

Comparative *In-Vitro* Dissolution Studies for Determination of Cefixime in an Innovator Product of Suprax Powder for Oral Suspension Dosage form Using Rp-Hplc Method



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Abstract

Dissolution testing is an *in vitro* technique of great importance in formulation and development of all solid oral dosage forms and is used in all phases of development for product release and stability testing. The aim of this work is to evaluate and compare the different official and unofficial dissolution tests and treatments of obtained data by using f_2 to determine whether all the formulations used are equivalent or significantly different. Accurate, simple and specific RP-HPLC method is performed for the determination of cefixime (CFX) in powder for oral suspension dosage form (POS) using FDA buffer media 0.05 M phosphate buffer, pH 7.2 is conducted for 12 doses from each brand for 45 min. by using dissolution testing apparatus USP type-II (Paddle). Samples are withdrawn at time intervals of 10, 20, 30 and 45 minutes, then are analyzed for drug content by using HPLC technique.

Cumulative drug release at each time interval is calculated for POS and the obtained data are calculated with statistical techniques to meet the FDA requirements for obtaining a waiver of bioavailability and bioequivalence studies. The method is evaluated on Supleco LC-18-DB (4.6 mm x 250 mm) 5 μ m or equivalent, using mobile phase as a mixture of 0.04 mM tetra butyl ammonium hydroxide: acetonitrile (72.5:27.5 v/v) adjusted to pH 7.0 with 10% ortho phosphoric acid at a flow rate of 2.0 mL/min with UV detection at 254 nm. The injection volume is 10 μ L, the retention time of cefixime is 3.195 \pm 0.679 min and the total run time is 6 min. The method has been applied for Aerocef 100 mg/5 mL POS and hence it is considered to be equivalent to the innovator product Suprax 100 mg/5mL using FDA media and the two products are considered similar.

Keywords: Cefixime Trihydrate; *In Vitro* Dissolution; Rp- Hplc; Stability Indicating Method; Generic Product; Innovator Product.

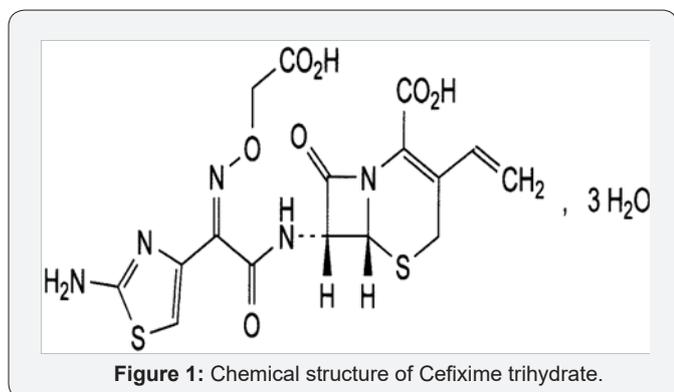
Abbreviations: CFX: Cefixime Trihydrate; IVIVC: *In vitro*-*In vivo* Correlations; PTFPE: Polytetra- Fluoroethylene; POS: Powder for Oral Suspension; FDA: US Food and Drug Administration; f_1 : The Difference factor; f_2 : Similarity factor.

Introduction

Dissolution testing is an *in vitro* technique can be used as a substitute for *in vivo* studies under strictly defined and specified conditions [1]. For the comparison of *in vitro* dissolution data and for use *in vivo* bioequivalence testing and *in vitro*-*in vivo* correlations (IVIVC), dissolution testing should be carried out under physiochemical and hydro dynamically defined conditions so that the obtained results are accurate and reproducible [1]. CFX, (Figure 1) is a semi synthetic cephalosporin antibiotic for oral administration. It is chemically designated as (6R, 7R)-7-[[[2-(2- Aminothiazol-4-yl)-2-[(carboxymethoxy) imino] acetyl] amino]-3- ethenyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-

2-ene-2-carboxylic acid trihydrate. It has a molecular formula of C₁₆H₁₅N₅ O₇ S₂ · 3H₂O and a molecular weight of 507.5 [2]. CFX as an antibiotic is a third-generation cephalosporin like ceftriaxone and cefotaxime. CFX is highly stable in the presence of beta-lactamase enzymes. Thus, many organisms resistant to penicillin's and some cephalosporins due to the presence of beta-lactamases may be susceptible to CFX. Its antibacterial effect results from inhibition of mucopeptide synthesis in the bacterial cell wall. CFX is an orally absorbed third generation cephalosporin with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and is highly resistant

to beta-lactamase degradation. In general serum and urinary concentrations of CFX achieved after recommended daily doses are well above the minimal inhibitory concentrations at 90% for indicated microorganisms.



