International Journal of Research in Engineering and Science (IJRES)
ISSN (Online): 2320-9364, ISSN (Print): 2320-9356
www.ijres.org Volume 10 Issue 11 ǁ November 2022 ǁ PP. 139-150

Formulation and Evaluation of Floating Alginate Beads of Cefadroxil

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ABSTRACT
The objective of this present investigation is to develop gastro retentive Controlled release alginate beads of Cefadroxil by the ionotropic gelation method. The floating beads were prepared by dispersing Cefadroxil together with CaCO3 (as gas forming agent) into a solution of sodium alginate. The resulting solution was then extruded through a 18 gauge syringe needle into 100 ml cross-linking solution containing calcium chloride (2 % w/v). Prepared beads were evaluated for FT-IR spectroscopy, Differential scanning calorimetry, encapsulation efficiency, buoyancy test, release studies, scanning electron microscopy (SEM). The drug entrapment efficiency was increased with the increment of polymer ratio. All of the formulations (F1 to F5) floated immediately or with a very short lag time and remained floating upto 12 hours. Spherical shape was observed in case of surface SEM of beads. In vitro dissolution studies were performed for twelve hours into 900 ml 0.1N HCl (pH 1.2) using USP Apparatus II (paddle type) maintained at a temperature of 37ºC and stirred at a speed of 50 rpm and λmax of 263nm. The dissolution study revealed that, after twelvehours the percent of drug release for five formulations were 25.76±0.60 (F1), 35.02±0.42 (F2), 44.29±0.50 (F3), 89.88±0.79 (F4), and 93.50±0.89 (F5) and all of the formulations followed zero order,First order, Higuchi model, and Peppas model.
Key words: *Floating-alginate beads, Cefadroxil, Differential scanning calorimetry, Scanning electron microscopy.*

Date of Submission: 04-11-2022 Date of acceptance: 16-11-2022

I. INTRODUCTION

Pharmaceutical dosage forms' medication bioavailability is influenced by a number of variables. Gastric residence time (GRT) [1] is one of them. Between a few minutes and 12 hours is the typical duration of the gastric emptying process from the stomach to small intestine. An oral dose form's bioavailability is variable due to this variability[2]. Additionally, the relatively quick gastric emptying period may cause a partial release of the medication from the dose form. One of the gastro retentive dosage forms that could extend GRT and achieve adequate drug bioavailability is the floating drug delivery system (FDDS)[3-6]. Since FDDS are less dense than gastric fluids, they float in the stomach for a longer duration without slowing the gastric emptying rate[4].

In our research, calcium carbonate (CaCO3) was used as a gas-forming agent in an alginate matrix for the floating drug delivery system. Alginate is a polysaccharide with variable concentrations of 1,4'-linked residues of -D-mannuronic acid and -L-guluronic acid[7]. With divalent cations like Ca2+, Sr2+, and Ba2+[8], it forms a bio-adhesive and stable gel as a biocompatible and biodegradable biopolymer. These characteristics have made the use of medicines with sustained release commonplace[9]. Alginate beads are readily degraded in alkaline conditions but stable in acidic media. Acetic acid and carbonate combine to form the floating medicine beads, which then release carbon dioxide. Alginate is penetrated by the developing gas, which leaves behind gas bubbles or pores[7].

In our studyCefadroxilis acid stable and Antibiotic, was used as model drug. This conventional dosage form of Cefadroxil need twice or thrice daily which may lead to Non-compliance[10-13]. Aim is to minimize the side effects and to reduce the frequency of dose.Thus, in this study, an attempt has been made to prepare controlled release sodium alginate beads containing Cefadroxil using calcium carbonate (CaCO3) as gas forming agent. The obtained beads were evaluated for encapsulation efficiency, infrared spectroscopy, scanning electron microscopy (SEM), Differential scanning calorimetry, *In-vitro* release behaviour.

II. MATERIALS AND METHODS

Materials

Cefadoxil from Himedia, Sodium alginate from Himedia, Calcium carbonate from Himedia.

Methods

Preparation of floating alginate beads[14].

Sodium alginate solutions of different concentrations were prepared by dissolving required amount of alginate in 100 ml of deionized water under gentle agitation. Cefadroxil and calcium carbonate (as gas forming agent) were dispersed in alginate solution under constant stirring for uniform mixing. The dispersion was stirred at 100 rpm for 30 minutes to remove any air bubbles. The resultant dispersion was dropped through a 18 gauge syringe needle into 100 ml of 2 % (w/v) calcium chloride solution at room temperature. Then the beads formed were allowed to dried at room temperature for 24 hrs and then performed the evaluation studies.

Table 1.Formulation design of floating alginate beads.

SI. No	Ingredients	F1	F2	F3	F4	F5
1	Cefadroxil	100mg	100mg	100mg	100mg	100mg
2	Sodium alginate	1gm	2gm	3gm	4gm	5gm
3	Calcium chloride	2gm	4gm	6gm	8gm	10gm
4	Distilled water	100ml	100ml	100ml	100ml	100ml

Evaluation of Cefadroxil loaded Alginate beads

Drug content (mg)

Powdered 100 mg microbeads were added to a 100 ml volumetric flask, filled to the appropriate level with 7.4 pH phosphate buffer, and left to stand for 12 hours while being sometimes shaken and filtered. After that, spectrophotometric analysis of the absorbance was performed at 263 nm. For each formulation, three determinations were made. The formula was used to determine the drug content;

Drug content = concentration × dil factor × conversion factor × amount of stock solution.

Drug loading (%) (DL)

The amount of Cefadroxil loaded in microbeads was determined by the following formula.

