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Formulation and Evaluation of Floating Microballons of Cefadroxil

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ABSTRACT
The objective of this present investigation is to develop gastro retentive Controlled release Microballons of Cefadroxil by the "emulsion solvent evaporation method". The floating Microballons were prepared by"emulsion solvent diffusion method" have been slightly modified in this technique. In a solution of ethanol: dichloromethane (1:1), a drug, polymers, and 0.1% surfactant like PEG are combined at room temperature. As an emulsifier, 80 ml of polyvinyl alcohol (0.46% w/w) is progressively added to the solution. For the purpose of evaporating the organic solution, this is agitated for 1 hour using a propeller agitator before being filtered. Prepared Microballons were evaluated for FT-IR spectroscopy, Differential scanning calorimetry, buoyancy test, release studies, scanning electron microscopy (SEM). 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 twelve hours the percent of drug release for five formulations were 49.95±0.94(F1), 52.95±0.76(F2), 64.88±0.68 (F3), 73.66±0.89 (F4), and 94.77±0.74 (F5) and all of the formulations followed zero order, First order, Higuchi model, and Peppas model.

KEY WORDS: *Floating-Microballons, Cefadroxil, Differential scanning calorimetry, scanning electron microscopy.*

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I. INTRODUCTION

For oral sustained or prolonged-release dosage forms, multiple units are more advantageous than single units because they disperse widely and uniformly along the gastrointestinal tract and could lessen intra- and intersubject variability. Gastric-retentive systems, multiple units, may have the advantage of avoiding all- or –nothing emptying, and increase the probability that some of the dosage form will remain in the stomach[1]. Approaches devising multiple unit floating systems include multiple unit HBS, polycarbonate microspheres[2], alginate beads[3], charged ion exchange resins with bicarbonate[4,5,6,] air compartment multiple unit systems, coated granules with a dual effervescent layer[7] and emulsion solvent diffusion[8,9,10]. There are various approaches in delivering substances to the target site in a controlled release fashion via oral route. One such approach is using polymeric hollow microsphere as carrier for drugs. Hollow microspheres are known as the Microballoons due to their low-density core[11]. Microballoons based drug delivery systems have received considerable attention in recent years. The most important characteristics of Microballons are microphase separation morphology, which endows it with a controllable variability in degradation rate and also drug release[12,13]Multiple unit systems such as Microballoons capable of floating on the gastric fluid have the advantage that they are not subjected to "all or nothing" gastric emptying nature of single unit systems. Drug loaded polymeric Microballoons and ion-exchange beads capable of floating on the gastric fluids have therefore been examined as FDF.

In our study Cefadroxil is 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[14-17]. 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 Microballons containing Cefadroxil. The obtained Microballons were evaluated for infrared spectroscopy, scanning electron microscopy (SEM), Differential scanning calorimetry, *In-vitro* release behavior.

II. MATERIALS AND METHODS

Materials

Cefadroxil from Himedia, PEG from Himedia, Ethanol from Himedia, Dichloromethane from Himedia, Polyvinyl alcohol from Himedia.

Methods

Preparation of Microballons of Cefadroxil[18].

Both the "emulsion solvent evaporation method" and the "emulsion solvent diffusion method" have been slightly modified in this technique. In a solution of ethanol: dichloromethane (1:1), a drug, polymers, and 0.1% surfactant like PEG are combined at room temperature. As an emulsifier, 80 ml of polyvinyl alcohol (0.46% w/w) is progressively added to the solution. For the purpose of evaporating the organic solution, this is agitated for 1 hour using a propeller agitator before being filtered. The optimal results of several process factors, such as the polymer ratio, drug: polymer ratio, stirring speed, and emulsifier concentration, are used to choose the best formulation. Five trial formulations F1 to F5 and their composition is given in **Table 1**.

Table 1. Formulation of Microballons

S.no	Ingredients	F1	F2	F3	F4	F5
1	Cefadroxil	100mg	100mg	100mg	100mg	100mg
2	HPMC,EC	1gm	2gm	3gm	4gm	5gm
3	PEG	0.1%	0.2%	0.3%	0.4%	0.5%
4	Ethanol	1ml	2ml	3ml	4ml	5ml
5	Polyvinyl alcohol	0.46%	0.92%	1.38%	1.84%	2.3%
6	Dichloromethane	1ml	2ml	3ml	4ml	5ml

Evaluation of Cefadroxil loaded Microballons

Drug content (mg)

100 mg Microballons 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)

Table 2. Drug content of Microballons

S.no	Formulation code	Drug content
1	F1	75.90±0.47
2	F2	79.23±0.66
3	F3	80.30±0.73
4	F4	81.82±0.41
5	F5	82.95±0.86

Percent yield of Microballons

The prepared Microballons were collected and weighed. The weight of Microballons was divided by the total weight of all the non-volatile components used for the preparation of the Microballons.

