

Preparation of Cefpodoxime Proxetil - Polymeric Microspheres by the Emulsion Solvent Diffusion Method for taste masking

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Abstract: Cefpodoxime Proxetil is a 3rd generation broad spectrum β -Lactam cephalosporin class of antibiotic administered orally in pediatric and adult patients and is extremely bitter in taste. Masking Bitter taste is a major challenge for better patient compliance particularly in an antibiotic treatment where dose and duration is important. Among the various techniques available for bitter taste masking microencapsulation is a useful technique as it has significant advantages over the other techniques. Also a polymer used provides protection to active moiety thereby increasing its stability. Floating Microspheres of Cefpodoxime Proxetil with Eudragit E100 plus HPMC and Eudragit E100 plus PEG were prepared by the emulsion solvent diffusion method to mask the bitter taste of an antibiotic. The effect of different polymers with different drug-polymer ratios on the taste masking and the characteristics of the microspheres were investigated. It was found that Eudragit E100 mask the taste but retard the drug release whereas combination of Eudragit E100 with PEG and with HPMC showed the better result for masking the unpleasant taste of Cefpodoxime Proxetil with floating ability as well as provide good drug release. Prepared microspheres were evaluated for taste masking ability, micromeritic properties, percentage yield, drug content, particle size, FTIR study and in vitro drug release study. Further dry powder for reconstitution was prepared from microspheres with respect to its use in pediatric population. The results of the present study will be helpful for the preparation of oral Dosage forms of Cefpodoxime Proxetil for pediatric population with an acceptable taste.

Key Words: Cefpodoxime Proxetil; Taste Masking; Floating drug delivery system; Microspheres.

INTRODUCTION

Most of the drugs have an unpleasant taste, often very bitter. The major consequence of the bitter taste is poor patient compliance in pediatric as well as adult patients. Particularly in an antibiotic therapy where dose and duration of therapy is important, patient compliance plays significant role in completing the course and thereby achieving required antibiotic concentration. Especially in pediatric population it is not acceptable for useful medicines to taste bitter. Pediatric patient compliance is better for the drugs that have nice taste and can be administered easily. Accordingly, it is important to mask the unpalatable taste of a drug, especially antibiotic in order to improve the

patient compliance and successful completion of therapy.

In order to mask bitter taste, various masking techniques have been described in the literature^{1, 2}. The simplest method is to add flavors or sweeteners which avoid the bitter drugs coming into direct contact with patients taste buds, reversibly anaesthetize patient's taste buds temporarily. Other way is the use of chemical methods by altering the chemical structure of the drug itself to remove the bitter taste without any loss of bioavailability after such modification^{1, 3}. However, in most cases, these are rather limited and may not be effective enough to mask the unpleasant taste of some drugs. A number of more useful approaches have been tried,

including capsule formulations, coating with water-insoluble polymers or pH-dependent water-soluble polymers, absorption to ion-exchange resin, microencapsulation with various polymers, inclusion complexes with cyclodextrins, chemical modification such as turning drugs into their milk-toast prodrugs without any reduction in bioavailability³.

From the various techniques microencapsulation is commonly used because of its significant advantages as far as taste masking is concerned and also polymers used provides protection to active moiety so increases its stability⁴.

In this study, Cefpodoxime Proxetil (CP) microspheres were prepared by a novel technique, called the emulsion solvent diffusion method as shown in figure 1¹, in which the water-insoluble drug and polymer are dissolved in a suitable solvent system mixed. The drug solution is poured slowly into an aqueous medium containing surfactant under constant stirring, and the o/w emulsion droplets are formed as soon as they meet each other. The droplets solidify gradually while the good solvent diffuses out of the droplets into the aqueous medium and finally forms microspheres. This method is suitable because of its feasibility, low cost and no need of any special equipment.

Cefpodoxime Proxetil is a 3rd generation broad spectrum β -LACTAM cephalosporin class of antibiotic administered orally. It is noncrystalline, slightly basic compound and after oral administration is absorbed from the gastro intestinal tract (stomach and duodenum). It has a better solubility in the acidic pH i.e. in the upper GI region which will further increase its absorption⁵⁻⁸. In this study, in order to mask the bitter taste of CP, we tried to prepare drug microspheres with different water-insoluble polymers in combinations using the emulsion solvent diffusion method. All the polymers used here were not regarded as materials for controlling drug release, but simply as taste-masking agents. The influence of all the

materials on taste-masking ability of microsphere was examined here. The drug release rate from the microspheres was monitored by an in vitro release test.

