PHARMACOKINETIC STUDIES OF CEPHALOSPORINS [CEFDINIR] MICROSPHERES

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A B S T R A C T

The prepared microspheres were evaluated for pharmacokinetic release study of sustained release microspheres preparations of cefdinir, using copolymers synthesized from acrylic and meth acrylic acid esters (Eudragit RS 100 and RL 100) as the retardant material.Solvent evaporation method was used by using acetone as solvent, magnesium state as droplet stabilizer and n-hexane was added as cross linking agent for hardening the microspheres. The studies include percentage yield, drug loading and release kinetics.In- vitro release studies were carried in pH 7.4, phosphate buffer. Theobtained microspheres were white, free flowing and spherical in shape. The drug-loaded microspheres showed 74-91% of entrapment and release was studied up to 12hrs. In-vitro release studies showed drug release from microspheres found slow releasing and following zero order kinetics, korsemeyer peppas and Higuchi model. The diffusion exponent "n" specified mechanism of drug release, anomalous transport and non fickian type. The release of cefdinir was influenced by the drug to polymer ratio and particle size showed drug release was diffusion controlled.

Keywords: Cefdinir, Eudragit, microspheres, sustained release.

1. INTRODUCTION

Taking drug for a long period , which can lead to increase in non-compliance. The problem arises due to drugs with short biological half-life,To solve such problems is to find a dosage form capable of releasing the drug gradually. Microencapsulation has been used as one of the methods to deliver drugs for longer period. These particles consist of core material and coating material[1]

Cefdinir is an expanded-spectrum, oral, third-generation cephalosporin antimicrobial agent active against Gram-positive and Gram-negative bacteria. It is used in the treatment of acute chronic bronchitis, rhino sinusitis, and pharyngitis and uncomplicated skin and skin-structure infections in adults and adolescents; it is indicated for acute otitis media, acute sinusitis, and community-acquired pneumonia. Cefdinir requires sustained release because of its short biological half-life of ~1.5 h. Microencapsulated techniques[2] have mostly been used for lipophilic drugs since hydrophilic drugs showed low loading efficiency. The objective of the present investigation was to prepare the sustained release microspheres of cefdinir by improving biological half-life and entrapment efficiency. In this present study, cefdinir microspheres were prepared by solvent evaporation technique using Eudragit RS 100 and RL 100[3] as a matrix polymer which have high permeability through cell membrane and these can be formulated as sustained release dosage forms. Liquid paraffin and acetone system were used for the preparation of microspheres. Magnesium stearate was used as a droplet stabilizer to prevent droplet coalescence in the oil medium and n-hexane was added as a non-solvent to the processing medium to solidify the microspheres. The effect of various processing and formulation factors such as drug to polymer ratio, stirring speed and surfactant concentration on the mean particle size of microspheres was investigated.

2. MATERIALS AND METHOD:

Materials:

Cefdinir was obtained as a gift from MSN Labs Ltd. (Hyderabad, India). Eudragit RS 100 and RL 100 were obtained from Rohm Pharma, GmbH, and Darmstadt, Germany. All other reagents and solvents used were of pharmaceutical or analytical grade

Method: Cefdinir microspheres were prepared by solvent evaporation technique [4]. Different amounts of Eudragit RS, RL and Eudragit RS: RL combination was dissolved in 35 ml acetone separately by using a magnetic stirrer. Pure cefdinir (600mg previously dissolved in 05 ml

methanol) and added in the polymer solution. The magnesium sterate was dispersed in the drug and polymer solution with the help of sonicator. The resulting dispersion was then poured into 500 ml beaker, containing the mixture of 60 ml of paraffin light oil and 10 ml n-hexane with continous stirring at 500-800rpm. The stirring was continued for 3hrs until acetone evaporated completely. After evaporation of acetone, the microsphere formed was filtered using what man no.1 filter paper. The residue was washed with 4-5 times in 50 ml petroleum ether (400 C-600 C) each. Microspheres were dried at room temperature for 24 h. Formulations containing 600mg of Eudragit RS only was assigned batch code as CFD1, formulation with Eudragit RL 600mg as CFD2, RS and RL combinations 350:150mg and 200:200mg were assigned batch code as CFD3 and CFD4 respectively.

