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Formulation and Evaluation of Ceftazidime Chewable Tablets

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ABSTRACT

Antimicrobial agents are among the most commonly used and misused of all drugs. The inevitable consequence of the widespread use of antimicrobial agents has been the emergence of antibiotic-resistant pathogens, feeling an ever-increasing need for new drugs. The Cephalosporin antibiotics are useful and frequently prescribed antimicrobial agents that share a common structure and mechanism of action ¾ inhibition of synthesis of the bacterial peptidoglycan cell wall. The β-lactams also include the cephalosporin antibiotics. Cephalosporium acremonium, the first source of the cephalosporins, was isolated in 1948 by Brotzu from the sea near a sewer outlet off the Sardinian coast. by determining the Quality assurance parameters during manufacturing, which influence the dissolution behavior of the drug hence its bioavailability. The formulation and evaluation done after the survey of literature, it shows the better result rather than first and second class of cephalosporin as chewable tablets.

Keywords: Antimicrobials, cephalosporin chewable tablets, Peptidoglycan, Penicillin binding proteins, Cephalosporium acremonium.

INTRODUCTION

Ceftazidime is a **3rd generation** broad spectrum β- Lactam **cephalosporin class of antibiotic** administered orally in pediatric and adult patients. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftazidime and other antibacterial drugs,The bactericidal action of cephalosporin is due to the inhibition of cell wall synthesis. It binds to one of the penicillin binding proteins (PBPs) which inhibit the final transpeptidation step of the peptidoglycan synthesis in the bacterial cell wall, thus inhibiting biosynthesis and arresting cell wall assembly resulting in bacterial cell death.

The cephalosporins have molecular weights of 400–450. They are relatively stable to pH and temperature changes. Numerous patients express complexity in swallowing tablets and hard gelatin capsules, resulting in non-compliance and ineffective therapy. Current advances in novel drug delivery systems endeavor to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach led to development of fast chewable tablets. Bacterial resistance to an antimicrobial agent is attributable to three general mechanisms: (1) The drug does not reach its target, (2) the drug is not active, or (3) the target is altered.

EXAMPLES	USEFUL SPECTRUM
First Generation	
Cefazolin (ANCEF, ZOLICEF, others)	Streptococci b; Staphylococcus aureus. C
Cephalexin monohydrate (KEFTAB)	Streptococci b; Staphylococcus aureus. C
Cefadroxil (DURACEF)	Streptococci b; Staphylococcus aureus. C
Cephradine (VELOSEF)	Streptococci b; Staphylococcus aureus. C
Second Generation	
Cefuroxime (ZINACEF)	Escherichia coli, Klebsiella, Proteus, Haemophilusinfluenzae, Moraxella catarrhalis. Not as active against gram-positive organisms as first-generation agents. Inferior activity against S. aureus compared to cefuroxime but with added activity against Bacteroidesfragilis and other Bacteroides
Cefuroxime axetil (CEFTIN)	
Cefprozil (CEFZIL)	
Cefmetazole (ZEFAZONE)	
Loracarbef (LORABID)	
Third Generation	
Cefotaxime (CLAFORAN)	Enterobacteriaceaed; Pseudomonas aeruginosa e; Serratia; Neisseria gonorrhoeae; activity for S. aureus, Streptococcus pneumoniae, and Streptococcus pyogenes f comparable to first-generation agents. Activity against Bacteroides spp. inferior to that of cefoxitin and cefotetan.
Ceftriaxone (ROCEPHIN)	
Cefdinir (OMNICEF)	
Cefditorenpivoxil (SPECTRACEF)	
Ceftibuten (CEDAX)	
Cefpodoximeproxetil(VANTIN)	
Ceftizoxime (CEFIZOX)	
Cefoperazone (CEFOBID)	Active against Pseudomonas
Ceftazidime (FORTAZ, others)	Active against Pseudomonas
Fourth Generation	
Cefepime (MAXIPIME)	Comparable to third-generation but more resistant to some β-lactamases.