% yield = weight of Microballons collected / wt. of all non-volatile components used for the preparation x 100

Table 3. Percentage yield of Microballons

S.no	Formulation code	Percentage yield
1	F1	89.9±0.35
2	F2	53.2±0.55
3	F3	48.1±0.90
4	F4	57.6±0.40
5	F5	58.9±0.85

Micromeritic properties, Particle density, Porosity

Angle of repose (θ) by funnel method

After thoroughly pouring the Microballons 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 Microballons 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. Evaluation parameters of prepared Microballons

Form-ulation code	Bulk density (gm/ ml)	Tapped density (gm/ml)	Angle of repose (θ)	Haus-ner's ratio	Carr's index	Particle density (g/cm3)	Percent porosity	D/T ratio
F1	0.19± 0.09	0.21± 0.05	35˚.52″± 1.02	1.51± 1.11	9.95± 0.71	08.0± 1.00	26.06± 2.71	0.702± 0.86
F2	0.12± 0.10	0.13± 0.08	51˚.79″± 0.72	1.68± 1.07	8.08± 1.09	0.73± 1.33	15.73± 0.81	0.747± 0.97
F3	0.23± 0.11	0.26± 0.09	38˚.65″± 1.18	1.10± 1.18	9.23± 1.05	0.6± 0.99	22.0± 0.58	0.66± 1.40
F4	0.19± 0.06	0.22± 0.10	35˚.21″± 0.95	1.18± 1.33	13.4± 0.83	0.05± 1.12	28.09± 1.06	0.62± 1.18
F5	0.10± 0.10	0.11± 0.12	34˚.63″± 0.75	1.07± 1.36	6.9± 0.66	0.4± 1.05	16.48± 1.43	0.612± 0.87

Buoyancy

Fifty milligrams of Microballons were placed in 100 ml simulated gastric fluid (SGF, pH 1.2) containing 0.02% Tween 20. The mixture was stirred at 100 rpm on a magnetic stirrer. After 8 h, the floating and settled Microballons were collected separately, dried at 40˚C and weighed.

Table 5. Buoyancy of prepared Microballons

S.no	Formulation Code	Buoyancy time (hrs)
1	F1	6
2	F2	4
3	F3	5
4	F4	9
5	F5	10

In vitro drug release studies

The Cefadroxil loaded polymeric Microballons, 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 Microballons

Time (hrs)	% Drug release				
	F1	F2	F3	F4	F5
1	19.67±0.59	23.20±0.87	25.32±0.78	26.64±0.57	27.79±0.69
2	23.64±0.85	26.91±0.61	28.82±0.53	32.26±0.97	38.79±0.56
3	24.44±0.96	29.88±0.69	33.14±0.68	36.58±0.67	42.79±0.44
4	25.67±0.63	36.58±0.91	43.64±0.89	49.02±0.88	56.55±0.73
5	27.52±0.50	39.82±0.85	46.58±0.92	52.91±0.72	59.17±0.95
6	31.14±0.82	40.08±0.78	49.61±0.86	58.05±0.83	61.26±0.89
7	35.84±0.73	41.38±0.84	52.67±0.84	61.22±0.84	67.59±0.97
8	38.28±0.79	43.66±0.87	54.86±0.94	63.64±0.93	75.99±0.95
9	41.99±0.84	45.78±0.79	57.33±0.92	66.89±0.79	78.37±0.85
10	44.45±0.82	47.27±0.84	60.28±0.87	68.29±0.85	84.66±0.83
11	47.64±0.95	49.61±0.79	63.78±0.75	70.11±0.82	88.89±0.79
12	49.95±0.94	52.95±0.76	64.88±0.68	73.66±0.89	94.77±0.74

***In-vitro* dissolution studies of Microballons:**

Dissolution studies were carried out for Cefadroxil loaded Microballons. The results are given in the **Table 7** and **fig 9**. The *in-vitro* drug release for prepared Microballons showed 96.80±0.97 after 12 hrs. In the present work all the prepared Microballons 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 Microballons

Time (hrs)	Cumulative % drug release				
	F1	F2	F3	F4	F5
1	34.58±0.98	41.67±0.92	52.26±0.97	61.02±0.96	66.76±0.84
2	35.31±0.94	42.11±0.87	54.14±0.89	63.90±0.83	67.57±0.98
3	38.08±0.87	43.79±0.90	57.96±0.78	65.84±0.90	69.58±0.86
4	41.11±0.85	45.46±0.88	58.42±0.82	66.23±0.81	70.65±0.94
5	43.19±0.73	46.89±0.84	60.84±0.85	68.33±0.86	73.56±0.98
6	44.66±0.72	47.14±0.98	63.42±0.94	70.33±0.94	76.55±0.83
7	47.84±0.73	49.38±0.84	64.67±0.84	73.22±0.84	78.59±0.97
8	49.28±0.79	50.66±0.87	68.86±0.94	77.64±0.93	80.99±0.95
9	50.99±0.84	52.78±0.79	70.33±0.92	79.89±0.79	84.37±0.85
10	53.45±0.82	57.27±0.84	73.28±0.87	80.29±0.85	87.66±0.83
11	58.64±0.95	62.61±0.79	75.78±0.75	83.11±0.82	89.89±0.79
12	59.95±0.94	66.95±0.76	77.88±0.68	84.66±0.89	95.77±0.74

