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Short communication

Stability and degradation kinetics of meropenem in powder for injection and reconstituted sample

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Abstract

The stability of broad-spectrum antibiotic meropenem was studied in order to investigate the kinetics of degradation of this drug in powder for injection and reconstituted sample. Carbapenem was submitted to conditions of accelerated thermal decomposition. Degradation of meropenem was adequately modeled by specific equations for order rate kinetics. The analyses of the degraded samples were performed by high-performance liquid chromatographic (HPLC) method and microbiological assay. At higher temperatures, the decomposition reactions of meropenem in powder for injection could be described by first-order kinetics. The higher rate of degradation was observed in meropenem reconstituted in 0.9% sodium chloride, and the thermal decomposition obeyed also first-order kinetics. The results obtained confirm the reliability of chromatographic method for determining the kinetics run of meropenem in the presence of its degradation products. The present study reveals the thermal lability of the drug, especially as reconstituted sample. Thus, appropriate thermal protection is recommended during the storage and handling.

Keywords: Meropenem; Stability; Kinetics of degradation; HPLC; Microbiological assay; Powder for injection; Reconstituted sample

1. Introduction

Meropenem (Fig. 1) is a parenteral carbapenem antibiotic with a very broad spectrum of antibacterial activity against the majority of gram-positive and gram-negative pathogens [1,2]. This antibiotic is stable to ring opening by human renal dehydropeptidase I (DHP-I) and consequently does not require concomitant administration of a DHP-1 inhibitor. Meropenem has shown clinical efficacy in the treatment of a wide range of serious infections such as intra-abdominal infections, urinary tract infections and lower respiratory tract infections [3,4].

Literature survey reveals several analytical methods reported for the quantitative estimation of meropenem in pharmaceutical dosage form, including high-performance liquid chromatography (HPLC) [5–7], ultraviolet spectrophotometry [6] and microbiological assay [8]. The quantitation of meropenem in the presence of its degradation products has been studied. Recently, in preliminary forced thermal testing, a liquid chromatographic method and a microbiological assay were performed for quantitative determination of this antibiotic in reconstituted sample submitted to thermal degradation [8]. In another work, a chromatographic method for determination of polymerized impurities in meropenem was proposed [9]. The separation of these impurities was carried out by gel filtration chromatography. Some investigators have reported the stability of meropenem under various conditions [10–12]. Patel and Cook [10] studied the stability of meropenem in 0.9% sodium chloride injection. The stability of commonly used meropenem concentrations in both PVC containers and a frequently used elastomeric infusion device was determined in a recent study [11]. In a solid state formulation for injection, meropenem was found to be stable at room temperature [13]. However, the formulation must be prepared under a controlled relative humidity of less than 40%.

Considering the few publications concerning kinetic studies of meropenem, the purpose of this paper was to establish the effect of temperature on the decomposition of this antibiotic in powder for injection and reconstituted sample, to determine the kinetics of degradation describing the concentration changes of meropenem as a function of time, and to determine the kinetics run parameters. The analysis of the degraded samples was

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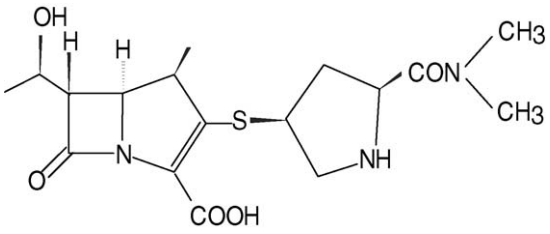

Fig. 1. The chemical structure of meropenem.

performed by stability-indicating HPLC method [6] and microbiological assay [8], developed and validated in our laboratory in compliance with ICH guidelines.

