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Preparation and Characterization of Floating Alginate Beads of Gastro-retentive Drug Delivery System

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ABSTRACT

Floating beads was formulated by ionotropic gelation method using various polymers. This research was prepared and evaluated for floating gastro-retentive beads of ciprofloxacin hydrochloride antibiotic drug to prolong gastric residence time increased drug bioavailability. The floating sodium alginate beads were evaluated for drug identification test ciprofloxacin hydrochloride, which include particle size, entrapment efficiency, in- vitro drug release, in-vitro buoyancy study. The morphology of shape or size and surface of beads was characterized by SEM. That floating alginate beads showed particle size calibration, drug entrapment efficiency, buoyancy and % yield in the ranges 96.08±0.4 to 99.12±1.15%. The % buoyancy of the preparation was found to be between 72.39 ± 0.13% to 95.23± 0.16% which was found to decrease with the increase in amount of drug loading. The % Drug loading and % Entrapment efficiency of the preparation was found to be in the range of 15.26 ± 0.28% to 18.31 ± 0.36% and 71.42± 0.05% to 88.37 ± 0.16%. Out of the six-drug loading formulation (A1,A2,A3, A4, A5, A6), the formulation A6 was to have maximum % drug loading and maximum % entrapment efficiency.

All the micrometric properties were found in the acceptable range for all the formulation evaluation. Preparation A6 was found to be optimized based on % yield buoyancy, percentage drug loading, %entrapment efficiency and micromeritic properties. Further studies i,e. FTIR study, SEM, drug release were performed on optimized formulation A6.

In- vitro drug release study confirms formulation A6 was best formulation, it releases 98.57% of ciprofloxacin hydrochloride at end of 12 hours-controlled manner in the floating drug delivery system and oral sustained administration of the ciprofloxacin hydrochloride.

KEYWORDS: Floating drug delivery system, Sodium alginate beads, Gastro-retentive drug delivery system, ciprofloxacin hydrochloride, In-vitro drug release study.

I. INTRODUCTION

Gastro-retentive delivery system (GRDDs) goes to controlled delivery system, that are capable to retain drug in stomach and avoiding gastric transit. These dosage form release drug in controlled manner for long time. The real trial in progress of gastro-retentive DDS is not objective to sustain drug released but including to prolonged existence of dosage form in abdominal till all the drug is totally released. **(1).** Oral delivery is the suitable choice for any drug. Drugs is certainly absorbed from (GIT) has short life- live is removed rapidly in systemic movement. This delivery system suffers from generally two difficulties short- gastric retaining period and changeable small gastric clearing time. **(2)**

GRDDS is method to prolonged GRT targeting to a specific-site and releasing drug in overhead GIT for local effect. Over the past some decades, numerous GRT drug delivery approaches to design and develop, as well as high density that is maintained the lowest of abdominal low-bulky system that reasons resistance within gastric liquid. **(1).**The GRT of dosage form is controlled by many factors include bulk, shape, size of dosage form natural of posture, food ingestion age, sex, posture gender, sleep physical activity body bundle index and disease state of specific (i.e, diabetes and chronic disease), administrations of drug and effect on gastrointestinal transit period such as drug action as opiates (e.g. codeine) anticholinergic agents (e.g. propantheline, atropine) prokinetic agents (cisapride and metodopramide). **(1)**

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Floating drug delivery system (FDDS)

The system of floating has density smaller in comparison with gastric fluids and therefore rest floating in abdominal without influence on gastric empty portion to long period. Through the system in moving completed in gastric materials, this drug released slowly at disagreeable amount, which results in enhanced GRT and more control of fluctuation. **(3).** The gastric evacuation time from stomach to small intestine remain from some minutes to 12 hours**. (4,6).**

Alginate beads

The multiple- unit floating system depend on crosslinked beads. It was finished by means of Ca^{2+} alginate. Round beads of almost 2.5 millimetre in size can be formulated by adding Na alginate in H_2O of $CaCl_2$, preparing precipitation medium of Ca^{2+}alginate. Then beads were divided into liquid nitrogen and freeze dry at temperature 40^0C for 23-24 hours, significant to development of porous medium, which continue to floating at least 10-12 hrs. **(3).**

