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Evaluation and Comparison of *In-Vitro* Dissolution Profiles for Different Brands of Cefixime Tablet

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ABSTRACT

Background: Cefixime is an oral semi-synthetic, cephalosporin class of antibiotics used to treat bacterial infections caused by susceptible microorganisms. It is usually prepared in capsule, tablet, and powder for oral suspension form. Solid dosage forms for oral administration pose bioavailability problems related to the absorption process. The World Health Organization (WHO) has promoted the use of generic brands to make the cost of medicines affordable. Generic substitution could be considered when a generic copy of a reference drug contains identical amounts of the same active ingredient in the same dose formulation and route of administration. However, the presence of generic products that is not interchangeable with that of the innovator and/or with each other has been reported. **Objective:** To evaluate and compare the *in-vitro* dissolution profiles of generic cefixime tablets with a different brand of cefixime tablets that are available in the market. **Methods:** Different brands and generic tablets contain cefixime 200mg which are available in the market were used to determine the dissolution profile as per United States Pharmacopoeia (USP, 2018). The obtained dissolution profile data of the three brands and one generic were evaluated and compared using single-factor ANOVA methods. Most brands cefixime tablets are not interchangeable with the generic (Better dissolution in generic was found). **Results:** By single factor, the ANOVA method calculates the P-value and compares it with the reference value (0.05). The P-value for CFX4 (generic) with CFX1, CFX2, and CFX3 was found to be 0.16, 0.0001, and 0.001, respectively and Calculated F-value was found to be lesser than critical in case of comparison of generic with CFX1 brand but higher in case of CFX2 and CFX3. Conclusion: **Most brand cefixime tablet is not interchangeable with the generic.**

INTRODUCTION

Cefixime chemically is (6R, 7 R)-7-[[(2Z)-2-(2-aminothiazol-4-y l)[(carboxymethoxy)imino]acetyl] amino]-3-ethenyl-8-oxo-5-thia1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It is clinically used in the treatment of susceptible infections including gonorrhea, otitis media, pharyngitis, lower respiratory tract infections such as bronchitis, and urinary tract infections. Cefixime exerts antibacterial activity by interfering with bacterial peptidoglycan synthesis after binding to the β- lactam-binding proteins [1,2].

It is official in Indian pharmacopeia (IP,2018), British Pharmacopoeia (BP,2016), United States Pharmacopoeia (The USP, 2018), and in European Pharmacopoeia (EP, 2013) and details procedure for dissolution study of Cefixime tablet was described in the United States Pharmacop[eia] [2,3,4,5,6]. Our study was performed according to pharmacopeia to evaluate and compare the dissolution criteria of the available brands of Cefixime 200mg tablet dosage forms of different brand and generic.

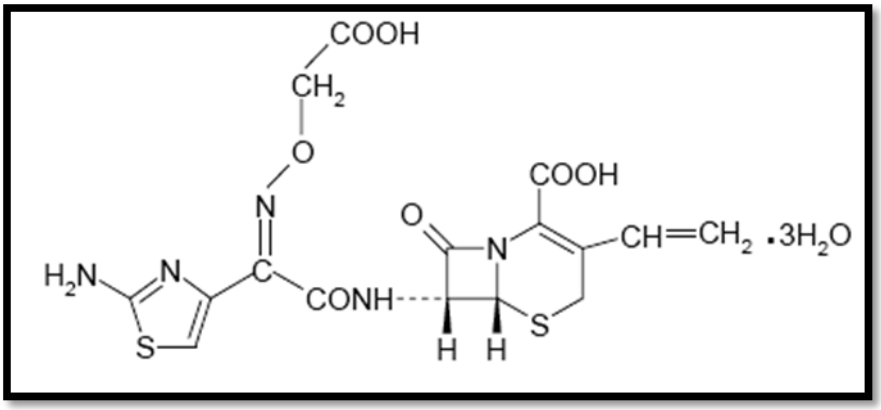


Figure No. 1: Chemical structure of Cefixime trihydrate [7,8]

Adequate oral bioavailability is a key pre-requisite for an orally administered drug to be systemically effective. Dissolution is defined as the rate of mass transfer from the surface of the dosage form to the bulk of the solution. "Dissolution is the process by which a solid substance enters into the solvent phase to yield a solution'' Dissolution is of primary importance for all conventional, solid oral dosage forms, and can be the rate-limiting step for the absorption of drugs administered orally especially for lipophilic drugs [9].