Table 1: Formulation Table of Cefdinir Microspheres

Ingredients	CDF1	CDF2	CDF3	CDF4
Cefdinir (mg)	500	500	500	500
Eudragit RS(mg)	500			
Eudragit RL(mg)		500		
Eudragit RS(mg)			350	250
Eudragit RL(mg)			150	250
Acetone	35	35	35	35
Methanol	05	05	05	05
n-hexane	08	08	08	08
Liq.Paraffin light oil	50	50	50	50
Magnesium sterate	62	62	62	62

2. Evaluation of microspheres

Percentage yield [5]

The percentage yield of cefdinir microspheres of various formulations were calculated by using the weight of the final product after drying with respect to the initial total weight of the drug and polymer used .It was calculated as per the formula mentioned.

$$\% \text{ yield} = \frac{\text{Amount of dried microspheres}}{\text{Amount of drug+ Amount of polymer}}$$

Drug entrapment efficiency [6]

About 100 mg of accurately weighed drug-loaded microspheres were added to 100 ml of phosphate buffer, pH 7.4. The resulting mixture was shaken in a mechanical shaker for 24 h. The solution was filtered with a 0.45 µm pore size filter and 1 ml of this solution was appropriately diluted to 25 ml using phosphate buffer, pH 7.4, and analyzed spectophotometrically at 286 nm using UV-Visible double beam Spectrophotometer.

$$\text{Drug Entrapment Efficiency} = \frac{\text{Estimated drug content}}{\text{Theoretical drug content}} \times 100$$

In-Vitro dissolution studies [7]

An accurately weighed amount of drug loaded microspheres are taken for dissolution studies. The study is carried out in USP Type-II apparatus using 900ml of buffer solution with rotating speed of 50 rpm at + 37^0c. First two hours study was carried in pH 1.2 and next 12hrs is carried out in pH 6.8 phosphate buffer. Samples are withdrawn every 1hr interval.1oml of sample is withdrawn from buffer medium, at the same time 10ml of fresh medium was added to maintain sink conditions. The withdrawn sample was diluted and analyzed for cefdinir by UV-visible spectrophotometer at 288nm.

Kinetic analysis of drug dissolution data (Release Kinetics):

The dissolution profile of most satisfactory formulation was fitted to zero order, first order, Higuchi's model and Korsmeyer-peppas model to ascertain the kinetic modeling of the

drug release. The methods adopted for deciding the most appropriate model were: Cumulative percent drug released versus time (zero order kinetic model [8]). Log Cumulative percent drug remaining versus time. (First-order kinetic model) [9] Cumulative Percent drug released versus square root of time (Higuchi's model) Log Cumulative percent drug released versus log time (Korsmeyer-Peppas model [10])

3. RESULTS AND DISSCUSSION

Percentage yield:

The % yield of cefdinir microspheres prepared by solvent evaporation method was found between 82.12-93.43%. It was found that the percentage of yield was more in the combination of Eudragit RS:RL100 formulation when it was compared with RS and RL alone formulation(CFD1&CFD2) .The % yield of CFD1,CFD2,CFD3 andCFD4 was observed 83± 6.30, 86±3.90 ,93.42± 1.87 and 82.12±5.77.

Drug entrapment efficiency:

The drug Entrapment efficiency of all formulations was in the range between 74.42-91.51%. Drug entrapment was more in eudragit combination formulation (RS:RL) .The viscosity of the polymer solution decreases diffusion of the drug in the external phase which results in higher entrapment efficiency.

