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Formulation and evaluation of dry suspension of taste masked coated pellets of cefixime

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Abstract
The present study was aimed to mask the bitter taste of cefixime trihydrate and formulate it for pediatric use. Taste masking was done by multi-unit particulate pellet coating technology using R & D coater in two step process. Initially drug layering was done on sugar pellet followed by polymer coating on drug layered pellets as taste masked layer. Good efficiency of drug layering was observed with 0.45 gm HPMC E5 as a binder. Drug layered pellets were coated with different concentrations of methacrylate copolymer as taste masking polymer. The prepared taste masked pellets were evaluated for taste and drug content, leaching of drug. From *in vitro* taste evaluation, bitter taste of cefixime trihydrate was masked with 1.25 gm of Eudragit EPO.

Keywords: Cefixime trihydrate, bitter taste, taste masking, HPMC E5, Eudragit EPO

Introduction
Even though, oral route is most easy and convenient for administration of various dosage forms; swallowing of solid dosage forms is a major difficulty encountered with pediatric population because many children cannot or will not swallow which leads to poor patient compliance. This can be easily overcome by designing liquid formulation. But most of the pharmaceutical substances either bitter in taste or can irritate the mucous membrane in oral cavity and can affect patient compliance [1]. Drugs with bitter taste can affect patient compliance and this becomes major constraints in success of therapy.
Various taste masking technologies are available depend upon the bitterness intensity of active ingredients [2]. Cefixime (CEF) is an oral third generation cephalosporin antibiotic. Clinically used in treatment of bacterial infection of otitis media, strep throat, pneumonia, urinary tract infection, gonorrhea and Lyme disease. Cefixime has bitter taste and this issue needs to be addressed while designing liquid formulation. This work describes taste masking of cefixime by pellet coating and formulation of dry suspension of same.
Eudragit EPO (exists as powder form) polymers which are basic butylated methacrylate copolymers provide an excellent coating with taste masking properties for fine particles and pellets. This polymer can form a film which is soluble below pH but insoluble at salivary pH and hence work efficiently for taste masking [4]. Films that are produced by Eudragit EPO types are sufficiently elastic and require no plasticizers. [5]

Materials and methods
Materials
Cefixime trihydrate (Cipla Ltd. Pharma R&D, Mumbai), sugar pellets (ACG worldwide. Pvt. Ltd.) were obtained as gift sample. Eudragit EPO was gifted from Degussa India Pvt.Ltd, Mumbai (India). Hydroxyl propyl methyl cellulose (E5) was purchased from Loba chemicals. All other Chemicals used were of Analytical Reagent grade and procured from the local suppliers.

Methodology
Evaluation of bitterness threshold of Cefixime trihydrate [5]
A panel of ten healthy human volunteer (age 20-25) was selected. A series of solution of cefixime trihydrate of concentrations 10, 20, 30, 40, 50, µg/ml was prepared.

Ten healthy human volunteer (age 20-25) were asked to taste and rate the taste after informed consent. The volunteers were asked to taste and rate on the scale from 0 to 4 where 0 meant no bitterness, 1 meant threshold bitterness, 2 meant bitter, 3 meant moderate bitter and 4 was for strong bitter taste. Based on the opinion of the volunteer, threshold bitterness concentration of drug was judged [5].

Preparation of taste masked pellets

R & D coater was used for the manufacturing of taste masked pellets. The process of taste masking technique was done in the following steps

1) Drug layering on inert core pellets i.e. Sugar pellets.
2) Polymer coating on the drug layered pellets as Taste masking layer

1) Drug layering on inert core pellets

Table3. Summarizes the various formulations used for the manufacturing of drug layered pellets with binder at various concentrations. Transferred required quantity of Methanol (18% w/w solids) into a suitable mixing vessel and Hydroxypropyl methylcellulose E5 was added to the vortex under stirring and continued the stirring to dissolve completely. Cefixime trihydrate was added slowly under stirring and continued the stirring for 30 minutes. After completion of spraying of drug dispersion, Drug coated pellets were dried for 15 minutes at a bed temperature of 40° – 45°C. Drug layered pellet were coated with different concentration of taste masked polymeric material of amino methacrylate copolymer (Eudragit EPO) as shown in table Required quantity of Eudragit EPO was added into methanol and stirred for 30 min. After completion stirring solution was sprayed onto drug layered pellet at bed temperature 35-40°C and pan speed 20 rpm. Polymer coated pellets were dried for 15 min.