II. MATERIALS AND METHOD

Materials: All the chemicals used, were either obtained as gift samples or purchased. Ciprofloxacin hydrochloride was obtained as gift samples from INTAS. Pharmaceutical Ltd., Dehradun INDIA. Sunflower oil was purchase from Prayagraj U.P. All other components were of systematic grade

Formulation of beads

Calcium chloride and sodium alginate solution of different concentration was prepared by emulsion gelation method. Different concentration of sodium alginate was dissolved in water with stirring at 100 rpm and different concentration of sunflower oil was added to the polymer solution. Then, 10 mg of ciprofloxacin hydrochloride was added to it and the homogenized mixture was eject through a 24G. syringe needle in to 100ml of various concentration of CaCl2 solution at the room temperature. The beads formed allowed to stand for 15 minutes in the solution, filtered out and finally dried overnight at the room temperature. **(4).**

Table 1. Different Formulations of calcium alginate bead.

Formulation code	Na alginate conc^n(W/V)	Sunflower oil conc^n (v/v)	Ciprofloxacin hydrochloride (mg)	$CaCl_2$(w/v)
A1	3%	5%	10	5%
A2	4%	5%	10	5%
A3	5%	5%	10	5%
A4	3%	10%	10	5%
A5	4%	10%	10	5%
A6	5%	10%	10	5%
A7	3%	15%	10	5%
A8	4%	15%	10	5%
A9	5%	15%	10	5%

Fourier transform infrared analysis (FTIR) study

FTIR used for examination of pure drug, polymer and drug load beads for identification of functional group present in compounds. The sample was scanned at wave numbers from 4000 $cm^{/1}$ to 400$cm^{/1}$ represent the molecular fingerprint (MF) of the specimen. FTIR spectra obtained was used for identifying interaction between the drug with excipients. **(6)**

FT-IR study for blank and drugs loaded formulation was performed to find any potential drugs polymer interrelation using FT-IR spectrometer in frequency (f) range of 4000 to 400 cm^{-1}

Characterization

Determination of particle size

Particle size determined by electric sieve shaker apparatus. Sieve sets were arranged with the coarsest sieve at the top. Sample was placed at the top sieve, sieves were fixed with the shaker machine tightly and allowed it to run for 20 minutes. Then particles were collected from different sieves, weight and particle size was determined.

Determination of % yield

The prepared formulation of calcium alginate beads was collection and weighed. The percentage yield was determined from formulagiven below **(8).**

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(Percentage Yield = (Actual mass of the product/Weight of the drug and excipients) ×100

In- vitro buoyancy study

Prepared beads equal to 10mg drug was spread onto the surface of 900 ml of dissolution fluid containing 0.1N HCL and 0.02 percentage tween 80 in an U.S.P dissolution device types (II) that was stirred with paddle, rotating at 100 round/minutes for 12 hours. Floating beads and settled beads were obtained separately. Then beads were dried, weighed & percentage resistance was considered by formula given below **(3).**

% buoyancy = (QF/QF+Qs) ×100

QF= mass of floating beads

Qs= mass of settled beads

Drug entrapment efficiency

The drug contents from dry beads were completed by crushing of beads with mortar pestle before dipping in 100ml of PBS (phosphate buffer solution 7.4 pH.) and regularly stirred using above stirrer for 60min that contribute completed bursting & swelling of beads. The resulting spreading was filtered by filter paper. Then concentration of drug in the solution was determined spectrophotometrically at 275 nm against blank afterward suitable dilution **(9).**

%EE= (Actual drug contents/theoretical drug loading) %

% Drug loading = (WD. WB^{-}) ×100

WD - Volume of drug loaded in beads

WB - Weight of beads

Micromeritic properties of beads

Floating beads were characterized by their micrometric properties like bulk density, haunser's ratio, tapped density, compressibility and angle of repose**. (8)**

- **Bulk Density**

The bulk density floating beads were placed in measuring cylinder and observed the quantity occupied by sample. The primary volume was measured and density was calculated by using formula.

