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Formulation and evaluation of floating microbeads of Ciprofloxacin HCl by emulsion gelation method

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Abstract

The present research work discusses the formulation and evaluation of floating microbeads of ciprofloxacin HCL by emulsion gelation method. The objective of this investigation is to develop a multi-unit gastro retentive sustained release dosage form of a water soluble drug, Ciprofloxacin, from a completely aqueous environment avoiding the use of any organic solvent. A new emulsion gelation technique is used to prepare emulsion gel beads using sodium alginate as the polymer. The gel beads containing is prepare by gently mixing or homogenizing oil and water phase containing sodium alginate which is then extruded in to calcium chloride solution. The effects of factors like concentration of oil, curing time, drug: polymer ratio, alginate: pectin ratio and curing agent on drug entrapment efficiency, floating lag time, morphology and drug release are study. Minimizing the curing time of beads leaded to enhanced drug entrapment efficiency. The use of sodium alginate and combinations of sodium alginate and pectin are used to study the effect on the sustaining property of the formed beads. It is found that sodium alginate was not sufficient to sustain the drug release at gastric pH. Instead of it, appropriate combination of alginate and pectin could provide the sustain release of drug. The results show that these beads can entrap even a water soluble drug as Ciprofloxacin in sufficient amount and also can successfully deliver the drug in stomach for a prolong duration of time. The Physical appearance and melting point of drug were found to be concordant with that mentioned in USP, 29 and Clarke's Analysis of Drugs and Poisons, 2006 respectively which shows the purity of the sample. IR spectrum of the drug sample was obtained by FT/IR. Its characteristic absorption bands proved its identity.

Key-Words: Floating Lag Time, Immediate release, Floating Lag time, Drug release, Drug entrapment efficiency

Introduction

Oral controlled release (CR) formulations have been developed in an attempt to release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time. Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation. Approaches to increase the GRT include: (i) bioadhesive delivery systems, ii) swellable delivery systems and (iii) density-controlled delivery systems, which either float or sink in gastric fluids. The floating system is intended to float in and over the gastric contents resulting in prolonged GRT. Furthermore, as the total gastrointestinal transit time of the dosage form is increased by prolonging the gastric residence time, these systems can also be used as sustained release devices with a reduced frequency of administration and therefore, improved patient compliance.

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Unfortunately, floating devices administered in a single-unit form such as hydrodynamically balanced systems (HBS) are unreliable in prolonging the GRT owing to their 'all-or none' emptying process and, thus, they may cause high variability in bioavailability and local irritation due to a large amount of drug delivered at a particular site of GIT. In contrast, multiple-unit particulate dosage forms (e.g. microspheres, gel beads) have the advantages that they pass uniformly through the GIT to avoid the vagaries of gastric emptying and provide an adjustable release, thereby, reducing the intersubject variability in absorption and risk of local irritation. Various types of drug delivery systems for oral administration such as drug release rate-controlled delivery systems, time-controlled delivery systems and site-specific delivery systems have been extensively developed. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. An important requisite for the successful performance of oral CRDDS is that the drug should have good absorption throughout the

gastrointestinal tract (GIT), preferably by passive diffusion, to ensure continuous absorption of the released drug. The average time required for a dosage unit to traverse the GIT is 3–4 h, although slight variations exist among various dosage forms. Certain types of drugs can benefit from using gastro retentive devices. These include: Drugs acting locally in the stomach, Drugs that are primarily absorbed in the stomach, Drugs those are poorly soluble at an alkaline pH, Drugs with a narrow window of absorption, Drugs absorbed rapidly from the GI tract, Drugs that degrade in the colon. Thus, when a drug possesses a narrow 'absorption window, design of the controlled release preparation requires both prolongation of gastrointestinal transit of the dosage form and controlled drug release.[1] The prolongation of gastric residence time (GRT) is expected to maximize drug absorption from Floating Drug Delivery Systems (FDDS) due to increased dissolution of drug and longer residence at the most favorable sites of absorption. It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time. Gastro retentive Dosage Forms (GRDFs) will provide us with new and important therapeutic options.[2] Thus control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drug exhibiting an 'absorption window' in the GI tract. The intimate contact of the DDS with the absorbing membrane and also the potential to maximize drug absorption may influence the rate of drug absorption. These considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities. Drug may not be absorbed uniformly over the length of the gastrointestinal tract, because dosage form may be rapidly transported from more absorptive upper regions of the intestine to lower regions where the drug is less absorbed and drug absorption from colon is usually erratic and inefficient. Moreover, certain drugs are absorbed only from the stomach or the upper part of small intestine.[3] The rate of drug absorption may not be constant in spite of the drug delivery system delivering the drug at constant rate into the gastrointestinal fluids. The drug is absorbed only from specific regions of the stomach or upper parts of the small intestine in case when the drug has a clear cut "absorption window".[4] Absorption windows in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of CDDS. It is apparent that for a drug having such an absorption window, an effective oral controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the upper parts of the gastrointestinal tract for a long period of time. The real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of drugs for more than 12 hrs but also to prolong the presence of dosage forms in the stomach or somewhere in the upper part of small intestine.[5]

