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"Formulation and Evaluation of Gastroretentive Floating Tablets of Cefadroxil by Using Natural Polymers"

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Abstract:

The floating tablets of Cefadroxil were prepared to increase the gastric retention and to improve the bioavailability of the drug. The floating tablets were formulated using Xanthan gum, Guar gum and its combination as the release retardant polymers. Sodium bicarbonate and citric acid as the gas generating agent to reduce the floating lag time. The tablets were prepared by direct compression. The floating tablets extended the drug release up to 12 hrs. The drug-polymer interaction was evaluated by Fourier transform infrared spectroscopy (FTIR). The FTIR study indicated the lack of drug-polymer interaction. The total formulation batches were F1 to F9.The optimized formulation (F2), containing drug 250mg and Xanthan Gum180mg showed very good result and extended the release up to 12 hours. The drug release from the optimized formulation followed zero order and Korsmeyer peppas equation. The drug release for batch F2 (optimized formulation) was 99.06%. The performance of developed formulation promises to be efficient in controlling the drug release rate with the Xanthan gum, a natural polymer.

Key words: Gastro-retentive; Cefadroxil; Xanthan gum; Guar gum; swelling index

INTRODUCTION:

Oral ingestion is the most convenient and commonly used method of drug delivery. These systems have the obvious advantages of ease of administration and patient acceptance, least sterility constraints and flexibility in the design of dosage form. One would always like to have an ideal drug delivery system that will possess two main properties:

(a) It will be a single dose for the whole duration of treatment.
(b) It will deliver the active drug directly at the site of action.

Unfortunately, such ideal systems are not available. Thus scientists try to develop systems that can be as close to an ideal system as possible. An oral drug delivery system providing a uniform drug delivery can only partly satisfy therapeutic and biopharmaceutical needs, as it doesn't take into account the site specific absorption rate within the gastrointestinal tract, therefore there is need for developing delivery system that release the drug at the right time, at the specific site and with the desired rate. Pharmaceutical products designed for oral delivery are mostly immediate release type, which are designed for immediate release of drug for rapid absorption. Invariably, conventional drug dosage forms do not maintain the drug blood levels within the

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therapeutic range for an extended period of time. To achieve the same, a drug may be administered repetitively using a fixed dosing interval. This causes several potential problems like saw tooth kinetics characterized by large peaks and troughs in the drug concentration-time curve, frequent dosing for drugs with short biologic half-life, and above all the patient noncompliance.

An ideal drug delivery system should aid in the optimization of drug therapy by delivering an appropriate amount to the intended site and at a desired rate. Hence, the delivery system should deliver the drug at a rate dictated by the needs of the body over the period of treatment. By and large, a delivery system may be employed for spatial placement (i.e., targeting a drug to a specific organ or tissue) or temporal delivery (i.e., controlling the rate of drug delivery to the target tissue)[1].

While developing a controlled release system one has to overcome basically three areas of challenges [2].

1) To develop a suitable system that delivers drug at a therapeutically effective rate at a predetermined site for a certain period of time required.
2) To develop a system that can be easily targeted to the site of action or the site of absorption and would reside there for sufficient period of time so as to release the drug in the vicinity of the site.
3) The drug should be delivered in such a way so that there is minimum first pass meta bolism[3-4].

OBJECTIVES OF STUDY:

The objective of the present research work was to provide a gastro-retentive system for sustained release of therapeutically active agent.

- ❖ To prepare floating sustained release drug delivery system of Cefadroxil.
- ❖ To select the polymers to achieve desired sustained release effect.
- ❖ Preliminary trials using hydrophilic polymers, gas generating agent or other recipients required for the formulation of the dosage forms with the desired characteristics.
- ❖ Optimization of concentration of release retarding polymers.
- ❖ To study the effect of combination of polymers.
- ❖ To evaluate prepared batches tablets.
- ❖ To perform statistical analysis by expert software.
- ❖ To perform model fitting

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EXPERIMENTAL AND METHODS: [5-12]

Table 1: Formulation Table

INGREDIENTS	FORMULATIONS (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefadroxil	250	250	250	250	250	250	250	250	250
Xanthan Gum	200	180	160	--	--	--	100	125	75
Gaur Gum	--	--	--	200	180	160	100	75	125
PVP k 30	10	10	10	10	10	10	10	10	10
Sod. Bicarbonate	75	70	72	75	70	72	75	70	72
Citric acid	25	30	28	25	30	28	25	30	28
Mg. stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	30	50	70	30	50	70	30	50	70
Total(mg)	600	600	600	600	600	600	600	600	600

Method of Preparation of Cefadroxil Tablets

Cefadroxil, lactose and hydrophilic polymers were passed from sieve of # 40 and mixed for 10 min.