MATERIALS AND METHODS:

MATERIALS

Cefpodoxime Proxetil (CP) was obtained as a gift sample from Maxim Pharmaceutical Ltd. (Pune, India). PEG and Hydroxypropylmethyl cellulose (HPMC K100M) was supplied by Colorcon Asia Ltd. (Goa, India). All solvents used were of analytical grades and were used as obtained.

METHODS

Preparation of microspheres:

All microspheres were obtained by the emulsion solvent diffusion method using distilled water as an external phase, in which 1% of PVA was dissolved as an emulsifier. The internal phase consisted of a good solvent and a bridging liquid including Cefpodoxime Proxetil with combination of polymers. Two combinations of Polymers were used, 1) Eudragit E100 and HPMC 2) Eudragit E100 and PEG

At first, the drug and polymer were co-dissolved in an organic solvent mixture that was composed of ethanol, iso-propyl alcohol (good solvent) and dichloromethane (bridging liquid) in 1:1:1 proportion. The drug solution was slowly injected via a syringe into the external water phase (poor solvent) under agitating. The system was stirred at 800 rpm continuously for about 1 h. Along with the good solvent diffusing into the poor solvent; the droplets gradually solidified and formed microspheres. Then, the system was filtered to separate the microspheres from the preparation system. The resultant product was washed with distilled water and dried. The whole process was carried out at room temperature¹. Ratio of drug and polymers were showed in Table 1.

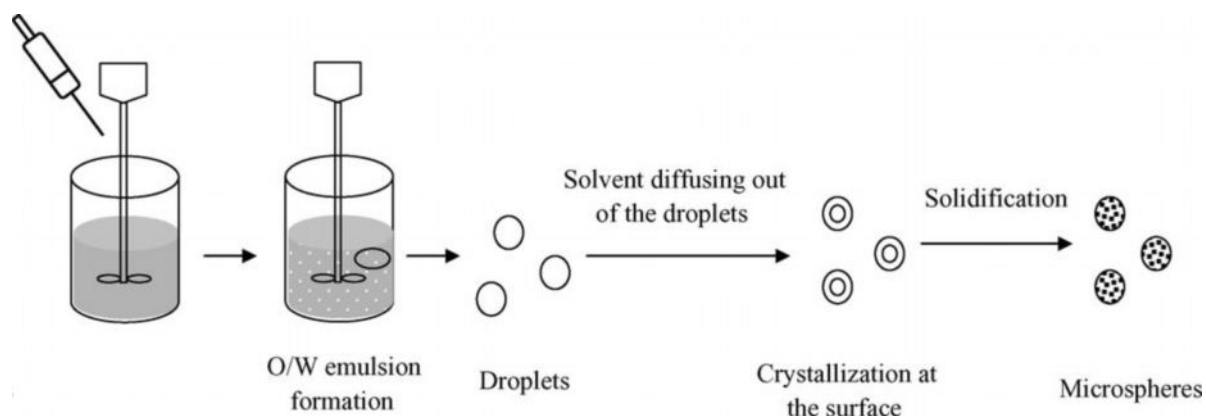


Figure 1: Mechanism of the emulsion solvent diffusion method.

Table 1: Preparation of microspheres

Batch No	Drug: Polymer	Ratio
A	CP: E 100	1:1
B	CP: E 100	1:0.5
C	CP: E 100: HPMC	1:0.1:0.1
D	CP: E 100: PEG	1:0.1:0.1

Assessment of the bitter taste of the Drug and microspheres

Estimation of Bitter taste of CP and CP microspheres

Estimation of bitter taste of CP and CP microspheres was determined based on the bitter taste recognized by the panel of ten healthy human volunteers (five females and five males).

50 mg of CP was dispersed in 5 ml phosphate buffer pH 6.8 and was placed on the tongue of each volunteer and was retained there for 30- 60 sec.

In similar manner microspheres equivalent to 50 mg CP were dispersed in 5ml phosphate buffer pH 6.8 and were placed on the tongue of each volunteer and was retained there for 30- 60 sec and compared with bitterness of pure drug.

Evaluation of the microspheres:

Micromeritic properties:

Prepared microspheres were tested for various micromeritic properties including angle of repose, bulk density, tapped density and carr's index ⁹.