Table: 1.1 Classification of Cephalosporin

Category: Antibacterial
Sub Category: Antibiotic

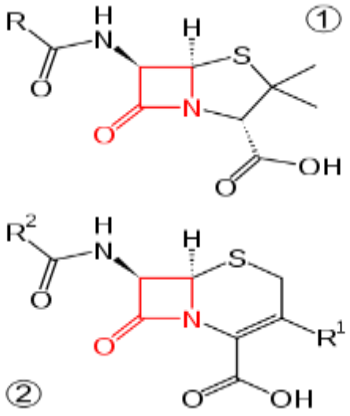

FIGURE 1: CHEMICAL STRUCTURE OF DRUG

Melting point: 240^0C

Appearance: yellowish-white crystalline powder

Solubility:

SOLVENT	SOLUBILITY
Propylene glycol	Very soluble
Methanol	Very Soluble
Ethanol	Soluble

Table: 1.2 Solubility of Different solvent

MATERIALS AND METHODOLOGY:

2.1 Visual Examination

A small quantity of Drug X powder was taken in butter paper and viewed in well-illuminated place for color observation.

2.2 Determination of absorption maxima (λmax) for analysis

For scanning the λmax of drug, standard solution was prepared. about 20 mg of pure drug was weighed and transferred to a 20 ml volumetric flask.10 ml of methanol was added and sonicated to dissolve and made up to mark with methanol. Further diluted 1 ml of resulting solution to 50 ml with methanol, mixed well and filtered through 0.45 Nylon filter. Standard solution was UV scanned between 200-400 nm and absorption maximum was determined spectrophotometrically. Methanol solvent was used as blank

2.3 Particle size distribution analysis

Particle size analysis of the micronized API was performed using Malvern Particle size analyser.

2.4 Water by KF (%w/w) andAssay

Equipment:

Karl Fischer Apparatus, Analytical Balance.

Chemicals & reagents:

Karl Fischer Reagent, Anhydrous methanol, Purified water.

Procedure:

- 500 mg of sample was taken and sufficient amount of anhydrous methanol added to the titration vessel and titrated to the electromeric end point with KF reagent.

- Quickly added 0.5 g of test samples mixed and again titrated to the electromeric end point with KF reagent.
- Water content was calculated by the following formula

Calculation:

$$\textbf{Water (\%m/m)} = \frac{v \times f \times 100}{w}$$

W = weight of sample taken (mg)

V = Volume of KF reagent consumed (ml)

F = Water equivalent factor of KF Reagent (mg/ml)

Water by KF was determined for Assay potency calculation

2.5 Flow property Determination

Flow property parameters like bulk density, tapped density, Hausner ratio, Compressibility index were calculated for determining flow properties of the drug.

2.6 Apparent Density / Bulk Density

Bulk density or apparent density is defined as the ratio of mass of a powder to the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

Method:

Weighed quantity of Drug X drug was weighed and transferred in graduated cylinder. Carefully leveling of the powder without compacting was done and unsettled apparent volume (V0) was noted. Then appearance bulk density in g/ml was calculated by the following formula:

$$\text{Bulk density} = \frac{\text{Weight of the API}}{\text{Bulk Volume}}$$

2.7 Tapped Density:

Weighed quantity of drug was taken and transferred in graduated cylinder. The cylinder containing the sample was mechanically tapped by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ±2 mm at a nominal rate of 300 drops per minute. Cylinder was tapped for 500 times initially and tapped volume (V_1) was measured to the nearest graduated units, repeated tapping of additional 750 times was done and tapped volume (V_2) was measured. Additional Repeated tapping was performed if the difference between the two successive volumes was less than 2% as per USP chapter <611>.

$$\text{T.D.} = \frac{Weight of API}{Final Tapped volume}$$

2.8 Compressibility index and Hausner Ratio: The Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particle interactions, and a greater difference between the bulk and tapped densities will be observed.

Hausner's Ratio indicate s the flow properties of the powder and is measured by the ratio of tapped density to bulk density. It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties.

Significance of Hausners ratio

Sr. No.	Hausner Ratio	Property
1	0–1.2	Free flowing
2	1.2–1.6	Cohesive powder

TABLE 2.1: HAUSNER'S RATIO

Method: The compressibility index and the Hausner ratio were calculated as follows:

$$Compressibility\ Index = \frac{T.D - B.D.}{T.D.} \times 100$$

$$Hausner\ Ratio = \frac{T.D.}{B.D}$$

Where B.D. = Bulk density
T.D. = Tapped density

3.0 FORMULATION DESIGN

Formulae for Preparation of Chewable Tablets of Ceftazidime.