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 8. Interpretation

Interpretation	WAVE NUMBER Interpretation	
	Cefadroxil	Cefadroxil Loaded Microballons
C-S	1117.44	1100.00
SNH	1568.72	1522.30
COOH	1759.06	1686.12
OH Stretch	3201.32	3411.47
C-O-C	1236.79	1230.5
Csp^{2}H	3028.33	2826.20

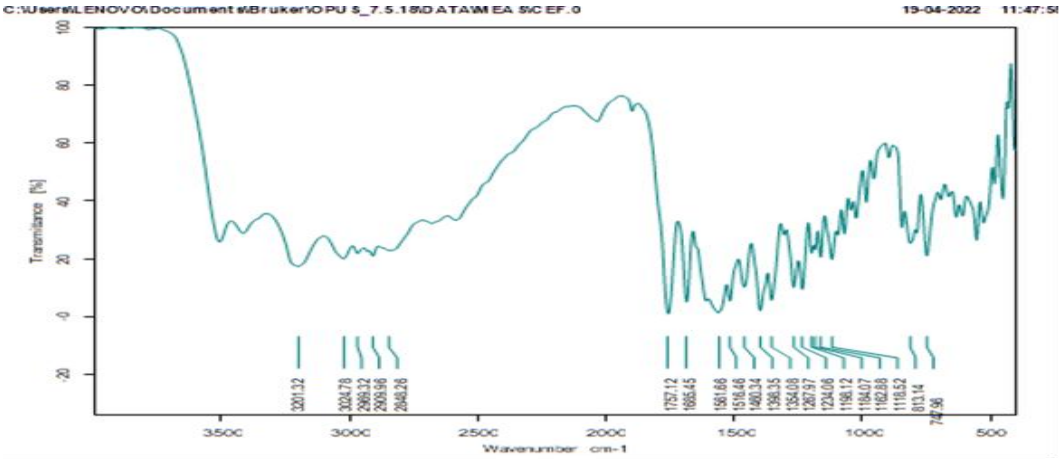

Fig 1. FTIR of Cefadroxil

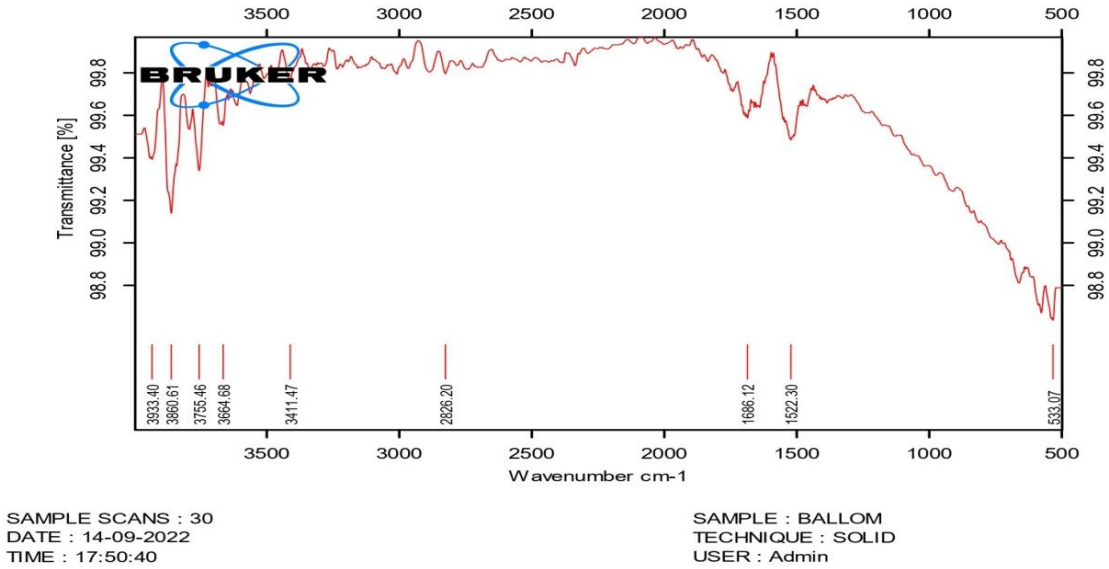

Fig 2. FTIR of Cefadroxil loaded Microballons

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.

