

“STABILITY STUDY OF CLAVULANIC ACID CONTAINING ORAL SUSPENSION”

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Abstract: Stability testing is now the key procedural component in the pharmaceutical development program for a new drug as well as new formulation. Stability tests have been carried out so that recommended storage conditions and shelf life can be included on the label to ensure that the medicine is safe and effective throughout its shelf life. Stability of a material or product to maintain a stated property value within specified period of time when stored under specific conditions is very significant for drug products. Cefixime $C_{16}H_{15}N_3O_7S_2$ and Clavulanate Potassium as Clavulanic acid $C_8H_9NO_5$ for oral suspension (50 mg/5ml + 31.25 mg) A combination of third generation cephalosporin (Cefixime) and β -lactamase inhibitor (Clavulanic acid) used for the treatment of various types of infections. Using HPLC method, the concentrations of Cefixime trihydrate and clavulanic acid brands, X, Y and Z at zero time were within the pharmacopial limit when reconstituted with distilled, decreases gradually with time and the reaction followed first order kinetics.

Keywords: Cefixime trihydrate, clavulanic acid, suspension, stability, market.

1. INTRODUCTION

Stability testing of pharmaceutical products is a complex set of procedures involving considerable cost, time consumption and scientific expertise in order to build in quality, efficacy and safety in a drug formulation. Stability testing thus evaluates the effect of environmental factors on the quality of the a drug substance or a formulated product which is utilized for prediction of its shelf life, determine proper storage conditions and suggest labelling instructions used for packaging¹⁻⁴. In oral suspension the reconstituted drug substances is very critical, because within the stability period drug can be utilized, so fixation of durability of reconstituted sample is very important^{5,6}.

Cefixime and Potassium clavulanate oral suspension contain the equivalent of not less than 80 % and not more than 120 % of labelled amount of Cefixime and not less than 80 % and not more than 125 % of labelled amount of Clavulanic acid after 5 days of reconstitution when stored in Refrigerator (2 to 8 °C) and 40°C ± 2°C & 75 % RH ± 5% and 25°C ± 2°C & 60 % RH ± 5%.

The chemical reactions like solvolysis, oxidation, reduction, racemization etc. that occur in the pharmaceutical products may lead to the formation of degradation product, loss of potency of activepharmaceutical ingredient (API), loss of excipient activity like antimicrobial preservative action and antioxidants etc.⁷⁻¹⁰.

2. MATERIALS AND METHODS:

2.1.Chemicals: Tetrabutylammonium hydroxide (10% aqueous solution), Acetonitrile (HPLC Grade), HPLC grade water (Milli Q or equivalent), Orthophosphoric acid (AR grade).

2.2. Mobile Phase Preparation: 6.5 pH Buffer: Tetrabutylammonium hydroxide solution: Dilute 25 ml 10% Tetrabutylammonium hydroxide solution with water to obtain 1000 ml of solution and adjust the pH to 6.5 with 1.5 M phosphoric acid.

Mobile Phase: Prepare a mixture of Acetonitrile, Buffer and Water in the ratio 40: 10: 50. Filter and degas. Adjust the pH to 5.0 ± 0.1 using 1 M phosphoric acid.

2.3. Experimental Methods: The Three Brands (X, Y & Z) of Market Sample Were Reconstituted With Distilled Water and Stored At 25°C And 40°C for Seven Days Period:

Instrumentation:	
Column C-18 DB)	: 250 mm x 4.6 mm x 5 µm, ODS (preferably Supelco 516
Flow rate	: 1.5 ml/min
Detector	: UV-VIS
Wavelength	: 220 nm
Injection Volume	: 20 µl.
Column Temperature	: 30°C

3.0 RESULT AND DISCUSSION:

The results of stability study show that the concentration of Cefixime trihydrate and clavulanic acid for three brand X,Y and Z collected from market at zero time were found within the pharmacopoeial limit and when reconstituted with distilled water and stored at different storage conditions decreases gradually with time.As illustrated in Table -1 , the concentration of Cefixime of reconstituted oral suspension stored at 40°C decreases gradually from 108.0 % to 68.3 %, 103.5 % to 58.9 % and 109.6 % to 52.9 % of brand X,Y and Z respectively and become out of pharmacopoeial specification limit on day 3. Similarly the concentration of Cefixime at 25°C became out of pharmacopoeial specification limit on day 4 for brand X and day 7 for brand Z. Similarly the concentration of Clavulanic acid at 40°C decreases gradually from 119.3 % to 48.3 %, 115.6 % to 15.8 % and 112.8 % to 22.8 % of brand X, Y and Z respectively and become out of pharmacopoeial specification limit on day 3. Similarly the concentration of Clavulanic acid at 25°C became out of pharmacopoeial specification limit on day 4 for all the brand.

