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Aripiprazole tablets: Development and Validation of a Dissolution Methodology

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ABSTRACT: *The aim of this work was to develop and validated a dissolution methodology for aripiprazole tablets by spectrophotometry on ultraviolet light (UV). The dissolution mediums tested were 0.1 M HCl, pH 4.5–citrate buffer and pH 6.8–phosphate buffer, and it was also tested the influence of apparatus and rotation speed. After an UV scan spectrum from 400 to 200 nm to determinate the maximum wavelength absorbance, samples were analyzed by UV visible spectrophotometric method. The selected parameters were 0.1 M HCl as dissolution medium, using paddles as apparatus at rotation speed of 50 rpm, with UV analysis at 249 nm. The method was validated per ICH guidelines, and the results showed that the dissolution methodology for aripiprazole tablets with 0.1 M HCl as dissolution medium, using paddles as apparatus at 50 rpm, with analysis at wavelength of 249 nm, with sampling points at 5, 10, 15, 30, 45 and 60 minutes is specific, linear, precise and accurate and could be applied for quality control of aripiprazole tablets, since there is no official monograph.*

Keywords: *Biopharmaceutical Classification System, Pharmaceutical Equivalence,Quality control,*

I. Introduction

Drug absorption from oral solid dosage form depends on drug release and dissolution under physiological conditions and permeability through gastrointestinal tract. Because of the critical nature of these conditions, *in vitro* dissolution can be relevant to try to predict the in vivo performance [1,2]. Validation of an analytical method is a process which establishes that performance characteristics of the procedure meet the requirements for the desired analytical applications, for the developed method meet the requirements of the analytical applications, ensuring theresultsreliability[3]. Some drugs products doesn't have an official monograph described in pharmacopeias. When these occurs, there's a need to develop and validated a method for tests such as identification, assay or dissolution [4].

Aripiprazole (ARI), an antipsychotic drug used to treat schizophrenia and bipolar disorder, act combining its parcial agonist activity on D2 and 5-HT1A receptors and 5-HT2A receptors antagonis activity [5]. The aim of this work was to develop and validated a dissolution method for aripiprazole tablets by an ultraviolet method.

II. Material and Methods

2.1 Materials and equipment

All chemicals and reagents were of analytical reagent grade. Pharmaceutical company Prati–Donaduzzi (Toledo, Brazil), kindly donated aripiprazole reference substance (99.94 %). The reference drug product (Aristab®), labelled as containing 10 mg of aripiprazole and the following excipients (microcrystalline cellulose, lactose, starch, hypromellose, magnesium stearate and red iron oxide dye) were obtained commercially.

Equipment and instruments used in the present study were analytical scale (Gehaka, AG–200 model), dissolution test apparatus (Nova Ética, 301-6 AUT model), ultrasonic bath (Químis, Q355D model) and UV spectrophotometer (UV-1600 Pró–Análise).

2.2 Methodology

2.2.1 Maximum wavelength absorption determination

It was prepared three different standard solutionswith 11.11 μg/mL of aripiprazole in the following medium: 0.1 M hydrochloric acid (HCl), pH 4.5-citrate buffer and pH 6.8–phosphate buffer. The samples were submitted to an UV scan spectrum between 400 to 200 nm in order to determinate ARI maximum wavelength absorption.

2.2.2 Dissolution test conditions

Dissolution testing of tablets was performed with the reference drug product (Aristab® 10 mg) in accordance with the USP to define the dissolution test conditions. Initially, this was performed using paddles (USP apparatus II) at a stirring speed of 50 rpm and 900 mL of the following dissolution media, pre-heated to 37°C ± 0.5°C: 0.1 M HCl; pH 4.5–citrate buffer and pH 6.8–phosphate buffer. Manual sampling aliquots of 20.0

mL were withdrawn at 5, 10, 15, 30, 45 and 60 minutes, filtered in a Millex® filter and analyzed on a UV/VIS Spectrophotometer (249 nm). There was no medium replacement after the sampling. The ARI standard solution was prepared in order to obtain a final concentration of 111,11 µg/mL. After these preliminary studies, tests to determinate the apparatus (paddles and baskets) and rotation speed (50 and 100 rpm for paddles; 75 and 100 rpm for baskets) were performed using as dissolution medium 0.1 M HCl maintained at 37°C ± 0.5°C. Also, sampling aliquots of 20.0 mL were withdrawn manually at the same minutes, filtered (Millex® filter) and analyzed on a UV/VIS Spectrophotometer (249 nm), together with a standard solution of ARI in 11.11 µg/mL final concentration.