Table 3: Physicochemical Characterization of Cefdinir Microspheres

Formulation code	Particle size(µm)	PercentageYield(%)	Entrapment efficiency	Angle of Repose(θ)
CFD1	463±17.34	83.45±6.30	91.51±1.42	6.87±2.30
CFD2	544±21.99	86.35±3.90	85.36±1.48	12.45±4.34
CFD3	606±30.61	93.43±1.87	89.33±0.77	10.59±4.57
CFD3	532±15.35	82.12±5.77	74.42±10.11	11.4±2.8

Release Kinetics:

The drug release were subjected for mathematical treatment to check whether the release is following zero order, first order and by incorporating the results in Higuchi and Korsemeyer

peppas model to known whether the release mechanism is diffusion controlled(Fickian or Non fickian) .

Formulation CFD1 was made with 1gm of Eudragit RS100 as rate limiting polymer showed drug release of 77.61% ,while formulation CFD2 was made with Eudragit RL100 and showed a drug release of 90.25%.The of order of release rate observed with various microspheres was CDF1<CDF2<CDF3<CDF4. The dissolution data for all the formulations were given in Table3.

Formulation CFD3and CFD4 was made with combination of Eudragit RS: RL100 and showed a drug release of 93 and90% respectively. The r^2 values of zero and first order plots for formulation CFD1,2,3and CFD4 were 0.934,0.980,0.983,0.953 and 0.863, 0.810,0.765,0.849 respectively. The r^2 values indicate all formulations followed zero order kinetics. The values of co-efficient correlation for all the formulation were fitted to korsemeyer peppas and Higuchi model showed the n values o.902,0.965,0.968,0.965 and 0.845,0.823,0.853,0.926 (CFD1,CFD2,CFD3,CFD4).

The r^2 values are closer to one in the zero order kinetics so it follows zero order kinetics and n value indicates both diffusion and sustained drug release (Non-fickian diffusion).The order of release and mechanism was showed in figures 1, 2, 3&4.

Table 2: In-vitro drug release profile of cefdinir microspheres

Time (hrs)	CFD1	CFD2	CFD3	CFD4
0	0	0	0	0
1	14.47	10.52	12.53	13.92
2	20.53	18.46	18.06	15.18
3	25.19	20.28	25.8	30.95
4	28.91	26.48	30.92	33.88
5	30.47	30.7	34.07	45.65
6	32.46	41.35	40.15	57.78
7	36.11	46	47.19	62.28
8	38.73	52.1	55.11	72.55
9	55.36	69.1	63.34	79.54
10	60.62	71.9	75.23	85.62
11	69.25	86.65	83.4	89.91
12	77.85	90.21	93.79	92.59

