ORIGINAL RESEARCH PAPER

Volume-7 | Issue-11 | November-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

METHOD DEVELOPMENT AND VALIDATION OF CEFOXITIN SODIUM IN POWDER FOR INJECTION DOSAGE FORM BY U.V-SPECTROSCOPY

Pharmaceutical

M.Meghana Department of Pharmaceutics

ABSTRACT

Spectrophotometry is one of the branches of spectroscopy where we measure the absoption of light by molecules that are in the gas or vapour state or dissolved molecules/ions. The word spectroscopy is used as a collective term for all the analytical techniques based on interaction of light and matter. Cefoxitin is a second generation cephalosporin with antibacterial activity. Develop and validate stability indicating, simple and accurate method for the determination of Cefoxitin sodium using accurate UV spectroscopic method for the determination of Cefoxitin sodium in powder for injection and perform validation of the method as per ICH guidelines. The standard solution of Cefoxitin sodium was taken and scanned in the range of 200-400nm in the UV- Visible spectrophotometer. From the spectrum obtained the wavelength at which the maximum absorption takes place has been found out. From the spectrum taken, it was found out that the lambda max for Cefoxitin sodium was observed at 231nm. Cefoxitin sodium is very soluble in water, soluble in methanol, sparingly soluble in dimethyl formamide, slightly soluble in acetone, insoluble in ether and in chloroform. The solubility of Cefoxitin sodium was determined by using different aqueous systems like distilled water, 0.1M NaOH, 0.1 M HCL. From the above mentioned solubility studies it was found that the drug has the solubility in water and 0.1 M NaOH. The solvent selected for this method was 0.1 M NaOH, because in water the drug doesnot show stable lambda max graph. The accuracy of the method was proved by performing recovery studies which were carried out by analyzing the formulation with three different levels like 10%, 20% and 30%. A value closer to 100% indicates that the proposed method is accurate for the analysis.

Thus, it was concluded that the above method was simple, precise and easy to perform and require short time to analyze the drug in the commercial formulations.

KEYWORDS

Spectrophotometry, Cefoxitin, Antibacterial activity, Wavelength, NaOH.

INTRODUCTION:

Spectrophotometry is one of the branches of spectroscopy where we measure the absoption of light by molecules that are in the gas or vapour state or dissolved molecules/ions. The word spectroscopy is used as a collective term for all the analytical techniques based on interaction of light and matter. Spectrophotometry investigates the absorption of the different substances between the wavelength limits 190nm and 780nm. In the wavelength range the absorption of the electromagnetic radiation is caused by the excitation of the bonding and non bonding electrons of the ions or molecules. A graph of absorbance against wavelength give the samples absorption spectrum. The measured spectrum is continuous, due to the fact that the different vibration and rotation states of the molecules make the absorption band wider.

Spectrophotometry is used for both qualitative and quantitative investigations of samples. The wavelength at the maximum of the absorption band will give information about the structure of the molecule or ion and the extent of the absorption is proportional with the amount of the species absorbing the light.

Quantitative measurements are based on Beer's Law which is described as follows:

A=ecl

Where, A=absorbance

e= molar absorbance or absorption coefficient

c=concentration of the compound in the solution

l= path length of light in the sample

Electronic transitions:

The absorption of UV or visible radiation corresponds to the excitation of outer electrons. These are three types of electronic transition which can be considered;

- Transitions involving π, sigma, n electrons.
- Transitions involving charge-transfer electrons.
- Transitions involving d and f electrons.

When an atom or molecule absorb energy, electrons are promoted from their ground state to an excited state. In a molecule, the atoms can rotate and vibrate with respect to each other. These vibrations and rotations also have discrete energy levels, which can be considered as being packed on top of each electronic level.

Instrumentation: (Gurdeep R chatwal, 2006; Beckett AH, 2007)

The essential components of spectrometers are

- Source of electromagnetic radiation.
- Monochromator
- Sample compartment
- Detector
- Recorder

Light Source: the distribution of energy through a spectrum is mainly a function of temperature. The higher the temperature of the light source the shorter the wavelength of the peak emission. Common energy sources for the various regions are indicated below.

Visible radiation: Tungsten filament lamp is a satisfactory light source for the region 350 to about 2000nm.

Ultraviolet radiation: The most convenient light source for measurement in the ultraviolet region is a deuterium discharge lamp, broaden to give a continuous spectrum in the range 185-380nm.