Bulk density (B.D) =M/V^{0-}

M = weight the beads sample

V^0 =volume the beads

- **Angle of Repose**

This property was evaluated by maximum angle probable b/w the outward of the pile of beads & parallel flat surface, its found by the funnel in a fixed location.

Tan A = (h/r)

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

A = Angle of repose

H = Height of pile

R = radius of pile

- **Tapped Density (T.D)**

T. D was calculated by mechanical tapping to graduated measuring cylinder which consists of the beads. Its ratio of the initial bead quantity with tapped -Volume of beads after tapping. Tapped density of the beads was considered by following equ^{n}.

Pt = M/Vt

Pt = Tapped density

M = weight (of bead)

Vt = Tapped volume

- **Compressibility index (Carr's index)**

The compressibility index is a tendency of the bead to be compressed. It is calculated by using this formula.

Compressibility Index = Tapped Density-Bulk Density /Tapped Density ×100

- **Hausner of Ratio**

Hausner fraction was calculated T.D and B.D hausner's ratio for bead were estimated and can be calculated by this formula.

Hausner of Ratio = Tapped Density/ Bulk Density

Scanning Electron Microscopy (SEM)

SEM is an important characterizing instrument. This is useful device in observing the surface and cress-section image of the beads. In the SEM sample is bombarded with the high intensity electron beam, that give information of topography morphology etc. Using SEM (NOVA NANO SEM 450) the surface morphology was determined at acceleration volt of 15KV. The SEM of ciprofloxacin hydrochloride containing sodium alginate beads is shown in figure.3. **(4,6).**

In- vitro release drug

The in- vitro drug release study of performance for all formulation use in USP dissolution apparatus. The exact weight of floating sodium alginate beads was taken into 200 millilitres of 0.1N Hydrochloric solution & dissolution fluid and temperature maintained at 37^{0}C and stirred at 100 rpm After 30 minutes of time interval 10ml sample were withdrawn then volume replaced within same quantity of the plain sample. The collected sample was analysed by UV-Spectrophotometer at 275nm **(4).**

In vitro kinetics

Drug release mechanism was investigated and the data obtained from in-vitro release studies were applied, first order kinetics, Higuchi condition and Korsmeyer-Peppas conditions. Different equation and models were studied in this in-vitro kinetics.

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III. RESULT AND DISCUSSION:

Drug polymer compatibility study

Fourier transform infrared analysis (FTIR)

FTIR testing was used for identification of drug. ciprofloxacin hydrochloride drug. FTIR spectra were recorded to measure compatibility of pure drug loaded and formulation compound. The FTIR spectrum of optimize A6 of the bead was recorded separately and compare with the spectrum of blank beads to verify the possible interaction b/w the constituent and characteristic peaks shown in Figure- 1, 2. In FTIR spectrum of Ciprofloxacin Hydrochloride frequency at 3376.38cm^{-1} shows bonded N-H stretch, 1703.09 cm^{-1} shows C = C stretching, 1388.23 cm^{-1}and 1314.98 cm^{-1} shows C -N stretch, 939.61 cm^{-1} and 805.32 cm^{-1} shows ortho substitution. In FTIR spectra of Ciprofloxacin Hydrochloride entrapped calcium alginate beads formulation A6 shows frequency at 3354.28 cm^{-1} which shows bonded N -H stretch at 1742.48 cm^{-1} shows aromatic C = C ring stretching, 943.24 cm^{-1}, 874.48 cm^{-1} and 819.93 cm^{-1} shows artho substitution the above frequency where absent in FT-IR spectrum of blank calcium alginate beads. The results showed that there is no chemical interaction took place during the formulation of beads and drug exhibits compatibility with polymer**(10).**