In Formulation (F1,F2,F3), Direct Compression method was selected for tablet compression.

S.NO.	INGREDIENTS	F1 (Direct Compression)
1	Ceftazidime	227.52 mg
2	Perlitol (200 SD)	540.48 mg
3	Crosspovidone (XL -10)	70 mg
4	Aspartame	15 mg
5	Strawberry Flavor	10 mg
6	FDC red No 40 aluminium lake	1 mg
7	Magnesium stearate	6 mg
Total weight of tablet		870 mg

TABLE 3.1: FORMULA FOR PREPARATION OF F1 BY DIRECT COMPRESSION

Assay potency or Quantity of API per tablet (For API having d0.9=210.65µm) =

$$\frac{Label\ Claim\ X\ 100\ X\ 100}{\%\ Assay\ of drug\ x\ (100 - \%Water\ by\ KF)}$$

$$Quantity\ of\ API\ per\ tablet\ (mg) = \frac{200\ X100\ X100}{99.1\ X\ (100-11.3)} = 227.52\ mg$$

Note: In F1, F2,F3,F4 API having (d0.9)=210.65 µm particle size was used.
In F1, poor flow of blend from hopper was observed due to micronized nature of API and low particle size pearlitoli.ePearlitol 200 SD. Therefore tablets were difficult to be compressed by this method.
To overcome this problem, in F2, Pearlitol 500 DC andAerosil was used to improve flow property.

S.NO.	INGREDIENTS	F2 (Direct Compression)	F3 (Direct Compression)
1	Ceftazidime	227.52 mg	227.52 mg
2	Pearlitol (500 DC)	510.48 mg	500.48 mg
3	Crosspovidone (XL -10)	70 mg	70 mg
4	Aspartame	15 mg	15 mg
5	HPC LH 21	----	10 mg
6	Aerosil	30 mg	30 mg
7	Strawberry Flavor	10 mg	10 mg
8	FDC red No 40 aluminium lake	1 mg	1 mg
9	Magnesium sterate	6 mg	6 mg
Total weight of tablet		870 mg	870 mg

TABLE 3.2: FORMULA FOR PREPARATION OF F2 AND F3 BY DIRECT COMPRESSION

In F2, Capping was observed due to absence of binder in formulation. To overcome this problem, HPC LH 21 was added as binder in formulation F3. Tablets were compressed and checked for friability but friability test for tablets failed due to which further compression not performed and tablets not given for dissolution.

Therefore due to above a problem, Direct Compression method was not choosen and Roller Compaction method was selected for further formulations (F4-F9).

S.NO.	INGREDIENTS	F4 (Roller Compaction)	F5 (Roller Compaction)
Intragranular			
1	Ceftazidime	227.52 mg	223.99 mg
2	Pearlitol (200 DC)	500.48 mg	504.01 mg
3	Crosspovidone (XL -10)	50 mg	50 mg
4	HPC LH-21	10 mg	10 mg
5	Aspartame	15 mg	15 mg
Extragranular			
6	Strawberry	10 mg	10 mg
7	FDC red No 40 aluminium lake	1 mg	1 mg
8	Crospovidone (XL - 10)	20 mg	20 mg
9	Colloidal silicon dioxide (Aerosil 200)	30 mg	30 mg
Lubrication			
10	Magnesium sterate	6 mg	6 mg
Total weight of tablet		870 mg	870 mg

TABLE 3.3: FORMULA FOR PREPARATION OF F5 BY ROLLER COMPACTION

Assay potency or Quantity of API per tablet (For API having d90= 11.3µm) =

$$\frac{Label\ Claim\ X\ 100\ X\ 100}{\%\ Assay\ of drug\ x\ (100 - \%\ Water\ by\ KF)}$$

$$Quantity\ of\ API\ per\ tablet\ (mg) = \frac{200\ X100\ X100}{100.1\ X\ (100-10.8)} = 223.99\ mg$$

In F4, same particle size API was used as used in Formulations F1-F3. Tablets were -compressed. Dissolution of Tablets was performed in Official medium (pH 7.2 Phosphate Buffer). Dissolution was very slow. So in F5, API having particle size d(0.9)-11 µm was used to check the effect of particle size on dissolution by keeping same concentration of all functional excipients (Disintegrant, Binder, Lubricant) and amount of API change due to assay potency was adjusted in diluent quantity. Tablets were compressed and dissolution of tablets was performed. As a result, dissolution was still very slow as compared to innovator but better than F4. So this optimised particle size API was selected for further formulation devlopment.