Other source: Xenon discharge lamp, Mercury arc, Hydrogen or deuterium discharge lamps, incandescent filament lamps (Tungsten halogen lamp).

Monochromators:

The function of monochromators is to isolate a particular wavelength or range of wavelengths.

Filters: Absorption filters.
Interference filters.

- **Absorption filters:** They absorb the unwanted radiation and transmit the rest of the radiation required for calorimetry. These are made up of gelatin, glass, liquid and plastic.
- **Interference filters:** Interferometric filters have an even narrower bandwidth (about 15nm).

Grating:

The dispersing element in the monochromatic of most modern ultraviolet, visible and infrared spectrophotometers is the diffraction grating. It consists of a very large number of equispaced lines (200-2000 per mm) ruled on a glass blank coated with a thin film of aluminum. They can be used either as transmission gratings or when aluminized, as reflection gratings, rotation of the grating permits appropriate wavelengths of the spectrum to emerge from the exit slit of the monochromator.

Prisms:

The prisms disperse the light radiation into individual colors or wavelengths. Prisms produce a non linear dispersion, with long

wavelength being less efficiently separated than short wavelengths. The two types of prisms available are

i. Refractive type
ii. Reflective type

Sample cell:-

For the analysis of liquids and gases in the ultraviolet -visible region above 320nm, cells or cuvettes constructed with optically flat fused glass may be used. For UV analysis cells made up of quartz are used, since glass absorbs UV radiation.

Detectors:

Detectors used in UV-Visible spectrophotometers can be called as photometric detectors. When a radiation is passed through a sample cell part of it is being absorbed by the sample solution and the rest is being transmitted. This transmitted radiation falls on the detector and the intensity of absorbed radiation can be determined or displayed. In these detectors light energy is converted to electrical signal which can be read or recorded.

The most commonly used detectors are

1. Photomultipliers
2. Photodiodes arrays
3. Barrier- layer cells
4. Phototubes
5. Recorder:

The signal from the detector is normally proportional to the intensity of light incident on the detector. The three common systems for displaying the absorbance are moving coil meter, digital display and strip-chart recorder.

Spectrophotometic Methods for Estimation Of Drugs : 9 Kasture vs 2010

1. One component analysis.
2. Methods for multi-component analysis.

One component analysis

1. Use of a standard absorptivity value.
2. Use of a calibration graph.
3. Single or double point standardization.

Methods for multiple- component analysis:

1. Simultaneous equation method or vierodt's method.
2. Derivative Spectrophotometry.
3. Absorbance ratio method (Q-absorbance method).
4. Difference Spectrophotometry.
5. Geometric correction method.
6. Orthogonal polynomial functional method.

Drug Profile

Drug name: Cefoxitin sodium.

Drug introduction: The cephalosporins are a class of beta lactum antibiotics originally derived from *Acremonium*, which was previously known as "Cephalosporium". Cephalosporin compounds were first isolated from cultures of *Cephalosporium acremonium* from a sewer in Sardinia in 1948 by Italian scientist Giuseppe Brotzu.

Mode of action: Cephalosporins are bactericidal and have the same mode of action as other beta-lactum antibiotics (such as pencillins) but are less susceptible to pencillinases. Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity.

Molecular formula: C16H16N3NaO7S2

Molecular weight: 449.44

Class: Cefoxitin is a second generation cephalosporin with antibacterial activity.

pH: Between 4.2 and 7.0 in a solution containing 100 mg per mL.

Description: White to off-white, granule or powder, having a slight characteristic odor. It is somewhat hygroscopic.

Melting point: >160 degree celcius.

Solubility: very soluble in water, soluble in methanol; sparingly soluble in dimethylformamide; slightly soluble in acetone; insoluble in either and in chloroform.

Pediatric Patients dose: The recommended dosage in pediatric patients three months of age and older is 80 to 160 mg/kg of body weight per day divided into four to six equal doses. The higher dosages should be used for more severe or serious infections. The total daily dosage should not exceed 12 grams.

Adverse Reactions:

Local Reactions: Thrombophlebitis has occurred with intravenous administration.

Allergic Rections: Rash, urticaria, flushing , pruritus, eosinophilia, fever, dyspnea and other allergic reactions including anaphylaxis, interstitial nephritis and angioedema have been noted.

Cardiovascular: Hypotension

Gastrointestinal: Marked changes in anaerobic, facultative and aerobic faecal flora have been noted with cefoxitin.

