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Formulation and Evaluation of Cefixime Loaded Microspheres for Extended Delivery

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A B S T R A C T

Microspheres of cefixime were prepared using the solvent evaporation method. The effect of different factor such as concentration of ethyl cellulose (polymer) on the characteristics of the microspheres was investigated. The morphology of microspheres was studied using optical and scanning electron microscopy and it was shown that microspheres had a spherical shape and slightly ellipsoidal. The particle size of microspheres analyzed by optical microscopic method was affected by concentrations of ethyl cellulose. When drug to polymer ratio was increased from 1:1 to 1:6, the proportion of larger particles formed became higher, which may be due to increase in viscosity of the solvent with increase in polymer to drug ratio. Larger microspheres showed greater drug loading. For formulation with drug: ethyl cellulose ratio 1:3 (batch M3) drug release was optimum. It revealed that increase in concentration of ethyl cellulose decreases the drug diffusion from microsphere.

Keywords: Cefixime, Ethyl Cellulose, Microspheres, SEM

A R T I C L E I N F O

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1. Introduction

The term microsphere is defined as a spherical particle with size varying with diameters in the micrometer range (typically 1µm to 1000µm), containing a core substance. The microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally having a particle

size less than 200 micrometer [1,2]. Cefixime trihydrate is a third generation cephalosporin antibiotic with bactericidal activity and used in the treatment of uncomplicated UTI, otitis media, pharyngitis [7], acute bronchitis and uncomplicated gonorrhea. Cefixime trihydrate having pKa value of 2.5 is a weak acid which will remain unionized at acidic pH thus increases absorption in the stomach region[4-6]. It is primarily absorbed from the stomach and upper part of intestine. In view of this absorption characteristic, the hypothesis of current investigation is that if the gastric residence time of Cefixime trihydrate containing formulation is prolonged the oral bioavailability might be increased. Cefixime trihydrate is not soluble in water after its oral administration [3,8,10], it is slowly and incompletely absorbed from the gastrointestinal tract, which resulting into the poor bioavailability around 40- 50 %. So, in order to improve the therapeutic effect of the drug by increasing its bioavailability [12], safe and effective levels are to be maintained for a long period time. It gives constant blood levels of active ingredient as compared to uncontrolled fluctuations observed when multiple dosage of quick releasing conventional dosage forms are administered to a patient [9,11].

2. Material and methods

Materials:

Cefixime trihydrate was received from MSN chemicals, Hyderabad, ethyl cellulose received from Biomedicare Pvt.Ltd., Ahmedabad, Polyvinyl alcohol& other material are received from Loba chemicals Pvt.Ltd., Mumbai.

Methods:

Preparation of Microspheres:

Microspheres were prepared by Solvent evaporation method. [7] Here, ethyl cellulose (EC) was dissolved into a 8 ml mixture of dichloromethane: ethanol in a ratio of 1:1. Then, required amount of drug was added to EC solution by stirring with a magnetic stirrer. The resultant solution was poured into 100 ml 2% polyvinyl alcohol solution, in a 250ml beaker. The resulting microspheres were filtered through whatman's filter paper. The residue was washed 4-5 times in distilled water each. Microspheres were dried at room temperature for 24 hrs.

Evaluation of Microspheres Percentage yield:

Prepared microspheres were weighed after drying, and percentyield was calculated by formula. The yield was calculated as the weight of the microspheres recovered from each batch divided by total weight of drug and polymer used to prepare that batch multiplied by 100. [8]

$$\% \text{ yield} = Yp / Yt \times 100 \quad \ldots\ldots\ldots\ldots (1)$$

Where,

Yp =Practical yield,

Yt = Theoratical yield.

Particle size analysis:

The microsphere size distribution was determined by the optical microscopy method using a calibrated stage micrometer (µm). The size of microsphere was calculated by using this equation. [9]

$$X = 10 \times [(ni \times \log Xi) / N] \quad \ldots\ldots\ldots (2)$$

Where,

X =particle's mean diameter,

ni =number of particle in range,

Xi = the midpoint of range,

N = total number of particles

Drug entrapment efficiency:

The amount of drug entrapped was calculated from the difference between the total amount of drug added and the amount of drug found in the filtered solution. About 100 mg of microspheres were completely dissolved in 500 ml of phosphate buffer solutions (pH 7.4), and stirred for 1h. Then, 2 ml of solution was filtered and the concentration of drug was determined spectrophotometrically by UV. [10, 11] Efficiency of drug entrapment was calculated in terms of percentage drug entrapment (PDE) as per the following formula:

$$PDE = (Pdl/Tdl) \times 100 \quad \ldots\ldots\ldots\ldots\ldots (3)$$

Where,Pdl =Practical drug loading,

Tdl =Theoretical drugloading.