As dissolution of F5 was very slow at both initial and end time points as compared to marketed drug formulation (Innovator) in the dissolution medium. To improve dissolution, In F6, quantity of crospovidone (Disintegrating agent) was increased in intragranular part. Dissolution increased at end time points but was slow in initial time points.

S.NO.	INGREDIENTS	F6 (Roller Compaction)	F7 (Roller Compaction)	F8 (Roller Compaction)
Intragranular				
1	Ceftazidime	223.99 mg	223.99 mg	223.99 mg
2	Perlitol (200 DC)	484.01 mg	474.01 mg	479.01 mg
3	Crosspovidone (XL -10)	70 mg	70 mg	70 mg
4	HPC LH-21	10 mg	10 mg	5 mg
5	Aspartame	15 mg	15 mg	15 mg
Extragranular				
6	Strawberry	10 mg	10 mg	10 mg
7	FDC red No 40 aluminium lake	1 mg	1 mg	1 mg
8	Crospovidone (XL - 10)	20 mg	30 mg	30 mg
9	Colloidal silicon dioxide (Aerosil 200)	30 mg	30 mg	30 mg
Lubrication				
10	Magnesium sterate	6 mg	6 mg	6 mg
Total weight of tablet		870mg	870 mg	870 mg

TABLE 3.8 : FORMULA FOR PREPARATION OF F6, F7, F8 BY ROLLER COMPACTION

Therefore in F7, quantity of crospovidone increased in extragranular part to increase dissolution at initial time points. Dissolution was improved.

In F8, quantity of HPC LH 21 was decreased to decrease disintegration time of tablet and to further improve dissolution. As a result disintegration time was decreased and increase in dissolution was also observed. Hence dissolution profile of F8 was found to be very similar with that of innovator in official medium (pH 7.2 Phosphate buffer).

Hence F8 was optimised and selected as final formula for further batches. Formulation F9 was taken as scale up batch keeping same formula as that of F8.

FORMULAE FOR SCALE UP BATCH CHEWABLE TABLETS OF CEPHALOSPORINS

F9 (SCALE UP)

S.NO.	INGREDIENTS	F9 (Roller Compaction)
Intragranular		
1	Ceftazidime	223.99 mg
2	Perlitol (200 DC)	479.01 mg
3	Crosspovidone (XL -10)	70 mg
4	HPC LH-21	5 mg
5	Aspartame	15 mg
Extragranular		
6	Strawberry	10 mg
7	FDC red No 40 aluminium lake	1 mg
8	Crospovidone (XL - 10)	30 mg
8	Colloidal silicon dioxide (Aerosil 200)	30 mg
Lbrication		
9	Magnesium sterate	6 mg
Total weight of tablet		870 mg

TABLE 3.9: FORMULA FOR PREPARATION OF F9 BY ROLLER COMPACTION

RESULT AND DISCUSSION:

4.1 Determination of absorption maxima (λmax) for analysis

The organic molecules in solution form, upon exposure to light in the ultra-violet region of the spectrum, absorb light of particular wavelength depending on the type of electronic transition associated with the absorption. Ceftazidimesolution (20µg/ml) was scanned between 200-400 nm and absorption maximum was determined spectrophotometrically. From the curve, λmax for Ceftazidimewas found at 288 nm,

4.2 Standard curve of Ceftazidime (optimized particle sized API)

The standard plot was prepared by taking concentration on x-axis and the absorbance on y-axis. The calibration equation for straight line was obtained.

