

POST-MARKET DISSOLUTION PROFILE STUDY AND COST COMPARISON OF CEFADROXIL BRANDS AVAILABLE IN KARACHI (PAKISTAN).

Najia Rahim^{*1}, S.. Baqir S. Naqvi², Sana Ghayas¹, Rehana Bibi³

¹Dow College of Pharmacy, Dow University of Health Sciences, Karachi.

²Department of Pharmaceutics, Faculty of Pharmacy, Hamdard University.

³Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi.

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***Correspondence for
Author**

Dr. Najia Rahim

Dow College of
Pharmacy, Dow
University of Health
Sciences, Karachi.

ABSTRACT

The present work was undertaken to evaluate the performance of locally available cefadroxil brands. Another objective was the cost comparison among generic brands and reference brand. Assay and dissolution profile was studied using USP 31. Dissolution profiles were investigated in four solutions as recommended by FDA (0.1 N HCl, acetate buffer (pH = 4.5), phosphate buffer (pH = 6.8) and distilled water). DDSolver® excel based Add in program was used for dissolution profile comparison. F_2 results revealed a mixed response, when drug release from cefadroxil marketed brands in four media was compared with that of reference brand. F_2 results concluded that brand B and D were similar in drug release to that of reference formulation.

Model dependent approach revealed that drug release was best fit in First order and Weibull model. Price comparison discovered that brand B, D and E have price differential in the range of 41.85-52.07%. Brand C has the lowest price differential of 23.32%. It was concluded that the pharmaceutical quality of local and multinational brands was analogous except few cases.

INTRODUCTION

Cefadroxil is a cephalosporin semi synthetic antibiotic, the p-hydroxy derivative of cephalexin, with a potential activity against many moderate to mild bacterial infections of upper respiratory tract, skin, soft tissues and urinary tract infections caused by *Staphylococci*, *Streptococci*, and *Enterobacteriae*.^[1] It is well tolerated orally, effective in the dose of 500-

1000 mg in single or divided doses.^[2] It is slightly soluble in water and in alcohol.^[3] It is well absorbed from the gastrointestinal tract and presenting 85% bioavailability.

Dissolution profile analysis of oral solid dosage forms is a very important test to judge product quality also for differentiating between formulations of the same therapeutic agent.^[4-5]

Dissolution of a drug from its dosage form is dependent on many factors, which include not only the physicochemical properties of the drug, but also the formulation of the dosage form, the process of manufacturing^[6], agitation, temperature, dissolution medium, pH of dissolution medium, surface tension and viscosity of the dissolution medium.^[7] Since the drug is generally absorbed in a unionized form^[8] the pH of dissolution media is controlled carefully during the development of a dissolution method. It effects ionization of the drug which in turn affects the absorption and *in-vivo* behavior of the drug. So, constant dissolution analysis of marketed drug brands is essential to ensure availability of quality medicines. The concept of generic substitution does not implemented in many developing countries, able to promote use of generic medicines; the primary purpose for generics is drug price containment via competition.^[9] Quality of generic medicines should be comparable with the innovator brand. The use of generic drugs that are not bioequivalent may result in treatment failure. Pharmacists reported such type of hazards in various studies on generic drug use.^[10]

The price discrepancy between generics and innovators reinforces the opinion among health practitioners and patients that generic drugs being cheaper than brand are substandard and incompetent.^[11] With the increase in number of manufacturers, there is further increment in competition on price among pharmaceutical companies^[12] leading to wide difference in generic products' prices. Proper quality tests that pledge pharmaceutical and therapeutic equivalence of generics are required. Lack of an effective system of screening the quality of generic drug products in the market results in prevalent supply of substandard and/or counterfeit drug products.

The present work was aimed on investigating dissolution kinetics of different brand of cefadroxil manufactured and marketed by local and multinational pharmaceutical companies in Pakistan. Due to the importance of cefadroxil as an antibiotic and its price variation among the running brands that are available in local market of Karachi, they were assayed and analyzed, in various dissolution media. Mathematical equations were applied to evaluate the methods used to compare the dissolution profile Model fitting was also done for different models such as zero order, first order, Hixon-Crowell, Weibull and Higuchi. Comparative

dissolution studies of cefadroxil brands available in Karachi have not been previously published. So, the present work was undertaken to evaluate the performance of our local brands due to the fact that people like to use generic brands as they are far cheaper than its branded versions. However, many developing countries do not have an effective mechanism of monitoring the quality of generic drug products in the market. This results in widespread distribution of substandard and/or counterfeit drug products. *In vitro* dissolution profile study can also be used in some cases not only to determine the quality of the pharmaceutical products but also to demonstrate in vivo performance comparable to the brand name product.