Percentage Yield of Microsphere Formation:

The prepared microspheres were collected and weighed. The yield was calculated by dividing the measured weight by the total weight of all non-volatile components.

The percentage yield of microspheres was calculated as follows. ¹

% Process yield =

$$\frac{\text{Total weight of microspheres} \times 100}{\text{Total weight of drug, polymer}} \text{-----(1)}$$

Floating ability:

Floating behavior of hollow microspheres was studied in a USP dissolution test apparatus by spreading the microspheres (100mg) on a 0.1M HCl containing 0.02% tween 80 as a surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 12 hr, both the floating and the settled portions of microspheres were collected separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres ^{4,10}.

Entrapment Efficiency

10 mg of floating microspheres were dissolved in 10 ml ethanol. The samples were assayed for entrapment efficiency by UV-spectrophotometer (Jasco-V530 and V550) at 263 nm after suitable dilution.

Entrapment efficiency is calculated with the help of following formula ¹.

%Drug Entrapment=

$$\frac{\text{Calculated drug concentration} \times 100}{\text{Theoretical drug concentration}} \text{-----(2)}$$

Table 2: In vivo taste assessment.

Volunteers	CP	Formulation Batches			
		A	B	C	D
1	+++	-	-	-	-
2	+++	-	-	-	-
3	++++	-	-	-	-
4	+++	-	-	-	-
5	+++	-	-	-	-
6	++	-	-	-	-
7	+++	-	-	-	--
8	+++	-	-	-	-
9	+++	-	-	-	-
10	+++	-	-	-	-

-: No bitterness, +: Threshold bitterness, ++: Bitter, +++: Moderate bitter, ++++: Strong bitter

Surface morphology

Size and Shape

Particle size analysis was carried out by using optical microscopy. About 1000 microspheres randomly selected and their sizes were determined by using optical microscope fitted with standard micrometer scale.

The surface morphology of the microsphere was examined by means of scanning electron microscope (*Model JSM 5400, Jeol, Tokyo, Japan*). The microspheres were previously fixed on a brass stub using double-sided adhesive tape and then were made electrically conductive by coating, in a vacuum, with a thin layer of platinum (3–5 nm), for 100 s and at 30 W.

FTIR-studies

Fourier transform infrared (FTIR) spectral data were taken on a (Jasco-430 Plus) instrument using KBr pellet technique to detect the reaction in prepared microspheres. FTIR spectra of the pure CP and prepared microspheres (batch C and D) were determined. All the samples were dried under IR-lamp and then triturated with potassium bromide to get powder blend. Spectral scanning was done in the range between 4000 and 500 cm^{-1}

Differential scanning calorimetry (DSC)

The DSC thermogram of microsphere was recorded using Differential scanning calorimeter (DSC 823 Mettler Toledo, Japan). Samples were accurately weighed onto aluminum pans and then hermetically sealed with aluminum lids. Thermograms were obtained at a scanning rate of 10°C/min conducted over a temperature range of 30-300° C in the environment of liquid nitrogen.

In vitro drug release studies

The drug release testing of the microspheres was conducted by using USP paddle apparatus. It was carried out for 1 h with 900 ml 0.1N hydrochloric acid solution maintained at 37±0.5 °C and agitated at 75 rpm. The amount of the microspheres were equivalent to 50 mg CP. 5 ml of dissolution medium was sampled filtered and diluted at regular intervals to determine the percentage drug release. The drug concentration was determined by calibration curve equation $Y = 0.035x - 0.007$ [$r^2 = 0.998$, $n=5$].

Formulation and evaluation of oral dosage form of taste masked microspheres:

Dry powder for reconstitution to be dispensed as multiple dose bottle was prepared from microspheres. Dosage form is prepared as a dry blend after various trials by adding preservatives, sweeteners and suspending agent and water was

supplied separately as a vehicle for reconstitution at the time of use. It is dispensed as blend sufficient for 6 doses which on reconstitution gives 30ml volume. After reconstitution a bottle is to be stored at 2-10 °C for 5 days till therapy is complete. The most suitable Formula is shown in table no 6. Prepared dosage forms of microspheres prepared with Eudragit E100 plus HPMC and Eudragit E100 plus PEG were evaluated for pH, sedimentation volume and taste.

RESULTS AND DISCUSSION

Bitter taste masking can be achieved by various techniques but in microencapsulation technique, particles of the bitter drug are entrapped in the polymers thereby offering a barrier between drug and taste receptors of the tongue. As a result drug can't bind with taste receptor and therefore taste is not sensed¹¹.