Material and Methods

Drug

Ciprofloxacin HCL was obtained as a gift sample from Alpa Pharmaceutical Ltd. Indore. Sodium alginate was purchased from, Alpa Pharmaceutical Ltd. Indore HPMC K100M was purchased from Peekay Scientific Center, Bhopal the other chemicals and reagents used in the study were of analytical grade.

Emulsion gelation method

Ciprofloxacin micro beads are prepared by emulsion gelation method.

Sodium Alginate (4%) was dissolved in distilled demineralised water with agitation. Ciprofloxacin and different concentrations of mineral oil are added to the solution. This solution (2.5g) containing Ciprofloxacin (125 mg) and oil (0-40% (w/w)) is dropped through 21 G needle in to 1%calcium chloride (10 ml) and left at room temperature for 2 h.The resultant hydro gel beads are washed twice with distilled water and kept for drying at room temperature up to 12 hours.

Preparation and optimization of alginate gel beads

All alginate gel beads were prepared following the emulsion gelation procedure. A pre-gelation liquid was prepared by mixing sodium alginate solution and HPMC K100M by dissolving in water with stirring. Sunflower oil was added to the polymer solution followed by drug. Twenty millilitres of each of the pre-gelation liquid was then added, through a 26 G syringe (0.8 mm diameter, into 100 ml of different concentration [1% (w/v), 2% (w/v)] of $CaCl_2$ solution dropped from 5 cm dropping at the rate of 2 ml/min. and kept for 20 min. The beads were then recovered from the $CaCl_2$ solution and washed with deionized (D.I.) water and air dried for 48 hours. Different formulations were prepared by varying the sodium alginate concentrations, sunflower oil concentrations and drug concentrations. The prepared formulations are given in Table 1.

Table 1: Different formulations of alginate gel beads

FC	Amt of Ciprofloxacin HCl (mg)	Amount of HPMC K100M (mg)	Amount of Sodium alginate	Amount of Calcium chloride	Amount of Sunflower oil (ml)
F1	250	250	4%	1%	1
F2	250	250	5%	1%	0.5
F3	250	250	6%	1%	1
F4	250	250	4%	1%	0.5
F5	250	250	5%	1%	0.5
F6	250	250	6%	1%	0.5
F7	250	250	5%	2%	0.5
F8	250	250	5%	3%	0.5

Characterization of floating alginate beads

Physical Appearance and Morphological Analysis

All the batches of Ciprofloxacin HCl beads were studied for colour and physical appearance. Surface and cross-sectional morphologies of beads were examined with a Scanning Electron Microscope (SEM Diya Laboratory Mumbai)**.** Beads were mounted on metal grids using double-sided tape and coated with gold under vacuum.

Size Analysis

The size of the 10 prepared floating alginate beads was measured by occular microscope. Least count of the instrument was found to be 0.01mm.

Buoyancy

The floating ability was determined using USP dissolution test apparatus I (Basket method). Fifty beads were introduced in the vessels and the Basket were rotated at 100 rpm in 900 ml of 0.1 N HCl, maintained at 37±0.5 ℃ for 10 hr. The floating ability of the beads was observed visually. The preparation was considered to have buoyancy only when all beads floated on the test solution for the prescribed time period. The experiment was conducted thrice.

