Development and Validation of a Dissolution Method for Desloratadine Coated Tablets

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Abstract

The aim of this work was the development and validation of a dissolution methodology for desloratadine-coated tablets by spectrophotometry on ultraviolet (UV). 0.1 M hydrochloric acid (HCl), pH 4.5-citrate buffer and pH 6.8 phosphate buffer were tested as dissolution medium. In addition, influences of apparatus, and rotation speed were evaluated. After an UV scan spectrum from 500 to 200 nm, to determine the maximum wavelength absorbance, samples were analyzed by UV visible spectrophotometric method. The parameters selected were 0.1 M HCl as dissolution medium, using paddles as apparatus at 50 rpm, with analysis at wavelength of 280 nm. The method was validated as per ICH guidelines, and the results showed that the dissolution methodology for desloratadine-coated tablets with 0.1 M HCl as dissolution medium, using paddles as apparatus at 50 rpm, with analysis at wavelength of 280 nm, with sampling points at 5, 10, 15 and 30 minutes is specific, linear, precise and accurate and could be applied for quality control of desloratadine tablets, since there is no official monograph.

1 Introduction

The dissolution tests allow to obtain information regarding the drug biological availability, being recognized also as an important tool to pharmaceutical companies on development and quality control, because helps on the research and development to guide the best formulation and ensure the lot-to-lot quality of pharmaceutical dosage forms or for justifying post-approval product changes such as in the formulation and the manufacturing process1-9.

Dissolution is the only test that addresses product performance, therefore when developing a dissolution methodology, the knowledge related to solubility, permeability, and pharmacokinetics of the drug should be considered and the test must be capable to display the maximum discriminative profile and, also to allow to detect any deviation in quality standards initially proposed. The results from dissolution assays provides important information, including to establish in vitro/in vivo correlation2, 7, 10-14.

Methodology validation enables to know limitations and reliability of measurements performed. Per official codex, validation process is essential to ensure that the analytical method is suitable for the intended purpose, demonstrating reliable information through parameters such as specificity, linearity, accuracy and precision suitable for analysis2, 15-21.

Desloratadine, (8-Chloro-11-piperidin-4-ylidene-6,11-dihydro-5H-cyclohepta[5,6]cyclohepta[1,2-b]pyridine), an off white powder, slightly soluble in water e very soluble in ethanol and propylene glycol, is used to relief of symptoms of seasonal allergic rhinitis, perennial (non-seasonal) allergic rhinitis by blocking the action of histamine, acting as an antihistamine drug, is commercially available in Brazil by the brand name of Desalex® as coated tablets with a labeled amount of 5 mg, and also available as 0.5 mg/mL syrup. Desloratadine is classified, according to Biopharmaceutical Classification System (BCS) as a Class I drug21-23.
Therefore, since there’s no official method describe in pharmacopoeias, this paper describes the development and validation of a dissolution test for desloratadine coated-tablets using a simple, fast and inexpensive ultraviolet method. The development and validation were carried out in compliance with the International Conference on Harmonization\textsuperscript{17}.

2 Materials and Methods

All chemicals and reagents were of analytical reagent grade. Desloratadine reference substance (99.82 \%) was kindly donated by the pharmaceutical company Prati-Donaduzzi (Toledo, Brazil). The reference drug product (Desalex\textsuperscript{5}), labelled as containing 5 mg of desloratadine and the following excipients (dibasic calcium phosphate, microcrystalline cellulose, starch, talc, hypromellose, titanium dioxide, polyethylene glycol, white wax and carnauba wax) 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 (Quimis, Q355D model) and UV spectrophotometer (UV-1600 Pró–Análise).

2.1 Methodology

2.1.1 Maximum wavelength absorption determination

Standard solutions with 5.56 \(\mu\)g/mL of desloratadine were prepared in the following medium: 0.1 M hydrochloric acid (HCl), pH 4.5-acetate buffer and pH 6.8 phosphate buffer. The samples were submitted to an UV scan spectrum between 500 to 200 nm to determine desloratadine maximum wavelength absorption.

2.1.2 Dissolution test conditions

Dissolution testing of tablets was performed with the reference drug product (Desalex\textsuperscript{5} 5 mg), to define the method conditions. Initially, to determine the more discriminating dissolution medium, using paddles (USP apparatus II) at a stirring speed of 100 rpm, a volume of 900 mL of the following dissolution media, pre-heated to 37 °C ± 0.5 °C, were tested: 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 and 60 minutes, filtered in a Millex\textsuperscript{6} 0.45 \(\mu\)m filter and analyzed on a UV/VIS Spectrophotometer (280 nm). There was no sample dilution nor medium replacement after the sampling. The desloratadine standard solution was prepared to obtain a final concentration of 5.56 \(\mu\)g/mL.

