INVESTIGATION ON PHARMACEUTICAL QUALITY OF DIFFERENT BRANDS OF CEFADROXIL MONOHYDRATE AVAILABLE IN KARACHI, PAKISTAN

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ABSTRACT

Many reports published in print and electronic media about the presence of substandard drugs in the local market of Pakistan which confuse the health care professionals. Therefore, the present study was aimed on pharmaceutical quality evaluation of different brand of Cefadroxil monohydrate manufactured by local and multinational companies of Pakistan. Study design was cross sectional and conducted at Institute of Pharmaceutical and Environment Research, Dow University of Health Sciences, Karachi during the month of September'2012 through Octtober'2012. Different pharmaceutical parameters, weight variation, thickness, hardness, disintegration time, dissolution testing and chemical assay were performed on all formulations of Cefadroxil monohydrate. These tests were performed as specified in United State Pharmacopeia (USP 28). Non pharmacopeia test (dissolution profile) was also performed to observe the drug release from dosage forms. Stastical test ANOVA was adopted to compare dissolution profile and chemical assay of Cefadroxil monohydrate from different brands using SPSS 20.0. Results of weight variation, thickness and hardness tests for all the samples were within the specified limit. The disintegration time for all the samples was within the range of 1.0 to 4.0 minutes. The dissolution test was passed for all samples analyzed during the study except one which passed in S-2 test limits according to USP. Percent dissolution in 30 minutes was in between 86.48 and 101.15%. F2 similarity results revealed that only three brands showed similarity in dissolution profile with that of reference brand, whereas, f2 factor for one brand was far from the FDA criteria (i.e. 50-100). Assay results of all samples were in the range of 95-118% of the label claim of Cefadroxil monohydrate. It is concluded that all the brands of Cefadroxil monohydrate are of good pharmaceutical quality. The pharmaceutical quality of local and multinational brands was comparable.

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INTRODUCTION

Cefadroxil monohydrate is a first generation cephalosporin antibiotic which is effectively used in treatment of mild to moderate infections of upper respiratory tract, skin, soft tissues and urinary tract infections. It is well tolerated orally, effective in the dose of 1000mg in single or divided doses [1]. Different brand of Cefadroxil are available in tablet, capsule and dry powder for suspension. Local and multinational pharmaceutical companies are involved in manufacturing and marketing of Cefadroxil formulations in Pakistan.

The World Health Organization (WHO) explains counterfeit drugs as the product which is intentionally mislabeled in terms of its identity, quality or purity [2]. Counterfeit not only involves the use of substandard active drug but also complete absence of active drug, reduced quantity of active drug, etc. Counterfeiting in pharmaceutical products is a growing health problem, resulting in poor treatment success. Substandard or poor quality pharmaceutical products are those which do not fall in the pharmacopeia limits specified for these products. These products not only results in treatment failure, adverse drug events, increased drug resistance, but also reduce the confidence of consumers on the pharmaceutical industry or health care system of the society [3,4]. Quality evaluation was performed on commercially available pharmaceutical products including tablets, capsules in different parts of the world [5, 6]. Reports were published in literature about the presence of low quality pharmaceutical products with reduced active ingredient or drugs in under developed countries [7]. In such countries, counterfeit or substandard drugs are marketed in large numbers [8]. Similarly, pharmaceutical quality of these products is also compromised. These substandard drugs marketed in developing countries are usually of the drugs used in life threatening ailments. Current status of health care system in countries like Pakistan can only be improved by uninterrupted supply of good quality and effective medicines available for general public [9].

Many reports published in print and electronic media about the presence of substandard drugs in the local market of Pakistan. These reports did not mention the results of quantitative analysis. Pharmaceutical products of different manufacturers are marketed. Bioavailability and effectiveness of these pharmaceutical products largely depends on their pharmaceutical quality. Most of the health care professionals (physicians and pharmacists) get confused in order to select suitable and good quality brand for better treatment outcomes. Keeping in view this situation, it is necessary that the quality of pharmaceutical products should be routinely assed to investigate the availability of counterfeit drug. Therefore, the present study was aimed on pharmaceutical quality evaluation of different brand of Cefadroxil monohydrate listed in local index of registered pharmaceutical products. This study gave an idea regarding the quality of different brands of cefadroxil monohydrate.

