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Formulation and Evaluation of Sustained Release Matrix Tablets of Cefadroxil by Using Direct Compression Method

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ABSTRACT

Cefadroxil is a first generation cephalosporin antibiotic intended for oral administration. In the Present investigation, an attempt has been made to increase the therapeutic efficacy to reduce the frequency of administration and to improve the patient compliance by developing the sustained release matrix tablets of Cefadroxil by using direct compression method. Excipients like Xanthun gum, HPMC K 15 M, PVP K 30 are used as matrix polymers. MCC used as diluents, magnesium stearate as lubricant, and talc act as a glidant. The different excipients were tested for their compatibility with the drug Cefadroxil by using FTIR and DSC, which revealed that there was no chemical and physical interaction occurred. Then the Preformulation parameters like bulk density, tapped density, compressibility index, and Hauser's ratio were analyzed for prepared powder before compression. The thickness of best formulation CF9 is 3.5mm, hardness of best formulation CF9 is 3.6kg/cm^2, friability of best formulation CF9 is 0.66%, weight variation of best formulation CF9 is 499±0.39.The *In-vitro* drug release were performed in the USP Apparatus (basket) using 0.1 N HCL as dissolution media at 50 rpm speed. The sample was done at periodic intervals of 1hr, 2hr, 3hr, 4hr, 5hr, and 6hrs and was replaced with equal volume of dissolution media to maintain the sink condition. The best *In-vitro* release shown by formula CF9 that is 95% .The results indicate that the selected formulation was stable during the period of accelerated stability studies. The optimized formulation CF9 compared with the marketed sample Cetil-500mg. Marketed sample in-vitro drug release is 98.85%. All evaluated formulations results were found to be satisfied.

Keywords: Cefadroxil, sustained release matrix tablets, xanthan gum, HPMC K15M, PVP K 30.

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INTRODUCTION

Sustained release dosage form is defined as "Any drug or dosage form modification there the drug release in prolongs the therapeutic activity". It' s delivery system is increasingly as been used in the treatment of acute and chronic diseases as they maintain the drug concentration in plasma above the minimum effective concentration of the drug and below the minimum drug concentrations in toxic level for an extended period of time. Sustained release, sustained action, prolonged action controlled release, extended action, timed release, depot and repository dosage forms are used to identify the drug delivery system and that are designed to achieved or prolonged therapeutic effect by continuously releasing of drug in an over extended period of time after the single dose administration of a drug[1]. *The Matrix tablets* may be defined as the "oral solid dosage forms in which the drug (or) active ingredient is homogeneously dispersed throughout the hydrophilic (or) hydrophobic matrices. A matrix which serves as release rate retardants. This matrix systems release the drug in continuous manner by dissolution and diffusion-controlled mechanisms. Under the gastric pH conditions present in the stomach, the matrix tablets gets slowly erodes. However the pH present in the upper small intestine, the tablet gets disintegrates rapidly to remove the coated particles, which in turn slowly releases the drug from the matrix. There are two different release mechanisms are operative, which one mechanism follows zero order erosion and decreasing surface area, and dissolution of coated particles, but the overall tablet drug release profile comprising the two mechanisms in sequence is nearly linear for most of the dose in the tablet. The result in the ability to control active pharmaceutical ingredient's blood level's in particular narrow range, above the minimum effective level and below toxic level[2].

MATERIALS AND METHOD

Cefadroxil, micro crystalline cellulose, lactose talc was purchased Drug India, Hyderabad, India. Xanthan gum, HPMCK15M, PVP K-30, was gifted by Tini Pharma, Tirupathi, India.

Drug and polymer compatibility studies:

The compatibility of the drug in the formulation was confirmed by FTIR spectral analysis. FTIR spectra of cefadroxil and xanthan gum, HPMC K15M, PVP K-30 were determined by using the shimadzu FT-IR 8300 spectrophotometer in the frequency range of 400- 4000 cm-1 with the resolution of 4 cm-1 using potassium bromide dispersion method. By using above mixture of sample there is no incompatibility in the mixtures[3].

Preparation of sustained release matrix tablets of Cefadroxil:

Matrix tablets containing 500mg of Cefadroxil were prepared by direct compression method using different polymers. The tablets were compressed using Rotary tablet compression machine[4].