The dissolution test for immediate or controlled release in solid oral dosage forms has recently widened to a variety of novel or special dosage forms such as suspensions, chewing gums, transdermal patches, implants and others. Because of the different characteristics of early dosage form, the site absorption and dosing routes and applications, it is essential to give appropriate consideration to the following factors in the development of the test method: apparatus selection, dissolution medium, agitation and temperature [3]. CFX is official in British Pharmacopeia (BP) [4]. European Pharmacopeia (EP) and United States Pharmacopeia (USP) [5]. They include the HPLC method for its estimation. It is still a limited number of analytical methods that were reported for the determination of CFX individually or in combination with other drugs including colorimetric and spectrophotometric [6-15], capillary electrophoresis and electrochemical methods [16-19], thin layer chromatography (TLC) [20,21], high performance liquid chromatography (HPLC) [22-33] and in vitro dissolution studies have been developed for the determination of CFX in capsule dosage forms using UV-VIS Spectrophotometer [34]. According to the best of our knowledge there is no in vitro dissolution study using HPLC method for determination CFX in Suprax powder for oral suspension dosage form by using FDA dissolution media. Consequently, the aim of this work was to establish and compare the obtained data by using f2 for official and unofficial products.

Materials and Reagents

Raw Materials and Reagents

Cefixime is kindly supplied as $C_{16}H_{15}N_5O_7S_2 \cdot 3H_2O$, Molecular Weight: 507.50 by Hikma pharmaceutical industries company, Beni-Suef, Egypt with claimed purity of 100.43%. Innovator Product Suprax® POS (Batch No. 2099) is manufactured by Hikma pharmaceutical industries company, Beni-Suef, Egypt. Each 5 mL are claimed to contain 100 mg of CFX. Generic product Aerocef POS (Batch No. 2000) is manufactured by Riva Parma Company, 6th October, Egypt. Each 5mL are claimed to contain 100 mg of CFX. Xanthan Gum is supplied by Semiramis

international trading, Sodium benzoate was supplied by Tenc Zhou Tenc Long Chemical Co., LTD, Strawberry powder flavour was supplied by Givaudan and Sucrose crystalline is supplied by Tereos pharmaceutical excipient company. Acetonitrile, methanol HPLC-grade, 40% tetra butyl ammonium hydroxide solution, purified water, potassium dihydrogen orthophosphate, di-sodium hydrogen phosphate anhydrous, sodium hydroxide, hydrochloric acid, hydrogen peroxide and ortho phosphoric acid analytical grades, are procured from (Scharlau, Spain).

Equipment and chromatographic conditions

Chromatographic separation of CFX is performed at room temperature in an HPLC (Shimadzu LC SPD 20 A) with a detector (dual wavelength), equipped with binary pumps, auto sampler, oven CTO-20A/20AC with temperature range (10-85 °C) and LC Solution software. Chromatography is carried out under isocratic conditions with a mobile phase consisting of a mixture of 0.04 mM tetra butyl ammonium hydroxide: acetonitrile (72.5:27.5 v/v) adjusted to pH 7.0 with 10% ortho phosphoric acid at a flow rate of 2.0 mL/min and UV detection at 254 nm with injection volume of 10 μ L using ACE C18 (4.6 mm x 250 mm) 5 μ m or equivalent and the total run time is 6 min. Dissolution apparatus (DIS 6000, Dr. Schleuniger, Germany) is used to study the drug dissolution profile. pH meter Mettler Toledo is used for the adjustment of the mobile phase and buffer solution.