Renal Function: Elevations in serum creatinine and/or blood urea nitrogen levels have been observed.

Drug Interactions: Probenecid reduces the renal clearance of cefoxitin. Amino glycosides may increase risk of nephrotoxicity.

Storage: Store powder in vials between 36° and 77°F.

Contraindications: Hypersensitivity to cephalosporins.

Pharmacokinetics: Cefoxitin is not absorbed from the gastro intestinal tract; it is given parentrally as the sodium salt. It has a plasma half life of 45 to 60 minutes which is prolonged in renal impairment. Cefoxitin is widely distributed in the body but there is normally little penetration into the CSF, even when the meninges are inflamed. It crosses the placenta and has been detected in breast milk.

Dosage forms available:

Cefoxitin powder for injection, Cefoxitin injection, Cefoxitin ophthalmic sterile solution.

Indications and usage for cefoxitin:

It is used for the treatment of susceptible injection. However, because of its activity against *Bacteroides fragilis* and other anaerobic bacteria, it is used principally in the treatment and prophylaxis of anaerobic and mixed bacterial injections, especially intra-abdominal and pelvic injections

1. Lower respiratory tract infections including pneumonia and lung abscess, caused by Streptococcus pneumonia, other streptococci (excluding enterococci, e.g., Enterococcus faecalis, Escherichia coli, Klebsiella species and Bacteroides.
2. Urinary tract infections caused by Escherichia cli, Klebsiella species, Proteus mirabilis, Morganella morgani, proteus vulgaris and Providencia species.
3. Intra-abdominal infections, including peritonitis and intra-abdominal abscess, caused by Escherichia coli, Klebsiella species, etc.
4. Gynecological infections.

LITERATURE REVIEW

A literature review is an objective, through summary and critical analysis of the relevant available research and non-research literature on the topic being studied (Hart, 1998). Its goal is to bring the reader up-to-date with current literature on a topic and form the basis for another goal, such as the justification for future research in the urea.

Lemus JM *et al.* (1993) have developed fluorescence method involving sample pre-treatment concerning the determination of cefoxitin. A fluorescent product is formed when samples containing cefoxitin are subjected to alkaline hydrolysis with 1M sodium hydroxide and heated for 60min at 90°C. The fluorescence is measured in ethanol/ water medium (50% v/v) at approximately pH 2.0 provided by adding of 0.1 M hydrochloride acid. The fluorescence excitation and emission maxima were 317 and 400 nm, respectively. The quantitative range is between 0.020 and 1.40µg/mL. A dectection limit of 2×10^{-1}µg/mL was found.

Salgado *et al*. (2007) developed a microbiological assay applying the cylinder plate method for determination of the activity of cefoxitin

sodium in injectables. Using a strain of Staphylococcus epidermidis ATCC 12226 as the test organism, cefoxitin sodium was measured in concentrations ranging from 50.0 to 200.0µg/mL. The validation showed that the method was lineae (r=0.9998), precise (RSD=0.81%) and accurate.

Charls BG *et al.* (1994) described a rapid, specific and precise method for the analysis of cefoxitin in plasma and urine by reversed- phase high performance liquid chromatography. Cefoxitin and the internal standard, 3-isobutyl-1-methyl xanthine were eluted after 5.3 and 7.5 min, respectively. The assay sensitivity limit is 1 to 2 mg/L of cefoxitin sodium at 254nm. Commonly prescribed antibiotics do not interfere. The assay is suitable for routine monitoring and pharmacokinetic studies of cefoxitin.

Robbs JV *et al.* (1989) developed HPLC method that successfully measured cefoxitin levels in subcutaneous tissue, muscle, aortic and peripheral arterial walls. Samples were obtained from 11 patients submitted to prosthetic aortic replacement. All patients received an intravenous bolus dose of cefoxitin 2 g just before induction of anaesthesia. Blood and tissue samples were taken at various intervals intra-operatively. The tissue samples were mechanically homogenized. Both plasma and the tissue homogenates were deproteinated with trichloracetic acid. The cefoxitin was separated by HPLC and measured by ultraviolet absorbance. The results show that the tissue concentration of the drug fell over a 4 hour period and that all levels exceeded the Minimum inhibitory concentration that inhibits growth of bacteria at the 90% level for most aerobic and anaerobic pathogens for at least 3 hours.