PARAMETERS FOR EVALUATION

Pre compression parameter[5]

Angle of repose:

The powder angle of repose was determined by using funnel method. For this study accurately weigh the powder. The funnel was fixed to stand and height of the funnel was adjusted up to 2-5cm tip of the funnel just touched the apex of the heap of powder. Now the powder was slowly allowed to flow through the funnel freely on to the surface. After the completion of the flowing powder, the diameter of cone was measured and angle of repose was calculated by using the following equation,

$$\text{Angle of repose } \Theta = \tan^{-1} h/r$$

Where

h= height of the file,

r= radius of the pile

Bulk density:

Bulk density is the ratio of total mass of powder to the bulk volume of the powder. It was measured by pouring the known weight powder (passed through standard sieve #20) in to a measuring cylinder and initial weight was noted. This initial volume is called as bulk volume, and it is expressed in g/ml and is given by,

$$\text{Bulk density} = \text{Mass of the powder} / \text{Bulk volume}$$

Tapped volume:

Tapped volume is the ratio of total mass of powder to the tapped volume of powder. It is determined by placing a graduated cylinder containing known weight of powder, by using mechanical tapper apparatus for fixed number of taps until the powder bed volume has reached a minimum volume. It can be expressed by g/ml.

$$\text{Tapped density} = \text{Mass of the powder/tapped volume}$$

Carr's index (compressibility index) CI:

The Carr's index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

$$\text{Carr's index} = (\text{Tapped density} - \text{Bulk density} / \text{Tapped density}) \, 100$$

Hausner's ratio:

Hausner's ratio is an indirect of the ease of powder flow. It is calculated by the following formula

Hausner's ratio= Tapped density/ Bulk density

Post compression parameter[6]

Hardness[7]:

The tablet strength was indicated by hardness. The resistance of the tablets for shipping/breakage during the conditions of storage, transportation and handling, before usage, depending upon its hardness. The hardness of the tablets was measured by using Monsanto hardness tester. The hardness can be expressed in Kg/cm2.

Thickness:

The thickness of the formulated tablets was determined by using a Vernier Callipers instrument. From the each formulation 20 tablets were randomly selected and average values were calculated. Thickness is expressed in Kg/cm2.

Weight variation[9]:

20 tablets are randomly selected from a batch and were individually weighed and then average weight was calculated. The weight variation of the tablets was meeting the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

Friability:

Strength of the tablets was measured by friability test. Roche Friabilator was used for the testing of friability. In this procedure 10 tablets were weighed accurately and placed in the Roche Friabilator plastic chamber to hold the tablets. The chamber revolves at 25 rpm for 4mins dropping the tablets through a distance of about 6 inches with each revolution. After completion of 100 revolutions the tablets were reweighed and % loss in tablet weight was measured by using below formula. It should not exceed 1%[10].

% loss = (Initial weight of tablets – Final weight of tablets)/ Initial Weight X 100

Content Uniformity:

The content uniformity test is mainly done to determine that every tablet contains the amount of drug substance intended with the little variation among the tablets within a batch. The five tablets were selected randomly from a batch and the average weight was calculated. Then the tablets were crushed in a mortar by using pestle and accurately weighed and the amount of average tablet was taken from the crushed blend. Then, the samples were transferred in to 100ml volumetric flasks and were diluted up to the mark with 0.1 N HCL solutions. The content was shaken periodically and kept for 24 hours for dissolution of the drug completely. Then the mixtures were filtered and

appropriate dilutions were made. The drug content in each tablet was estimated at λ max 270 nm against blank reference and reported[11].

***In vitro* dissolution study:**

In vitro drug release rate of Cefadroxil was determined using type-II Apparatus (basket type) dissolution test. The dissolution test carried out using 900ml of 0.1NHCL at 37±0.5 ˚C at 50rpm for 6hr. A 5ml of sample was withdrawn from the dissolution apparatus at specified time point and sample was replaced with the same quantity of fresh medium. The sample was filtered with Whatman filter paper No 40. The dissolution media at different time intervals at 1, 2, 3, 4, 5, and 6 hours and absorbance of solution were measured at 270nm using UV –spectrophotometer[12].

Stability study:

The tablets were charged for the accelerated stability studies according to ICH guideline temperature 40±2 ˚C and RH 75±5% for the three months and sample were taken out at 0, 30,60 and 90 days and evaluated for the drug content, *In-vitro* dissolution rate, physical parameter, and hardness, thickness, weight variation and the friability[13].