MATERIALS AND METHODS

In this study, seven different brands of cefadroxil available in local market and listed in local index of pharmaceutical products were randomly selected and purchased from medical stores including retail and wholesalers and coded as A, B, C, D and E. Among them brand A (brand leader) was considered as a reference. No specific sampling procedure was used and samples were purchased by one of the author as regular customer. The study was cross-sectional and done during the month of January' 2014 through June' 2014.

Cost Comparison

The differences in retail price of all test brands were compared with innovator price by following formula: $(\text{Price of innovator} - \text{price of test}) \div \text{Price of innovator} \times 100$.^[13]

Apparatus

Analytical balance (Kern), disintegration apparatus (Pharmatest, DISINT 3, Germany), dissolution apparatus (Pharmatest DT70, Germany), sonicator, spectrophotometer (Spekol 2000 series, Analytikjena) and High performance liquid chromatography (Agilent, Germany, 1200 series A).

Assay

Chemical assay on different brands of cefadroxil was performed using HPLC (Agilent, Germany, 1200 series A) as mentioned in USP 2008. Buffer preparation: 13.6 gm of monobasic potassium phosphate was dissolved in distilled water to make 2000 ml of buffer solution and adjust pH 5.0 with potassium hydroxide 10 N. Mobile phase preparation: Mobile phase was prepared using pH 5.0 buffer and acetonitrile in the ration of 960:40 and filtered. Standard preparation: Accurate quantity of USP cefadroxil RS was dissolved in buffer pH 5.0 to get the solution containing 1.06 mg/ml. Sample preparation: Content of ten capsules were

removed completely, the powder content equivalent to 200 mg cefadroxil was accurately weighed and mixed with buffer pH 5.0 to make 200 ml of the solution. Procedure: Equal volume (10 microliter) of standard solution and sample solution was injected and chromatogram was recorded with 230 nm detector.

Dissolution Testing

Dissolution profile was also studied using USP 32.^[14] USP dissolution Apparatus 1 (Pharmatest DT70, Germany), at 100 rpm for 60 min. All brands were evaluated using 900 ml of deaerated distilled water at $37 \pm 0.5^\circ\text{C}$. Dissolution profiles were also investigated in three solutions: 0.1 N HCl, acetate buffer (pH = 4.5), phosphate buffer (pH = 6.8). Six replicates of each brand were used. Five ml aliquots were withdrawn at six time points i.e. 0, 10, 20, 30, 40 and 60 minutes and replaced by fresh dissolution medium (5 ml) to maintain sink conditions. The samples were filtered, diluted with buffer to prepare concentration of 0.0011 % of cefadroxil solution. The same procedure was followed for acetate buffer of pH 4.5 and phosphate buffer of pH 6.8 USP. All the samples were assayed using previously calibrated spectrophotometer (Spekol 2000 series, Analytikjena) at 263 nm. Percent cefadroxil dissolved at different time points was calculated.

Dissolution profiles comparison methods

(1) Model independent method

According to US FDA guidance^[15] for dissolution data equivalence, model independent approach is suggested which involves use of similarity factor (f_2) providing simple means to contrast the data. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the dissolution % of two curves as in Eq. [1].

$$f_2 = 50 \times \log \left\{ \left(1 + \frac{1}{N} \sum_{t=1}^n (R_t - T_t)^2 \right)^{-0.5} \times 100 \right\}$$

Where

N = number of dissolution sample times and R_t and T_t = individual or mean percents dissolved at each time point for the reference and test brands respectively.

The difference factor can also be calculated with Eq. [2],

$$f_1 = \left\{ \frac{(\sum_{t=1}^n |R_t - T_t|)}{\sum_{t=1}^n R_t} \right\} \times 100$$

Where

R_t and T_t = percentage release of reference and test brands respectively.

The FDA suggests that f_2 values of 50-100 % ensure equivalence and f_1 values less than 50 % ensure the difference of two dissolution profiles.

(2) Model-dependent methods

Model-dependent approaches including zero order, first order, Hixson-Crowell, Higuchi, and Weibull models as described in table 1 were applied considering amount of drug release from 0 to 60 mins.