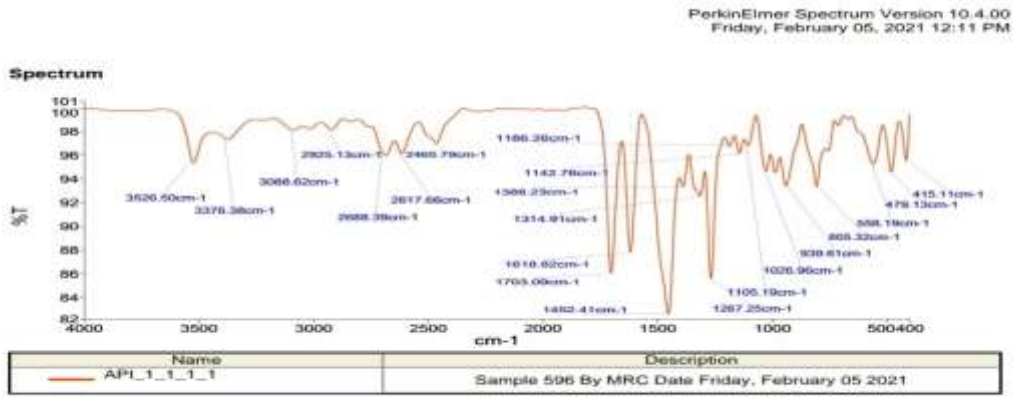

Figure .1. FTIR spectrum of ciprofloxacin hydrochloride.

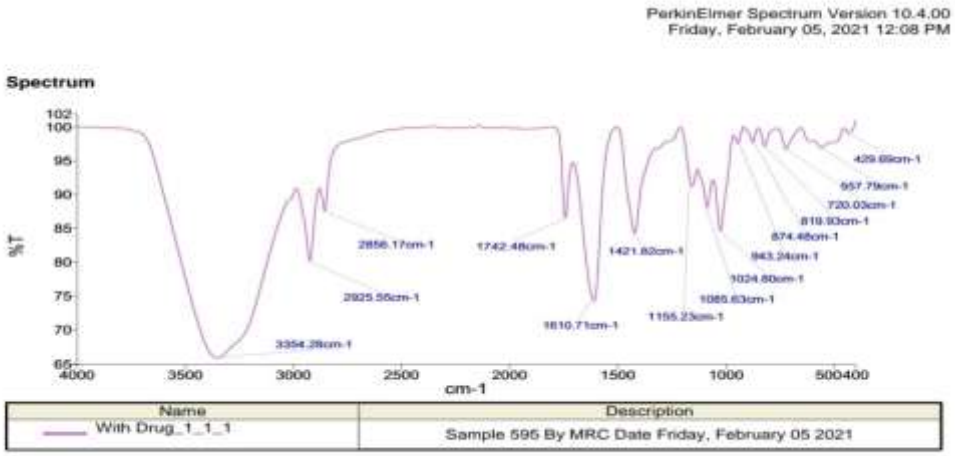

Figure .2. FTIR spectrum of Ciprofloxacin hydrochloride entrapped calcium alginate beads.

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Characterization and optimization of formulation

Particle size

The particle sizeof the optimized formulation was determined by electric sieve shaker apparatus. This particle size of sodium alginate beads was found to be in range between 1.04± 0.20 mm to 1.74±0.98 mm. The particle size of all the formulation are shown in Table.2. Due to leaching of oil from the formulation, F7, F8, F9, the beads are were found adhered to each other**(7).**

Table .2. Particle size and percentage yield %

Batch no.	Particle size (mm)	Percentage Yield
A1	1.04 ± 0.20	97.68±0.98%
A2	1.11 ± 0.25	96.08±0.04%
A3	1.22 ± 0.35	98.32±1.10%
A4	1. 14 ± 0.27	98.09±1.11%
A5	1.18 ± 0.30	99.06±1.14%
A6	1.24 ± 0.37	99.12±1.15%
A7	1.43 ± 0.54	96.52±0.06%
A8	1.54 ± 0.78	97.45±0.85%
A9	1.74 ± 0.98	98.89±1.13%

Percentage yield

The % yield was found to be in range of 96.08±0.04% to 99.12±1.15% formulation A6 showing highest loading of 99.12±1.15% and second highest loading A5 of 99.06±1.13%. formulation A2showed lowest drug loading of the 96.08 ±0.04% the drug loading was increased with decrease in polymer concentration for highest viscosity. It was found that obtain % yield was larger than 90% for all formulation. All the formulation are shown in table. 2.