Gas generating agent was then passed through sieve of # 60 added to the above mixture.

- Magnesium stearate was passed through sieve of # 60 and added to the above mixture.
- The whole bulk of powder was then mixed thoroughly for 15 min.
- The powder was then compressed into round shaped tablets on eight station tablet press. The tablets were evaluated for parameters like hardness and friability.

Experimental Data: -[12-27]

Pre-compression evaluation parameters:-

Solubility

After the preparation of supersaturated solution of Cefadroxil in 0.1N HCl was found to be 20 mg/ml.

Melting Point

The melting point of the drug was determined by using capillary method. It was found to be 197^{o} C.

Identification Test

The identification test for Cefadroxil was carried out by using IR spectroscopy and UV absorbance spectra.

For IR spectroscopy, KBr powder was dried at 60^{o} C for one hour. The dried KBr powder was uniformly mixed with drug and IR spectra was taken for this mixture.

For UV identification of Cefadroxil the solution of concentration from 2-8 µg/ml in 0.1N HCl was prepared. The solution was scanned from 200-400 nm and a spectrum was observed for absorption maxima.

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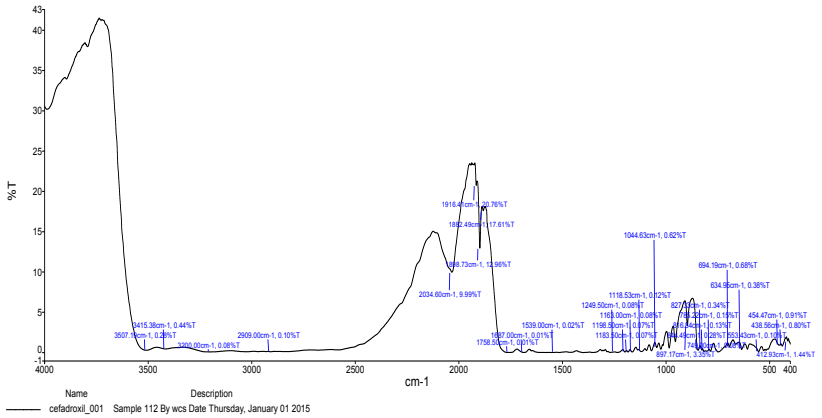