Table 1: Assay % Result of Cefixime

Test Interval	Brand X 40 °C	Brand Y 40 °C	Brand Z 40 °C	Brand X 25 °C	Brand Y 25°C	Brand Z 25 °C
0 Day	108.0 %	103.5 %	109.6 %	108.0 %	103.5 %	109.6 %
Day 1	99.0 %	99.6 %	99.8 %	105.2 %	108.6 %	105.9 %
Day 2	90.3 %	86.9 %	85.3 %	99.6 %	97.8 %	101.3 %
Day 3	78.6 %	76.9 %	73.8 %	95.8 %	98.5 %	99.7 %
Day 4	76.9 %	81.9 %	76.2 %	89.3 %	96.3 %	92.8 %
Day 5	83.6 %	75.2 %	71.6 %	83.5 %	93.8 %	86.9 %
Day 6	73.5 %	71.8 %	64.3 %	70.6 %	92.9 %	88.7 %
Day 7	68.3 %	58.9 %	52.9 %	69.8 %	91.7 %	78.6 %

Table 2: Assay % Result of Clavulanic Acid

Test Interval	Brand X 40 °C	Brand Y 40 °C	Brand Z 40 °C	Brand X 25 °C	Brand Y 25°C	Brand Z 25 °C
0 Day	119.3 %	115.6 %	112.8 %	119.3 %	115.6 %	112.8 %
Day 1	98.5 %	99.1 %	90.7 %	99.6 %	104.3 %	101.3 %
Day 2	90.8 %	92.3 %	89.2 %	94.6 %	97.3 %	96.5 %
Day 3	87.6 %	75.3 %	76.3 %	91.5 %	91.3 %	88.6 %
Day 4	77.6 %	65.2 %	71.3 %	89.2 %	86.1 %	70.6 %
Day 5	70.6 %	42.7 %	50.4 %	74.6 %	84.6 %	65.7 %
Day 6	63.7 %	37.3 %	41.3 %	70.8 %	52.3 %	60.4 %
Day 7	48.3 %	15.8 %	22.8 %	62.3 %	41.3 %	51.6 %

4. CONCLUSION:

Usually the temperature has a pronounced effect on drug stability and a rise in temperature increases the frequency of collision of the reactants molecules and hence increase the degradation, while a decrease in temperature reduce collision and reduce degradation with confirm results obtain. We can conclude that the Cefixime and Clavulanic acid suspension reconstituted with distilled water are affected by an increase in temperature, so it should be store below the room temperature.

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6. REFERENCES:

6.1. Journals:

1. J.T. Carstensen, C.T. Rhodes, Accelerated Conditions of Temperature and Humidity in the Absence and the Presence of light, Clin. Res. Drug Reg. Affairs. 1993; 10:177-185.
2. Oyetunde Olubukola and Akinleye Moshood, Stability of reconstituted amoxicillin clavulanate potassium under simulated in-home storage, Journal of Applied Pharmaceutical Science, 2012, 02 (01);28-31.
3. A.H. Samir, Stability-Kinetics, Pharmaceutical Dosage forms. Tablets, Vol.3, Marcel Dekker Inc., New York and Basel, 1982, 339-340, 364-366.
4. Swarbrick, J, Boylan, J.C., Encyclopedia of Pharmaceutical Technology - 2nd Ed., Vol.2, Marcel Dekker Inc., New York, 1992, 577, 1211-1218.

6.2 Books:

5. British Pharmacopoeia, British Pharmacopoeia Commission. Vol. 1, London: Her Majesty's Stationary Office; 2009. p. 397.
6. Indian Pharmacopoeia 2010, Volume II, 6th edition, 1 sep 2010, p 1012
7. <http://www.fda.gov/cder/guidelines.htm>
8. <http://www.fda.gov/cber/gdlns/ichstabdta.htm>
9. Proposed guidelines for stability studies for human drugs and biologicals, Food and Drug Administration, Washington, DC, March, 1984.
10. IDMA BULLETIN. Weekly publication. India drug manufacturer's association, Bombay, India, Vol. XXVII, 21st March 1997

6.3 Theses:

11. McMillan, A. and Young, H. The treatment of pharyngeal gonorrhoea with a single oral dose of Cefixime, International Journal of STD and AIDS, (2007), 18, 253-254.
12. Mayorga C, Torres M, Blanca M. Cephalosporin allergy. N Engl J Med 2002; 236:380-381
Norrby S. Side effects of cephalosporins. Drug 1987; 34(Suppl 2):105-120.
13. [Jump up](#) Joint Formulary Committee. [British National Formulary](#), 47th edition. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2004.

6.4 Proceeding papers:

14. **Samir, A.H.**, Stability-Kinetics, Pharmaceutical Dosage forms. Tablets, Vol.3, Marcel Dekker Inc., New York and Basel, 339-340, 364-366, **1982**.
15. The United States Pharmacopeia 28, The National Formulary 23, Asian edition. United States Pharmacopeial convention Inc., Rockville, MD, 143-148, 488-489, 2727-2728, **2005**.
16. Proposed guidelines for stability studies for human drugs and biologicals, Food and Drug Administration, Washington, DC, March, **1984**.