STABILITY OF CEFUROXIME AXETIL ORAL SUSPENSION AT DIFFERENT TEMPERATURE STORAGE CONDITIONS

Alija Uzunović[1*], Edina Vranić[2]

[1] Institute for Quality Control of Medicines, Titova 9, 71 000 Sarajevo, Bosnia and Herzegovina

[2] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Sarajevo, Čekaluša 90, 71 000 Sarajevo, Bosnia and Herzegovina

[*] Corresponding author

Abstract

Stability testing of an active substance or finished product provides information of the variation of drug substance or final product with time influenced by a variety of environmental factors such as temperature, humidity and light. Knowledge gained from stability studies enables understanding of the effects of the environment on the drugs.

The aim of our study was to determine the stability of cefuroxime axetil oral suspension at different temperature storage conditions (stored at room /20°C/ and refrigerated /5°C/ conditions). Determination of cefuroxime (as cefuroxime axetil) was performed by dissolution testing.

Fractions of the released cefuroxime axetil were compared using *f*2 value. After interpolating data for dissolution profiles at room and refrigerated conditions the following f2values were obtained: 62,56; 56,32 and 36,18 on 3rd, 6th and 10th day, respectively. These values indicate similarities in drug release from analyzed cefuroxime axetil oral suspension on 3rd, 6th day, and differences on 10th day.

Based on our results, we may assume that cefuroxime axetil oral suspension preserves its stability for 10 days after reconstitution under room and refrigerated conditions. It is obvious, according to the *f*2 value obtained on the 10th day, that there is a difference between the released ceforoxime axetil from oral suspension at room (87,68%) and refrigerated (92,35%) conditions. Concentration changes can be caused by the mechanisms associated with drug release and hydrolytical decomposition of the sample and higher temperatures during longer period of storage.

KEY WORDS: cefuroxime axetil, suspension, stability

Introduction

Cefuroxime axetil (1-acetoxyethyl ester of cefuroxime) is orally active prodrug of cefuroxime, second generation semi-synthetic cephalosporine antibiotic. Upon oral administration, cefuroxime axetil is absorbed from gastrointestinal tract and rapidly hydrolyzed by non-specific esterase in the intestinal mucosa and blood releasing microbiologically active form (free acid), cefuroxime. Cefuroxime exerts its bactericidal effect against a range of gram-positive and gram-negative bacteria by inhibiting the synthesis of bacterial cell wall (1,2,3). Cefuroxime axetil (Figure 1.) has a carbamoyl group in position 3, which accounts for considerable metabolic stability, and a methoxyimino group in position 7, which provides resistance to β-lactamase attack and, together with a furyl ring, contributes to the antibacterial properties of the molecule by enhancing its activity against Gram-negative bacteria. A 1-acetoxyethyl ester group in the position 4 of cefuroxime axetil ensures its lipophilicity and promotes the intestinal absorption of cefuroxime. For the preparation of pharmaceutical formulations only the amorphous form is used. It has better physicochemical and biological properties than the crystalline form, e.g. significantly higher solubility and bulk density as well as higher degree of absorption after oral administration (4,5). Due to their possible composition, pharmaceuticals are especially sensitive to environmental factors. Strict storage conditions are necessary for the maintenance of integrity and product activity. Stability is defined as the capacity of a drug substance or drug product to remain within the established specifications to maintain its identity, strength, quality, and purity throughout the retest or until expiry date period (6). Stability testing of an active substance or finished product provides information on how the quality of drug substance or drug product varies with time influenced by a variety of environmental factors such as temperature, humidity and light. Knowledge from stability studies enables understanding of the long-term effects of the environment on drugs (7). Stability testing also provides information about the degradation mechanisms, potential degradation products, possible degradation pathways of drug as well as interaction between the drug and the excipients in drug product. The gained information is applied in the development of manufacturing processes, selection of proper packaging and storage conditions, and determination of product's shelf life and expiration date (8). The aim of present study was to determine the stability of cefuroxime axetil oral suspension at different temperature storage conditions (stored at room /20°C/ and refrigerated /5°C/ conditions). Determination of cefuroxime (as cefuroxime axetil) was performed by dissolution testing.

