Research Paper

Pharmaceutical Evaluation of Cefuroxime Axetil Tablets Available in Drug Market of Pakistan

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Cefuroxime is a second generation cephalosporin antibiotic with a broad spectrum activity against Gram positive and Gram negative bacteria. The purpose of this research work was to evaluate the pharmaceutical quality standards of four different brands of cefuroxime axetil 125 mg tablets with different price ranges purchased from retail pharmacies of Pakistan. The brands were tested for physicochemical evaluation and *in vitro* dissolution studies in different medium like 0.07N HCl, distilled water, 0.1N HCl of pH 1.2 and phosphate buffers of pH 4.5 and pH 6.8. Statistical analysis, model dependent (zero order, first order, Korsmeyer-Peppas, Hixson-Crowell, Weibull) and model independent (Difference *f1,* similarity *f2*) approaches were applied to multiple dissolution profile of all brands. All brands were found to be similar with reference and meeting the compendial quality standard. Inter brand variation was observed in disintegration time and assay which was resulted in significant differences (P<0.05) in drug release data and Weibull was observed as best fill model.

Key words: Cefuroxime axetil, different brands, dissolution studies, statistical analysis, model dependent and independent approaches

Recent advances in pharmaceutical technology and drug delivery system has greatly helped to design and formulate pharmaceutical products. In addition, recent advances in excipients sciences have also supported the phenomena for better understanding and success of such formulations. The safety and efficacy of pharmaceutical products greatly depends on its quality attributes, formulation properties and manufacturing methods[1]. Generic products are marketed throughout the world and increasing in number of generic products has become more difficult for the health care persons as well as for patients to select one from among a number of apparently equivalent products[2]. In case of orally administered drugs the conventional generic products are considered to be therapeutically equivalent to a reference innovator when their pharmaceutical and bioequivalent parameters have been developed and correlated with each other[3]. Although physician and patient acceptance of generics may vary from country to country, a common factor in the decision to use a generic is price[4]. Various studies reported that the generic products were significantly differing from the reference brands and amongst themselves in terms of cost and quality[5]. For example, one of two marketed amoxicillin generics from Italian market was not bioequivalent to the brand leader product[6]. In another study significant difference was observed in dissolution release of branded and generic tablets of Ibuprofen[7]. The generic brands (drugs) available on the market should be analyzed for their chemical and biopharmaceutical equivalence, strength, quality, purity and releasing profile of active ingredient in comparison to the innovator drug. This is important especially for second and third world countries[8].

Cefuroxime is a second generation broad spectrum cephalosporin antibiotic used to treat upper and lower respiratory tract infections, skin, soft tissues, urinary tract, bone and joint infections, meningitis and lyme disease[9]. According to biopharmaceutical

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classification system cefuroxime axetil (prodrug of cefuroxime) is a poorly water soluble drug having class II qualities with low solubility but high permeability, therefore it's *in vitro* dissolution profile could be expected to reflect the *in vivo* performance of the formulation[10].

Thus the present study was undertaken with the aim to perform comparative pharmaceutical evaluation of four different brands of cefuroxime axetil 125 mg tablets included physical appearance and parameters along with dissolution in different medium was performed. Multiple point dissolution results were further analyzed by statistical analysis tool like one-way ANOVA and *in vitro* kinetic studies (model dependent and independent approaches).

MATERIALS AND METHODS

Cefuroxime axetil was procured from Nectar Life Sciences, Ltd. India. Cefuroxime axetil 125 mg tablet brands were purchased from national and multinational companies of Pakistani market coded as Ref. A1 (Reference test brand) and A2, A3, A4 (Test brands). Hydrochloric acid, sodium hydroxide, methanol, ammonium phosphate and potassium dihydrogen phosphate all were purchased from Merck, Darmstadt, Germany.

Software used were adds in program DD solver®, SPSS® 20.0 for Windows (IBM SPSS Statistics Inc., Chicago, USA) and Microsoft Excel 2010® for statistical analysis and dissolution profile comparison.

Tablets testing:
The quality parameters of reference and brands were evaluated by USP36/NF31, 2013 pharmacopeial test procedure[11] and non-pharmacopeial procedures as stated below.

Weight variation:
The weight variation evaluation of reference (Ref. A1) and test brands (A2, A3, A4) were carried out by individually weighing twenty tablets on an analytical balance (Sartorius GmbH; type A 6801) and then mean weight and standard deviation were calculated.

Tablet thickness:
Thickness of twenty tablets, each of the innovator and test brand, were determined by a vernier caliper in mm (CD-6, CSX, Mitutoyo, Japan) and mean, standard deviation was calculated.

Tablet length and width:
Length and width variation test of oblong shaped reference and test brands were determined by a vernier caliper in mm (CD-6, CSX, Mitutoyo, Japan). Average of 20 tablets length and width was recorded and the data was presented using a quality control chart on MS Excel® 2010.

Disintegration test:
Disintegration of innovator and test brand were performed by placing six tablets of each brand in a tube of basket rack assembly of disintegration apparatus[12] (Erweka, ZT2, Heusenstamm Germany).

Assay method:
Assay of Cefuroxime axetil brands were performed according to USP 36/NF 31, 2013 pharmacopeial test procedure[11] using HPLC (LC-10AT VP, No.C20973806986 LP, Shimadzu Corporation, Kyoto, Japan) and column Promosil® (Agela Technologies, USA) C-18, 4.6×250 mm containing 5 µm packing with injection volume about 10 µl. The suitably filtered and degassed mixture of mobile phase composed of 0.2M monobasic ammonium phosphate and methanol (620:380) with a flow rate of 1.5 ml/min. Randomly selected twenty tablets of each brand were pulverized and quantity equivalent to 240 µg/ml strength prepared in methanol and 0.2M monobasic ammonium phosphate. Sonicated and filtered solution was then injected and peaks were detected at 278 nm. Each determination was carried out in triplicate.

