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RESEARCH ARTICLE

FORMULATION AND IN VITRO EVALUATION OF CEFIXIME MICROSPHERES PREPARED MULTIPLE EMULSION TECHNIQUE

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ABSTRACT

The purpose of the research work was to prepare and evaluate the microspheres of cefixime as a model drug by multiple emulation method with gelatin as polymer in various proportions. A total of six formulations were prepared i.e. F1, F2, F3, F4, F5 and F6. The microspheres were evaluated for micromeritic properties, particle size, % yield, Drug content and Drug release. The size or average diameter of prepared microspheres was in between 4µm-16 µm. Cefixime release from these microspheres was sustained by various rations of gelatin. The formulation F2 and F5 showed consistent drug release for up to 8 h time period. Among all the formulations, F4 contains gelatin ratio (1:4) showed the reproducible results with best release profile and good surface morphology.

KEYWORDS: Cefixime, gelatin, Tween-20, isopropyl alcohol.

INTRODUCTION:

Microencapsulation for oral use has been employed to sustain the drug release and to reduce or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This result in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Microencapsulation is used to modify and retard drug release. Due to its small particle size, are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa.[3,4]. The conventional dosage forms of cefixime (MCP) contains drawbacks like dose related side effects like Stomach upset/pain, diarrhea, nausea, gas, headache, or dizziness may occur. Micro encapsulation can be described as a process in which contain of polymeric material are deposited around particles of solids.

Microencapsulation technique produces the two most common types of products.

1. Microcapsules
2. Microspheres

PREPARATION OF MICROCAPSULES: [7]

PHYSICAL METHODS:

1. Pan coating
2. Air-suspension coating
3. Centrifugal extrusion
4. Vibrational Nozzle

PHYSICO-CHEMICAL METHODS: [8]

1. Coacervation-phase separation:

Process consist 3 steps carried out under continueous agitation.

1) Formation of 3 immiscible chemical phases.
2) Deposition of coating.
3) Rigidization of coating.

1) Formation of 3 immiscible chemical phases: - Liquid manufacturing vehicle phase, core material phase & coating material phase.

2) Deposition of coating:- Core material is dispersed in the coating polymer solution coating polymer material coated around core. Deposition of liquid polymer coating around core by polymer adsorbed at the interface formed between core material & vehicle phase.

3) Rigidization of coating:- Coating material is immisible in vehicle phase & it gets rigid form It done by thermal, cross-linking, or dissolvation techniques.

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CHEMICAL METHODS:

1. Interfacial polycondensation
2. Interfacial cross-linking
3. In-situ polymerization
4. Matrix polymerization

The aim of the work is to formulate the gelatin microspheres contain cefixime .gelatin was selected because it is cheap and free from toxicity. In the present work the microspheres prepared by co- acersavation phase separation technique to encapsulate cefixime.

MATERIALS AND METHODS:

All the materials are listed in table no: 1,

EXPERIMENTAL WORK:

PREPARATION OFMICROSPHERES: [13]

Formulation of microspheres with drug and polymer various ratios are prepared by multiple emulsion technique through co-acervation phase separation technique. Weight accurately gelatin and dissolve in distilled water and make a clear solution of gelatin which is previously heated to 50^{o}C then add gelatin polymer solution is heated to 50^{o}Cthen ground nut oil also heated to 50^{o}C seperately.add previously sieved cefixime powder.Stirr the mixture to form a fine emulsion. To the oil phase add tween-20.Then this mixture was poured into the water bath with continuous stirring then the emulsion was cool to 10^{o}C by using ice bath for 3hrs, then place in fridge for 24hrs.then the phase is separated at low temperature.After the formed microspheres obtained by washing with isopropyl alcohol. Excess oil is removed by isopropyl alcohol with the help of vacuum pump. The oil free microspheres are obtained and dried at room temperature for one day. Six batches of microspheres were prepared by taking drug: polymer ratio as 1:1, 1:1.2, 1:3, 1:4 1:5, and 1:6with cefixime as drug and gelatin polymer.

EVALUATION OF MICROSPHERES:

MICROMERETIC PROPERTIES:

PARTICLE SIZE ANALYSIS: [9, 10]

Microsphere size was determined by using an optical microscope under regular polarized light, and the mean microsphere size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer. The average particle size was determined by using the Edmondson's equation.

Dmean= Σ nd/ Σ n

Where, n =number of microspheres observed,
d = mean size range.

The particle size of Micro spheres was given in table -3

DETERMINATION OF BULK DENSITY:

Transfer known quantity of microsphers to 50ml of measure cylinder and fix the 100 tapping in the bulk density apparatus. Note down the initial and final volume of microsphers and calculate the bulk density by using Bulk density formula. Bulk density was determined by the following formula.

Bulk density = Sample initial volume/Sample final volume

The bulk density of Micro spheres was given in table -4

TAPPEDBULKDENSITY:

Tapped Bulk density was determined by transferring known quantity of microspheres to 50ml measuring cylinder and tapping 100 times from 1 inch at 2 sec interval. The tapped density was calculated by the following equation:

Tapped density (Pp) = M/Vo

COMPRESSIBILITY INDEX (CI), HAUSSNER'S RATIO:

Carr's index (% compressibility index), Hausner ratio were determined to predict flowability and these can be determined by following equations.

$$\text{Compressibility index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100$$

Haussner's ratio = Tapped density/Bulk density

DETERMINATION OF ANGLE OF REPOSE: [12]

The angle of repose was determined by funnel method. Flow property of microspheres is usually assessed by determining angle of repose of microspheres. The angle of repose was determined according to the following formula.

$$\theta = \tan^{-1}(h/r)$$

Where, h= height of pile
r = radius of the pile formed by the microspheres
The angle of repose of microspheres was given in table -4.