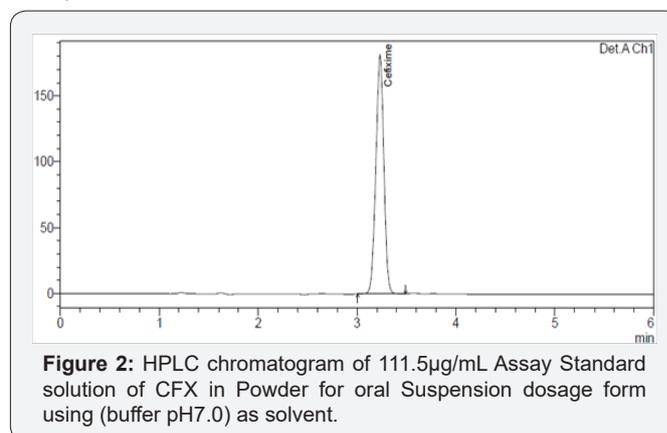
Preparation of solvent, stock solutions and calibration standards

Solvent is prepared by transferring 6.8mL of concentrated phosphoric acid to 1000mL volumetric flask, addition of 300 mL of water, adjusting to pH 7.0 \pm 0.1 with 10 N NaOH then dilution to volume with water.

Stock standard solutions of cefixime (1115 μ g mL⁻¹)

Accurately transfer 111.5 mg of the standard CFX (equivalent to 100 mg cefixime base) into 100-mL volumetric flask, add about 70 ml diluents, sonicate for 10 min till complete dissolution then complete to volume with the same diluents. Filter through suitable syringe filter.

Working standard solutions of Cefixime (111.5 μ g mL⁻¹)



Accurately transfer 10 mL from the stock standard solution of CFX into 100 mL volumetric flask, add diluents and sonicate to dissolve. Makeup to the mark with the same diluents and mix well. Inject into the chromatographic system. The chromatogram obtained is shown in (Figure 2).

Calibration curves Construction

Different aliquots of CFX equivalent to 27.87-223µg/mL are separately transferred from their respective stock standard solutions into separate series of 100mL volumetric flasks and volume is completed to the mark with diluents and mixed well. Triplicate 10µL injections are performed for each concentration maintaining the flow rate at 2.0mL/min and the effluent is UV-scanned at 254nm. The chromatographic separation is carried out following the procedure under chromatographic conditions. The chromatograms are recorded and the peak areas of CFX are determined and the calibration curves relating the obtained integrated peak areas to their corresponding concentrations are constructed and the regression equations are computed.

Application to pharmaceutical formulation (Suprax®100 mg POS and Aerocef® 100 mg POS)

Constitute Suprax as directed in the labeling, dilute 5mL (equivalent to about 100mg of cefixime) in 500mL volumetric flask. Sonicate if necessary to ensure complete dissolution of cefixime. Transfer 10mL into 20mL volumetric flask to obtain a final concentration of (111.5µg/mL⁻¹). Filter through 0.45µm PTFE membrane filter to obtain the clear assay preparation.

Content Uniformity

The test for content uniformity is required for all dosage forms not meeting the conditions for the mass variation test. Alternatively, products that do not meet the 25mg/25 per cent threshold limit may be tested for uniformity of dosage units by mass variation instead of the content uniformity test on the following condition: the concentration Relative Standard Deviation (RSD) of the active substance in the final dosage units is not more than 2 per cent, based on process validation data and development data, and if there has been regulatory approval of such a change. The concentration RSD is the RSD of the concentration per dosage unit (m/m or m/V), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit mass [2].

In Vitro Dissolution Studies

Dissolution Parameters:

- Apparatus: USP II (paddle type).
- Speed: 50rpm.
- Medium: 900 mL FDA dissolution medium.
- Temperature: 37.0±0.5 °C.
- Time: 25mL sample aliquots are withdrawn at 10, 20, 30 and 45 min using a hypodermic glass syringe equipped with

a stainless-steel needle, and replaced with equal volume of the fresh medium at the same temperature to maintain constant total volume. The solutions are immediately filtered through a 0.45 µm membrane. Drug release is assayed by HPLC method. Cumulative percentages of the dissolved drug are calculated and plotted versus time.

Dissolution Medium Preparation (phosphate buffer pH 7.2): Dissolve 81.6 g of anhydrous potassium dihydrogen phosphate in 12.0 liters with de ionized water so as to obtain 0.05M solution. If necessary, adjust the pH to 7.2 ± 0.05 with 1N phosphoric acid or 1N NaOH. For mobile phase and chromatographic conditions; proceed as directed under assay method.