Related substances:
Related substances examined by liquid chromatography as described under assay[11]. The method was performed by preparing test solution to dissolve tablet substance equivalent to 10 mg of cefuroxime axetil in to the mobile phase composed of 0.2M monobasic ammonium phosphate and methanol (620:380) and dilute to 50 ml with the mobile phase. Reference solution (*a*) prepared by diluting 1 ml of test solution to 100 ml with the mobile phase, for reference solution (*b*) heat 5 ml of test solution at 60º for 1 h to generate the Δ3-isomers and for reference solution (*c*) expose 5 ml of test solution to ultraviolet light at 254 nm for 24 h to generate E-isomers. Reference solution (*d*) prepared by dissolving 10

mg of cefuroxime axetil in the mobile phase and dilute to 50 ml with the mobile phase. Inject 20 µl each of reference solutions (*a*), (*b*), (*c*) and (*d*) and chromatograms recorded at 278 nm with a flow rate of 1.5 ml/min. Percentage content of the related substances calculated from the areas of the peaks in the chromatogram by the normalization procedure.

Multiple point dissolution:

The dissolution studies of the reference and test brand were performed in USP dissolution medium i.e. 0.07 N HCl[11] and also established in distilled water, 0.1 N HCl of pH 1.2 and phosphate buffers at pH 4.5 and 6.8 by using a USP apparatus II (Erweka DT, Heusenstamm, Germany). Dissolution was performed in 900 ml of dissolution medium at 37±0.5º with 100 rpm. An aliquot of 10 ml of solvent was taken out from vessels at 5, 10, 15, 20, 25, 30, 45, 60, 90 and 120 min and volume was compensated by fresh medium. Drug concentration was calculated by UV/Vis spectrophotometer 1800 (Shimadzu, Kyoto, Japan) at 278 nm with dissolution medium taken as blank. Each experiment was repeated in triplicate.

Dissolution data analysis:

Single group univariate repeated measures analysis (One way ANOVA) was applied to the dissolution profile in each dissolution medium. Then post hoc procedures were performed by multiple comparisons using Dunnett's *t*-test (two-sided) and repeated contrasts were applied separately to each drug product for the comparison of percent dissolved at the sequential times in all dissolution medium.

Model independent methods:

A simple model independent approach was used in the present investigation that was difference factor (*f*1) and similarity factor (*f*2). The *f*1 values should be close to 15, and *f*2 values should be close to 100[13] (Eqns 1-2): $f_1=\{[\sum_{t=1}^{n}|R_t-T_t|]/[\sum_{t=1}^{n}R_t]\} \times 100$…[1] and $f_2=50\times\log\{[1+(1/n)\sum_{t=1}^{n}(R_t-T_t)^2]^{-0.5}\times 100\}$…[2].

Model dependent methods:

The mathematical models shown in Table 1, were fitted to individual dissolution data evaluated by DD Solver® software.

RESULTS AND DISCUSSION

Pakistan is a developing country where 70-80% of the population could not be able to pay for costly medication. In cost analysis of various brands it was determined that the innovator is 50% more expensive than test brands. Many drugs that are manufactured in developing countries are implicated to be substandard[20,21]. For minimizing the health risk factors and to maximizing the safety of health products and food; it is necessary to monitor all the pharmaceutical services on a regular basis that promoting the conditions and providing information on the base of which the people become enable to make healthy choices and they can make correct decisions about their health. The aim of the present work as a surveillance study, was to assess the product quality of different brands of cefuroxime axetil tablets (125 mg) available in the local market to determine the appropriateness of their inter-changeability. Four different brands of cefuroxime axetil tablets were tested with variable price ranges and among them innovator A1 brand was considered as reference for comparison with other brands.

TABLE 1: MODELS FOR FITTING DRUG RELEASE DATA

Model	Equation	Parameter*	Reference
Zero order	$F=k_0.t$	R^2, k_0	[14]
First order	$F=100.(1-e^{-k1.t})$	R^2, i_1	[15]
Korseemyer and peppas	$F=k_{KP}.t^n$	R^2, k_{KP}, n	[16,17]
Hixson crowell	$F=100.[1-(1-k_{HC}.t)^3]$	R^2, k_{HC}	[18]
Weibull	$F=100.[1-e^{(t-Ti)\beta/\alpha}]$	R^2, β	[19]

*In all models, F is the fraction (%) of drug released in time *t*; k_0 is the zero-order release constant; R^2 is the Regression coefficient; k_1 is the first-order release constant; k_{KP} is the release constant incorporating structural and geometric characteristics of the drug-dosage form; n is the diffusional exponent indicating the drug-release mechanism; k_{HC} is the release constant in Hixson-Crowell mode; *α* is the scale parameter which defines the time scale of the process; *β* is the shape parameter which characterizes the curve.

Different pharmaceutical parameters were successfully performed and different weights were observed in different brands like A1, A2 and A3 had weights ranges from 208.10±0.86 to 277.58±0.85 mg while brand A4 were of 307.73±1.04 mg. Differences in weights variation is might be due to their different formulation compositionof excipients. Thickness range was found to be 3.30±0.07 to 4.12±0.02 mm in all selected formulations within the pharmacopeial limits. Disintegrations are required to break up tablets into primary powder particles and USP states that the tablets should be disintegrate within the prescribed period of time[11]. The reference and all tested brands showed disintegration time not more than 60 s and compliance with the USP criteria. All of the obtained brands were assayed as recommended by USP36/ NF31, 2013 pharmacopeial test procedure[11] and it could be concluded that the assayed products were observed with satisfactory results (Table 2).