Bead Water Uptake

Bead water uptake in this case was presented as normalized weight gain ratio as defined below:

$$Y = m_w/m_d$$

Where Y is the normalized weight gain ratio, m_w the bead weight after swelling (including water uptake), and m_d is the initial dry bead weight. Weight gain ratio at equilibrium, Y of different floated formulations is the average of three determinations.

% Yield

% Yield for the different formulations was calculated by the formula given below.

% Yield =Total weight of floating beads produced × 100 / Total weight of drug and polymer

% Drug entrapment

50 mg of prepared floating alginate beads of Ciprofloxacin HCl were dissolved in 50 ml of 0.1N HCl (pH 1.2) and the drug content was analyzed at 277 nm using a UV/visible spectrophotometer (Shimadzu-1800). Encapsulation efficiency was calculated as the percentage (w/w) of the theoretical drug content.

% Drug Entrapment = (Actual drug content / Theoretical drug content) x 100

***In Vitro* Drug Release Studies**

The *in vitro* drug release studies of different formulations (F-1, F-7, and F-8) were conducted to ensure the effect of sodium alginate concentration, calcium chloride concentration and drug loading concentration on the release of Ciprofloxacin HCl from the formulations.The *in vitro* dissolution studies of the floating formulations were carried out using USP dissolution test apparatus I (basket method). The basket of USP dissolution test apparatus I, each containing an amount of beads equivalent to 250 mg Ciprofloxacin HCl, were rotated at 100 rpm in 900 ml of 0.1N HCl maintained at 37°C±0.5 °C. An aliquot of 10 ml of the solution was withdrawn at predetermined time intervals and replaced by fresh dissolution medium. The withdrawn samples were analyzed for Ciprofloxacin HCl content spectrophotometrically at λ_{max} 277 nm.

Effect of sodium alginate concentration

Formulations F-1 and F-8 were prepared by 4% and 5% sodium alginate concentrations (w/v of alginate solution), respectively. *In vitro* drug release study was performed to observe the effect of sodium alginate concentration on Ciprofloxacin HCl release.

Effect of calcium chloride concentration

Formulations F-1, F-7 and F-8 were prepared by syringing the pre-gelation liquid in 1%, 2% and 3% $CaCl_2$ concentration (w/v) solutions, respectively. *In vitro* drug release study was performed to observe the effect of calcium chloride concentration on Ciprofloxacin HCl release.

Release kinetics

The dissolution release kinetics and result of best fit model among the preparations were also compared. To study the mechanism of drug release from the optimized formulation of matrix tablets, the release data were fitted to the following equations:

Zero-order equation: $Q_t = Q_0 + k_0t$

Where, Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and k_0 is the zero order release rate.

First-order equation: $\ln Q_t = \ln Q_0 + k_1t$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and k_1 is the first order release rate constant.

Higuchi's equation (Higuchi, 1962): $Q = k_H t^{1/2}$

Where, Q is the amount of drug release at time t, and k_H is the Higuchi diffusion rate constant.

Korsmeyer et al's equation (Koresmeyer et. al, 1983): $M_t/M_\infty = Kt^n$)

Where, M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, and k is a kinetic constant incorporating structural and geometric characteristics of the tablet and n is the diffusion exponent indicative of the drug release mechanism. The mechanism of drug release was dependent on the value of '**n**'.

Table 2: Value of 'n' and corresponding mechanism of drug release

Value of 'n'	Mechanism of drug release
n = 0.5	Case – I (Fickion) diffusion or square root of time kinetics
0.5 < n < 1	Anomalous (non-Fickion) diffusion
n = 1	Case – II transport
n > 1	Super Case – II transport (Costa and Mannuel, 2001)

