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Formulation and Evaluation of Cefuroxime Axetil Oral Suspension

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ABSTRACT

The oral route is considered the most convenient and easy route of drug delivery. Yet, patient noncompliance, termed "intelligent noncompliance," due to feeling better, bad taste, etc., which is reasoned out by the patient but may not necessarily be wise, is one of the key causes of failure of oral dosage regimen. Paediatric and geriatric populations are most sensitive to the bad taste of medicaments. Also, currently there is a rising trend to formulate drugs in the form of orally disintegrating dosage forms due to their easy ingestion and absorption process. Thus, in these cases a good taste is indispensable to patient compliance. Moreover, high palatability gives a competitive advantage, especially in the case of over-the-counter products. In this review, we will discuss how taste is perceived, what techniques are available for taste masking, selection of appropriate taste masking technique, and evaluation tests for the same. Initial six formulations were taken by without adding IPA & talc to the Complexation part. So the dissolution was not improving. But in the formulations F7-F9 IPA and talc was incorporated into the Complexation part. Here talc improved the solubility of the Cefuroxime axetil: Betacyclodextrin complex. For initial 2 formulations taste was not good, bitter taste and the dissolution was not in the limit. For formulations F3-F6 taste was good, slightly bitter taste and the dissolution was not in the limit. For formulations F7-F9 the taste was good, slight bitter after taste and the dissolution were increasing with increasing the concentration of Talc. In the case of F9 slight irritation on the throat occurs when increasing the talc concentration. So F7 was chosen as best formulation.

Keywords: Cefuroxime axetil, Oral suspension, Beta cyclodextrin, IPA, Betalactum antibiotic.

INTRODUCTION

A variety of delivery systems are being developed for different routes of administration like the oral, parenteral, nasal, and transdermal, the oral route remains attractive for drug delivery because this mode of administration is an easy, convenient, non- invasive and familiar method of drug delivery. The common oral dosage forms include: liquid mixtures like solutions, suspensions, solid dosage forms like tablets and capsules and liquid filled capsules etc. However, patients at the extremes of age, such as children and the elderly, often experience difficulty in swallowing solid oral dosage forms. For these patients the drugs are mostly provided in liquid dosage forms such as emulsions and suspensions. These dosage forms usually lead to perceptible exposure of the active drug ingredient to taste buds and this is a very serious problem when the drug has an extremely unpleasant or bitter taste.[1,2]

The current work is concerned with pharmaceutical compositions containing the 1- acetoxyethyl ester of

cefuroxime, which has the approved name Cefuroxime axetil. The presence of 1-acetoxyethyl esterifying group results in significant absorption of the compound from the gastro-intestinal tract, whereupon the esterifying group is hydrolysed by enzymes present to yield the antibiotically active acid. Cefuroxime axetil has therefore extended the valuable therapeutic potential of cefuroxime by making available a form of antibiotic which may be administered orally.[3]

The oral route is considered the most convenient and easy route of drug_delivery. Yet, patient noncompliance, termed "intelligent noncompliance," due to feeling better, bad taste, etc., which is reasoned out by the patient but may not necessarily be wise, is one of the key causes of failure of oral dosage regimen. Paediatric and geriatric populations are most sensitive to the bad taste of medicaments. Also, currently there is a rising trend to formulate drugs in the form of orally disintegrating dosage forms due to their easy ingestion and absorption process. Thus, in these cases a good taste is indispensable to patient compliance. Moreover, high palatability gives a competitive advantage, especially in the case of over-the-counter products. In this review, we will discuss how taste is perceived, what techniques are available for taste masking, selection of appropriate taste masking technique, and evaluation tests for the same.[4]

A convenient means of presenting antibiotics for oral administration is in the form of granules which may be administered as a solution or suspension. Syrups are particularly convenient for oral administration of antibiotics to children. They are particularly aimed at patients with nausea, vomiting, motion sickness and institutionalised patients. However Cefuroxime axetil has an extremely bitter taste which is long lasting and this remains a challenge.[5]

Dry syrups are oral reconstitutable suspensions commercially available as dry mixtures that require the addition of water at the time of dispensing.The aim of this study is formulation development and evaluation of taste masked Cefuroxime Axetil Oral suspension. Many conventional tablets are available in adult strength and the administration of accurate dosage for children is critical. Oral suspension can be formulated in paediatric strength. Swallowing difficulty is another drawback with conventional tablet dosage form that can be overcome by Oral suspension formulation.[6]

Cefuroxime Axetil is a second generation cephalosporin antibiotic. It is used in the treatment of uncomplicated urinary tract infections, respiratory tract infections, otitis media, and Lyme disease.