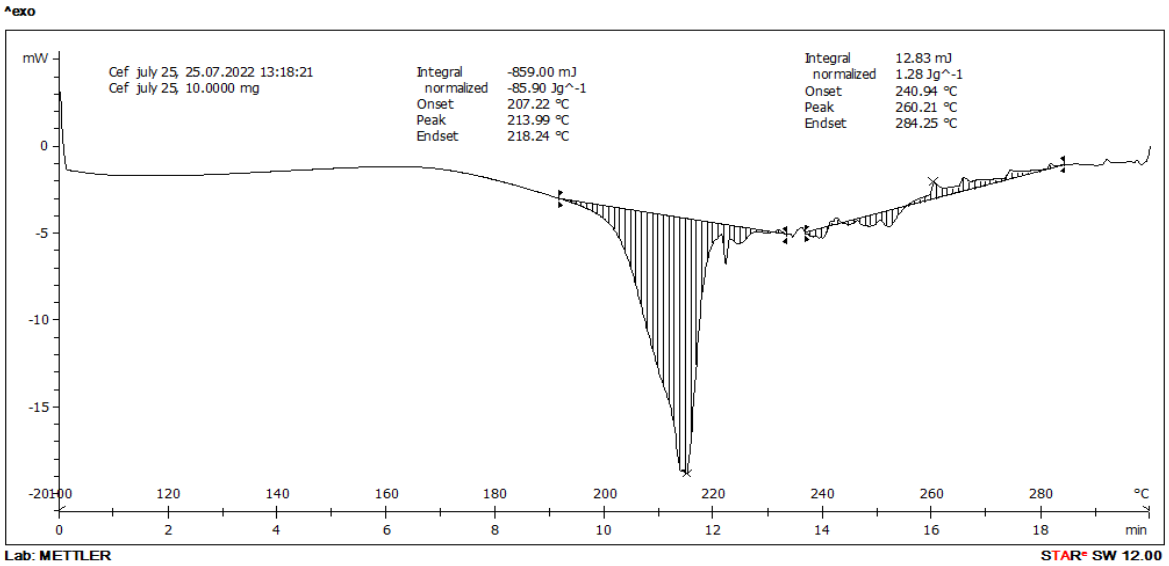

Fig 3. DSC of Cefadroxil

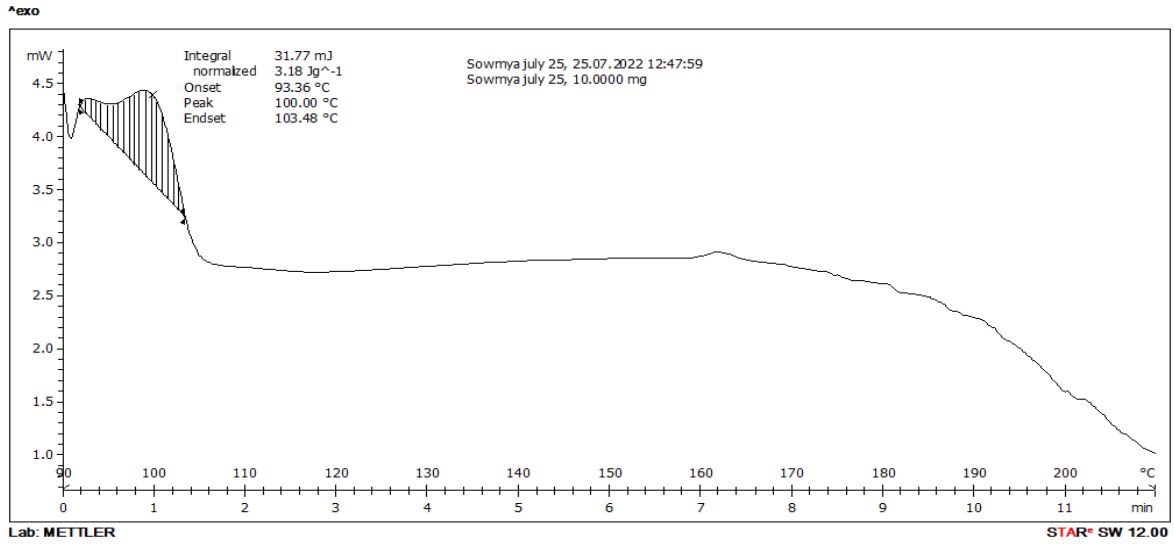

Fig 4.DSC for Cefadroxil loaded Microballons

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.

