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RESEARCH ARTICLE

EFFECT OF LIGHT, HEAT AND AIR EXPOSURE ON SHELF LIFE AND STABILITY OF CEFTAZIDIME

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ABSTRACT

Stability study of ceftazidime was performed as per ICH guidelines with an emphasis to accelerated, stress and photo degradation of this drug in powder for injection and in solution form after reconstitution. Ceftazidime sample was exposed to simulated accelerated, thermal and photodegradation conditions as observed during hot and humid summer conditions in Indian subcontinent. The samples were analyzed by a pre validated high performance liquid chromatographic method. Results obtained confirmed the photo and thermolabile nature of ceftazidime powder and solution after reconstitution. Thus, an appropriate protection is recommended during storage and handling of this antibiotic after reconstitution such that assay, purity and potency of the drug is maintained.

INTRODUCTION

The stability of a drug substance or drug product is described as its ability to remain within established pharmacopoeial specifications to maintain its identity, strength, quality, and purity throughout the retest or expiration dating periods, under stated or reasonably expected conditions of storage and use [1-3].

As pharmaceutical drugs have varied chemical compositions, these are especially sensitive to environmental factors. This high sensitivity factors necessitates strict storage conditions to maintain the desired product integrity and activity. In view of these concerns, the stability of drug product is considered to be of utmost importance and a secure way to establish and ensure delivery of therapeutic values to patients [4].

The stability testing of an active substance or finished product provides evidence on how the quality of a drug substance or drug product changes over a period of time under the influence of a variety of environmental factors such as temperature, humidity, light and storage after reconstitution etc. The long-term effects of the drug environments are understood by these stability studies [5]. Information pertaining to degradation mechanisms, potential degradation products, possible degradation pathways of drug as well as interaction between drug and excipients in pharmaceuticals are gained through these stability studies. These results are further applied to develop a suitable manufacturing process, selecting proper packaging, storage conditions which directly impact product's shelf life and expiration dates [6,7]. The International Conference on Harmonization (ICH) guidelines determines the temperature and humidity zones specifications under which, the stability studies have to be performed.

Ceftazidime is a third-generation cephalosporin widely used for the treatment of serious infections caused by Gram-negative bacteria, including *Pseudomonas aeruginosa*, especially in cystic-fibrosis patients.. The usual dose of ceftazidime is administered by slow intravenous infusion over 24 hours. Infusion solutions are prepared at the time of administration or in advance [8-20].

For dry powder parenteral drug products intended through intravenous infusion route as aqueous solution, various environmental factors such as pH, temperature, light and oxidizing atmosphere can sometimes affect the maximum recommended shelf life of the drug [21- 22]. Thus the stability of both ceftazidime powder for injection and reconstituted solution under several environmental conditions such as temperature, humidity, photo degradation and reconstitution stability testing is required to be conducted as per ICH

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guidelines to evaluate the degradation kinetics as a function of time. Analysis of the degraded samples were performed by high performance liquid Chromatography assay [23], developed and validated in our laboratory in compliance with ICH guidelines [27].

MATERIAL AND METHODS

Chemicals

Ceftazidime reference substance (assigned purity 99.98%) was procured from Govt testing lab Kolkata and ceftazidime powder for injection was purchased from market. Ceftazidime powder for injection was claimed to contain ceftazidime pentahydrate equivanent to ceftazidime 1000 mg (as anhydrous base). Water HPLC grade was obtained from Milli Q. Anhydrous dibasic sodium phosphate (AR grade) and Acetonitrile (HPLC grade) were obtained from Merck, Hohenbrunn, Germany. Monobasic potassium phosphate (AR grade) was obtained from CDH chemicals, Lucknow, India.

Instrumentation and analytical conditions

Thermal degradation

Stress studies under thermal conditions simulating extreme summer temperature of June month in Indian Terrain were performed using a hot air oven (Oven Universal, Model No NSW -143, New Delhi, India). Susceptibility of the drug in powder for injection to dry heat was studied by exposing it to 50ºC. For reconstituted sample, ceftazidime was dissolved in sterile distilled water when procured fresh and for the stress exposed samples.

Stability studies

Stability studies were carried out at different temperature and humidity conditions as per ICH guidelines, viz. 30°C±2°C/65%RH±5%RH and 40°C±2°C/75%RH±5%RH. The tests were carried out as per ICH guidelines as suggested from time to time.

