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FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF CIPROFLOXACIN HCL

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ABSTRACT

Design of a controlled release formulation for a water soluble drug unstable at a high pH. A controlled oral delivery may be needed to achieve prolonged exposure or time based release for water - soluble drug under certain circumstances. It could offer advantages in improving efficacy, reducing side effect, or achieving a more desirable dose regimen. Ciprofloxacin HCl is a water soluble drug but it shows better solubility in biological fluids but not at high pH. Different formulations were prepared by varying the concentration of water soluble polymers by using direct compression method. The effect of varying concentration of hydrophilic polymers was studied on the release pattern of ciprofloxacin gastro retentive floating tablets.

KEYWORDS

Ciprofloxacin HCl, Gastro retentive floating tablets and Direct compression method.

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INTRODUCTION

Controlled drug delivery systems[1]

Oral drug delivery systems, in particular, have required innovation in materials science to provide materials biocompatible during prolonged contact with body tissues, bioengineering to develop drug delivery modules, and clinical pharmacology for elucidation of drug action under conditions of continuous controlled drug administration. Recent work in advanced oral delivery has been primarily focused on liposome technology and concept that substances that are normally destroyed by the stomach can be protected long enough before they

could be absorbed downstream. Besides, where delivery rate control is critical, oral delivery, even when possible, would probably insufficiently precise. The Oral delivery system would also limit the substance has to bloodstream delivery to the Disease site. Even so, oral controlled drug delivery systems will likely find primary usefulness in specific carefully controlled therapies and prophylactic situations with due regard for drug interactions. This system represents a potentially very significant therapeutic modality. The purpose of present article is to review oral controlled-release drug delivery systems, with particular emphases on the practical aspects of testing and fabricating these systems and the underlying mechanisms by which control over drug release rate is accomplished conventional oral controlled dosage forms suffer from mainly two adversities.

The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulations of single daily dosage forms. These problems can be overwhelmed by altering the gastric empting.

SUSTAINED RELEASE FORMULATION

Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels as shown in Figure No.1a. To overcome these problems, controlled drug delivery system were introduced three decades ago. The delivery systems have been a number of advantages over traditional systems such as improved efficiency, reduced toxicity, and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies.

Simple definition of sustained release drug system is "any drug of dosage form modification that prolongs the therapeutic activity of the drug ''ideally a sustained release oral dosage form is designed to release rapidly some predetermined fraction are the total dose into GI tract. This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response and the remaining fraction of the total dose (maintenance dose) is then release at a constant rate. The drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. Thus, the release commences as soon as the dosage form is administered as in the case of conventional dosage forms. Controlled drug delivery is delivery of drug at a rate are at a location determined by needs of body are disease state over a specified period of time.

Ideally to main objectives exist for these systems: Spatial delivery, which is related to the control over the location of drug release. Temporal drug delivery, in which the drug is delivered over an extended period of time during treatment.

Formulation Design

Formulation of Ciprofloxacin floating tablet

The effervescent floating tablets of ciprofloxacin were prepared by direct compression technique. For each tablet formulation, drug, sodium alginate, poly vinyl pyrolidine, sodium bicarbonate and diluents were blended homogeneously for 10 min followed by addition of magnesium stearate and talc. The resultant mixture was compressed in to tablets in 10mm and 10mm die cavities using Riddhi mini tablet press punching machine. Six formulations were prepared by changing the amount of the ingredients as shown in table.

MICROMERITIC PROPERTIES

The resultant formulation mixtures were characterized by their micromeritic properties, such as angle of repose, bulk density, tapped density, compressibility index and hausners ratio (values used in prediction of flow ability).

Pre-compression parameters

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. Accurately weighted amount of sample (5gm) was transferred into a 25ml measuring cylinder. The volume of packing was recorded. The measuring cylinder was then tapped 100 times on a plane hard wooden

surface and the tapped volume of packing was recorded. LBD and TBD were calculated by the following formula:

$$\text{LBD (Loose bulk density)} = \frac{\text{Weight of granules}}{\text{Volume of packing}}$$

$$\text{TBD (Tapped bulk density)} = \frac{\text{Weight of granules}}{\text{Tapped volume of packing}}$$