The taste of Cefuroxime Axetil is extremely bitter. Marketed preparations of Cefuroxime Axetil currently available are not completely devoid of bitterness problem. So children cannot tolerate the bitter taste of the drug and vomit out during administration. The formulation of taste masked oral suspension was aimed to administer Cefuroxime Axetil in a more palatable form to obtain a "patient-friendly dosage form" especially for paediatric patients and hence that will increase the patient compliance. In the present work the problem is addressed and better taste masking methodologies were used for rectification.[7]

METHODS AND PROCEDURE

The formulation development progressed with different trials each differing in one or the other parameter. Initially preliminary trials F1 to F9 were taken to optimize each parameter and then the final formulations F7 was developed. The formulations are listed below.

Table 1: Preliminary Formulation F1 – F6

S.NO.	INGREDIENTS	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)
1	CA:BetaCD complex	481.033	481.033	481.033	481.033	481.033	481.033
2.	Sucrose	967.467	952.467	967.467	952.467	967.467	952.467
3.	Ratio	1:1	1:1	1:1	1:1	1:1	1:1
4.	Water	100%	100%	-		50%	50%
5.	Isopropyl alcohol	-	-	100%	100%	50%	50%
6.	Xanthan gum	4.00	4.00	-	-	4.00	4.00
7.	Talc	-	15.00	-	15.00	-	15.00
8.	Aspartame	17.50	17.50	17.50	17.50	17.50	17.50
9.	Acesulfame K	12.50	12.50	12.50	12.50	12.50	12.50
10	Tutti frutti flavour	17.50	17.50	17.50	17.50	17.50	17.50
	Avg. weight in mg/5ml	1500.00	1500.00	1500.00	1500.00	1500.00	1500.00

The quantity of sucrose compensates the final average weight per 5ml.

Table 2: Complexation Using Beta Cyclodextrin with the Incorporation of IPA & Talc

Sl No	INGREDIENTS	F7 (mg)	F8 (mg)	F9 (mg)
	FOR COMPLEXATION			
1	Cefuroxime axetil	158.875	163.875	158.875
2	Beta cyclodextrin	353.179	364.294	353.179
3	IPA	40%	30%	20%

4	Water	60%	70%	80%
	FOR BLENDING			
5	CA:B CD Complex	529.425	543.386	536.014
6	Sucrose	912.575	902.114	905.986
7	Acesulfame K	12.500	12.500	12.500
8	Aspartame	17.500	17.500	17.500
9	Xanthan gum	3.000	3.000	3.000
10	Talc	7.500	4.000	7.500
11	Tutti frutti flavour	17.500	17.500	17.500
	TOTAL	**1500.000**	**1500.000**	**1500.000**

Manufacturing procedure

1. The solvent was prepared.
2. The solvent was stirred under the mechanical stirrer.
3. The API and beta cyclodextrin were sifted through sieve # 30, and then transferred to solvent solution.
4. Stirred for 30 minutes.
5. The formation of smooth slurry was obtained.
6. The slurry was dried in the oven at 45ºc at 8 to 10 hrs.
7. Sifted the granules through sieve # 60.
8. The granules after cooling were used for formulation.
9. The sugar was dried at 60˚C for 2 hours.
10. Divided the sugar into two equal portions.
11. The first portion of the sugar was milled and sifted through sieve # 60.
12. Sifted the excipients through sieve# 40.
13. Geometrically blended the milled sugar with the granule.
14. Geometrically blended the excipients with the above blend.
15. The above portion was mixed with unmilled portion of sugar.
16. The powder was blend thoroughly.
17. Weighed and dispensed in bottles.