% DL = Weight of drug in Alginate beads/ Total weight of Alginate beads taken× 100

% Encapsulation efficiency (EE)

The amount of Cefadroxil entrapped within microbeads was determined by the following formula

% EE = Practical Drug Loading/ Practical Drug Loading× 100

Table 2. Drug content, % Drug loading, %Encapsulation efficiency of Alginate beads

Formulation code	Drug content	% Drug loading	%Encapsulation efficiency
F1	80.80±0.81	45.62±0.18	47.80±0.28
F2	83.15±0.93	47.15±0.25	58.28±0.39
F3	85.59±0.55	48.59±0.37	76.86±0.47
F4	87.55±0.64	48.55±0.49	83.82±0.52
F5	92.65±0.98	49.65±0.50	87.59±0.61

Percentage yield

The prepared microspheres, which ranged in size from 1 to 1000 micrometres, were gathered and weighed from several formulations. The measured weight was divided by the sum of all the non-volatile ingredients that went towards making the microspheres.

%Yield=Actual weight of product/Total weight of drug and polymer × 100

Table 3. Percentage yield of Alginate beads

S.no	Formulation code	Percentage yield
1	F1	64.70 ±0.52
2	F2	42.18 ±0.93
3	F3	72.34 ±0.84
4	F4	58.06 ±0.74
5	F5	51.29 ±0.92

Micromeritic properties

Angle of repose (θ) by funnel method:

After thoroughly pouring the microbeads into the funnel and shutting the other end, a jet of beads of known weight was obtained and allowed to pass through. The formula,

θ = tan-1 h / r

Where, θ = Angle of Repose.

h = Height of the heap.

R = Radius of the base of the heap.

Bulk density, tapped density (g/cc) and Carr's index (%): Calculated by placing microbeads with a specified weight in a measuring cylinder (bulk volume), tapping the cylinder 100 times (tapped volume), and then calculating Carr's index (%).

BD = Mass / Bulk volume × 100

TD = Mass / Tapped volume × 100

% CI = Tapped Density – Bulk Density/ Tapped Density x 100

Where, BD is bulk density

TD is tapped density

Table 4. Micromeritic characteristics

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Hausner's ratio	Carr's index
F1	0.23±0.32	0.14±0.27	28˚.17′± 0.22	1.657±0.021	39.9±0.152
F2	0.31±0.43	0.27±0.34	26˚.16′±0.35	1.126±0.035	11.21±0.28
F3	0.56±0.66	0.52±0.64	18˚.37′±0.42	1.082±0.046	7.59±0.47
F4	0.62±0.73	0.56±0.67	17˚.26′±0.59	1.110±0.052	9.96±0.59
F5	0.74±0.855	0.70±0.83	16˚.86′±0.70	1.06±0.069	5.66±0.71

Particle size

Using scanning electron microscopy, the microbeads' shape and surface were examined. The dried microbead samples were scattered across platinum-coated metallic studs and examined at the micrometre scale.

Table 5. Particle size

Formulation code	Mean particle size (μm)
F1	710±0.87
F2	520±0.81
F3	480±0.52
F4	595±0.75
F5	650±0.78

In vitro drug release studies

The cefadroxil loaded polymeric microbeads, equivalent to 100 mg of cefadroxil were suspended in paddle of USP dissolution apparatus II containing 1.2 pH HCl for 12 hrs (simply the beaker containing gastric medium was replaced with fresh media) operating under the standards of 37°C Temp., at 50 rpm. The samples were collected at specified time interval and analyzed at 263 nm after suitable dilutions if necessary using UV Spectrophotometer.

Table 6. *In-vitro* % Drug release studies of prepared Alginate beads

Time (hrs)	F1	F2	F3	F4	F5
	% Drug release (1.2 pH HCl buffer (gastric pH)				
1	13.23±0.60	21.26±0.64	29.11±0.99	38.91±0.78	50.20±0.93
2	14.20±0.96	23.11±0.70	30.88±0.62	45.38±0.88	51.35±0.71
% Drug release (7.4 pH Phosphate buffer (intestinal pH)					
3	16.32±0.53	25.32±0.71	34.05±0.89	47.64±0.78	58.58±0.87
4	17.20±0.69	26.20±0.99	35.47±0.66	48.05±0.62	63.11±0.88
5	18.44±0.73	28.14±0.74	37.50±0.79	49.14±0.84	65.67±0.89
6	21.08±0.81	21.08±0.85	38.47±0.51	50.44±0.77	78.05±0.61
7	21.88±0.95	30.17±0.80	39.88±0.55	57.55±0.67	79.32±0.65
8	22.32±0.73	31.32±0.87	41.29±069	58.82±0.56	83.20±0.59
9	26.11±0.68	31.85±0.54	42.17±0.96	66.05±0.68	89.17±0.40

10	24.52±0.98	33.44±0.73	43.05±0.54	79.58±0.45	90.70±0.90
11	25.41±0.75	34.32±0.84	43.94±0.73	81.02±0.87	92.88±0.91
12	25.76±0.60	35.02±0.42	44.29±0.50	89.88±0.79	93.50±0.89

***In-vitro* dissolution studies of Alginate beads:**

Dissolution studies were carried out for Cefadroxil loaded Alginate beads. The results are given in the **Table 7** and **fig 9**. The *in-vitro*drug release for prepared Alginate beads showed 96.80±0.97 after 12 hrs. In the present work all the prepared Alginate beads of formulation F1 to F5 evidenced sustained for 12 hrs. Among all formulation F5 is considered as ideal formulation due to its percent release of 96.80±0.97.

