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Development and evaluation of cefadroxil sustained release pellets by extrusion spheronization technique

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Abstract
Objective: The aim of the present study is to design and develop sustained release pellets of cefadroxil. cefadroxil is widely used in the management of anti-biotics and in the treatment of urinary tract infection. Cefadroxil is freely soluble in water and possesses pKa 1.5. Cefadroxil ($C_{16}H_{14}N_3O_5S$) a first-generation antibiotic. To carry out compatibility studies by FTIR. Pellets are evaluated for their bulk density, tapped density, angle of repose, carr's index, flow rate, friability, drug-content and *in-vitro* drug release.
Methods and results: Cefadroxil pellets were prepared by using HPMC K100 M or ETHYL CELLULOSE by extrusion and spheronization technique. The *in-vitro* release studies of pellets were carried out in 6.8 phosphate buffer for 12 hours. The studies indicated that the drug release can be modulated by varying the concentration of the PEG 4000 as release modulator with polymers. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order, and Zero-order to evaluate the kinetics and mechanism of the drug release. Kinetic modelling of in-vitro dissolution profiles revealed the release mechanism ranges from Quasi-Fickian transport to Anomalous (non-Fickian transport), which was only dependent on the type and amount of release modulator used. The drug release of the optimized formulation (F4) is 98.86% in 12 hours, follows then first order release kinetics (R^2: 0.864 to 0.988), Zero order kinetics shows (R^2: 0.903 to 0.998), and the 'n'value lies between (0.026 to 0.8421). The mechanism was found to be diffusion controlled. The compatibility studies were performed by using FTIR which reveals that there is no interaction between the drug and the polymer/excipients mixture.

Keywords: cefadroxil, extrusion spheronization, HPMC, ethyl cellulose, PEG 4000, Pellets

Introduction

Cefadroxil, a semisynthetic first-generation cephalosporin with antibacterial activity. Cefadroxil binds to and inactivates penicillin-binding proteins (PBPs) located on the inner membrane of the bacterial cell wall. PBPs are enzymes involved in the terminal stages of assembling the bacterial cell wall and in reshaping the cell wall during growth and division. Inactivation of PBPs interferes with the cross-linkage of peptidoglycan chains necessary for bacterial cell wall strength and rigidity. This results in the weakening of the bacterial cell wall and causes cell lysis. It is a long-acting, broad-spectrum, water-soluble, cephalexin-derivative. Like all beta-lactam antibiotics, (PBPs) located inside the bacterial cell wall, causing the inhibition of the third and last stage of bacterial cell wall synthesis[1]. Peak plasma concentration of about 16 and 30 micrograms/ml, respectively, are obtained after 1.5 to 2.0 hours. Plasma concentration are more sustained about 20% of cefadroxil is reputed to bound in plasma protein. The average elimination half-life in plasma is 1.5 hours. Dose of cefadroxil is 0.5 to 1.0g (every 12hr). Urinary excretion is 88% (renal deposition),

Multiple unit extended release dosage forms are becoming very popular dosage forms relative to single unit dosage forms because of their ability to spread uniformly in the gastrointestinal tract, thus minimizing the plasma level variability and reduced risk of local irritation [2, 3]. Pharmaceutical pellets may be defined as spherical, free-flowing granules with a relatively narrow size distribution (500-1500 μm) [4] since it offers some important pharmacological as well as technological advantages [5, 6]. In the present study, Extrusion-Spheronization method was adopted for the preparation of sustained release pellets of cafadroxil. Extrusion-Spheronization may be defined as a process in which a wet mass is extruded through a specific sieve with fixed diameter and subsequently spheronized into spherical particle called as spheroids, pellets or beads depending upon materials and process used for Extrusion – Spheronization [7].

Drug Selection

The half-life of cefadroxil is about 1.5 hours and dosing frequency is about 0.5 to 1g (every 12 hrs) modified release multiple unit preparation. To reduce the frequency of administrations and to improve patient compliances, cefadroxil is suitable for making sustain release dosage form such as pellets.