Optimization of formulation [7]

Selection of suitable experimental design

In a full factorial design, all the factors are studied in all the possible combinations, as it is considered to be most efficient in estimating the influence of individual variables (main effects) and their interactions, using minimum experimentation. In the present study, fitting a cubic model is considered to be better as the values of the response surfaces are not known from the previous findings. Hence, 3^2 Factorial design (FD), was chosen for the current formulation optimization study. Amount of HPMC E5 and Eudragit EPO were selected as independent factors whereas drug content and leaching of drug were measured as responses. Based on initial trials, levels of HPMC E 5 were selected as 0.15, 0.3 and 0.45 mg whereas Eudragit EPO levels were 0.31, 0.78 and 1.35 mg. Nine formulations were prepared according to 3^2 factorial design and evaluated. The responses were analyzed for ANOVA using Design Expert version 10 statistical modal was generated for each response parameter. The mathematical models were tested for significance. Response surface plots were generated for each response to study the behavior of the system.

Validation of statistical model

Levels of HPMC E5 and Eudragit EPO were selected at six different points and responses predicted by the statistical models were calculated. Taste masked pellets were prepared using these levels and responses were measured practically. The predicted responses were compared against observed responses and closeness between them was checked.

Taste evaluation of Taste masked pellets

In-vitro taste evaluation

In vitro taste evaluation of taste masked pellets of cefixime trihydrate was done by UV VIS spectrophotometrically. A quantity of taste masked pellets equivalent to 100 mg of cefixime was added to each of the six volumetric flasks containing 10 ml of phosphate buffer of pH 6.8. The mixtures were vortexed for 0, 15, 30, 60,120 and 300 seconds and filtered. Content of cefixime in each filtrate was determined. For satisfactory taste masking, the amount of drug dissolved at the end of 120 seconds should not be more than the threshold bitterness concentration of the drug. [8]

Characterization of taste masked pellets

Shape and surface morphology

The surface morphology of pellets was determined by Scanning Electron microscope. Photograph was taken with suitable magnification. (Instrument – FEI, modal – Nova Nano SEM 450)

Drug content

Taste masked pellets equivalent to 100 mg of cefixime trihydrate was stirred in 100ml of 0.1 N HCl for 3 hour, till the entire drug leached out, and then the solution was filtered through a Whatman filter paper. Further dilutions were made with 0.1 N HCl and the drug content was determined spectrophotometrically at 283 nm using 0.1 HCl as blank.

Determination of the leakage of drug from pellets

Pellets equivalents to 100 mg of cefixime was suspended in phosphate buffer 6.8 and leakage of drug was measured for 3 successive days by UV spectrophotometrically [8].

***In vitro* release of cefixime trihydrate from taste masked pellets**

Weighed quantity of taste masked pellets equivalent to normal dose of drug was subjected to dissolution studies using USP II Type dissolution test apparatus at 50 rpm with temperature of 37 ± 0.5 ºC and 900ml 0.1 N HCL used as the dissolution medium. An aliquot equal to 5 mL was withdrawn at specific time interval, and it was filtered through Whatman filter paper. Absorbance of the filtered solution was checked by UV VIS spectrophotometrically at 283 nm and quantity of drug released was determined periodically.

Formulation of oral suspension of taste masked pellets of cefixime trihydrate

Suspending medium plays an important role in suspension stability and acceptability of suspension as oral drug delivery system. Syrup based suspending medium were developed for suspending the taste masked product previously prepared.