Results and Discussion

Eight formulations were prepared with the optimization of sodium alginate concentration, sunflower oil and calcium chloride. The variations of calcium chloride and sodium alginate were 1%, 2% and 3% with varying combinations. Also Oil concentration is changed to 0.5 and 1mL. The drug loading and HPMC K100M concentration was constant in each formulation. Physical appearance of various formulations of Ciprofloxacin HCl beads by using different carrier (in different ratio) was given in (Table 3). The size analysis was done by Occulometer and the average size for each formulation was found out as shown on Table 4. The buoyancy of each of the eight formulations were find out and the maximum floating time was observed for formation F-8 since the oil was in optimized concentration and sodium alginate concentration was more, which binds water. Both the constituents help in maximum floating time. Formulations F-3 and F-6 showed less floating time, so these formulations were discarded from further characterizations. Weight of bead was taken before and after putting in 0.1N HCl, the weight gained showed which formulation shows sticking and leaching of oil, thus the stability of formulation can be found out.Leaching of oil from beads was seen in formulations F-2, F-4 and F-5 containing 1% and 0.5% oil, respectively. As beads of these formulations were found sticking to each other so formulations were discarded from further characterization. Also, further formulations were prepared with 0.5% sunflower oil incorporation only.

Drug content is found to be between 85.79 % and 96.75 %. All the formulations show presence of high drug content and low standard deviations of results. It indicates that the drug is uniformly dispersed in the formulations. Therefore, the method used in this study appears to be reproducible for the preparation of beads. Formulation F-8 prepared with 5% sodium alginate and 0.5ml Sunflower oil was selected and further observed for the effect of calcium chloride concentrations on drug release. Formulation F-8 prepared with 5% sodium alginate, 0.5ml Sunflower oil and syringing in 3% calcium chloride solution was selected. In vitro drug release profile of Ciprofloxacin HCl beads formulation F-1 is given in (Table 11).

Table 3: Physical appearance of Ciprofloxacin HCl beads

Formulation Code	Physical Appearance	
	Colour	Appearance
F-1	Creamy white	Oval
F-2	Creamy white	Oval
F-3	Creamy white	Oval
F-4	Creamy white	Oval
F-5	Creamy white	Oval
F-6	Creamy white	Round
F-7	Creamy white	Round
F-8	Creamy white	Round

Table 4: Average size of different formulations

Formulation Code	Average size (mm)± SD
F-1	1.543±0.079
F-2	1.522±0.107
F-3	1.534±0.107
F-4	1.440±0.104
F-5	1.452±0.109
F-6	1.572±0.076
F-7	1.557±0.122
F-8	1.566±0.102

Table 5: Buoyancy of different formulations

Batches	Buoyancy	Floating time
F-1	Floating	7hr
F-2	Floating	6hr
F-3	Floating	-
F-4	Floating	7hr
F-5	Floating	6.5hr
F-6	Floating	-
F-7	Non-floating	8hr
F-8	Non-floating	9hr

Table 6: Bead water uptake of different formulations

Batches	Weight gain ratio at equilibrium, Y ± SD
F-1	0.284±0.00244
F-2	0.369±0.00453
F-4	0.495±0.00432
F-5	0.544±0.00106
F-7	0.615±0.000551
F-8	0.6423±0.0007

Table 7: Drug content uniformity studies and percentage practical yield of Ciprofloxacin HCl beads

Formul n Code	Drug Content uniformity %				% Practical Yield
	1st	2nd	3rd	Mean ± SD	
F-1	92.62	92.37	92.12	92.37 ± 0.25	94.23
F-7	85.75	86.37	85.25	85.79 ± 0.56	96.44
F-8	96.75	97.0	96.5	96.75 ± 0.25	98.24

Table 8: % Yield and % drug entrapment of different formulations

Formulation Code	% Drug loading	% Drug entrapment± SD
F-1	94.23	85.6
F-7	96.44	95.2
F-8	98.24	98.4

Table 9: Cumulative % drug released from floating beads (F-1 and F-8) of different sodium alginate concentration

Time (hr)	Cumulative % drug released ± SD	
	F- 1	F -8
0.5	24.45±1.27	41.53±1.12
1.0	36.39±0.81	54.66±1.09
2.0	46.16±1.10	58.56±0.94
3.0	55.23±0.98	60.5±0.88
4.0	58.39±0.95	64.53±1.25
5.0	62.31±0.85	71.13±1.42
6.0	71.39±0.56	81.3±0.75
7.0	76.41±1.05	87.26±0.80
8.0	80.26±0.97	97.43±0.83

Table 10: Cumulative % drug released from floating beads (F-1, F-7 and F-8) prepared in different calcium chloride concentration