Variable therapeutic responses to therapeutically equivalent drug products have been reported with so-called branded generics and batch-to-batch inconsistencies have also been

reported. Different products with the same amount of API have shown distinct differences in their therapeutic effects. The reasons may be either due to the differences in rate and extent of absorption, or difference between the purity of active ingredients, type of excipients, the proportion between them and the manufacturing variables such as the influence of mixing method and granulation procedure as well as coating parameters[10].

The dissolution of the drug is extremely important as it determines the bioavailability as well as the therapeutic efficacy of the drug. Hence, the dissolution analysis of pharmaceutical solid dosage forms has emerged as a very important test of product quality as well as for differentiating among the formulation of the same therapeutic agent[11,12]. So we perform a dissolution test to compare the dissolution profile of the different brand and generic cefixime tablets and the result was evaluated by the ANOVA method to find out having significance differences or not.

MATERIALS AND METHODS

Apparatus:

A USP standard dissolution apparatus (Electrolab) with Basket System (USP-1) having six vessels for dissolution was used to perform the dissolution study. UV-VIS Spectrophotometer (UV-1800), Shimadzu, Japan with the appropriate cell was used to measure the absorbance of all solutions. All the samples were weighted in electronic balance (CX-200 Citizen). pH meter (DO-505, Digital Instrument Corporation) was used to measure the pH of the buffer. Some other apparatus e.g Sonicator, Filter paper (Whatman), measuring cylinder, volumetric flask, tripod stand, and pipette were also used.

Material and Reagents:

The cefixime 200mg tablet of different 3 brands and 1 generic were collected from the market. The brand tablet was coded randomly as CFX1, CFX2, CFX3 and generic as CFX4. Standard of Cefixime trihydrate was provided by B.K. MODY government pharmacy college Rajkot, Gujrat (INDIA). Monobasic Potassium Phosphate **(**Molychem), Sodium Hydroxide **(**Molychem) and Methanol (Finisar Pvt. LTD) was also used in the study.

Preparation of Phosphate Buffer (0.05M) PH 7.2:

According to U.S. Pharmacopoeia, 6.8 gm of monobasic potassium phosphate (KH_2PO_4)

was dissolved in 1000ml of water. pH was adjusted to 7.2 with 1N sodium hydroxide (NaOH) solution [3,4].

Preparation of calibration curve:

Weigh accurately 10mg of cefixime and dissolve in 5ml methanol in a 100ml volumetric flask. Make up the volume with phosphate buffer pH 7.2 (Stock Solution). Take 10ml from the above solution and makeup to 50ml with the same phosphate buffer. Prepare further diluted solution of 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, 12 µg/ml, 16 µg/ml, and 18 µg/ml with same buffer. Take UV absorbance at 288nm and plot calibration curve to get (y=mx+c) equation.

Procedure for *in-vitro* dissolution study:

Dissolution studies were conducted on a USP standard Dissolution apparatus having six Basket assembly (USP-1 apparatus)[4]. Each of 6 dissolution vessels was filled with 900 ml of phosphate buffer pH 7.2 and waited for equilibrating the temperature of the dissolution medium to 37˚c± 0.5˚c. Six samples in six dry baskets of the metallic shaft were placed and taken care to exclude air bubbles from the surface of the tablets, immediately operated the apparatus at 100 RPM [2-6]. 10ml sample was withdrawn from each jar at the time point of 10, 20, 30, &45minutes and filter it. Take 1ml from the above solution and add 1-2 drops of methanol and then the volume is made up to 10ml with the same buffer. The absorbance of sample solutions was measured in a UV-VIS spectrophotometer at wavelength 288 nm against the blank (buffer) solution. Calculate the drug concentration from y=mx+ C (slope of standard curve of cefixime) and find out the % drug release or % drug dissolved.