Preparation of Stock Standard Solution for Dissolution Test (1115µg mL⁻¹): Similar to the previously prepared solution, accurately transfer 111.5 mg of the standard CFX (equivalent to 100 mg cefixime base) into 100-mL volumetric flask, with the aid of 20 mL methanol, sonicate for about 5 minutes and complete to volume with the pH 7.2 buffer solution and mix well. Filter through suitable syringe filter.

Working standard solutions of cefixime (111.5 µg mL⁻¹): Accurately transfer 10mL from the stock standard solution of CFX into 100mL volumetric flask, add the dissolution medium and sonicate to dissolve. Makeup to the mark with the same diluents and mix well. Inject into the chromatographic system. The obtained chromatogram is shown in (Figure 3).

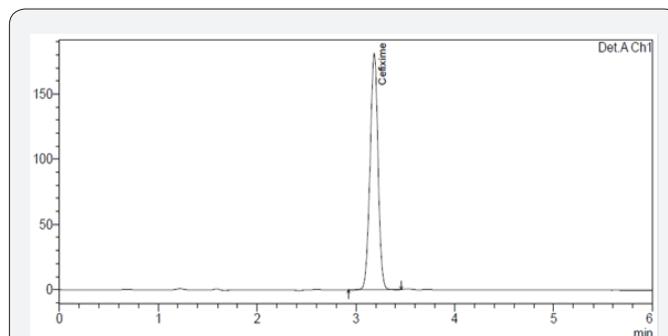


Figure 3: HPLC chromatogram of 111.5µg/mL dissolution standard solution of CFX in powder for oral suspension dosage form using dissolution media (buffer pH7.2) as diluents.

Test Preparation for Dissolution of (Suprax®100 mg POS and Aerocef® 100 mg POS):

Place 12 doses each in a vessel from Aerocef® 100 mg POS the generic product and Suprax®100 mg POS, the innovator product. Operate using the above conditions. After 10, 20, 30 and 45 minutes period.

Results and Discussion

Methods development and optimization

Mobile phase and wavelength selection: Many systems of different compositions and ratios were tried including: methanol

(100%); methanol: purified water (70:30, v/v); acetonitrile: purified water (70:30, v/v) and methanol: purified water (95:5, v/v). All the solvents of the mobile phase were filtered through 0.45µ membrane to remove particulate matter and degassed by sonication; also (0.8, 1.0, 1.5 and 2.0mL/min) flow rates were tried, to get the optimum wavelength for the CFX solution, a solution of 40 µg/mL of CFX was measured at 200 to 400nm (Figure 4). Thus, 254nm was selected as the most suitable wavelength. Preliminary studies involved trying C18 reversed-phase columns. The best developing system was the mobile phase composed of a mixture of 0.04mM tetra butyl ammonium hydroxide: acetonitrile (72.5:27.5 v/v) adjusted to pH 7.0 with 10% ortho phosphoric acid at a flow rate of 2.0mL/min and UV detection at 254nm. Another advantage is the relatively short run time (6min) of the analysis, under isocratic conditions. This selected developing system allows good separation with good R_f values without tailing of the separated bands and good theoretical plates.

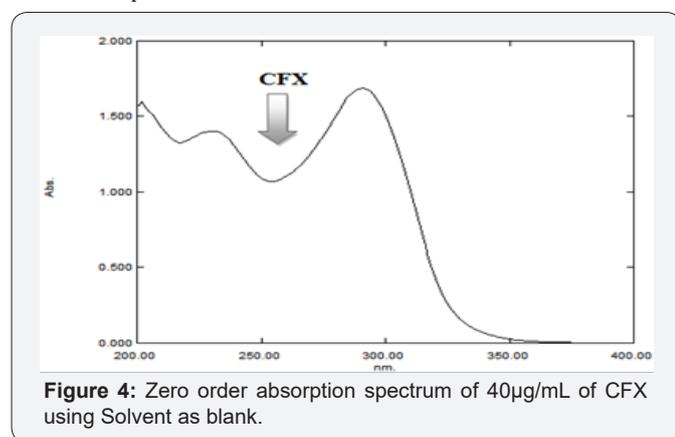


Figure 4: Zero order absorption spectrum of 40µg/mL of CFX using Solvent as blank.