Biader Ceipidor U *et al.* (1982) analyzed a series of sodium salts of antibiotics belonging to the cephalosporin group has by thermoanalytical techniques as TG, DTG, and DSC. No melting processes have been identified. The heating process, mainly carried out in a stream of oxygen, shows thermal reactions starting at about 150°C. Sodium sulphate was found as residue at temperatures around 600-650°C. From the residue, which has a well-defined composition, it is possible to dose the sodium to a higher degree of accuracy than that obtained by flame photometry.

Rudolf PB *et al.* (1974) quantitatively analyzed cefoxitin, cephalothn and their deacylated metabolites, decarbamylcefoxitin and deacetylcephalothin in whole human urine using high performance anion-exchange liquid chromatography with UV detection. The rate of excretion and extent of deacylation for the two compounds were determined after intravenous injection with or without probenecid and after intramuscular injection. Recoveries of intact cefoxitin were considerably higher than those of cephalothin in all the cases studied, owing to the almost total resistance of cefoxitin to inactivation by deacylation. Cephalothin was found to be deacylated rapidly and to a relatively large extent.

Abdel Khalek MM *et al.* (1984) developed a colorimetric method for the determination of five cephalosporins (cefoxitin sodium, cefotaxime sodium, cephapirin sodium, cephalothin sodium and cephaloridine), based on the blue color formed by reaction of the cephalosporins with ammonium molybdate is described. The proposed method has been applied to the analysis of cephalosporin injections, the results of which are in good agreement with those obtained by the official method of the British Pharmacopoeia (BP).

Gortajzar P *et al.* (1995) analyzed 200 urine samples from 61 subjects by circular dichroism spectroscopy. The results proved that this technique can be applied to the direct determination of optically active absorbing drugs in urine of subjects under multiple drug administration, independently of the presence of proteins, which can simultaneously be determined. A list of non interfering drugs is included. The validity of he present method was confirmed by analysis of variance, the beta-lactum antibiotics ampicillin, cefoxitin, and cephalexin being chosen as model drugs and human albuminas the analytical standard for protein determination. The results demonstrated that the proposed method is accurate and precise, the correlation coefficients being higher than 0.9996. A circular dichroism and HPLC data comparision was successfully performed.

AIM AND PLAN OF WORK

Objective:

The objective of the present work is to develop and validate stability indicating, simple and accurate method for the determination of Cefoxitin sodium using accurate UV spectroscopic method for the determination of Cefoxitin sodium in powder for injection and perform validation of the method as per ICH guidelines (International Conference on Harmonization of Technical requirements for registration of pharmaceuticals for human use).

Plan of present work

- Selection of solvent
- Development of simple, cost effective and accurate UV method.
- Validation of proposed analytical method.

MATERIALS AND METHODS

Instruments:

- Digital balance - Model No: US- 500C.
- UV-Visible spectrophotometer - Systronics 2201 Double beam with pair of 10mm

Matched Quartz cells

- Calibrated glass wares

Reagents and chemicals:

All the chemicals and reagents used were of analytical grade

- Distilled water
- 0.1 M sodium hydroxide - Merck- AR grade

Drug Samples:

Cefoxitin active pharmaceutical ingredient was obtained from orchid chemicals and pharmaceutical LTD.
Cefoxitin sodium – 99.7%

Formulation used:

The finished product Cefoxitin sodium powder for injection was used which was formulated by Hospira Health care PVT LTD.

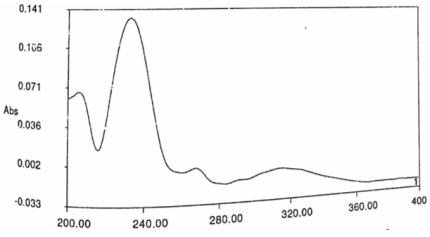
METHOD DEVELOPMENT

Preliminary solubility studies of pure drug Cefoxitin sodium

Cefoxitin sodium is very soluble in water, soluble in methanol; sparingly soluble in dimethyl formamide, slightly soluble in acetone, insoluble in ether and in chloroform. The solubility of Cefoxitin sodium was determined by using different aqueous systems like distilled water, 0.1 M NaOH. The solvent for the UV study was 0.1 M NaOH.

Selection of wavelength:

The standard solution of Cefoxitin sodium was taken and scanned in the range of 200-400nm in the UV- Visible spectrophotometer. From the spectrum obtained the wavelength at which the maximum absorption takes place has been found out. From the spectrum taken, it was found out that the lambda max for Cefoxitin sodium was observed at 231nm.