Time (hr)	Cumulative % drug released ± SD		
	F- 1	F- 7	F- 8
0.5	24.45±1.27	25.73±0.97	41.53±1.12
1.0	36.39±0.81	42.33±0.96	54.66±1.09
2.0	46.16±1.10	55.43±0.86	58.56±0.94
3.0	55.23±0.98	65.3±0.85	60.5±0.88
4.0	58.39±0.95	70.33±1.05	64.53±1.25
5.0	62.31±0.85	77.5±0.80	71.13±1.42
6.0	71.39±0.56	85.63±1.11	81.3±0.75
7.0	76.41±1.05	88.2±1.17	87.26±0.80
8.0	80.26±0.97	91.53±0.75	97.43±0.83

Table 11: Dissolution Profile of F-1 Ciprofloxacin beads

Time (hr)	Amt. found (µg/ml)	Amt. in 900 ml (mg)	% drug release
0.5	2.716	2.445	24.45
1	4.135	3.722	37.22
2	5.128	4.616	46.16
3	6.146	5.532	55.23
4	6.487	5.839	58.39
5	6.923	6.231	62.31
6	7.932	7.139	71.39
7	8.49	7.641	76.41
8	8.917	8.026	80.26

Table 12: Dissolution Profile of F-7 Ciprofloxacin HCl beads

Time (hr)	Amt. found (µg/ml)	Amt. in 900 ml (mg)	% drug release
0.5	2.858	2.573	25.73
1	4.703	4.233	42.33
2	6.158	5.543	55.43
3	7.255	6.53	64.3
4	7.814	7.033	70.33
5	8.695	7.826	78.33
6	9.514	8.563	85.63
7	9.8	8.82	88.2
8	10.17	9.153	91.53

Table 13: Dissolution Profile of F-8 Ciprofloxacin HCl beads

Time (hr)	Amt. found (µg/ml)	Amt. in 900 ml (mg)	% drug release
0.5	4.614	4.153	41.53
1	6.073	5.466	54.66
2	6.506	5.856	58.56
3	6.722	6.05	60.5
4	7.17	6.453	64.53
5	7.903	7.113	71.13
6	8.947	8.053	80.53
7	9.695	8.726	87.26
8	10.82	9.743	97.43

Table 14: Kinetic data of Ciprofloxacin HCl beads

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Peppas R^2
F-8	0.9405	0.9922	0.904	0.5277

Conclusion

The Ciprofloxacin HCl was obtained as a gift sample from Alpa Pharmaceuticals, Indore (M.P.). The Physical appearance and melting point of drug were found to be concordant with that mentioned in USP, 29 and Clarke's Analysis of Drugs and Poisons, 2006 respectively which shows the purity of the sample. IR spectrum of the drug sample was obtained by FT/IR. Its characteristic absorption bands proved its identity.

Most beads were found nearly spherical in shape. There were no large differences in size between the bead samples prepared with different alginate and oil concentrations or by gelation in different $CaCl_2$ concentrations. However, formulation F-3 loaded with high polymer concentration was found spherical in shape. This was due to the increased viscosity of pre-gelation liquid with increased polymer (HPMC K100M) concentration. Also, tailing of beads were found in formulation F-6 containing 6% alginate concentration due to increase in viscosity of the pre-gelation liquid. Figure 1, 2 and 3 shows beads with nearly spherical shape and a rough surface without any pore. Drug particles were seen on the surface. Figure shows cross-sectional bead with no internal cavity but uniform matrix within the bead. Drug particles were also seen embedded within the matrix of the bead.