Level	Concentration (µg/ml)	Absorbance		Average absorbance
		Replicate-I	Replicate-II	
0%	0.00	0.000	0.000	0.000
10%	1.82	0.055	0.057	0.056
20%	3.64	0.115	0.115	0.115
40%	7.28	0.223	0.223	0.223
60%	10.91	0.335	0.335	0.335
80%	14.55	0.441	0.440	0.441
100%	18.19	0.537	0.538	0.538
Y-intercept		0.0095		
Slope		0.0292		

Square of correlation coefficient(R^2)	0.9994
Residual sum of square	0.00061

Table 4.1: Absorbance versus Concentration Values

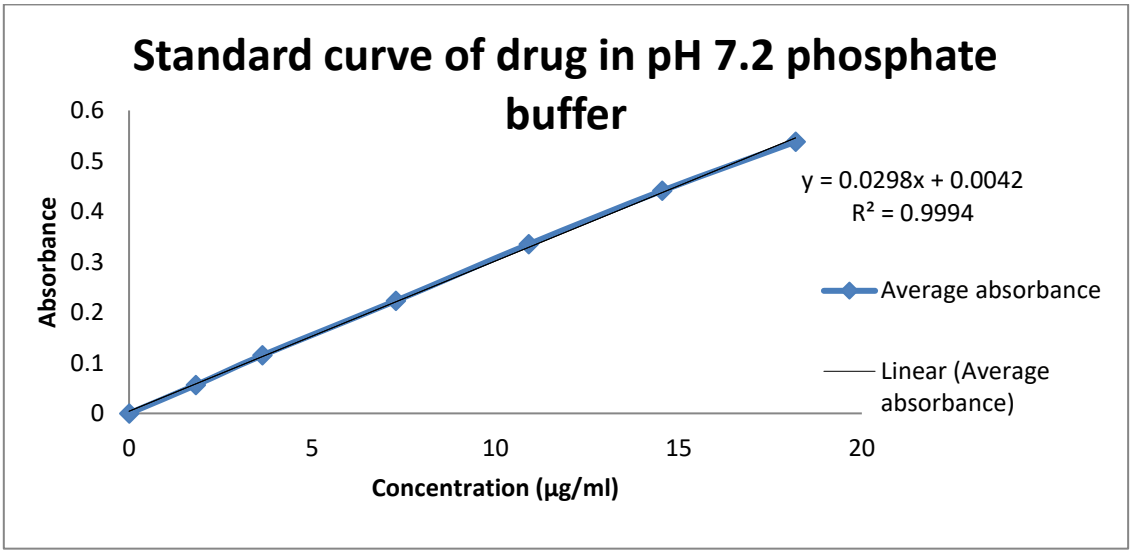

Figure 2- Standard Curve of Drug

4.3 FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR) STUDIES

FTIR of optimized particle size API was performed using KBr disc method.

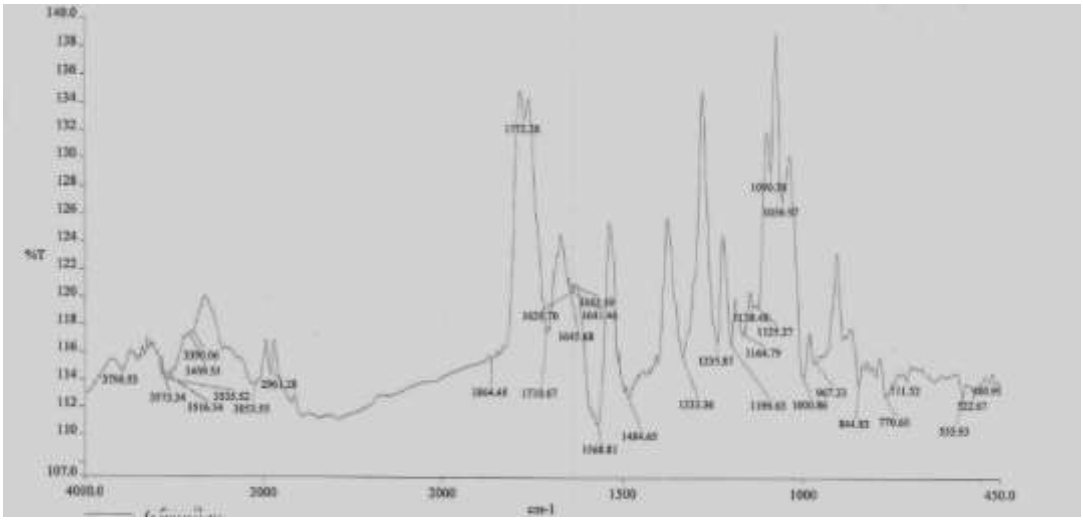

Figure 3: FTIR Spectrum of Ceftazidime

Note: Optimization of particle size was done on basis of dissolution results of the formulation.