2.3 Validation

To demonstrate the method's suitability for use as a dissolution test, it was validated based on specificity, linearity, precision and accuracy parameters [6].

2.3.1 Specificity

Placebo samples of ARI reference drug (a mix of the excipients from aripiprazole tablets) were prepared empirically in their usual compositions, according to literature [7]. The placebo samples were transferred to different vessels (n=6) with 900 mL of 0.1 M HCl as dissolution medium at 37°C ± 0.5°C and stirred for 1 h at 50 rpm using a paddle (USP apparatus II). Aliquots of these solutions were filtered through a Millex® filter and analyzed by the UV method (249 nm).

2.3.2 Linearity

A stock solution was prepared containing 111.11µg/mL of ARI using 0.1 M HCl as solvent. Aliquots of this solution were transferred to volumetric flasks to obtain final concentrations of 4.44; 6.67; 8.89; 11.11; 13.33 and 15.56µg/mL. Each solution was prepared in triplicate. The linearity was evaluated by linear regression analysis, which was calculated by the least squares regression method and analysis of variance (ANOVA).

2.3.3 Precision

The evaluation of intermediate precision (inter-day precision) of the dissolution test was performed on three different days. The repeatability was evaluated on the same day for intra-day precision in six vessels used for the dissolution test. The relative standard deviation (RSD) from the results was calculated.

2.3.4 Accuracy

Accuracy was determinate by the recovery percentage of a known amount of ARI reference substance added to a placebo solution. A recovery study was conducted by adding known amounts of the ARI stock solution to the dissolution vessels containing the placebo solution (50, 100 and 150%) of the nominal assay (10 mg). Each concentration was prepared in triplicate and analyzed by the UV method at 249 nm.

III. Discussion

2.4 Dissolution method development

The first test was performed to determinate the ARI maximum wavelength absorption under UV light. The UV scan spectrum resultsshowed a maximum absorption at 249 nm, which find relation with other studies [8, 9, 10].

To develop a dissolution method, tablets must be tested in dissolution mediums ranging physiological pH (1.2 to 6.8). So, 0.1 M HCl, pH 4.5–citrate buffer and pH 6.8–phosphate buffer were evaluated to determinate which medium showed better discriminative dissolution profile to ARItablets. The results from Fig. 1 showed that there was no complete ARI dissolution on pH 6.8–phosphate buffer, where the final drug dissolution was a litter higher than 20%. Drug complete dissolution also was not achieved in pH 4.5–citrate buffer as dissolution medium, showing a final drug dissolution close to 80%. The dissolution medium which showed complete ARI dissolution was 0.1 M HCl, where the final drug release was 98.14%. Also, the dissolution profile at six points (5, 10, 15, 30, 45 and 60 minutes) showed that ARI dissolved more than 90% in 15 minutes (Fig1).

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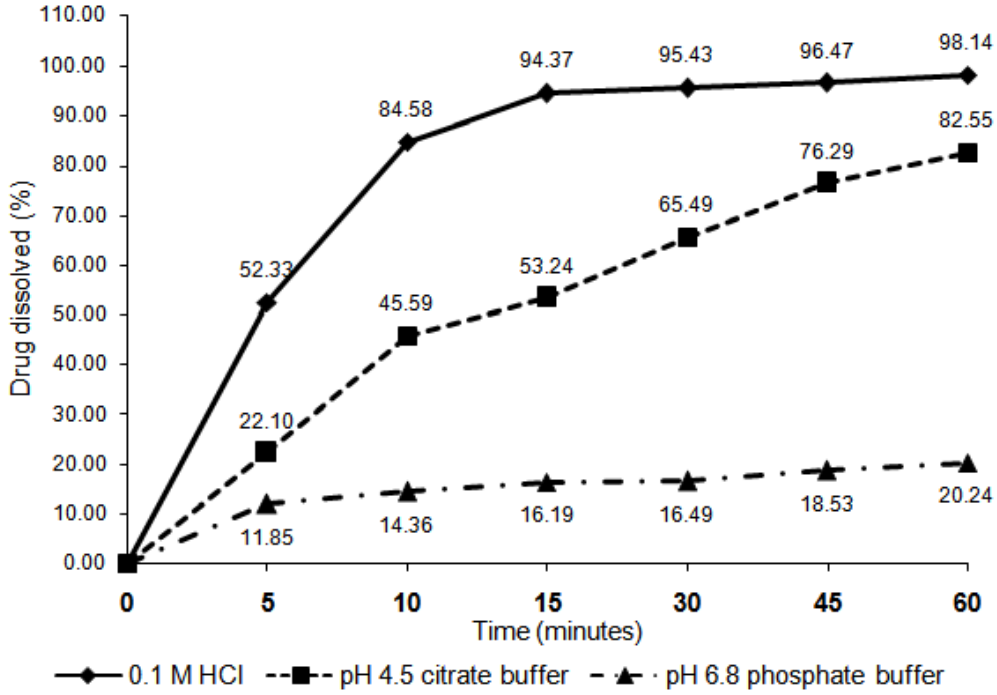

