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Research Article

FORCED OXIDATIVE DEGRADATION STUDY OF DORIPENEM BY UV SPECTROPHOTOMETRIC METHOD

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ABSTRACT

A forced degradation study of doripenem in bulk and injectable form was conducted under Oxidized condition. The study was conducted as per available guidelines and main references. Stability indicating RP- HPLC method has been reported for analysis of doripenem injectable formulation in Brazil. To evaluate the stability of drug substance and formulation, a stress testing of drug substance and formulation by exposing to various stress condition has been recommended. Doripenem is a beta-lactam antibiotic belonging to the carbapenem group, with a broad antibacterial spectrum. Extensive degradation was observed under oxidized condition, and the degraded products were analysed by standard comparison method of UV spectrophotometry.

Forced degradation was performed in bulk drug and injectable formulation using hydrogen peroxide solution (30%). Doripenem was subjected to oxidative degradation at different time intervals based on references. The assay value of degraded doripenem after 90 mins was found to be 73%. Complete degradation of doripenem was observed at the end of 5th day. It was concluded that doripenem was found unstable under oxidative condition.

Keywords: Doripenem, UV spectrophotometry, Oxidative degradation, Hydrogen peroxide.

INTRODUCTION

Doripenem is a novel, broad-spectrum parenteral carbapenem antimicrobial. Doripenem is a new carbapenem similar to meropenem and imipenem but different than ertapenem. Doripenem, like other carbapenems, is stable to most beta-lactamases including ampC beta-lactamases and extended-spectrum beta-lactamases (ESBLs). Doripenem also effective against infections caused by Gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Enterobacteriaceae*, including strains of these bacteria that are resistant to other therapies. It is approved for complicated intra-abdominal and complicated urinary tract infections (UTI) in the United States and in Europe. It is also approved for nosocomial pneumonia. All carbapenems (except for ertapenem) have very similar pharmacokinetics, including half-life (1 hour), protein binding (2-20%), distribution properties (0.23-0.35 L/kg), and temporal plasma profiles. Stability- Indicating RP- HPLC method has been reported for analysis of doripenem injectable formulation [1]. Determination of doripenem by Charge Transfer and Kinetic methods have been reported [2]. Antimicrobial activity of doripenem has been determined [3]**.** It is very important to conduct the degradation study to understand the relative chemistry of the drug substance; also to determine intrinsic stability of a drug substance. Doripenem powder for injection was subjected to forced oxidative degradation. The identification and evaluation of degraded product was conducted by standard comparison method of UV spectrophotometry.

MATERIAL AND METHODS

Materials and reagents

Hydrogen peroxide solution (30%) has been purchased from E-Merck. Distilled water was used as a solvent. Doripenem powder for injection was obtained from reputed pharmaceutical company. The determinations were carried out at room temperature. All absorption spectra were measured using Shimadzu UV-1650PC (UV-visible) spectrophotometer with a scanning speed of 200 nm min-1 and a band width of 2.0 nm, equipped with 1 cm matched quartz cells.

Forced degradation (stress study) of Doripenem: Intraday

Standard preparation

Doripenem was transferred to volumetric flask and dissolved in distilled water to achieve a concentration of 1 mg mL^{-1}. An aliquot solution was diluted with distilled water to get a final concentration of 20 µg mL^{-1}. The solution was scanned in the UV region and the λ maximum was recorded at 298 nm.

Standard stress preparation

Doripenem was transferred to volumetric flask and dissolved in hydrogen peroxide solution (30%) to achieve a concentration of 100 µg mL^{-1}. After 30 mins, an aliquot solution was diluted with distilled water to get a final concentration of 20 µg mL^{-1}. The solution was scanned in the UV region and the λ maximum was recorded at 298 nm. The same procedure was repeated for 60 mins and 90 mins time interval.

Sample preparation

Doripenem powder for injection was transferred to volumetric flask and dissolved in hydrogen peroxide solution (30%) to achieve a concentration of 100 µg mL^{-1}. After 30 mins, an aliquot solution was diluted with distilled water to get a final concentration of 20 µg mL^{-1}. The solution was scanned in the UV region and the λ maximum was recorded at 298 nm. The same procedure was repeated for 60 mins and 90 mins time interval.

