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Formulation And Evaluation Of Calcium Pectinate Floating Beads Of Clarithromycin

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Abstract: The objective of this investigation was to develop an intra gastric floating drug delivery system of Clarithromycin and also attempts were made to sustain the release of clarithromycin. Multiple-unit floating beads of clarithromycin were prepared from sodium alginate solution containing low methoxy pectin and sunflower oil by using emulsion gelationmethod.These beads were evaluated for Swelling index Particle sizeentrapment efficiency, drug loading, buoyancy,scanning electron microscopy and *in vitro* drug release.No significant drug-polymer interactions were observed in FT-IR studies. All formulations were the floating lag time below two minutes and shows total floating duration more than eight hours. It was observed that entrapment efficiency,drug loading and buoyancy was greater with formulation containing two percent sodiumalginate solution and five percent calcium chloride solution along with 500mg pectin and five ml sunflower oil (i.e.*F14*) and also the result of *in-vitro* dissolution studies reveals that theformulation F14 gave sustained release pattern of clarithromycin upto 12 hrs.
Keywords: Clarithromycin, Floating alginate beads, emulsion gelation.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract[1]. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time along with gastric emptying time is an important parameter for drugs that are incompletely absorbed.Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It has application also for local drug delivery to the stomach and proximal small intestine[2].

The concept of floating drug delivery system was described as a method for overcoming the difficulty experienced by some people of gagging or choking while swallowing medicine pills[3]. It was suggested that this difficulty could be overcome by providing pills having density of less than 1.0 gm/ml, so that pills will float on water surface. Since then many types of gastric retention drug delivery systems[4] were tested to overcome the limited region and times for drug absorption in gastrointestinal tract.

Calcium alginate gel beads have been developed in recent years as a unique vehicle for drug delivery system. Various categories of drug have been encapsulated such as nonsteroidal antiinflammatorydrugs,

enzymes, peptides/proteins, and acid labile drugs[5] Clarithromycin wasselected as a model drug for incorporation in calcium alginate beads. Clarithromycin, amacrolide antibiotic is widely used as an anti-bacterial as well as to prevent recurrence of peptic ulcer disease caused by *Helicobacter pylori*.[6]

In the present investigation, a controlled release formulation of clarithromycin capable ofproviding detectable blood levels over 10 hr was formulated using expandable and swellable polymer along with the sunflower oil.[7] The polymer used was sodium alginatewhich is an inexpensive, nontoxic product extracted from kelp. Sodium alginate has been used as thickening and gelling agent. Additionally it also reduces interfacial tension between an oil and water phase and is efficient for preparation of emulsion. Pectin was also used to achieve a controlled drug release.[8]

MATERIALS AND METHODS

Sodium alginate, Pectin and calcium chloride were purchased from Nice Chemicals, Bangalore Clarithromycin was donated by Micro labs ltdAll other chemicals used were of analytical grade.

Preparation of clarithromycin floating microbeads

Clarithromycin floating beads were prepared using emulsion-gelation method. Sodium alginate and Pectin were dissolved in water with stirring. Sunflower oilwas added to polymer solution followed by clarithromycin. The homogenized mixture was extruded into calcium chloride solution with gentle agitation at room temperature. The formed beads were allowed to stand for 30 min in the solution for curing then separated by filtration anddried at room temperature and used for further studies.[9]

Process variables and process optimization

To investigate the contribution of formulation variables on the release profile of clarithromycinfrom alginate beads, the different batches were produced and analyzed for size, shape, ease ofpreparation, drug loading, entrapment efficiency, buoyancy and drug release. The formulationparameters investigated are concentration of sodium alginate, concentration of calcium chloride,amount of sunflower oil, % entrapment efficiency, % drug loading and buoyancy.

Three factors were evaluated at three levels and experimental trials were performed at allpossible levels and 27 formulations were prepared as shown in Table1 .Actual physical values of coded variables are given in the table2.[10]

Evaluation of Floating Microbeads:

Percentage Practical Yield:

The yield of floating microbeads was determined by comparing the whole weight of microbeads formed against the combined weight of the copolymer and drug.

%Practical yield=(Mass of microbeads obtained/ Total weight of drug and polymer used)100

Particle Size Analysis:

The sample of prepared floating microbeads was randomly selected and their size was determined using an optical microscope with the help of eye piece and stage micro meter. In all measurements at least 50 beads in five different fields were examined. Each experiment was carried out in triplicate[7].