Fig.1- FTIR spectrum of Cefadroxil

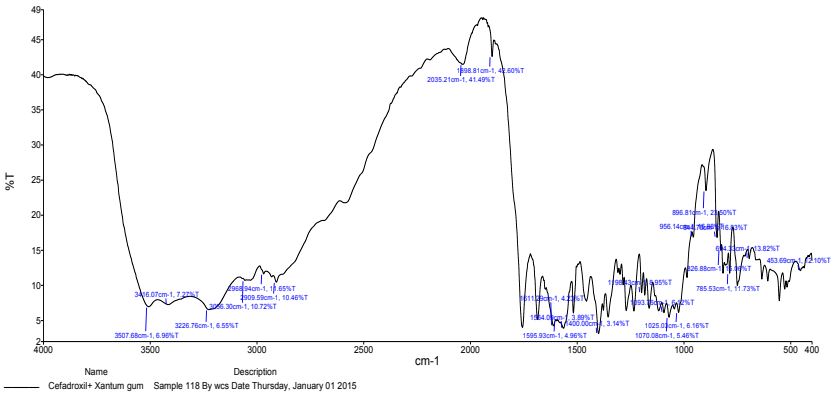

Fig.2- FTIR Spectrum of Cefadroxil+Xanthan gum

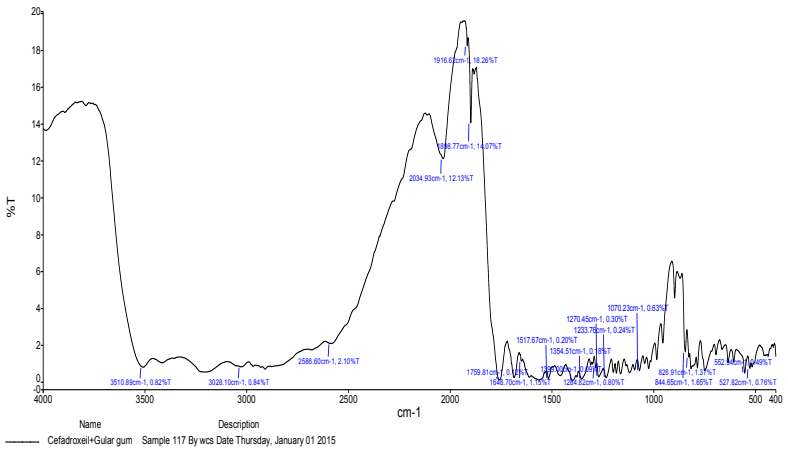

Fig.3: FTIR Spectrum of Cefadroxil+Guar gum

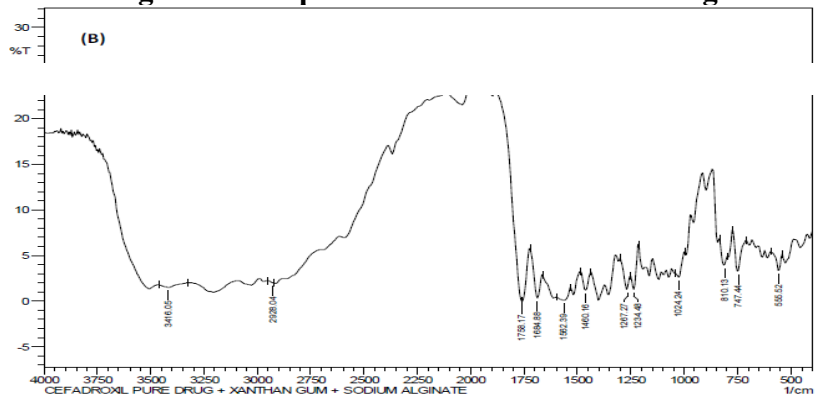

Fig.4-FTIR Spectrum of Cefadroxil+Xanthan gum+Gaur gum

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Table.2- Characterization of Formulation Blends

Formulation code	Bulk Density (gm/ml)	Tap Density (gm/ml)	Carr's Index (%)	Hausner's ratio	Angle of Repose (Deg)	Flow Rates (gm/ml)
F1	0.57	0.61	6.57±0.69	1.07± 0.00	28.81±0.16	10.34
F2	0.55	0.60	8.33±0.36	1.09±0.00	27.02±0.26	11.56
F3	0.53	0.60	11±0.25	1.13± 0.01	25.15±0.24	8.15
F4	058	0.65	10.7±1.03	1.12± 0.01	21.79±0.96	10.56
F5	0.51	0.53	3.77±096	1.03± 0.00	20.23±0.23	8.46
F6	0.53	0.58	8.60±0.72	1.09± 0.01	23.25±0.17	9.29
F7	0.53	0.56	5.35±0.69	1.06±0.00	22.29±0.56	11.33
F8	0.55	0.58	6.12±0.25	1.08±0.00	20.33±0.65	9.25
F9	0.53	0.59	8.89± 0.71	1.09±0.02	25.13±0.16	10.36

(n=3;mean±S.D)

Particle Size analysis of formulation Blend:

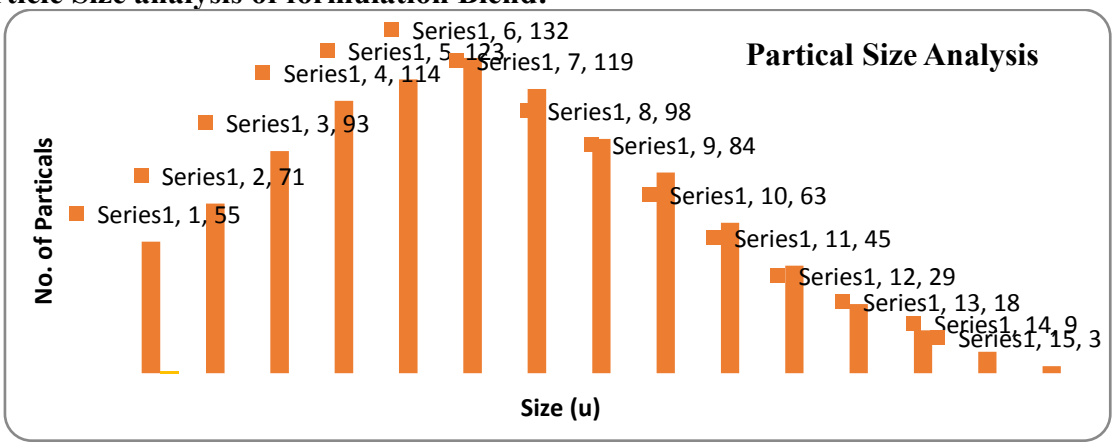

Fig.5- Particle Size Analysis

Evaluation of Floating Tablet

Table.3-Tablet Evaluation Parameters

Formulation Code	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm^2)	Friability (%)	Floating Lag Time(Sec)	Total Floating time (hrs)
F1	3	12	4.9±0.65	0.557	27	17
F2	3	12	4.7±0.46	0.370	15	20
F3	3	12	4.6±0.26	0.000	26	15
F4	3	12	4.9±0.74	0.545	25	18

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F5	3	12	4.7±0.36	1.107	32	16
F6	3	12	4.8±0.69	0.712	28	17
F7	3	12	4.7±0.36	0.000	40	14
F8	3	12	4.9±0.89	0.732	35	20
F9	3	12	4.7±0.84	0.735	17	19

(n=3; meanS.D) (n=20; meanS.D.)

Swelling Study of formulation Batches

Table.4- Swelling Study of F1, F2, F3 Batches

TIME(Hrs.)	F1 (%)	F2 (%)	F3 (%)
0	0	0	0
0.5	18.26±0.01	28.08±0.01	14.89±0.01
1	28.66±0.00	47.11±0.01	40.25±0.01
2	35.69±0.02	56.61±0.02	55.15±0.00
3	41.25±0.00	71.5±0.01	86.5±0.01
4	66.45±0.03	83.25±0.00	97.22±0.01
5	88.56±0.00	95.4±0.00	115±0.00
6	105±0.00	152.51±0.00	117±0.01

(n=3: mean ±S.D.)

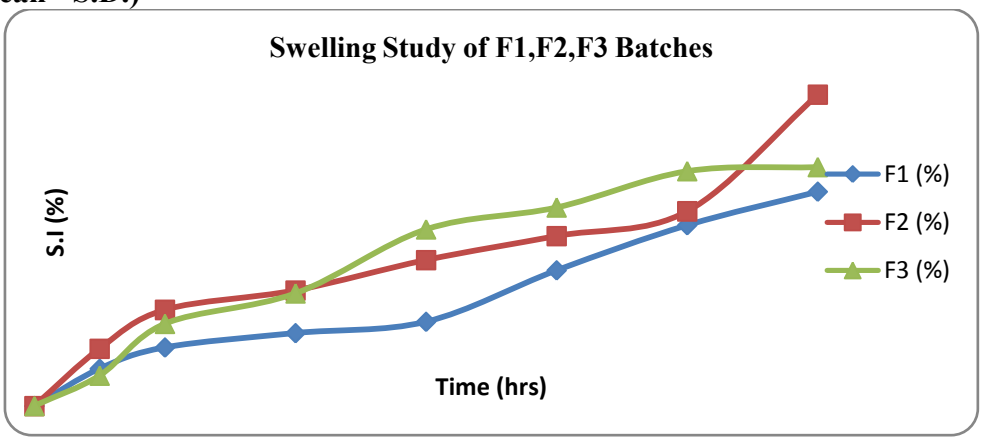

Fig .6-Swelling Index of F1, F2, and F3 Batches

Swelling Study of formulation Batches

Table.5-Swelling Study F4, F5, F6 Batches

TIME(Hrs.)	F4 (%)	F5 (%)	F6 (%)
0	0	0	0
0.5	29.25±0.00	23.25±0.02	31.55±0.00
1	49.16±0.01	36.78±0.027	39.15±0.01

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2	60.36±0.00	56.56±0.01	62.56±0.01
3	75.41±0.00	73.56±0.00	72.56±0.025
4	79.14±0.00	84.47±0.00	93.16±0.00
5	96.83±0.01	106.65±0.01	97.56±0.01
6	120.69±0.00	115±0.01	106±0.01