Dissolution Specifications

Table No. 1: Dissolution specifications

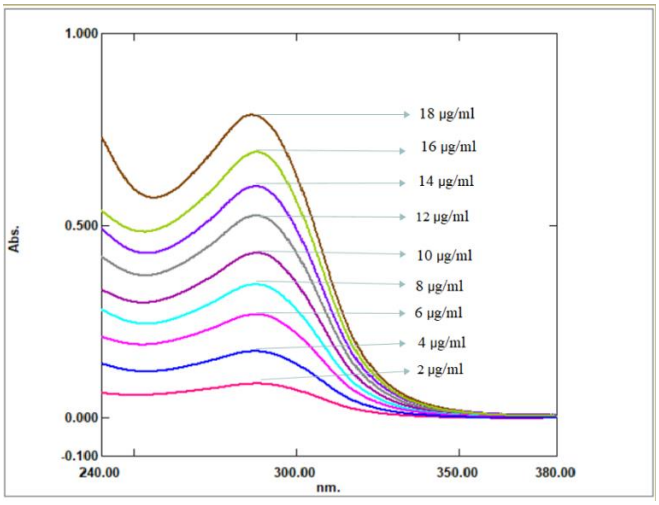
Drug name:	Cefixime tablet
Temperature:	37± 0.5 ◦C
Speed of rotation:	100 rpm
USP apparatus:	Type 1 (Basket)
Medium:	Phosphate buffer pH 7.2
Volume:	900 ml
Sampling times:	At 10, 20, 30, and 45minutes
Dissolution tester:	Dissolution tester (USP) TDT-08L

RESULTS AND DISCUSSION

RESULTS

The calibration curve for cefixime was obtained linear over the concentration range of 2-18 µg/ml with R^2 = 0.9996 and dissolution was performed for all brand and generic cefixime tablets. In dissolution test generic and 1 brand (CFX1) passed the test as per USP(2007) but 2 brand tablet CFX2 and CFX3 do not pass the test as per USP(2007). For comparison of the dissolution profile of the different brands and generic cefixime tablets use a single factor ANOVA method. By this method, we calculate P-value and compare it with the reference value (0.05). Calculated P-value for CFX4 (GENERIC) and CFX1 was found to be 0.16 and it is greater than a reference value or Calculated F-value is lesser than F-critical so the difference was not significance and both dissolution profile is comparable. Calculated P-value for CFX4 (GENERIC) and CFX2 was found to be 0.0001 and it is lesser than a reference value or Calculated F-value is greater than F-critical so the difference was significance and both dissolution profile is not comparable. Calculated P-value for CFX4 (GENERIC) and CFX3 was found to be 0.001 and it is lesser than a reference value or Calculated F-value is greater than F-critical so the difference was significance and both dissolution profile is not comparable.

Calibration Curve of Cefixime:



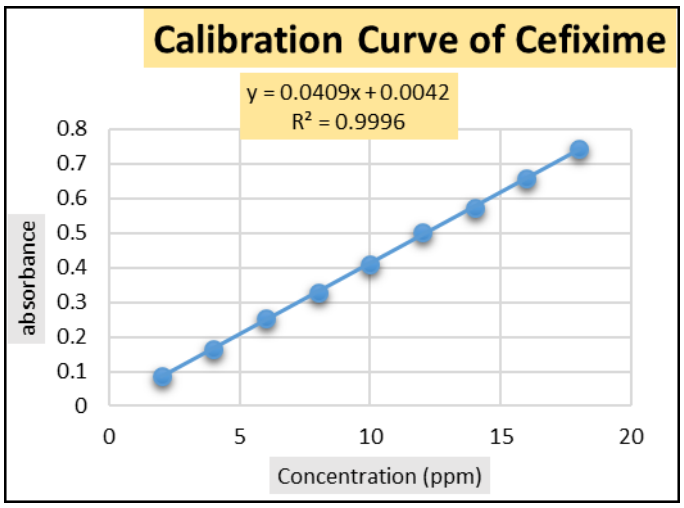


Figure No. 2: Calibration curve graph

PERCENT DRUG RELEASE OF DIFFERENT BRAND OF CEFIXIME:

Table No. 2: CFX1 drug release

Time (min)	Avg. Abs. of 6 Jar	Conc.in 1ml (mg)	Dilution	Actual conc. (mg/ml)	Conc. in 10ml	Cumulative release (in 10ml)	Conc. in 900ml (mg)	Actual conc.in 900ml(mg)	% Drug release
0	0	0	10	0	0	0	0	0	0
10	0.964	0.023	10	0.235	2.35	2.35	211.17	211.16	105.58
20	1.035	0.025	10	0.252	2.52	4.87	226.79	229.13	114.56
30	1.010	0.025	10	0.246	2.46	7.33	221.36	226.22	113.11
45	1.001	0.024	10	0.244	2.437	9.76	219.31	226.63	113.31

Table No. 3: CFX2 drug release

Time (min)	Avg. Abs. of 6 Jar	Conc.in 1ml (mg)	Dilution	Actual conc. (mg/ml)	Conc. in 10ml	Cumulative release (in 10ml)	Conc.in 900ml (mg)	Actual conc.in 900ml(mg)	% Drug release
0	0	0	10	0	0	0	0	0	0
10	0.545	0.013	10	0.132	1.32	1.32	119.08	119.08	59.54
20	0.545	0.013	10	0.132	1.32	2.65	119.08	120.40	60.20
30	0.549	0.013	10	0.133	1.33	3.98	119.96	122.60	61.30
45	0.543	0.013	10	0.132	1.32	5.29	118.45	122.43	61.22

Table No. 4: CFX3 drug release

Time (min)	Avg. Abs. of 6 Jar	Conc.in 1ml (mg)	Dilution	Actual conc. (mg/ml)	Conc. in 10ml	Cumulative release (in 10ml)	Conc. in 900ml (mg)	Actual conc.in 900ml (mg)	% Drug release
0	0	0	10	0	0	0	0	0	0
10	0.520	0.013	10	0.126	1.26	1.26	113.49	113.43	56.71
20	0.517	0.013	10	0.125	1.25	2.51	112.80	114.07	57.03
30	0.520	0.013	10	0.126	1.26	3.77	113.54	116.05	58.03
45	0.511	0.012	10	0.124	1.24	5.01	111.45	115.22	57.61

Table No. 5: CFX4 drug release

Time (min)	Avg. Abs. of 6 Jar	Conc.in 1ml (mg)	Dilution	Actual conc. (mg/ml)	Conc. in 10ml	Cumulative release (in 10ml)	Conc. in 900ml (mg)	Actual conc.in 900ml (mg)	% Drug release
0	0	0	10	0	0	0	0	0	0
10	0.771	0.019	10	0.187	1.87	1.87	168.66	168.66	84.33
20	0.899	0.022	10	0.219	2.19	4.06	196.97	198.85	99.42
30	0.954	0.023	10	0.232	2.32	6.38	208.93	212.99	106.50
45	1.012	0.025	10	0.246	2.46	8.85	221.84	228.22	114.11

% Drug release of a different brand of cefixime:

Table No. 6: CFX4 drug release

TIME (min)	CFX1	CFX2	CFX3	CFX4(GENERIC)
10	105.58	59.54	56.71	84.33
20	114.57	60.20	57.03	99.42
30	113.11	61.30	58.03	106.50
45	113.32	61.22	57.61	114.11