Compressibility Index

Percent compressibility of granules as determined by Carr's compressibility index was calculated by the following formula:

$$\text{Carr's Index} = \frac{\text{TBD - LBD}}{\text{TBD}} \times 100$$

Hausner Ratio

Hauser ratio was calculated by the following formula:

$$\text{Hausner ratio} = \frac{\text{TBD}}{\text{LBD}}$$

Angle of Repose (θ)

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$\tan \theta = h/r$

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

Where θ = Angle of repose

h = height of the heap

r = radius of the heap

Post-Compression Parameters

The tablets were evaluated for the various parameters enlisted below:

Appearance
Weight variation
Thickness
Hardness
Friability
Drug content
Tablet density
Floating test
Swelling study
In-vitro dissolution studies
Kinetics of drug release

Appearance

The compressed tablets were examined under the magnifying lens for its appearance.

Weight Variation

The procedure described in IP 1996 was employed to determine the weight variation of the tablets. Ten tablets were randomly selected from each batch and weighed to determine the average weight and were compared with individual tablet weight. The percentage was calculated and checked for weight variation.

Thickness

The tablet thickness is essential for consumer acceptance and to maintain tablet to tablet uniformity. The thickness of the tablets was measured using vernier caliper. It is expressed in mm. 5 tablets of each batch was picked randomly and its thickness were measured individually.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Five tablets were randomly picked from each batch and the hardness of the tablets was determined.

Friability

Friability of the tablets were determined using Roche friabilator. It is expressed in percentage (%). Ten tablets was initially weighed ($W_{initial}$) and placed into the friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions, and then the tablets were weighed again (W_{final}). They loss in the tablet weight due to abrasion or fracture was the measure of tablet friability.

% Friability was calculated by:

$$F = \frac{\text{W(initial) - W(final)}}{\text{W(initial)}} \times 100$$

% Friability of less than 1% is considered acceptable.

Drug Content

Ten tablets from each batch were weighed and powdered. Powder equivalent to the average weight

of the tablet was accurately weighed in a 100ml volumetric flask and dissolved in a suitable quantity of 0.1 N Hcl. Then the volume was made upto 100ml with 0.1 N Hcl and filtered. 2ml of filtrate was transferred to a 100ml volumetric flask and volume was made with 0.1 N Hcl. The absorbance of the resulting solution is measured by UV spectrophotometer at 276nm.

Tablet Density

Tablet density is important parameter for floating tablets. The tablet will only float when its density is less than that of gastric fluid (1.004g/cm^3). The density was determined using following relationship.

V = lbh

d = m/V

V = volume of tablet (cc)

l = length of tablet (cm)

b = width of tablet (cm)

h = crown thickness of tablet (cm)

m = mass of tablet (g)

d = density of tablet (g/cc)

Floating Test

The tablets was placed in a 100ml beaker containing 0.1 N Hcl. The time between introduction of dosage form and its buoyancy on 0.1 N Hcl, and the time during which the dosage form remains buoyant were measured (Figure No.5). The time taken for the dosage form to emerge on surface of medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time during which the dosage form remains buoyant is called Total Floating Time (TFT).

Swelling Study

The swelling behavior of a dosage form is measured by studying its weight gain or water uptake (WU). The study was done by immersing the dosage form in 0.1 N Hcl at 37ºC and determining these factors at regular intervals up to a period of 8 hours.

$WU = (W_t - W_o) \times 100 / W_o$

W_t = Weight of the dosage form at time t. W_o = Initial weight of the dosage form.

PREFORMULATION STUDIES

Organoleptic Properties

These tests were performed as per procedure given in materials and methods part. The results are illustrated in Table No.4.

Melting point

It was determined as per procedure given in material and method part. The results are illustrated in Table No.5.

The result of indicate the drug ciprofloxacin was pure one.

Solubility

Compatibility Studies

Compatibility studies were performed using FT-IR spectrophotometer and the FTIR spectrum of the obtained drug and drug with polymers were studied. The characteristic absorption peaks of ciprofloxacin obtained at 1710cm^{-1}-1702cm^{-1} were seen in the FT-IR spectrum of drug with polymers, indicating compatibility of drug with polymer components. The FT-IR spectrum of the drug and drug with polymers are shown in Figure No.2 and No.3 respectively.

Discussions

Gastro retentive systems have potential to remaining in the gastric region for several hours and hence significantly prolong the gastric residence time of drug. Prolonged gastric retention improves bioavailability, reduces drug waste.

