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Development and validation of a dissolution test for rabeprazole sodium in coated tablets

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Abstract

The aim of this work is to develop and validate a dissolution test for rabeprazole sodium coated tablets using a reverse-phase liquid chromatographic method. After test sink conditions, dissolution medium and stability of the drug, the best conditions were: paddle at 75 rotations per minute (rpm) stirring speed, HCl 0.1 M and borate buffer pH 9.0 as dissolution medium for acidic and basic steps, respectively, volume of 900 ml for both. The quantitation method was also adapted and validated. Less than 10% of the label amount was released in the acid step, while more than 95% was achieved over 30 min in the basic one. The dissolution profile for tablets was considered satisfactory. The dissolution test developed was adequate for its purpose and could be applied for quality control of rabeprazole tablets, since there is no official monograph.

Keywords: Rabeprazole sodium; Dissolution test; HPLC; Method validation; Stability; Quality control

1. Introduction

Dissolution test has emerged in the pharmaceutical field as a very important tool to characterize drug product performance [1]. It provides measurements of the bioavailability of a drug as well as can demonstrate bioequivalence from batch-to-batch. Besides, dissolution is a requirement for regulatory approval for product marketing and is a vital component of the overall quality control program [2,3].

Rabeprazole (±)-sodium 2-[[4-(3-methoxypropoxy)-3-methylpyridine-2-yl]methylsulfinyl]-1*H*-benzimidazole (Fig. 1) is a proton pump inhibitor that covalently binds and inactivates the gastric parietal cell proton pump (H^+/K^+ ATPase). It has proven efficacy in healing, symptom relief and prevention of relapse of gastric ulcer, duodenal ulcer and gastro-oesophageal reflux disease [4]. Since it is an acid labile drug, it is commercialize as enteric coated tablets [5].

Although there is a crescent number of works describing the determination of rabeprazole in biological fluids [6–11] and pharmaceutical formulation [12–15] by several methods, this drug is not listed in any pharmacopoeia and there is no dissolution test for tablets reported in literature.

The aim of the present work is to develop and validate a dissolution test for rabeprazole sodium coated tablets using a high performance liquid chromatographic method (HPLC) adapted from the previously published method for drug determination in tablets [13].

2. Experimental

2.1. Chemicals

Rabeprazole sodium reference standard, 99.3% purity, was supplied by Janssen-Cilag (São Paulo, SP, Brazil) and was used as received. The coated tablets (Pariet®), containing 20 mg of rabeprazole sodium, were obtained commercially. The excipients of the pharmaceutical formulation were mannitol, hydroxypropyl cellulose, magnesium oxide, low-substituted hydroxypropyl cellulose, magnesium stearate, ethylcellulose, hydroxypropyl methylcellulose phthalate, diacetylated monoglycerides, talc, titanium dioxide, carnauba wax, and ferric oxide (yellow) as a coloring agent. All of them were obtained from different local distributors. Water was purified using Millipore®

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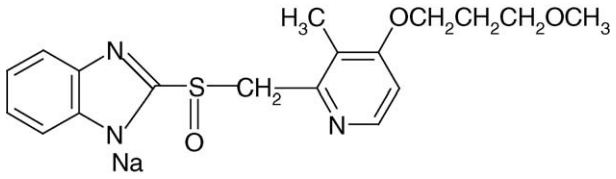

Fig. 1. Chemical structure of rabeprazole sodium.

system. All the other reagents were of analytical grade (Merck, Darmstadt, Germany). Buffer solutions were prepared according to USP 28 [16].

2.2. Instrumentation

The dissolution test was performed in a Sotax AT7 multi-bath ($n = 6$) dissolution test system (Basel, Switzerland), in accordance with the United States Pharmacopeia (USP) general methods [16].

A liquid chromatograph (Shimadzu, Kyoto, Japan) equipped with a model LC-10ADvp binary pump, SIL-10ADvp autosampler, CTO-10ACvp column oven, SPD-M10Avp PDA detector, SCL-10Avp system controller and CLASS-VP software was used to quantify the samples.

The Digimed potenciometer, model DM-20 (São Paulo, Brazil) was used to determine the pH of all solutions.

The ultrasonic bath used for deaeration was the model USC 2850 (Unique, São Paulo, Brazil) and the 0.45 μm nylon membranes were Millex (Millipore, São Paulo, Brazil).