Drug release kinetics:

Kinetics studies were conducted for CF1-CF10 formulations[14]. Zero order plot, fast order plot, Higuchi plot and Korsmeyer-Pappas were plotted for all formulation CF1-CF10.

RESULTS AND DISCUSSION

Drug – Excipients compatibility studies FTIR

Cefadroxil drug and also Cefadroxil + different excipients were made into pellets by using KBr at a ratio of 1:100. Physical mixture of drug and polymers was characterized by FTIR and DSC spectral analysis for any physical as well as chemical alteration of the drug. From the results, it was concluded form there no interference in the functional group as the principle peaks of the cefadroxil were found to be drug and polymer mixture, FTIR spectra are shown in figure and interpreted values shown in the table respectively.

Drug excipient compatibility study DSC

The pure drugs of DSC sample of spectra the exothermic peak 122.5and-10.65. The mixtures contain the drug cefadroxil, Xanthan gum, PVPK30, HPMCK15M the endothermic peak is 134.5 and -9.29mw, the endothermic peak of the mixture 287.5 and -5.62mw. The compatibility of drug and excipients shows there is no compatibility in the formulation. So the suitable for performing formulation of sustained release matrix tablets. The DSC spectra as shown in figure 6.

Pre-compression parameter of Cefadroxil

Bulk density:

The bulk density for all formulations CF1 to CF10 values varied from 0.41gm/cm^3 to 0.48gm/cm^3, which indicates good property.

Tapped density:

The tapped density for all formulations CF1 to CF10 values varied from 0.44gm/cm^3 to 0.58gm/cm^3, which indicates good property.

Hausner's ratio:

The Hausner's ratio of powder mix was determined by the data of loose bulk density and tapped density. The Hausner's ratio for all the formulations CF1 to CF10 lies within the range of 1.06 to 25, which indicates flow of powder is good.

Percentage compressibility (Carr's consolidation index):

The % percentage compressibility of powder mix was determined by the equation given for Carr's consolidation index. The percentage compressibility for all CF1 to CF10 formulations lies within the range of flow of the tablet mixture 12.5% to 20% which indicates that that the flow of the tablet mixture of various formulations is good

Post- compression parameter:

The Cefadroxil tablets of different formulation were physically characterized by parameter like hardness, thickness, weight variation, friability and assay results were shown in table 4

Thickness:

The thickness of all formulation was checked using Vernier Calipers. The average thickness of all batches CF1 – CF10 is in the range of 2.9±0.16 to 3.5±0.15.

Hardness:

The hardness of all the formulation was checked using Monsanto hardness tester, the average hardness of all the batches CF1-CF10 is in range of 3.3±0.11 to 3.6±0.13 kg/m^2.

Friability:

The percentage friability for all the formulation checked, the ranges of all batches CF1 – CF10 in the range of 0.47±0.14 % to 0.66±0.15%.

Weight variation:

All the formulation passed weight variation test as the % weight variation was within the pharmacopoeia limits of all formulations CF1 – CF10 it was found to be 494±1.200 to 499±0.39mg.

Drug content:

The drug content values for all the formulation in the range of all batches CF1 – CF10 was found to be 98.12±0.12% to 101.28±0.13%.

***In-vitro* dissolution study**

The *in-vitro* dissolution study of cefadroxil tablet is tested by using 0.1N HCL dissolution medium. The *in-vitro* drug release study of sustained release matrix tablets for all formulation CF1 to CF10 was carried out by using 0.1N HCL for 6 hours. The sample were withdrawn at specified time interval and analyzed by UV-spectrophotometer. The cumulative % drug release of cefadroxil was plotted against time to obtain drug release profiles. The *In-vitro* cumulative % drug release CF1 to CF10 values are calculated in table no 12.Form the *in-vitro* dissolution data it was found that the formulation containing Xanthum gum(CF1, CF2, and CF3) showed 92.00%, 93.5%, and 92.5% drug release respectively. Form the *in-vitro* dissolution data, it was found to be formulation containing HPMC K 15M (CF4, CF5, and CF6) showed 94.0%, 92.8%, and 93.9% drug release respectively. Form the *in-vitro* dissolution data, it was found to be formulation containing PVP K 30(CF7, CF8, and CF9) showed 94.5%, 92.7%,and 95.00%drug release respectively.