The aim of the study was to formulate and evaluate the floating tablets of Ciprofloxacin by direct compression technique with sodium alginate, poly vinyl pyrolidine as polymers in different concentration.

In the present work, total 6 formulations were prepared and the detailed composition is shown in Table No.8. The prepared Ciprofloxacin floating tablets were then subjected to FTIR, Hardness, Weight variation, *In vitro* buoyancy study, drug content, *In vitro* dissolution, release kinetics.

PREFORMULATION STUDIES

The solubility of Ciprofloxacin in 10mg/10ml of buffer was carried out and it reveals that it is freely soluble in 0.1N HCL.

The melting point of ciprofloxacin was found to be 257^{o}C, which complied with IP standards thus indicating purity of obtained drug sample.

A solution of Ciprofloxacin containing concentration 10µg/ml was prepared in water and UV spectrum was taken using thermo scientific, evaluation 2010 UV visible.

Spectrophotometer and scanned between 200-400nm. The maxima obtained in the graph were considered as max for the drug ciprofloxacin.

Compatibility studies

Drug polymer interaction (FTIR) Study

FTIR Spectra were obtained for ciprofloxacin, physical mixture of ciprofloxacin and polymer presented in Figure No.2 to Figure No.4. The characteristic peaks of the ciprofloxacin were compared with peaks is obtained for physical mixture of ciprofloxacin and polymer. The characteristic peaks found in ciprofloxacin, physical ciprofloxacin and polymer and it can be concluded that the characteristics bands of ciprofloxacin were not affected.

PRE COMPRESSION STUDIES

Angle of repose

The formulations with sodium alginate, poly vinyl pyrolidine, show angle of repose value in the range of 23.59^{o}C given in Table No.7. i.e., less than 30, which shows good flow properties.

Tapped density

The formulations with sodium alginate, poly vinyl pyrolidine show tapped density value in the range of 0.34 to 0.45 given in Table No.7.

Carr's index

The formulations with sodium alginate, poly vinyl pyrolidine were subjected to hardness test the values in the range of 4.5-5 kg/cms.

Weight variation

The prepared ciprofloxacin floating tablets were subjected to weight variation test and values within the limits as per IP.

Friability

The prepared LP floating tablets with sodium alginate, poly vinyl pyrolidine were subjected to friability test and the values within limits and the values given in Table No.8.

Table No.1: Composition of ciprofloxacin floating tablets

S.No	Drug	F1	F2	F3	F4	F5	F6
1	Ciprofloxacin HCl	500	500	500	500	500	500
2	Sodium alginate	25	50	75	-	-	-
3	Poly vinyl pyrolidine	-	-	-	25	50	75
4	Sodium bicarbonate	100	100	100	100	100	100
5	Citric acid	20	20	20	20	20	20
6	Micro crystalline cellulose	120	95	70	120	95	70
7	Magnesium stearate	5	5	5	5	5	5
8	Total tablet weight	750	750	750	750	750	750

Table No.2: Scale of flow property

S.No	Flow property	Angle of Repose (θ in degrees)	Compressibility Index (CI in %)	Hausner Ratio
1	Excellent	25 - 30	< 10	1.00 - 1.11
2	Good	31 - 35	11 - 15	1.12 - 1.18
3	Fair	36 - 40	16 – 20	1.19 - 1.25
4	Possible	41 - 45	21 – 25	1.26 - 1.34
5	Poor	46 - 55	26 – 31	1.35 - 1.45
6	Very Poor	56 - 65	32 – 37	1.46 - 1.59
7	Very, very poor	> 66	> 38	> 1.60

Table No.3: Percentage deviation of Average weight

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

Table No.4: Organoleptic properties

S.No	Test	Specification / limits	Observations
1	Color	White or almost white, powder	faintly yellowish to light yellow
2	Taste	Bitter	Bitter
3	Odour	Pungent	Pungent

Table No.5: Melting point

S.No	Material	Specification	Melting point range
1	Ciprofloxacin HCl	257^{o}C	255-257^{o}C