Figure 1: Aripiprazole tablets 10mg dissolution profiles in 0.1 HCl, pH 4.5–citrate buffer and pH 6.8–phosphate buffers as dissolution mediums.

After the dissolution medium was determinate, apparatus type and speed were tested. The most common dissolution conditions are basket (USP apparatus I) at 75 or 100 rpm as rotation speed and paddles (USP apparatus II) in a rotation of 50 or 100 rpm. According with Table 1 and Fig. 2, the results were similar from both apparatus types, with drug dissolution close to 100% at the end of the test. Thus, since there was no difference between the amount of ARI dissolved in both apparatus, and because the most common to tablets is paddles, the conditions selected were paddles (USP apparatus II) in a rotation of 50 rpm, because there is no need for a higher apparatus speed to provide a good drug dissolution profile.

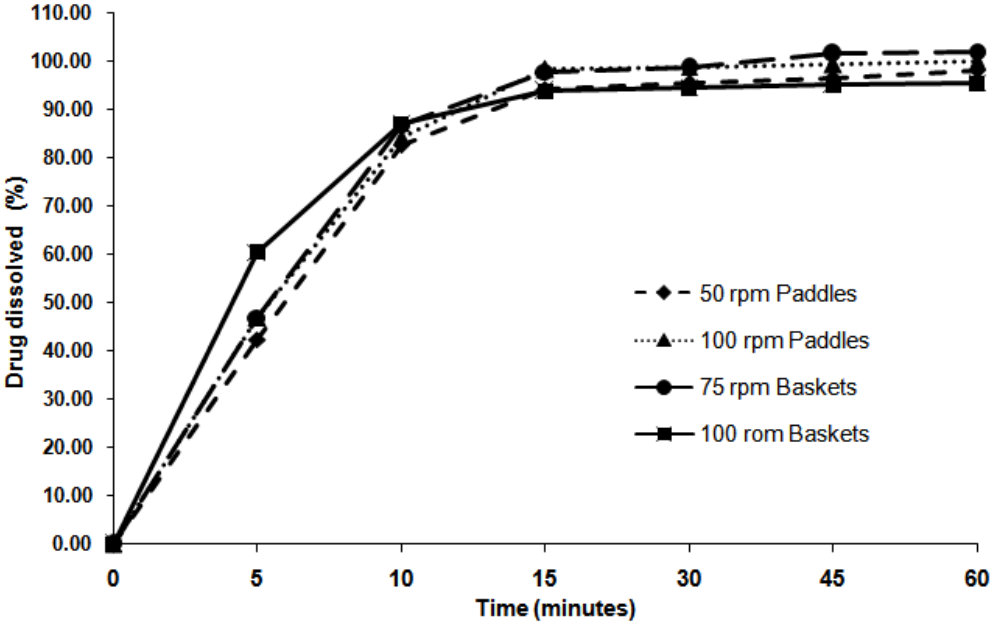

Figure 2: Dissolution profile of aripiprazole tablets 10mg in paddles (50 and 100 rpm) and baskets (75 and 100 rpm) using 0.1 M HCl as dissolution medium.

Table 1:Percentage (%) of dissolved aripiprazole tablets 10mg in paddles (50 and 100 rpm) and baskets (75 and 100 rpm) using 0.1 M HCl as dissolution medium.

Time (min)	Drug dissolved (%)			
	50 rpm Paddles	100 rpm Paddles	75 rpm Baskets	100 rpm Baskets
5	42.33	46.94	47.02	60.49
10	82.58	84.21	86.86	87.08
15	94.37	98.26	97.90	93.81
30	95.43	98.77	98.57	94.48
45	96.47	99.25	101.49	95.14
60	98.14	99.89	101.89	95.45

Based on the results, is possible to determinate that a good dissolution method for ARI tablets is using 900 mL 0.1 M HCl as dissolution medium with paddles at 50 rpm, samples withdraw at 5, 10, 15, 30, 45 and 60 minutes, filtered and analyzed at spectrophotometer at 249 nm.