% Yield and encapsulation efficiency of the different prepared formulations are given in Table 5. % Yield of the prepared formulation was found to be between 94.23 to 98.24%. Encapsulation efficiency was found to decrease with the increase in oil concentration from 0.5% to 1% (v/v) due to the hydrophilic nature of drug, Ciprofloxacin. But encapsulation efficiency was found to increase with the increase in sodium alginate concentration from 4% to 6% (w/v) due to the hydrophilic nature of Ciprofloxacin as the drug partitions more in alginate matrix than in sunflower oil. Encapsulation efficiency was found to increase with the increase in concentration of gelation and curing ($CaCl_2$) solution from 1% to 3% (w/v). Table 2 shows how the oil loadings affect the buoyancy of the alginate beads. Any non-oily beads failed the buoyancy test as several specimens began sedimentation either upon contact with the 0.1N HCl or soon after agitation started. As the oil concentration was increased from 0.5% to 1%, all beads were found floating except F-3 and F-6 and leaching of oil from beads was seen in the formulations. So, 0.5 % oil was incorporated in rest of the formulations. There was no effect of the increase in alginate concentration from 4% to 6% or increase in $CaCl_2$ concentration and increase the polymer (HPMC K100 M) from 1% to 3% on the buoyancy of the beads.The results show that the buoyancy decreased for the beads with less oil inclusion. All the floating formulations immediately float as soon as they were put in the 0.1N HCl. Therefore, no lag time in floatation was seen.Emulsification of sunflower oil in the alginate solution and fast gelation encapsulation of the oil with the alginate gel matrices resulted in a large number of tiny oil pockets either on the gel bead surface or deep within the bead matrices. This was the reason for the beads buoyancy.

In general, the beads achieved relatively low degrees of swelling, probably because the ionization of –COOH in alginate hydrogel was suppressed in acidic pH. Oil encapsulation inhibits bead water uptake as equilibrium weight gains of beads of the same crosslink density decreases with increasing initial oil concentration. As the sodium alginate concentration increased from 4% to 6%, equilibrium weight gain ratio increased because the crosslink density of the beads increased with increase in alginate concentration. and increased the polymer(HPMC K 100M) ratio.Ciprofloxacin HCl incorporation seemed to have made the beads more hydrophilic and the equilibrium weight gain ratio increased.

The release profile show that Ciprofloxacin HCl released from beads in a considerable burst during the initial hours of release. Figure shows that as the concentration of sodium alginate increased from 4 to 6%, increased the polymer (HPMC K100 M) ratio Ciprofloxacin HCl was found to be released in a slow manner. As the concentration of $CaCl_2$ increased (1% to 3%) in formulations the Ciprofloxacin was found to be released rapidly. The formulation F-8 prepared in 3% $CaCl_2$ solution released Ciprofloxacin faster than the formulation F-1 prepared in 1% $CaCl_2$ solution but the encapsulation efficiency of formulation F-8 (97.43%) was much higher than the formulation F-1 (80.26%) so further formulations were prepared by gelation in 3% $CaCl_2$ solution.It is clearly seen that Ciprofloxacin HCl released from beads in a considerable burst during the initial hours of release due to rapid water ingress and creation of aqueous channels for the Ciprofloxacin HCl to permeate out as the drug is hydrophilic in nature.

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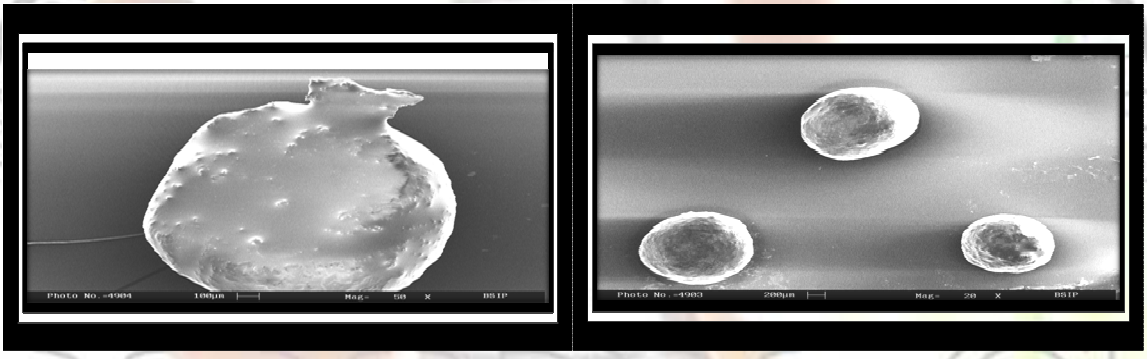

Fig 1: a) SEM photomicrograph of alginate beads (F-6) b) SEM photomicrograph of cross-sectioned alginate bead (F-6)