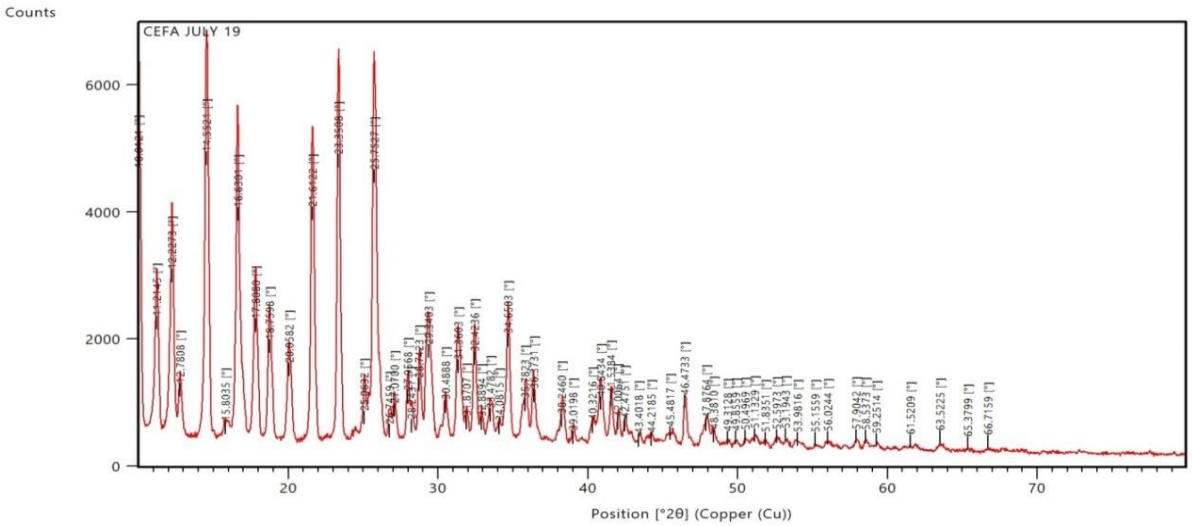

Fig 5. XRD of Cefadroxil

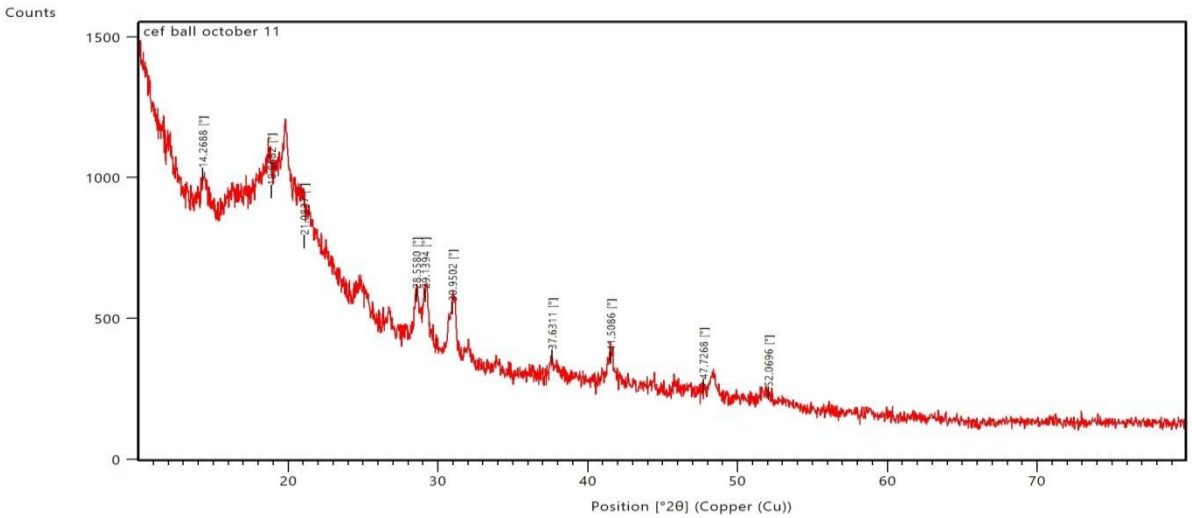

Fig 6. XRD for Cefadroxil loaded Microballons

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.