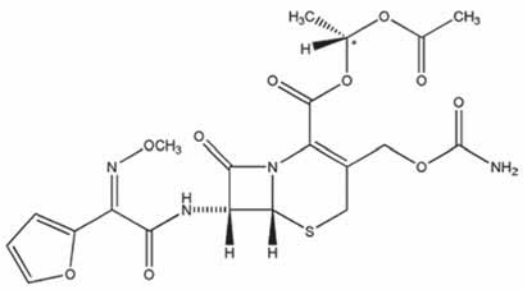

FIGURE 1. Structural formula of cefuroxime axetil

Material and Methods

Reagents

The reagents used were of analytical grade, unless otherwise stated. Cefuroxime axetil working standard was provided by GlaxoSmithKline. Sodium dihydrogen phosphate and disodium hydrogen phosphate were provided by Carl Roth GmbH & Co. (Karlsruhe, Germany).

Preparation of standard solutions

A standard curve of absorbance versus concentration was constructed using dilutions of cefuroxime axetil in the dissolution medium (phosphate buffer, pH=7,0; previously degassed) ranging in concentration from 0,0027 to 0,0133 mg/ml. Absorbance versus concentration plot was linear over this concentration range and was used to determine percent of drug dissolved in the dissolution experiments. UV absorbance of each standard solution was measured spectrophotometrically at 280 nm.

Dissolution test conditions and analysis procedure

The dissolution tests of cefuroxime axetil oral suspension (n=6) were performed using USP apparatus 2 , Van Kel VK 7010 dissolution tester, at a stirring speed of 50 rpm (Van Kel, Cary, NC, USA). The dissolution apparatus was maintained at 37°C throughout the experiment. Cefuroxime axetil oral suspension, when reconstituted in water, provides the equivalent of 125 mg of cefuroxime per 5 ml of suspension. Reconstituted oral suspension in the amount of 5 ml was transferred into test tube and slowly added to dissolution medium. Samples in the amount of 5 ml were withdrawn at the following intervals: 5^{th}, 15^{th}, 30^{th} and 45^{th} min. Prior to use, the dissolution medium was equilibrated at 37°C overnight to

deaerate the medium. The dissolution tests of cefuroxime axetil oral suspension (n=3) at different temperature storage conditions (stored at room /20°C/ and refrigerated /5°C/ conditions) was performed on 3rd, 6th and 10th day.

Dissolution samples were collected for the analysis. Correction for volume was calculated mathematically, considering that withdrawn samples were not supplemented with an equal volume of fresh dissolution fluid to maintain a constant total volume. The samples were filtered using a 0,45 μm membrane filter (Sartorious GmbH, Goettingen, Germany). The dissolution apparatus was connected with UV/VIS spectrophotometer Shimadzu 1601 (Shimadzu, Kyoto, Japan). Determination of dissolution rates for the active ingredient in oral suspension is carried out according to the previously mentioned spectrophotometric method. All dissolution tests were performed in triplicate. Model independent approach that compare the dissolution profiles was applied to the dissolution data in this study. The data were analyzed using pharmacopeial test for similarity of dissolution profiles (f_2 equation), previously proposed by Moore and Flanner (9).