Buoyancy study

The time between the introduction of the floating alginate beads into the medium and the time taken to rise on the surface was measured as floating lag time and the duration for which the formulation constantly floated on the surface of the medium was measured as total duration of floating.[12]

Swelling Index Study:

The extent of swelling was measured in terms of % weight gain by the beads. The swelling behaviors of all the formulations were studied. In this test 20 mg of beads from each formulation was kept in petridish containing distilled water. At the end of 1 hour, the beads were withdrawn, soaked with tissue paper and

weighed. Then for every 1 hour, weights of beads were noted and the process was continued till the end of 8 hours. The % weight gain by the beads was calculated by the following formula[8]:

Swelling Index (SI) = [{$W_t - W_0$}/ W_0)] x 100
Where, W_t= Mass of swollen beads at time t
W_0= Mass of dry beads at t=0

Table 1: Composition of various formulations of microbeads.

Formulation code	Amount of clarithromycin(mg)	Pectin (mg)	Sodim alginate(%)	Calciumchloride (%)	Sunfloweroil (ml)
F1	250	500	1	4	2
F2	250	500	2	4	2
F3	250	500	3	4	2
F4	250	500	1	5	2
F5	250	500	2	5	2
F6	250	500	3	5	2
F7	250	500	1	6	2
F8	250	500	2	6	2
F9	250	500	3	6	2
F10	250	500	1	4	5
F11	250	500	2	4	5
F12	250	500	3	4	5
F13	250	500	1	5	5
F14	250	500	2	5	5
F15	250	500	3	5	5
F16	250	500	1	6	5
F17	250	500	2	6	5
F18	250	500	3	6	5
F19	250	500	1	4	10
F20	250	500	2	4	10
F21	250	500	3	4	10
F22	250	500	1	5	10
F23	250	500	2	5	10
F24	250	500	3	5	10
F25	250	500	1	6	10
F26	250	500	2	6	10
F27	250	500	3	6	10

Table 2.Actual physical values of the coded variables

Coded value	Sodium alginate(X1)	Calcium chloride(X2)	Sunflower oil(X3)
-1	1%	4%	2ml
0	2%	5%	5ml
1	3%	6%	10ml

Evaluation of Drug LoadedFloating Microbeads:

Percentage Drug Entrapment Efficacy (%DEE):

Accurately weighed microbeads equivalent to 100mg were suspended in 100ml of simulated intestinal fluid of pH 1.2±0.1 and kept for 24hrs. Next day it was stirred for 5min and filtered. After suitable dissolution, the drug content in the filtrate was analyzed spectrophotometrically at 268nm using Shimadzu UV spectrophotometer[11]. Finally, drug encapsulation efficiency is calculated by;

Percentage Drug Entrapment Efficiency =(Actual drug content/ Theoretical drug content)100

Loose Surface Crystal Study (LSC):

This study was conducted to estimate the amount of drug present on the surface of the microbeads which showed immediate release in dissolution media. 100mg of microbeads were suspended in 100ml of phosphate buffer (pH 1.2), simulating the dissolution media. The samples were shaken vigorously for 15min in a mechanical shaker. The amount of drug leached out from the surface was analyzed spectrophotometrically at 268 nm. Percentage of drug released with respect to entrapped drug in the sample was recorded[4].

Fourier Transform Infrared Spectroscopy:

FTIR spectral measurement was performed using Shimadzu FTIR spectrophotometer to confirm the presence of any interaction between the polymer and drug. The polymer and the drug were finely ground with KBr to prepare the pellets under a hydraulic pressure of 600psi and spectra were scanned between 400 and 4000cm^{-1} [10].

Scanning Electron Microscopy:

The surface morphology of drug-loaded beads obtained from various percentages of polymer, $CaCl_2$ and drug were studied by using a scanning electron microscope (model JEOL JSM-6360, Japan). The beads were mounted on an appropriate stub and then coated with carbon and gold (100 and 50 Å thickness respectively) sputter module in a vacuum evaporator in an argon atmosphere. The coated samples were then observed under a scanning electron microscope operated at 15 KV.

Invitro Dissolution Study:

Dissolution studies of Carvedilol microbeads was performed according to USP XXII type I dissolution apparatus in pH 1.2 for first 2 h and rest of the release study was performed in phosphate buffer of pH 7.4. The temperature was maintained at 37±0.5°C and the rotation speed was 100 rpm. The 5 ml of sample was withdrawn at various time intervals and replenished with an equal volume of fresh dissolution media. The drug content in the sample was analyzed spectrophotometrically at 268nm[13].

