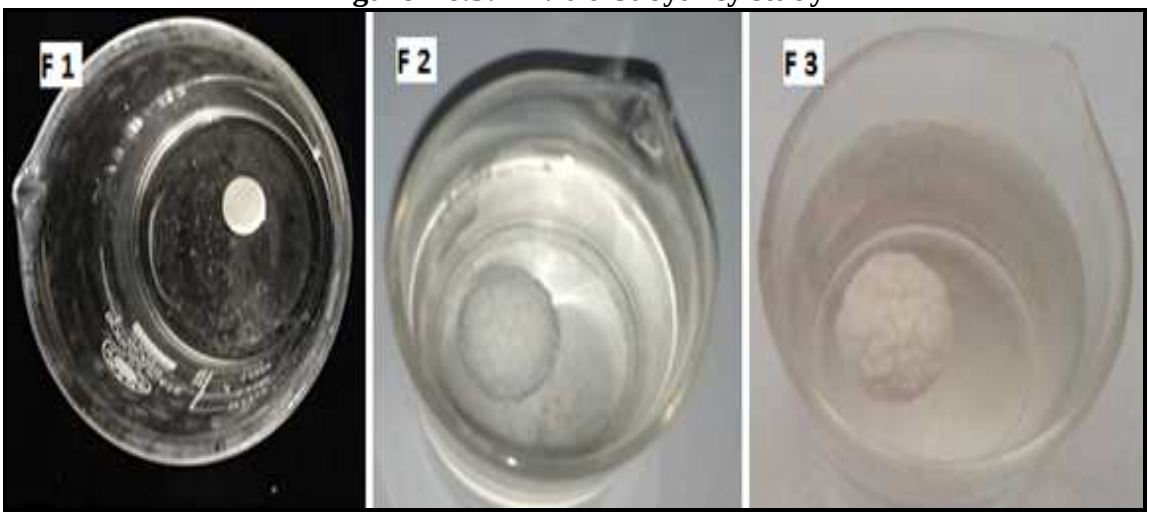


Figure No.4: Swelling index test

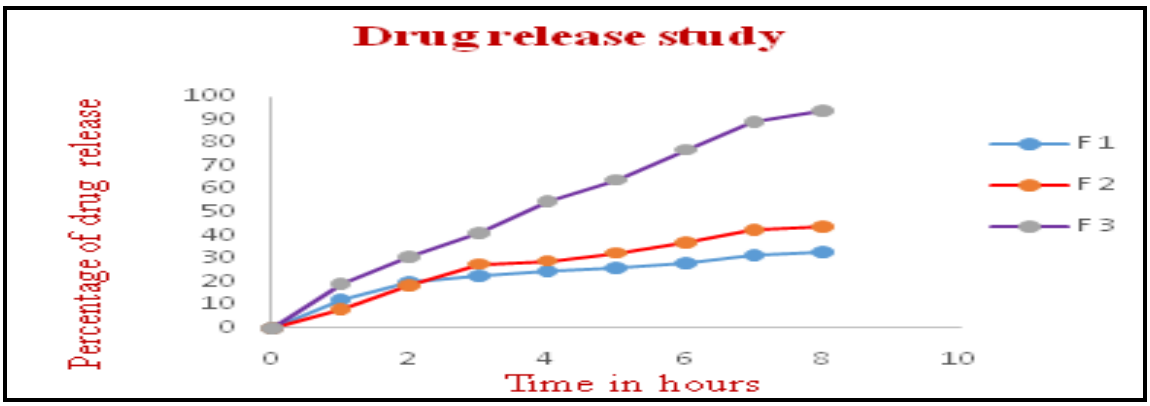


Figure No.5: Dissolution profile of formulated drug release

CONCLUSION

It was concluded, that Ciprofloxacin hydrochloride can be successfully formulated as floating tablets using various grades of low density polymers in different concentrations by direct compression method. The formulation containing 10% of HPMC K-100, 28%of microcrystalline cellulose and 10% of sodium bicarbonate (F3) was found to be outstanding than other formulations in terms of quick buoyancy time of 2 seconds, drug retardation release rate of 94.04 % in 8 hour, and comparatively high swelling index of 325 %, in those parameter would drive the F-3 formulation as a best comparatively.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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