Formula optimisation

Based on the preliminary formulations inferences are drawn and the trials are focused to optimise the formulation.

Table 3: Optimized Formula

S.NO	INGREDIENTS	F7
1.	API	158.875
2.	Beta CD	353.179
3.	IPA	40%
4.	Water	60%
5	CA: B Cd complex	529.425
6.	Sucrose	912.575
7.	Aspartame	12.500
8.	Acesulfame K	17.500
9.	Xanthan gum	3.000
10.	Talc	7.500
11.	Tutti frutti flavour	17.500
Avg weight in mg/5ml		**1500**

Evaluation of oral suspension[8]

Taste Evaluation (Sensory Evaluation)

Sensory evaluation is defined as a scientific discipline used to measure, analyze and interpret reactions to those characteristic of materials as they are perceived by the senses of sight, smell, taste, touch and hearing.

Taste evaluation was done by taste panels. The method chosen was ranking test. For this purpose 20 human volunteers were selected. The suspension of the pure drug and formulations were coded and given to the volunteers. The intensity of bitterness was asked from volunteers. By using ranking test best taste masking technique was screened from all the adopted taste masking methods. Excellent; good; fair; bitter; extremely bitter;

Mouth feel

The mouth feel of the suspension is an important parameter with respect to its acceptance by the patient and thereby compliance. Gritty suspensions are usually not preferred. The data can be collected from the volunteers when given to taste.

Flow property

This is measured in terms of angle of repose, bulk density, tapped density, compressibility index, Hausner ratio which has been described earlier.

TASTE EVALUATION

Taste evaluation is done by taste panels. The method chosen is ranking test. The suspension of the pure drug and formulations prepared by various techniques were coded and

given to the volunteers. The intensity of bitterness was asked from volunteers. By using ranking test best taste masking technique was screened.

pH stability study

The formulation was studied for stability of pH. After reconstitution the suspension was stored at 2-8˚C and pH of the suspension was checked for 10 days.

Scale up

Once the optimised formula was finalised a higher batch of the final formulation is taken by extrapolating the same formula for 100 bottles.

RESULTS AND DISCUSSION

Taste Masking By Inclusion Complex Formation

Table 4: Results of Preliminary Formulations F1-F6

Parameters	F1	F2	F3	F4	F5	F6
Taste	Bitter	Bitter	Slightly	Slightly	Slightly	Slightly
Flavour	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient
Mouth feel	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth
Pourability and viscosity	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient
Bulk density	0.689	0.758	0.656	0.736	0.794	0.749
Tapped density	0.746	0.887	0.883	0.820	0.846	0.883
Angle of repose	30.68	31.61	32.52	32.4	29.98	31.59
Compressibility index	6.84	11.5	11	10.5	6.84	4.52
Hausner ratio	1.074	1.142	1.136	1.13	1.09	1.12
Dissolution	40.76	43.20	50.37	48.68	38.73	34.70
pH	5.38	6.38	6.07	6.28	6.32	6.30