(n=3, Mean± SD)

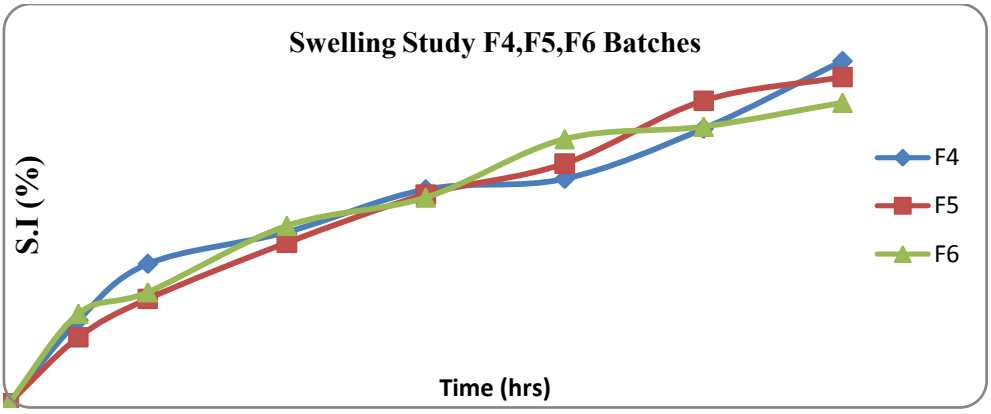

Fig.7 -Swelling Index of F4, F5, and F6 Batches.

Table.6-Swelling Study of F7, F8, F9 Batches

TIME(Hrs.)	F7 (%)	F8 (%)	F9 (%)
0	0	0	0
0.5	29.14±0.03	28.16±0.00	34.10±0.01
1	40.36±0.02	37.43±0.01	42.56±0.02
2	62.31±0.00	63.85±0.00	58.36±0.03
3	73.89±0.02	76.51±0.03	73.63±0.01
4	92.01±0.01	86.78±0.01	90.54±0.00
5	96.32±0.00	94.22±0.00	108.00±0.00
6	108.27±0.00	108.25±0.03	112.18±0.00

(n=3, Mean± SD)

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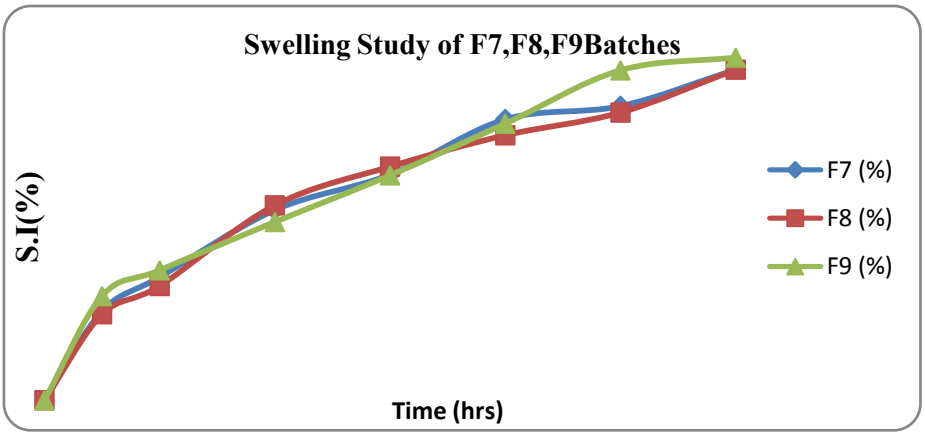

Fig .8-Swelling Index of F7,F8,F9 Batches

Assay of formulation Batches[28-38]

Table .7- Assay of Formulation Batches

ASSAY TABLETS							
BATCH	CONC µg/ml	ABSORBANCE			AVERAGE	S.D.	DRUG CONTENT %w/w
		1	2	3			
F1	15µg/ML	0.887	0.893	0.889	0.890	0.0031	92.32%
F2	15µg/ML	1.056	1.045	1.052	1.051	0.0056	99.12%
F3	15µg/ML	1.036	1.046	1.055	1.046	0.0095	95.23%
F4	15µg/ML	0.756	0.859	0.877	0.831	0.0653	92.32%
F5	15µg/ML	1.046	1.045	1.089	1.060	0.0251	90.36%
F6	15µg/ML	0.998	0.997	0.994	0.996	0.0021	90.12%
F7	15µg/ML	1.163	1.170	1.248	1.194	0.0472	95.56%
F8	15µg/ML	0.847	0.838	0.854	0.846	0.0080	91.02%
F9	15µg/ML	1.038	1.055	1.067	1.053	0.0146	92.25%
ASSAY OF BRANDED TABLET							

