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Research Article

FORMULATION AND EVALUATION OF TASTE MASKED ORAL SUSPENSION OF CEFUROXIME AXETIL USING HYDROXYPROPYL-BETA-CYCLODEXTRIN

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ABSTRACT

Objective: Cefuroxime axetil is a prodrug of Cefuroxime, which is extremely bitter in taste, which reduces the patient compliance when taken as oral suspension especially in pediatric population. The objective of this study was to mask the bitter taste of Cefuroxime axetil using Hydroxy propyl betacyclodextrin [HP- Betacyclodextrin] by inclusion complexation method.

Methods: The complexation of Cefuroxime axetil and HP- Betacyclodextrin was carried out at 1:1, 1:2, 1:2.5 and 1:3 ratios respectively. The prepared suspension was evaluated for various parameters like pH, viscosity, redispersibility, pourability, assay and invitro dissolution profile. A comparative evaluation of the taste masking was carried out for the developed formulations and marketed product.

Results: All the formulations and the marketed product were meeting all the quality parameters. Formulations with 1:3 and 1:2.5 ratios showed better taste masking compared to the marketed product and the formulation with 1:2.5 ratio shown to have better invitro dissolution pattern.

Conclusion: Considering the invitro dissolution profile and taste evaluation with marketed product, formulation with 1:2.5 ratio of Cefuroxime axetil and HP- Betacyclodextrin was selected as the optimum formulation.

Keywords: Cefuroxime axetil, Taste masking, Betacyclodextrin, Inclusion complexation.

INTRODUCTION

The bitter taste of the drugs, which are orally administered, is disadvantageous in several aspects. Taste is an important parameter governing the compliance. *"The worse the taste of the medication, the better the cure"* was once the prevailing attitude. A change in patient attitude and development of taste masking technique has reversed this opinion. Patients now expect and demand formulations that are pleasantly, or at least tolerably, flavored. The disagreeable taste of drugs causes difficulties in swallowing (dysphagia) or causes patients to avoid their medication thereby resulting in low compliance of patients [1-5].

The current work is concerned with pharmaceutical compositions containing the 1-acetoxyethyl ester of cefuroxime, which has the approved name cefuroxime axetil, which is formulated in the form of dry powder for oral suspension for pediatric patients. However, cefuroxime axetil has an extremely bitter taste which is long lasting, and this remains a challenge [6-12].

In this study, an attempt has been made to mask the taste of cefuroxime axetil oral suspension 125 mg using hydroxypropyl-beta-cyclodextrin. Cyclodextrins are used for a long time to mask the unpleasant taste of drugs by forming an inclusion complex with the drug [13-16]. HP-betacyclodextrin is selected due to its improved water solubility and safety compared to other cyclodextrins [17]. A leading market sample is used in this study as a competitor product, which has used spray drying technology with Stearic acid to mask the taste [18,19]. The market sample has grittiness feeling in mouth while administration which could be due to the Stearic acid: Drug granules, which may lead to rejection of medicine by pediatric patients.

METHODS

Materials

Cefuroxime axetil for the study was procured from Covalent Laboratories private limited, Hyderabad, India. Hp-Betacyclodextrin was purchased from Signet Chemical Corporation Pvt. Ltd., India (manufactured by Roquette). Sucrose was received from EID Parry Ltd., India, Xanthan was procured from Deosen, China. Acesulfame K potassium was procured from Ningbo Hi Tech Biochemicals Co- Ltd., China. Aspartame was received from Nutrasweet, China. Tutti frutti flavor and Peppermint flavor were procured from Firmenich, Switzerland.

Preparation of cefuroxime axetil: HP-betacyclodextrin complex by inclusion complexation method

Cefuroxime axetil and HP-Betacyclodextrin were taken at 1:1, 1:2, 1:2.5, and 1:3 combinations at molecular weight ratio (Table 1).

Accurately weighed cefuroxime axetil and HP-betacyclodextrin were sifted through #30 mesh and mixed together to get a uniform blend. The resulting mixture was slowly added to purified water in a beaker under stirring using mechanical stirrer. The stirring process continued for 6 h to get a thick slurry of cefuroxime axetil and HP-betacyclodextrin complex. The slurry was transferred to a tray and dried in hot air oven at 45°C until the complex is adequately dried. The dried complex was passed through #60 mesh and mixed thoroughly. The resulted cefuroxine axetil: HP-betacyclodextrin complex in different ratios were used for further processing to make a dry suspension.