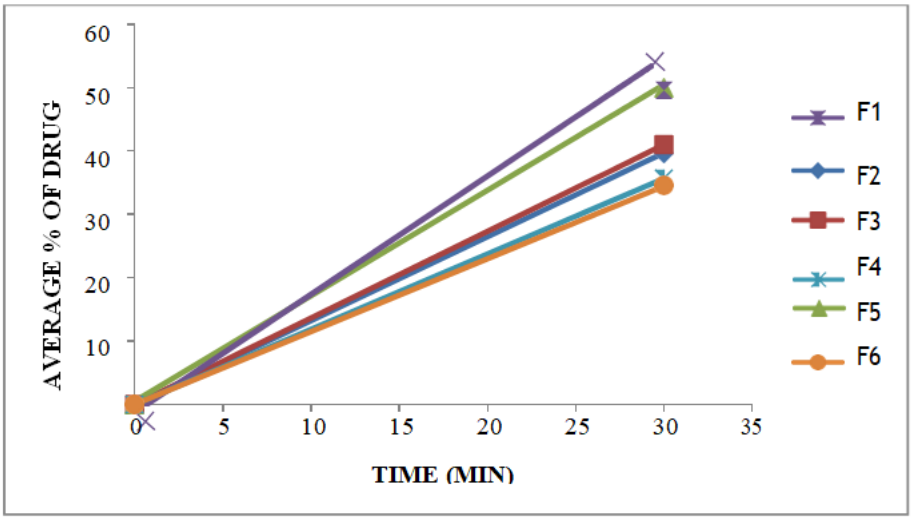


Fig 1: Dissolution Profile of Trails F1-F6

Table 5: Results Of Preliminary Formulations F7-F9

Parameters	F7	F8	F9
Taste	Slightly bitter	Slightly bitter	Slightly bitter
Flavour	Sufficient	Sufficient	Sufficient
Mouth feel	Smooth	Smooth	Smooth
Pourability and Viscosity	Sufficient	Sufficient	Sufficient
Bulk density	0.769	0.787	0.736
Tapped density	0.836	0.845	0.753
Angle of repose	29.41	28.94	29.98
Compressibility index	8.69	8.4	6.76
Hausner ratio	1.078	1.048	1.065
Dissolution	75.94	69.39	75.77

pH	6.39	6.58	6.15
Assay	101.6	98.22	98.54

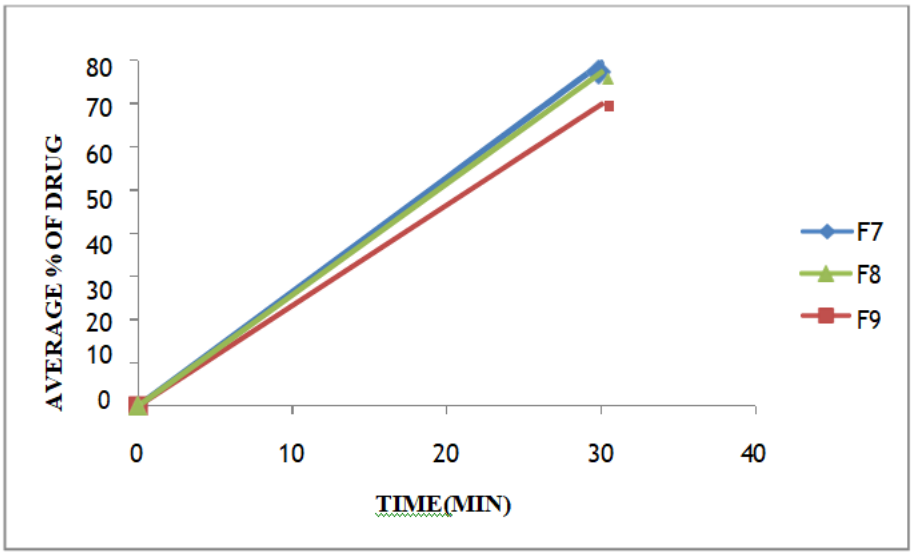


Fig 2: Dissolution Profile 0f Formulations F7-F9

DISCUSSION

Initial six formulations were taken by without adding IPA & talc to the Complexation part. So the dissolution was not improving. But in the formulations F7-F9 IPA and talc was incorporated into the Complexation part. Here talc improved the solubility of the Cefuroxime axetil: Betacyclodextrin complex.[9] For initial 2 formulations taste was not good, bitter taste and the dissolution was not in the limit. For formulations F3-F6 taste was good, slightly bitter taste and the dissolution was not in the limit. For formulations F7-F9 the taste was good, slight bitter after taste and the dissolution were increasing with increasing the concentration of Talc. In the case of F9 slight irritation on the throat occurs when increasing the talc concentration. So F7 was chosen as best formulation.[10-12]

Inferences from preliminary formulations

From the 9 preliminary formulations certain inferences were drawn. They are as follows.

1. The ideal ratio of drug: beta cyclodextrin was found to be 1: 1 taken on weight basis.
2. The fill weight was optimised at 1.5 grams per 5ml.
3. The taste of the bitter drug is improved when isopropyl alcohol and water (40% - 60%) is used in the solvent.
4. Ideal volume of complexing medium is 500 ml.
5. Ideal stirring time is 30 mins to 1 hrs.
6. The sweeteners along with sucrose contribute to taste abatement.
7. Talc enhances dissolution.
8. A 15-17.5mg/5ml Tutti frutti flavour works good at masking the bitter taste.
9. As the pH of the formulation remains below 6.5 there was no need to add any buffer.