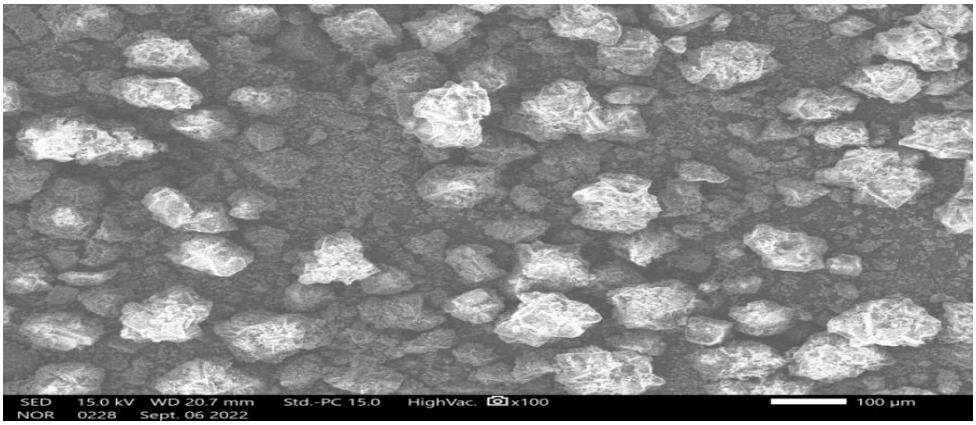

Fig 7. SEM of Cefadroxil

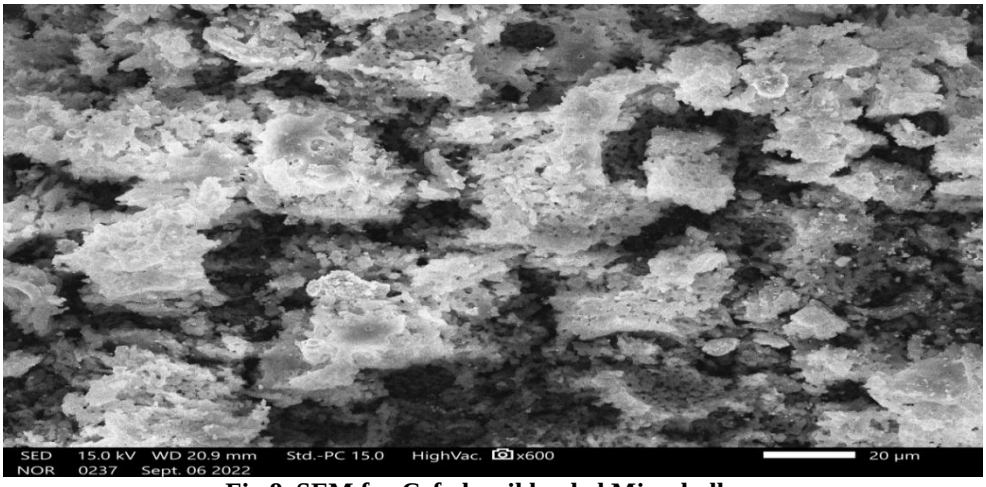

Fig 8. SEM for Cefadroxil loaded Microballons

III. Results and discussion

Cefadroxil Microballons were prepared by slight modification of both "emulsion solvent evaporation method" and "emulsion solvent diffusion method", with different combinational polymers like PEG, PVP, Ethanol, and Dichloromethane. The prepared Microballons were found to be good floatation controlled release characteristics in simulated gastric fluid in vitro has been successfully developed using the solvent evaporation and diffusion method.

SEM Analysis

The micrographs of Cefadroxil Microballons re as shown in **fig 8** and they indicate that the Microballons was found to be smooth, dense and porous in shape with outer surface.

Drug content

The percent drug content of Microballons determines the amount of drug entrapped in the Microballons. The formulation F5 has shown maximum release of 82.95±0.86.Among all the formulation F5 was considered as optimized formulation due to its drug content.

Percentage yield

The percentage yield of all the 5 formulations in Table 26 was in the range of 48.1±0.90 to 89.9±0.35 and formulations F1 showed highest percentage yield of72.34 ±0.84.

Micromeritic properties, Particle density, Porosity

The micromeritic properties of prepared Microballons are shown in **Table 4**of all formulation F1 to F5, value of Angle of repose, Hasner's ratio, Carr's index shows good flow ability.

Diameter to thickness ratio and percentage porosity decreased as the size range decreased and this could be interpreted as a decrease in the size range resulted in an increase in thickness of the wall.

Buoyancy

Buoyancy nature in all formulations from F1 to F5 was found to be in the range of 5 hrs to 10 hrs shown in **Table 5**. Among all the formulation F5 shows highest buoyancy time.

***In-vitro* dissolution studies**

Dissolution studies were carried out for Cefadroxil loaded Microballons. The results are given in the **Table 7** and **fig 9**. The *in-vitro* drug release for prepared Microballons showed 95.77±0.74 after 12 hrs. In the present work all the prepared Microballons 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 95.77±0.74.