Photodegradation

Photodegradation studies were carried out in a photostability chamber. For photo-stability testing, a cool, white, fluorescent lamp designed to produce an output similar to that specified in ISO 10977 (1993) and a near-UV fluorescent lamp having a spectral distribution from 320 to 400 nm (with maximum energy emission between 350 and 370 nm; a significant proportion of UV in both bands of 320-360 nm and 360-400 nm) of ICH Q1B (Option-2) were used in the photo-stability chamber (Model no: TP 200S) manufactured by Thermolab Scientific Equipments (Thane, Maharashtra, India)[24]. Samples were exposed to the cool white fluorescent light providing overall illumination of not less than 1.2 million lux hours and an integrated near-UV energy of not less than 200 W h/m^2 [25]. The controls of temperature and relative humidity were maintained appropriately constant throughout within 30 ± 2°C and 65 ± 5% relative humidity, respectively, to minimize the effect of localized temperature and humidity changes.

High performance liquid chromatographic assay

At the end of the exposure period, samples were examined for any changes in physical properties (e.g., appearance, disintegration and dissolution) and analyzed for assay by a suitably validated analytical method as per United States Pharmacopoeia. When Ceftazidime API was involved, sampling was ensured by a representative portion that was to be used in individual tests. For Ceftazidime finished product, testing was conducted on an appropriately sized composite of 2 vials. The analysis of the exposed sample was performed concomitantly with that of protected samples used as dark controls.

Sample preparations for assay procedures (by HPLC)

Standard preparations

About 29 mg of Ceftazidime working standard was transferred and accurately weighed, to a 25 ml volumetric flask containing 2.5 ml of pH 7 Buffer, and was shaken until dissolved. Then it was diluted with water and made upto volume, and was mixed well. [Note—Protect this solution from light.] Immediately prior to chromatography, 5.0 ml of this stock solution was transferred to a 50 ml volumetric flask, diluted with water to volume and mixed. This solution contains about 100 µg of ceftazidime ($C_{22}H_{22}N_6O_7S_2$) per ml.

Sample preparation

About 115 mg of Ceftazidime was accurately weighed and transferred to a 100 ml volumetric flask containing 10.0 ml of pH 7 Buffer and was shaken until dissolved. Then it was diluted with water to volume and mix. [Note—Protect this solution from light.] Immediately prior to chromatography, 5.0 ml of this solution was transferred to a 50 ml volumetric flask, diluted with water to volume, and mixed.

Resolution solution

A solution of Ceftazidime working standard, Delta-3-Isomer RS in pH 7 Buffer containing about 0.1 mg per ml was prepared. Immediately prior to chromatography, 1 ml of this solution was mixed with 8 ml of water and 1ml of the stock solution used to prepare the Standard preparation.

pH 7 Buffer*:* 42.59 g of anhydrous dibasic sodium phosphate and 27.22g of monobasic potassium phosphate were dissolved in water to make 1000 ml of solution.

Mobile phase*:* 40 ml of acetonitrile and 200 ml of pH 7 Buffer were mixed and diluted with water to obtain 2000 ml of solution. Then it was filtererd, using a filter having a porosity of 1 µm or finer, and degas.

Chromatographic parameters: **An Agilent 1200 series HPLC system** equipped with a variable-wavelength photo diode array detector, an injector and a data processor.

Column: A stainless steel column (15 cm × 4.6 mm) packed with octadecylsilyl silica gel for chromatography (5 µm) (ODS Hypersil is suitable).

Detector	: 254 nm
Flow rate	: 2.0 ml per minute
Injection volume	: 20µl
Retention time of Ceftazidime	: About 11 minute
Run time	: 20 minute

Procedure: Separately inject equal volumes of the Standard preparation and Assay preparation into the chromatograph, record the chromatograph, and measure the responses for the major peaks.

Calculation

Calculate the quantity, in percentage, of $C_{22}H_{22}N_6O_7S_2$ in the portion of ceftazidime on dried basis taken by the formula:

$$\frac{AT}{AS} \times \frac{WS}{25} \times \frac{5}{50} \times \frac{100}{WT} \times \frac{50}{5} \times \frac{P \times 100}{(100 - LOD)}$$

AT **:** Average area of ceftazidime peak obtained in standard preparation.
AS **:** Average area of ceftazidime peak obtained in test solution.
WS **:** Weight in mg of standard preparation.
WT **:** Weight in mg of Test preparation.
P **:** is the potency of Ceftazidime working standard on as is basis.
LOD: % Loss on draying.