Mucoadhesive Test:

The mucoadhesive property of microbeads was evaluated by an in vitro adhesion testing method known as wash-off method. Freshly excised pieces of chicken stomach mucosa were mounted on to glass slides with cotton thread. About 20 microbeads were spread on to each prepared glass slide and immediately thereafter the slides were hung to USP II tablet disintegration test. When the test apparatus was operated, the sample is subjected to slow up and down movement in the test fluid at 37 ^{0}C contained in a 1-litre vessel of the apparatus. At an interval of 30min up to 8 hours the machine is stopped and number of beads still adhering to mucosal surface was counted. The test was performed at intestinal (phosphate buffer pH 1.2) condition[7].

RESULTS AND DISCUSSION

The floating beads of clarithromycin were prepared by emulsion-gelation method and influence of amount of sunflower oil on floating property and particle size of the beads, as well asconcentration of pectin on the release profile of clarithromycinfrom floating alginate beads were studied. The yield of all the formulations was within the range of 90.2± 3.01 to 97.14 ± 2.55.The production yields are summarized in table 2. The mean particle sizes of the various formulations of microbeads were obtained in the range between 1113.22±0.007 and 2450.22±0.009µm (Table 2).By increasing the concentration of sunflower oil, the mean particle size of floating microbeads increased. From results it can be seen that larger microbeads were obtained by increasing the amount of sunflower oil. The swelling behavior of the beads was studied by measuring the weight of the beads after exposure to phosphate buffer, pH 1.2 for 8 hours. Degree of swelling is proportional to ratio of drug to polymer, and it affects the property of drug release from polymer, which was shown in table 2.

Table 2:Characteristics of drug loaded microbeads

Formulation code	Percentage yield(%)	Particle size(µm)	Swelling index(%)
F1	96±0.3	1196.42±0.76	1371.2±0.09
F2	96±0.13	1182±0.55	1395±0.08
F4	92±0.23	1181.47±0.84	1374.4±0.03
F5	90.2±0.4	1180.34±0.98	1400.8±0.01
F7	92.8±0.18	1160.24±0.54	1377.4±0.04
F8	91.42±0.17	1170.34±0.32	1404.4±0.04
F10	93.6±0.14	1193.92±0.12	1380.4±0.07
F11	93.1±0.15	1150.24±0.13	1402.4±0.08
F13	96±0.16	1193.92±0.78	1377.2±0.07
F14	97.14±0.19	1113.22±0.77	1411±0.06
F16	94.4±0.3	1164.25±0.65	1382±0.02
F17	96.57±0.2	1179.34±0.64	1397.4±0.04
F19	93.6±0.1	1193.25±0.33	1370.4±0.01
F20	94.28±0.8	1195.34±0.73	1391.6±0.04
F22	95.2±0.12	2018.54±0.62	1360.4±0.03
F23	94.28±0.8	2220.12±0.13	1396±0.05
F25	92.8±0.1	2312.25±0.75	1365.6±0.05
F26	92.7±0.21	2450.22±0.15	1390±0.012

Buoyancy

Formulation code	Buoyancy
F1	8
F2	8
F4	8
F5	9
F7	>10
F8	>10
F10	7
F11	10
F13	7
F14	>12
F16	7
F17	8
F19	6
F20	7
F22	6
F23	8
F25	6
F26	6

Based on the characterization of floating microbeads, 3% concentration sodium alginate was not found to be the floated so the rest was taken as optimized formulation. The drug loading was done in the optimized formulation and the drug entrapment efficiency is summarized in table 3. The encapsulation efficiency determines the percentage of encapsulated drug with respect to the total drug introduced into polymer solution. Loose surface crystal (LSC) study was an important parameter giving an indication of the amount of drug on the surface of the microbeads without proper entrapment. Its results are given in table 3.