RESULTS AND DISCUSSION

During the present study, cefadroxil oral solid dosage forms available in local market were purchased and label information was noted that were within their stated expiration date also indicating the difference of prices, expressed in percentage in comparison to the innovator as mentioned in table 2. Assay was also performed to check compliance with the pharmacopoeial requirement. Results were in the specified limit mentioned in cefadroxil monograph (USP 32).^[14] In cost analysis of various brands it was observed that the innovator is 52% more expensive than test brands. The lowest priced brand among these five is Brand B i.e. PKR Rs 150 per 12 units and highest is Brand A i.e. PKR Rs 313 per 12 units (Table 2). This fluctuation in the price of same drug makes it difficult for the health care professionals in selection.

As in vitro drug release profile predicts in vivo performance of oral solid dosage forms. The samples were subjected to drug release study in the recommended dissolution media (FDA). Before testing the brands into different dissolution mediums (pH 1.2, 4.5, 6.8) it was run in distilled water because under the normal circumstances, the dissolution testing should be conducted at 37°C in distilled water unless otherwise noted USP 32. The dissolution test was passed for all samples analyzed during the study. Percent dissolution in 30 minutes was between 86.48 - 101.15% in distill water (figure 1-4). Dissolution profiles in four different media are mentioned in figures 1-4. DDSolver® an excel based add in program was used to compare cefadroxil release from samples. This program was introduced by Zhang in 1991.^[16] Now-a-days it is frequently used for drug release comparison by many scientists.^[17-18]

Dissolution data of innovator brand was compared with the commercial brands using model independent methods as described by Moore and Flanner.^[19] F_2 similarity results revealed a

mixed response when drug release was compared in four different media (table 3). The recommended range of f_2 is 50-100% (FDA). In distilled water, drug release from different formulation was similar to the reference formulation (innovator brand A) and F_2 values ranged 50.24 - 64.17. In buffer pH 4.5 and pH 6.8, brand C and E fails in f_2 test. However, all the brands were similar to innovators at pH 1.2 in drug release to reference formulation (F_2 values ranged between 54.11-73.49). The dissolution data in various pH media is useful in predicting the bioavailability of the drug product. Likewise the work of Carlson *et al* in case of ketoconazole tablets found lower dissolution rate at high pH.^[20] This might be due to the physicochemical characteristics of active ingredient and the dissolution medium employed in these studies. Brands B and D showed similarity with the innovator whereas C and E does not (Table 3). This might be due to changes in sources of active drug, excipients utilized and the manufacturing process. This dissimilarity in dissolution profiles indicates monitoring of commercial brands from time to time. Similar finding were also explained by Arshad et al. in Pharmaceutical Quality Control Studies on Gatifloxacin 200 mg Tablets Available in the Pakistani Market compare similarity of the dissolution profile of the different formulation with reference and showed formulations having more than 50% f_2 value was similar.^[21] Another researcher evaluated the pharmaceutical quality and equivalence of different brands of amlodipine besylate (5 mg) tablets available in the Pakistani drug market: all brands passed the quality control tests f_1 and f_2 values from the results indicated that the dissolution profile of the tests were similar and different to the profile of reference.^[22]

In order to explain drug release from cefadroxil formulations, these formulations were compared applying model dependent approach using mathematical models i.e. Zero order, First Order, Higuchi, Hixson-Crowell and Weibull models (Table 1) in various dissolution media (0.1N HCL pH 1.2, buffer pH 4.5, buffer pH 6.8 and distilled water). The best goodness of fit was the criterion of selecting the most appropriate model. Correlation (R^2) of samples with applied equations is mentioned in table 4. The drug release from the dosage form is dependent on the drug concentration remaining. Therefore first order kinetic model best explain the drug release from all the samples. The values of R^2 were in the ranges of 0.9940 – 0.9355 in distilled water, 0.9938 – 0.9588 at pH 1.2, 0.9678 – 0.8280 at pH 4.5 and 0.9456 – 0.7889 at pH 6.8. Similarly weibull model was also seemed to be followed by cefadroxil release data from all the samples. R^2 values were in the range of 0.9202 for brand E in distilled water and 0.9980 for brand D at pH 4.5. Amongst five models applied at all the

formulations. First order as well as Weibull models were the most appropriate models fits for majority of the formulations.