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1	15µg/ML	1.058	1.048	1.063	1.071	0.0036	99.58%

***In vitro* Release Profile**

Table.8-*In vitro* Release Profile of F1, F2 and F3 Batch

Time (Hrs)	% Cumulative Release		
	F1	F2	F3
0	0	0	0
0.5	7.53	5.91	4.28
1	11.99	10.20	10.86
2	18.47	16.59	14.43
3	26.68	26.64	21.92
4	32.41	37.54	28.64
5	39.20	46.18	36.99
6	49.13	58.10	41.18
7	57.93	61.97	48.85
8	66.13	72.82	56.59
9	72.56	82.21	63.75
10	80.90	89.82	77.59
11	88.14	92.58	81.84
12	94.61	99.06	90.56

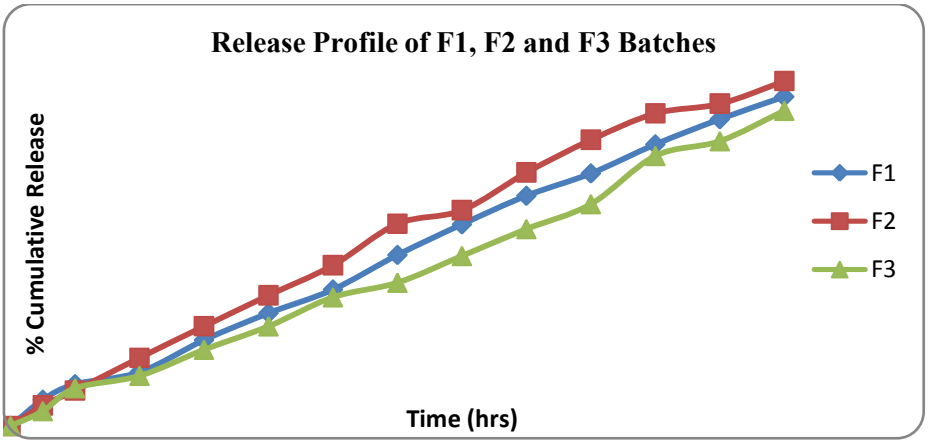

Fig.9-*In vitro* Release Profile of F1, F2 and F3 Batches

Table.9-*In vitro* Release Profile of F4, F5 and F6 Batch

Time (Hrs)	% Cumulative Release		
	F4	F5	F6
0	0	0	0
0.5	3.93	7.21	8.43
1	7.55	10.25	11.35

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2	14.02	15.88	15.47
3	21.48	26.91	28.46
4	25.39	36.52	37.89
5	32.23	40.73	43.97
6	42.19	48.96	50.65
7	52.04	53.89	54.65
8	57.43	58.43	60.77
9	62.08	64.08	66.41
10	67.67	72.63	71.63
11	73.85	77.30	76.25
12	83.37	87.62	84.14