Final dosage form selected is powder for reconstitution for pediatric use. Therefore polymers for microsphere preparation should be able to retain microspheres in original form even after reconstitution for specified duration. At the same time when formulation is administered, it should be able to release the drug in upper GI tract as CP is having absorption window in upper GIT. Eudragit E100 is a cationic polymer based on dimethyl aminoethyl methacrylate and other neutral methacrylic acid esters. It is nonswellable in aqueous fluid and is soluble in acidic pH. Also Eudragit E100 is having well ability of microencapsulation and can formulate floating microspheres. This helps to mask the bitter taste and to maintain microspheres in floating form thereby retaining CP in its absorption window where it has better solubility and stability too. As CP is having its absorption window in acidic pH and Eudragit E100 is also soluble in acidic pH with microencapsulation ability¹², Eudragit E100 is a choice of polymer here.

HPMC and PEG have been widely used as low-density hydrocolloid system; which upon contact with water form a hydrogel layer that acts as a gel boundary for the delivery system and swells at stomach pH¹². Hence HPMC and PEG when used in combination with Eudragit E100 it helps to maintain floating nature of microspheres and also helps to release the drug from microspheres when administered.

Selection of dispersing agent i.e. Polyvinyl Alcohol was done on the basis of solubility criteria in external phase.

Solvent system selected was such that CP and the polymers are soluble in it and also helps to form microspheres and with required size.

All the four batches were evaluated for assessment of the bitter taste and in vitro drug release study. All the four batches showed acceptable taste but only batch C and D showed required drug release. Hence only those two batches were selected for further evaluation.

Assessment of the bitter taste of the microspheres

When microspheres equivalent to 50 mg CP were dispersed in 5ml water and was made to taste by a panel of 10 volunteers, microspheres didn't show any bitterness. This indicates that the polymers must have formed barrier around CP particles and therefore bitter taste is not sensed. DSC studies also shows disappearance of endothermic peak of CP when combined with Eudragit E100. This indicates that CP is uniformly dispersed in the polymer. The dry powder for reconstitution prepared from these microspheres was also made to taste and was not showing any bitterness immediately after reconstitution. It was stored at required condition for 5 days and then tasted again. Even after 5 days no bitterness was sensed. This indicates that the drug is not released prematurely before administration. Also selected polymers can successfully entrap the drug even after reconstitution to mask the bitterness.

Micromeritic properties:

Micromeritic properties of microspheres were evaluated such as bulk density, angle of repose and compressibility (Carr's index) (Table 3). It was found that the flow and compressibility of microspheres were satisfactory. This helps to form free flowing powder blend for reconstitution and

thereby ensuring dispensing of required dose accurately in the bottle.

Percentage Yield of Microsphere Formation:

The percentage yield the microspheres were in the range of 78% to 86.87% all the batches. These showed that production yield is quite satisfactory. (Table 4)

Floating ability:

The floating ability test was carried out to investigate the floatability of the prepared microspheres. The purpose of preparing floating microspheres was to maintain the drug in its absorption window. The microspheres containing polymeric combination of Eudragit E100 with HPMC and PEG showed good floating ability i.e. 83.37% and 81.95% respectively (Table 4). It helps to maintain CP [as microspheres] in its absorption window and this may help to have better absorption.

Entrapment Efficiency

% Drug entrapment in the microspheres includes drug entrapped within the polymer matrices. Entrapment efficiency depends on drug solubility in the solvent system used for processing and also on physicochemical properties of drug. As the CP has maximum solubility in selected solvent system and poorly soluble in aqueous medium, homogeneous solution of drug and polymer obtained for processing and hence drug entrapment was up to its maximum level. The drug entrapment efficiency of microspheres for both batches C and D was 89.56% and 86.06% respectively. (Table 4)

Table 3: Micromeritic properties:

Sr. No.	Property	Batch C	Batch D
1	Bulk density(g/ml)	0.3046	0.2785
2	Tap density(g/ml)	0.3987	0.3012
3	Angle of repose (°)	27.98	28.49
4	Carr's index (%)	6.87	6.44