Table 7.Cumulative % drug release of Cefadroxil loaded Alginate beads

Time (hrs)	Cumulative % drug release				
	F1	F2	F3	F4	F5
1	23.37±0.94	41.37±0.87	59.99±0.92	75.7±0.86	79.53±0.88
2	27.43±0.84	44.37±0.93	63.52±0.84	80.29±0.91	80.98±0.89
3	30.52±0.90	48.43±0.83	64.93±0.87	81.02±0.98	82.99±0.92
4	33.52±0.96	51.52±0.79	69.52±0.96	82.69±0.94	84.18±0.73
5	35.64±0.81	54.34±0.93	72.97±0.91	84.19±0.85	85.57±0.86
6	39.52±0.90	57.08±0.90	75.97±0.85	85.08±0.87	86.69±0.95
7	42.9±0.72	59.11±0.85	78.35±0.88	86.49±0.83	87.85±0.81
8	44.2±0.95	61.49±0.97	81.17±0.92	89.37±0.92	90.33±0.95
9	48.43±0.89	63.17±0.76	83.46±0.93	90.87±0.85	92.37±0.98
10	50.63±0.75	65.29±0.91	85.22±0.81	92.63±0.96	93.46±0.97
11	49.63±0.86	67.76±0.84	86.99±0.86	93.66±0.93	94.78±0.84
12	51.17±0.96	69.34±0.93	88.23±0.96	94.22±0.72	96.80±0.97

Swelling Ratio

A known weight of microbeads were placed in a test tube containing 10 ml of 0.1 N HCl buffer and 7.4 pH phosphate buffer at 37 ± 0.5˚ C with occasional shaking. The microbeads were periodically removed, blotted with filter paper and their changes in weights were measured during the swelling unit equilibrium was attained. Finally the weight of the swollen microbeads was recorded after a time period of 4 hrs and the swelling ratio (SR) was then calculated using the formula.

Swelling ratio (SR) = Ws – Wo/ Wo

Where, Wo = initial weight of dry microbeads

Ws = swollen weight of microbeads at equilibrium

Table 8.Swelling studies of prepared microbeads

Formulation Code	Initial weight of microbeads (mg)	Final weight after 4 hrs in 1.2 pH HCl (mg)	Final weight after 4 hrs in 7.4 pH phosphate buffer (mg)
F1	100	103.8±3.12	105.9±2.33
F2	100	107.9±2.25	109.2±0.85
F3	100	104.3±3.29	125.6±2.15
F4	100	128.7±1.90	137.2±3.10
F5	100	130.2±1.16	145.6±1.39

Buoyancy

The floating ability was determined using USP dissolution test apparatus. 10mg beads we introduced in the vessels and were rotated at 100 rpm in 900 ml of 0.1N HCL, maintained at 37±0.5˚c for 10 hr.The floating ability of the beads was observed visually.

Table 9. Buoyancy of different formulations of Alginate beads

S.no	Formulation Code	Buoyancy	Floating time (hrs)
1	F1	Floating	5
2	F2	Floating	9
3	F3	Floating	10
4	F4	Floating	7
5	F5	Floating	11

Fourier transform infra-red measurements (FTIR)

FTIR measurements were taken at ambient temperature using a Nicolet, Model BRUKER ALPHA-II. About 2 mg of the samples were ground thoroughly with KBr and pellets were formed under a hydraulic pressure of 600 kg/cm^2.

Table 10. Interpretation

Interpretation	WAVE NUMBER Interpretation	
	Cefadroxil	**Cefadroxil Loaded Alginate beads**
C-S	1117.44	1120.02
SNH	1568.72	1549.12
COOH	1759.06	1750.3
OH Stretch	3201.32	3410.84
C-O-C	1236.79	1234.26
Csp^2H	3028.33	3300.00