Decomposition studies

The commercial sample of ceftazidime (1000 mg) was heated at 50ºC for 7 days to carry out accelerated thermal degradation study. The specified amounts of degraded samples (three flasks for each time) were dissolved in sterile distilled water at concentration of 1000 µg/mL at predetermined time intervals. For reconstitution purpose, commercial samples of ceftazidime (1000 mg) were reconstituted to 10 mL with sterile water for injection and analyzed. At suitable time points, aliquots were withdrawn (samples in triplicate for each time) and diluted in sterile distilled water to give final concentration of 1000 µg/mL.

Similarly, Photodegradation studies were performed in a photostability chamber. The commercial samples of ceftazidime (1000 mg) were exposed to ultraviolet radiation and visible radiation for 1, 2, 7, 14, and 21 days. At the predefined time intervals, amounts of the degraded samples (samples in triplicate for each time point) were dissolved in sterile distilled water at concentration of 1000 µg/mL. For reconstituted sample, commercial samples of ceftazidime (1000 mg) were reconstituted to 10 mL with sterile distilled water and exposed to ultraviolet and visible radiation for 6, 12 and 24 hours in a photostability chamber . Aliquots were withdrawn at suitable time intervals (three aliquots for each time) and diluted in sterile distilled water to give final concentration of 1000 µg/mL.

The respective dilutions were prepared in potassium phosphate buffer solution pH 6.0 to give final concentrations of 100.0, 200.0 and 400.0 µg/mL, and assay was performed against solutions of the reference substance at the same concentrations (linearity range)[23].

RESULTS AND DISCUSSION

The quality of a pharmaceutical product is the key important factor to ensure patient's safety. The efficacy and safety of a pharmaceutical product may be jeopardized due to the presence of impurities which may arise due to improper storage conditions. The Impurities and potential degradation products can bring about changes in chemical, pharmacological and toxicological properties of drugs which may further impact product quality and safety [31].

It is mandatory to carry out stability studies of pharmaceutical preparations to assure the purity, safety, potency and the stress studies are mainly useful in determining accidental exposures to conditions other than those proposed as deleterious to the product [such as stress testing at 50°C (25 degree celsius of air temperature corresponds to 50 degree celsius goods temperature inside brown painted cargo container)], for evaluating which specific test parameters may be the best indicators of product stability and in revealing patterns of degradation. Stress testing conditions were also observed in reports pertaining to the establishment of stability-indicating assays in the literature. The results of the different types of studies, such as hydrolysis in acid, alkaline and neutral conditions, oxidation, photolysis and thermal degradation was reported earlier [33].

Accelerated stability studies mainly uses elevated temperatures to increase the rate of reactions. It can be noted that to estimate the ambient stability, the reaction rate at single or different temperature, and the extrapolation to the desired temperature [4].

Temperature has a high degree of influence on all varieties of chemical reactions and it is usually accelerated by raising the temperature. This is understandable since with increased temperature, molecules tend to move faster with increased kinetic energy. Additionally, the rate of collision molecules increases greatly. Finally, greater available energy causes more molecules to have enough activation energy and the fraction of collisions with suitable energy increases. It is typically said that a 10ºC increase in temperature produces a 2-5 fold increase in decomposition [35-36].

In current pharmaceutical testing programs, the formation rate of individual products, independent of whether they are primary or secondary decomposition products of the drug, is the determining factor in setting shelf-life expiration. The drugs mainly get chemically decomposed to give various impurities, the shelf-life is rarely determined by the overall drug decomposition rate, but rather by the rate of formation of individual products as determined by their toxicity limits[4,34]. Light can have deleterious effects on the active photosensitive pharmaceutical ingredient in a drug formulation, as well as on the final product. The loss of potency of a drug is the most

obvious result of drug photodecomposition. As a further consequence, this can lead to a drug formulation, which is therapeutically inactive. Besides, amounts of photodegraded products formed in the pharmaceutical preparation may lead to adverse effects [31].

There is an urgent need of information about photo reactivity of compounds to provide the methodologies about handling, packaging, labeling and use of the drug substance or drug product.