Table 4: Evaluation aspect of microspheres

Batch Code	Practical Yield (%)	Mean Particle Size (µm)	Drug Entrapment Efficiency (%)	Drug Release (%)	Floating ability (%)
A	86.67	-	-	23.56±2	-
B	84.71	-	-	30.21±2	-
C	78	245	89.56%	99.07±1.5	83.37
D	81.34	253	86.06%	99.68±1.5	81.95

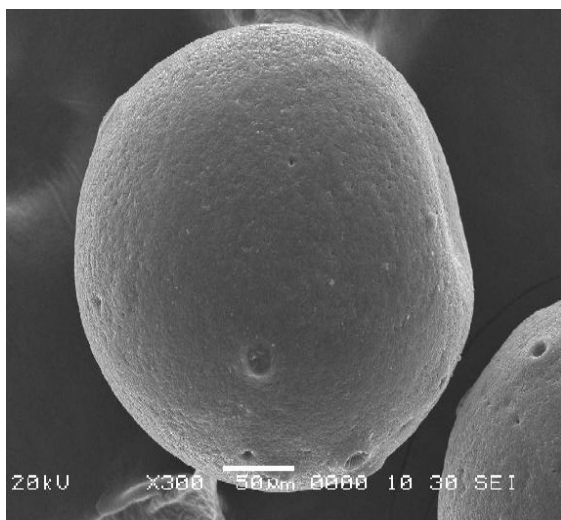


Figure 2 A : Scanning electron microscopy results for Batch C



Figure 2 B : Scanning electron microscopy results for Batch D

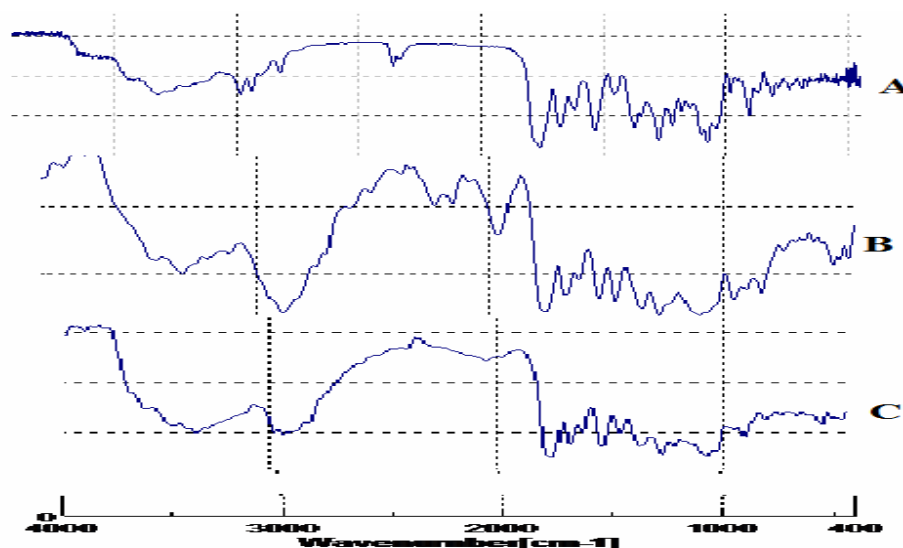


Figure 3: FTIR study.

A- DRUG

B- PEG + E100+ Drug

C-HPMC + E100 + Drug

Surface morphology

The particle size of microspheres determined by using optical microscope fitted with standard micrometer scale was in the range of 100-275 μm . (Table 4). Morphology of microspheres was examined by scanning electron microscopy. The view of the microspheres showed a hollow spherical structure with a smooth surface morphology and exhibited a range of sizes within each batch. Some of the microspheres showed a dented surface structure but they showed good floating ability on the surface of the medium, indicating intact surface. Scanning electron

microscopy results of both the batches C and D are shown in Figure 2.

FTIR-studies

The spectral observations indicated that the principal IR absorption peaks observed in the spectra of CP were close to those in the spectra of the CP microspheres. IR spectrums of the microspheres indicate that there is no strong interaction between the drug and the polymers. Hence drug excipients compatibility was established also which indicates the stable nature of drug during the entrapment process. (Figure 3)

Differential scanning calorimetry (DSC) studies

The DSC thermogram of CP recorded using Differential scanning calorimeter (DSC 823 Mettler Toledo, Japan). Its the most widely used calorimetric techniques to characterize the physical state of drug in the polymeric matrix. Figure 4A and 4B depict the DSC thermogram of pure CP and combination of CP with Eudregit E100. The DSC thermogram of CP exhibited a single sharp endothermic peak at 89° corresponding to its melting transition temperature. The thermograms of the combination of CP with Eudregit E100 showed no such characteristic peak, indicating that the drug was uniformly dispersed at the polymeric matrix. These studies also support the hypothesis of formation of an envelop surrounding the bitter drug particles thereby masking bitter taste.