Polymer selection

Ethyl cellulose and HPMC K100 M is selected as sustained releasing agents for the formulation of sustained release pellets. Ethyl cellulose and HPMC K100 M is a non-toxic, biocompatible, hydrophobic and cost effective and also reduces the risk of systemic toxicity due to dose dumping. ethyl cellulose and HPMC K100 M remains same but the release pattern is found to be changed as the porosity and viscosity of ethyl cellulose and HPMC K100 M differs. So, they were used to sustain the release of the drug according to specification given in USP.

Selection of Binder for Preparation of Pellets[8]

Pellets prepared without binder (i.e. only with water) & with binders i.e. HPMC K4M, HPMC K15M (in water) were

observed for their consistency and strength. Among the binders used, HPMC K4M was chosen on the basis of good consistency of the mass to be extruded and spheronized. Mass of HPMC K15M did not get spheronized due to its relatively higher viscosity. The effect of binder on extrusion and spheronization ability is shown in Table 1.

Table 1: Selection of Binder

Binder (solvent)	Concentration (w/v)	Response
----- (Water)	- - -	No extrudability due to very low binding force
HPMC K4M (water)	1-3 %	Good consistency and extrudate formed
HPMC K15M (water)	1-3 %	Improper extrudates due to high viscosity, Not spheronizable

Binder Level Optimization (HPMC K4M) [9]

Binder solution of HPMC K4M was prepared in the concentration range 1-3%. Response was analyzed for consistency of the damp mass and its ability to form proper extrudates and spherical pellets with smooth surface. HPMC K4 as a binder with concentration of 1% and 1.5% failed to extrude because of its poor binding capacity. At binder concentration of 2%, it was observed that the damp mass extruded and spheronized well to provide spherical pellets due to optimum binding capacity and plasticity. At concentration of 2.5%, it was found to give good extrudate but failed to spheronize because of its high viscosity. Concentration of 3% was unable to extrude due to stickiness and high viscosity. Hence, binder concentration of 2% was selected for further study. The effect of binder concentration is shown in Table 2.

Table 2: Binder Level Optimization (HPMC K4M)

Binder Concentration (% w/v)	Response
1%	Failed to extrudates
1.5%	Improper extrudates
2%	Good extrudates and spheronizable
2.5%	Good extrudates, unable to spheronizer
3 %	Sticky extrudates

Material and Methods

Preparation of cefadroxil pellets

Cefadroxil sustained release pellets were prepared by a laboratory scale mini melt extruder and spheronizer by extrusion and spheronization technique. All the ingredients of sustained release pellets (F1-F8) were passed through the sieve no 40 and weighed according to the formulation. Ingredients were blended for 10 min. Adequate volume of binder solution was then added to the powder mixture and the mass was kneaded for 10 min of time after binder solution addition. Finally, the dry powder was made into dough mass [10].

Extrusion

The wet powder mass was immediately extruded at 25 rpm through a radial screen with a 1mm aperture screen.

Spheronization

A radial plate spheronizer with a plate diameter (12cm) was used. The friction plate speed in the spheronizer was maintained at 1000 rpm. The was spheronized for 20 min. the wet pellets were dried in a hot air oven at 40^0 c for 12 hours and then stored in desiccator [10].

Table 3: composition of cefadroxil SR pellets

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Cefadroxil (30%)	1.5gm	1.5gm	1.5gm	1.5gm	1.5gm	1.5gm	1.5gm	1.5gm
HPMC K100 (10%)	0.5gm	0.5 gm	0.5gm	0.5gm	------	-----	------	-----
Ethyl cellulose (10%)	-----	----	-----	--------	0.5gm	0.5gm	0.5gm	0.5gm
PEG 4000(1-3%)	------	0.05gm	0.10gm	0.15gm	------	0.05gm	0.10gm	1.15gm
MCC (58-60%)	3gm	2.95gm	2.9gm	2.85gm	3gm	2.95gm	2.90gm	2.85gm
2% HPMC K4M (w/v) in water	q. s	q. s	q. s	q. s	q.s	q. s	q. s	q. s

Melting Point Determination [11]

Melting point of the drug was determined by using melting point apparatus (Thiele's tube). This was compared with the literature melting point value of drug

Compatability study of drug with excipients [11].

FTIR study of Cefadroxil with excipients

FTIR spectra of the selected formulation were taken and compared with the spectrum of pure drug. The characteristic peaks of drug were checked in the formulation spectra.