Procedure for preparation of Dry suspension

Preparation of dry suspension

In the suspension formulations, Guar gum was used as suspending agent. To produce dry mixture for reconstitution, all the powder components were reduced to more or less the same particle size. Ingredients present in

small quantities (preservative, colourant and flavourant) were mixed homogeneously [14]. The same procedure was followed for coated pellets (equivalent to 100mg cefixime). Such ingredients were mixed with a portion of flavourant according to the principle of the geometric dilution. The representative formulations for the preparation of dry mixtures are tabulated in Table 1

Table 1: Composition of dry suspension of Cefixime

Ingredient	Formulation Code		
	A1 (gm)	A2 (gm)	A3 (gm)
Coated pellets (eq. to 100 mg of Cefixime)	2.4	2.4	2.4
Sugar	12.3	12.2	12.1
Guar gum	0.2	0.3	0.4
Sodium benzoate	0.05	0.05	0.05
Orange flavour	0.05	0.05	0.05
Total	15	15	15

Evaluation of taste masked dry suspension

1) Taste masked suspensions

Micromeritics properties: Compressibility, angle of repose, and bulk density were determined using the methods described in literature [8].

Sedimentation characteristics: To study the sedimentation in reconstituted suspension, the sedimentation volume was measured at selected time intervals during storage without agitation for a period of 10 days and was recorded in terms of the ratio of the ultimate settled height (Hu) to the original height (Ho), as expressed in the following equation F= Hu/ Ho

Redispersibility: The redispersibility of a suspension was evaluated qualitatively. The test consisted of manually shaking the cylinder after the sedimentation experiments were completed. Based on the time and the effort required to convert the sediment to homogenous suspension, the formulations were evaluated. One inversion was considered as 100% easy to be redispersed. Every additional inversion decreased the percent ease of redispersibility by 5% [11].

Viscosity: The viscosity of each formulation after constitution, in terms of viscosity, was determined by using the Brookfield viscometer.

PH values: The pH of suspensions was measured with the aid of a pH meter.

Assay of suspension: The suspension samples were subjected for assay. 1 ml of sample withdrawn from top, middle and bottom and dissolved in 0.1 N HCl and absorbance were taken by UV VIS spectrophotometer.

***In vitro* taste evaluation:** Suspension equal to normal dose of drug was added to each of the 3 volumetric flasks containing 10 ml of phosphate buffer of pH 6.8. The mixtures were vortexes for 20, 40 and 60 seconds and filtered. Content of cefixime in each filtrate was determined. For satisfactory taste masking, the amount of drug dissolved at the end of 60 seconds should not be more than the threshold bitterness concentration of the drug.

***In vitro* drug release profile:** The suspension samples were subjected to in-vitro dissolution studies using USP Type II dissolution apparatus at 37±2°C and 50 rpm speed. 900 ml of 0.1 N HCl was used as dissolution medium. Aliquot equal to 5 ml was withdrawn at specific time intervals and amount of cefixime released from the film sample was determined.

Results and discussions

Threshold bitterness of Cefixime trihydrate

Most volunteers reported threshold bitterness at 20µg/ml (table 3).

Table 2: Threshold bitterness of Cefixime trihydrate

Volunteer No	Rating on the scale of bitterness				
	10µg/ml	20µg/ml	30µg/ml	40 µg/ml	50µg/ml
1	0	0	0	1	2
2	0	1	2	3	4
3	0	1	2	3	4
4	0	0	1	1	1
5	0	1	1	2	3
6	0	0	0	1	2
7	0	1	2	3	4
8	0	1	2	3	3
9	0	1	1	2	2
10	0	1	2	3	3

0=No bitterness, 1=threshold bitterness, 2=bitter, 3=moderate bitter, 4=strong bitter

Table 3: Factor combination and responses as per the experimental design for formulation of coated pellets

Formulation code	Factor A Polymer (Eudragit EPO)gm	Factor B Binder (HPMC E5)gm	Response 1 Drug content	Response 2 Leaching of drug
1	0.31	0.15	7.94	19.64
2	0.31	0.31	8.72	19.48
3	0.31	0.45	9.81	7.3
4	0.78	0.31	13.01	20.8
5	0.78	0.15	13.45	15.94
6	0.78	0.45	13.91	5.5
7	1.25	0.15	19.44	17.89
8	1.25	0.31	24.23	14.38
9	1.25	0.45	24.14	3.21