From the *in- vitro* dissolution data, it was found to be formulation containing xanthan gum, HPMC K 15 M, PVP K 30 (CF10) showed 93.5% drug release respectively. Among all the formulations CF9 has shown maximum drug release. So the sustained drug release for the cefadroxil tablets with PVP K 30 may fulfill our objective.

Comparison of dissolution profile of optimized formulation with marketed product

Out of 10 formulations, tablets made with combination of PVPK30 (CF9) showed better dissolution rate 95.0% at 6 hrs. The in-vitro drug release of marketed product was found to be 99.9%. From the above observations, it may be concluded that optimized formulation (CF9) is near to the marketed formulation in release rate of drug.

Stability Studies

The optimized formulation was subjected to the different temperature and different humidity conditions up to three month and analysis the every one month condition for drug content release studies. The analyzed values are tabulated in table 8. The based ideal storage conditions for Cefadroxil tablets are 25±2^{o}C/ 60%RH. It is shown the decreases the less amount of drug content studies.

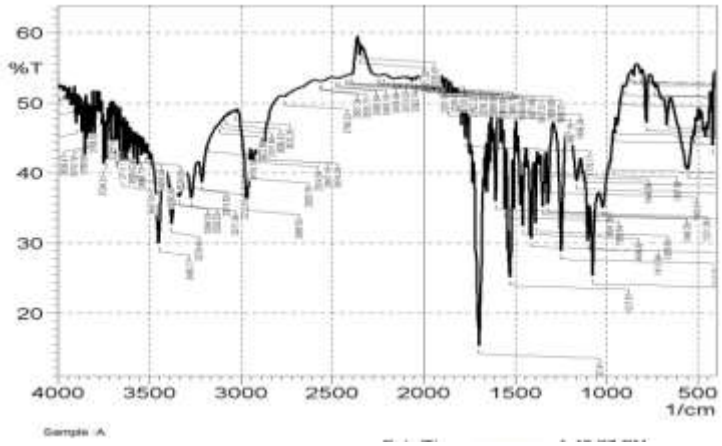

Figure 1: FTIR spectrum of cefadroxil

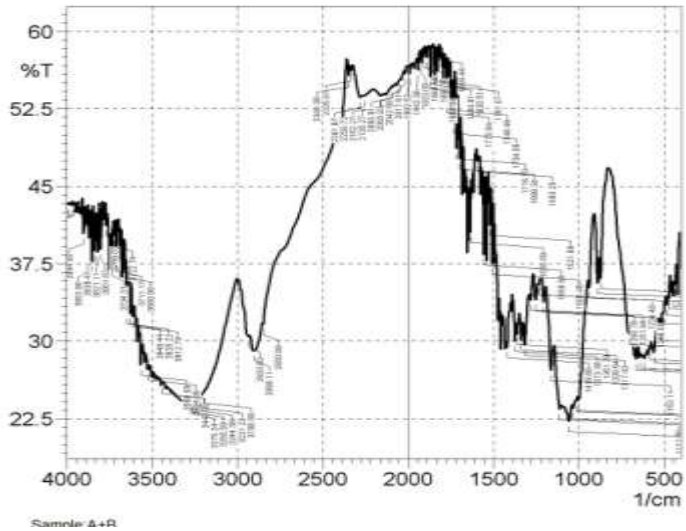