The USP test for related substances in cefuroxime axetil tablets is a semiquantitative test that is based on HPLC[11]. The test states that the percentage sum of the pairs of peaks of cefuroxime axetil diastereoisomers A and B obtained with reference solution (*a*) not greater than 1.0%, for Δ^3-isomers (*b*) not more than 1.5%, E-isomers (*c*) not greater than 1.0% and the area of any other secondary peaks not greater than 0.5%. The results indicates that in all of the tested brands Ref. A1, A2, A3 and A4 percentage sum of the pairs of peaks (cefuroxime axetil diastereoisomer A and B) were observed as 0.11%, 0.25%, 0.19% and 0.32% respectively. Percentages of Δ^3-isomers peaks were found within the prescribed limits i.e. 0.25% (Ref. A1), 0.42% (A2), 0.32% (A3) and 0.65% (A4). Results of E-isomers were found 0.12%, 0.18%, 0.21% and 0.32% correspondingly for all brands. The sum of the related substances is not greater than 3.0%. This suggests that all of the tested products met the pharmacopoeial specifications pertaining to related substances.

Dissolution profile is believed to reflect the *in vivo* bioavailability of drugs, particularly for those drugs which are belong to class II type drugs. Such drugs are known as low solubility and high permeability drugs[22]. The multiple point dissolution studies of different brands of cefuroxime axetil tablets were performed in five different dissolution medium i.e., 0.07N HCl (USP dissolution medium), 0.1N HCl of pH 1.2, phosphate buffers (pH 4.5 and 6.8) and in distilled water, according to the Food and Drug Administration-US[13]. From the Figs. 1-5, it can be seen that all products including reference brand (Ref. A1) released considerable amount of drug within fifteen minutes (more than 70%). In 0.07N HCl test brand A2 exhibited the lowest percentage release at five minutes (70.14%±1.35) which were promisingly increased and become maximum (91.03%±0.71) at 45 min. Test brand A3 exhibited low drug release in 0.1N HCl medium (pH 1.2) at first five minutes (65.87%±1.97) with increased in release profile up to 90% within two hours of dissolution. In distilled water dissolution medium all products presented more than 80% of drug release within 15 min and more than 85% of drug release at 45 min with maximum drug release (90.42%±1.28) observed at 2 h in reference A1 release pattern. Highest drug release at 45 min of all brands was observed in pH 4.5 phosphate buffer medium i.e. 90.31±0.80% to 94.95±0.57% and in pH 6.8 phosphate buffer medium all brands showed more than 80% of drug release (82.32±0.92% to 89.05±0.74%) within 45 min according to USP 36/ NF 31, 2013 prescribed test procedure[11]. Cefuroxime axetil is a poorly water soluble drug with BCS class II characters and use of appropriate solubility enhancing agent (surfactant) and

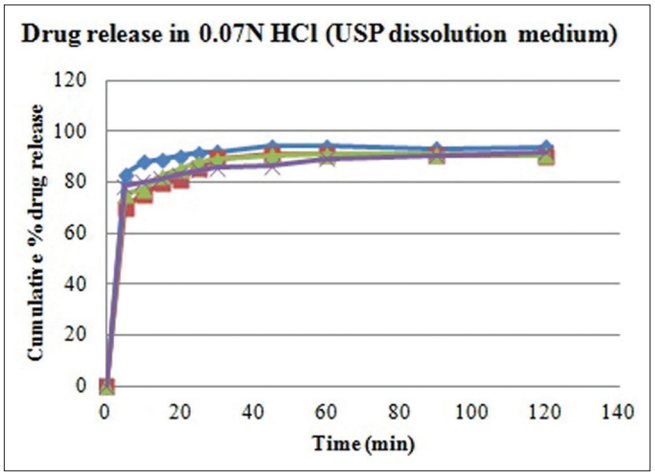

Fig. 1: Cefuroxime axetil percent release from immediate release brands in 0.07N HCl (USP dissolution medium).
N=6; -♦- Ref A1; -■- A2; -▲- A3 and -×- A4.

TABLE 2: PHYSICAL APPEARANCE AND PHARMACEUTICAL CHARACTERISTICS OF DIFFERENT BRANDS

Product code	Physical appearance	Expiry (years)	Price/14 units (PKR)	Weight. variation (mg)	Dimensions (mm)			Disintegration time (s)	Assay (%)
					Thickness	Length	Width		
Pharmacopoeial limits (USP 36)	-	-	-	**±5%**	**±5%**	-	-	**NMT 15 min**	**90-110**
Ref. A1	Oblong caplet shaped tablet, white, coated	2	295.72	227.10±1.16	3.43±0.04	12.00±0.02	5.06±0.06	47.33±0.58	98.84±0.29
A2	Oblong caplet shaped tablet, white, coated	2	210.00	208.10±0.86	3.30±0.07	12.07±0.06	5.11±0.06	55.33±1.15	99.56±0.67
A3	Oblong caplet shaped tablet, blue, coated	2	252.00	307.73±1.04	4.12±0.02	13.05±0.06	6.07±0.05	49.33±0.58	97.78±0.97
A4	Oblong caplet shaped tablet, white, coated	2	240.00	277.58±0.85	4.03±0.02	12.51±0.10	5.50±0.05	55.00±1.00	95.36±0.60

n=20, Ref. A1: Reference test brand 1, A2: test brand 2, A3: test brand 3, A4: test brand 4, USP: United States Pharmacopeia

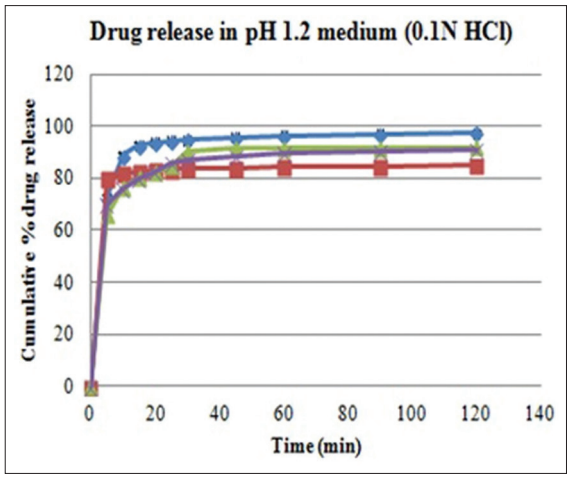

Fig. 2: Cefuroxime axetil percent release from immediate release brands in pH 1.2 (0.1N HCl).
N=6; -♦- Ref A1; -■- A2; -▲- A3 and -×- A4.