Characterisation of pellets [11]

Shape

Shape and morphological features of pellets were observed by shape and size.

Angle of repose

The angle of repose of Cefadroxil pellets was determined by the funnel method (Repos gram). The accurately weighed quantity of pellets was taken in a funnel. The pellets were allowed to flow through the funnel freely onto the surface. The diameter of the pellet cone was measured and angle of repose was calculated using the following equation.

Angle of repose (θ) = $\tan^{-1}$ (h/r)

Where h and r are the height and radius of the pellets cone, respectively

Determination of bulk density and tapped density

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_0) was measured. Then the graduated cylinder was set into the density determination apparatus. The density apparatus was set for 100 taps and after that, the volume was measured. The bulk density, and tapped density were calculated using the formulae**.**

Bulk density = Mass of the pellets/ Bulk volume

Tapped density = Mass of the pellets / Tapped volume

Flow rate

30 grams of pellets were filled in a glass funnel with a 6 mm internal stem diameter fixed on a clamp. The time was

recorded from when the pellets started to flow until finish. Flow rate was expressed as g.s-1.

Compressibility index (Car's indices) Carr's compressibility index
Compressibility indices are a measure of the tendency for arch formation and the ease with which the arches will fail. It is calculated by using the formula,

Carr's index (%) = [(TBD – LBD) x 100]/TBD
Where,
TPD is Tapped bulk density LBD is loose bulk density

Hausner's Ratio
Hausner's ratio was measured by the ratio of tapped density to bulk density.

Hausner's ratio = Tapped density/ Bulk density

Friability
The friability of pellets was determined by using USP friability tester. Friability of the pellet formulation was evaluated over 5g sample in Roche friabilator at 25rpm for 4min. Prior to and following the test, the weights of the formulation were accurately recorded and friability ratios were calculated with the given equation

$F = W_1\text{-}W_2/W_1 \times 100$

Where, W1 = Initial weight of the formulation,
W_2 = Final weight of the formulation

Loss on drying:
The empty crucible was taken and it is dried for about 30 minutes and weighed (W1), place the sample 1gm and again crucible was weighed (W2), now the crucible was kept in furnace for about one hour which is maintained at a temperature of 250-300^{0}C. Now the crucible is taken out from the furnace and kept for cooling in desiccator. After the crucible was cooled it is again weighed (W3). Now LOD is calculated in percentage using the following formula.

LOD = W2-W3/ W2-W1 X 100

Where,
W1= weight of empty crucible,
W2= weight of crucible+ weight of the sample,
W3= weight of crucible+ weight of the sample (after drying).

Assay by UV
Standard Preparation
Transfer an accurately weighed quantity of about 100mg of Drug to 100ml volumetric flask. Make up the volume to the mark with buffer solution of pH-6.8 and mix. Transfer 5ml of the above solution to 50ml volumetric flask and make up with buffer solution of pH-6.8

Sample preparation
Weigh a quantity of pellets equivalent to 200mg of cefadroxil pellets were taken in mortar and pestle. 50mg of powder is taken from mortar and pestle and transfer 50ml volumetric flask. Make up the volume to the mark with phosphate buffer solution of pH-6.8 and mix. Transfer 1ml of the above solution to 10ml volumetric flask and make up with phosphate buffer solution of pH-6.8

Procedure
Measure the absorbance at the wave length of maximum at about 263nm using filtered portions of the solution under test, in comparison with the standard solution, using buffer solution of pH-6.8 as the blank and calculate as per the below formula.
Total weight of ingredients in formulation is 5000 mg and the drug weight is kept constant to 1500 mg.

$$Theoritical\ yield = \frac{wt\ of\ drug\ in\ mg}{wt\ of\ excipients\ in\ mg} \times wt\ of\ crushed\ pellets\ taken\ in\ mg$$

$$Theoritical\ yield = \frac{1500\ mg}{5000\ mg} \times 25\ mg = 7.5\ mg$$

Therefor Theoretical yield = 7.5 mg

Practical yield = Concentration of sample (µg/ml) × dilution factor × volume / 1000

Assay = $\frac{practical\ yield}{theoritical\ yield} \times 100$

***In-vitro* release study [12].**
In-vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consists of 900 ml of pH 6.8 phosphate buffer for 12 hours, maintained at 37 ± 0.50^{0}C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Labindia, Mumbai, India) at 263nm.