Table 3: Composition and characteristics of drug loaded microbeads

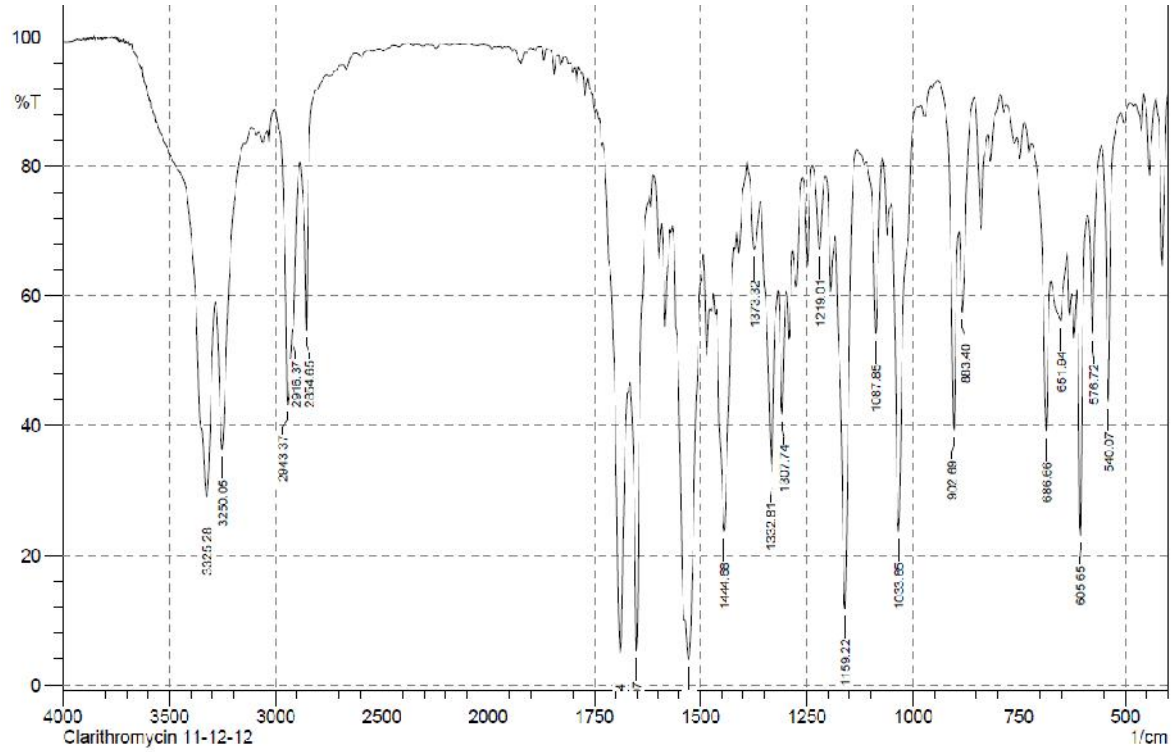
Formulation code	Drug content(mg)	%drug entrapment	%loose surface crystal
F1	8.1	81±0.34	5.2±0.09
F2	5.84	72±0.56	6.16±0.09
F4	7.84	78.4±0.45	6.6±0.07
F5	6.28	87.95±0.34	2.8±0.02
F7	7.64	76.4±0.87	6.8±0.01
F8	5.68	79.55±0.88	5.88±0.02
F10	7.72	77.2±0.78	6.4±0.03
F11	5.92	82.91±0.46	3.64±0.04
F13	8	80±0.68	4.6±0.05
F14	6.52	91.31±0.59	1.68±0.05
F16	7.9	79±0.39	5.4±0.01
F17	5.64	78.99±0.34	6.16±0.03
F19	7.78	77.8±0.23	5.8±0.023
F20	5.74	80.39±0.12	4.76±0.03
F22	8.64	86.4±0.78	3.8±0.02
F23	5.92	82.91±0.57	3.6±0.04
F25	7.92	79.2±0.99	5.6±0.01
F26	5.62	78.71±0.23	4.48±0.03

The compatibility of Clarithromycin with various polymers was investigated by IR-spectroscopy study. The IR spectra of the drug and polymer combination were compared with the spectra of the pure drug. In which no shifting of peaks was significantly found, indicating the stability of the drug during encapsulation process. The spectra are included as figure 1. The morphological evaluation of the optimized micro beads formulation (sodium aginate floating micro beads coated with pectin) was done by scanning electron microscopy (Figure 2). SEM study revealed that the microspheres were almost spherical in shape with rough outer surface.