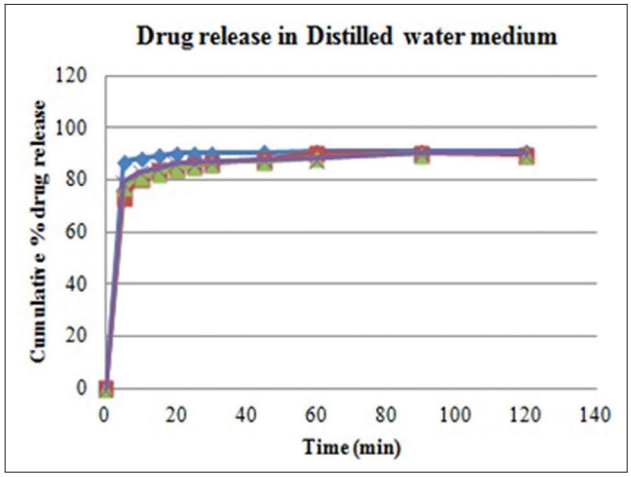

Fig. 3: Cefuroxime axetil percent release from immediate release brands in distilled water medium.
N=6; -♦- Ref A1; -■- A2; -▲- A3 and -×- A4.

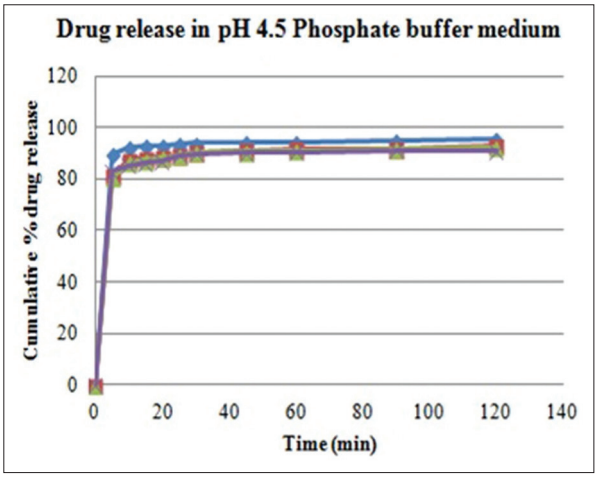

Fig. 4: Cefuroxime axetil percent release from immediate release brands in pH 4.5 Phosphate buffer medium.
N=6; -♦- Ref A1; -■- A2; -▲- A3 and -×- A4.

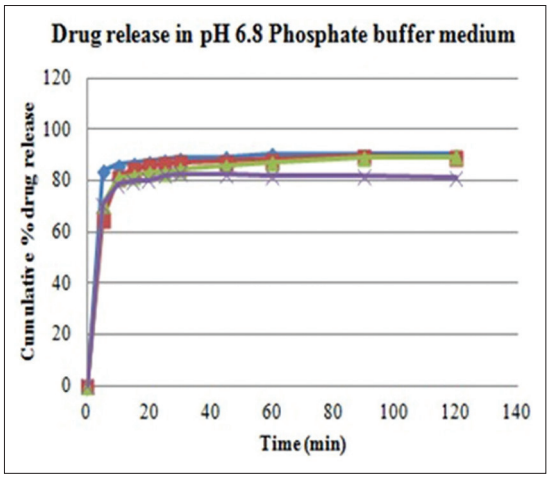

Fig. 5: Cefuroxime axetil percent release from immediate release brands in pH 6.8 Phosphate buffer medium.
N=6; -♦- Ref A1; -■- A2; -▲- A3 and -×- A4.

disintegrator increase the dissolution rate of the active component[10]. In the present study, all the marketed brands (A1-A4) were disintegrated quickly within one minute and get dissolved to show highest drug release pattern i.e. greater than 70% in all medium at two time points of 15 and 45 min.

Multiple comparison by Dunnett's *t*-test[23] were applied to compare all brands in 0.07N HCl (USP medium) dissolution profile with different dissolution medium profiles at each time interval. The FDA document, mentions the *in vitro* bioequivalence testing protocol for a prescribed strengths, based on dissolution studies of the dosage form in at least three distinctive dissolution medium pH 1.2, 4.5 and 6.8[13]. In the present work, results revealed that dissolution profile of Ref. A1, in 0.07N HCl medium in comparison with other medium showed a significant difference ($P<0.05$) at 60, 90 and 120 min time interval. Significant results ($P<0.05$) were observed for brand A2 evaluation at 5, 10, 15 and 20 min time intervals. In case of brand, A3 and A4 in 0.07N HCl dissolution profiles of both formulation were found to be nonsignificant ($P>0.05$) with 0.1N HCl, distilled water and pH 4.5 phosphate buffer medium at 90 min time intervals (Tables 3 and 4). These findings indicates that cefuroxime axetil has the ability to show a promising drug release in different pH medium at different time points gaining the waiver studies that the drug is well absorb and bioavailable at different body pH. *In vitro* dissolution testing is of pivotal importance, as the *in vitro* evaluation surrogates the in vivo outcomes.