2.5 Dissolution method validation

The results from specificity, defined as the ability to assess unequivocally the substance in the presence of components that may be expected to be present [12] showed that the UV method suffer no interference from the formulation of the tablet evaluated. As there was no interference from the excipients with the selected wavelength (249 nm), UV can be used in order to quantify ARI.

Generally, UV is usually used in quality control of pharmaceuticals because most of drugs absorbed energy in UV region, and is a method, which does not require a complex or expensive equipment, and there is no need for toxic solvents. In addition, by using UV method, results can be obtained faster, analysis is simpler and fewer solvents are used, making this valuable in routine analysis.

To assess linearity, three calibration curves of ARI were constructed and plotted graphically as concentration (µg/mL) versus absorbance. The results (Fig. 3) showed a good correlation coefficient (R^2: 0.9986) in the studied concentration range (4.44 to 15.56 µg/mL). The obtained representative linear equation was y = 0.0281x – 0.0053 and the data were validated by means of analysis of variance (ANOVA), which demonstrated a significant linear regression and no significant linearity deviation ($p < 0.01$). According to obtained results, linearity was proved because an appropriate linear correlation was found since the obtained correlation coefficients showed values higher than 0.99 [6].

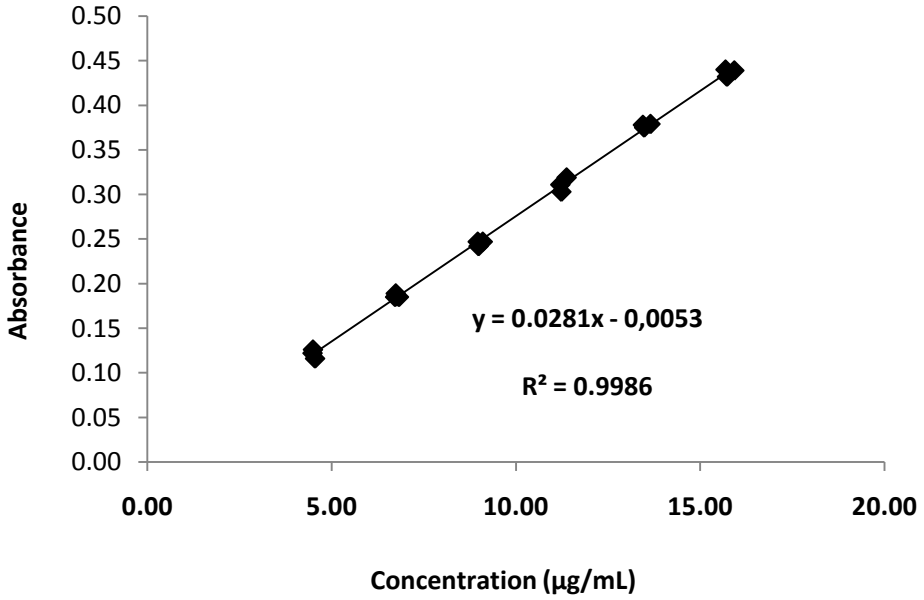

Figure3: Linearity curve of aripiprazole standard solution in 0.1 M HCl (µg/mL).

Precision of the method was determined by measuring the repeatability and intermediate precision. The results showed a low relative standard deviation (RSD) ranging from 0.15 to 0.38% for intra-day precision and 0.24% for inter-day precision. As RSD values were lower than 5%, the results indicated the good precision of this method [13].

The accuracy of the analytical procedure, which is the accordance between the accepted value and the value found, was demonstrated by the recovery of known amounts of ARI in the dissolution vessels. In the present study, three concentrations were evaluated (5.56; 11,11 and 16.65 μg/mL) and each concentration was measured three times. The recovery percentage found ranged from 100.30 to 100.44%, with a RSD of 0.32%, indicating method's accuracy. As the measured recovery is typically 95–105%, the results indicated good accuracy of the method. The recovery percentage was calculated in triplicate and the mean value was considered [13].

IV. Conclusion

A discriminative dissolution method to evaluate aripiprazole tablets was successfully developed and demonstrate to be an easy, fast and simple method. The conditions allowing dissolution determination were 900 mL of 0.1 M HCl as dissolution medium at 37.0 ± 0.5 ºC, using USP type II apparatus (paddles) at 50 rpm and analysis by spectrophotometric detection in a wavelength of 249 nm. The spectrophotometric method was validated and showed to be specific, linear, precise and accurate. The developed method is suitable for its purpose and could be applied in routine quality control of aripiprazole tablets since there is no official monograph using spectrophotometric method for this drug in the pharmacopoeias.

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