Table No.6: Solubility of ciprofloxacin HCl

S.No	Medium	Water	0.1 N HCl
1	Solubility	1g/25ml	25mg/ml

Table No.7: Pre-Compression Parameters

S.No	Formula Code	Angle of repose (°)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's ratio
1	F1	31.5±0.13	0.3750±0.25	0.4091±0.15	8.3333	1.0909
2	F2	27.4±0.52	0.3750±0.32	0.4500±0.25	14.6345	1.2000
3	F3	29.4±0.01	0.3750±0.22	0.4500±0.32	14.6666	1.2000
4	F4	26.2±0.20	0.3461±0.13	0.409±0.42	15.3846	1.1818
5	F5	29.26±0.01	0.3214±0.18	0.3461±0.34	7.1428	1.0769
6	F6	28.29±0.23	0.3228±0.13	0.3477±0.14	7.1428	1.0769

Table No.8: Post Compression Properties of Ciprofloxacin HCl Floating Tablets

S.No	Formula Code	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content (%)
1	F1	5.75±0.15	4.3±0.07	749.15±1.16	0.58±0.01	98±1.14
2	F2	4.90±0.14	4.4±0.07	750.2±1.17	0.30±0.10	100±0.80
3	F3	5.12±0.07	5.4±0.05	748.4±3.21	0.41±0.20	99±2.47
4	F4	5.30±0.11	4.7±0.04	753.1±2.21	0.43±0.03	100±1.87
5	F5	5.25±0.15	4.4±0.07	748.5±3.21	0.64±0.05	98±1.22
6	F6	5.05±0.14	5.2±0.09	748.4±2.78	0.75±0.06	100±1.37

Table No.9: Floating test of ciprofloxacin HCL tablets

S.No	Formula Code	Floating lag time (or) Buoyancy lag time (sec)	Total Floating time (hrs)
1	F1	15	>8
2	F2	34	>8
3	F3	41	>8
4	F4	11	>8
5	F5	36	>8
6	F6	26	>8

Table No.10: Swelling index

S.No	Time (hr)	F1	F2	F3	F4	F5	F6
1	1	59.25	67.85	82.14	50	61.76	74.38
2	2	81.48	103.57	114.28	76.47	97.05	114.38
3	3	100	146.42	153.57	91.17	120.58	145.71
4	4	122.22	160.71	178.57	111.76	155.88	168.57
5	5	133.33	178.57	203.57	123.52	179.41	197.14
6	6	148.14	196.42	228.57	138.23	197.05	217.14
7	7	159.25	207.14	253.57	152.94	217.64	237.14
8	8	174.07	221.42	275	170.58	229.40	254.28