Formula Optimization

Table 6: Result o f Optimized Formula

Parameters	**F7**
Taste	Slightly bitter
Flavour	Sufficient
Mouth feel	Smooth
Pourability and viscosity	Sufficient
Bulk density	0.769
Tapped density	0.836
Angle of repose	29.41
Compressibility index	8.69
Hausner ratio	1.078
Dissolution (%)	75.94

pH	6.39
Assay	101.6

Formulation F7 was chosen as the optimised formula. The bitter taste of the drug was masked to a larger extent by the complexation method. The flavour together with sweeteners have further improved the taste of the formulation. The average dissolution values lies at 75.94. The pH of the formulation was maintained below 6.39 which omits the use of any buffer.[13]

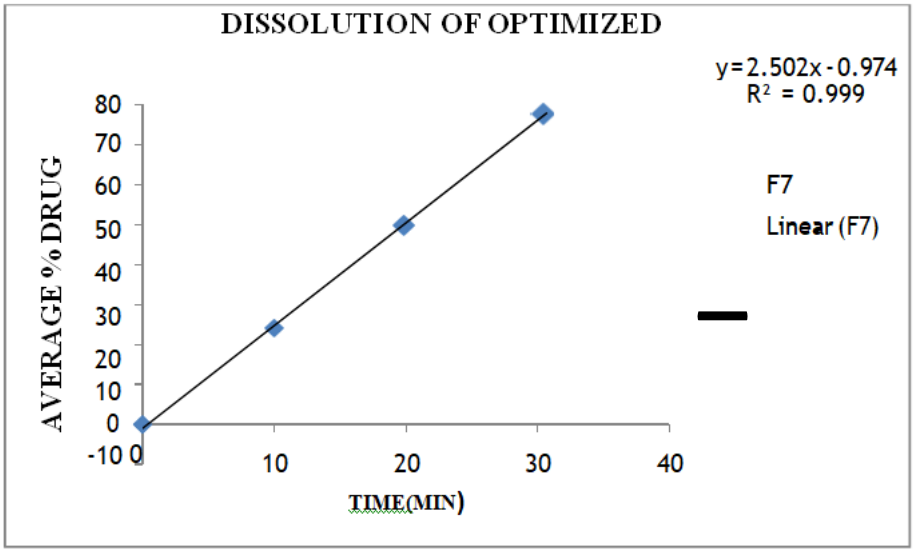
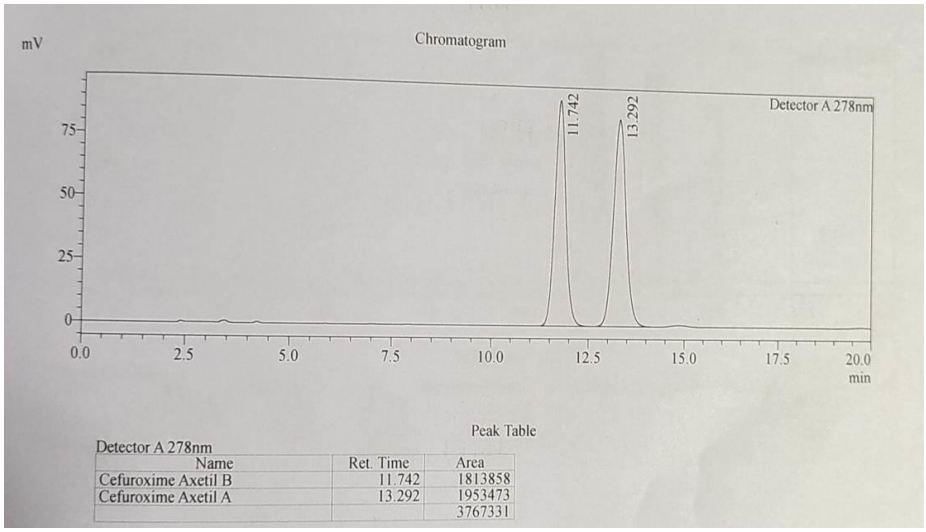