Optimization of dissolution test conditions

Dissolution is an official test used by pharmacopoeias for drug evaluation release of solid and semisolid dosage forms, and it is routinely used in Quality Control (QC) and Research & Development (R&D) laboratories. The purpose of in vitro dissolution studies in QC is batch to batch consistency and detection of manufacturing deviation while in R&D the focus is to provide some predictive estimate of the drug release in respect to the *in vivo* performance of a drug product. For QC, an over-discriminatory test might be suitable to detect even small production deviations. However, for prediction of the *in vivo* performance of drug product, a dissolution test should be sensitive and reliable [35]. The accomplishment of dissolution profile is recommended as a support in the development and optimization of drug formulation as well as in the establishment of in vitro/*in vivo* correlation. When dissolution test is not defined or if the monograph is not available, comparison of drug dissolution profiles is recommended on three different dissolution mediums (pH 1–7.5) [36]. In vitro dissolution is used to perform the release rate of drug products and to assure the quality of suspension dosage forms by the pharmaceutical industry and regulatory agencies [37].

Method validation

The method was validated, in accordance with ICH guidelines (ICH Q2R1), for system suitability, precision, accuracy, linearity, specificity, ruggedness, robustness, LOD and LOQ [38].

Linearity and range

The linearity of the proposed methods is obtained in the concentration range (55.75 - 446µg/mL) for CFX at FDA buffer media of pH 7.2. From the graphical presentation, the relation of peak response (A) plotted at X axis and concentration (C) plotted at Y axis is evaluated on the base of least-square linear regression equation ($A = \text{slope } C + Y \text{ intercept}$). The LOD and LOQ of the method are calculated using the expression ($3.3\sigma / \text{slope}$) and ($10\sigma / \text{slope}$) respectively. The obtained coefficient of regression is 0.9999. Linearity results are shown in (Table 1).

Table 1: Regression and validation parameters of the proposed HPLC method for determination of CFX at FDA dissolutionMedium.

CFX	Parameter
Linear	
Range (µg/mL)	27.87-223
Slope	9221.9027
Intercept	5189.9130
Correlation coefficient	0.9999
Precision	0.857
LOD ^a (µg/mL)	1.24
LOQ ^a (µg/mL)	3.78

^aLimit of detection ($3.3 \times \sigma / \text{Slope}$) and limit of quantization ($10 \times \sigma / \text{Slope}$).

Repeatability

Repeatability is conducted using 6 replicates of the standard solution of the compound being studied (111.5 µg/mL). The system is precise as the relative standard deviation $RSD \leq 2\%$. Precision of the method is illustrated in (Table 1).

Accuracy and recovery

Table 2: Data of Accuracy for CFX at FDA dissolution Medium.

Cefixime	µg/ mL (injected)	µg/ mL (found)	Recovery%
55.75	55.75	54.84	98.36
	55.75	54.85	98.39
	55.75	55.83	100.14
111.5	111.5	110.34	98.96
	111.5	111.11	99.65
	111.5	111.13	99.67
167.25	167.25	167.69	100.26
	167.25	167.64	100.23
	167.25	167.51	100.15
Accuracy (Mean) ± RSD	99.53±0.78		

The recovery was calculated for triplicate of three concentrations (55.75, 111.5 and 167.25µg/mL) comparing the individual peak response with that of the reference solution. Table 2 showed the recovery percent of 99.53±0.78 of the spiked analyte.

Formulation assay

The study is performed by assaying six samples from the finished product with the same concentration prepared from a homogenous sample starting from the first step of the analysis procedure to the final one. The results of the assay indicate that the method is selective for the analysis of Suprax® and Aerocef® Cap without interference from the excipients used to formulate. The results are displayed in (Table 3).

Table 3: Assay results for the determination of CFX in its pharmaceutical formulations by the proposed HPLC method.

Limit %	CFX	Pharmaceutical formulation
Suprax 100mg POS CFX, 100mg (claimed)	103.54	90-120
	103.68	
	105.17	
	103.90	
	105.61	
	105.29	
Mean ± RSD	104.53±0.92	
Aerocef 100mg Cap CFX, 100 mg (claimed)	99.99	
	101.93	
	100.87	
Mean ± RSD	102.04	
Aerocef 100mg Cap CFX, 100 mg (claimed)	101.51	
	102.20	
Mean ± RSD	101.42±0.84	

Intermediate precision (ruggedness)

Intermediate precision expresses the within-laboratories variations: different days, different analysts, different equipments, etc. Good results are obtained and presented in (Table 4).