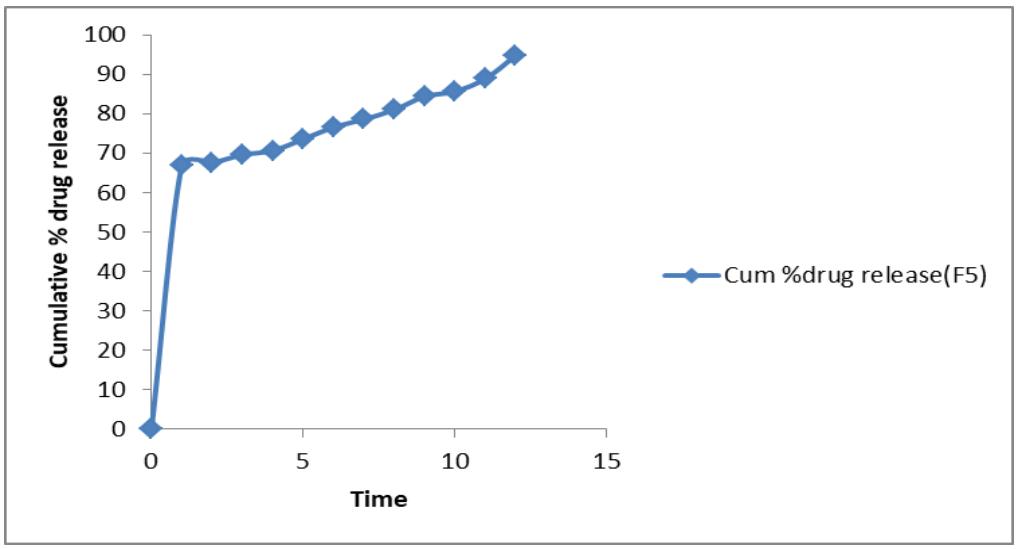

Fig 9.Cumulative % drug release of Cefadroxil loaded Microballons(F5)

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 Cefadroxil 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.