Preparation of taste masked dry suspension of cefuroxime axetil 125 mg/5 ml

Cefuroxime axetil taste masked dry suspension was formulated by mixing cefuroxime axetil: HP betacyclodextrin complex along with other

Table 1: Combinations of cefuroxime axetil and HP-betacyclodextrin for complexation

Ingredients	Ratio (mg/5 ml)			
	1:1	1:2	1:2.5	1:3
Cefuroxime axetil	158.250	158.250	158.250	158.250
HP-betacyclodextrin	477.915	955.830	1194.790	1433.750
Total weight	636.165	1114.080	1353.040	1592.000

inactive ingredients as shown in Table 2. Formulations were prepared with each combinations of cefuroxime axetil: HP betacyclodextrin complexes (1:1, 1:2, 1:2.5, and 1:3).

Cefuroxime axetil: HP betaccyclodextrin complex, Sucrose (#80 mesh), Acesulfame K, Aspartame, Xanthan gum, Tutti frutti flavor, and Peppermint premium flavor were sifted through mesh #40 and mixed together. Sucrose (#40 mesh) was sifted through mesh #30 and added to above blend and mixed well. 18 g of the blend was filled in 30 ml high-density polyethylene (HDPE) bottle and closed with HDPE cap. Each bottle needs to be reconstituted with water before administration to make the oral suspension.

Evaluation of cefuroxime axetil oral suspension 125 mg/5 ml

Physiochemical properties of suspension

The physiochemical properties of suspension like color, pH, redispersibility, viscosity, assay, and pourability were evaluated.

In vitro dissolution studies

In vitro dissolution of all the combinations and market sample were tested using ELECTROLAB dissolution apparatus as per the method specified in United States Pharmacopoeia. 900 ml of pH 7.0 phosphate buffer was used as dissolution medium with USP apparatus 2 (Paddle), at 50 rpm. The temperature of the dissolution medium was maintained at 37 ±0.5°C. The dry suspension was reconstituted with water and a quantity equivalent to 125 mg of cefuroxime axetil was used for the dissolution study. During the dissolution study, 5 ml samples were withdrawn at 10 minutes 20 minutes, and 30 minutes intervals. The samples were filtered through 0.22 µm filter, and the concentration of Cefuroxime axetil in the filtrate was tested using a spectrophotometer. The limit for dissolution as per USP is not less than 60% (Q) in 30 minutes.

Taste evaluation of the suspension

Taste evaluation of the oral suspensions was carried out using ten human volunteers. Cefuroxime axetil pure drug was used as the standard for the study and the market sample also was used to compare the formulations. Formulations were classified into four categories (1) No bitter taste/taste masked, (2) Slightly bitter/acceptable, (3) Bitter, (4) Very bitter. Volunteers were provided with adequate drinking water and a break time of 1 hr between each sample to avoid carry over.

RESULTS AND DISCUSSION

Physiochemical properties of suspension

Physiochemical properties of reconstituted suspension were carried out as part of quality control tests, the results of which are shown in Table 3.

Cefuroxime axetil dry suspension was reconstituted with an adequate quantity of water. The color of the suspensions was observed to be white. The pH of all the formulations was within the specified limit of 3.5-7 as in USP. Adequate viscosity was observed in all the formulations, providing sufficient stability, and pourability of suspension. All the formulations were easy to re-disperse with water by shaking by hand for some time. All the suspensions were easily pourable making it easy to dispense. The Assay of all the formulations was meeting the specified limit of 90-110% as per USP.

***In vitro* dissolution studies**

In vitro dissolution of all the combinations and market sample were tested using ELECTROLAB dissolution apparatus as per the method specified in the United States Pharmacopoeia. The results of *in vitro* dissolution studies are given in Fig. 1.