In-Vitro drug release studies

The *in vitro* dissolution studies of the prepared batches were performed to investigate the dependant variable i. e. percentage drug release at 1 hr (Q1), 6 hr (Q6), and 12 hr (Q12). Fromthe results of in vitro dissolution studies, it revealed that the floating alginate beads (F5, F8, F13and F14) showed controlled release of clarithromycin for about 12 hr. Amongst the formulations,formulation F14 shows maximum % cumulative release within 1 hr, 6 hr and 12 hr. also. Thissuggested that formulation F14 was having the good sustained release of the clarithromycin up to the 12 hr. Hence it can be concluded that a new sustained release system of oil entrapped calciumalginate beads were designed and prepared by an emulsion-gelation method and it'smorphological and release characteristics were studied. The prepared beads were easy to prepareand evaluate. The beads showed excellent sustaining properties as compared to the conventionalbeads which were due to incorporation of pectin. Thus, oil entrapment technique can become a useful tool for the development of multiparticulate system even for a water-insoluble drug.

FT-IR spectrum of Clarithromycin



FT-IR spectrum of Clarithromycin+polymer

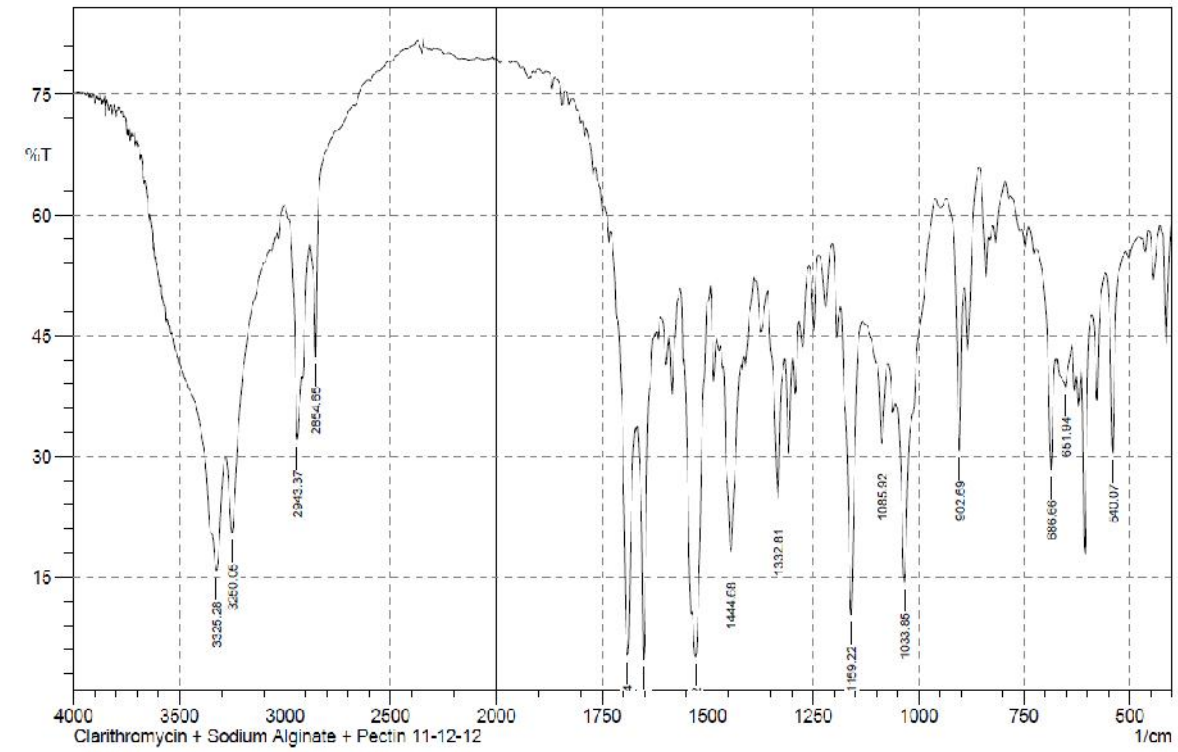