2. Experimental

2.1. Chemicals

Meropenem reference standard was kindly supplied by Sumitomo Pharmaceuticals Co. Ltd. (Osaka, Japan) and AstraZeneca (São Paulo, Brazil). Pharmaceutical dosage form (Meronem®) containing meropenem was obtained commercially and was claimed to contain 500 mg (as anhydrous base) of the drug and 104 mg of the anhydrous sodium carbonate as excipient. Acetonitrile for chromatography LiChrosolv®, potassium dihydrogenphosphate p.a., orthophosphoric acid p.a., Grove Randall number 11 agar and Grove Randall number 1 agar were obtained from Merck (Darmstadt, Germany). Sodium chloride was obtained from Quimibrás (Rio de Janeiro, Brazil). Ultrapure water was obtained from a Milli-Q® UF-Plus apparatus (Millipore). Ultrapure water was used to prepare all solutions for the HPLC method and distilled water was used to prepare all solutions for the microbiological assay.

2.2. Instrumentation and analytical conditions

2.2.1. Thermal degradation

Stress studies under thermal conditions were performed using a dry air oven De Leo® (São Paulo, Brazil). Susceptibility of the drug in powder for injection to dry heat was studied by exposing to 70, 80 and 90 °C. For reconstituted sample, meropenem was dissolved in 0.9% sodium chloride and the solution was heated at 25, 35 and 45 °C.

2.2.2. HPLC method

The HPLC method was performed as described in an earlier publication [6].

2.2.3. Microbiological assay

Microbiological assay, applying the cylinder-plate method, was performed as described in an earlier publication [8].

2.3. Decomposition studies

Accelerated thermal degradation study was performed by heating the commercial sample of meropenem (500 mg) at 70, 80 and 90 °C for 335, 295 and 95 days, respectively. At time intervals, aliquots of degraded samples (three aliquots for each time) were diluted in ultrapure water at concentration of 50 μg/ml and analyzed by HPLC method. All solutions were injected in triplicate.

For reconstituted sample, commercial samples of meropenem (500 mg) were reconstituted in 10 ml of 0.9% sodium chloride and stored at 25, 35 and 45 °C for a period of 36 h. Aliquots were withdrawn at suitable time intervals (three aliquots for each time) and subjected to HPLC analysis at concentration of 50 μg/ml. All solutions were also injected in triplicate.

The decomposition rate of meropenem was also evaluated by microbiological assay. Aliquots of degraded samples (one aliquot for each time) were diluted in distilled water at concentrations of 6.0 and 10 μg/ml which were assayed against solutions of reference standard and sample at concentrations of 1.5, 3.0 and 6.0 μg/ml (linearity range). This assay was carried out only with meropenem stored at 90 and 45 °C. For each aliquot of degraded sample, the assay was performed using five plates.

2.4. Kinetic calculations

The degradation rate kinetics were determined by plotting log of concentration of drug remaining versus time (first-order process). The kinetic parameters such as apparent order degradation rate constant (k), half-life ($t_{1/2}$) and t_{90} (i.e. time where 90% of original concentration of the drug is left unchanged) were obtained from the slopes of the straight lines at each temperature. Each experiment was done in triplicate (analysis by HPLC method) and average values were taken for the analysis.

3. Results and discussion

In this study, thermal stability of meropenem was carried out through employment of stress conditions. The thermal degradation profile of meropenem was studied at different temperatures for different time periods. For reconstituted sample, the drug was found to degrade extensively after reconstitution in saline solution. Almost 80% drug degradation was observed on exposure to heating at 45 °C for 36 h. A yellowish color developed thereupon exposure of the meropenem reconstituted sample at heat. Fig. 2 shows the changes observed during degradation of the reconstituted drug in comparison with the initial sample. Three degradation product peaks at around 3.0 and 17.0 min were seen, especially at 220 nm.

On exposure of meropenem to dry heat in solid state (powder for injection), this drug was found to be stable. In this work, the experiments were carried out using commercial samples, in sealed glass vials, protected from humidity. Thus, significant degradation was verified only at higher temperatures and long storage time. The extent of degradation was much lesser than in solution. At 70 °C, only 8% of the drug degraded after exposing for 115 days. It was observed that around 75% of the drug degraded on heating for 95 days at 90 °C but there was no corresponding formation of degradation products. Very small degradation product peaks at around 3.0 min were seen, especially at 220 nm (Fig. 2).