Fig 3: Dissolution Profile of Optimized Formulation



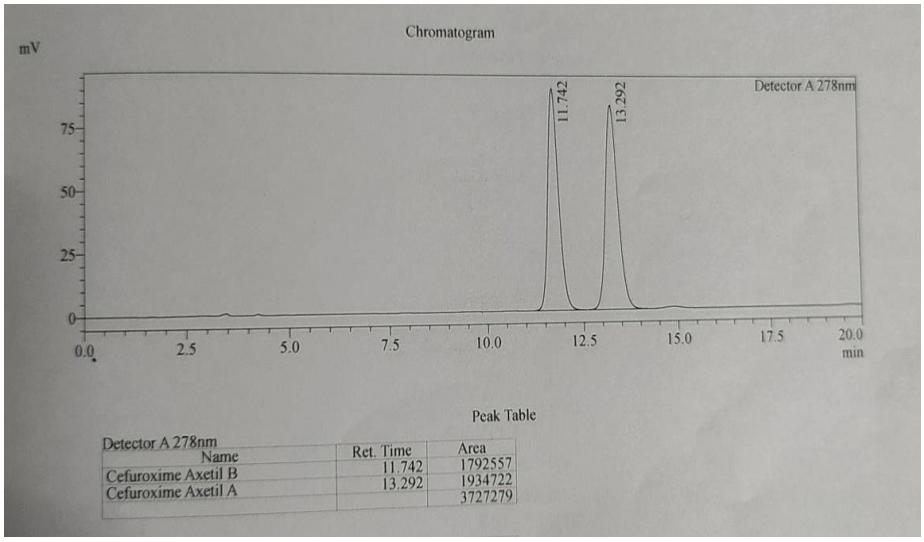


Fig 4: Assay of Optimized Formula F7

Comparison of Innovator Product with the Optimzed Formulation

The dissolution profile of the innovator product and the optimised formulation was compared and the results are shown below.

Table 7: Comparison of Innovator Product with the Optimzed Formulation

Time	Average % drug released	
	Innovator product	F7
10	24.6	25.1
20	45.2	47.3
30	75.03	75.94

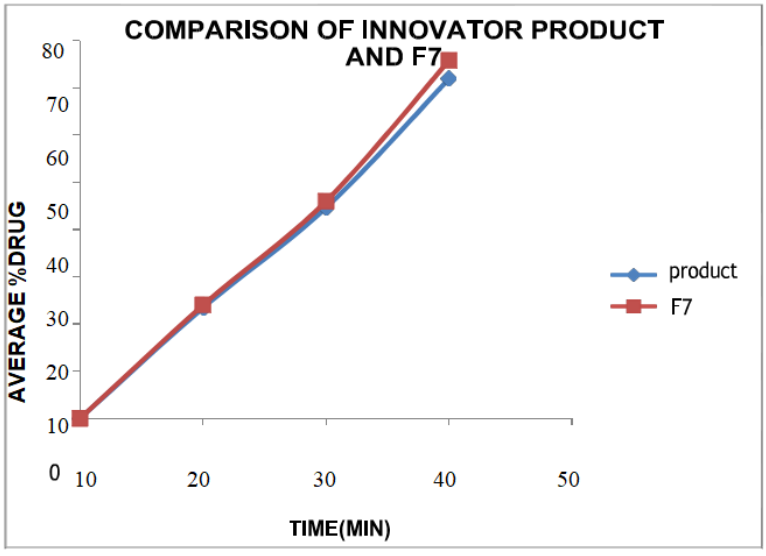


Fig 5: Comparison of Dissolution Profile

pH Stability Study

The dry powder after reconstitution were packed in HDPE bottles of 30 ml capacity and stored at 2-8˚C. The pH of the formulation was checked for 10 days.