2.3. Chromatographic conditions

The HPLC method was adapted from a previously published one [13] validated for rabeprazole sodium coated tablets analysis. The chromatographic conditions are listed in Table 1.

Standard preparation for content uniformity. An amount of powder equivalent to 10 mg of rabeprazole sodium was weighed and transferred to a 50 ml volumetric flask with 5 ml of water pH 10 (adjusted with ammonium hydroxide). The volume was completed with acetonitrile. An aliquot of 4 ml of this standard solution was transferred to 20 ml volumetric flask and diluted with acetonitrile obtaining the final concentration of 40.0 μg ml^{-1}. The solution was filtered in a 0.45 μm nylon membrane filter before the analysis. For the dissolution test, the solution was diluted to 11 μg ml^{-1} using the mixture of acetonitrile-borate buffer pH 9.0 (50:50, v/v) as solvent.

Table 1
Chromatographic conditions for rabeprazole sodium determination in tablets [13]

Equipment	Shimadzu SPD-M10A diode array detector
Column	Keystone Betabasic C8 (250 mm × 4.6 mm, 5 μm)
Mobile phase	Acetonitrile–water (35:65, v/v)
Flow rate	1.0 ml min^{-1}
Wavelength	282 nm
Injection volume	20.0 μl
Temperature	30 ± 1 °C

Sample preparation for content uniformity. One tablet was transferred to each 100 ml volumetric flask containing 10 ml of water pH 10 (adjusted with ammonium hydroxide). They were kept in the ultrasonic bath for 25 min, shaken for 15 min and the volume was completed with acetonitrile. Aliquots of 4 ml of the solutions were transferred to 20 ml volumetric flasks and diluted with the mixture of acetonitrile obtaining the final concentration of 40.0 μg ml^{-1}. The solutions were filtered in a 0.45 μm nylon membrane filter before the analysis. This procedure is according to the previous published method for tablets [13].

Sample preparation for acidic step. One tablet was transferred to each 100 ml volumetric flask containing 10 ml of water pH 10 (adjusted with ammonium hydroxide). They were kept in the ultrasonic bath for 25 min, shaken for 15 min and the volume was completed with acetonitrile. Aliquots of 1 ml of the solutions were transferred to 20 ml volumetric flasks and diluted with the mixture of acetonitrile-borate buffer (50:50, v/v) obtaining the final concentration of 10.0 μg ml^{-1}. The solutions were filtered in a 0.45 μm nylon membrane filter before the analysis.

2.4. Determination of sink conditions

Rabeprazole sodium sink conditions were determined in different solvents, such as: phosphate buffer pH 6.8, phosphate buffer pH 7.5 and borate buffer pH 9.0 (using an amount of drug equivalent a three times of the dose in the pharmaceutical formulation in 900 ml of medium).

2.5. Validation

In order to demonstrate the method was adequate for dissolution test purposes, it was validated through the analysis of stability, specificity, linearity, precision and accuracy parameters [17,18].

Stability. The rabeprazole stability were evaluated for at least 10 h in phosphate buffer pH 6.8, phosphate buffer pH 7.5 and borate buffer pH 9.0. The solutions were kept at 37 °C during the period of the test, verifying the chromatograms obtained by the HPLC method (peak area and degradation products formation).

Specificity. It was evaluated by preparing a placebo sample of commercial formulation of tablets in their usual concentration. This sample was transferred to a vessel with 900 ml of the dissolution medium and stirred for 2 h at 150 rpm using paddle (USP apparatus 2) and temperature of 37 °C. Aliquots of this solution were filtered and analyzed by HPLC and UV methods.

Linearity. Aliquots of a 100 μg ml^{-1} solution of rabeprazole sodium reference standard, prepared in a mixture of acetonitrile-borate buffer (50:50, v/v), were transferred to 25 ml volumetric flasks to obtain the final concentrations of 1.0, 2.0, 4.0, 5.0, 10.0 and 20.0 μg ml^{-1}. Each solution was prepared in triplicate. The linearity was evaluated by linear regression analysis, which was calculated by the least square regression method.

Precision. The evaluation of the intermediate precision of the dissolution tests was performed using a well-characterized lot of the drug product of tight content uniformity (according to USP 28) and compared with the results of the dissolution tests. The