It was concluded that drug release from oral solid dosage forms can be simply be explained by using model independent approach however model dependent approach is more discriminatory. The comparatively low dissolution profile observed is a quality issue and should be addressed. The presence of the active drug ingredient in the right quantity is not a sufficient condition but drug should be release in time to get required release pattern. In Pakistan local manufacturer usually apply for registration of their generic products without paying attention towards dissolution profile data as recommended by FDA.^[15] The manufacturing technique, source of active drug and choice of excipient should be properly monitored as it greatly affects drug release as well as in vivo performance.

Table 1: Mathematical models used to describe dissolution curves.

| | |
|-----------------------|---|
| Zero order | $Q_1 = Q_0 + K_0t$ |
| First order | $\ln Q_1 = \ln Q_0 + Kt$ |
| Hixson-crowell | $Q_0^{1/3} - Q_1^{1/3} = K_s t$ |
| Higuchi | $Q_1 = K_H t^{1/2}$ |
| Weibull | $\text{Log}[-\ln(12(m))]= \text{blogt}-\text{loga}$ |

Table 2: Information written on labels of different brands of Cefadroxil.

| Sr. No | Brand Code | Batch No. | Price/12 Units (Pkr*) | Price Differential With Innovator | Manufacturing Date | Expiry Date |
|--------|------------|-----------|-----------------------|-----------------------------------|--------------------|-------------|
| 1 | Brand A | 2g552 | 313 | Innovator | 7/2012 | 7/2015 |
| 2 | Brand B | 12647 | 150 | 52.07 | 6/2012 | 5/2015 |
| 3 | Brand C | Cd5991 | 240 | 23.32 | 1/2012 | 1/2014 |
| 4 | Brand D | 134 | 182 | 41.85 | 9/2012 | 9/2015 |
| 5 | Brand E | 43 | 180 | 42.49 | 8/2012 | 7/2014 |

*PKR = Pakistani Rupees

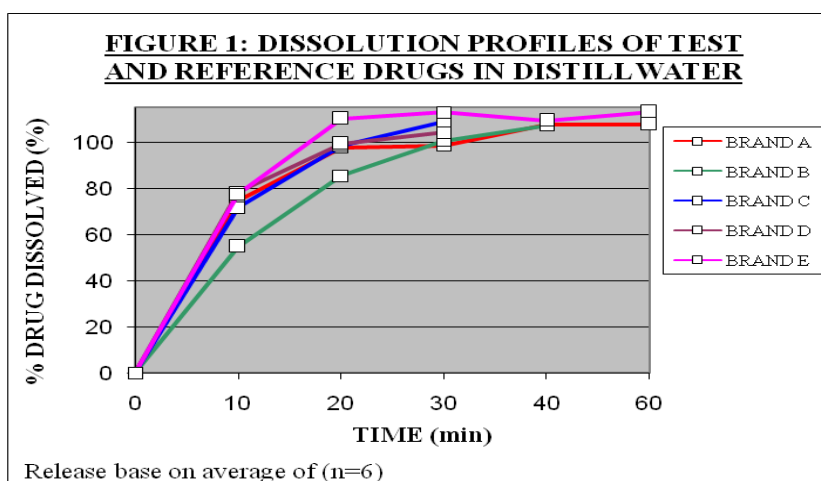
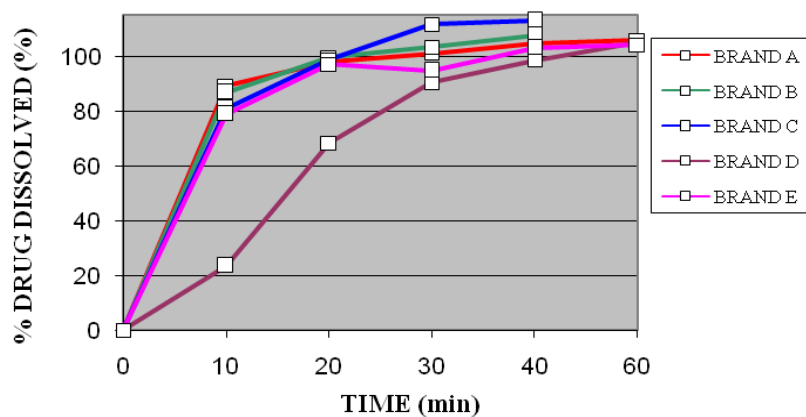
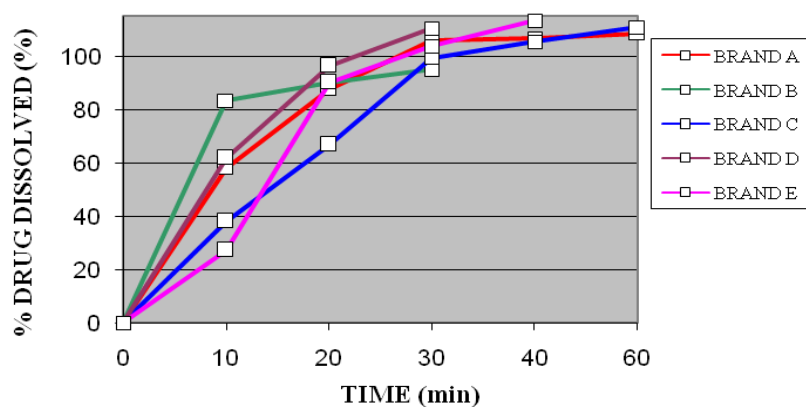