Table 8: pH Stability study

DAYS	pH
Day 1	6.39
Day 2	6.28
Day 3	6.46
Day 4	6.54
Day 5	6.36
Day 6	6.24
Day 7	6.57
Day 8	6.42
Day 9	6.46
Day 10	6.56

Scale up study

The formulation F7 was selected as the lead for the scale up. The composition of scale up batch is listed below.

Table 9: Composition for Scale Up

SL NO	INGREDIENTS	Qty/5ml(mg)	Qty/30ml(g)	Qty/Batch in g
	FOR COMPLEXATION			
1	Cefuroxime axetil	158.875	0.953	9.530
2	Beta cyclodextrin	353.179	2.119	21.190
3	IPA	40%	40%	40%
4	Water	60%	60%	60%
	FOR BLENDING			
5	CA:B CD Complex	529.425	3.177	31.770
6	Sucrose	912.575	5.475	54.750
7	Acesulfame K	12.500	0.075	0.750
8	Aspartame	17.500	0.105	1.050
9	Xanthan gum	3.000	0.018	0.180
10	Talc	7.500	0.045	0.450
11	Tutti frutti flavour	17.500	0.105	1.050
	TOTAL	**1500.000**	**9.000**	**90.000**

The scale up batch was an extension of the formulation. The dry powders were filled into HDPE bottles of 30 ml capacity using dry syrup filling machine. The cap was sealed by induction sealing.

Stability studies

Short term accelerated stability studies were performed on the optimized oral suspension formulations packed in HDPE bottles of 30 ml capacity. Fifty oral suspensions were subjected to stability studies at 40°C/75% RH in a stability chamber for a period of 2 months. Initial evaluation of the suspension was done and at the end of first and second month the suspensions were again analyzed for its physical appearance, assay, water content and in vitro drug release profile.[14]

Study conditions: 40°C/75%RH Packing: HDPE bottles of 30 ml Equipment: Humidity chamber.

Table 10: Accelerated Stability Study Report

	Dissolution		Assay	
INITIAL	75.94	6.39	101.3	White Colour
1st MONTH	77.4	6.44	99.57	White Colour
2nd MONTH	79.5	6.53	98.20	White Colour

The accelerated stability studies reveal that the formulation has not undergone any physical or chemical degradation during the period. There are no significant differences in the in vitro drug release, pH and the drug content of the optimized formulation.

Anti Microbial Assay of Cefuroxime Axetil[15]

Three different wells were made in each petriplates for blank (B) and two dilutions (10^{-1} and 10^{-2}). Test sample was serially diluted in saline upto 10^{-2} dilutions.

Table 11: Diameter of inhibition zones

		Diameter of inhibition zones in different	
		10^{-1}	10^{-2}
1	E.coli	26mm	16mm
2	Bacillus subtilis	21mm	8mm
3	Salmonella typhi	24mm	14mm

SUMMARY AND CONCLUSION

The bitter taste of drugs remains a big challenge to the pharma sector especially when it deals with oral pharmaceutical to paediatric population. Cefuroxime axetil is a Betalactum antibiotic used for infections in the urinary tract, sinusitis, otitis media, angioedema, leukopenia, urticaria, seizure, erythema multiforme, renal dysfunction and so on. The highly bitter taste of drug reduces its patient compliance. In the present work the taste masking of the drug employed various techniques like masking with sweetener and flavour, drug particle coating with stearic acid and finally complexation with betacyclodextrin.

The inclusion complex formation with betacyclodextrin proved to be highly efficacious, cost effective and simple method. The drug is entrapped within the hydrophobic core of cyclodextrin thus reducing the solubility of drug in saliva. The complex is thought to separate inside the gastric environment thus releasing the drug. The drug is better absorbed from the upper part of intestine.

The complexation method is the simplest method. All the formulation parameters were crucially scrutinised and optimised the final formula. This final formula F7 is easily scale up to increase the batch size and less time consumed and fast output in production. The data of drug, complexing agent and optimised formulation confirms complexation. The suspension was taken on a scale up quantity and charged for stability studies. The report of the same has been furnished. The suspensions were evaluated as per USP standards. The in vitro studies of the suspension conclude here. Thus an attempt to mask the bitter taste of second generation cephalosporin antibiotic has been made.

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