Results and Discussion

The results of our studies are summarized in Tables 1-4, and Figures 1-4, which show the fraction of the dissolved drug as a function of time. In vitro release of cefuroxime axetil from oral suspension fulfilled official requirements if the dissolution of each of the six samples was not less than 60% of the declared contents in 30 minutes. Our tests were carried out for a period of 45 minutes. In our study, in vitro release of cefuroxime axetil fulfilled these requirements and exhibited release profile: 91,49 and 95,71%, for 30 and 45 minutes, respectively. Concentration changes of cefuroxime axetil under the experimental (room and refrigerated) conditions were assessed by means of dissolution testing and spectrophotometry, too. Fractions of cefuroxime axetil released in dissolution medium were calculated from calibration curves. The data were analyzed using pharmacopeial test for similarity of dissolution profiles (f_2 equation). The f_2 value between 50 and 100 suggests that the dissolution profiles are similar. The value of 100 suggests that the test and reference dissolution profiles are identical. Fractions of the released cefuroxime axetil were compared using this value. After interpolating data for dissolution profiles at room and refrigerated conditions the following f_2 values were obtained: 62,56, 56,32 and 36,18 on 3rd, 6th and 10th day, respectively. These values indicate similarities in drug release from analyzed cefuroxime axetil oral suspension on 3rd, 6th day, and differences on 10th day.

	Time			
	5 min	15 min	30 min	45 min
% dissolved	58,17	77,79	88,27	90,85
	57,04	81,13	90,84	94,87
	58,88	84,32	92,93	98,53
	59,68	84,36	94,36	98,00
	56,31	82,42	91,47	95,98
	54,56	81,65	91,09	96,04
$\overline{X}$	57,44	81,94	91,49	95,71
S.D.	1,863	2,437	2,061	2,747
R.S.D	3,24	2,97	2,25	2,87

TABLE 1. Fraction of dissolved cefuroxime axetil from oral suspension as a function of time (freshly reconstituted suspension -"0" day).

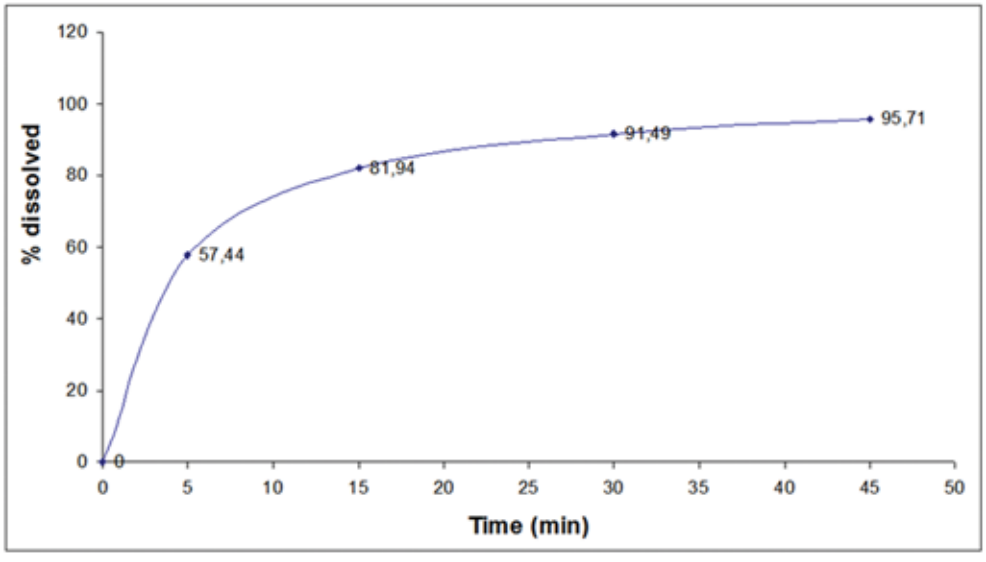

FIGURE 1. In vitro release of cefuroxime axetil from oral suspension ("0" day)

	Time							
	Refrigerated conditions				Room temperature conditions			
	5 min	15 min	30 min	45 min	5 min	15 min	30 min	45 min
% dissolved	50,02	75,44	86,61	91,69	44,71	80,12	93,77	97,08
	52,41	78,67	88,98	94,60	43,56	77,71	90,34	94,15
	54,92	81,20	91,73	95,06	43,02	78,67	92,41	97,72
$\overline{X}$	52,45	78,44	89,11	93,78	43,77	78,83	92,17	96,32
S.D.	2,454	2,889	2,559	1,826	0,865	1,215	1,725	1,899
R.S.D	4,68	3,68	2,87	1,95	1,98	1,54	1,87	1,97

TABLE 2. Fraction of dissolved cefuroxime axetil from oral suspension as a function of time (3rd day).