Figure 2 : FTIR spectrum of cefadroxil + xanthan gum

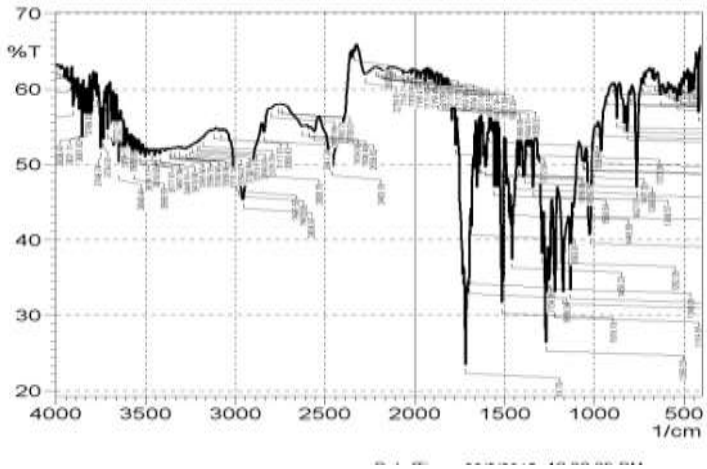

Figure 3: Drug + PVPK 30

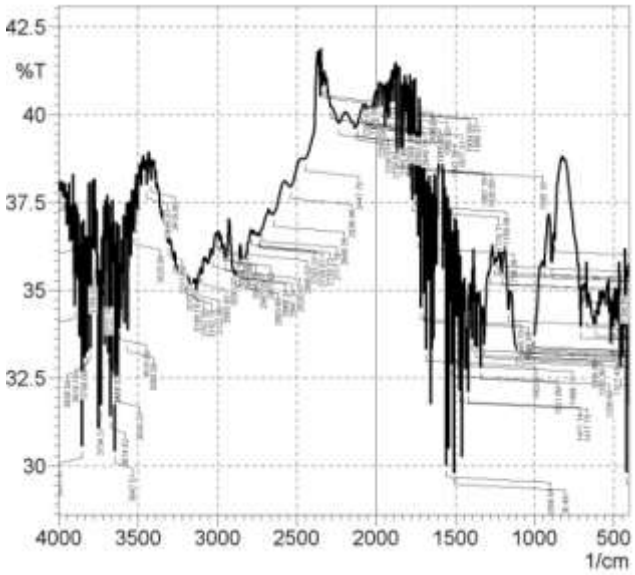

Figure 4: Cefadroxil +HPMCK15M

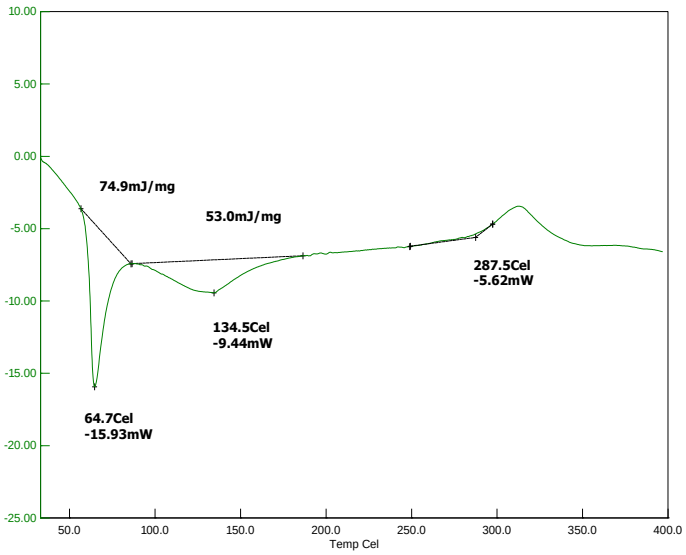

Figure 5: DSC of Cefadroxil+Polymers

Table 1: Development of formulations

Ingredients	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9	CF10
Cefadroxil	100	100	100	100	100	100	100	100	100	100
Xanthan gum	80	90	100	-	-	-	-	-	-	30
HPMC K 15 M	-	-	-	80	90	100	-	-	-	30
PVP K– 30	-	-	-	-	-	-	80	90	100	30
MCC	208	205	200	208	205	200	208	205	200	205
Lactose	92	85	80	92	85	80	92	85	80	85
Mg.Stearate	10	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10	10
Total weight	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**

Note: All ingredients taken in milligrams (mg)

Table 2: Pre-compression parameter of Cefadroxil

Formula Code	Bulk density(g/cc)	Tapped density(g/cc)	Hausner's ratio	Compressibility index (%)	Angle of repose (θ)
CF1	0.41	0.44	1.06	16.06	33.69
CF2	0.43	0.50	1.14	12.50	34.21
CF3	0.45	0.56	1.24	19.35	34.00
CF4	0.46	0.53	1.15	13.33	36.60
CF5	0.44	0.54	1.21	17.85	34.01
CF6	0.45	0.56	1.19	18.00	32.61
CF7	0.45	0.55	1.24	19.35	35.83
CF8	0.46	0.55	1.20	16.66	34.60
CF9	0.48	0.58	1.25	20.00	36.60
CF10	0.45	0.54	1.18	15.78	34.99