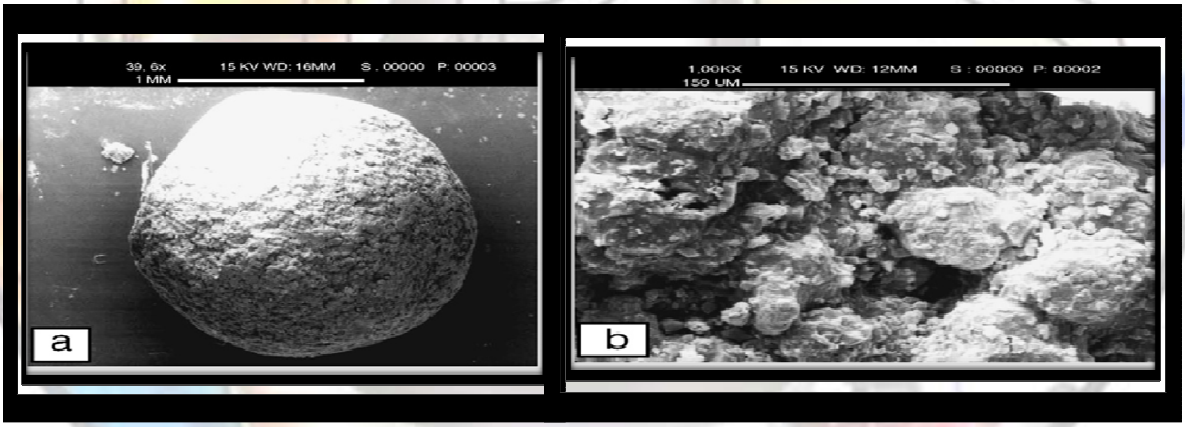

Fig 2: SEM graphs of alginate beads (a) and (b) Surface morphology

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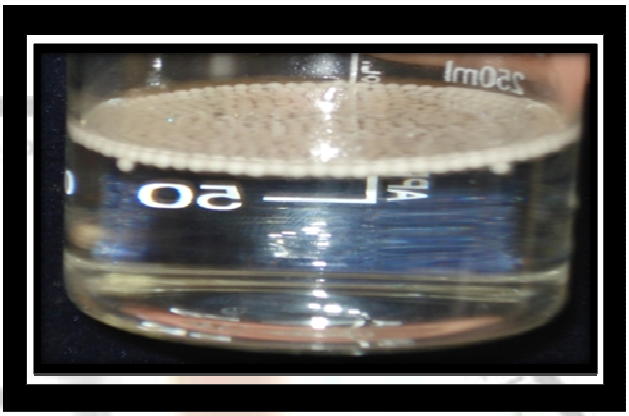

Fig 3: Sodium alginate beads (F-8) floating in 0.1NHCl in a beaker (top view) after 9 hours
Fig 4: Sodium alginate beads (F-8) floating in 0.1N HCl in a beaker (side view) after 10 hours

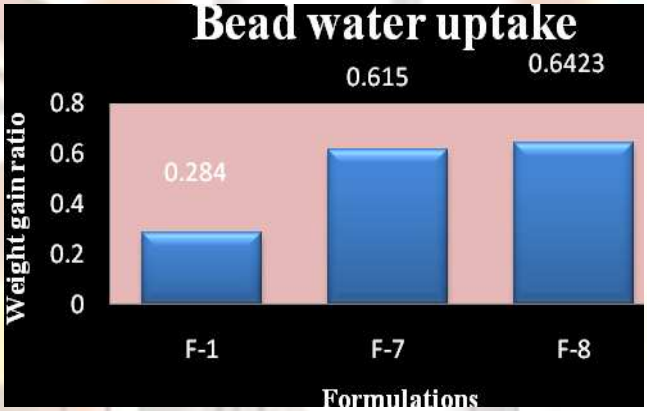

Fig 5: Effect of sunflower oil concentration on bead water uptake of different formulations