Kinetic analysis of in-vitro release rates of controlled release pellets of Cefadroxil
The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows: -

1. Zero - order kinetic model – Cumulative % drug released versus time.
2. First - order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model - Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa„s model - Log cumulative percent drug released versus log time.

Results and discussion
Melting Point Determination
Melting point was found to be 197^{0}C and it is within the range specified in the official limits.

Compatibility Study
Compatibility study is important to understand the interaction between the drug and polymers. It saves costs and it makes easier to choose a few excipients from the long list of excipients for a better formula. Drug–excipients compatibility studies were carried out at an accelerating condition. A small quantity of each mixture was evaluated by FTIR with the control i.e., the pure cefadroxil and the excipients were studied. It was found that all peaks corresponding to different functional groups of pure drugs

were present in the drug-excipient mixture. That shows the absence of interaction between the drug and excipients studied.

FT-IR Spectroscopy

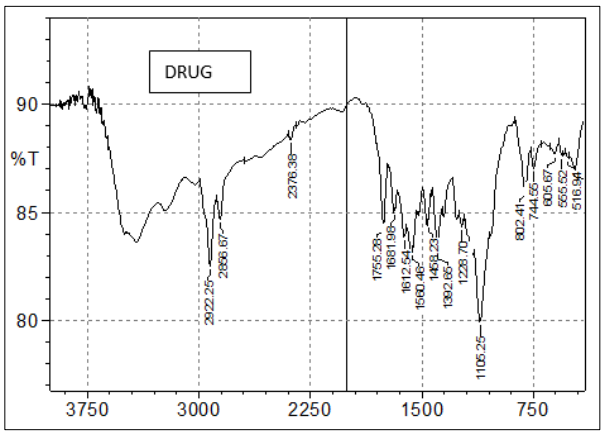

Fig 1: FTIR of pure cefadroxil

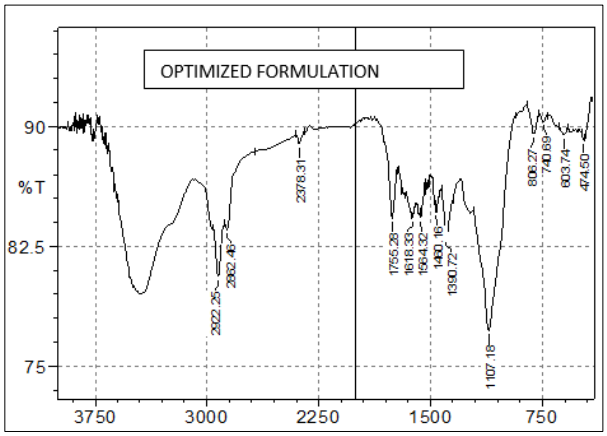

Fig 2: FTIR of optimized formulation F4

Table 4: Drug and formulation frequency of FTIR studies

Functional groups	Frequency		literature
	Pure drug	In formulation	
N-H Stretching	2922.25 cm^{-1}	2922.25 cm^{-1}	3200-2900 cm^{-1}
C-H Stretching	2856.67 cm^{-1}	2862.46 cm^{-1}	3000-2840 cm^{-1}
C=O Stretching	1755.28 cm^{-1}	1755.28 cm^{-1}	1770-1750 cm^{-1}
O-H Stretching	2376.38 cm^{-1}	2378.31 cm^{-1}	3390-2310 cm^{-1}
C-N Stretching	1392.65 cm^{-1}	1390.73 cm^{-1}	1392-1266 cm^{-1}

The above Table 4 identifies the corresponding functional groups of the observed peaks of the drug. For example, as per the literature the absorption peak of C-H stretching 3000-2840 cm^{-1} the absorption peak of C-H group is also retained in the spectra of formulation (2856.67 cm^{-1} to 2862.46 cm^{-1}) similarly the remaining absorption peaks of different functional groups of drugs are retained in the formulation. Hence there is no interaction between drugs and excipients of the pellets.