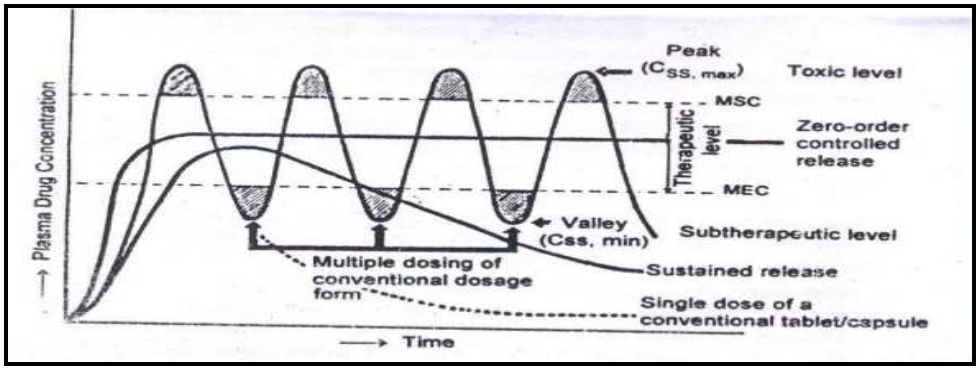


Figure No.1a: Drug levels in the blood with Conventional drug delivery system

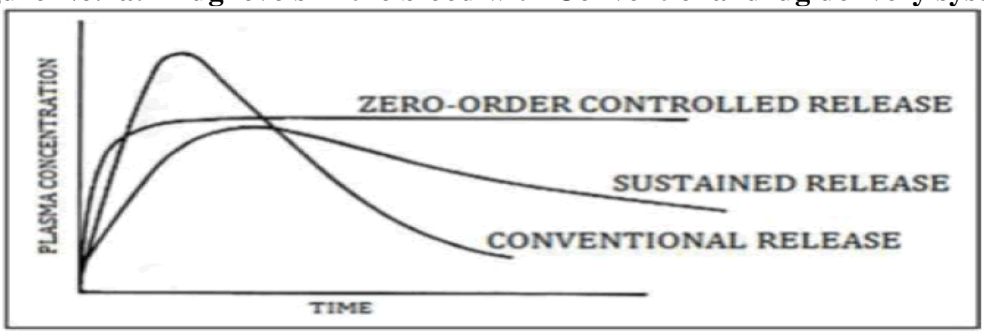


Figure No.1b: Drug levels in the blood with Controlled drug delivery system

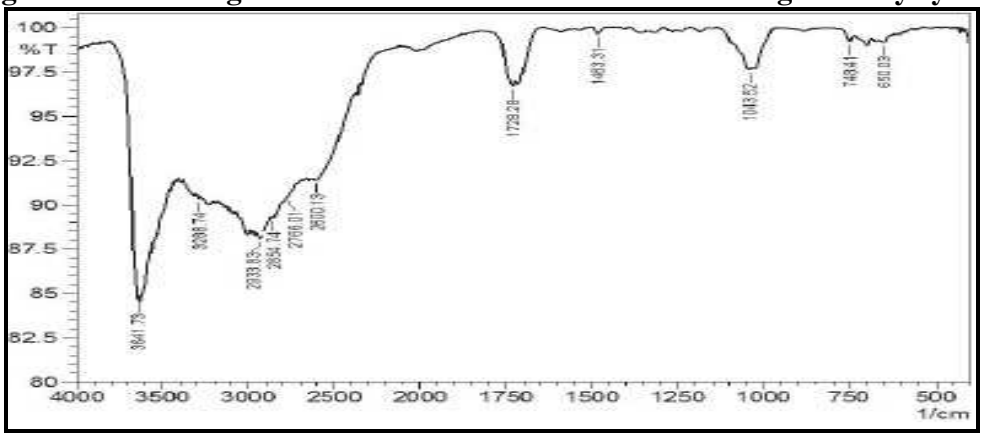


Figure No.2: FT-IR spectrum of pure drug Ciprofloxacin HCl

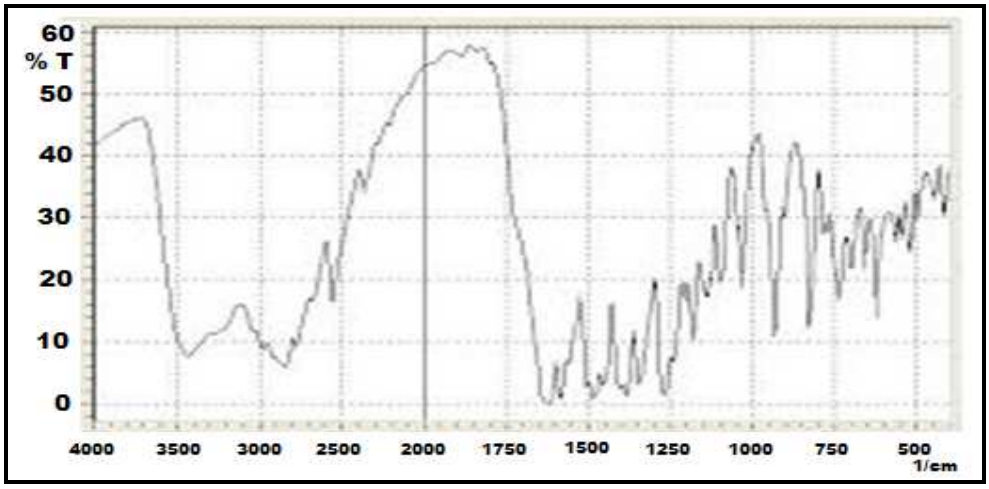


Figure No.3: FT-IR spectra data of Ciprofloxcin HCl and Sodium alginate

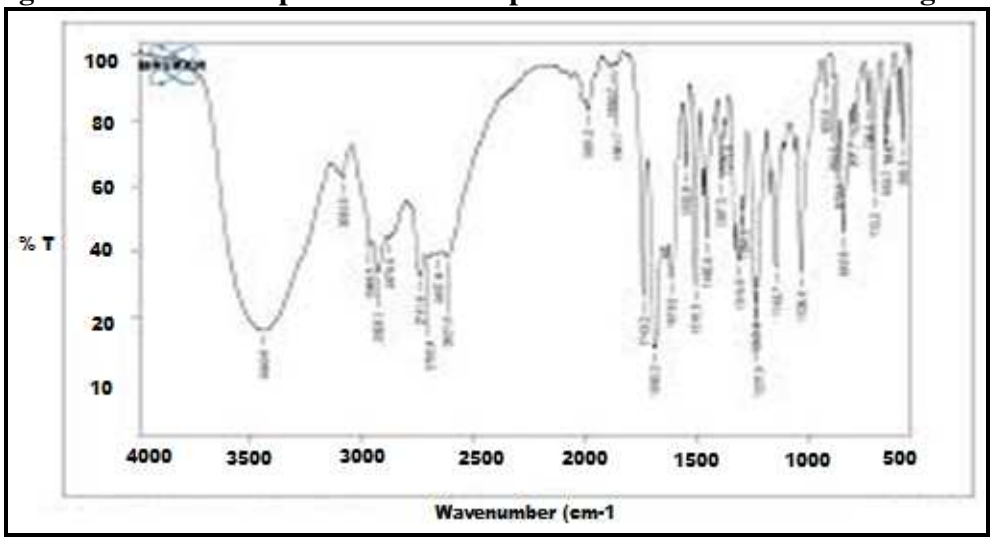
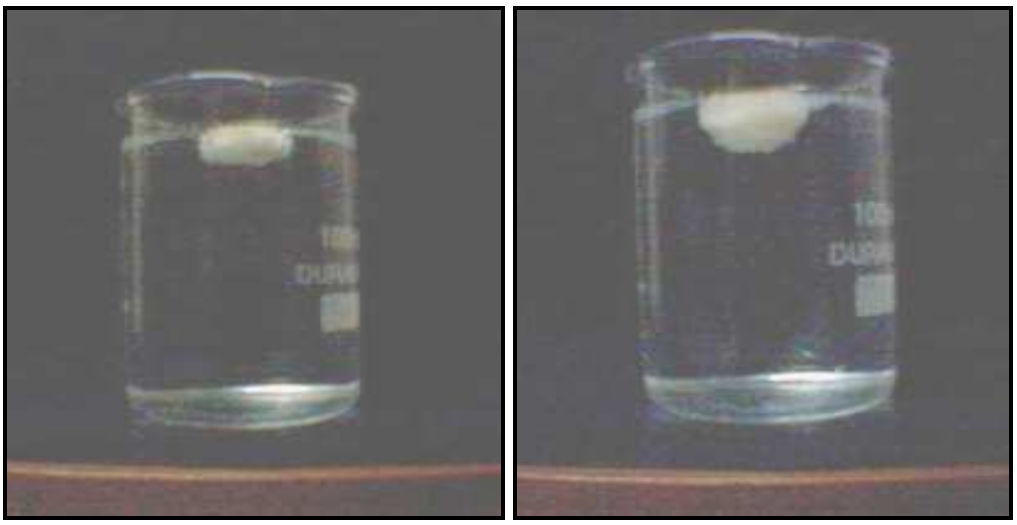


Figure No.4: FT-IR spectra data of Ciprofloxacin HCl and PVP

At initial time **After 12 second**



After 45 second **After 8 hrs**

Figure No.5: Buoyancy character of formulated tablets

SUMMARY AND CONCLUSION

The goal of present work is to provide a therapeutic amount of ciprofloxacin HCl to the proper site in the body and also to achieve and maintain the desired ciprofloxacin concentration. ciprofloxacin is a anti-biotic used in the treatment of bacterial infection .Because of its poor solubility in high pH, short half life and therapeutic use in chronic disease it is considered as an ideal drug candidate for the design of controlled release dosage form. An attempt was made to prepare floating tablets of ciprofloxacin by direct compression technique by using polymer /drug carrier like sodium alginate, PVP with a view to prevent the gastric side effects and to achieve sustained release of ciprofloxacin

In the present study six formulations were formulated by using sodium alginate, PVP in various proportions. All the formulations were subjected for evaluation. Results of pre formulation studies, FTIR, drug content, *in vitro* dissolution and release kinetics had shown satisfactory results. Pre formulation studies like melting point solubility and UV analysis of ciprofloxacin were complied with IP standards. The FTIR spectra revealed that, there was no interaction between polymer and ciprofloxacin. The polymer used was compatible with ciprofloxacin.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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