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Taste masking and improvement of anti microbial activity of cefuroxime axetil oral suspension

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ABSTRACT

Objective

Cefuroxime axetil is a second generation cephalosporin antibiotic active against wide range of organisms, which is a prodrug of Cefuroxime. Cefuroxime axetil 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 and to evaluate the improvement in antimicrobial activity of oral suspension, compared to a leading marketed product.

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. Comparative evaluation of the taste masking and antimicrobial sensitivity tests were 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. The optimized formulation was found to have better antimicrobial activity against selected organisms compared to the marketed product.

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, which also demonstrated improved antimicrobial activity.

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 attempt has been made to mask the taste of Cefuroxime axetil oral suspension 125mg using Hydroxy propyl betacyclodextrin. Cyclodextrins are used for a long time to mask the unpleasant taste of drugs by forming inclusion complex with the drug [13-16]. Most of the studies in this field carried out using plain Betacyclodextrin which is toxic if given intravenously and at high concentrations in oral route. HP-Betacyclodextrin is selected in this study due to its improved water solubility and safety compared to other cyclodextrins. Since HP-Betacyclodextrin is known to improve the antimicrobial activity of drugs, a comparative evaluation of the antimicrobial sensitivity of optimized formulation and marketed product has been conducted [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]. 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.

MATERIALS AND 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 (mfg. by: Roquette). Sucrose was received from EID Parry Ltd, India; Xanthan was procured from Deosen, China. Acesulfame potassium was procured from Ningbo Hi Tech Biochemicals Co- Ltd China. Aspartame was received from Nutrasweet, China. Tutti fruiti 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 (shown in table-1).

Table 1: Combinations of Cefuroxime axetil and HP -Betacyclodextrin for complexation

Ingredients	Ratio (mg/5ml)			
	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**

Accurately weighed Cefuroxime axetil and HP-Betacyclodextrin were sifted through #30 mesh and mixed together to get uniform blend. The resulting mixture was slowly added to purified water in a beaker under stirring using mechanical stirrer. Stirring process continued for six hours to get thick slurry of Cefuroxime axetil and HP-Betacylcodextrin 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 dry suspension.

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

Cefuroxime axetil taste masked dry suspension was formulated by mixing Cefuroxime axetil: HP Betacyclodextrin complex along with other 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).

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

Sr. No	Ingredients	Ratio (mg/5ml)			
		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	Aspartame	30.000	30.000	30.000	30.000
6	Xanthan gum	8.000	8.000	8.000	8.000
7	Tutty friuty premium flavour	35.000	35.000	35.000	35.000
8	Peppermint premium flavour	10.000	10.000	10.000	10.000
	Average Weight:	**3000.000**	**3000.000**	**3000.000**	**3000.000**

Cefuroxime axetil: HP- Betacyclodextrin complex, Sucrose (#80 mesh), Acesulfame K, Aspartame, Xanthan gum, Tutti fruity 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. 18g of blend was filled in 30 ml High density polyethylene [HDPE] bottle and closed with HDPE cap. Each bottle need to be reconstituted with water before administration to make the oral suspension.

Evaluation of cefuroxime axetil oral suspension 125mg/5ml

Physiochemical properties of suspension

The physiochemical properties of suspension like colour, pH, redispersibility, Viscosity, Assay and pourability were evaluated.

Invitro dissolution studies

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

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 hour between each sample to avoid carry over.

Comparative antimicrobial sensitivity evaluation

The comparison of the inhibition of growth of various microorganisms by the pure drug, the optimized formulation (F21) and the marketed product were tested by Kirby-Bauer antibiotic sensitivity test.

In this method filter paper disc of uniform size were impregnated with known concentration of pure drug, the optimized formulation (F21) and the reference product and then placed on the surface of an agar plate that has been seeded with the organism to be tested. The efficacy of the formulations was determined by measuring the diameter of the zone of inhibition that resulted from diffusion of the drug into the medium surrounding the disc.

Media

Mueller Hinton Agar No-2
The media consists of Caseine acid hydrolysate, Beef heart infusion, Starch soluble and Agar.

Preparation of media

Suspend 38gms of Mueller Hinton Agar media in 1000ml distilled water, mixed well and heated to boiling to dissolve the medium completely. Then it was sterilized by autoclaving at 15lbs per square inch pressure at 121^0c for 15 minutes.

Organisms

The test organisms selected were, Escherichia coli, Staphylococcus aureus and Salmonella abony.

Procedure

1. The covers of each of the agar plates were labeled with the name of the test organism to be inoculated and the positions of discs of each test samples.
2. Using sterile techniques, all agar plates were inoculated with their respective test organisms as follows:

a. A sterile cotton swab was dipped into a well mixed saline test culture and excess inoculum was removed by pressing the saturated swab against the inner wall of the culture tube.
b. Using the swab, the entire agar surface were streaked horizontally, vertically and around the outer edge of the plate to ensure a heavy growth over the entire surface and all culture plates were allowed to dry for about 5 minutes.