Formulation development

The present study was undertaken to formulate sustained release cefadroxil pellets with HPMC, ethyl cellulose. Drug coated pellets prepared by extrusion spheronization technique. Initially Analytical method was developed; pre-formulation studies were performed for active pharmaceutical ingredient as well as excipients.

Shape and morphological features

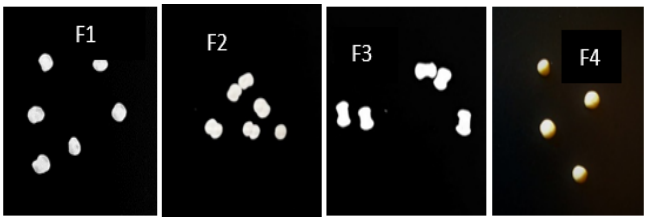

Fig 3: morphology of pellets F1 to F4

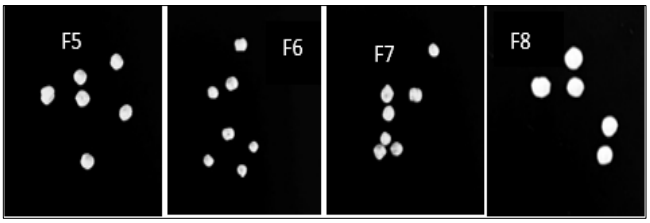

Fig 4: morphology of pellets F5 to F8

Table 5: shape of pellets

Formulations	Shape
F1	Oval + spherical
F2	Dumbbell
F3	Dumbbell
F4	Spherical
F5	Spherical
F6	Oval + Spherical
F7	Oval + Spherical
F8	spherical

Evaluation parameters

The angles of repose of the pellets were in the range of 20.01° to 24.9°. They are particularly sensitive to changes in particle size distribution and to the moisture content, and they provide a rapid means of monitoring significant batch to batch differences in these respects. Values of Carr's Index (Compressibility) below 15% usually give rise to good flow properties but readings above 25% indicate poor flow properties. It was found that the compressibility values of the pellets were below 15% and hence they exhibit good flow characteristics.

The Carr's index (compressibility) of the pellets was in the range of 8.42 to 11.80 (Table 6).

Friability and loss of drying:

The friability of the pellets was found to be less than 1% and it was within the range of standard specification. Loss on drying was found to be in the range of 0.172 to 0.263% (Table 6). It was within the range of monograph specification.

Assay

Assay was conducted for all the batches and it was also found to be in the range of 98 to 99.9% (Table 6)

Table 6: evaluation parameters of Cefadroxil sustained release pellets (F1 to F8)

Parameters	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Angle of repose	20.56º	22.35º	21.2º	23.2º	24.9	20.1º	21.65º	23.48º
Loose bulk density (LBD) (g/ml)	0.350	0.282	0.270	0.279	0.262	0.262	0.276	0.268
Tapped bulk density (TBD) (g/ml)	0.390	0.310	0.295	0.295	0.261	0.289	0.296	0.291
Compressibility index (%)	10.25	9.032	8.474	8.42	10.02	9.342	6.756	7.903
Hausner's ratio	1.114	1.099	1.092	1.057	1.002	1.103	1.072	1.085
Flow rate (g/s)	9.235	7.843	7.625	7.389	7.262	8.913	8.782	8.478
Loss on drying (%)	0.263	0.199	0.249	0.198	0.249	0.198	0.235	0.242
Assay (%)	98.2	98.68	97.32	99.15	98.3	99.5	99.35	99.97

In-vitro release studies

In-vitro release studies were carried out for all the formulations as per USP XXII tablet dissolution tester employing paddle at 50rpm. These studies were conducted for 12 hours in 6.8 pH phosphate buffer. The results were evaluated for 12hrs. The results of all the formulations for different tests found to be within the limits.

The dissolution test was carried out for all the formulations. F4 release was found to 98.86 at 12 hours which is due to the concentration of polymer. The further formulations were prepared by changing the PEG 4000 along with MCC concentration. F4 formulation was found to be greater release of drug were the ratio of drug and polymer concentration was used to be at 2:1:3 ratio of drug: polymer: spheronizing aid.

Table 7: *In vitro* drug release of Cefadroxil F-1 to F-4.