Table 4: Ruggedness of the method.

Parameter(%RSD)	CFX
Day to Day	0.308
Analyst to Analyst	0.526
Column to Column	0.725

Robustness

The method’s capability to remain unaffected by small but deliberate variations in method parameters as: influence of variations of the pH in the mobile phase, influence of variations in its composition, different columns (different lots and/or suppliers), temperature, flow rate and wave length. Table 5 indicates the robustness of the proposed method.

Table 5: Robustness of the method.

Parameter(%RSD)	CFX
Flow rate change (±0.1 mL/min)	0.835
pH change of mobile phase (±0.2)	1.165
Wave length change (254±2.0nm)	1.430
Column temperature change (30,25°C)	0.927

System suitability

System suitability testing is an integral part of much analytical procedure. The tests are based on the concept that the equipments, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability is checked by calculating the tailing factor (T), column efficiency (N), resolution (Rs) factors. All calculated parameters are found to be within the acceptable limits indicating good selectivity of the method and assuring system performance (Table 6).

Table 6: System suitability testing parameters of the developed method.

Item	Obtained value	Reference values
	CFX	
Tailing factor	1.027	T ≤ 2
Injection precision	0.35	RSD ≤1%
Number of theoretical plates (N)	6235.506	N > 2000

Stability of the analytical solution

After preparing the standard solution, part of it was stored in fridge and another one was stored at room temperature. After about 24 hours, these solutions were tested against freshly prepared standard; relative standard deviation should be less than 2%. These results are displayed in (Table 7).

Table 7: Results of the stability of the analytical solution.

Condition	CFX*
Fridge	100.11
Room temperature	99.65

Potency of CFX standard=100.43%.

Content Uniformity

Select not less than 30 units, and proceed as follows for the dosage form designated. Where different procedures are used for assay of the preparation and for the content uniformity test, it may be necessary to establish a correction factor to be applied to the results of the latter. Assay 10 units individually using an appropriate analytical method. Calculate the acceptance value (AV) using the formula:

$$AV = |M - \bar{x}| + KS$$

Where, T: label claim (100.0%), unless otherwise specified in the individual monograph,

\bar{x} : mean of individual contents (x_1, x_2, \dots, x_n),

x_1, x_2, \dots, x_n : individual contents of the units tested, expressed as a percentage of the

label claim,

n: sample size (number of units in a sample),

k: acceptability constant, k=2.4 when the sample size is 10, and k=2.0 when the sample

size is 30.

s: standard deviation of the sample = cf. (Table 8).

Table 8: Uniformity of Dosage Unit.

Variable	Definition	Condition	Value
K	Acceptability Constant	If N=10, then	24
		If N=30, then	20
S	Sample standard deviation		$\sqrt{\frac{1}{N} \sum_{i=1}^N (x_i - \bar{x})^2}$
RSD	Relative standard deviation		100 s \bar{x}
M (case I) To be applied when T≤101.5	Reference Value	≤ 101.5 percent \bar{x} If 98.5 percent ≤ < 98.5 percent, then \bar{x} If > 101.5 percent, then If	\bar{x} M= (Av=ks) M=98.5 percent +ks) \bar{x} (Av=98.5- M=101.5 percent 101.5+ks) (Av=-
M (case II) To be applied when T>101.5	Reference Value	≤ T, then If 98.5 percent ≤ < 98.5 percent, then If > T, then If	\bar{x} M= (Av=ks) M=98.5 percent +ks) \bar{x} (Av=98.5- M=101.5 percent 101.5+ks) (Av=-
L1	L1=15, Unless otherwise specified	On the low side, no dosage unit result can be less than 0.75 M while on the high side, no dosage unit result can be greater than 1.25 M (this based on L2 value of 25)	Maximum allowed Acceptance Value
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of M		L1=25, Unless otherwise specified

Table 9: Results of Content Uniformity.