3. The individual discs were distributed on the respective points with sterile forceps.
4. Each disc was gently pressed down with the sterile forceps to ensure that the discs adhere to the surface of the agar.
5. All the plates were incubated in an inverted position for 24 to 48 hours at 37^0c.
6. Then the plates were examined for the presence of growth inhibition and the susceptibility of the organism to the test samples was determined by the diameter of the zone.

RESULTS

Physiochemical properties of suspension

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

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 to 7)	5.98	6.01	5.92	6.02
3	Viscosity	319cps	340cps	395cps	410cps
4	Redispersibility	Easy	Easy	Easy	Easy
5	Pourability	Easily Pourable	Easily Pourable	Easily Pourable	Easily Pourable
6	Assay (Limit: 90 to 110 %)	97.85 %	96.89 %	99.50 %	97.68 %

Cefuroxime axetil dry suspension was reconstituted with 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 to 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 redisperse 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 to 110 % as per USP.

Invitro dissolution studies

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

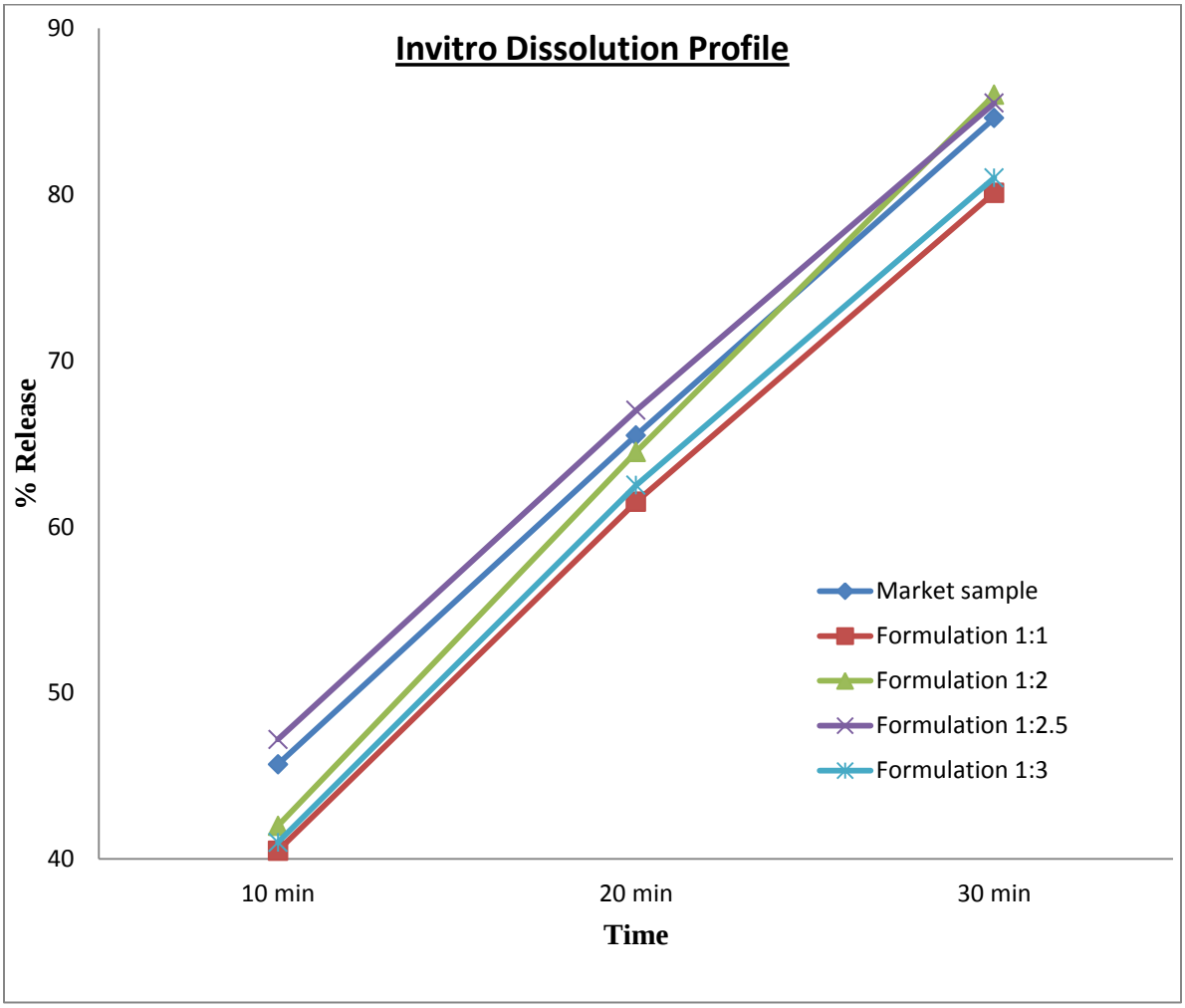


Figure 1: Invitro dissolution studies- All values are represented as mean±SD, n=6

From the dissolution studies it was found that all the formulations and marketed sample were meeting the dissolution criteria of not less than 60 % (Q) in 30 min. Among these formulation 1:2.5 seemed 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.

