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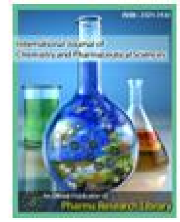

Research Article Open Access

Formulation and *In-vitro* Evaluation of Eudragit® Microspheres of Cefdinir

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A B S T R A C T

The aim of this study was to formulate and evaluate microencapsulated controlled release preparations of a highly water-soluble drug, cefdinir, using Copolymers synthesized from acrylic and methacrylic acid esters (Eudragit RS 100 and RL 100) as the retardant material. Microspheres were prepared by solvent evaporation method using an acetone / liquid paraffin system. Magnesium stearate was used as the droplet stabilizer and n-hexane was added to harden the microspheres. The prepared microspheres were characterized for their micromeritic properties and drug loading, as well by Fourier transform infrared spectroscopy (FTIR), and scanning electron microscopy. The in vitro release studies were performed in pH 6.8, phosphate buffer. The prepared microspheres were white, free flowing and spherical in shape. The drug-loaded microspheres showed 67-91% of entrapment and release was extended up to 6 to 8 h. The infrared spectra showed stable character of cefdinir in the drug-loaded microspheres and revealed the absence of drug polymer interactions. Scanning electron microscopy study revealed that the microspheres were spherical and porous in nature. The best-fit release kinetics was achieved with Higuchi plot followed by zero order and First order. The release of cefdinir was influenced by the drug to polymer ratio and particle size & was found to be diffusion controlled.

Keywords: Cefdinir, Eudragit, microspheres, controlled release, polymethacrylate.

A R T I C L E I N F O

CONTENTS

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1. Introduction

The population of patient with chronic disease or complications of other disease has recently been increasing. These situations necessitate taking drug for a long period and / or multiple medicines simultaneously, which can lead to increase in non-compliance. The problem would be worse for drugs with short biological half-life. One method 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 in a controlled manner. Cefdinir is an expanded-spectrum, oral, third-generation cephem antimicrobial agent active against Gram-positive and Gram-negative bacteria. It is used in the treatment of acute chronic bronchitis, rhinosinusitis, 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 controlled release because of its short biological half-life of ~1.5 h. Microencapsulated techniques have mostly been used for lipophilic drugs since hydrophilic drugs showed low loading efficiency. The objective of the present investigation was to prepare the controlled release, microspheres of cefdinir by improving biological half-life and entrapment efficiency. One method of ensuring high entrapment efficiency of water-soluble active ingredients is to use a hydrophobic processing medium into which the hydrophilic drug molecule is unlikely to migrate out . In this present study, cefdinir microspheres were prepared by solvent evaporation technique using Eudragit RS 100 and RL 100 as a matrix polymer. 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. The prepared spherical microspheres were evaluated for micromeritic properties and drug content, and also by FTIR, SEM as well as for in vitro drug release studies.

2. Materials and Methods

Materials:

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

Methods: Cefdinir microspheres were prepared by solvent evaporation techniques. Different amounts of Eudragit RS or Eudragit RS: RL combination was dissolved in 25 ml acetone separately by using a magnetic stirrer (Remi Equipments, model 2MIH). Pure cefdinir (600mg previously dissolved in 10 ml methanol) and magnesium stearate [100 mg] were dispersed in the polymer solution. The resulting dispersion was then poured into 1000 ml beaker, containing the mixture of 270 ml liquid paraffin light and 30 ml n-hexane, while stirring. A mechanical stirrer with a blade [4 cm diameter] (Remi Motors, Model No.RO-123R, Mumbai) was used. Stirring (at 500-700 rpm) was continued for 3 h, until acetone evaporated completely. After evaporation of acetone, the microsphere formed was filtered using Whatman 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 1, 2 and 3 g of Eudragit RS only were assigned batch code as: FA1, FA2 and FA3 respectively and formulation with Eudragit RS: RL combinations as, 0.8:0.2,1.8:0.2 and 2.8:0.2 g were assigned batch code: FA4, FA5 and FA6 respectively. All batches were prepared in triplicate. Microspheres dried at room temperature were then weighed.

Measurement of Micromeritic properties of microspheres

Measurement of Micromeritic properties of microspheres:

The flow properties of prepared microspheres were investigated by measuring the bulk density, tapped density, Carr's index and packing factor. The bulk and tapped densities were measured in a 10 ml graduated measuring cylinder. The sample contained in the measuring cylinder was tapped mechanically by means of constant velocity rotating cam. The initial bulk volume and final tapped volume were noted from which, their respective densities were calculated. Each experiment was carried out in triplicate.

Drug entrapment efficiency

About 50 mg of accurately weighed drug-loaded microspheres were added to 50 ml of phosphate buffer, pH 6.8. 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 6.8, and analyzed spectophotometrically at 277 nm using Systronic 2101 UV-Visible double beam Spectrophotometer.