INVITRO DRUG RELEASE STUDIES:

The dissolution studies were carried out usingUSP basket type apparatus at 60 rpm and 37±0.5°C. The microspheres equivalent to 250 mg of microspheres were filled in to basket separately. The dissolution medium phosphate buffer pH 7.4 was selected 5ml of sample solution was withdrawn at predetermined

time intervals, filtered through a Whitman filter paper, diluted suitably and analyzed spectrophotometrically. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Samples were analyzed at 320 nm. The Percentage drug dissolved at different time intervals was calculated using the Lambert-Beer's equation ***(y=0.03194x + 0.01523, R2=0.9989)*** described above. All the results are given in Table no-5.

DRUG ENTRAPMEN TSTUDIES:

The methodology of Levy&Hayes forms the basis of this technique. In their initial work they used a400cm beaker containing 250ml of dissolution medium, which was agitated my means of a three bladder polyethylene stirrer which a diameter of 50mm the stirrer was immersed to a depth of 27mm in dissolution medium and rotated at known times, filter and absorbance was measured at 320nm. Polymer did not interfere with the absorbance of the drug at the specified wavelength. All the results are given in Table no-6.

$$\text{Drug incorporation efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

RESULTS:

MATERIALS:

Table: 1

Sr. No	Ingredients	source
1	Cefixime	gift sample
2	Gelatin	S.D fine Chemicals Mumbai
3	Span-30	S.D fine Chemicals Mumbai
4	Purified water	Daro chemicals Tirupathi
5	Iso propyl alcohol	S.D fine Chemicals Mumbai

EQUIPMENTS:

Table 2:

Equipment's	Model And Manufacturer
Digital balance	Infrainstrumentspvt.LTD, Chennai.
Tablet dissolution test apparatus	Labindia DS 8000 Mumbai.
UV-Visible spectrophotometer	Elico Ltd., SL 150, Hyderabad
Compression machine.	Cadmach Machinery , Kolkata
Roche Friabilator	Campbell Electronics, Mumbai.
Monsanto Hardness Tester	Cadmach, Ahmedabad, India.
Disintegration apparatus	ThermonicCampbellelectronics,
Digital pH meter	Digisum Electronics, Hyderabad.

Particle size analysis:

Table: 3

Parameter	Formulation code					
	F-1	F-2	F-3	F-4	F-5	F-6
Average particle size (µm)	21.3 µm	4.1 µm	20.5 µm	16 µm	10.7 µm	50.1 µm

MICROMERITIC PROPERTIES:

Table: 4

Parameters	Formulation code					
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
Angle of repose	24° 37’	25° 24’	26° 51’	23° 48’	25° 40’	23° 17’
Bulk density (gm/ml)	0.46	0.57	0.49	0.44	0.53	0.52
Tapped density (gm/ml)	0.52	0.64	0.55	0.50	0.61	0.60
Compressibility index (%)	11.53	10.93	10.90	12.00	13.11	13.33

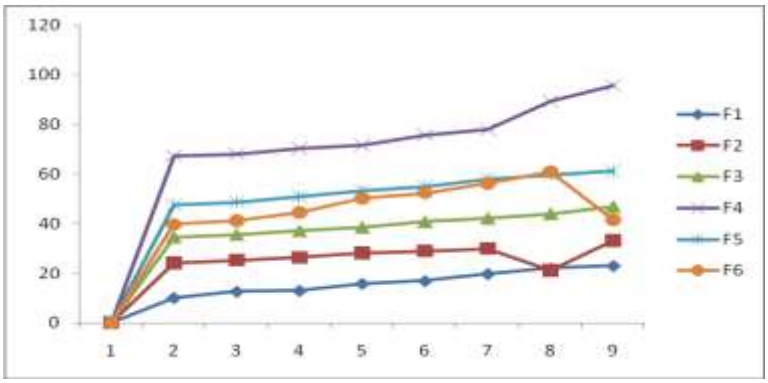
Dissolution Profile of F1-F6 formulations (1:1, 1:2, 1:3, 1:4, 1:5, 1:6 of gelatin)

Table: 5

Time (Hrs.)	F1	F2	F3	F4	F5	F6
1	10.08	24.12	34.56	67.32	47.56	39.72
2	12.62	25.22	35.56	68.04	48.67	41.16
3	12.96	26.28	37.08	70.24	50.91	44.53
4	15.84	28.08	38.52	71.56	53.28	50.19
5	16.92	28.87	40.68	75.67	55.08	52.35
6	19.8	29.88	42.12	77.98	57.96	56.17
7	21.96	20.96	43.92	89.21	59.76	60.94
8	23.04	33.12	46.87	95.67	61.29	41.5

***In vitro* drug release profile of gelatin microspheres formulation F-1 to F-6**

Figure: 1



DRUG ENTRAPMENT:

Table: 6

Parameters	Formulation code					
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
Drug content (%)	38.84	49.71	51.92	74.29	69.25	23.16

SUMMARY:

Various formulations of extended release microspheres of cefixime were developed using various polymer ratios in different proportions and prepared by co-acervation phase separation technique. The microspheres were evaluated for particle size analysis, *in vitro* release study. Observations of all formulations for physical characterization had shown that, all of them comply with the specifications of official pharmacopoeias and/or standard references. Results of in vitro release profile indicated that formulation (F4) was the most promising formulation as the extent of drug release from this formulation was high as compared to other formulations. Results of in vitro drug release study indicate that the formulation F4 was having considerable drug release.

CONCLUSION:

From the above summary it is concluded that formulation of extended release microspheres of cefixime containing gelatin (1:4), batch F4 can be taken as an ideal or optimized formulation of extended release for 8 hour release as it fulfills all the requirements for extended release microspheres.

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