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FORMULATION AND *IN VITRO* EVALUVATION OF CEFIXIME MICROSPHERES

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ABSTRACT

The aim of the present study was to microencapsulate the antibiotic drug (cefixime) to provide sustained release delivery system. Cefixime is a third generation cephalosporin antibiotic which is highly effective against various infections. Microspheres containing cefixime was prepared by ionotropic gelation technique by using different ratios of polymers.(sodium alginate&HPMCK$_4$) . The prepared microspheres were subjected to drug loading, Invitro drug release and scanning electron microscopy. The drug loaded microspheres sodium alginate and HPMCK$_4$ (1:1:3) shows 70-85% drug entrapment. The release kinetics was carried up to 8-12hrs in phosphate buffer (P^H - 7.4) at 270nm.The drug release from microspheres of 1:1:3 ratio shows the most constant and prolonged release. The characteristics of the prepared microspheres are conductive to the formulation of sustained release drug delivery system.

KEY WORDS

Ionotropic gelation, sustained release, cefixime

INTRODUCTION

An appropriately designed controlled release drug delivery system can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size and number of doses required[1]. One approach for controlled release formulation of different polymeric gel beads can increase the bioavailability of drugs. Numerous studies have been reported, concerning the use of alginate beads as a controlled release carrier. Alginate, is a linear unbranched polysaccharide composed of varying proportion of 1, 4-linked beta-D mannuronic acid (M) and alpha- L guluronic acid (G) residues. Alginate has a unique gel-forming property in the presence if multivalent cations, such as calcium ions in an aqueous medium, which takes place mainly at junctions in the G-G sequence rich chain region known as egg box junctions[2]. When divalent metal ions such as calcium, barium diffuse into an alginate solution, the rapid ion binding and formation of a polymeric network produces an inwardly moving gelling zone. In fact alginate moves from the gel core towards this gelling zone, leading to the deletion of the alginate within the core. Varying proportions of HPMC were used in few of the formulations along with alginate as the main polymer. HPMC forms water soluble complexes with several drugs and may be useful in release of drug.HPMC is a biodegradable polymer [3]The low methoxy polysaccharide less than 50%can form rigid gels by the action of calcium ions which cross link the galacturonic acid chains of pectin to yield hydrogels that are stable at low Ph[4]. Sodium alginate has been used as a food additive, an antacid adjuvant, cell immobilizer and viscosifier. Cefixime Trihydrate was taken as a model drug. Cefixime is an orally active third generation semi synthetic cephalosporin type of beta lactam antibiotic. Chemically, Cefixime is 5-Thialazabicy clo [4, 2, 0] oct-2-ene-2-carboxylic acid, 7-[(2 amino 4 thizolyl) (carboxy methoxy) imino] acetyl] amine]-3-ehenyle-80x0, trihydrate. It is soluble in methanol and 0.1M NaoH insoluble water and 0.1M HCL.

MATERIAL AND METHODS

Cefixime Trihydrate was a kind gift from Micro Laboratories Pvt Ltd, Banglore. Sodium alginates, $HPMCK_4$, Calcium chloride were provided by SR College of Pharmacy. All other chemicals were of analytical grade and used without further purification.

Preparation of Microspheres: Four different concentrations of the polymer were used in different formulations. The polymer was used in 1, 2 and 3 percent concentrations. Sodium alginate was dissolve in suitable quantity of delionized water. It was sonicated for 5 minutes. Then after required stirring, cefixime was added to the solution. Then each of these drug suspensions was dropped (10 ml/min) through a syringe nozzle (#22) into calcium chloride solution made in distilled water. Whole of the procedure took place at room temperature. Different concentrations of sodium alginate, HPMC and calcium chloride as well as varying curing times were examined. The obtained beads were filtered using wattman filter papers washed twice by deionized water and dried at 37 degree Celsius for 24 hours.**Table-1** shown different formulations of cefixime microspheres.

Table-1: Different Formulation of Cefixime Microspheres and their Composition Data

S.NO	Ingredients	$F_{1(1:1)}$	$F_{2(1:1:1)}$	$F_{3(1:1:2)}$	$F_{4(1:1:3)}$
1	Cefixime	4	4	4	4
2	Sodium alginate	4	4	4	4
3	$HPMCK_4$	-	4	8	12

CHARACTERIZATION OF MICROSPHERES

1. Particle size measurement:

The size of the prepared microspheres was measured by the optical microscopy method using a calibrated stage micrometer. Particle size was calculated by using equation.

Xg = 10 x [(ni x log Xi)/N]

Where Xg is geometric mean diameter, ni is number of particle in range

Xi is the midpoint of range and N is the total number of particles.

All the experimental units were analyzed in triplicate form (n=3) and data's were given in **Table 2**

Table 2: Mean particle Size, % Yield and Encapsulation efficiency of various formulations

Formulation code	Mean Particle Size (µm) X+S.D	Yield (%)	Encapsulation Efficiency X+S.D
F1	41.360+ 0.016	97.56 + 0.023	98.61 + 0.22
F2	23.78 + 0.031	88.71 + 0.015	82.03 + 0.19
F3	37.22 + 0.021	90.23 + 0.019	98.23 + 0.14
F4	38.85 + 0.015	70.13 + 0.012	60.05 + 0.17

2. Determination of drug content:

Drug content of microspheres was determined by UV-Vis spectrophophotometer (Shimadzu UV 1700). The weighed amounts (100 mg) of drug-loaded polymer microspheres were powdered and suspended in 100 ml methanol: water (1:99 v/v) solvent system. The resultant dispersion was kept for 20 min for complete mixing with continuous agitation and filtered through a 0.45 µm membrane filter. The drug content was determined. Spectrophotometrically (UV-Visible-1700, Shimadzu, Japan spectrophotometer) at 270nm.