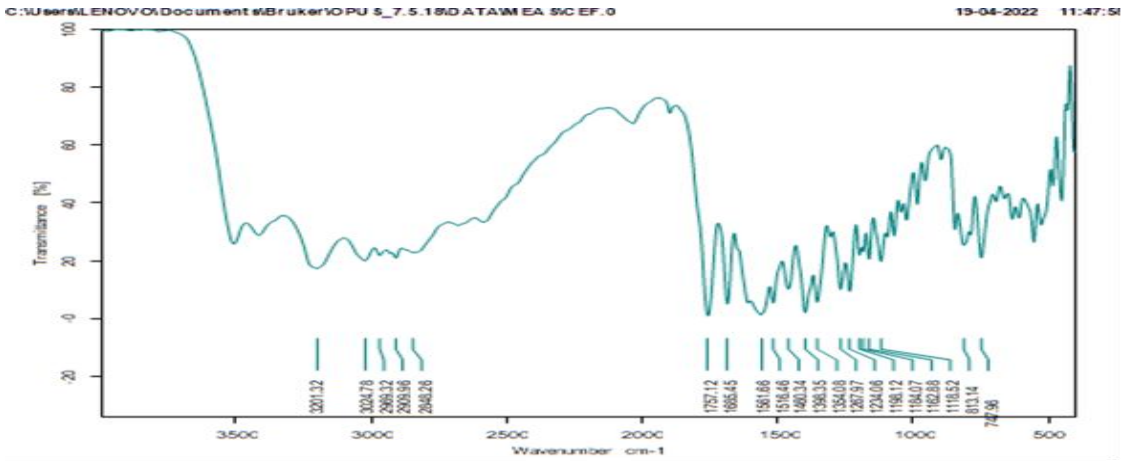


Fig 1. FTIR of Cefadroxil

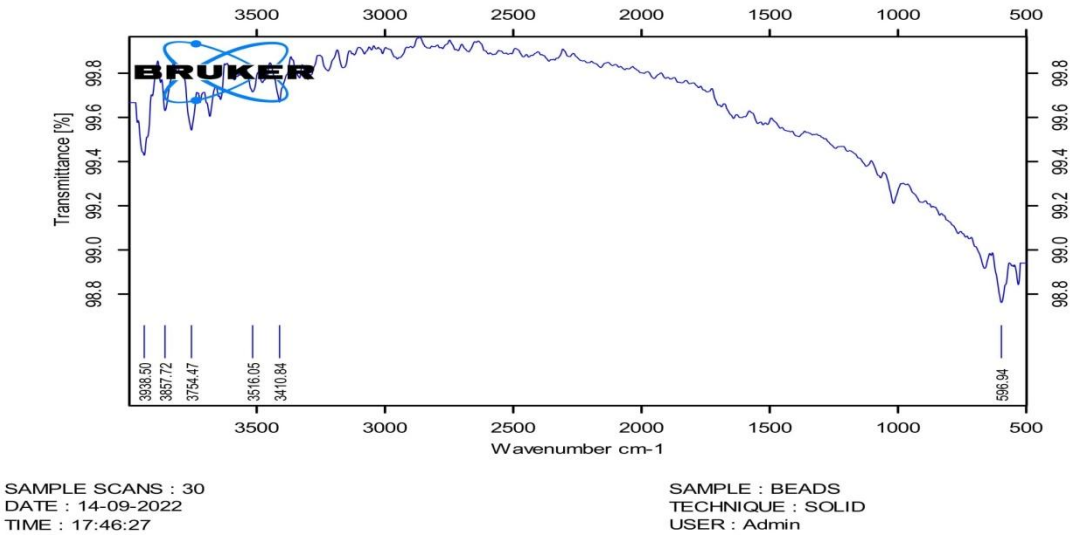


Fig 2.FTIR of Cefadroxil loaded Alginate beads

Differential scanning calorimetric (DSC) analysis

DSC experiments were performed on the beads, pure Cefadroxil and the Cefadroxil-loaded beads using a DuPont-2000 micro calorimeter (made in USA). The samples were heated at a rate of 5˚C/min under a constant flow of nitrogen gas.

