

To Evaluate Critical Process Parameters of Cefixime Dry Powder Suspension at Different Time Intervals

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ABSTRACT

Cefixime is a new orally active third-generation cephalosporin with a broad spectrum of activity against a variety of both gram-positive and -negative bacteria including many beta-lactamase-producing strains of streptococci, Hemophilus influenzae, Neisseria gonorrhoeae, and the majority of the Enterobacteriaceae. Cefixime is used to treat a wide variety of bacterial infections. This medication is known as a cephalosporin antibiotic. It works by stopping the growth of bacteria. These antibiotic treats only bacterial infections. It will not work for viral infections (such as common cold, flu). Using any antibiotic when it is not needed can cause it to not work for future infections. In previous studies, bioequivalence studies of cefixime as oral solid dosage form, HPTLC determination of cefixime in tablet dosage form was reported. In this article, we perform evaluation of various parameters of cefixime in dry suspension as dosage form at different time intervals within a year.

Dry powder suspension is commercial dry mixtures that require addition of water at the time of dispensing. The major consequence of the bitter taste is to restrict greatly the further development of oral preparations and clinical applications of these drugs. People wish to take effective drugs that have a nice taste can be administered easily. Accordingly, it is important to mask the unpalatable taste of a drug in order to improve the product quality. The suspension prepared was evaluated for various critical process parameters like pH, Weight variation and Assay of Cefixime. All the critical process parameters were found to be within limits. When the results were compared with marketed preparation suspension was found to be better with respect to marketed preparation.

Keywords: Critical process parameters, Dry powder suspension, pH, Weight Variation, Assay Limit

INTRODUCTION

Cefixime is 3rd generation oral cephalosporin effective against a wide spectrum of sensitive gram +ve, gram -ve and anaerobic bacteria including β -lactamase producing strains. The antibacterial activity of cefixime results from inhibition of mucopeptide synthesis in the bacterial cell wall. Chemically, it is [6R, 7R] – 7- [[(2Z)- 2- (2-amino thiazole- 4-yl)- [(carboxy methoxy) imino] aetyl] amino]-3-ethenyl -8 oxo 5-thia 1-aza bicyclo [4.2.0] oct-2- ene-2 carboxylic trihydrate. The molecular formula is C₁₆H₁₅N₅O₇S₂·3H₂O and molecular weight (M.W) is 507.50. It has an absolute bioavailability of 40 to 52%, and food does not obstruct with the overall extent

of absorption of drug. It is used in lower respiratory tract (LRT) infections, acute sinusitis, acute urinary tract

infections, acute otitis media and helicobacter pylori infection⁽¹⁾.

Dry powders for oral suspensions are pharmaceutical preparations intended to be reconstituted with the prescribed liquid in order to produce a liquid preparation for oral use. APIs that are chemically unstable in solution in the presence of an aqueous vehicle for a long period of time (e.g. antibiotics) usually come on the market as a mixture of dry powders that need to be reconstituted before being dispensed to the patient⁽²⁾.

Critical process parameter (CPP)

A process parameter whose variability has an impact on a critical quality attribute and, therefore, should be monitored or controlled to ensure the process produces the desired quality.⁽³⁾

Critical process parameters (CPPs) and their associated process controls are crucial to drug development and process validation and to the evaluation of every manufacturing unit operation. Although every manufacturer and regulator requires effective process control systems, few companies are satisfied with the performance of their internal controls. In many cases, process controls fail to perform adequately due to the fragmented nature of selection, application, and implementation⁽⁴⁾.

The dry suspensions were evaluated by various critical process parameters like Filled weight variation, pH and Assay limit. All the parameters were found to be within limits⁽⁵⁾.

Literature review shows that previously many articles reported relate to cefixime^(6, 7)

METHODOLOGY

Literature review shows that previously many articles reported relate to cefixime related to their methods evaluation^(8, 9)

Following are the collection of data about critical process parameters; we collected 24 random samples of dry suspension manufactured in a year. 06 Samples were evaluated by their critical process parameters at every 03 months intervals.

We gathered all the data for analysis of critical process parameters in dry suspension samples containing cefixime as active pharmaceutical ingredient to evaluate the concentration of a drug compared to its labelled amount and used to confirm uniformity of the dosage unit and therefore also to support product safety, identity and quality.

pH

Model: Handilaz pH meter

Volume after Reconstitution: 60ml

Sample Volume: sufficient Quantity that electrode bulb dip easily

Acceptance Criteria: 2.5-4.5

Working: Reconstitute the amount of labelled claim of dry suspension with water in amber glass bottle. Then shake well for uniform distribution of content than transfer sufficient Quantity of reconstituted suspension in beaker and dip the electrode of calibrated pH meter in it. Then start the pH meter until and unless constant pH is shown on screen. Repeat the above process for 06 samples in each 03 months interval and take the mean of 06 measured pH.

The mean pH of 06 samples should lie within acceptance criteria.