TABLE 3: MULTIPLE COMPARISON OF UNITED STATES PHARMACOPEIA DISSOLUTION MEDIUM WITH OTHER MEDIUM FOR REFERENCE A1 AND SAMPLE A2

Time (min.)	DM (I)	DM (J)	Ref. A1				A2			
			Mean difference (I–J)	Significance	95% CI		Mean difference (I–J)	Significance	95% CI	
					Lower bound	Upper bound			Lower Bound	Upper Bound
5	0.1N HCl	0.07N HCl	3.457	0.000	1.905	5.008	9.807	0.000	8.184	11.429
	Distilled water	0.07N HCl	3.645	0.000	2.094	5.196	2.975	0.000	1.353	4.597
	pH 4.5	0.07N HCl	6.437	0.000	4.885	7.988	11.410	0.000	9.788	13.032
	pH 6.8	0.07N HCl	0.692	0.603	−0.860	2.243	−5.195	0.000	−6.817	−3.573
10	0.1N HCl	0.07N HCl	3.507	0.002	1.174	5.840	6.533	0.000	4.738	8.328
	Distilled water	0.07N HCl	0.557	0.924	−1.776	2.890	5.200	0.000	3.405	6.995
	pH 4.5	0.07N HCl	3.412	0.003	1.079	5.745	12.040	0.000	10.245	13.835
	pH 6.8	0.07N HCl	−1.750	0.183	−4.083	0.583	6.110	0.000	4.315	7.905
15	0.1N HCl	0.07N HCl	1.403	0.061	−0.053	2.860	3.088	0.001	1.219	4.958
	Distilled water	0.07N HCl	1.158	0.148	−0.298	2.615	3.883	0.000	2.014	5.753
	pH 4.5	0.07N HCl	3.037	0.000	1.580	4.493	8.578	0.000	6.709	10.448
	pH 6.8	0.07N HCl	−1.503	0.042	−2.960	−0.047	5.012	0.000	3.142	6.881
20	0.1N HCl	0.07N HCl	0.545	0.763	−0.990	2.080	1.975	0.017	0.309	3.641
	Distilled water	0.07N HCl	0.533	0.776	−1.001	2.068	3.232	0.000	1.566	4.897
	pH 4.5	0.07N HCl	2.632	0.001	1.097	4.166	7.195	0.000	5.529	8.861
	pH 6.8	0.07N HCl	−3.198	0.000	−4.733	−1.664	4.888	0.000	3.223	6.554
25	0.1N HCl	0.07N HCl	−1.547	0.050	−3.094	0.000	−2.203	0.014	−4.020	−0.387
	Distilled water	0.07N HCl	−0.912	0.368	−2.459	0.635	−0.075	1.000	−1.892	1.742
	pH 4.5	0.07N HCl	1.858	0.015	0.311	3.405	3.415	0.000	1.598	5.232
	pH 6.8	0.07N HCl	−4.222	0.000	−5.769	−2.675	1.007	0.420	−0.810	2.823
30	0.1N HCl	0.07N HCl	−3.608	0.000	−4.918	−2.299	−5.568	0.000	−7.408	−3.729
	Distilled water	0.07N HCl	−0.700	0.451	−2.009	0.609	−3.113	0.001	−4.953	−1.274
	pH 4.5	0.07N HCl	1.883	0.003	0.574	3.193	1.308	0.220	−0.531	3.148
	pH 6.8	0.07N HCl	−4.212	0.000	−5.521	−2.902	−2.220	0.015	−4.060	−0.380
45	0.1N HCl	0.07N HCl	−6.340	0.000	−7.463	−5.217	−7.083	0.000	−8.728	−5.438
	Distilled water	0.07N HCl	−3.200	0.000	−4.323	−2.077	−3.398	0.000	−5.043	−1.753
	pH 4.5	0.07N HCl	0.480	0.636	−0.643	1.603	0.292	0.972	−1.353	1.937
	pH 6.8	0.07N HCl	−5.425	0.000	−6.548	−4.302	−3.580	0.000	−5.225	−1.935
60	0.1N HCl	0.07N HCl	−6.967	0.000	−8.266	−5.667	−6.893	0.000	−8.283	−5.503
	Distilled water	0.07N HCl	−3.215	0.000	−4.514	−1.916	−0.893	0.296	−2.283	0.497
	pH 4.5	0.07N HCl	1.357	0.039	0.057	2.656	0.440	0.825	−0.950	1.830
	pH 6.8	0.07N HCl	−3.707	0.000	−5.006	−2.407	−3.005	0.000	−4.395	−1.615
90	0.1N HCl	0.07N HCl	−6.345	0.000	−7.927	−4.763	−6.063	0.000	−7.423	−4.703
	Distilled water	0.07N HCl	−3.217	0.000	−4.798	−1.635	−0.037	1.000	−1.397	1.323
	pH 4.5	0.07N HCl	−1.820	0.021	−3.402	−0.238	1.172	0.106	−0.188	2.532
	pH 6.8	0.07N HCl	−6.750	0.000	−8.332	−5.168	−1.010	0.190	−2.370	0.350
120	0.1N HCl	0.07N HCl	−9.675	0.000	−11.108	−8.242	−5.422	0.000	−6.708	−4.135
	Distilled water	0.07N HCl	−3.437	0.000	−4.869	−2.004	−0.365	0.872	−1.652	0.922
	pH 4.5	0.07N HCl	−4.427	0.000	−5.859	−2.994	2.653	0.000	1.367	3.940
	pH 6.8	0.07N HCl	−8.693	0.000	−10.126	−7.261	−0.890	0.240	−2.177	0.397

Multiple comparison of USP dissolution medium 0.07N HCl with other medium (0.1N HCl, distilled water, pH 4.5 and pH 6.8 phosphate buffer) by Dunnett's *t*-test (two-sided) of immediate release cefuroxime axetil brands (n=6). SE: Standard error, CI: confidence interval, DM: dissolution medium, Ref. A1: reference test brand 1, A2: test brand 2, A3: test brand 3, A4: test brand 4, USP: United States Pharmacopeia