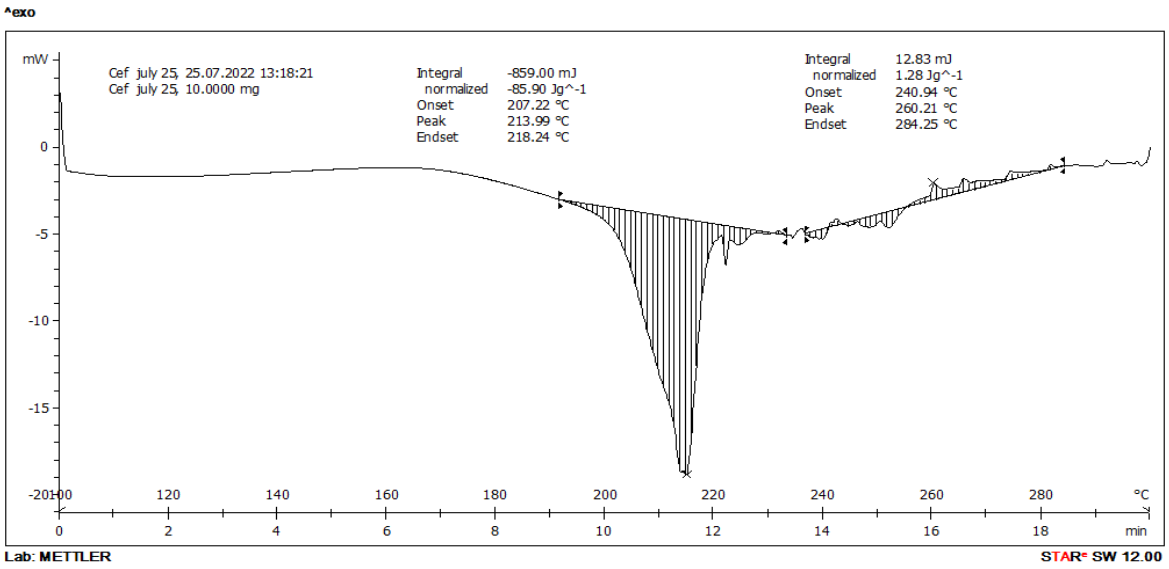


Fig 3.DSC of Cefadroxil

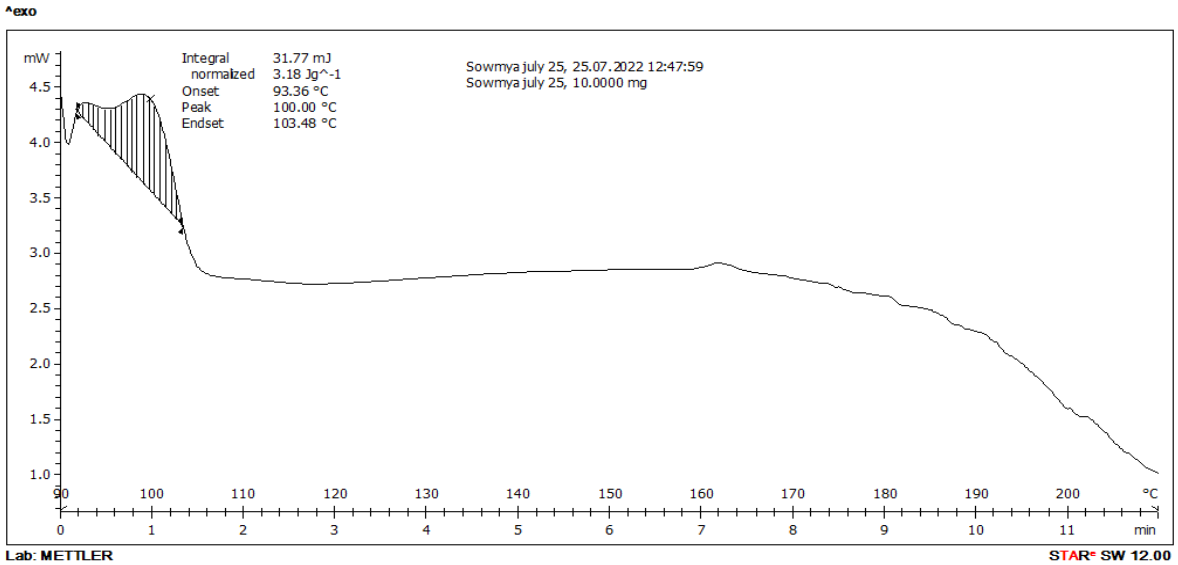


Fig 4.DSC of Cefadroxil loaded Alginate beads

X-ray diffraction (XRD)

The crystalline phase was determined by using XRD using a x-ray diffractometer with cu kα radiation. The x-ray powder diffraction patterns were recorded in the angular range of 20˚-80˚ with a step size of 0.01˚ using monochromatic x-rays. The x-ray wavelength, the full width at half-maximum (FWHM) of the diffraction line and the diffraction angle were measured by X'Pert High Score version 2.0a software

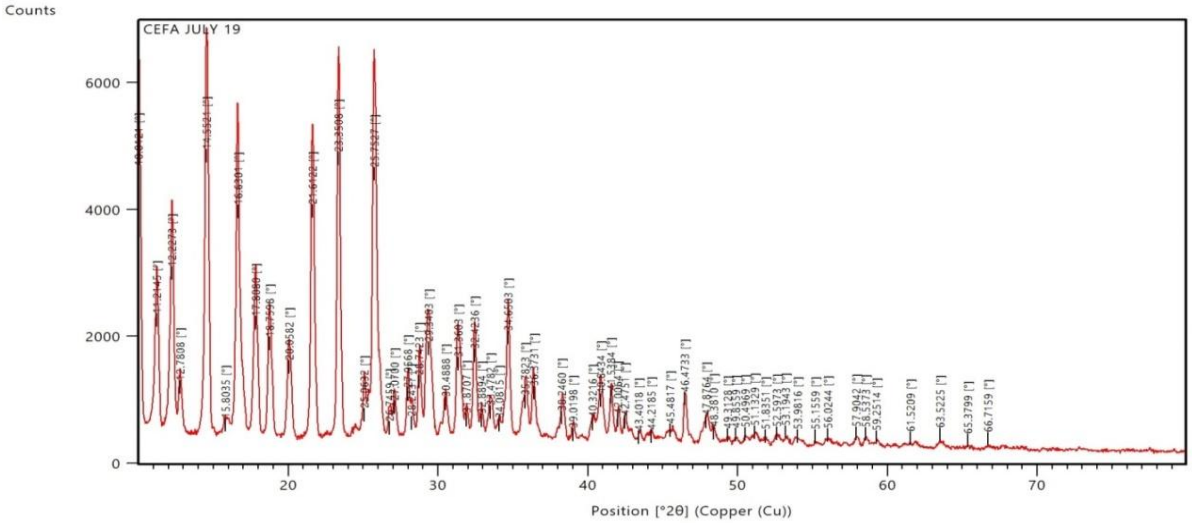


Fig 5.XRD of Cefadroxil

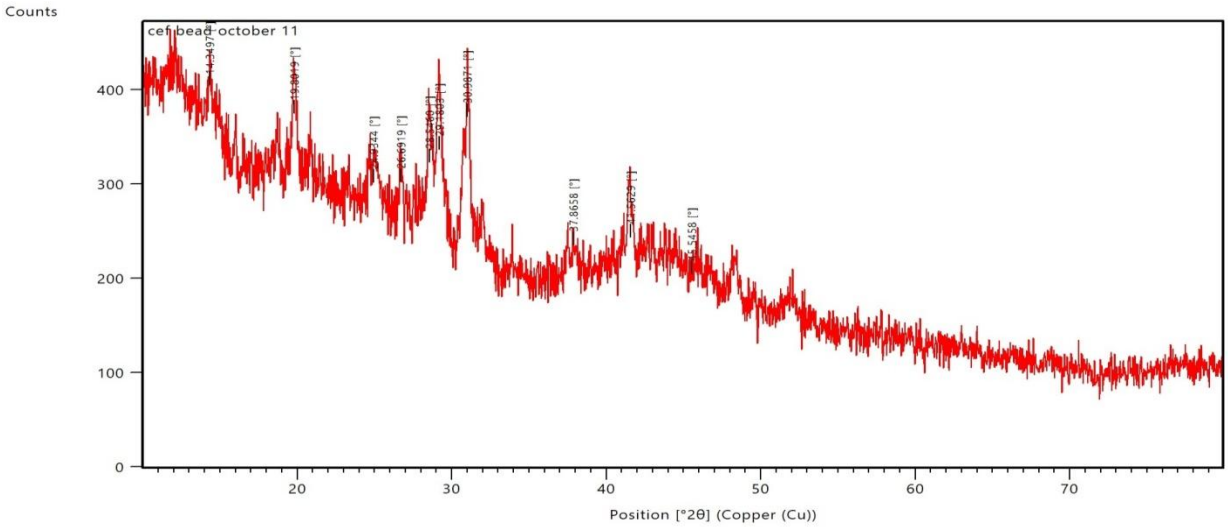


Fig 6. XRD of Cefadroxil loaded Alginate beads

Scanning electron microscopy (SEM)

The sample was deposited on a brass holder and sputtered with gold. The SEM photographs were then taken with JSM-IT500 model scanning electron microscope (Japan) at the required magnification at room temperature. The working distance of 39 mm was maintained and the acceleration voltage used was 20 kV, with the secondary electron image (SEI) as a detector.