4.3 FORMULATION TESTING

Direct Compression method

In F1-Poor flow of blend from hopper was observed due to micronized nature of API and low particle size pearlitoli.ePearlitol 200 SD. Therefore tablets were difficult to be compressed by this method.
To overcome this problem, in F2, Pearlitol 500 DC andAerosil was used to improve flow property.

In F2- Capping was observed due to absence of binder in formulation. To overcome this problem, HPC LH 21 was added as binder in formulation F3.

In F3- Tablets were compressed and checked for friability but friability test for tablets failed due to which further compression not performed and tablets not given for dissolution.

Therefore due to above problems, Direct Compression method was not choosen and Roller Compaction method was selected for further formulations (F4-F9).

In F4 and F5, particle size optimisation and selection of particle size was done to check effect on dissolution. **In F4**, API having d(0.9)-210.60 µm particle size was used as used in F1 and F2. As in **F5**, API having particle size d(0.9)-11 µm was used, dissolution was better than that of F4. Therefore for further formulation development this optimised particle size d(0.9)-11 µm was selected for further formulation.

In F5, disintegrating agent crospovidone added in extragranular part increased dissolution at initial time points.

In F6, disintegrating agent crospovidone added in intragranular part increased dissolution at end time points.

In F7, disintegrating agent crospovidone added in extragranular part as compaired to F5 increased dissolution at initial time points.

In F8, added amount of Hydroxypropyle cellulose (LH-21) decreased, decreased disintegration time and further increased dissolution. Dissolution profile of F8 tablets was found to be similar with innovator.

In F9, dissolution profile of tablets also found to be similar with innovator.

Evaluation of tablets

Formulation Code	Weight Variation	Friability (%)	Thickness (mm)	Hardness (kp)	Disintegration Time
F3	Passed	0.210	4.40-4.56	7.2-8.3	35 sec - 45 sec
F4	Passed	0.198	4.26-4.48	7.4-8.1	45 sec - 56 sec
F5	Passed	0.223	4.50-4.40	7.0-8.5	40 sec - 45 sec
F6	Passed	0.321	4.40-4.55	7.0-8.1	39 sec - 42 sec
F7	Passed	0.305	4.73-4.90	7.0-8.2	25sec - 30sec
F8	Passed	0.279	4.80-4.90	7.4-8.3	35 sec - 45 sec
F9	Passed	0.298	4.75-4.85	7.4-8.1	35 sec - 45 sec

FormulationCode	**Thickness(mm)**	**Disintegration time**	**Assay (%)**
F8	4.80-4.90	35 sec - 45 sec	100.2
F9	4.75-4.85	35 sec - 45 sec	98.5

Table 4.2: Evaluation of tablets of all formulations

Comparative dissolution profile of various formulations with Innovator in pH 7.5 phosphate buffer medium.

Time (in min.)	Innovator (% CDR)	F3 (% CDR)	F4 (% CDR)	F5 (% CDR)	F6 (% CDR)	F7 (% CDR)	F8 (% CDR)
0	**0**	0	0	0	0	0	0
10	**65**	30	49	40	42	52	61
15	**85**	43	59	64	68	70	83
20	**94**	52	67	70	80	86	95
30	**99**	69	77	97	98	100	100
45	**102**	77	80	98	99	101	101

Table 4.3: Comparative Dissolution Profile In Various Formulation pH 7.2 phosphate buffer medium