3^2 Factorial design

A statistical model, $Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1X_1 + b_{22}X_2X_2$, incorporating interactive and polynomial terms was used to evaluate the responses; where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate nonlinearity. The % drug content and leaching of drug for the nine batches (A1 to A9) showed wide variation (i.e. 7.94 to 24.14% and 3.21 to 19.64 respectively). The data clearly indicate that the % drug content and leaching of drug were strongly dependent on the selected independent variables. The fitted full equations relating the responses % drug content and leaching of drug to the transformed factors are as:

Drug content = $13.70+6.95A+1.28B+0.82AB+2.38A^2-047B^2$ (1)

Leaching of drug = $18.05-1.74A-6.16B-0.46AB-0.10A^2-631B^2$ (2)

Table 4: ANOVA for selected factorial model

Responses	R^2	F- value	p-value	Adequate precision
Drug content	0.9827	34.12	0.0076	14.85
Leaching of drug	0.9591	14.08	0.0270	9.331

Table 4 shows the results of the analysis of variance (ANOVA), which was used to generate mathematical models. The high values of correlation coefficient for Drug content and leaching of drug indicate a good fit i.e. good agreement between the dependent and independent variables. The equations may be used to obtain estimates of the response as a small error of variance was noticed in the replicates. The F value in the ANOVA table is the ratio of model mean square (MS) to the appropriate error mean square. The larger the ratio, the larger the F value and the more likely that the variance contributed by the model is significantly larger than random error. If the F ratio - the ratio of variances - lies near the tail of the <F>distribution then the probability of a larger F is small and the variance ratio is judged to be significant. Usually, a probability less than 0.05 is considered significant. The F distribution is dependent on the degrees of freedom<DF>for the variance in the numerator and the<DF>of the variance in the denominator of the F ratio. The outcomes of ANOVA are shown in Table 4. The model F-value of 34.12 Drug content and 14.08 for leaching of drug and high R square values suggest that these models are significant. There is only 2.70% chance that a 'Model F-value' this large could occur due to noise. Values of 'Prob>F' less than 0.0500 indicate model terms are significant. In this case both the models generated for % Drug content and leaching of drug are significant. As there are no insignificant terms, model reduction is not required. Adeq Precision" measures the signal to noise ratio.A ratio greater than 4 is desirable. The ratios of 14 and 9.33 respectively for Drug content and leaching of drug models indicate an adequate signal for each.

Validation of statistical model

A good evaluation of a model is not how well it fits the data, but how well it predicts the points. The predicted responses of the nine formulations and corresponding actual experimentally observed values were found to be in close agreement as indicated in Table 5. Thus the models developed to predict the responses were not only significant statistically but they were found to be valid to predict values that were very close to the practical observations.

Table 5: Comparision of predicted values and experimental values.

Reponses	Experimental value	Predicted value	Error
Drug content	24.14	24.31	0.17
Leaching of drug	3.21	3.351	0.14

Response surface plots

It was observed that Drug content and leaching of drug were dependent on both the factors. There was a linear increase drug content as increase in binder. While there is linear decrease in leaching of drug with increase in polymer concentration.