Spectrum of Cefoxitin sodium scanned between 200-400nm

Preparation of Standard solutions for calibration curve:

Accurately weighed 100mg of Cefoxitin sodium pure drug was taken in separate 100ml volumetric flask and diluted with 0.1M NaOH solution further dissolution was made by pipetting out 10ml of standard stock solution and by transferring into 100ml volumetric flask, diluted with 0.1M sodium hydroxide solution. Final dilutions were made by transferring 1,1.5,2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0 ml from the 100µg/ml solution into the 10ml volumetric flask and then volume made with 0.1 M sodium hydroxide to obtain 10, 15, 20, 25, 30, 35, 40, 45, 50 µg/ml solutions. Evaluation was performed with ultra-violet detector for Cefoxitin sodium at 231nm. Plots of concentration Vs absorbance were prepared.

Formulation used

Cefoxitin sodium for injection 1 gm.

Preparation of sample solution for assay of formulation:
One vial was taken and was weighed. Then one vial was reconstituted with 10ml of water for injection or as per labeling to get 95mg/ml of cefoxitin. Then entire contents was withdrawn from the vial using a suitable calibrated Hamilton syringe and transferred the solution to 250ml volumetric flask and diluted to volume with 0.1 N NaOH and mixed well. 0.5ml of resulting solution was further diluted to 100ml with 0.1 N NaOH to get final concentration of 20µg/ml Cefoxitin respectively. The absorbance of final solution was measured at 231nm.

METHOD VALIDATION

The method was validated according to, US FDA guidelines and USP. Method validation provides an assurance of reliability during normal use, and is sometime referred to as "The process of providing documented evidence that the method does what it is intended to do".

Assay of Cefoxitin sodium for injection:
The absorbance of the sample solution in the concentration of 20µg/ml was measured at 231nm and percentage drug content was calculated in replicate.

Concentration (µg/mL)	Label claim (mg)	Percentage Content *
20	1000	99.47 %

(*n=3)

Linearity and range:
Linearity of the proposed method was verified by analyzing different concentrations in the range of 10-50µg/ml for cefoxitin sodium. They were established along the standard curve. The regression coefficient y-intercept and slope of the regression line were calculated for the drug.

Precision-system precision:
The interday precision of the developed method was evaluated by analyzing aliquots of Cefoxitin sodium sample from homogeneous lot for six times on the same day. The intraday precision was evaluated from the same concentration on six consecutive days.

Accuracy:
The accuracy of the method was performed by conducting the recovery studies at three level (10, 20 and 30%). The actual and measured concentrations were then compared. Three concentrations of the drug solution were prepared and analyzed in triplicates. The percentage recovery and percentage RSD was calculated.

LOD and LOQ
For the determination of LOD and LOQ, the method is based on residual standard deviation of regression line and slope. To determine LOD and LOQ the specific calibration curve was studied using the sample containing analyte in the range of detection limit and quantization limit.

RESULTS AND DISCUSSION

Solubility:
Cefoxitin sodium is very soluble in water, soluble in methanol, sparingly soluble in dimethyl formamide, slightly soluble in acetone, insoluble in ether and in chloroform. The solubility of Cefoxitin sodium was determined by using different aqueous systems like distilled water, 0.1M NaOH, 0.1 M HCL. From the above mentioned solubility studies it was found that the drug has the solubility in water and 0.1 M naOH. The solvent selected for this method was 0.1 M NaOH, because in water the drug doesnot show stable lambda max graph.

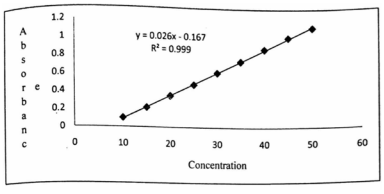
Parameters for calibrated curve:
The optical characteristics such as absorption maxima, BEER law limit, molar absorptivity and Sandell's sensitivity of standard drug were calculated from the average of six measurements and results were tabulated in below table.