Weight Variation

Model: Analytical Weighing Balance

Standard Label Claim: 15g

Acceptance Criteria: 15g $\pm$ 3% (14.55gm -15.45gm)

Working: Place the empty petri dish in calibrated analytical weighing balance. Tare the weight of empty petri dish. Then transfer the amount of powder present in our sample bottle in petri dish.

Then note the weight in grams shown on display screen. Repeat the above process for 06 samples in each 03 months interval and take the mean of 06 measured weights.

The mean weight variation of 06 samples should lie within acceptance criteria.

Assay

Solution A: 0.4 M tetrabutylammonium hydroxide solution and water (1:39). Adjust with 1.5 M phosphoric acid to a pH of 6.5.

Solution B: 13.6 mg/mL of monobasic potassium phosphate mg

Solution C: 14.2 mg/mL of anhydrous dibasic sodium phosphate.

Adjust a volume of this solution with a sufficient volume of Solution B to a pH of 7.0. Mobile phase: Acetonitrile and Solution A (1:3) System suitability solution: 1 mg/mL of USP Cefixime [NOTE—Heat this solution at 95° in an oil bath for • ORGANIC IMPURITIES 45 min, cool, and use promptly.] **Standard solution:** 0.2 mg/mL of USP Cefixime RS in phase, System suitability solution, Standard solution, Solution C. [NOTE—Use this solution promptly.]

Sample solution: Constitute Cefixime for Oral Suspension as directed in the labelling. Quantitatively dilute a suitable aliquot of the suspension, freshly mixed and free from air bubbles, with Solution C to obtain a solution having a nominal concentration of 0.2 mg of cefixime/mL.

Chromatographic system Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 12.5-cm; 4-μm packing L1

Temperature: 40°

Flow rate: Adjust flow rate of cefixime so that the retention time is about 10 min.

Observe the Peaks of 06 samples on display screen and calculate the assay for all 06 Samples individually and calculate the average of 06 assay results. Repeat the above process for 06 samples in each 03 months interval. The mean assay results of 06 samples should lie within acceptance criteria.

Acceptance Criteria: 90-120%

Reagents:

Water, tetrabutylammonium hydroxides, phosphoric acid, monobasic potassium phosphate, anhydrous dibasic sodium phosphate, Acetonitrile.

RESULTS AND DISCUSSION

The acceptable limit of pH is 2.5 – 4.5. The results of pH evaluation were lies within the limit for each of 24 samples of cefixime containing dry suspension evaluated in every 3 months interval as represented in Fig 1. The average of every 6 samples evaluated in 3 months regular interval were also lies within the limit.

The acceptable limit of weight variation is 15g ±3% that is 14.55gm -15.45gm. The results of weight variation evaluation were lies within the limit for each of 24 samples cefixime containing dry suspension evaluated in every 3 months interval as shown in Fig 2. The average of every 6 samples evaluated in 3 months regular interval were also lies within the limit. The average of every 6 samples evaluated in 3 months regular interval were also lies within the limit.

The acceptable limit of assay is 90-120%. The results of assay evaluation were lies within the limit for each of 24 samples cefixime containing dry suspension evaluated in every 3 months interval as manifest in Fig 3. The average of every 6 samples evaluated in 3 months regular interval were also lies within the limit.

The present work done on evaluation of Critical process parameters for 24 random samples of cefixime containing dry suspension. The critical process parameters evaluated were pH, weight variation and assay, performed in every 03 months interval by selecting 06 samples in each interval. In this, we took total 24 samples for evaluation and also took average of six samples in every 03 months interval that also lies within the acceptable criteria as per product specification mention in monograph.

In pH evaluation, all 04 intervals average were having slight differences in their values after decimal that were 3.223333, 3.346667, 3.438333, 3.801667. This indicate that pH of given samples were not showing drastic variation in all 24 samples.

In weight variation evaluation, all 04 intervals average shown slight differences in their values after decimal that were 14.99567, 14.94867, 14.98533, 15.02767. This indicate that weight variation of given samples were not showing huge variation in all 24 samples.

In assay evaluation, all 04 intervals average shown differences in their values that were 103.44%, 106.19%, 110.52%, 116.16%. This indicate that assay limit of given samples were showing variation in all 24 samples. Although, all 04 intervals assay average lies within acceptable limit that is 90-120%. But, assay results of 03 samples taken in last interval were lies slightly towards higher side of acceptable limit which leads its average towards higher side.