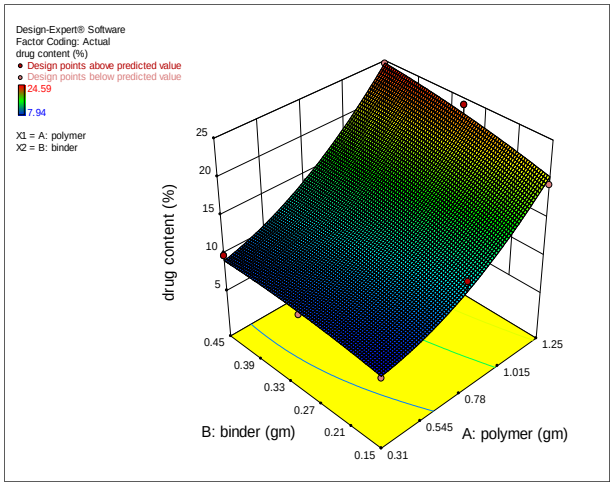

Fig 1: Response surface plot for % Drug content

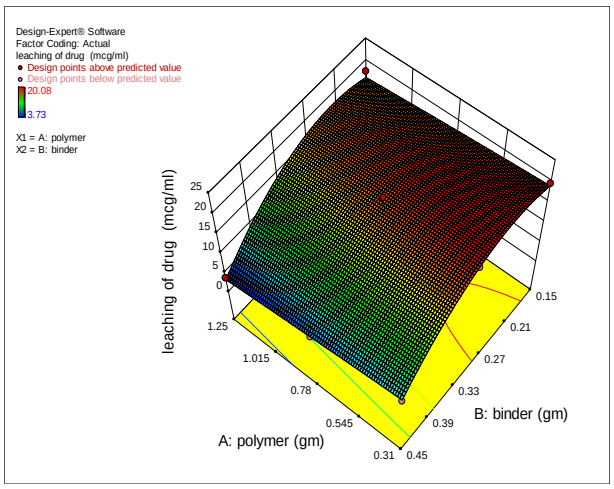

Fig 2: Response surface plot for leakage of drug

Taste evaluation of Taste masked pellets

In-vitro taste evaluation of pellets

The objective for this test was to check whether the pellets releases any drug at salivary pH during a time interval of 300 S. No detectable amount of cefixime trihydrate dissolved in the phosphate buffer of pH 6.8 was detected at the end of 300 S. Thus the pellets did not release any drug at salivary pH.

Table 6: *In vitro* taste evaluation of pellets

Sr no	Time (sec)	Concentration (µg/ml)
1	5	5.52±0.12
2	15	8.96±0.22
3	30	11.63±0.16
4	60	12.63±0.19
5	120	13.56±0.17
6	300	15.63±0.13

Characterization of taste masked pellets

Shape and surface morphology

From SEM pictures of taste masked pellets and uncoated pellets (Fig 4) ; drug layered pellet coated with 1.25 g Eudragit EPO appeared smooth and continuous, constituting as a barrier for bitter taste drug layered pellets. In contrast, uncoated pellet appeared rough uneven surface.

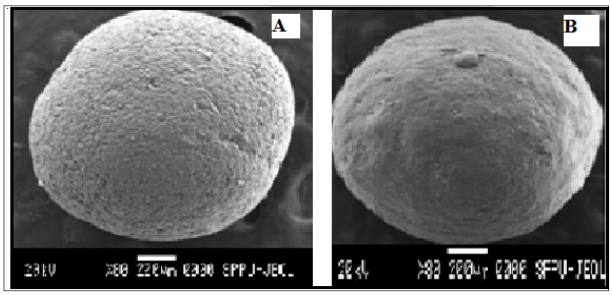

Fig 3: SEM pictures of A] Uncoated sugar pellets B] Coated sugar pellet

Drug content

The percentage content of cefixime trihydrate in taste masked pellets were determined by UV- Visible spectrophotometer and the results are presented in table 3.

In vitro release of cefixime trihydrate from taste masked pellets

In vitro profile of pellets shows drug release of 93.57 % within 30 min (Fig 3). Film form by Eudragit EPO dissolved readily in acidic environment. Hence doesn't affect bioavailability.

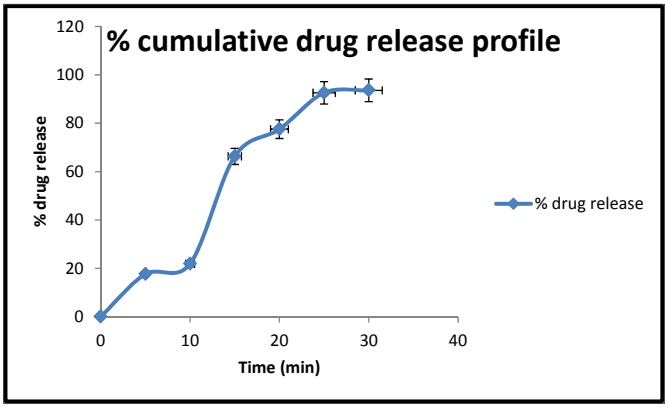

Fig 4: *In vitro* drug release profile from pellets

Determination of the leakage of drug from pellets

Leakage of drug was measured by UV VIS spectrophotometrically (table 3). No detectable amount of cefixime trihydrate dissolved in the phosphate buffer of pH 6.8 was detected at the end of 3rd day. Thus the pellets did not leak any drug from pellet.