With the results of the dissolution medium, tests to determine 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 that one with better results, maintained at 37 °C ± 0.5 °C. Again, samples of 20.0 mL were withdrawn manually at 5, 10, 15, 30, 45 and 60 minutes, filtered (0.45 \(\mu\)m Millex\textsuperscript{6} filter) and analyzed on a UV/VIS Spectrophotometer (280 nm), along with a desloratine standard solution in 5.56 \(\mu\)g/mL final concentration.

To perform the filter evaluation, tests were performed in the mentioned dissolution mediums and the samples withdrawn were not filtered. Filtration of dissolution samples is usually necessary to prevent undissolved drug particles from entering the analytical sample and removes insoluble excipients that otherwise cause high background or turbidity. The filter evaluation is necessary to verify whether it can be used in the dissolution test without adsorption of the drug into the filter\textsuperscript{24}.

2.1.3 Validation

To demonstrate the method’s suitability for use as a dissolution test, it was validated based on specificity, linearity, precision and accuracy parameter\textsuperscript{16, 25}.

2.1.3.1 Specificity

Placebo samples of desloratadine, a mix of the excipients from the desloratadine reference drug tablets (Desalex\textsuperscript{5}) were prepared in their usual compositions, according to literature\textsuperscript{22, 26}. 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 30 minutes at 50 rpm using a paddle (USP apparatus II). Aliquots of these solutions were filtered through a Millex\textsuperscript{6} filter and analyzed by the UV method (280 nm).

2.1.3.2 Linearity

Desloratadine stock solutions at 55.55 mg/mL, using 0.1 M HCl as solvent, were prepared. Aliquots of this solution were transferred to volumetric flasks to obtain final concentrations of 1.11; 2.78; 4.17; 5.56; 6.94 and 8.33 \(\mu\)g/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).

2.1.3.3 Precision

Precision was evaluated on two levels, repeatability and intermediate 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, in a concentration of 5.56 \(\mu\)g/mL. The relative standard deviation (RSD) from the results was calculated.

2.1.3.4 Accuracy

Accuracy was determinate by the recovery percentage of a known amount of desloratadine reference substance added to a placebo solution. A recovery study was conducted by adding known amounts of the desloratadine stock solution to the dissolution vessels containing the placebo solution at 50 % (2.78 \(\mu\)g/mL), 100 % (5.56 \(\mu\)g/mL) and 150 % (8.25 \(\mu\)g/mL) of

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the nominal assay (5 mg). Each concentration was prepared in triplicate and analyzed by the UV method at 280 nm.

3 Results and Discussion

3.1 Dissolution method development

To determine which wavelength desloratadine shows UV absorption, an UV scan spectrum between 500–200 nm was performed. The results demonstrated that desloratadine showed a maximum absorption at 280 nm (Figure 1).

![Fig. 1: UV spectrum of desloratadine solution at 5.56 µg/mL in 0.1 M HCl](image)

During the development of a dissolution methodology, different parameters were evaluated. As dissolution method development for immediate release drugs must be tested in dissolution mediums ranging physiological pH (1.2 to 6.8), the dissolution medium selected 0.1 M HCl, pH 4.5-citrate buffer and pH 6.8-phosphate buffer were evaluated to determine which medium showed better discriminative dissolution profile. The results (Table 1 and Figure 2) demonstrated that pH 4.5-citrate buffer and pH 6.8-phosphate buffer as dissolution mediums showed dissolution profiles very similar, with an initial dissolution around 70 % (71.64 % and 14.72 %, respectively). However, both medium doesn’t allowed total desloratadine dissolution, since the final drug dissolution was 74.76 % for pH 4.5-citrate buffer and 80.79 % for pH 6.8-phosphate buffer.

The dissolution medium where desloratadine showed complete dissolution, was 0.1 M HCl. Also, the dissolution profile at five points (5, 10, 15, 30 and 60 minutes) showed that the drug dissolved more than 85% in 15 minutes (Table 1 and Figure 2), classifying desloratadine as very rapidly dissolving drug. As desloratadine is an antihistamine drug used to relieve allergy symptoms, it must be ready to act in the body around 30 minutes after the drug intake, a rapidly drug dissolution is required for immediate-release dosage forms. This results, corroborates with the fact that desloratadine is classified as a Class I drug (high solubility and high permeability) in Biopharmaceutical Classification System (BCS). The results indicated that 0.1 M HCl was selected as dissolution medium.