MATERIALS AND METHODS

Different brands of Cefadroxil monohydrate available in local market and listed in local index of pharmaceutical products were randomly selected and purchased from medical stores including retail and wholesalers. 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 October'2012 through November'2012.

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).

Reagents:

De-ionized double distilled water, Acetonitrile HPLC Grade, Monobasic Potassium Phosphate, Potassium Hydroxide (analytical grade) and Cefadroxil monohydrate RS.

Pharmaceutical analysis:

Weight uniformity, thickness, hardness, disintegration time and dissolution test on all samples were performed according to USP 2008 [10]. For weight uniformity, weight of randomly selected twenty tablets/capsules was determined using digital balance. Disintegration time was determined by disintegration apparatus (Pharmatest) in distilled water at 37°C. The dissolution test was performed using dissolution apparatus (Pharmatest). The dissolution apparatus 1 (basket) and 2 (paddle) was used with dissolution medium i.e. distilled water at 37°C for about 30 minutes, for capsules and tablets, respectively. The dissolved amount of Cefadroxil monohydrate was determined by UV-spectrophotometer at 263nm.

Chemical assay:

Chemical assay on different brands of Cefadroxil monohydrate ($C_{16}H_{17}N_3O_5S$) was performed using HPLC 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 10N. Mobile phase preparation: Mobile phase was prepared using pH 5.0 buffer and acetonitrile in the ration of 960:40 and filtered using 0.5 micrometer porosity. Standard preparation: Accurate quantity of USP Cefadtoxil monohydrate RS was dissolved in buffer pH 5.0 to get the solution containing 1.06 mg per ml. Sample preparation: Content of ten capsules were removed completely, the powder content equivalent to 200mg Cefadroxil monohydrate 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 noted with 230 nm detector.

System suitability test:

Standard solution was repeatedly injected five times and peak area was recorded for these consecutive injections. This was done before the injection of sample solution to check the consistency of performance of HPLC on repetitive injections. The criteria of acceptability of the system was

- RSD >2% for five consecutive injections of standard solution
- Tailing factor not more than 2.2 for cefadroxil

Qualification of HPLC system:

Equal injection volume of standard solution i.e. 10microliter was injected cautionary two times at the end of the analysis and peak response was recorded. Acceptance limit was 3% to use and conclude the study. Formula is given below:

$$\text{Formula} = \frac{\text{Maximum peak area} - \text{Minimum peak area}}{\text{Maximum peak area}} \times 100$$

Dissolution profile study:

Dissolution profile was also studied using apparatus 2 (paddle type) at 50rpm for tablets and apparatus 1 (basket type) at 100 rpm for capsules using deaerated distilled water at 37$\pm$1°C.Six replicates of each sample (SMP) were used. Ten ml of dissolution medium at six time points i.e. 0, 10, 20, 30, 40 and 60 minutes were pipetted out and replaced by fresh dissolution medium (10ml) to maintain sink conditions. UV spectrophotometer determination at 263nm was performed. Percent of Cefadroxil monohydrate dissolved at different time points was calculated. F2 similarity factor was also determined taking SMP 4 (multinational brand) as reference.

Stastical analysis:

Data was entered in stastical software SPSS 20.0. ANOVA was performed to compare results of assay and dissolution profile of different brands of Cefadroxil monohydrate at 0.05 level of significance.

RESULTS

During the study, seven samples of oral dosage forms of Cefadroxil monohydrate available in local market of Pakistan were analyzed including two tablets and five capsules of five manufacturers. Two manufacturers were multinational. Sample information including strength, price of package, price per unit dosage form, expiry date

and manufacturing date is summarized in table-1. Results of weight variation test for all the samples were within the specified limit. The disintegration time for all the samples was within 4 minutes. The dissolution test was passed for all samples analyzed during the study. Assay was performed using HPLC as mentioned in USP monograph of Cefadroxil. Assay results of all samples were in the USP specified limit i.e. not less than 90% and not more than 120% of the label claim of Cefadroxil. Pharmaceutical evaluation and assay results are mentioned in table-2 and 3. Dissolution profiles of these brands are summarized in figure 2, 3 and 4. F2 similarity results comparing different brands with SMP 4 as reference brand were 70.26, 52.72, 62.24, 47.72, 31.08 and 42.13 for SMP 1, 2, 3, 5, 6 and 7, respectively.