FIGURE 2: DISSOLUTION PROFILES OF TEST AND REFERENCE DRUGS AT pH 1.2



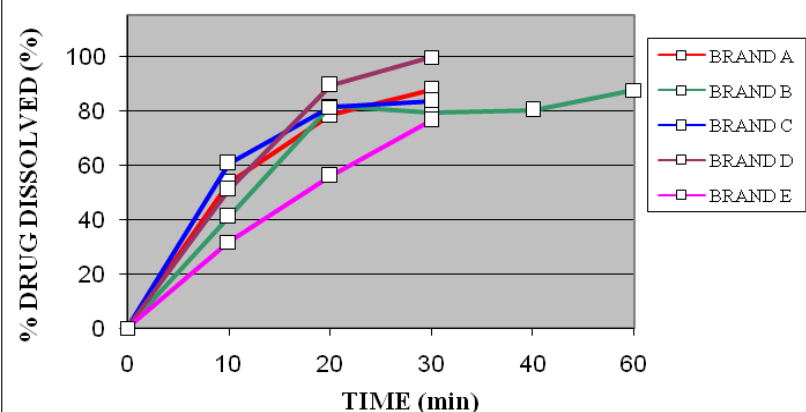
Release base on average of (n=6)

FIGURE 3: DISSOLUTION PROFILES OF TEST AND REFERENCE DRUGS AT pH 4.5



Release base on average of (n=6)

FIGURE 4: DISSOLUTION PROFILES OF TEST AND REFERENCE DRUGS AT pH 6.8



Release base on average of (n=6)

Table 3: Similarity (f_2) and dissimilarity (f_1) values for different brands in four dissolution media.

| Brand Code | Dissolution Media Used | | | | | | | |
|------------|------------------------|-------|--------|-------|--------|-------|-----------------|-------|
| | pH 1.2 | | pH 4.5 | | pH 6.8 | | Distilled water | |
| | f_2 | f_1 | f_2 | f_1 | f_2 | f_1 | f_2 | f_1 |
| Brand A | Reference brand | | | | | | | |
| Brand B | 73.49 | 4.44 | 50.36 | 4.33 | 51.14 | 13.28 | 50.24 | 8.29 |
| Brand C | 59.09 | 10.94 | 45.72 | 10.89 | 46.83 | 18.77 | 59.56 | 5.54 |
| Brand D | 64.17 | 7.23 | 67.19 | 9.94 | 76.6 | 3.46 | 64.17 | 5.19 |
| Brand E | 54.11 | 5.44 | 44.07 | 17.72 | 42.0 | 11.34 | 54.11 | 7.64 |

*FDA recommended ranges of f_2 and f_1 are 50 – 100 and 1 – 15.

Table 4: Model dependent release kinetics of cefadroxil brands in 0.1 HCl at pH 1.2, buffer pH 4.5, buffer pH 6.8 and distilled water.