Table 4: Comparative taste evaluation of the oral suspensions

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

Taste evaluation of oral suspensions was carried out using ten human volunteers. Ranking of samples done on the basis of bitterness and are compared with the marketed product. Formulation of 1:3 combination found to be the most taste masked one, followed by the 1:2.5 combination and marketed sample. Considering the optimum dissolution profile and taste masking, formulation with 1:2.5 combination was selected as optimized formulation (F21)

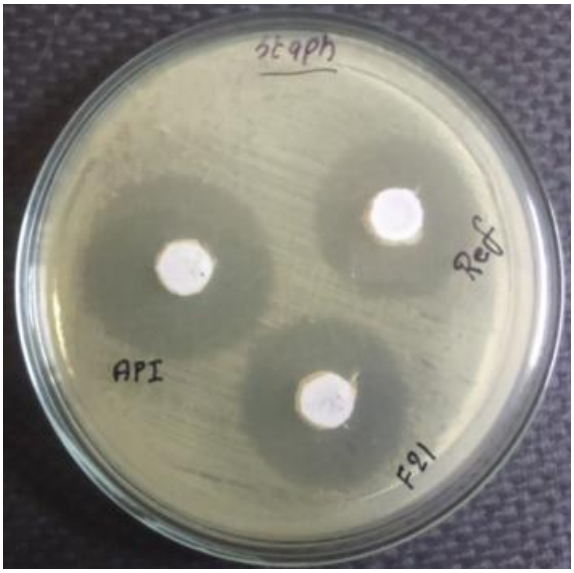
Comparative antimicrobial sensitivity evaluation

The comparison of the inhibition of growth of various microorganisms by the pure drug, the optimized formulation and the reference product were tested by Kirby-Bauer antibiotic sensitivity test. The test results are given below,

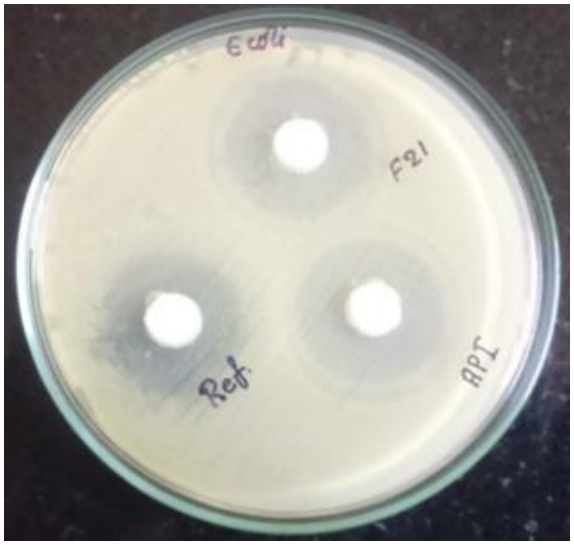
Table 5: Comparative Antimicrobial Sensitivity Evaluation

Organism ⟶	Escherichia coli	Staphylococcus aureus	Salmonella abony
Optimized formulation (F21)	28.40mm	25.20mm	20.80mm
Reference product	21.0mm	23.0mm	15.20mm
Pure drug	26.70mm	27.50mm	18.10mm

Organism: Salmonella abony



Organism: Staphylococcus aureus



Organism: Escherichia coli

Figure 2: Comparative Antimicrobial Sensitivity Evaluation

The diameters of zone of inhibition of all the samples were measured for *Escherichia coli*, *Staphylococcus aureus* and *Salmonella abony*, which demonstrated a significant increase in the antimicrobial activity of optimized formulation compared to the marketed product, suggesting that inclusion complexation with HP-Betacyclodextrin could improve the antimicrobial activity of Cefuroxime axetil oral suspension.

DISCUSSION

Taste masked oral suspension of Cefuroxime axetil 125mg/5ml was developed by inclusion complexation method using HP- Betacyclodextrin at 1:1, 1:2, 1:2.5 and 1:3 ratios respectively. All the formulation developed were subjected to various quality control test including physiochemical parameters, invitro dissolution and taste evaluation. The physiochemical parameters were found within the acceptance limits for all the formulations.

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

Taste evaluation of the oral suspensions was carried out using ten human volunteers. 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 invitro 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.

The comparison of the inhibition of growth of various micro organisms by the optimized formulation and the marketed product were conducted by Kirby-Bauer antibiotic sensitivity test. It is observed that the diameters of inhibition by optimized formulation (F21) were significantly increased compared to the marketed product, suggesting that inclusion complexation with HP-Betacyclodextrin could improve the antimicrobial activity of Cefuroxime axetil oral suspension.

In this study HP-Betacyclodextrin is selected instead of plain Betacyclodextrin due to its improved water solubility and safety profile. So it is an additional advantage to the patients to have tastier and safer medicine.

CONCLUSION

Extremely bitter taste of Cefuroxime axetil suspension was successfully masked using complexation method using HP-Betacyclodextrin. 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. The antimicrobial sensitivity of optimized formulation and the marketed product were compared and found that the zones of inhibition of optimized formulation were larger than the marketed product, so it can be concluded that the inclusion complexation with HP-Betacyclodextrin could improve the antimicrobial sensitivity of Cefuroxime axetil oral suspension.

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