Evaluation of suspension

Physiological characteristics of suspension: Suspending agent acts as thickening agent. They increase viscosity of solution which is necessary to prevent sedimentation of suspended particles Sedimentation study shows that the sedimentation volume of all formulations is in the range of 0.98 to 1, which indicates that formulation is acceptable. [5]

Table 7: Evaluation of suspension

Sr. no	Evaluation parameters	A1	A2	A3
1	Colour	Orange	Orange	Orange
2	Taste	Sweet	Sweet	Sweet
3	pH	5.6	5.6	5.5
4	Viscosity (cps)	1133	1295	1317
5	Sedimentation volume	0.92	0.93	0.94
6	Redispersibility (%)	85	90	85
7	Assay	%Assay		
	Top	99.38	99.59	99.12
	Middle	99.59	100.15	99.6
	Bottom	99.70	99.8	100.5

Viscosity of suspension is very important factor for the stability of suspension because viscosity contributes to rate of sedimentation, higher the viscosity, lower is the rate of sedimentation. The in- vitro taste evaluation of suspension in the buffer of salivary pH 6.8 showed that the drug does not get released in saliva to attain threshold bitterness concentrations. As shown in table 8 indicates satisfactory taste masking.

Table 8: *In vitro* taste evaluation of suspension

Formulation code	Drug release in phosphate buffer of pH 6.8		
	20 sec	40 sec	60 sec
A1	2.10 µg/ml	5.60 µg/ml	7.68 µg/ml
A2	2.40 µg/ml	5.14 µg/ml	7.18 µg/ml
A3	2.12 µg/ml	5.23 µg/ml	7.05 µg/ml

n=3

Dissolution studies

The formulation showed 94.96% release within 50 min table 7 (fig 4). The concentration of suspending agent (guar gum) does not affect drug release in formulations. (Fig 4)

Table 9: *In vitro* drug release

Time (min)	% Drug release		
	A1	A2	A3
0	0	0	0
5	10.11	12.12	13.56
10	21.85	22.35	26.32
15	66.29	65.54	63.25
20	77.54	73.25	76.23
25	82.23	81.32	83.26
30	87.76	85.36	89.67
35	90.23	90.12	91.87
40	93.57	92.36	93.54
45	96.35	93.62	94.12
50	96.23	95.69	96.32

n=3

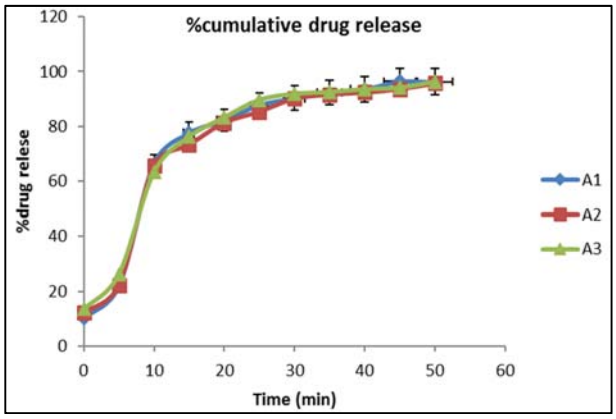

Fig 5: *In vitro* drug release profile of pellets

Conclusion

It was concluded that the bitter taste of Cefixime can be masked by coating sugar pellet with Eudragit EPO polymer. Taste masked dry suspension of Cefixime having good stability can be prepared using as a binder for sugar pellet coating HPMC E5 and Eudragit EPO as polymer. Factorial design and statistical models can be successfully used to optimize the formulations.

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