Scanning Electron microscopy (SEM)

Scanning electron microscope (JEOL JSM -5200) was used to characterize the Shape and surface topography of the microspheres8. Prior to examination, samples were gold sputtercoated to render them electrically conductive.

Fourier Transform Infrared Spectroscopy (FTIR)

Drug-polymer interactions were studied by FTIR spectroscopy. The spectra were recorded for pure drug and drug-loaded microspheres using FTIR JASIO (Model No. 410). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400-4000 cm -1 and the resolution was 2 cm -1.

Drug release studies

The in vitro release studies of drugloaded microspheres were carried out at 37^0 C and 100 rpm using phosphate buffer pH 6.8 (500 ml) in a USP dissolution apparatus (LABINDIA, DISSO-2000, Mumbai, India) under sink conditions. Accurately weighed samples of microspheres (containing approx. 50 mg of drug, size fraction 250 µm) were added to dissolution medium and at preset time intervals 2 ml aliquots were withdrawn and replaced by an equal volume of fresh dissolution medium. After suitable dilution, the samples were analyzed spectophotometrically at 277 nm. The concentration of stavudine in test samples was corrected and calculated using a regression equation of the calibration curve.

Release Kinetics

Data obtained from in vitro release studies were fitted to various kinetics equations10 to find out the mechanism of drug release from microspheres. The kinetics models used were zero order, first order, and Higuchi models. The rate constants were also calculated for the respective models.

3. Results and Discussion

Effect of various processing and formulation parameters on mean particle size. It was observed that when the speed of stirrer was below 500 rpm, there was no formation of spherical microspheres. This could be due inadequate agitation to disperse the inner phase in the total mass. Therefore, particles were found to settle at the bottom of vessel. At stirrer speeds of 700-1000 rpm, the resulting high turbulence, caused frothing and adhesion to the container wall. Therefore, the mean particle size of microshperes decreased. The desired spherical microspheres were obtained at stirring speeds of 500-700 rpm. When 50 mg magnesium stearate was incorporated, microspheres were not formed because the low magnesium content failed to prevent droplet coalescence in the oil medium; as a result mean particle size was increased. The mean particle size decreased with increasing amount of magnesium stearate (150 mg). This is probably a consequence of stabilization of the oil droplets with magnesium stearate.

Spherical microspheres were formed when the magnesium stearate content was maintained at 100 mg. When the drug: polymer ratio was 1: 1, there was formation of microspheres with small and irregular size, and as the polymer concentration was increased, solution viscosity also increased, resulting in large particles. Thus, mean particle size also increased. Flow properties of Microspheres the flow properties are expressed in terms of Carr's Index (see Table 1.).

The Carr's index for all formulations was less than 20, which indicates excellent flow compared to the original drug crystals. Also the microspheres were found to exhibit higher packing properties than the original drug crystals. The improvement in flow properties suggests that the microspheres can be easily handled during processing.

Table 1: Physical characteristics of the microspheres.

Batch Code	Yield (%)	Mean Particle Size (µm)	Entrapment efficiency	Carr's Index	Packing Factor
Cefdinir	***	***	***	23.62 ± 0.615	1.27 ± .015
FA1	82 ± 6.30	462 ± 17.34	90.71 ± 1.46	6.87 ± 2.30	1.16 ± 0.023
FA_2	86 ± 3.90	531 ± 21.99	84.35 ± 1.59	12.45 ± 4.39	1.02 ± 0.083
FA_3	92.43 ± 1.87	602 ± 30.61	83.67 ± 1.34	12.59 ± 4.57	1.09 ± 0.047
FA_4	81.12 ± 5.77	461 ± 12.66	88.33 ± 0.77	5.74 ± 1.91	1.36 ± 0.023
FA_5	91.93 ± 1.68	544 ± 15	72.42 ± 1.10	7.49 ± 2.78	1.77 ± 0.037
FA_6	90.42 ± 3.78	606 ± 22.69	64.92 ± 1.60	6.55 ± 2.06	1.3 ± 0.026

Scanning Electron Microscopy (SEM)

SEM study shows that particles were spherical. The surface of the drug-loaded microspheres manifested the presence of drug particles (see Fig. 1). The spherical nature and size of the microspheres did not change after the dissolution tests, but the number of pores increased. When a cross section of the microspheres was viewed it showed a spongy appearance.

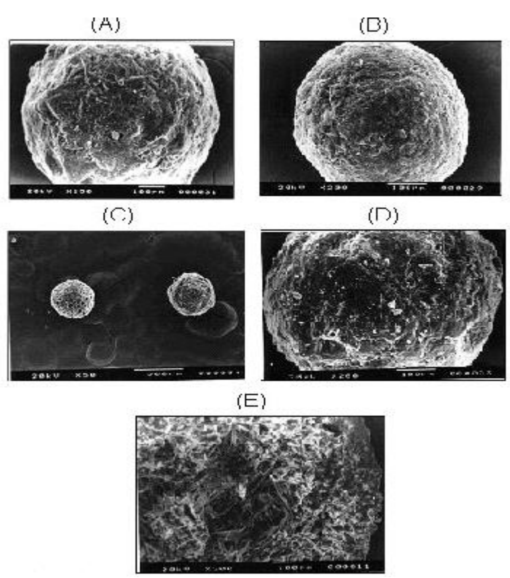

Figure 1: SEM of cefdinir microspheres.