S.No	Optimal parameters	Values
1	λ-Max (nm)	231
2	Linearity (µg/mL)	10-50
3	Regression equation	Y= 0.026X – 0.167
4	Correlation coefficient	0.999
5	Slope	0.026
6	Intercept	0.167
7	Molar absorptivity (L $mol^{-1}cm^{-1}$)	8.451×10^3
8	Sandell's sensitivity (µg/cm^2/0.001)	0.056
9	LOD (µg/mL)	1.391
10	LOQ (µg/mL)	4.214

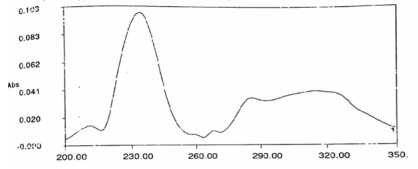
Linearity:
The linearity of an analytical procedure is its ability to obtain test results which are directly proportional to the concentration of analyte in the sample. The lambda max for Cefoxitin sodium was determined in 0.1 M NaOH at 231 nm. At selected lambda max and in it selected solvent system the drug showed a linear relationship in the concentration range of 10-50µg/ml. The linear regression equation for Cefoxitin sodium obtained was Y=0.026-0.167. The data were shown in below table.

Linearity of regression equation was demonstrated from the high correlation coefficient value and very low values of intercept. Hence it was suggested that the calibration line of Cefoxitin sodium in selected solvent system did not deviate from the origin and its values were within the acceptable range.

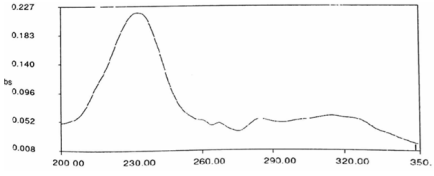
Sr.No	Concentration(µg/mL)	Absorbance
1	10	0.099
2	15	0.217
3	20	0.35
4	25	0.476
5	30	0.61
6	35	0.741
7	40	0.879
8	45	1.01
9	50	1.12



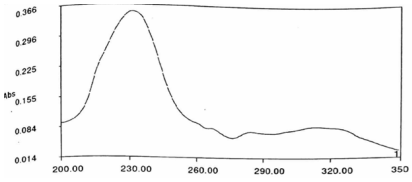
Linearity graph for Cefoxitin sodium



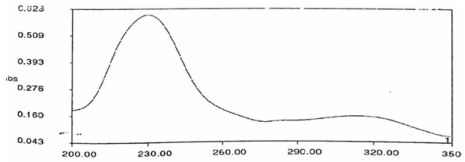
UV spectrum for 10µg/mL of Cefoxitin sodium



UV spectrum for 15µg/mL of Cefoxitin sodium



UV spectrum for 15µg/mL of Cefoxitin sodium



UV spectrum for 30µg/mL of Cefoxitin sodium

Accuracy:

Accuracy of the proposed method was studied by analyzing the powder for injection formulation in three different concentration levels like 10%, 20% and 30% under similar condition of the above procedure. The percentage recoveries of the three concentrations were found to be close to 100%. The results were tabulated below

S.NO	Levels of std drug added (%)	Label claim of Cefoxitin sodium (mg)	Percentage recovery*	%RSD
1	10 %	1000	98.71	0.270
2	20 %	1000	99.52	0.306
3	30 %	1000	99.36	0.309

(*n=3)

Precision:

To validate the precision ability of the proposed method, 20µg/mL concentration of cefoxitin sodium sample was prepared. Six replicates on the same day and on six consecutive days were carried out. The very low % relative standard deviation values for intraday and interday indicated that the precision of the method was good and data's were summarized in below table.

Concentration	*Interday* precision			*Intraday* precision		
	Duration	% Content	% RSD	Day	% Content	% RSD
20µg/mL	9.0 am	99.34	0.736	1	98.29	0.511
	11.05 am	99.13		2	98.97	
	1.03 pm	99.51		3	99.71	
	3.10 pm	98.7		4	99.11	
	5.05 pm	97.20		5	98.47	
	7.11 pm	97.05		6	99.05	

Intra and Interday precision for Cefoxitin sodium assay in powder for injection dosage form.

SUMMARY AND CONCLUSION

A rapid, cheap, reliable and simple spectrophotometric method for the quantitative determination of Cefoxitin in powder for injection dosage forms was developed.

LOD and LOQ were found to be 1.39µg/mL and 4.21µg/mL for cefoxitin sodium respectively.

The accuracy of the method was proved by performing recovery studies which were carried out by analyzing the formulation with three different levels like 10%, 20% and 30%. A value closer to 100% indicates that the proposed method is accurate for the analysis.

Thus, it was concluded that the above method was simple, precise and easy to perform and require short time to analyze the drug in the commercial formulations.

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