Table 3: Post–compression parameter of Cefadroxil

Formula code	Hardness (kg/cm2)	Thickness (mm)	Weight variation(mg)	Friability (%)	Assay (%)
CF1	3.3±0.15	3.3±0.17	495±1.39	0.60±0.15	99.89±0.13
CF2	3.3±0.11	3.2±0.15	498±0.79	0.62±0.15	98.12±0.12
CF3	3.4±0.12	3.4±0.16	498±0.79	0.64±0.16	98.99±0.15
CF4	3.3±0.13	2.9±0.15	498.6±0.99	0.61±0.14	100.21±0.13
CF5	3.4±0.14	3.5±0.13	494±1.200	0.61±0.15	97.54±0.12
CF6	3.4±0.15	3.1±0.14	495±0.56	0.52±0.13	97.69±0.14
CF7	3.5±0.14	2.9±0.16	497±0.28	0.52±0.14	97.87±0.16
CF8	3.3±0.12	3.0±0.15	499±0.38	0.56±0.13	98.58±0.12
CF9	3.6±0.13	3.5±0.11	499±0.39	0.66±0.15	101.28±0.13
CF10	3.4±0.15	3.4±0.12	499±0.33	0.47±0.14	98.74±0.15

Table 4: Interpretation of DSC Spectrum

S. No	Drug & Excipients	Exothermic peak	Endothermic peak
1	Cefadroxil	122.5^{o}c & -10.65 mw	----------
2	Drug+HPMCK15M+Xanthumgum+ PVPK30	134.5^{o}c & -9.44 mw	287.5^{o}C & -5.62mW

Table 5: *In-vitro* dissolution profile for the CF1 to CF10 formulations

Hours	% cumulative drug release									
	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9	CF10
0hr	0	0	0	0	0	0	0	0	0	0
1hr	23.0	25.6	22.5	23.5	31.0	29.0	28.4	24.6	28.4	25.6
2hr	39.8	42.0	50.3	41.6	45.1	40.5	43.3	34.5	43.5	42.0
3hr	50.3	59.0	61.9	63.5	60.2	68.1	54.6	54.7	61.7	58.3
4hr	68.9	71.9	79.6	77.8	78.8	79.4	76.1	68.0	72.8	69.9
5hr	81.9	85.0	86.5	87.8	86.1	86.9	89.1	81.9	84.3	80.1
6hr	92.0	93.5	92.5	94.0	92.8	93.9	94.0	92.7	95.0	93.5

Table 6: Regression coefficient and m values for the CF1 to CF 10

Release order kinetics	CF1		CF2		CF3		CF4		CF5		CF 6		CF 7		CF 8		CF 9		CF 10	
	R^2	M	R^2	M	R^2	m	R^2	M	R^2	M	R^2	m	R^2	M	R^2	m	R^2	M	R^2	M
Zero order	0.93	20.6	0.97	23.1	0.94	25.1	0.96	23.5	0.95	26.1	0.94	25.5	0.97	23.8	0.98	20.4	**0.99**	**14.9**	0.97	22.9
First order	0.95	2.25	0.93	2.25	0.98	2.24	0.97	1.89	0.97	2.24	0.97	2.27	0.86	2.32	0.93	2.27	**0.86**	**2.34**	0.92	2.26
Higuchi	0.96	29.9	0.97	32.3	0.97	34.1	0.96	33.0	0.98	34.8	0.96	34.6	0.96	33.2	0.95	29.9	**0.89**	**25.4**	0.97	31.8
Korsmeyer-Pappas	0.81	3.16	0.99	2.15	0.95	2.20	0.98	2.19	0.99	2.11	0.96	2.13	0.98	2.13	0.97	2.13	**0.98**	**2.17**	0.99	2.13

Table 7: Comparison of dissolution profile of CF9 and marketed product (Cetil– 500) containing Cefuroxime exitil)

Time (hrs)	CF9	Marketed
0	0	0
1	28.4	33.39
2	43.5	48.40
3	61.7	66.41
4	72.8	73.04
5	84.3	80.70
6	95	98.93

Table 8: Accelerated stability studies for optimized formulation F9

parameters	Initial	One month	Two months
Colour	Cream or White	Cream or White	Cream or White
Surface	Smooth	Smooth	Smooth
Thickness	3.3-3.4	3.3-3.4	3.3-3.4
Hardness	4	4	4
Assay	99.3	100.6	99.5

CONCLUSION

The objective of the present study is to develop sustained release matrix tablets of Cefadroxil by using direct compression technique. In this present study an attempt was made to improve the bioavailability of drug. Preparations of tablets are directly compression method. That among the all formulation (CF1-CF10), an optimized batch CF9 shows good *In-vitro* drug release. So formulation CF9 was found to be the best formulation among others.

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