Table 1: Information written on labels of different brands of Cefadroxil monohydrate.

Sample code	Dosage form	Strength (mg)	Price per pack (rupees)	Price per unit dosage form (rupees)	Manufacturing date	Expiry date	Batch no.	Manufacturer type
SMP-1	Capsule	500	150	12.5	6/2012	5/2015	12647	Local
SMP-2	Capsule	500	240	20	1/2012	1/2014	CD5991	Multinational
SMP-3	Capsule	500	182	15.13	9/2012	9/2015	134	Local
SMP-4	Capsule	500	313	26	7/2012	7/2015	2G552	Multinational
SMP-5	Tablet	1000	265	22	5/2012	4/2015	12584	Local
SMP-6	Tablet	500	180	15	6/2012	6/2016	56	Local
SMP-7	Capsule	500	180	15	8/2012	7/2014	43	Local

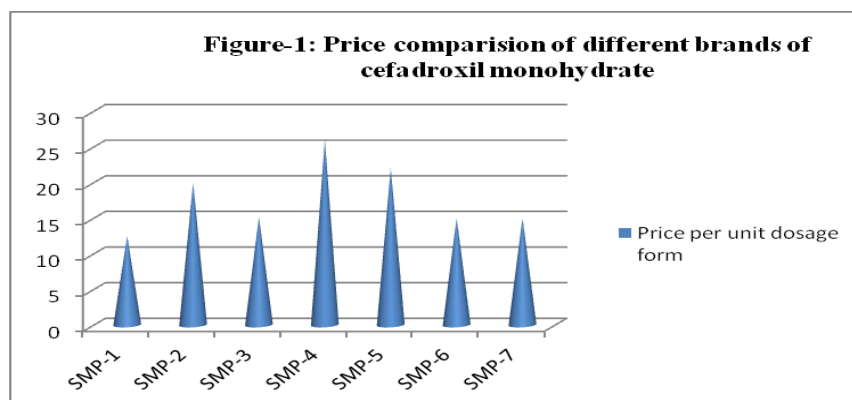Figure-1: Price comparision of different brands of cefadroxil monohydrate

Table 2: Pharmaceutical evaluation assay of different brands of Cefadroxil monohydrate.

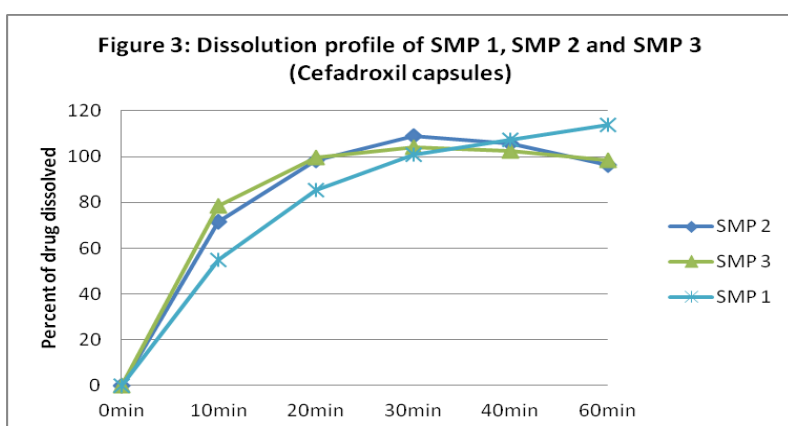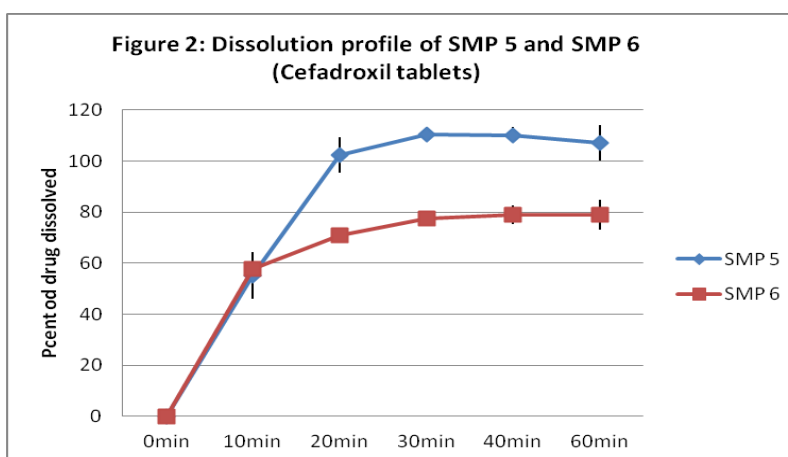| Sample code	Weight variation (mg) X ± SD	Thickness Variation (mm) X ± SD	Hardness (N) X ± SD	Disintegration time (min)	Dissolution testing (%)
SMP-1	647.5+21.4	NA*	NA	3.0	86.48
SMP-2	642.11+11.67	NA	NA	3.5	97.6
SMP-3	660.2+13.7	NA	NA	3.3	98
SMP-4	633.38+19.1	NA	NA	2.25	101.15
SMP-5	1347+16.6	7.32+0.028	189.5+28.9	4.0	93.6
SMP-6	638.75+9.83	5.48+0.049	184.4+34.9	1.0	88.3
SMP-7	627.25+22.06	NA	NA	4.0	93.49