TABLE 4: MULTIPLE COMPARISON OF UNITED STATES PHARMACOPEIA DISSOLUTION MEDIUM WITH OTHER MEDIUM FOR SAMPLE A3 AND SAMPLE A4

Time (min.)	DM (I)	DM (J)	A3				A4			
			Mean difference (I−J)	Significance	95% CI		MD (I-J)	Significance	95% CI	
					Lower Bound	Upper Bound			Lower bound	Upper bound
5	0.1N HCl	0.07N HCl	−9.363	0.000	−11.480	−7.247	−8.115	0.000	−9.520	−6.710
	Distilled water	0.07N HCl	1.997	0.068	−0.120	4.113	1.162	0.126	−0.243	2.567
	pH 4.5	0.07N HCl	5.325	0.000	3.209	7.441	4.773	0.000	3.368	6.178
	pH 6.8	0.07N HCl	−4.600	0.000	−6.716	−2.484	−7.713	0.000	−9.118	−6.308
10	0.1N HCl	0.07N HCl	−0.993	0.298	−2.543	0.556	−3.898	0.000	−5.365	−2.431
	Distilled water	0.07N HCl	4.088	0.000	2.539	5.638	3.103	0.000	1.636	4.570
	pH 4.5	0.07N HCl	9.002	0.000	7.452	10.551	5.333	0.000	3.866	6.800
	pH 6.8	0.07N HCl	3.972	0.000	2.422	5.521	−1.803	0.013	−3.270	−0.336
15	0.1N HCl	0.07N HCl	−2.333	0.018	−4.317	−0.350	−1.302	0.184	−3.039	0.436
	Distilled water	0.07N HCl	0.308	0.983	−1.675	2.292	3.212	0.000	1.474	4.949
	pH 4.5	0.07N HCl	5.065	0.000	3.081	7.049	4.720	0.000	2.982	6.458
	pH 6.8	0.07N HCl	−0.310	0.982	−2.294	1.674	−1.625	0.072	−3.363	0.113
20	0.1N HCl	0.07N HCl	−2.845	0.001	−4.564	−1.126	−0.620	0.718	−2.246	1.006
	Distilled water	0.07N HCl	−0.935	0.436	−2.654	0.784	3.035	0.000	1.409	4.661
	pH 4.5	0.07N HCl	3.022	0.000	1.303	4.740	3.540	0.000	1.914	5.166
	pH 6.8	0.07N HCl	−2.495	0.003	−4.214	−0.776	−3.080	0.000	−4.706	−1.454
25	0.1N HCl	0.07N HCl	−2.890	0.000	−4.543	−1.237	0.820	0.576	−0.958	2.598
	Distilled water	0.07N HCl	−2.348	0.004	−4.001	−0.696	1.978	0.026	0.201	3.756
	pH 4.5	0.07N HCl	1.650	0.050	−0.003	3.303	4.368	0.000	2.591	6.146
	pH 6.8	0.07N HCl	−4.207	0.000	−5.859	−2.554	−2.635	0.003	−4.413	−0.857
30	0.1N HCl	0.07N HCl	0.988	0.528	−1.035	3.011	1.408	0.143	−0.347	3.163
	Distilled water	0.07N HCl	−2.297	0.023	−4.320	−0.274	1.328	0.178	−0.427	3.083
	pH 4.5	0.07N HCl	1.150	0.399	−0.873	3.173	4.107	0.000	2.352	5.862
	pH 6.8	0.07N HCl	−4.500	0.000	−6.523	−2.477	−2.918	0.001	−4.673	−1.163
45	0.1N HCl	0.07N HCl	0.863	0.523	−0.893	2.620	2.102	0.004	0.630	3.573
	Distilled water	0.07N HCl	−3.358	0.000	−5.115	−1.602	1.237	0.118	−0.235	2.708
	pH 4.5	0.07N HCl	0.192	0.995	−1.565	1.948	3.777	0.000	2.305	5.248
	pH 6.8	0.07N HCl	−4.827	0.000	−6.583	−3.070	−4.212	0.000	−5.683	−2.740
60	0.1N HCl	0.07N HCl	0.457	0.616	−0.584	1.497	0.455	0.883	−1.201	2.111
	Distilled water	0.07N HCl	−2.647	0.000	−3.687	−1.606	−1.105	0.267	−2.761	0.551
	pH 4.5	0.07N HCl	0.043	1.000	−0.997	1.084	1.328	0.143	−0.328	2.984
	pH 6.8	0.07N HCl	−3.887	0.000	−4.927	−2.846	−7.433	0.000	−9.089	−5.777
90	0.1N HCl	0.07N HCl	0.755	0.191	−0.263	1.773	−0.328	0.964	−2.045	1.388
	Distilled water	0.07N HCl	−0.907	0.091	−1.925	0.111	−0.243	0.988	−1.960	1.473
	pH 4.5	0.07N HCl	0.840	0.127	−0.178	1.858	0.555	0.814	−1.161	2.271
	pH 6.8	0.07N HCl	−1.708	0.001	−2.726	−0.690	−8.915	0.000	−10.631	−7.199
120	0.1N HCl	0.07N HCl	1.210	0.006	0.307	2.113	−1.007	0.421	−2.824	0.811
	Distilled water	0.07N HCl	−0.498	0.424	−1.402	0.405	−1.685	0.075	−3.502	0.132
	pH 4.5	0.07N HCl	1.470	0.001	0.567	2.373	−0.902	0.515	−2.719	0.916
	pH 6.8	0.07N HCl	−1.298	0.003	−2.202	−0.395	−10.873	0.000	−12.691	−9.056