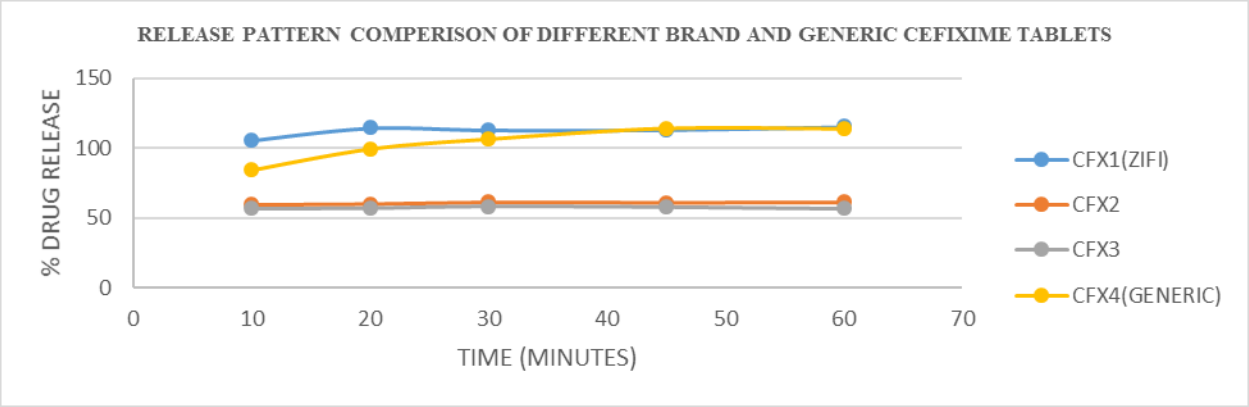


Figure No. 3: Release pattern comparison

Evaluation by ANOVA:

For comparison of the dissolution profile of different marketed cefixime tablets by using a single factor ANOVA method and analyze the result data to find out the difference is significant or not.

Table No. 7: Comparison of CFX4 (GENERIC) and CFX1

ANOVA: Single Factor

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
CFX4(GENERIC)	4	404.36	101.09	160.81
CFX1	4	446.58	111.64	16.74

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	222.82	1	222.82	2.51	0.164	5.98
Within Groups	532.69	6	88.78			
Total	755.52	7				

ANOVA: Single Factor

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
CFX4(GENERIC)	4	404.36	101.09	160.81
CFX2	4	242.25	60.56	0.72

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	3284.82	1	3284.82	40.67	0.001	5.98
Within Groups	484.60	6	80.76			
Total	3769.42	7				

Table No. 8: Comparison of CFX4 (GENERIC) and CFX2

ANOVA: Single Factor

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
CFX4(GENERIC)	4	404.36	101.09	160.81
CFX3	4	229.38	57.34	0.34

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	3827.13	1	3827.13	47.49	0.001	5.98
Within Groups	483.48	6	80.58			
Total	4310.61	7				

DISCUSSION

In the present study, the dissolution profile comparison is carried out by a single factor ANOVA method. In this method calculated P-value is compared with reference P-value (0.05). Calculated P-value for CFX4 (GENERIC) and CFX1 was found to be 0.16 and it is greater than the reference value (or Calculated F-value is lesser than F-critical) so the difference was not significance and both dissolution profile is comparable. Calculated P-value for CFX4 (GENERIC) and CFX2 was found to be 0.0001 and it is lesser than the

reference value (or Calculated F-value is greater than F-critical) so the difference was significance and both dissolution profile is not comparable. Calculated P-value for CFX4 (GENERIC) and CFX3 was found to be 0.001 and it is lesser than the reference value (or Calculated F-value is greater than F-critical) so the difference was significance and both dissolution profile is not comparable.

CONCLUSION

In the present study, dissolution is carried out using USP apparatus-I, 100RPM and 900ml phosphate buffer 7.2 as a dissolution medium and results of different brand and generic cefixime tablets were carried out using single-factor ANOVA method. As per result, it concludes that CFX1 and CFX4 (generic) passes the test as per USP-2018 and both dissolution profile is comparable but CFX 2 and CFX3 fail to complies and these marketed brand is not comparable. From the above study, we also conclude that dissolution is depended only on the formulation, process, and excipient used in it, not on brand and generic category so we cannot say that generic tablet is secondary to branded.

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