*NA= not applicable for capsules, X = mean, SD= standard deviation

Table-3: Chemical assay of different brands of Cefadroxil monohydrate.

Sample	Assay-1 (%)	Assay-2 (%)	Mean
SMP-1	101.7	101.8	101.75
SMP-2	95.2	95.38	95.29
SMP-3	101.2	101.29	101.25
SMP-4	98.8	99	98.9
SMP-5	104.28	104	104.14
SMP-6	103.3	102	102.65
SMP-7	98.3	98.5	98.4

Table 4: Results of ANOVA adopted to compare percent assay of different brands of Cefadroxil monohydrate

Source of variation	SS	df	MS	F	p-value
Between groups	108.639	6	18.106	136.366	0.000
Within groups	0.929	7	0.133		
Total	109.568	13			

Figure 2: Dissolution profile of SMP 5 and SMP 6 (Cefadroxil tablets)

Figure 3: Dissolution profile of SMP 1, SMP 2 and SMP 3 (Cefadroxil capsules)

DISCUSSION

Pharmaceutical counterfeiting is now a great problem both in developed and less developed countries. It does not only harm the consumers in terms of health but also manufacturer in terms of reputation, physicians in terms

of confidence of patient and government in terms of large number of cases [11]. Many countries like Bangladesh, India, Thailand and Nigeria are facing the problem of counterfeiting [12-14]. Affordability is a major reason of counterfeit drugs in less developed countries. The situation of pharmaceutical counterfeiting in poor countries is not clear yet. It is general perceptions that drug product of multinational companies although expensive are more effective than that of local companies. Reports from Pakistan were published but did not comment on pharmaceutical quality of local and multinational manufacturer brands. The present study analyzed data for statistical association of such type. According to WHO, the contribution of antibiotics to the total percentage of counterfeit drugs was 28% (from Jan' 1999 till Dec '2002) [15]. The substandard antibiotics result in development of resistance in clinical isolates [16]. In this background, Cefadroxil was selected for the present study. The pharmaceutical parameters including weight variation, thickness, harness, disintegration time, dissolution and chemical assay was performed according to USP 2008 on all the brands of Cefadroxil available in local market in oral solid dosage forms.