In vitro drug release studies

As floating microspheres were prepared to keep the drug in an absorption window, dissolution was checked in vitro in 0.1 N HCl. The drug release from microspheres in 0.1N HCl is shown in Figure 5. Release of drug from batches A and B was only 25- 30 % in even after 1 hr, while drug released from batch C and D was 96-99% within 45 mins.

Microspheres release the drug quickly upon contact with acidic environment although it does not release any drug at salivary pH 6.8. Thus both taste masking and required drug release is achieved. No formulation is showing burst release which indicates the absence of free particles on the surface of microspheres which is further confirmed by SEM. The dissolution study shows that if only E100 is used to mask the taste, it may not be satisfactory as it the drug release is poor. (batch A and B). But when HPMC and PEG are added to formulation along with Eudragit E100 (batch C and D) drug release is good.

Formulation of dosage form of taste masked microspheres

Dry powder for Reconstitution was prepared as dosage form for microspheres for pediatric use. The required amount of microspheres were mixed with the xanthan gum, flavours and sweeteners and resultant powder was reconstituted by sufficient quantity of water to prepare suspension. Dry blend was evaluated for flow properties by angel of repose and reconstituted suspension was evaluated for pH, taste. Result obtained concludes that dosage form shows satisfactory taste masking. (Table 6)