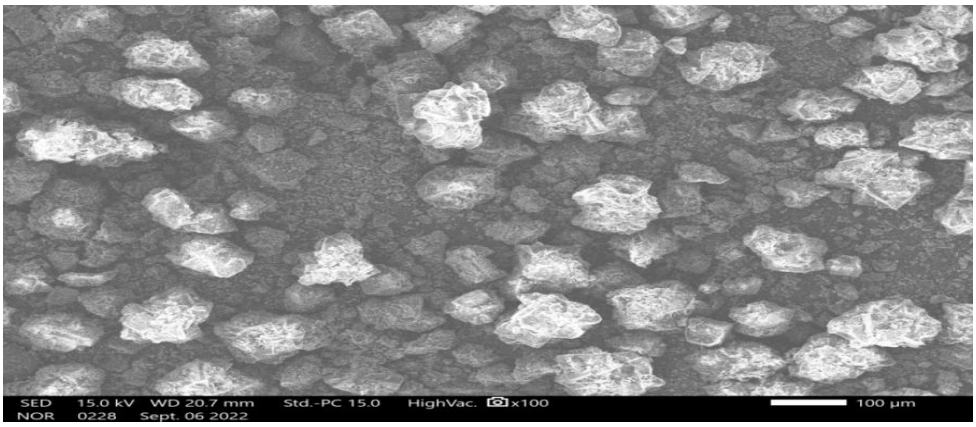


Fig 7.SEM of Cefadroxil

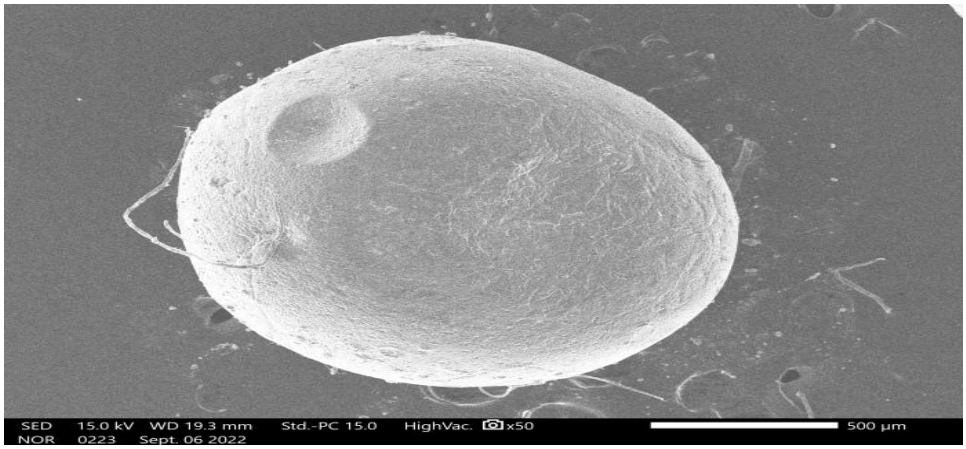


Fig 8.SEM of Cefadroxil loaded Alginate beads

III. Results And Discussion

Cefadroxil microbeads were prepared by "Ionotropic gelation technique" with different combinational polymers and sodium carboxy methyl cellulose using sodium alginate in common. The prepared microbeads were found to be discrete and free flowing.

SEM Analysis

The micrographs of Cefadroxil microbeads re as shown in **fig 8** and they indicate that the microbeads were almost
spherical in shape, with smooth outer surface.

Drug content and % Encapsulation Efficiency

The percent drug content of microbeads determines the amount of drug entrapped in the Microbeads. The formulation F5 has shown maximum release of 92.65±0.98. Among all theformulation F5 was considered as optimized formulation due to its drug content.

The encapsulation efficiency determines the percentage of encapsulated drug with respect to the total drug introduced into polymer solution. The encapsulation efficiency ranged from 76.80± 0.28 to 93.59± 0.61, as the results shown in **Table 2.**

Swelling ratio

Swelling studies of the prepared microbeads were carried out in both 1.2 and 7.4 pH buffer
Solutions and found that the microbeads showed higher swelling ratio value in pH 1.2 after 4 hrs
than that in pH 7.4 medium as the results are shown in **Table 8**.

In vitro dissolution studies

Dissolution studies were carried out for Cefadroxil loaded Alginate beads. The results are given in the **Table7**and **fig 9**. The *in-vitro* drug release for prepared Alginate beads showed 96.80±0.97 after 12 hrs. In the present work all the prepared Alginate beads of formulation F1 to F5 evidenced sustained for 12 hrs. Among all formulation F5 is considered as ideal formulation due to its percent release of 96.80±0.97.