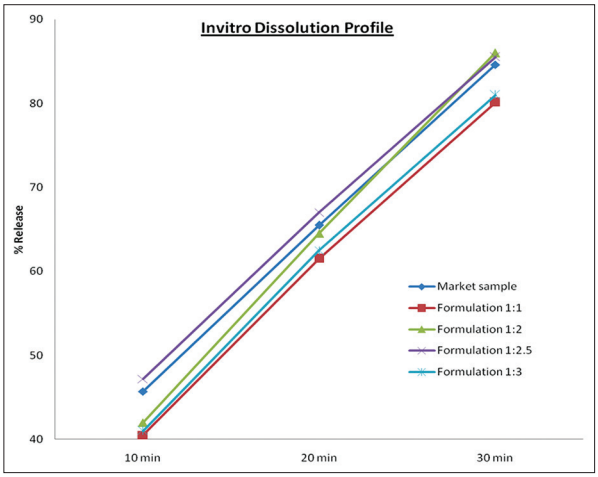

Fig. 1: *In vitro* dissolution studies

Table 2: Formula for cefuroxime axetil taste masked dry suspension 125 mg/5 ml

Sr. No	Ingredients	Ratio (mg/5 ml)			
		1:1	1:2	1:2.5	1:3
1	Cefuroxime axetil: HP-betacyclodextrin complex	636.165	1176.468	1454.518	1634.984
2	Sucrose (#40 mesh grade)	1691.876	1286.649	1078.111	942.762
3	Sucrose (#80 mesh grade)	563.959	428.883	359.371	314.254
4	Acesulfame K	25.000	25.000	25.000	25.000
5	Aspartam	30.000	30.000	30.000	30.000
6	Xanthan gum	8.000	8.000	8.000	8.000
7	Tutti frutti premium flavor	35.000	35.000	35.000	35.000
8	Peppermint premium flavor	10.000	10.000	10.000	10.000
	Average weight	3000.000	3000.000	3000.000	3000.000

Table 3: Physiochemical properties of suspension

Sr. No	Tests	Formulations			
		1:1	1:2	1:2.5	1:3
1	Color	White	White	White	White
2	pH (limit: 3.5-7)	5.98	6.01	5.92	6.02
3	Viscosity	319 cps	340 cps	395 cps	410 cps
4	Re-dispersibility	Easy	Easy	Easy	Easy
5	Pourability	Easily pourable	Easily pourable	Easily pourable	Easily pourable
6	Assay (limit: 90-110%)	97.85	96.89	99.50	97.68

Table 4: Taste evaluation of the suspension

Volunteer	Drug	Market sample	Formulations			
			1:1	1:2	1:2.5	1:3
1	4	1	2	1	1	1
2	4	2	3	2	1	2
3	4	1	2	2	2	1
4	4	1	2	2	1	1
5	4	2	3	2	2	1
6	4	2	2	3	2	2
7	4	2	2	2	1	1
8	4	1	2	2	1	1
9	4	2	3	2	2	1
10	4	1	3	2	1	1
Average score	4	1.5	2.4	2.0	1.4	1.2

1: No bitter taste/taste masked, 2: Slightly bitter/acceptable, 3: Bitter, 4: Very bitter

From the dissolution studies, it is found that all the formulations and marketed sample are meeting the dissolution criteria of not <60% (Q) in 30 minutes. Among these formulations, 1:2.5 seems to have better release pattern than the marketed sample.

Taste evaluation of the suspension

The main objective of this study was to mask the extremely bitter taste of cefuroxime axetil. The degree of taste masking was evaluated using human volunteers. Cefuroxime axetil pure drug was used as a base for this study and the marketed sample also was included for a comparative purpose. Each volunteer were asked to taste the samples and rank the same into four categories, (1) No bitter taste/taste masked, (2) Slightly bitter/acceptable, (3) Bitter, (4) Very bitter. The results are given in Table 4.

The evaluation results show that the drug is extremely bitter. All other samples were having considerable taste masking including the marketed sample. Formulation of 1:3 combination found to be the most taste masked one, followed by the 1:2.5 combination and marketed sample. Since the *in vitro* dissolution profile is better in formulation 1:2.5, the same can be considered as the optimum formulation with good taste masking and improved drug release when compared to the marketed sample.

CONCLUSION

The extremely bitter taste of cefuroxime axetil suspension was successfully masked using complexation method using HP-betacyclodextrin. All the formulation developed were subjected to various quality control test including physiochemical parameters, *in vitro* dissolution, and taste evaluation, where all the formulations were meeting the quality parameters. Among the four formulations prepared formulation with 1:2.5 ratio of cefuroxime axetil and HP-betacyclodextrin showed better taste masking along with improved dissolution compared to the marketed sample. So, formulation 1:2.5 can be selected as the optimum formulation.

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