In -vitro buoyancy study

The percentage buoyancy of formulation was found to be between 72.39% to 95.23%. That so large amount of the alginate beads remain floating after12 hours. The formulations A1 and A2 had the floating capability in the range 72.39 to 79.36%. Alginate beads formulations F3 and A4 have present buoyancy between 81.89% to 92.45%. Formulation A5 and A6 have buoyancy between 95.23 to 94.52%. Low buoyancy is due to low oil concentration of 5% v/v. Formulation A7, A8, A9 have low buoyancy due to leakage of oil from the Calcium alginate matrix of beads. All the formulation are shown in table no.3.

Percentage of drug loading and Drug entrapment efficiency (EE)

The percentage drug loading and EE of prepared sodium alginate beads was found to be in the range of 15.26% to 18.31% and 71.42% to 88,37% respectively. Out of the five drug- loaded formulation, the formulation A6 was to have maximum% drug loaded and maximum % entrapment efficiency due to higher amount of drug content. The drug loaded and entrapment efficacy were determined by the extraction method and results are shown in Table no.3. Due to oil leaching from the matrix formulation A7, A8, and A9 was not included in % drug entrapment as well as % drug loading study.

Table .3. %Drug loading, drug entrapment efficiency and In- vitro buoyancy %

Batch no.	% Drug Loading	Entrapment efficiency (%)	In -vitro buoyancy (%)
A1	15.26 ± 0.28	71.42 ± 0.05	72.39 ± 0.13
A2	15.38 ± 0.20	76.25 ± 0.09	79.36 ± 0.09
A3	16.25 ± 0.32	82.54 ± 0.12	81.89 ± 0.04
A4	17.21 ± 0.36	72.12 ± 0.06	92.45 ± 0.16
A5	18.31 ± 0.48	84.21 ± 0.14	95.23 ± 0.20
A6	18.19 ± 0.46	88.37 ± 0.16	94.52 ± 0.09

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Micromeritic Properties

The floating beads of ciprofloxacin hydrochloride was prepared. The Angle of Repose of preparation were found in range 19.15±0.9 to 27.29±0.02. Angle of repose of less than 25 shows is excellent flow property. Result suggest excellent flowability of beads. The (BD) bulk density of formulation is in the range between 393±0.06 to 745±0.08. The tapped density (TB) of the preparation were found in the range b/w 0.422±0.20 to 0.609±0.041. Hausner ratio of the preparation was found in the range b/w 1.15±0.34 to 1.25±0.84 the formulation all batches shown Hausner ratio of less than 1.30, the excellent flowability for all the preparation. The Compressibility of preparation A1- A6 was found in range of all formulation batches that was found to have excellent compressibility. All batches A1-A6 results are shown in the table 4. Formulation A7, A8, and A9 were discarded because these formulations were found adhered to each other due to leaching of oil from the formulation.

Table .4. Micromeritic Properties

Formulation	Angle of Repose	Bulk Density	Tapped Density	Hausner's Ratio	Carr's Index
A1	27.29 ± 0.02	0.566 ± 0.92	0.494 ± 0.29	1.17 ± 0.58	9.87
A2	21.12 ± 0.08	0.745 ± 0.08	0.602 ± 0.04	1.29 ± 0.12	20.67
A3	24.30 ± 0.05	0.695 ± 0.82	0.514 ± 0.22	1.25 ± 0.22	13.57
A4	19.15 ± 0.9	0.712 ± 0.17	0.609 ± 0.41	1.25 ± 0.84	8.90
A5	25.42 ± 0.06	0.425 ± 0.66	0.520 ±0.031	1.15 ± 0.34	6.97
A6	20.25 ± 1.6	0.515 ± 0.16	0.422 ± 0.20	1.16 ± 0.68	5.13

Scanning Electron Microscopy study (SEM)

The cross- section of floating beads was examined in SEM image of bead revealed the spherical shape and rough surface. (Figure. 3) showed the appearance of beads with many hollow and small pores found in the alginate matrix.