Statistical Evaluation

We have statistically analysed our result and plotted graphs for Number of samples vs. critical process parameters (pH, weight variation and assay). Results were as follows:

Table 1: Evaluation of pH

Time Interval (Months)	No. of Samples	pH (Acceptance Criteria: 2.5-4.5)	Statistical Evaluation
1 – 3	1.	3.25	Average: 3.223333
	2.	3.29	
	3.	3.26	
	4.	3.24	
	5.	3.17	
	6.	3.13	
4 - 6	7.	3.38	Average: 3.346667
	8.	3.39	
	9.	3.36	
	10.	3.38	
	11.	3.34	
	12.	3.36	
7 - 9	13.	3.41	Average: 3.438333
	14.	3.40	
	15.	3.45	
	16.	3.46	
	17.	3.45	
	18.	3.46	
10 – 12	19.	3.97	Average: 3.801667
	20.	4.31	
	21.	4.08	
	22.	3.49	
	23.	3.49	
	24.	3.47	

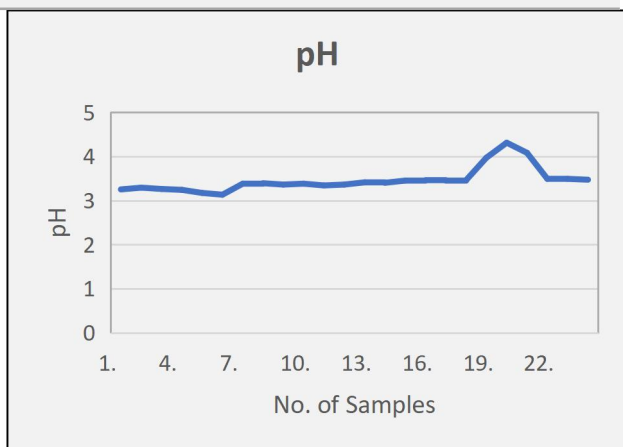


Figure 1: Evaluation of pH

Table 2: Evaluation of Weight Variation

Time Interval (Months)	No. of Samples	Weight Variation (Acceptance Criteria: 15g $\pm$ 3%) 14.55gm - 15.45gm	Statistical Evaluation
1 - 3	1.	14.998g	Average: 14.99567g
	2.	14.995g	
	3.	14.993g	
	4.	14.993g	
	5.	14.998g	
	6.	14.997g	
4 - 6	7.	14.886g	Average: 14.94867g
	8.	14.942g	
	9.	14.962g	
	10.	14.972g	
	11.	14.960g	
	12.	14.97g	
7 - 9	13.	14.983g	Average: 14.98533g
	14.	14.981g	
	15.	14.987g	
	16.	14.989g	
	17.	14.983g	
	18.	14.989g	
10 – 12	19.	15.03g	Average: 15.02767g
	20.	15.02g	
	21.	15.08g	
	22.	15.012g	
	23.	15.00g	
	24.	15.024g	

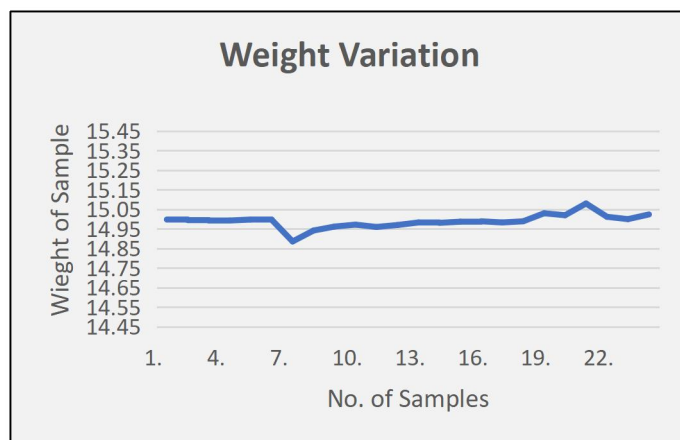


Figure 2: Evaluation of Weight Variation

Table 3: Evaluation of Assay

Time Interval (Months)	No. of Samples	Assay (Acceptance Criteria: 90-120%)	Statistical Evaluation
1 – 3	1.	104.498%	Average: 103.44%
	2.	104.233%	
	3.	104.547%	
	4.	102.547%	
	5.	101.271%	
	6.	103.547%	
4 – 6	7.	106.23%	Average: 106.19%
	8.	105.247%	
	9.	106.247%	
	10.	105.537%	
	11.	106.349%	
	12.	107.543%	
7 – 9	13.	109.342%	Average: 110.52%
	14.	109.547%	
	15.	108.247%	
	16.	109.349%	
	17.	113.270%	
	18.	113.344%	
10 – 12	19.	114.53%	Average: 116.16%
	20.	115.33%	
	21.	116.013%	
	22.	118.697%	
	23.	116.611%	
	24.	115.803%	

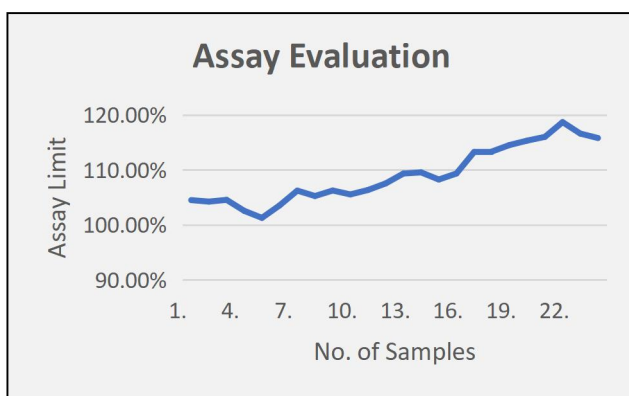


Figure 3: Evaluation of Assay

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