Time In Hours	F1	F2	F3	F4
0.5	10.52	12.54	13.71	15.65
1	12.25	18.76	15.99	23.85
2	22.5	26.34	28.64	31.83
4	28.59	35.66	32.03	55.64
6	36.2	52.20	65.57	65.75
8	46.3	63.89	70.52	83.83
10	47.85	70.96	89.13	89.34
12	60.6	89.23	95.51	98.86

Table 8: *In vitro* drug release of Cefadroxil F-5 to F-8

Time In Hours	F5	F6	F7	F8
0.5	13.82	14.44	19.96	20.41
1	17.65	24.68	32.48	36.8
2	36.5	47.85	48.79	61.95
4	50.45	60.12	56.66	70.40
6	56.51	67.32	61.54	86.22
8	62.6	73.24	68.86	90.12
10	67.85	77.53	72.36	92.81
12	70.2	81.75	84.20	93.90

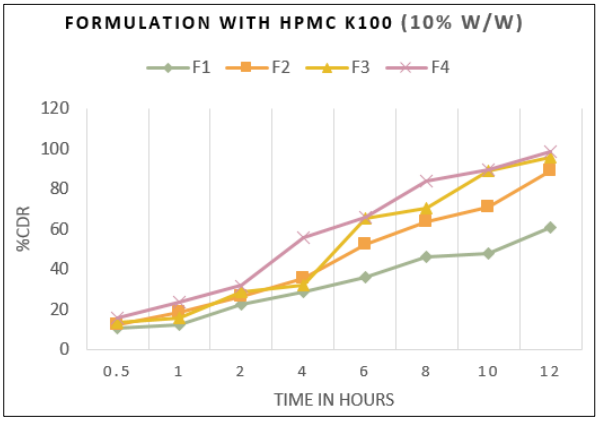

Fig 5: *In-vitro* Drug release profile of Cefadroxil formulations F1-F4

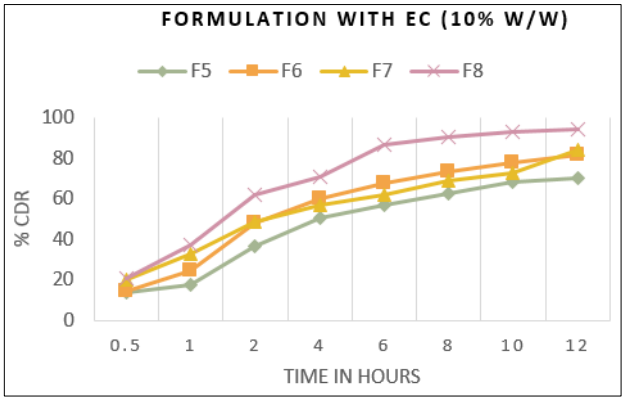

Fig 6: *In-vitro* Drug release profile of Cefadroxil formulations F5-F8

Release Kinetics

The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations F-1 to F-8 could be best expressed by zero order equation as the plots showed highest linearity (R^2: 0.879 to 0.992), then first order release kinetics (R^2: 0.814 to 0.938)

Table 9: Co-relation coefficients of different mathematical models for formulations F-1 to F-8.

Formulation Code	Zero order R^2	First order R^2	Higuchi R^2	Peppas-model	
				R^2	Slope N
F1	0.967	0.9313	0.9625	1.000	0.0266
F2	0.918	0.9888	0.9424	0.9967	0.4839
F3	0.9031	0.9525	0.8012	0.9938	0.7266
F4	0.9668	0.86	0.9668	0.8912	0.724
F5	0.998	0.895	0.998	0.998	0.693
F6	0.9305	0.956	0.9737	0.9848	0.8605
F7	0.9362	0.9654	0.9617	0.9847	0.4004
F8	0.945	0.932	0.9983	0.9976	0.4432

Table 10: Kinetic fitting model for optimized formulation (F4).