3. Drug entrapment efficiency (DEE) and Percentage Yield:

Drug loaded microspheres were evaluated for percentage yield and the drug entrapment efficiency (DEE). The percentage yield was calculated by the equation. All the experimental units were analyzed in triplicate form (n=3) and data's were given in **Table 2**.

Percentage yield =Weight of microsphere recovered / Weight (drug + polymer) X 100

Drug entrapment efficiency was calculated by the equation.

DEE = (Pc / Tc) X 100

Where –Pc is practical content, Tc is the theoretical content.

4. **In Vitro Drug Release Studies:**

In vitro dissolution studies were performed using USP type I dissolution apparatus (LABINDIA, DISSO-2000, Mumbai, India) at 50 rpm. The microspheres were weighed and filled in empty capsule shells and placed in the basket. The dissolution medium (900ml) consisted of 0.1M hydrochloric acid for the first 2 hours and then changed to phosphate buffer pH 7.4 from 8^{rth} to 12th hour; Temperature was maintained at 37^{0}C±5^{0}C. An aliquot (5mL) was withdrawn at specific time intervals and replenished with an equivalent volume of dissolution fluid. Drug content was determined by UV – visible spectrophotometer (Schimadzu, V-1700 E 23) at 270 nm. The release studies were conducted in triplicate and the results are showed in **Table 3 & Fig 1**.

Table 3: In-vitro drug release studies of Cefixime Microspheres

S.NO	Time	F_1	F_2	F_3	F_4
1	0	0	0	0	0
2	1	06.31	05.55	04.31	02.33
3	2	09.10	08.86	08.34	05.21
4	3	19.25	17.45	13.45	10.34
5	4	25.56	22.71	20.12	19.31
6	5	39.17	35.67	34.55	32.12
7	6	48.12	51.22	40.35	38.01
8	7	68.99	63.72	55.32	50.55
9	8	78.55	69.25	62.81	59.32
10	9	80.12	72.12	68.56	65.32
11	10	83.65	79.33	71.91	69.12
12	11	85.11	82.24	77.32	71.11
13	12	87.11	84.55	84.00	74.32

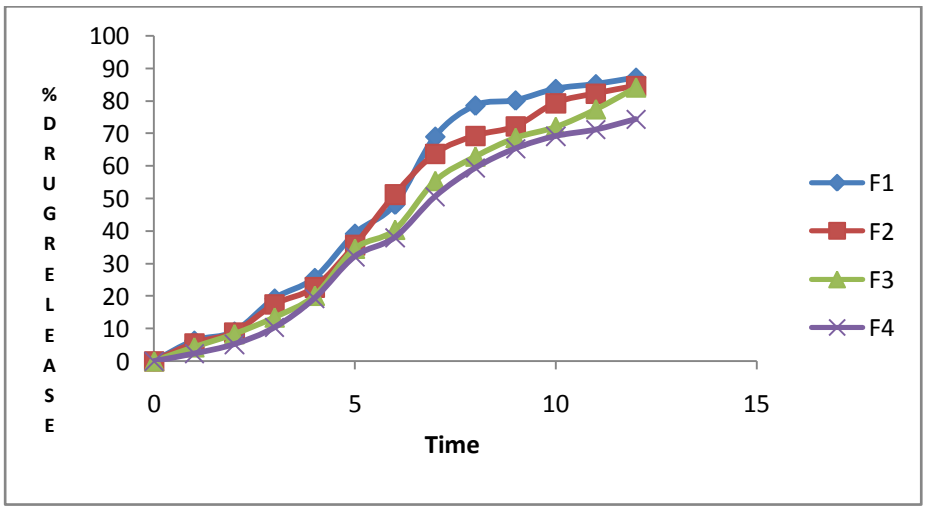

Fig 1: In vitro drug release profile of Cefixime microspheres

RESULTS AND DISCUSSIONS

Cefixime release from the microspheres was studied for 8-12hrs in phosphate buffer 7.4 pH. All the preparations showed good release properties but the F_3 formulation showed sustained drug release because the concentration of the polymer is minimum. When drug release compared with F_2 formulation the drug release was fast due to less amount of polymer and in F_4 formulation the drug release was very low due to high concentration of polymer. The obtained microspheres are smaller in size due this it gets larger surface area for drug release .the formulation F_3 showed the drug release 84.21% in phosphate buffer of pH 7.4 for 12hrs, when compared with other formulations. The yield was high and encapsulated efficiency was good for all preparations but it was higher for F_3 formulation as the polymer concentration increases the particle size increased. The method employed gives spherical, discrete and free flowing microspheres of cefixime. Cefixime released from microspheres was found to be slow and spread over extended period of time, drug release depends on the percentage of coat materials, wall thickness and size microspheres.

CONCLUSION

The yield was high and encapsulated efficiency was good for all preparations, but the F_3 formulation showed sustained drug release because the concentration of the polymer is minimum. The method employed gave spherical, discrete, and free flowing microspheres of cefixime. The size could be readily separated, drug content was found to be uniform in all batches of microspheres. Erythromycin released from microspheres was found to be slow and spread over extend period of time, drug release depends on the percent of coat material, wall thickness, and size of microspheres.

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