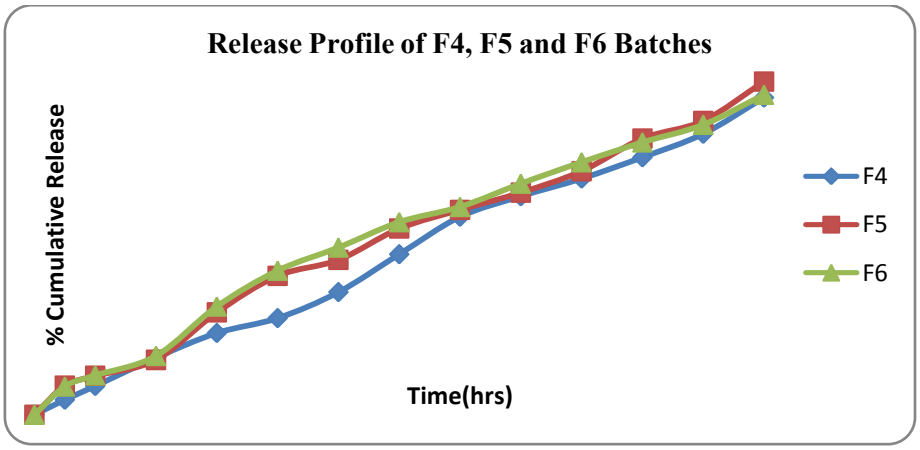

Fig.10- *In vitro* Release Profile of F4, F5 and F6 Batch

Table.10-*In vitro* Release Profile of F7,F8 and F9 Batch

Time (Hrs)	% Cumulative Release		
	F7	F8	F9
0	0	0	0
0.5	7.21	5.93	5.67
1	14.53	15.77	14.12
2	19.80	20.32	19.37
3	27.43	28.12	27.26
4	32.41	33.27	33.27
5	40.22	40.90	43.63
6	51.84	52.51	53.53
7	58.10	58.94	58.94
8	65.62	66.46	64.12
9	70.90	70.90	71.06
10	74.45	75.61	76.10

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11	81.24	82.51	85.56
12	90.89	91.79	95.74

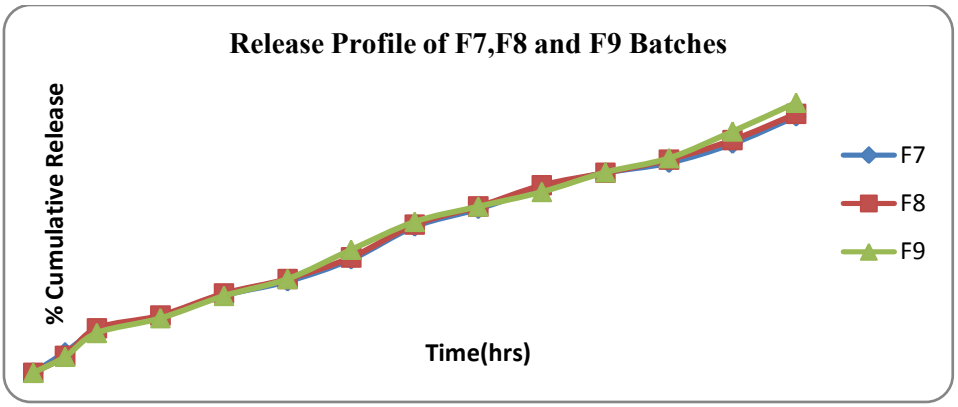

Fig.11- *In vitro* Release Profile of F7, F8, and F9 Batch

Release Kinetics Study of Batches[39-42]

Table: 11 Release Kinetics Study of Batches

Batch	Regression coefficient (R^2)									
	Zero order		First order		Higuchi		Korsmeyer-Peppas		HixonCrowell	
	k	R^2	k	R^2	k	R^2	k	R^2	K	R^2
F1	8.091	0.997	0.891	-0.170	22.796	0.932	8.349	0.999	-0.049	0.957
F2	8.808	0.995	-0.233	0.869	24.991	0.947	10.567	0.999	-0.0513	0.961
F3	7.345	0.997	0.138	0.921	20.628	0.922	7.820	0.998	-0.034	0.984
F4	7.407	0.992	-0.132	0.957	21.102	0.955	11.047	0.990	-0.0351	0.992
F5	7.480	0.986	-0.131	0.975	21.400	0.964	11.324	0.993	-0.035	0.998
F6	7.475	0.987	-0.132	0.978	22.127	0.998	12.131	0.991	-0.037	0.984
F7	7.807	0.993	-0.148	0.952	22.226	0.954	11.411	0.997	-0.038	0.985
F8	7.907	0.994	-150	0.948	24.498	0.953	9.782	0.996	-0.039	0.983
F9	7.906	0.995	-153	0.945	22.496	0.996	9.785	0.993	-0.0391	0.988

Stability studies:

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Table.12- Stability study of all formulation Batches

S.N	Time	DRUG CONTENT %w/w								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	92.32	99.12	95.23	92.32	90.36	90.12	95.56	91.02	92.25
2	1 Month	91.25	97.23	93.26	89.26	87.23	88.36	92.s58	91.23	91.16

DISCUSSION

The main aim of this work was to develop new floating tablets of Cefadroxil with natural polymers to increase its oral bioavailability by prolonging its gastric residence time and allowed to float in the stomach for a long period.