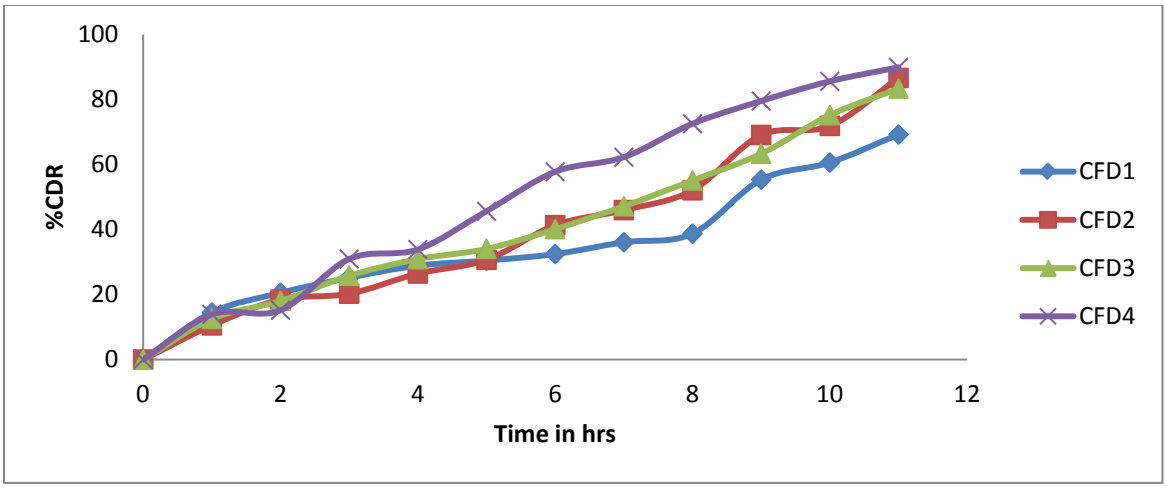

Fig.1 In- vitro percentage drug release profile of cefdinir micro spheres

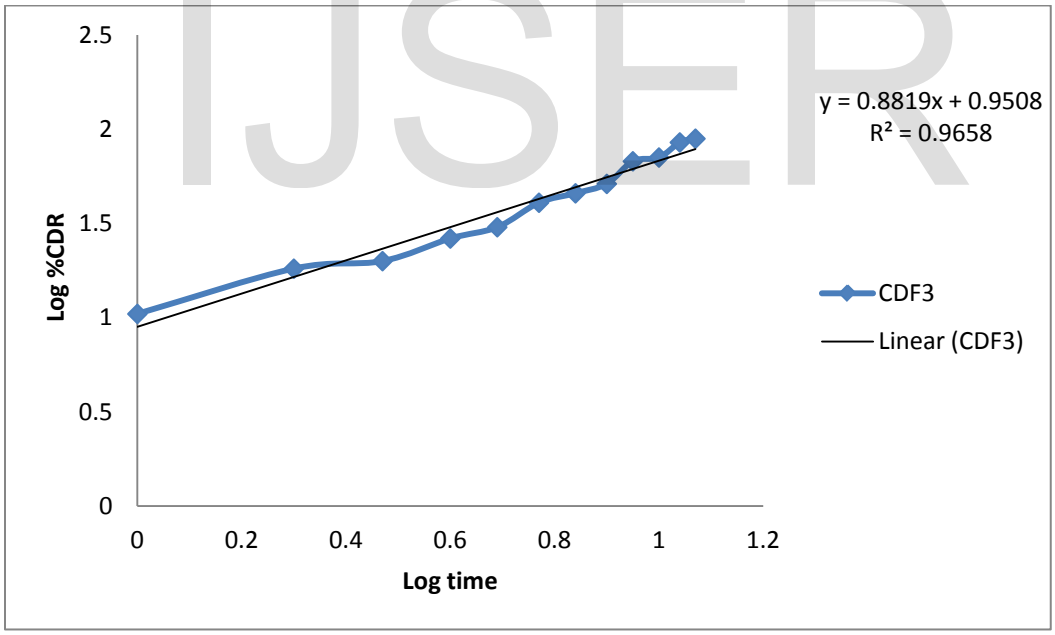

Fig.2 Korsemeyer-peppas Model release kinetics of cefdinir (CDF3)