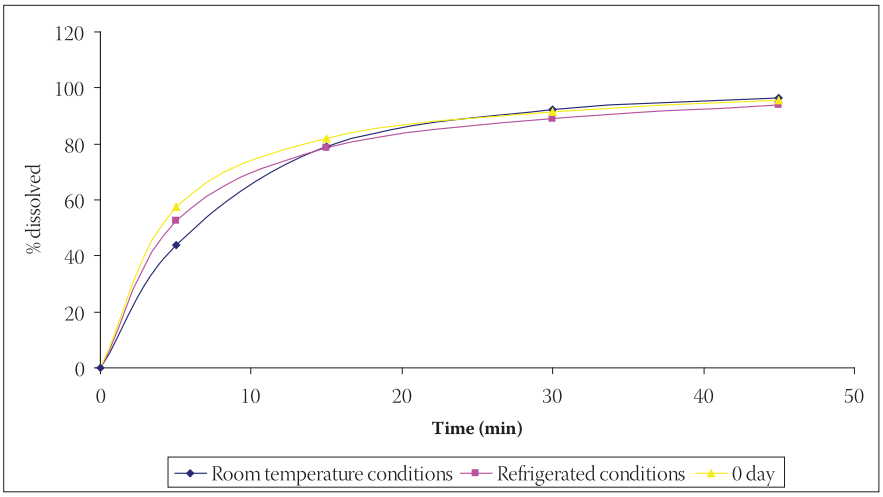

FIGURE 2. Comparison of *in vitro* release of cefuroxime axetil from oral suspension (3rd day)

	Time							
	Refrigerated conditions				Room temperature conditions			
	5 min	15 min	30 min	45 min	5 min	15 min	30 min	45 min
% dissolved	44,84	78,37	90,18	94,66	32,39	74,28	95,34	99,74
	47,74	80,10	93,33	97,41	33,64	75,25	91,29	96,17
	43,13	80,77	94,03	96,87	36,46	71,16	92,30	98,44
$\overline{X}$	45,24	79,75	92,51	96,31	34,16	73,56	92,98	98,12
S.D.	2,332	1,236	2,052	1,459	2,084	2,135	2,106	1,805
R.S.D	5,16	1,55	2,22	1,52	6,10	2,90	2,27	1,84

TABLE 3. Fraction of dissolved cefuroxime axetil from oral suspension as a function of time (6th day).

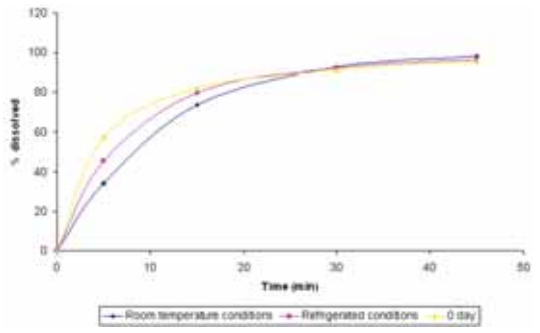

FIGURE 3. Comparison of *in vitro* release of cefuroxime axetil from oral suspension (6th day)

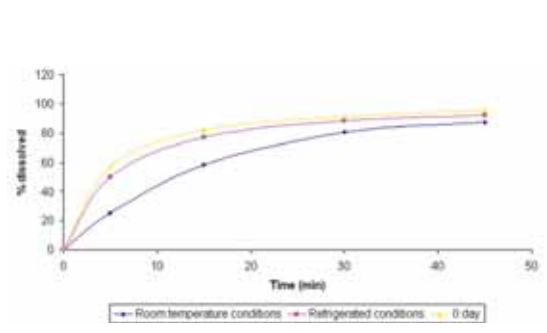

FIGURE 4. Comparison of *in vitro* release of cefuroxime axetil from oral suspension (10th day)