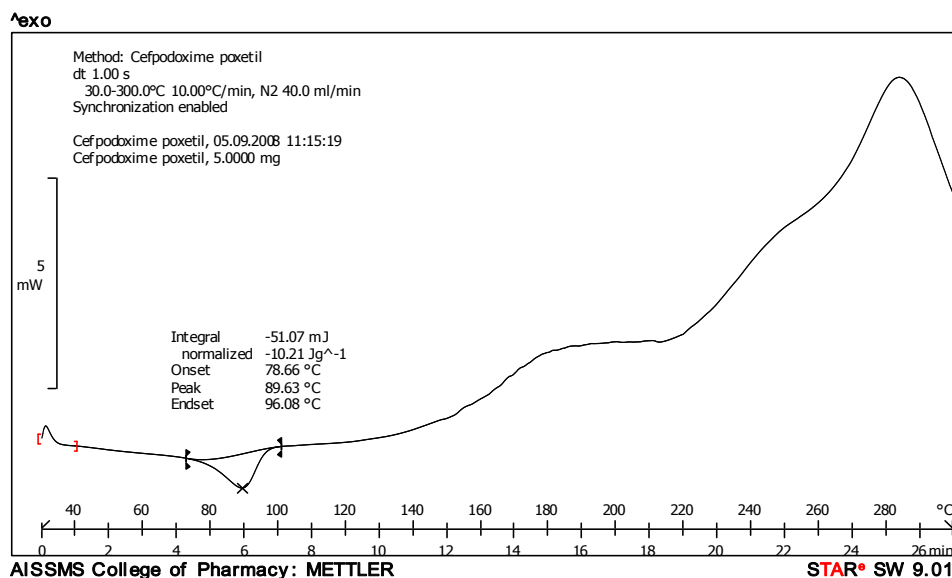


Figure : 4 A Differential scanning calorimetry (DSC)of CP

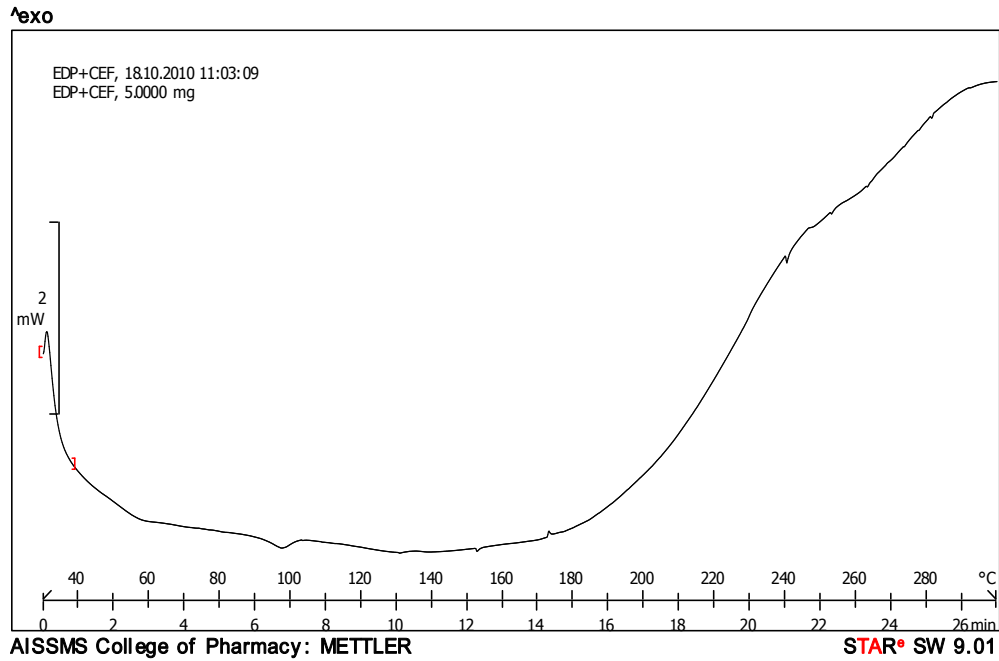


Figure : 4 B Differential scanning calorimetry (DSC) of CP+ Eudragit E100

Table 5: Formula for dry powder for reconstitution (mg/bottle)

Sr.No.	Name of ingredients	Quantities g/bottle [6 doses]
1	Microspheres*	600mg
2	Xanthan gum	150 mg
	Citric acid	10 mg
3	Magnesium stearate	20 mg
4	Flavor	125 mg
5	Pharma grade sucrose	q. s. 9000 mg

*microsphere equivalent to 50 mg CP per dose

Table 6: Evaluation of the dosage forms

Sr. No.	Properties	Batch C	Batch D
1	pH	5.1	5.0
2	Taste	Palatable	Palatable
3	Sedimentation Volume	1	1

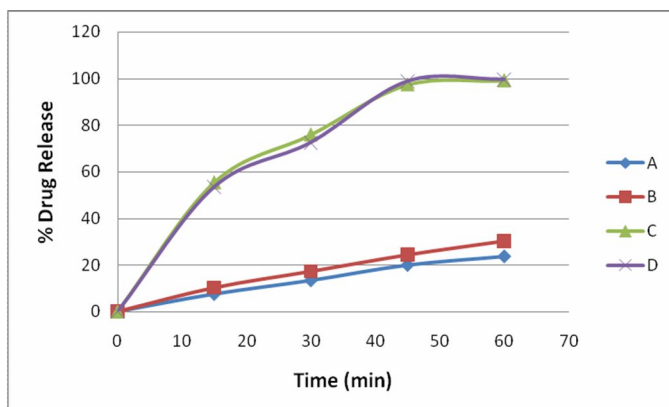


Figure 5: In vitro drug release studies

CONCLUSION

The present study has been a satisfactory attempt to formulate a floating microspheres of Cefpodoxime Proxetil with Eudragit E100, HPMC and PEG by the emulsion solvent diffusion method to mask the bitter taste of an antibiotic, at the same time maintaining the drug in its absorption window. The effect of different polymers with different drug-polymer ratios on the taste masking and the characteristics of the microspheres were investigated. In vivo taste evaluation reveals that bitter taste masking is satisfactory. It was found that Eudragit E100 masks the taste but retards the drug release whereas combination of Eudragit E100 with PEG and HPMC showed the best result for masking the unpleasant taste of Cefpodoxime Proxetil with floating ability as well as provide required drug release. Further dry powder for reconstitution was selected as dosage form for

microsphere with respect to its use in pediatric population. The dosage form maintains palatable taste even after reconstitution and storage for specified duration.

In summary biocompatible and cost-effective polymers like Eudragit E100, HPMC and PEG can be used to formulate an efficient floating microparticulate system with acceptable taste, good percentage entrapment efficiency and practical yield. The particle size analysis revealed that the particles were of the size range of 100-275 micrometer, showed good flow properties.

Hence the present study is a successful attempt to formulate a taste masked floating microparticulate system of an antibiotic i.e. Cefpodoxime Proxetil, with a view of conventional delivery of the drug and its conversion to a suitable dosage form with respect to its use in pediatric population.

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