Table 1: Different batches of Microspheres

Batch	Drug (mg)	EC (mg)	Ethanol (ml)	DCM (ml)	PVA (ml)
M1	200	200	4	4	100
M2	200	300	4	4	100
M3	200	400	4	4	100
M4	200	500	4	4	100
M5	200	600	4	4	100

Table 2: Percentage yield, Particle size & entrapment efficiency of cefixime loaded microspheres

Batch	Yield (%) (X ± S.D.)	Particle size (µm) (X ± S.D.)	Entrapment Efficiency (%) (X ± S.D.)
M1	82.66 ± 0.368	143.2 ± 8.30	70.46 ± 0.59
M2	83.85 ± 0.716	167.0 ± 13.7	74.96 ± 0.64
M3	87.13 ± 0.575	234.8 ± 19.3	87.45 ± 0.22
M4	87.38 ± 0.464	200.3 ± 23.3	78.50 ± 0.86
M5	84.93 ± 0.378	267.4 ± 18.6	67.05 ± 0.72

The *In-Vitro* dissolution study

These studies were performed by using USP type II dissolution test apparatus. Dissolution medium used was phosphate buffer (pH 7.4), each 900 ml, temperature was maintained at 37 ± 2°C and 100 rpm stirring was provided for each dissolution study. Cefixime microspheres equivalent to 100 mg of pure drug were used for each dissolution study. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through whatman no. 1 filter paper, concentration of cefixime was determined spectrophotometrically at 288.8 nm. [12]

Scanning electron microscopy (SEM) study

SEM of the cefixime microsphere was performed by scanning electron microscope. The samples were prepared by lightly sprinkling the microspheres powder on a double side adhesive tape which already shucked to on aluminum stubs. The stubs were then placed into fine coat ion sputter for gold coating. After gold coating samples were randomly scanned for particle size and surface morphology. [14, 15]

Table 3: *In-vitro* drug release study of M1 to M5 batches of microspheres

Time (hr)	Cumulative % drug release				
	M1	**M2**	**M3**	**M4**	**M5**
1	18.47±1.09	7.52±1.37	14.06±1.84	23.92±1.82	14.85±1.98
2	20.53±2.32	12.46±2.03	17.06±2.83	26.75±1.48	20.38±1.94
3	25.19±2.12	13.28±1.39	19.80±4.05	30.95±1.05	27.83±2.04
4	28.91±2.23	26.48±1.87	34.07±3.72	35.85±1.93	30.86±2.03
5	30.47±2.45	30.70±1.94	40.15±2.91	42.68±1.73	41.77±3.41
6	32.46±2.78	41.35±3.87	49.19±2.81	46.78±1.83	48.56±3.12
7	36.11±3.09	46.00±5.32	55.11±2.91	50.28±1.82	51.70±1.42
8	38.73±3.94	48.10±2.34	63.34±2.73	58.55±1.09	55.83±1.21
20	55.36±3.72	69.10±1.83	89.40±2.84	81.91±1.89	74.48±1.67
24	60.62±2.86	71.90±2.89	93.79±2.04	91.59±1.92	78.14±1.86

3. Results and Discussion

In preformulation studies we concluded that UV analytical method was found to shown good linearity. The melting point of cefixime was found within range. From the above studies FT-IR, it was concluded that the excipients and drug did not interact with each other and are compatible. Controlled release microspheres were prepared by the solvent evaporation method using a gradually increase in stirring rate and ethyl cellulose concentration, to assess the effect of polymer concentration on the size of microspheres. The batch specifications were shown in Table.1. The mean particle size of the microspheres significantly increased with increasing ethyl cellulose concentration and was in the range 140.2 ± 8.3 to 245.4 ± 18.6and drug entrapment efficiency of all formulations was found to more than 60 % as shown in Table.2. For formulation with drug: ethyl cellulose ratio 1:3 (batch M3) drug release was optimum. It revealed that increase in concentration of ethyl cellulose decreases the drug diffusion from microsphere. The scanning electron micrograph of cefixime loaded microsphere shows that microspheres obtained were slightly ellipsoidal and spherical in shape.

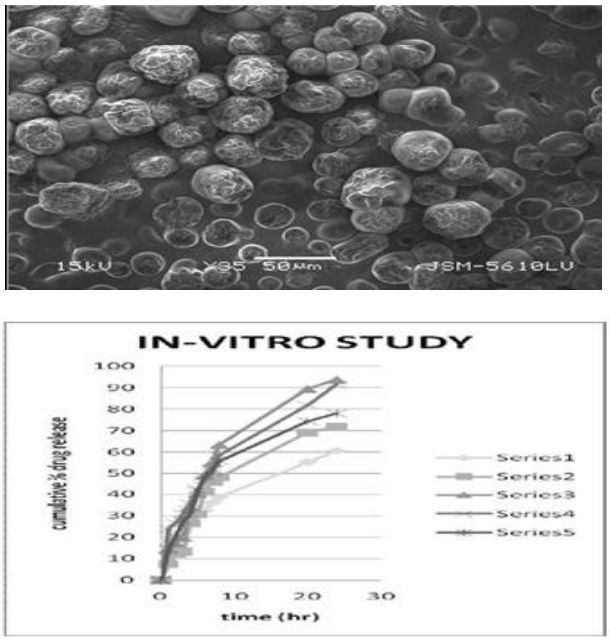

Figure 3: Scanning electron micrograph of cefixime loaded microsphere

4. Conclusion

In-vitro data obtained for microspheres of cefixime showed good drug entrapment and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. Diffusion was found to be the main release mechanism. Thus, the prepared microspheres may prove to be potential candidates for various delivery devices.SEM of cefixime loaded microsphere shows that microspheres obtained were slightly ellipsoidal and spherical in shape.

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