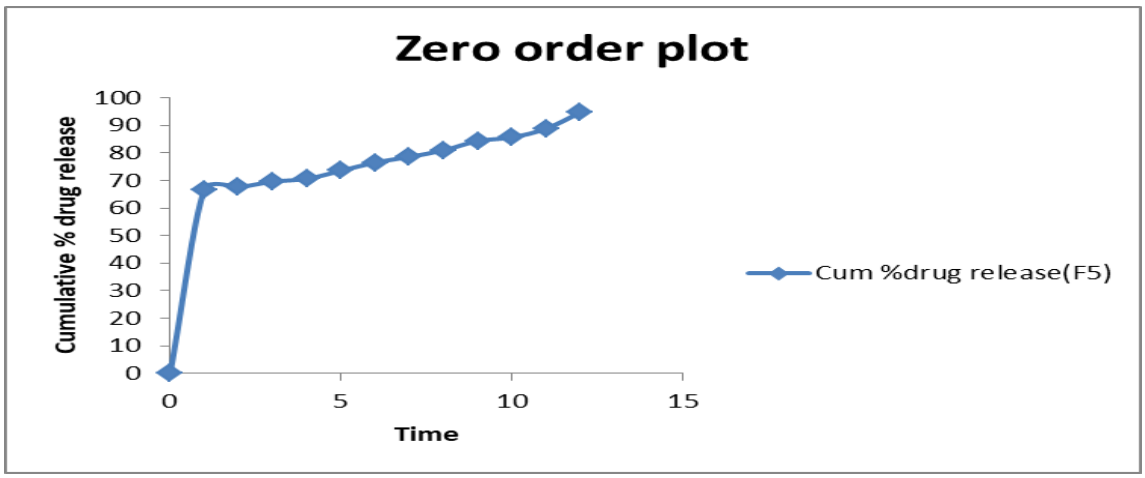

Fig 10

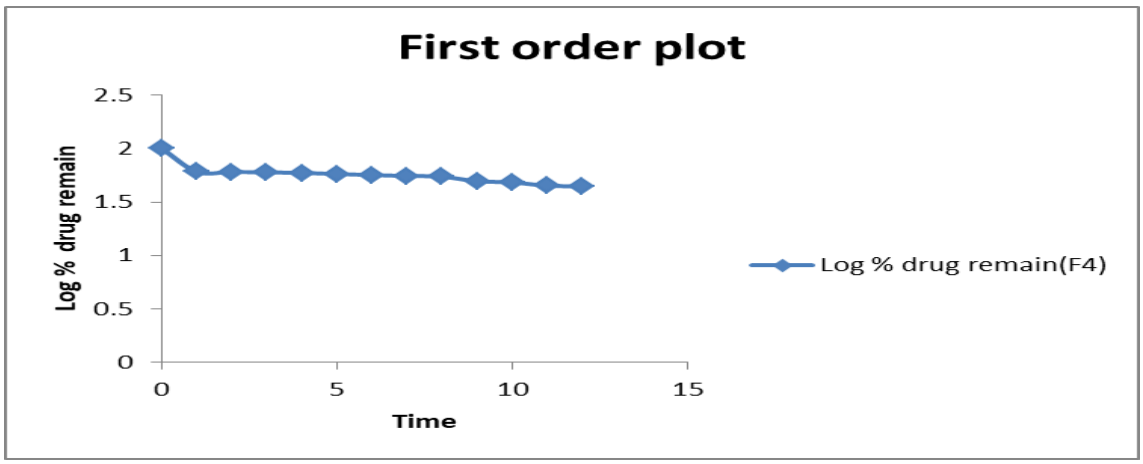

Fig 11

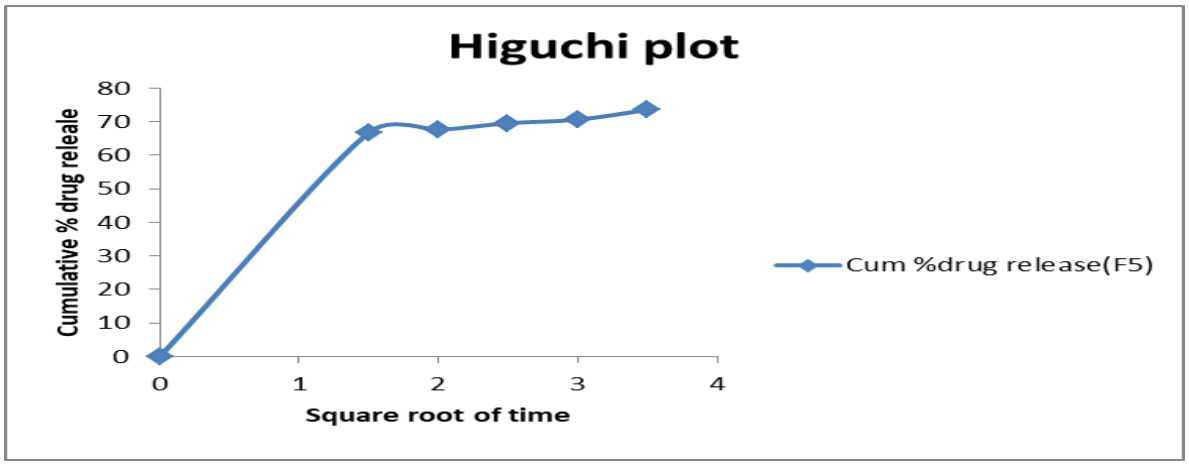

Fig 12

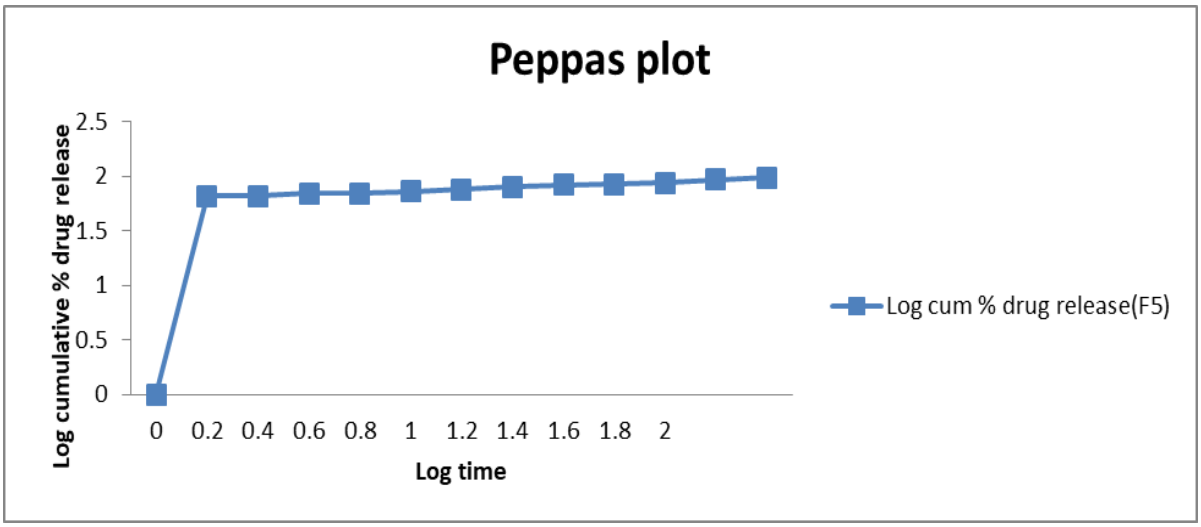

Fig 13

Table 9. Correlation coefficient(r^2)

Formulation code	Correlation coefficient(r^2)			
	Zero order	First order	Higuchi plot	Peppas plot
F5	0.88	0.82	0.80	0.84

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 9**. The drug release kinetics following mixed mechanism of zero and first order and the mechanism of release is "diffusion" as r^2 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 Microballons containing Cefadroxil using surfactant such as PEG, polyvinyl alcohol as emulsifier. The obtained Microballons were evaluated for Particle density, Porosity, infrared spectroscopy, scanning electron microscopy (SEM), Differential scanning calorimetry, *In-vitro* release behavior. The dissolution study revealed that, after twelve hours the percent of drug release for five formulations were 49.95±0.94 (F1), 52.95±0.76 (F2), 64.88±0.68 (F3), 73.66±0.89 (F4), and 94.77±0.74 (F5) and all of the formulations followed zero order, First order, Higuchi model, and Peppas model.

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Conflicts of interest: Nil

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