Blank preparation

A blank solution of hydrogen peroxide solution (30%) was prepared in a similar manner.

The procedure was repeated thrice. After the stipulated time, the absorbance of the resulting solutions showed maxima at 298 nm (Table 1) against reagent blanks treated in the same way. Three such determinations were made and the assay value was estimated. The obtained values were concurrent.

Table 1: Summary of forced degradation study of doripenem: Intraday

Stress condition (Oxidation)	Time	Std (stress)	Powder for Injection Assay (% w/w)	Assay (% w/w)	Remarks
Hydrogen peroxide solution (30%)	30 mins	78.75%	78.18%		Degradation observed
	60 mins	77.52%	77.22%		Degradation observed
	90 mins	73.08%	72.93%		Degradation observed

Inter-day

Standard preparation

The standard preparation was prepared in similar manner which was mentioned in Intraday preparation.

Standard stress preparation

Same method was followed, but the final solution was scanned and absorbance was recorded at the following time intervals 1st, 3rd & 5th day.

Sample preparation

Same method was followed, but the final solution was scanned and absorbance was recorded at the following time intervals 1st, 3rd & 5th day.

Blank preparation

Similar to intraday preparation.

The procedure was repeated thrice. After the stipulated time, the absorbance of the resulting solutions showed maxima at 298 nm (Table 2) against reagent blanks treated in the same way. Three such determinations were made and the assay value was estimated. The obtained values were concurrent.

Table 2: Summary of forced degradation study of doripenem: Inter-day

Stress condition (Oxidation)	Time	Std (stress) Assay (% w/w)	Powder for Injection Assay (% w/w)	Remarks
Hydrogen peroxide solution (30%)	1st day	7.32%	4.26% observed	Degradation
	3rd day	0%	0%	Complete degradation observed
	5th day	0%	0%	Complete degradation observed

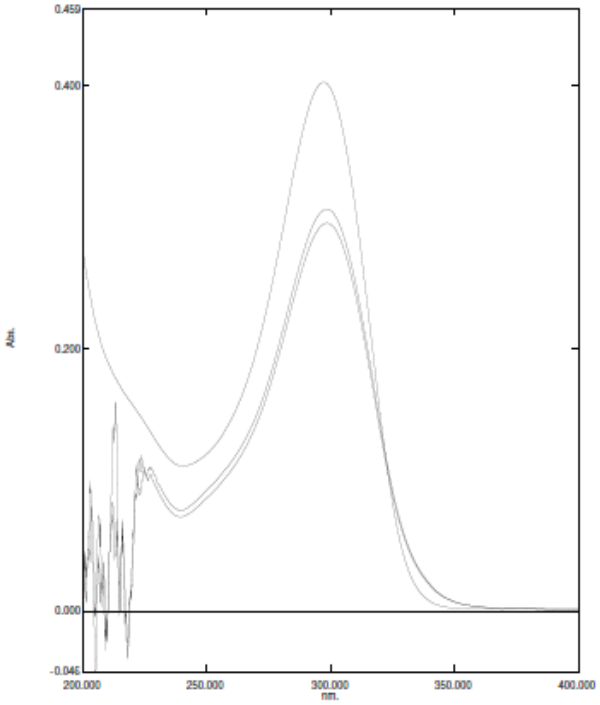

Fig. 1: Absorbance Spectrum of doripenem powder for injection

RESULTS AND DISCUSSION

Doripenem was found to be unstable under oxidative condition. It was found that the stress induced standard and the test were found to degrade to 73 % w/w at the end of 90 mins after the exposure to H_2O_2 (30% v/v). Complete degradation of the stressed standard and sample was recorded on 3rd & 5th day; whereas it was only 4 % w/w at the end of the 1st day. Therefore the drug doripenem has to be stored under such condition where the possibility of oxidation does not arise.

CONCLUSION

The forced oxidative degradation of doripenem was studied by UV spectroscopy at various time intervals (30 mins, 60 mins & 90 mins; 1st, 3rd & 5th day); it was established that the drug doripenem is vulnerable to oxidized condition.

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