During the study, seven samples of oral dosage forms of Cefadroxil monohydrate available in local market were analyzed including two tablets and five capsules of five manufacturers. Two manufacturers were multinational. Sample information including strength, price of package, price per unit dosage form, expiry date and manufacturing date is summarized in table-1 and figure-1. Results of weight variation test for all the samples were within the specified limit i.e. the weight of not more than two tablet/capsule of twenty can diverge from average weight not more than $\pm 7.5\%$. Tablets should be hard enough to withstand the friction during distribution, handling and storage and should not be too hard that overdue disintegration. Hardness testing was performed to tablets and was in the recommended range i.e. 4 kg. Disintegration time was determined in distilled water in 30 minutes at 37°C. If in any condition disintegration delays, the dissolution and intestinal absorption of drugs from oral solid unit dosage form is adversely affected. The disintegration time for all the samples was less than 4 minutes (table-2).

For the intestinal absorption of drugs from oral solid dosage form, it is obligatory that it must be in dissolved form. In cases of worried dissolution, absorption and bioavailability is also affected. Dissolution test was performed as per USP 2008 specifications using UV- spectrophotometer. The limit of dissolved drug in 30 minutes in distilled water is not less than 80% for capsules and not less than 75% for tablets. Results of dissolution test for all samples are mentioned in table-2. One brand (SMP-6) failed in S-1 limit of dissolution test i.e. less than 75% of drug dissolved in 30 minutes. For this sample, test was repeated with six more tablets and the average amount of drug dissolved of 12 tablets was more than 75%, so the sample passed the S-2 limit of dissolution test (USP 28). F2 similarity results revealed that only three brands showed similarity in dissolution profile with that of reference brand, whereas, f2 factor for one brand was far from the FDA criteria (i.e. 50-100). Assay was performed using HPLC as mentioned in USP monograph of Cefadroxil tablet and capsule. HPLC enables one to proceed with automation, higher resolution, quicker analysis, and getting accurate results. HPLC analysis requires small volume of samples which increase its implementation in pharmaceutical evaluations [17]. For all seven samples, assay results were in the USP specified limit, ranged 95% to 104% of the label claim of Cefadroxil (table-3). There was stastical significant variation among different brands of cefadroxil monohydrate (table-4) whereas, passed quality control tests. Similar work was also undertaken by other researchers i.e. quality evaluation of other drugs available in local market [18-20].

Dissolution profile was also studied and mentioned in figure 2, 3 and 4. ANOVA was adopted to compare dissolution profile of Cefadroxil monohydrate from different brands (tablets and capsules). For seven samples, %RSD was ranged from 10-20%. Results of ANOVA showed that there was significant influence of brand on the cumulative amount of drug dissolved over a period of 60 minutes (p-value<0.0001). Even though most of the samples showed satisfactory pattern of dissolution profile which prove that the release of Cefadroxil monohydrate from dosage form vary from one product to another but are satisfactory to make drug available for gastrointestinal absorption. These variations were due to formulation and manufacturing differences.

It was observed that the pharmaceutical quality of both local and multinational manufacture's product was good. The study gave an idea that the perception of general public about the drug product of local manufacturer may be wrong. Local manufacturers are working to make available the pharmaceutical products in low price especially for the people having affordability problems. This is true that reports were published in literature

about pharmaceutical counterfeiting, especially in less developed countries including Pakistan. Print and electronic media also excauade the situation of the availability of substandard drugs in Pakistan. This may result in under and over estimations of the actual situation. It is recommended that studies should be conducted routinely on different drugs with large sample size and collecting samples from different cities, including rural and urban localities to get the clear picture of the situation of pharmaceutical counterfeiting in Pakistan.

CONCLUSION

Quality control tests carry out during manufacturing and essential to be carried out post-marketing by regulatory agencies and researchers. Seven brands of Cefadroxil monohydrate have been evaluated using set quality control test of weight variation, hardness, disintegration, dissolution and assay with intention to judge whether these seven brands are pharmaceutically equivalent or not. The outcomes obtained have been matched with USP standards and indicated that all the brands have met the requirements of the quality control test proved to be pharmaceutically equivalent. Though, there were variations among these brands due to the different manufacturing process and excipients, all the brands have complied with the requirements for quality control tests. As quality control parameters are interrelated to one another from chemical purity of active ingredient through manufacturing to intended effect of the drug, high-quality pharmaceutical products should meet all the standard requirements for getting its therapeutic response in the human body.

Conflict of interest

The authors declare no conflict of interest.

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