Cefadroxil floating tablets were prepared using Xanthan gum (F1, F2 & F3), Gaur gum (F4, F5, F6), and in combination of Xanthan gum and Gaur Gum (F7, F8, F9). The powder evaluation suggested that all the prepared powders exhibited good flow properties, as the angle of repose value were less than 30^0. A good packing ability of the powder was indicated by carr's compressibility index. The weight, Thickness and drug contents of all the tablets were found to be uniform. The hardness was in the range of 4.5 to 5 kg/cm^2 and friability was in the range of 0 to 1.107 %.Drug content was in the range of 90.12 % to 99.12 %.

The FTIR study indicated that the characteristic peaks related to drug were also noticed in the spectra of drug & other polymers .Hence there is no drug –polymer interaction.

Among all the formulations F2 & F9 formulation batches were optimized based on floating time and drug release profile. The floating study of the prepared tablets was carried out in 0.1N HCL buffer. Formulation F2 containing Xanthan gum and formulation F9 containing combination of Xanthan gum & Gaur gum found to be best not only in floating behavior but also in best drug release profile.

The polymers used were Natural, biodegradable, low density, highly swellable in shortest possible time and which upon contact with water; a hydrogel layer is formed to act as a gel would be gel boundary for the release of drug. Mixture of citric acid and sodium bicarbonate was incorporated in the formulation in such a way that when it contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen polymers, which provides buoyancy to the dosage form. The swelling study of the prepared tablets was carried out in 0.1N HCL buffer. The swelling behavior of tablets was expressed as the ratio of initial weight of tablet to the final weight of swollen tablet as a function of time. In formulations maximum swelling was seen with the formulation containing Xanthan gum (F2) & Guar gum (F4). Results indicate that xanthan gum and Gaur gum shows the good swelling index.

The in-vitro drug release study was performed using dissolution rate test apparatus in 0.1 N HCl (pH 1.2) till end of the study. The dissolution profiles are given in release profiles of all batches and data are presented in Tables 20 to 22. From dissolution data it is evident that designed formulations have displayed in the range of 83.37% to 99.06% drug release in 12hrs.

Among all the formulations, formulation F2 containing Xanthan gum & formulation F9 containing Xanthan gum & Gaur gum showed maximum drug release of 99.06% and 95.74% respectively at the end of 12 hr. Drug release data were shown that as the concentrations of Xanthan gum was decreased the initial drug

release was also decreased (F1, F2, F3) While concentration of Gaur gum was decreased the initial drug release was increased (F4, F5, F6).

The Drug release kinetic models suggesting that the drug was released by non-fickian diffusion mechanism. All the formulation were subjected for short term stability studies. It was observed for drug content 40^0c for 1 month. There is no physical changes in appearance, flexibility and colour. The % of degradation with respect to drug content was 0.2 - 3% thus the formulations were stable. Based on the results of evaluations data of all the 9 formulations F2& F9 were optimized because of their good sustained release data.

CONCLUSION

In the present study, an attempt was made to retain the dosage form in stomach for longer period of time. This can be achieved by developing gastro-retentive drug delivery system i.e., floating drug delivery system. For the formulation of floating tablets Xanthan gum, Gaur gum and in combination of Xanthan and Gaur gum were used as matrix forming agent. Other excipients were used a PVP and sodium bicarbonate, citric acid (gas generating agent), talc and magnesium stearate (lubricating agent). Among all the 9 formulations F2 and F9 showed good floating property while formulations F1, F3, F4, F5, F6, F7, and F8 showed moderate floating property while all the 9 formulations showed controlled drug release. Stability studies were carried out for all 9 formulations showed good stability. Drug release data were shown that as the concentrations of Xanthan gum was decreased the initial drug release was also decreased (F1, F2, F3) While concentration of Gaur gum was decreased the initial drug release was increased (F4, F5, F6).

It was observed that F2 and F9 gave maximum drug release upto 99.06% within 12 hrs. Thus conclusion can be made that stable dosage form can be developed for Cefadroxil by using natural polymers (xanthan gum and Gaur gum) for the controlled release. Swelling index study indicates that all the formulations showed significant swelling.

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