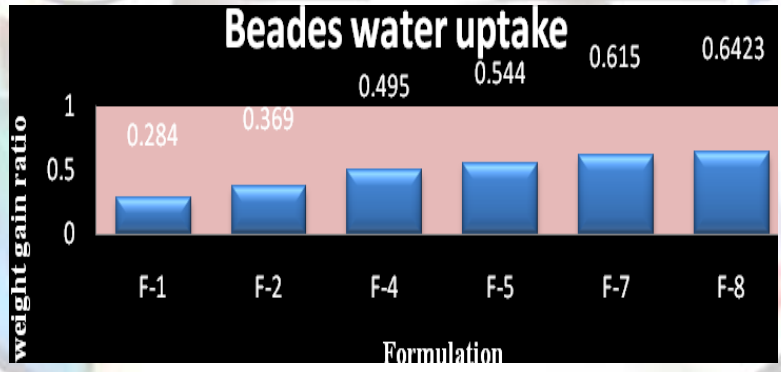

Fig 6: Effect of sodium alginate concentration on bead water uptake of different formulations

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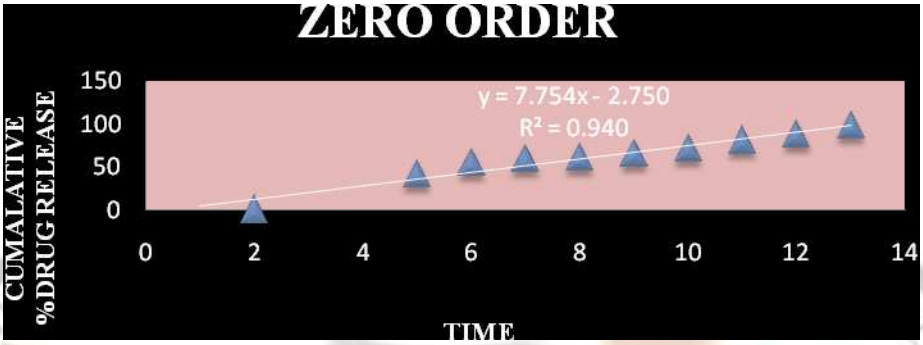

Fig 7: Cumulative % drug release of Ciprofloxacin HCl from F8

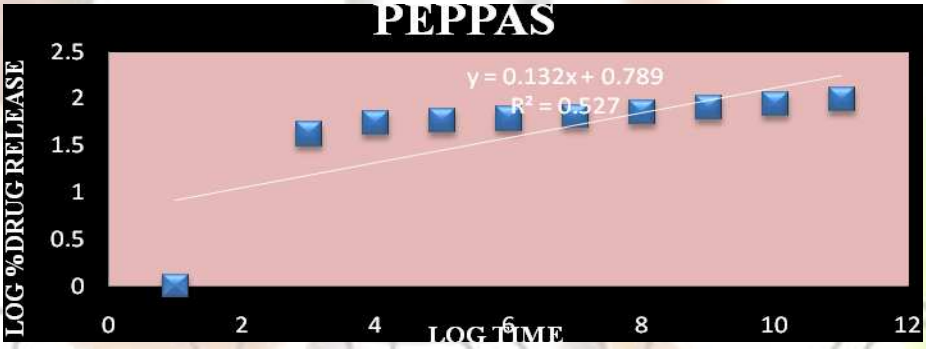

Fig 8: Peppas exponential plot of Ciprofloxacin HCl from F8

Fig 9: First order plot of Ciprofloxacin HCl from F8

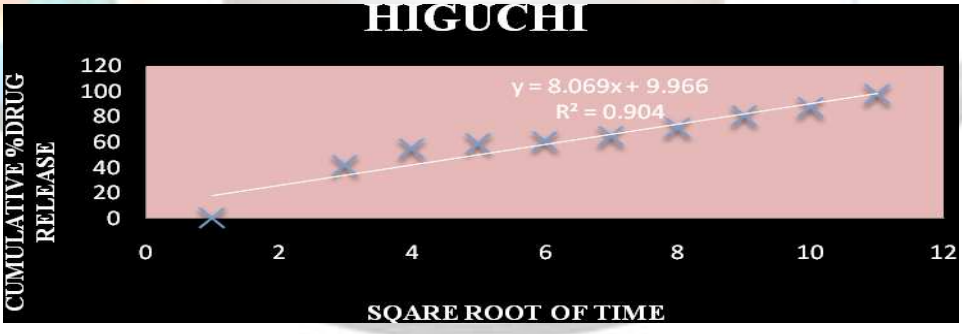

Fig 10: Higuchi diffusion plot of Ciprofloxacin HCl from F8