The mechanistic knowledge about the photodegradation process is of utmost importance in stabilizing the product. The solution state stability after reconstitution is of critical nature as most of the dry powder injectables are prone to degradation either by pH, temperature, oxidation, photodegradation and hydrolytic cleavage. It can be noted that the solution state for cephalosporin dry powder products is the most unstable state and any changes in the above mentioned parameters can cause drastic alteration and stability issues of the product.

Light-sensitive drugs can be affected either by sunlight (especially ultraviolet irradiation) or artificial light sources (e.g. fluorescent light) and contribute to the photodegradation of the active substance, occurring changes in physicochemical properties of the product, e.g. discoloration or cloudy appearance, viscosity loss, change in dissolution rate or precipitation which is usually more evident after reconstitution because that stage is unstable [31].

In this study, thermal and photostability studies of ceftazidime were carried out through employment of stress conditions. Thermal degradation profile of ceftazidime was studied at both 40ºC and 50ºC for different time periods and the photodegradation of reconstitution product was studied for different time periods to mimic the possible environmental conditions as suggested by ICH guidelines and the temperatures which are prevalent in Indian subcontinent during summer seasons with a particular reference to hot and humid conditions.

In reconstituted sample, drug was found to degrade extensively after reconstitution in aqueous solution. About 35% drug degradation was observed in samples exposed to heating at 50ºC just after 30 minutes of reconstitution as compared to 40 °C sample where there was no degradation for 30 min, however storage for more than 2 hrs prior to injection degrades product faster (Table 1). A yellowish color developed there upon exposures of ceftazidime in reconstituted sample to heat indicating that reconstituted samples if not injected timely can degrade faster.

On exposures of ceftazidime to drug heat and radiation in solid state (powder for injection), this drug was found to be stable below 30 ºC. In this work, experiments were carried out using commercial samples, in sealed glass vials, protected from humidity. At 40ºC with visible radiation, about only 8% of drug degraded after exposition for 28 days; at 50 ºC the loss of drug was about 19% (Table 2). When reconstituted at 30 ºC and above along with concomitant exposure to light, the degradation was much faster (around 17% after 30 min (at 30 ± 2°C and 65 ± 5% relative humidity and around 30% after 30 min (at 40°C±2°C/75%±5% relative humidity).

For reconstituted sample, drug was found to degrade extensively after reconstitution in aqueous solution. About 85 to 90% drug degradation was observed on exposures to heating at 50ºC and to ultraviolet and visible radiation for 24 h (Table 3). A yellowish color developed there upon exposures of ceftazidime in reconstituted sample to heat and ultraviolet radiation. The 1st and 3rd month stability samples when reconstituted at temperatures above 30 ºC, showed a degradation in the range of 15 to 60% (Table 4) with a development of mild yellowish colour. Thus it can be noted that higher temperature along with photo exposure has a deleterious effect on the ceftazidime dry powder parenteral formulation as well as after reconstitution and can render the therapeutic ineffective. Thus a suitable container closure system which provides appropriate protection from light and excursion temperature below 30 ºC is recommended for this product.

Table 1 Stability study results of ceftazidime powder for injection exposed at 30°C±2°C/65%RH±5%RH, 40°C±2°C/75%RH±5%RH and at 50°C.

Period (months)	Assay Ceftazidime pentahydrate equivalent to Ceftazidime USP (Between 90.0% and 115.0%) at 30°C±2°C/65%RH±5%RH	Assay Ceftazidime pentahydrate equivalent to Ceftazidime USP (Between 90.0% and 115.0%) at 40°C±2°C/75%RH±5%RH	Assay Ceftazidime pentahydrate equivalent to Ceftazidime USP (Between 90.0% and 115.0%) at 50°C
Initial	100.4%	100.4%	100.40%
After 1st month	97.1%	95.8%	83.20% (After 7 days)
After 3rdmonth	82.8%	71.7%	--

Table 2 Photostability studies results of the determination of ceftazidime powder for injection after exposing to photostability chamber as per ICH guidelines.