Time	Log Time	Sqrt	% cdr	Log % Cdr	% crr	Log of % drug unreleased
1	0	1	23.85	1.377	76.15	1.886
2	0.30	1.41	31.83	1.50	68.17	1.833
4	0.60	2	55.64	1.74	44.36	1.645
6	0.77	2.44	65.75	1.81	34.25	1.534
8	0.90	2.82	83.83	1.92	16.17	1.208
10	1	3.16	89.34	1.95	10.66	1.02
12	1.07	3.464	98.86	1.99	1.144	0.056

Conclusion

In this study sustained release pellets of cefadroxil was prepared by extrusion and spheronization technique, using HPMC K100M, Ethyl cellulose as polymers alone as retardant material. FTIR Indicates no incompatibility

between drug and polymer. In the initial trial formulations are done using 15% on HPMC K100 and Ethyl cellulose, these polymers did not allow complete release of drug within 12 hours, later the polymer concentration decrease to 10%. with also did not give satisfactory result, by keeping 10% of polymer concentration, to modulate the release of drug. PEG 4000 was added in the formulation at different levels. Because PEG 4000 hydrophilic in nature which may enhance the percentage of drug release. It was found that as the concentration of PEG 4000 increased (F1 to F4) the drug release found to be increased and also able to sustain for 12 hours. The formulation F4 containing 10% w/w HPMC K100M with 1.5% of PEG4000 showed good drug release over a period of 12 hours and in-turn the release was found to be within the limits specified in monograph.

The entire pellet formulations showed acceptable quality control properties like loss on drying, drug content uniformity etc. and complied with in the specifications for tested parameters. Thus, formulation F-4 was found to be the most promising formulation on the basis of acceptable pellets properties.

The kinetic treatment of selected optimized formulation shows that the regression coefficient for first-order kinetics were found to be higher when compared with those of the zero-order kinetics, indicating that drug release from all the formulations followed first-order kinetics and the ‘n’ value lies between (0.026 to 0.8421) (Korsmeyer-Peppas model) demonstrating that the mechanism controlling the drug release of formulations F-1 to F-8 was Quasi-Fickian diffusion. Therefore, the results of the kinetic study obtained permit us to conclude that cefadroxil pellets are suitable for oral administration for the purpose of sustain release of the drug.

References

1. Available from: http://pubchem.ncbi.nlm.nih.gov/ compound/47967 (Accessed on 22 May 2021) for drug cefadroxil.
2. Bodmeier R. Tableting of coated pellets. Eur J Pharm Biopharm,1997:43:1-8.
3. Bechgaard H, Nielsen GH. Controlled release multiple units and single unit doses. Drug Dev Ind Pharm,197:4:53-57.
4. Ghebre-Sellassie. Pellets: A general overview. In: I. GhebreSellassie (eds). Pharmaceutical Pelletization Technology, New York and Basel; Marcel Dekker Inc, 1989, 1-13. 13. Bodmeier R. Tableting of coated pellets. Eur J Pharm Biopharm,1997:43:1-8.
5. Marijima T, McGinity JB. Pharm Dev Tech. Extrusion Spheronization as a drug delivery system: A technical note,2000:116:211-221.
6. Bodmeier R. Tableting of coated pellets. Eur J Pharm Biopharm,1997:43:1-8.
7. Mohamed RK, Dinesh BM, Sateesh SB. Development of matrix tablets by extrusion/spheronization process using laboratory extruder: study of the effects of the process parameters. Int J Pharm Pharm Sci,2010:2:203-205.
8. Makoto O, Jian G, Yoshihisa M. Effect of amount added water during extrusion-Spheronizer process on pharmaceutical properties of granules. Drug Dev Ind Pharm,1994:20:29772992.
9. Millili GP, Schwartz JB. The strength of MCC pellets. The effect of granulating with water/ethanol mixture. Drug Dev. Ind. Pharm, 1990, 1411-1426.
10. Farhan MK, Prashanth KP. Formulation and evaluation of Aceclofenac loaded SR matrix pellets: extrusion spheronization. Int J Phar Pharm Sci,2013:5(3):781-9.
11. Kanwar N, Kumar R, Sinha VR. Preparation and Evaluation of Multi-Particulate System (Pellets) of Prasugrel Hydrochloride. Open Pharmaceutical Sciences Journal, 2015, 2(1).
12. Akbar MA, Uddin MM. Formulation and Evaluation of in-Vitro Release Kinetics of Ketoprofen from Coated Pellets Prepared by Extrusion... Journal of Pharmacy Research,2012:5(3):15925.