Figure 2: SEM of Clarithromycin floating microbeads

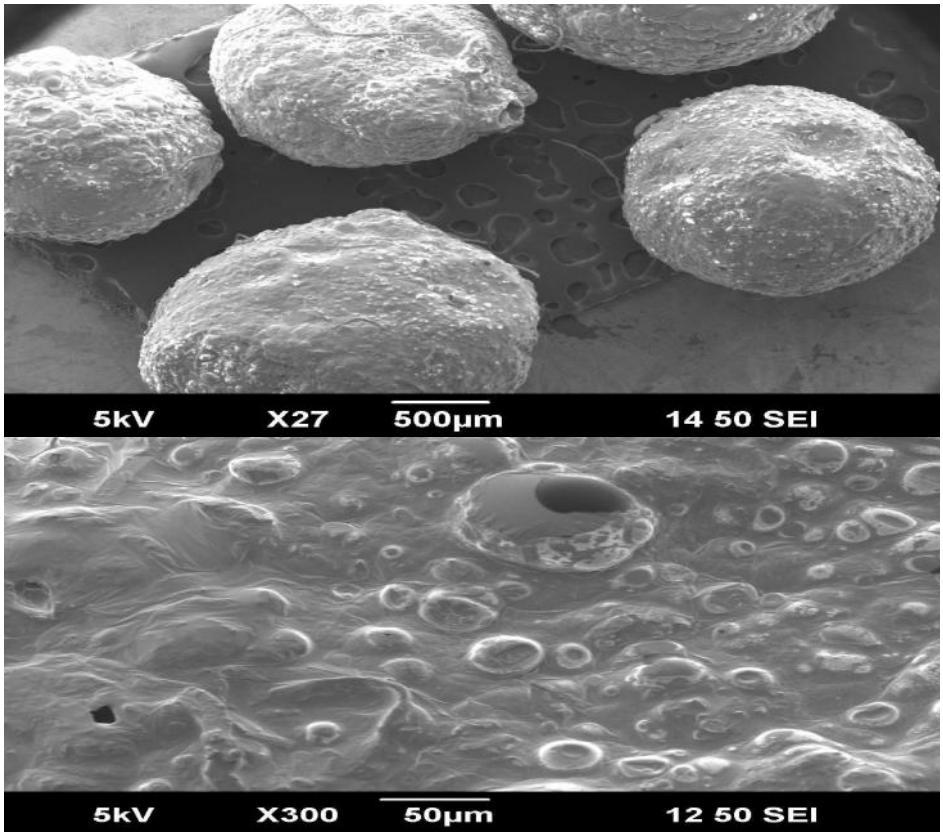
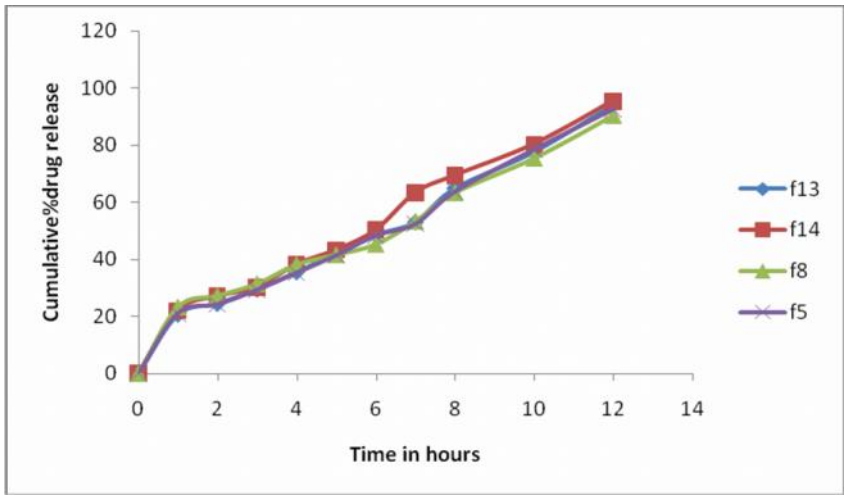


Figure 3a: *In Vitro* Drug release studies for Prepared floating Clarithromycin coated with Pectin



CONCLUSION

The emulsion gelation method was successfully utilized for formulation of floating alginatebeads of clarithromycin. The adopted method for estimation of clarithromycin showed goodlinearity. The formulated floating alginate beads have shown higher percentage of drug loading,encapsulation efficiency, particle size and very low moisture content. The scanning electronphotomicrographs of floating alginate beads reveals that the beads are almost spherical and the matrix showed densely populated sunflower oil droplets, which provides floating property. The rheological parameters like angle of repose and bulk density reflects better flowability of floatingalginate beads. In-vitro dissolution study showed that, amongst the formulations, formulationF14

released clarithromycin for prolonged duration (12 h). Formulated floating beads ofclarithromycin showed good swelling behavior. The optimized formulation F14 showed best fitin zero order model.

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