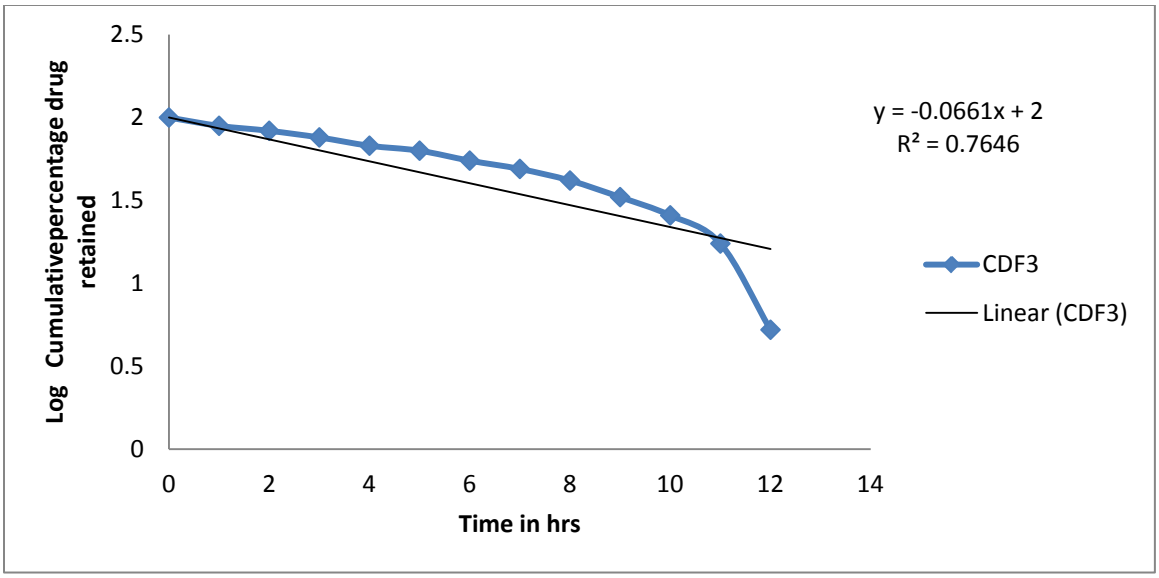

Fig.3 First order release kinetics of cefdinir (CDF3)

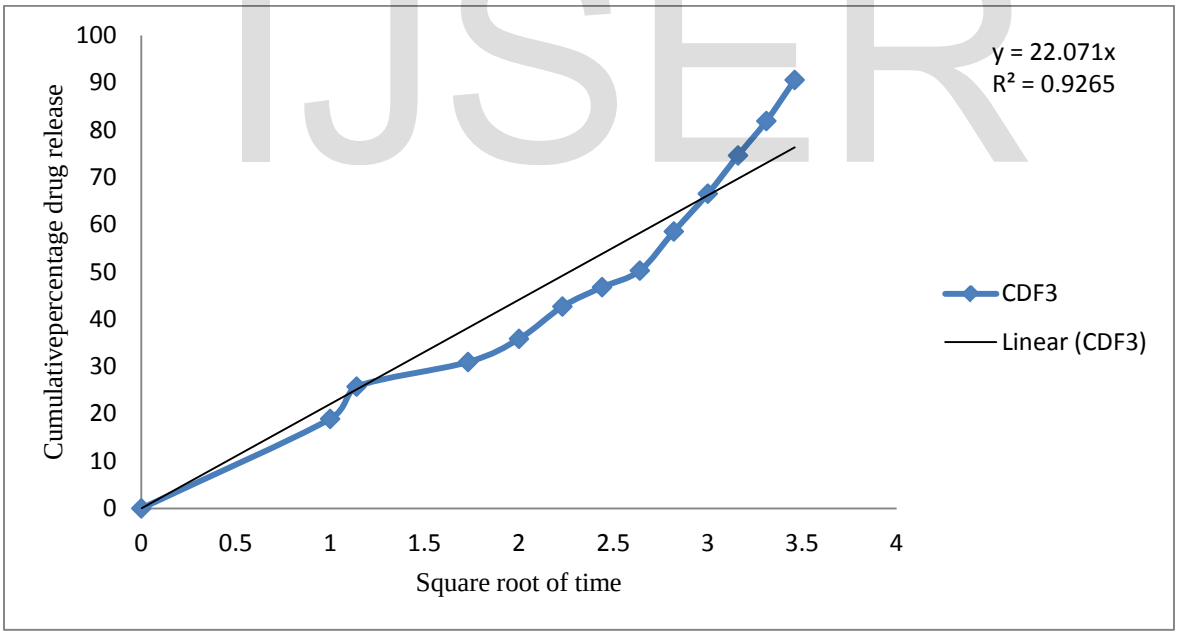

Fig.4 Higuchi Model release kinetics of cefdinir (CDF3)

Conclusion:

Cefdinir release from Eudragit was slow and extended over a period of 12hrs and these formulations were found suitable for oral sustained release formulations. It was observed that the increasing stirring speed decrease mean particle size of microspheres and results showed that average particle size decreased with increasing amount of magnesium state. CFD3 formulation showed highest release of drug and highest r^2 value nearly to one. Higuchi and korsmeyer peppas plot showed highest r^2 and n values for CDF3 formulation. The assessment of the release kinetics revealed that the drug release from cefdinir microspheres followed zero order and korsmeyer peppas model. It was suggested that mechanism of drug release from microspheres was non-fickian diffusion.

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