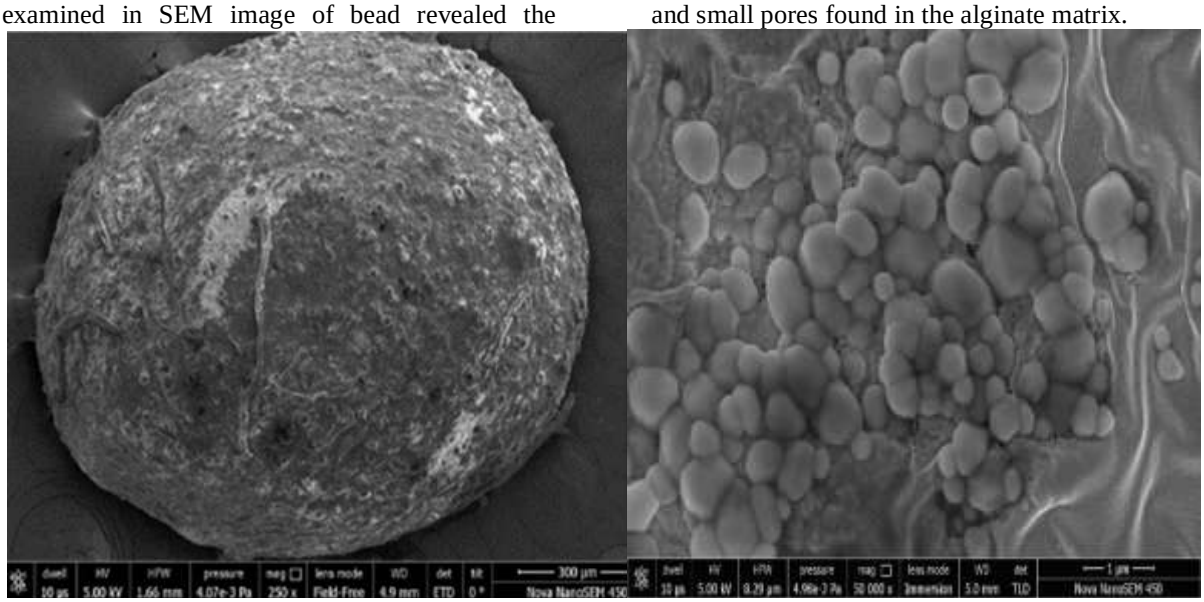

Figure. 3: Scanning Electron Microscopy transverse section (TS) of A6 Formulation

In- Vitro Drug Release

In vitro drug release study data display that drug release from beads is mostly dependent on polymer swelling and drug diffusion. The percentage drug release was in the range from 40.87 ± 0.18% to 98.57 ± 0.009%. The in- vitro drug release of the formulation, F6 is shown in the Table 5. The data obtained in- vitro release studies were fitted to various kinetic equations to find out the mechanism of drug release from the optimized drug loaded formulation F6. The kinetic models used were Zero-order equation, First order equation, Higuchi model and Korsmeyer-Peppas model. Drug release kinetics was best fitted for korsmeyer-peppas model as the R^2 value for the model was 0.9841 which was nearer to 1. The drug release mechanism was of Fickian diffusion the release exponent, n was found to be 0.2698, which

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was < 0.43 **(11)**.The graphical illustrations of the kinetic models for in-vitro drug release profile are shown in Tables 5 and Figures 4.