Multiple comparison of USP dissolution medium 0.07N HCl with other medium (0.1N HCl, distilled water, pH 4.5 and pH 6.8 phosphate buffer) by Dunnett's *t*-test (two-sided) of immediate release cefuroxime axetil brands (n=6). SE: Standard error, CI: confidence interval, DM: dissolution medium, Ref. A1: reference test brand 1, A2: test brand 2, A3: test brand 3, A4: test brand 4, USP: United States Pharmacopeia

Dissolution data were further analyzed by one way ANOVA (Dunnett's *t*-test) method to compare mean percentage drug release of each brand with reference in all dissolution medium at each time intervals. Results of post hoc procedure, the pair wise comparison of test products against reference product by Dunnett's *t*-test in 0.07N HCl are given in Table 5 detected a significant difference ($P<0.05$). In other dissolution medium like 0.1N HCl of pH 1.2 showed no significance difference for test formulations A3 ($P=0.198$) and A4 ($P=0.855$) with respect to the reference at 30 min time interval, similarly brand A2 found parallel with reference at 90 ($P=0.119$) and 120 min ($P=0.998$) time points. In distilled water medium percent dissolved of all test formulations were significantly difference ($P<0.05$) until time point 45 min and that the dissolution profile were parallel ($P>0.05$) at the time point up to 120 min for all brands (A2, A3 and A4). Whereas significant difference ($P<0.05$) observed in release profile of all brands at phosphate buffer of pH 4.5 and 6.8 medium. In one study comparing 13 products of alendronate, significant differences in dissolution and disintegration of tablets were revealed[24].

Comparison of *in vitro* dissolution profile is recommended based on dissimilarity factor (*f1*) and a similarity (*f2*) factor that compares an innovator brand's dissolution data with the test formulation and establishes similarity profile[13]. The value of *f1* and *f2* factor for test brands (A2, A3, A4) versus reference (Ref. A1) were calculated and listed in Table 6. The results indicates that the dissolution profile of tests were found similar to the profile of reference in all dissolution medium except the *f2* value of test brand A2 in 0.1N HCl was 48.35 as compare to the reference formulation (Table 6). The goodness of results in all medium of test

TABLE 5: MULTIPLE DISSOLUTION COMPARISON OF IMMEDIATE RELEASE CEFUROXIME AXETIL TEST PRODUCTS AGAINST REFERENCE PRODUCT IN UNITED STATES PHARMACOPEIA DISSOLUTION MEDIUM

Time (min)	Formulations (I)	Formulation (J)	Mean difference (I−J)	SE	Significance	95% CI	
						Lower boundary	Upper boundary
5	Test A2	Ref. A1	−13.220	0.616	0.000	−15.903	−10.537
	Test A3	Ref. A1	−8.132	0.611	0.000	−10.789	−5.474
	Test A4	Ref. A1	−5.018	0.457	0.000	−6.878	−3.158
10	Test A2	Ref. A1	−12.748	0.589	0.000	−15.102	−10.394
	Test A3	Ref. A1	−10.633	0.664	0.000	−13.336	−7.930
	Test A4	Ref. A1	−7.853	0.670	0.000	−10.584	−5.122
15	Test A2	Ref. A1	−9.692	0.427	0.000	−11.469	−7.914
	Test A3	Ref. A1	−6.803	0.333	0.000	−8.135	−5.472
	Test A4	Ref. A1	−7.822	0.654	0.000	−10.812	−4.831
20	Test A2	Ref. A1	−8.863	0.420	0.000	−10.556	−7.171
	Test A3	Ref. A1	−4.708	0.539	0.000	−6.994	−2.422
	Test A4	Ref. A1	−6.802	0.473	0.000	−8.748	−4.855
25	Test A2	Ref. A1	−5.805	0.544	0.000	−7.983	−3.627
	Test A3	Ref. A1	−3.885	0.519	0.000	−5.956	−1.814
	Test A4	Ref. A1	−6.770	0.629	0.000	−9.350	−4.190
30	Test A2	Ref. A1	−2.628	0.564	0.019	−4.884	−0.373
	Test A3	Ref. A1	−2.802	0.441	0.010	−4.829	−0.775
	Test A4	Ref. A1	−6.207	0.488	0.000	−8.250	−4.164
45	Test A2	Ref. A1	−3.440	0.515	0.002	−5.567	−1.313
	Test A3	Ref. A1	−3.883	0.509	0.001	−5.998	−1.769
	Test A4	Ref. A1	−7.935	0.442	0.000	−10.043	−5.827
60	Test A2	Ref. A1	−2.855	0.286	0.000	−4.119	−1.591
	Test A3	Ref. A1	−2.855	0.314	0.000	−4.150	−1.560
	Test A4	Ref. A1	−4.743	0.297	0.000	−6.012	−3.474
90	Test A2	Ref. A1	−2.583	0.393	0.002	−4.176	−0.991
	Test A3	Ref. A1	−2.202	0.309	0.001	−3.449	−0.955
	Test A4	Ref. A1	−2.668	0.364	0.001	−4.129	−1.208
120	Test A2	Ref. A1	−3.642	0.291	0.000	−4.833	−2.450
	Test A3	Ref. A1	−3.205	0.254	0.000	−4.356	−2.054
	Test A4	Ref. A1	−1.982	0.435	0.030	−3.790	−0.174

Multiple dissolution comparison by Dunnett's *t*-test (two-sided) of immediate release cefuroxime axetil test products against reference product (ref. A1) in USP dissolution medium 0.07N HCl ($n=6$). SE: Standard error, CI: confidence interval, Ref. A1: reference test brand 1, A2: test brand 2, A3: test brand 3, A4: test brand 4, USP: United States Pharmacopeia

formulations could possibly be due to the formulation composition, appropriate use of disintegrator and presence of adequate amount of solubility enhancing agent established similarity inference.