	Time							
	Refrigerated conditions				Room temperature conditions			
	5 min	15 min	30 min	45 min	5 min	15 min	30 min	45 min
% dissolved	49,47	75,95	85,43	90,69	26,04	59,91	80,88	87,95
	50,04	77,27	89,26	92,42	23,44	54,24	75,24	81,54
	50,91	79,20	90,20	93,94	26,00	60,84	86,31	93,55
$\overline{X}$	50,14	77,47	88,30	92,35	25,16	58,33	80,81	87,68
S.D.	0,727	1,634	2,526	1,627	1,492	3,573	5,535	6,009
R.S.D	1,45	2,11	2,86	1,76	5,93	6,13	6,85	6,85

TABLE 4. Fraction of dissolved cefuroxime axetil from oral suspension as a function of time (10^{th} day).

Conclusion

- ◊ *In vitro* release of cefuroxime axetil from oral suspension fulfilled official requirements
- ◊ After interpolating data for dissolution profiles at room and refrigerated conditions the following f_2 values were obtained: 62,56, 56,32 and 36,18 on 3^{rd}, 6^{th} and 10^{th} day, respectively. These values indicate similarities in drug release from analyzed cefuroxime axetil oral suspension on 3^{rd}, 6^{th} day, and differences on 10^{th} day.
- ◊ On the basis of the results in this study, we can assume that cefuroxime axetil oral suspension preserves its stability during 10 days after reconstitution under room and refrigerated conditions. It is obvious, according to the obtained f_2 value on the 10th day, that there is difference between released ceforoxime axetil from oral suspension at room (87,68%) and refrigerated (92,35%) conditions.
- ◊ Changes in concentration may be caused by the mechanisms associated with drug release and hydrolytical decomposition of the sample and higher temperatures during longer period of storage.

References

(1) Deguchi K., Yokota N., Koguchi M., Suzuki Y., Fukayama S., Ishihara R., Oda S., Tanaka S, Nakane Y., Fukumoto T. Antimicrobial activities of cefuroxime against recent clinical isolates. Jpn. J. Antibiot. 1994; 47: 365.

(2) Scott L.J., Ormrod D., Goa K.L. Cefuroxime axetil: An updated review of its use in the management of bacterial infections. Drugs 2001; 61: 1455–1500.

(3) Dellamonica P. Cefuroxime axetil. Int. J. Antimicrob. Agents 1994; 4: 23–26

(4) Oszczapowicz I., Tejchman B., Zimniak A., Szatyłowicz H. Esters of cephalosporins. Part VI. Properties of the beta-form of 1-acetoxyethyl ester of cefuroxime Acta Pol. Pharm. 1998;55: 197–204.

(5) Raw A.S., Furness M.S., Gill D.S., Adams R.C., Holcombre F.O. Jr., Yu L.X. Regulatory considerations of pharmaceutical solid polymorphism in Abbreviated New Drug Applications (ANDAs). Adv. Drug Deliv. Rev. 2004; 56: 397–414.

(6) Anonymous. Draft Guidance for Industry: Stability Testing of Drug Substances and Drug Products, FDA, Rockville, MD, 1998.

(7) International Conference on Harmonization (ICH), Guidance for Industry, Q1A(R2): Stability Testing of New Drug Substances and Products, IFPMA, Geneva, 2000.

(8) Carstensen J.T., Rhodes C.T. Drug Stability, Principles and Practices, Marcel Decer, Inc., New York, 2000.

(9) Moore J.W., Flanner H.H. Mathematical comparison of dissolution profiles. Pharm. Tech. 1996;20: 64-74.