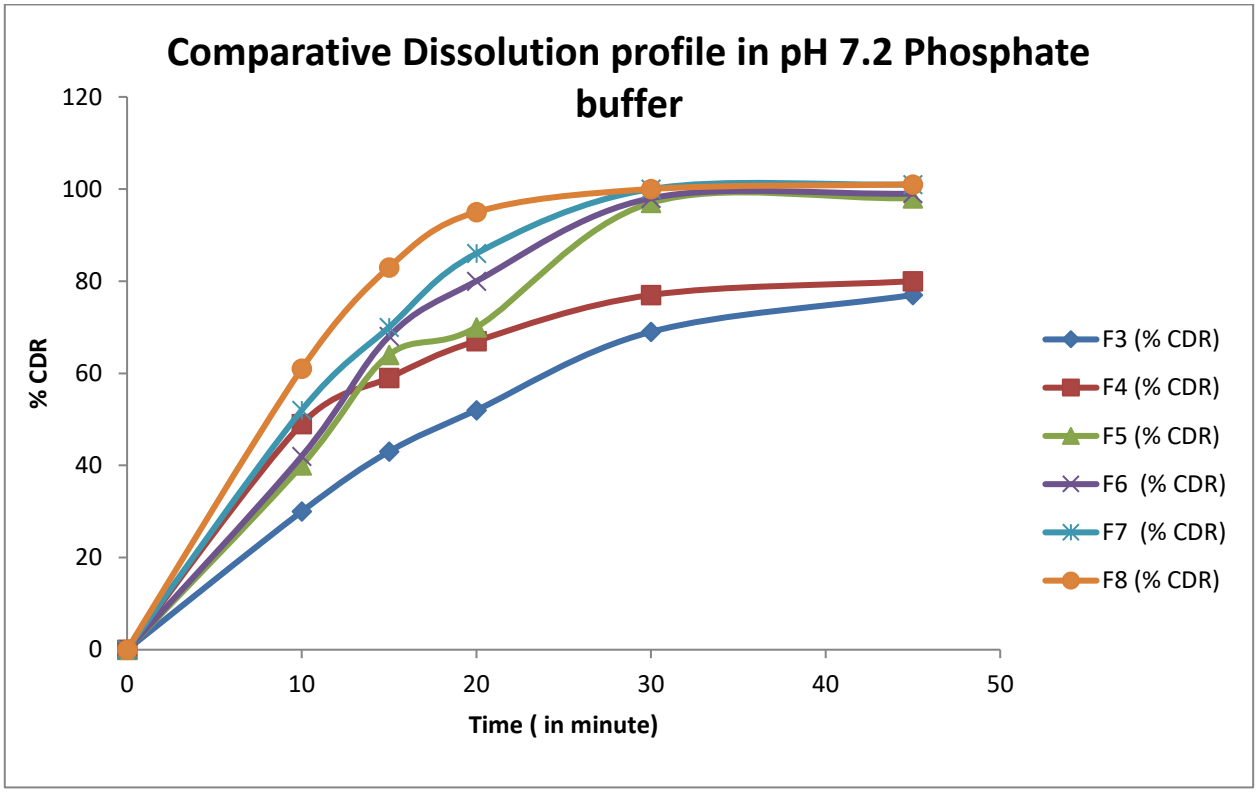

Fig. 3: Comparative Dissolution Profile InVarious FormulationpH 7.5 phosphate buffer medium.
F2 value for best formulation (F8) - 71

Comparative dissolution profile of final formulations F7 and F8 tablets with Innovator in pH 7.2 phosphate buffer medium.

Time (in min.)	Innovator (% CDR)	F8 (%CDR)	F9 (%CDR)
0	**0**	0	0
10	**65**	60	61
15	**85**	82	83
20	**94**	93	95