Model dependent *in vitro* kinetics like zero order, first order, Korsmeyer-Peppas, Hixson-Crowell and Weibull model were employed to elaborate the mode of release as well as to describe the best model fit data on the basis of determination coefficient R^2[14]. As seen from the Table 7, that all brands including reference brand were not successfully fitted with zero, first and Hixon Crowell model but Weibull gave highest determination coefficient at all dissolution medium. Calculated Weibull β parameter was <1 for all brands specified a parabolic curve with steeper initial slope than is consistent with the exponential and the values of regression R^2 was found to be 0.914-0.997 (Table 7). Davit *et al*., explained dissolution properties of tablet by using Weibull model[25]. In another study, Weibull model considered as a best model of comparison after comparing four models first order, Hixson-Crowell, quadratic and Weibull[26].

TABLE 6: DIFFERENCE FACTOR (*f1*) AND SIMILARITY FACTOR (*f2*) AT DIFFERENT DISSOLUTION MEDIUM WITH REFERENCE A1 AS REFERENCE BRAND

Brands and test comparison	Factor	0.07 N HCl (USP dissolution medium)	Distilled water	pH 1.2 (0.1N HCl)	pH 4.5 phosphate buffer	pH 6.8 phosphate buffer
Ref. A1 versus A2	*f1*	7.20	5.32	9.85	4.52	4.20
	f2	55.54	60.30	48.35	66.76	59.35
Ref. A1 versus A3	*f1*	5.40	5.06	8.35	5.00	5.17
	f2	62.39	63.47	53.79	64.62	62.13
Ref. A1 versus A4	*f1*	6.35	3.95	8.86	5.51	9.25
	f2	60.36	69.10	52.87	63.38	53.63

USP: United States Pharmacopeia, Ref. A1: reference test brand 1, A2: test brand 2, A3: test brand 3, A4: test brand 4

TABLE 7: MODEL DEPENDENT *IN VITRO* KINETICS OF DIFFERENT BRANDS OF CEFUROXIME AXETIL IN DIFFERENT DISSOLUTION MEDIUM

Brands	Zero order		First order		Korsmeyer peppas			Hixson-crowell		Weibull model	
	R^2	k_0 (h^{-1})	R^2	k_1 (h^{-1})	R^2	k_{KP} (h^{-n})	n	R^2	k_{HC} ($h^{-1/3}$)	R^2	β
0.07N HCl (USP dissolution medium)											
Ref. A1	−304.711	1.284	−4.149	0.306	0.841	80.902	0.035	−101.001	0.014	0.946	0.11
A2	−50.037	1.227	−1.283	0.145	0.84	64.031	0.082	−13.029	0.013	0.918	0.229
A3	−88.528	1.236	−2.579	0.18	0.844	69.582	0.063	−25.55	0.013	0.914	0.186
A4	−147.753	1.224	−7.366	0.2	0.985	71.194	0.053	−45.839	0.013	0.990	0.234
0.1N HCl (pH 1.2)											
Ref. A1	−64.962	1.324	0.669	0.236	0.662	74.243	0.065	−19.565	0.014	0.997	0.171
A2	−1408.95	1.163	−105.952	0.222	0.913	78.59	0.017	−483.904	0.013	0.989	0.033
A3	−37.014	1.239	−0.364	0.139	0.844	61.63	0.094	−9.041	0.013	0.961	0.234
A4	−60.616	1.221	−1.928	0.149	0.898	64.856	0.077	−16.389	0.013	0.973	0.195
Distilled water											
Ref. A1	−2129.515	1.253	−50.394	0.354	0.865	85.925	0.014	−748.654	0.014	0.965	0.036
A2	−105.931	1.222	−3.868	0.181	0.885	69.776	0.059	−31.456	0.013	0.985	0.13
A3	−184.626	1.218	−8.356	0.204	0.963	72.816	0.047	−57.829	0.013	0.991	0.126
A4	−302.952	1.224	−12.391	0.236	0.942	76.301	0.037	−98.581	0.013	0.987	0.093
pH 4.5 phosphate buffer											
Ref. A1	−1527.976	1.306	−12.732	0.423	0.898	88.502	0.016	−547.165	0.014	0.99	0.057
A2	−324.794	1.261	−7.075	0.281	0.870	79.539	0.034	−107.283	0.014	0.984	0.084
A3	−287.282	1.255	−6.646	0.267	0.857	78.645	0.036	−93.935	0.014	0.993	0.085
A4	−445.38	1.245	−13.499	0.284	0.902	79.864	0.030	−148.269	0.013	0.935	0.094
pH 6.8 phosphate buffer											
Ref. A1	−830.438	1.237	−27.016	0.3	0.928	81.822	0.023	−283.004	0.013	0.971	0.063
A2	−55.634	1.215	−1.152	0.16	0.648	67.001	0.069	−15.498	0.013	0.993	0.091
A3	−99.868	1.202	−4.753	0.167	0.855	68.413	0.060	−29.755	0.013	0.985	0.103
A4	−221.8	1.124	−20.221	0.147	0.536	71.750	0.033	−71.567	0.013	0.916	0.029

Ref. A1: Reference test brand 1, A2: test brand 2, A3: test brand 3, A4: test brand 4, USP: United States Pharmacopeia

In the present study, pharmaceutical evaluation of various brands of cefuroxime axetil by applying different comparison approaches with the intent to investigate several methods. All tested products were within the quality control limits and found to be similar in terms of physicochemical evaluation. The tested generic differs mostly in their dissolution behavior when tested in different dissolution medium and showed a significant difference ($P<0.05$). The model independent approach revealed similarity between reference and test brands, while model dependent approach explained the release kinetics and parameters of the Weibull model that suggest a homogeneity in profile shape.

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