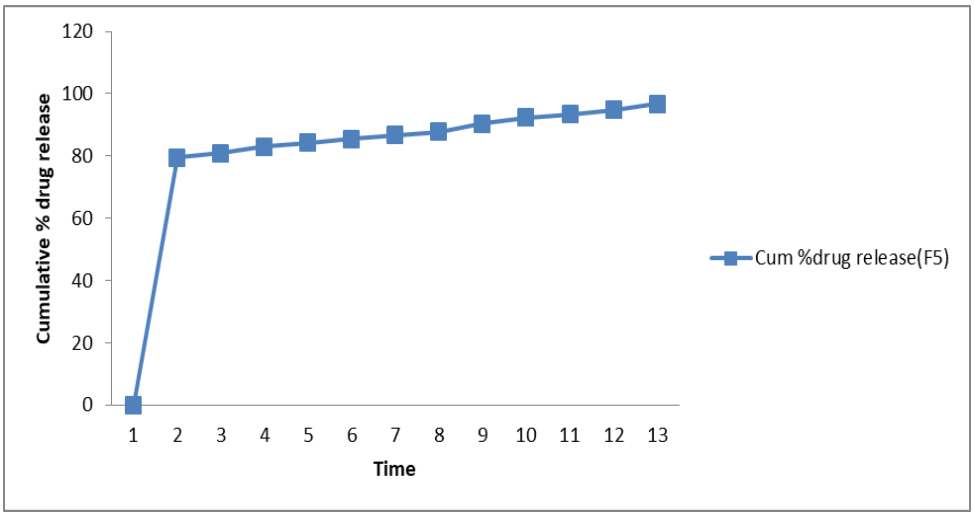


Fig 9.Cumulative % drug release of Cefadroxil loaded Alginate beads (F5)

Drug release kinetic data analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsemeyer-Peppas equation (Plotted as Log cumulative percentage of drug released vs Log time). To study the release kinetics of Cefadoxil from the Floating microspheres the release data was fitted to these three equations.

Zero order equation

When a graph of the cumulative percentage of the drug released from the matrix against time is plotted, zero order release is linear in such a plot, indicating that the release rate is independent of concentration.

Qt = k0.t …… (1)

Where Qt is the percentage of drug released at time t and k0 is the release rate constant;

First order equation

In (100-Qt) = In 100- kI.t …….. (2)

Where kI is the release rate constant;

Higuchi's equation (Wagner, 1969):-

Qt = kH.t1/2 …….. (3)

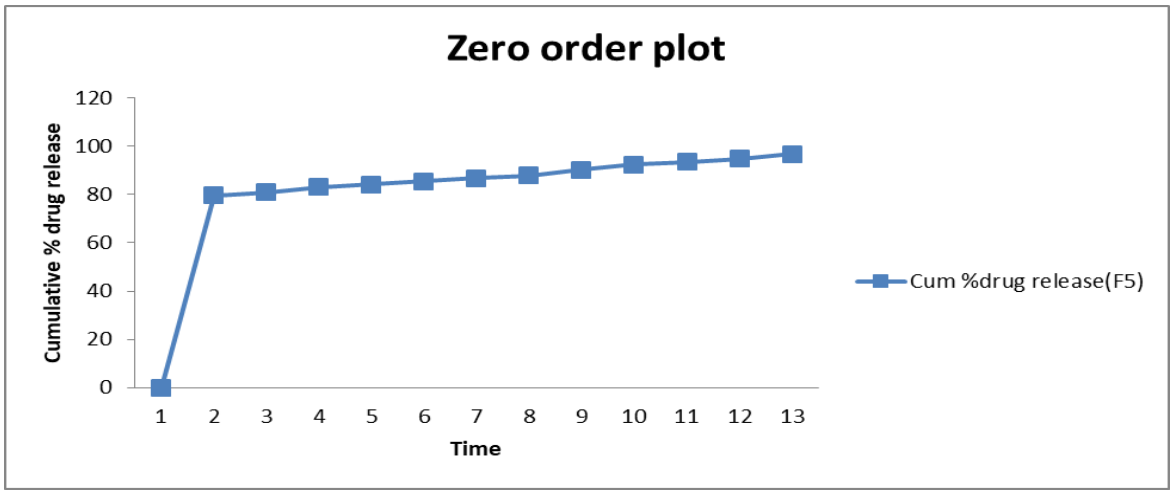
Where KH is the Higuchi release rate constant

Korsemeyer-Peppas

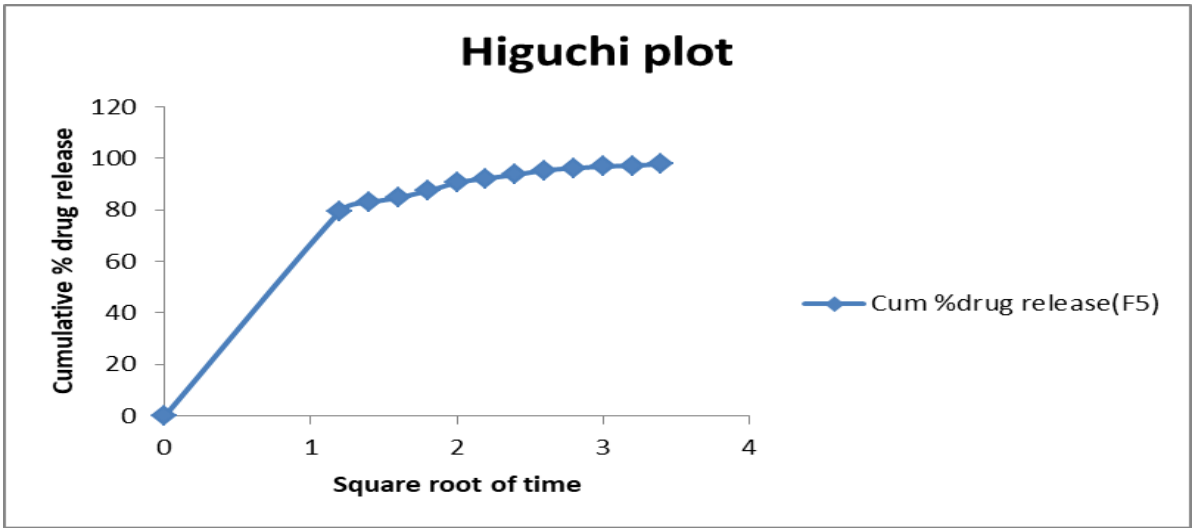
The curves plotted may have different slopes, and hence it becomes difficult to exactly pin-point which curve follows perfect zero order release kinetics. Therefore, to confirm the kinetics of drug release, data were also analyzed using Korsemeyer's equation.