Aerocef 100mg POS	Suprax 100mg POS	Parameter
Content Uniformity	99.99	103.54
	101.93	103.68
	100.87	105.17
	102.04	103.90
	101.51	105.61
	99.03	103.34
	100.11	102.46
	100.85	105.52
	97.94	105.27
	102.20	105.29
Mean ± RSD	100.64±1.38	104.36±1.06
AV	3.3	2.7
L1 :15	Pass, Stop here	Pass, Stop here
L2:25	NA	NA

RSD: Relative Standard Deviation of the active substance in the final dosage units is not more than 2 per cent, based on process validation and development data, and if there has been

regulatory approval of such a change = RSD results are illustrated in (Table 9).

Application of In Vitro Dissolution of Powder for oral Suspension dosage form

A simple model independent approach uses a difference factor (f1) and a similarity factor

(f2) is applied to compare the dissolution profiles. The difference factor (f1) calculates the

percent (%) difference between the two curves at each time point and is a measurement of the relative error between them. The equation of the similarity factor proposed by Moore and Flanner [39] is presented in equations (1, 2).

$$f_1 = \left\{ \left[\frac{t-1}{n} | R_t - T_t | \right] / \left[\frac{t-1}{n} R_t \right] \right\} * 100 \quad (1)$$

Where n is the number of time points, R_t is the dissolution value of the reference

(pre-change) batch at time t and T_t is the dissolution value of the test (post change) batch at time t. The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f_2 = 50 * \log \{ [1 + (1/n) t = 1^n (R_t - T_t) 2]^{0.5} * 100 \} \quad (2)$$

A specific procedure to determine the difference and similarity factors is as follows:

Determine the dissolution profile of the two products (12 units each) of the test (post change) and reference (pre-change) products using the mean dissolution values from both curves at each time interval. Calculate the difference (f1) and similarity (f2) factors using the above equations. Results are summarized in (Table 10). To obtain the in vitro dissolution profile of the product, the cumulative percentage of Aerocef and Suprax released is plotted against time (Figure 5).

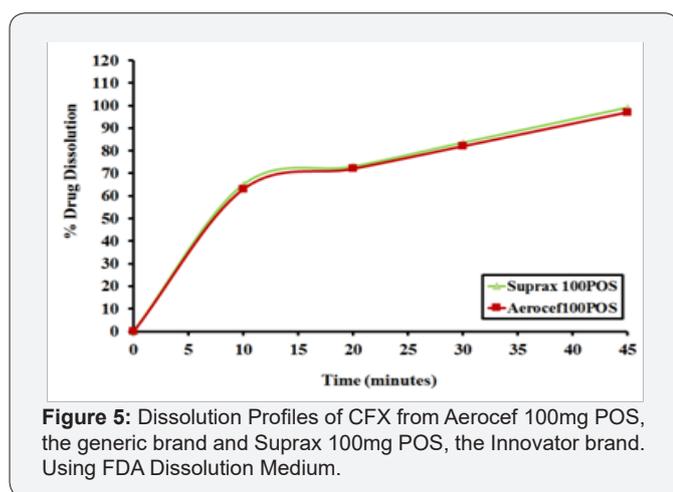


Figure 5: Dissolution Profiles of CFX from Aerocef 100mg POS, the generic brand and Suprax 100mg POS, the Innovator brand. Using FDA Dissolution Medium.

Table 10: Results of comparative dissolution studies.

	Suprax 100 mg POS	Aerocef 100 mg POS
Time	CFX	CFX
10	65	63
20	73	72
30	83.5	82
45	99	97
f1(≤10)	2	
f2(50-100)	86	

Specificity

Method specificity was determined for the samples of the compound being studied and placebo matrix containing all excipients of the finished product. No interference was detected at the retention time of CFX in the placebo solution.

Conclusion

Successful in vitro dissolution studies have been applied for Aerocef 100mg/5mL powders for oral suspension and hence it is considered as equivalent to the innovator product Suprax 100mg/5mL powders for oral suspension at FDA dissolution media. The proposed RP-HPLC method for the determination of CFX in dosage forms is simple, precise, specific and accurate. The results of stress testing that have been undertaken according to the International Conference on Harmonization (ICH) guidelines

revealed that the analytical method is valid, fit for use and can be applied for regular routine analysis and stability study.

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