- **Zero- order kinetics**

In zero order models, data obtained from in-vitro drug release study was plotted as % Cumulative drug release

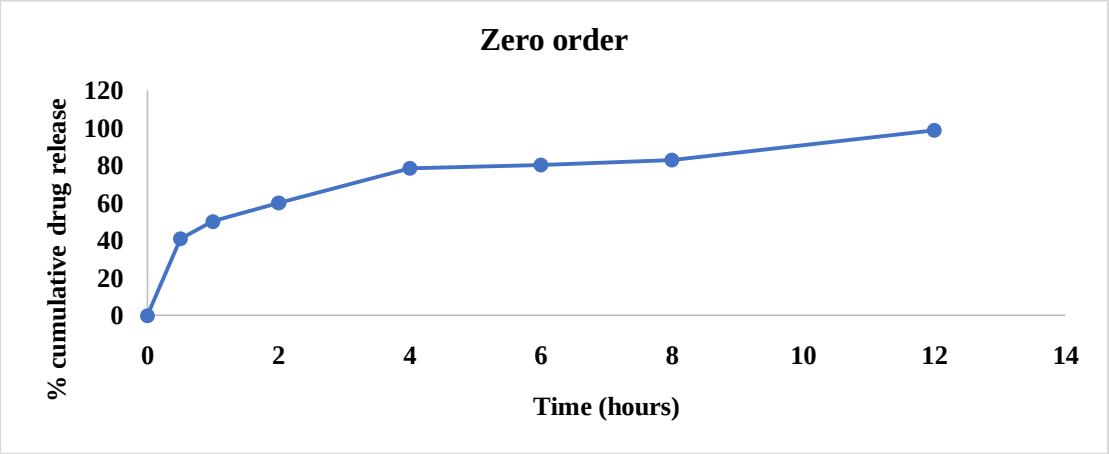

Figure4. Zero-order release kinetics

- **First order kinetics**

In first order release study, data found from in-vitro drug release studies was plotted as log % Cumulative drug unreleased v/s time.

- **Higuchi model**

In Higuchi model, data found from in-vitro drug release studies was plotted as %Cumulative drug release v/s square root of time.

- **Korsmeyer - Peppas model**

In Korsmeyer- peppas model, information found from in- vitro drug release studies were plotted as log % Cumulative drug release v/s log time.

Table.5. Release kinetics study of formulation F6

Release kinetics	Parameter	F6
Zero order	R^2	0.7063
	K_0	6.2038
First order	R^2	0.3042
	K_1	0.1978
Higuchi model	R^2	0.9086
	K_H	25.555
Korsmeyer-Peppas	R^2	0.9841
	K_{KP}	0.2698
	N	0.2698

IV. CONCLUSION:

The floating beads present in gastro-retentive have controlled release property so that floating completed gastric content & remaining in the abdomen for prolonged period of time. Calcium alginate beads were prepared by ionotropic gelation technique that used $CaCl_2$as a cross-linking agent. In this study, solubility and melting point was checked and was found that ciprofloxacin hydrochloride is soluble in the distilled water and methanol. The melting point is between 256-257^{o}c of ciprofloxacin hydrochloride. The % yield was found to decrease with increasing drug amount. The maximum %yield was found to be 96.08±0.04 to 99.12±1.15. The particle size 1.04 ± 0.20 mm to 1.74 ± 0.98 mm. The high % buoyancy of the preparation was found to be 72.39 ± 0.13% to 95.23 ± 0.16%. The drug loading was found to be 15.26 ± 0.28% to 18.31 ± 0.36% and the % drug EE was found in range between 71.42 ± 0.05% to 88.37 ± 0.16% which showed the increased concentration of the polymer used in experiment. That morphology of sodium alginate beads was observed by SEM which showed that the floating

beads was spherical and rough surface with hollow and small pores.

The FTIR spectrum of optimized formulation A6, the identification of the drug ciprofloxacin hydrochloride and other excipients and bonds were identified.

The in-vitro release studies display that floating bead was capable to release drug up to 12 hrs in gastric fluid and determined that optimized batch A6 showed great EE & drugs release casually and totally for 12 hrs and continue in floating state throughout dissolution study. Drug release kinetics of F6 formulation was best fitted for korsmeyer-peppas model the R^2 value for the model was 0.9841 which was nearer to 1, then the R^2 value for the other model. The drug release mechanism was of Fickian diffusion the release exponent, n was found to be 0.2698, which was < 0.43.

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