Period (months)	Assay Ceftazidime pentahydrate equivalent to Ceftazidime USP (Between 90.0% and 115.0%)	Degradation (%)
Initial	100.4%	--
After 1st Day	99.89%	0.51%
After 2nd Day	99.62%	0.78%
After 7th Day	97.98%	2.40%
After 14th Day	97.26%	3.14%
After 21st Day	95.69%	4.71%

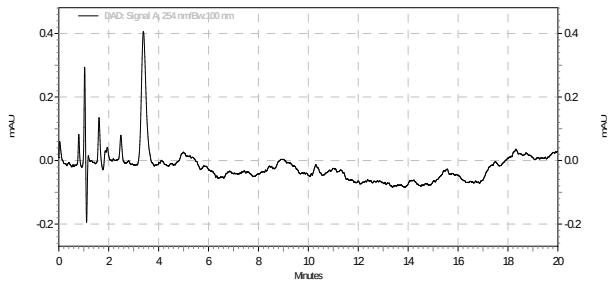
Table 3 Experimental values obtained for the determination of ceftazidime (reconstituted sample) after exposition to temperature, and both ultraviolet and visible radiation in a photostability chamber.

Time (hours)	Temperature (50°C)	UV radiation (254 nm)	Visible Radiation (320 nm)
0	100.4%	100.40%	100.40%
6	80.68%	81.26%	82.22%
12	61.25%	65.26%	59.73%
24	10.94%	14.98%	13.80%

The representative HPLC chromatograms of ceftazidime blank, reference standard and test sample is given in Figure (1A), (1B) and (1C) respectively.

Segregation and quantification of antibiotic components was carried out by high-performance liquid chromatography which was further confirmed by antimicrobial assay.

Ceftazidime Blank

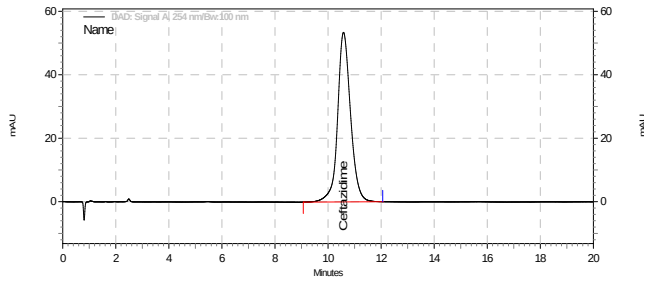


DAD: Signal A, 254 nm/Bw:100 nm Results

Pk #	Name	Retention Time	Area	Theoretical plates (USP)	Asymmetry

(1A)

Ceftazidime Reference

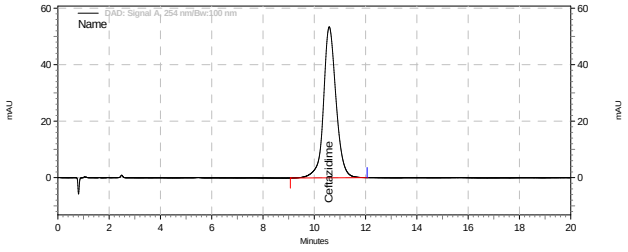


DAD: Signal A, 254 nm/Bw:100 nm Results

Pk #	Name	Retention Time	Area	Theoretical plates (USP)	Asymmetry
1	Ceftazidime	10.580	3796034	2410	1.06374
Totals			3796034		

(1B)

Ceftazidime Test



DAD: Signal A, 254 nm/Bw:100 nm Results

Pk #	Name	Retention Time	Area
1	Ceftazidime	10.553	3801271
Totals			3801271

(1C)

Figure 1 HPLC Chromatogram of representative samples of (1A) Ceftazidime Blank, (1B) Ceftazidime Reference standard and (1C) Ceftazidime test

Stability study of drugs has as main goal to exposure the nature, kinetic course and degradation, as well as determining for how much time the product can conserve its original constitution [37-38]. Quality control in pharmaceutical industries is very important to guarantee effectiveness and confirm the quality of medicines commercialized for the population.

CONCLUSIONS

In this study, accelerated, stress stability and photodegradation kinetic study of ceftazidime was performed with a view to detect the effect of thermal, photo and moisture degradation on ceftazidime.

The degradation of ceftazidime under stress conditions is found to follow first-order reaction kinetics. Extensive decomposition was observed for ceftazidime in aqueous solution at a temperature exceeding 30ºC when compared with solid state (powder for injection), therefore Ceftazidime is recommended to be stored below 30 degrees in controlled temperature ware houses and transported in temperature controlled vans. Consequently, an appropriate protection is recommended during storage and handling of this antibiotic even after reconstitution which renders the therapeutic ineffective by decreasing the assay, purity and potency of the drug. This procedure can avoid the degradation of the drug and consequent loss of effectiveness and security of the product. These studies are important to establish storage type and adequate places for pharmaceutical preparations to prevent degradation after exposures, and guarantee the drug integrity, quality and security for users.

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