Qt/Q∞= kKP.tn

Where Qt/ Q∞ is the fraction of drug released at time t, kKPa constant compromising the structural and geometric characteristics of the device and n is the release exponent.


Zero order plot
Cumulative % drug release
120
100
80
60
40
20
0
1 2 3 4 5 6 7 8 9 10 11 12 13
Time
Cum %drug release(F5)


First order plot
log % drug remain
2.5
2
1.5
1
0.5
0
0 5 10 15
Time
Log % drug remain(F5)


Higuchi plot
Cumulative % drug release
120
100
80
60
40
20
0
0 1 2 3 4
Square root of time
Cum %drug release(F5)

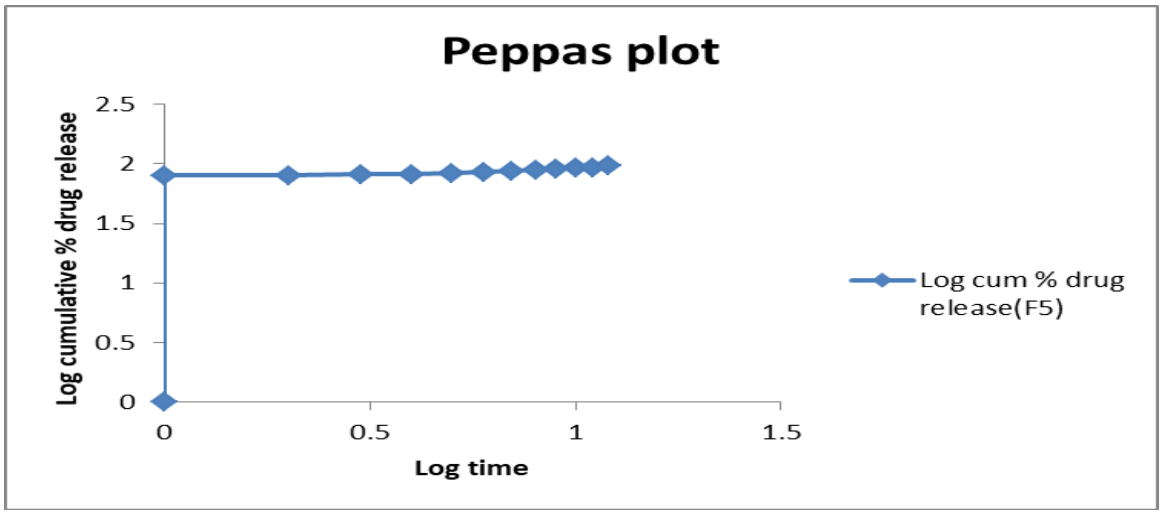


Table 11.Correlation coefficient(r^2)

Formulation code	Correlation coefficient(r2)			
	Zero order	First order	Higuchi plot	Peppas plot
F5	0.97	0.84	0.86	0.79

X-ray diffraction (XRD) pattern was recorded on dif-fractometer (RigakuMiniflex, Japan) at a scan rate of 0.05 2h/s. The transmission electron microscope (TEM, model TecnaiG2,F2OS-Twin,FEI,USA,200kV),wasusedto study the internal structure and morphology. The spectral response of the catalyst material was evaluated using UV–visible diffuse reflectance spectra using a UV–DRS spectrophotometer (Shimadzu UV-2200, Japan). The photoluminescence spectrum was recorded using a pho-toluminescence spectrometer (Perkin Elmer LS55, USA)for studying the trap states X-ray diffraction (XRD) pattern was recorded on dif-fractometer (RigakuMiniflex, Japan) at a scan rate of 0.05 2h/s. The transmission electron microscope (TEM, model TecnaiG2,F2OS-Twin,FEI,USA,200kV),wasusedto study the internal structure and morphology. The spectral response of the catalyst material was evaluated using UV–visible diffuse reflectance spectra using a UV–DRS spectrophotometer (Shimadzu UV-2200, Japan). The photoluminescence spectrum was recorded using a pho-toluminescence spectrometer (Perkin Elmer LS55, USA) for studying the trap state

In-vitro release data obtained was fitted to different kinetic models like Zero order, First order, Higuchi plot, Peppas plot. As per the results shown in **Table 11**. The drug release kinetics following mixed mechanism of zero and first order and the mechanism of release is "diffusion" as r2 values in case of Higuchi plot is almost equal to 1.

IV. Conclusion

In this study, an attempt has been made to prepare controlled release sodium alginate beads containing Cefadroxil using calcium carbonate (CaCO3) as gas forming agent. The obtained beads were evaluated for encapsulation efficiency, infrared spectroscopy, scanning electron microscopy (SEM), Differential scanning calorimetry, Invitro release behaviour.The dissolution study revealed that, after twelve hours the percent of drug release for five formulations were 25.76±0.60 (F1), 35.02±0.42 (F2), 44.29±0.50 (F3), 89.88±0.79 (F4), and 93.50±0.89 (F5) and all of the formulations followed zero order,First order, Higuchi model, and Peppas model.

Acknowlegments: Authors are thankful to Sri padmavathi mahila visvavidyalayam, Tirupati.
Funding: No funding received
Conflicts of interest: Nil

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