Fourier Infrared Spectroscopy (FTIR)

As shown in Fig. 2, there was no significant difference in the IR spectra of pure cefdinir and drug-loaded microspheres (Both Eudragit RS and RS: RL loaded microspheres). The characteristic OH stretching, NH stretching of secondary amine, C-H stretching and C=O stretching of pure drug was unchanged in case of microspheres. The results suggest drug stability during the encapsulation process.

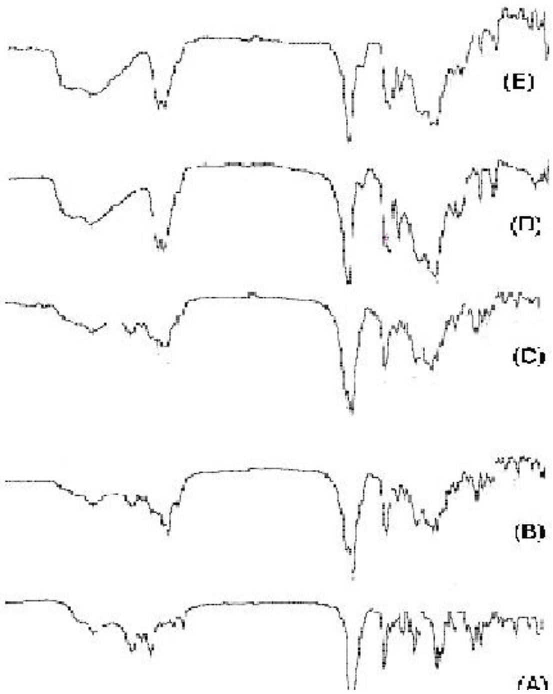

Figure 2: FTIR Spectra of pure cefdinir (A), Eudragits RS loaded microspheres (B), Eudragit RS: RL loaded Microspheres (C), Eudragit RS blank Microsphered (D), Eudragit RS : RL blank Microspheres (E).

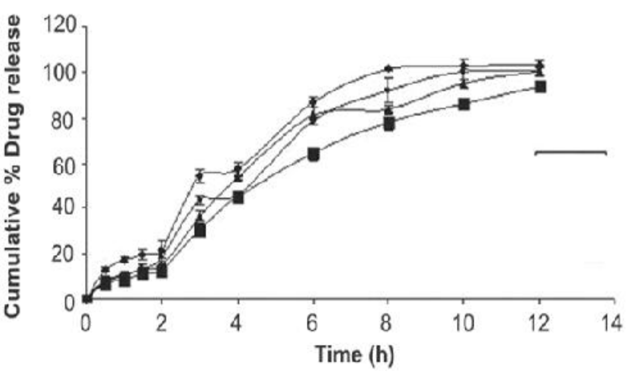

Figure 3: Drug release behavior

Drug release behavior

The pure cefdinir showed a fast release as 98 % was released within 7 min. When it was encapsulated, sustained release up to 8 h was observed. For FA3, It was found that the release rate of drug from size fractions of 355 and 250 µm was faster than that of 500 µm. This is because the smaller the particle size the larger the surface area available for drug release. The drug release from formulation containing Eudragit RS only was slow, but when RL was used in combination with RS, cefdinir release from micro spheres was faster that is: FA4 > FA1, FA5 >FA2 and FA6 >FA3 (see fig. 3). This is due to the fact that the amount of quaternary ammonium groups of Eudragit RS is lower than that of Eudragit RL, which renders Eudragit RS is less permeable. It was also found that as the proportion of Eudragit RS was increased relative to drug concentration, the release rate of cefdinir was decreased due to slower rate of diffusion through the polymer matrix.

Release Kinetics

The release mechanism of cefdinir from various formulations was determined by comparing their respective correlation coefficient. It would appear that the mechanism of drug release from microspheres was diffusion controlled. When the release rate constants of cefdinir microspheres were compared, it was found to follow the following order: FA4 >FA1>FA5>FA6 >FA2 > FA3.

4. Conclusion

Cefdinir microspheres were prepared successfully using the solvent evaporation method. Polymer: drug ratio, stirring speed and the content of magnesium stearate influenced the sphericity of the microspheres. The yield and entrapment efficiency were high for all formulations. It was observed that with increase in polymer concentration, the mean particle size of the microspheres increased but increasing the stirring speed and magnesium stearate content, resulted in a decrease in the mean particle size of microspheres. The assessment of the release kinetics revealed that drug release from cefdinir microspheres followed Higuchi Model. It was suggested that mechanism of drug release from microspheres was diffusion-controlled. Controlled release without initial peak level achieved with these formulations may reduce dose frequency and side effects as well as improve patient.

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