30	**99**	100	100
45	**102**	101	101
Similarty factor (f2) Value		**69**	**71**

Table 4.4: Comparative between F7, F8 Tablet with Innovator

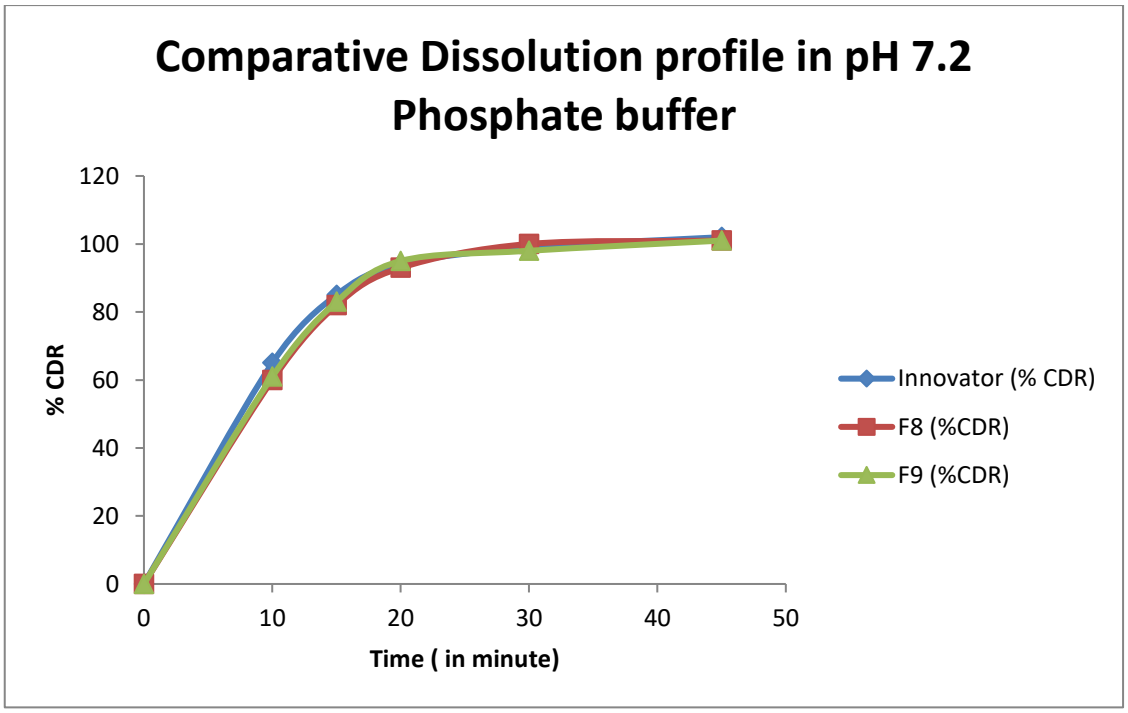

Figure 4: Comparative Dissolution Profile In pH 7.5 phosphate buffer medium.

Stability data of Final Formulation (F9) at accelerated conditions (40º C±2/75%±5 RH) at 3 months

Sr. No .	**Test**	**Specifications**	**Initial (RT)**	**After 1 month (40ºC/75%RH)**	**After 2 Months (40ºC/75%RH)**	**After 3 Months (40ºC/75 %RH)**
1	Description	Pink colour ,round shaped,smooth tablets, debossed with 'C13' on one side and plain on other side	Complies	Complies	Complies	Complies
2	Assay (By HPLC) (%)	90-110	98.5	97.8	97.1	96.9
3	Dissolution	NLT 75 % Q at 45 minutes	99	101	102	101

	(in pH 7.2 phosphate buffer)					

Table 4.5: Physical and chemical parameter analysis before and after Accelerated Stability Study (40º C±2/75%±5 RH).

Tablets were found to be stable as all the physical and chemical properties were found within limits mention in monograph.

Hence Formulation, development, evaluation of stable and bioequivalent chewable tablet was attained.

CONCLUSION

The aim was to develop a stable chewable tablet of cephalosporins whose in-vitro dissolution profile is similar or to the nearby with that of marketed dosage form, so that a dosage form having same therapeutic efficacy at a low cost can be available in the market.

As Drug X has poor dissolution property. Therefore dissolution was improved by using micronised API, binder, disintegrant in the formulation.

Preformulation study was performed. In-vitro parameters of formulations were evaluated. As according to USFDA guideline, similarty factor (f2) value should be between 50-100 in official medium. Therefore Formulation F8 was selected as best formulation as its dissolution profile was found to be similar (On basis of similarty factor f2 value 66) with that of Innovator in official medium (pH 7.2 phosphate buffer medium). Tablets dissolution was performed. Dissolution profile of F8 tablets also was found to be similar with that of innovator.

It was optimised and Scale up (F9). Dissolution profile of F9 tablets was also found to be similar in pH 7.2 phosphate buffer medium (Similarty factor f2 value 63). Stability studies of final batch F9 (after packing) were performed and the product was found stable. Thus objective of Formulation, development and evaluation of a stable and bioequivalent chewable tablet was attained.

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