| Brands | Zero Order | | First Order | | Higuchi model | | Hixson-Crowell Model | | Weibull Model | | |
|------------------------|------------|-------------|-------------|-------------|---------------|-------------|----------------------|-------------|---------------|---------|-------------|
| | K_0 | R^2_{adj} | K_1 | R^2_{adj} | K_H | R^2_{adj} | K_{HC} | R^2_{adj} | α | β | R^2_{adj} |
| pH 1.2 | | | | | | | | | | | |
| Brand A | 2.489 | 0.0546 | 0.222 | 0.9929 | 17.230 | 0.7088 | 0.026 | 0.8663 | 1.966 | 0.787 | 0.9918 |
| Brand B | 2.576 | 0.1834 | 0.207 | 0.9752 | 17.731 | 0.7729 | 0.027 | 0.8947 | 3.074 | 1.071 | 0.9594 |
| Brand C | 2.594 | 0.1366 | 0.177 | 0.9588 | 17.869 | 0.7774 | 0.026 | 0.8941 | 9.051 | 1.316 | 0.9349 |
| Brand D | 2.201 | 0.2549 | 0.163 | 0.9646 | 15.377 | 0.6057 | 0.024 | 0.8244 | 0.410 | 0.010 | 0.9954 |
| Brand E | 2.418 | 0.0577 | 0.157 | 0.9938 | 16.647 | 0.7724 | 0.025 | 0.9222 | 1.490 | 0.598 | 0.9899 |
| pH 4.5 | | | | | | | | | | | |
| Brand A | 2.470 | 0.4256 | 0.103 | 0.9678 | 16.704 | 0.9080 | 0.025 | 0.9879 | 41.533 | 1.528 | 0.9667 |
| Brand B | 2.517 | 0.2910 | 0.120 | 0.9576 | 17.160 | 0.8525 | 0.025 | 0.9640 | 93.885 | 1.929 | 0.9600 |
| Brand C | 2.359 | 0.7442 | 0.068 | 0.9346 | 15.563 | 0.9514 | 0.018 | 0.9641 | 1063.9 | 2.254 | 0.9567 |
| Brand D | 2.191 | 0.7668 | 0.056 | 0.9363 | 14.373 | 0.9176 | 0.015 | 0.9655 | 70.540 | 1.565 | 0.9980 |
| Brand E | 2.425 | 0.5874 | 0.078 | 0.8780 | 16.165 | 0.8519 | 0.021 | 0.9186 | 11277 | 3.294 | 0.9681 |
| pH 6.8 | | | | | | | | | | | |
| Brand A | 1.994 | 0.2002 | 0.069 | 0.9456 | 13.658 | 0.8228 | 0.019 | 0.9077 | 0.804 | 0.119 | 0.9917 |
| Brand B | 1.708 | 0.5579 | 0.038 | 0.9381 | 11.443 | 0.9121 | 0.010 | 0.8902 | 2.354 | 0.336 | 0.9660 |
| Brand C | 1.702 | 0.2707 | 0.063 | 0.8572 | 12.070 | 0.4483 | 0.018 | 0.4435 | 0.846 | 0.037 | 0.9229 |
| Brand D | 1.986 | 0.2131 | 0.068 | 0.9279 | 13.590 | 0.8116 | 0.019 | 0.8889 | 0.655 | 0.053 | 0.9790 |
| Brand E | 1.770 | 0.0615 | 0.053 | 0.7889 | 12.242 | 0.6942 | 0.016 | 0.7180 | 0.766 | 0.027 | 0.9532 |
| Distilled water | | | | | | | | | | | |
| Brand A | 2.488 | 0.1745 | 0.145 | 0.9844 | 17.045 | 0.8240 | 0.026 | 0.9471 | 6.244 | 1.117 | 0.9774 |
| Brand B | 2.485 | 0.5515 | 0.095 | 0.9598 | 16.675 | 0.9514 | 0.025 | 0.9921 | 40.96 | 1.483 | 0.9529 |
| Brand C | 2.421 | 0.2763 | 0.142 | 0.9774 | 16.752 | 0.7316 | 0.024 | 0.9190 | 1.355 | 0.781 | 0.9753 |
| Brand D | 2.412 | 0.1738 | 0.163 | 0.9940 | 16.724 | 0.7087 | 0.025 | 0.9022 | 5.570 | 1.238 | 0.9945 |
| Brand E | 2.658 | 0.3365 | 0.178 | 0.9355 | 18.287 | 0.7809 | 0.027 | 0.8958 | 8.312 | 1.366 | 0.9202 |

COCLUSION

Comparative dissolution study of different market available brands of cefadroxil was performed. According to the analysis, Brand B and D were similar in drug release to that of reference brand (A). This similarity is a guide to conclude that these two brands will show

similar in vivo performance to reference formulation. First order and Weibull model best explained cefadroxil release from different oral solid dosage forms analyzed. From the present study, it is also evident that a slight change in pH might affect dissolution kinetics and hence *in-vivo* performance of the drug. Significant difference was detected in buffer pH 4.5 and pH 6.8 that indicated these brands can not be used interchangeably. The results also emphasized the need of constant surveillance on marketed drug product by the government, manufacturers and independent research groups to ensure supply and availability of quality medicines for the patients.

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