<table>
<thead>
<tr>
<th>Time</th>
<th>0.1 M HCl</th>
<th>pH 4.5-acetate buffer</th>
<th>pH 6.8-phosphate buffer</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>90.56%</td>
<td>74.72%</td>
<td>74.72%</td>
</tr>
<tr>
<td>10 min</td>
<td>95.35%</td>
<td>74.35%</td>
<td>78.88%</td>
</tr>
<tr>
<td>15 min</td>
<td>97.69%</td>
<td>78.74%</td>
<td>81.06%</td>
</tr>
<tr>
<td>30 min</td>
<td>98.84%</td>
<td>79.16%</td>
<td>84.98%</td>
</tr>
<tr>
<td>60 min</td>
<td>100.75%</td>
<td>83.79%</td>
<td>87.14%</td>
</tr>
</tbody>
</table>

![Fig. 2: Dissolution profiles of desloratadine tablets in 0.1 M HCl, pH 4.5-acetate buffer and pH 6.8-phosphate buffer as dissolution mediums](image)
with values higher than 99 % of drug dissolved, the time of the dissolution test was set on 30 minutes, because since there was no more drug to be dissolved after 30 minutes of test, there’s no reason to keep the test performing for 30 minutes longer.

Table 2: Percentage of dissolved desloratadine tablets in paddles (50 and 100 rpm) and baskets (75 and 100 rpm) using 0.1 M HCl as dissolution medium

<table>
<thead>
<tr>
<th>Time</th>
<th>50 rpm Paddles</th>
<th>100 rpm Paddles</th>
<th>75 rpm Baskets</th>
<th>100 rpm Baskets</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>84.72%</td>
<td>91.17%</td>
<td>82.35%</td>
<td>88.13%</td>
</tr>
<tr>
<td>10 min</td>
<td>92.67%</td>
<td>94.40%</td>
<td>83.65%</td>
<td>88.88%</td>
</tr>
<tr>
<td>15 min</td>
<td>94.74%</td>
<td>97.15%</td>
<td>87.34%</td>
<td>91.06%</td>
</tr>
<tr>
<td>30 min</td>
<td>96.09%</td>
<td>98.78%</td>
<td>89.19%</td>
<td>94.96%</td>
</tr>
<tr>
<td>60 min</td>
<td>98.08%</td>
<td>99.90%</td>
<td>92.32%</td>
<td>96.16%</td>
</tr>
</tbody>
</table>

Fig. 3: Dissolution profile of desloratadine tablets in paddles (50 and 100 rpm) and baskets (75 and 100 rpm) using 0.1 M HCl as dissolution medium.

Based on the results, is possible to determinate that a good dissolution method for desloratadine-coated tablets is using 900 mL 0.1 M HCl as dissolution medium with paddles at 50 rpm, samples withdraw at 5, 10, 15 and 30 minutes, filtered and analyzed at spectrophotometer at 280 nm.

3.2 Dissolution method validation

For the developed dissolution method meets the requirements of the analytical applications, ensuring results reliability, it should be validated.

To the results of specificity, analysis of desloratadine placebo solutions showed that the UV method suffer no interference from the formulation of the tablet evaluated, demonstrating to be specific (Figure 4). Since there was no interference from the excipients with the selected wavelength (280 nm), UV can be used to quantify desloratadine. Analysis by UV are 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 desloratadine were constructing and plotted graphically as concentration (µg/mL) versus absorbance. The results showed a good correlation coefficient (R²: 0.9994) in the studied concentration range (1.11; 2.78; 4.17; 5.56; 6.94 and 8.33 µg/mL). Also, the representative linear equation was y = 0.0432x + 0.0019 and the data were validated by means of the analysis of variance (ANOVA), which demonstrated significant linear regression and no significant linearity deviation (p < 0.01). According to the results, linearity was proved because an appropriate linear correlation was found since the obtained correlation coefficients showed values higher that 0.99.

The method showed precision by measuring the repeatability and intermediate precision on the concentration of 5.56 µg/mL. The results from intra-day precision showed a relative standard deviation (RSD) of 0.82, 0.71 and 1.58 % from each of the three days and an RSD of 1.04 % for inter-day precision. As RSD values were lower than 5 %, the results indicated the good precision of this method.

The accuracy of the analytical procedure, the accordance between the accepted value and the value found, was demonstrated by the recovery of known amounts of desloratadine in the dissolution vessels. In the present study, three concentrations were evaluated (2.78, 5.56 and 8.25 µg/mL) and each concentration was measured three times. The average recovery percentage found was 101.37 % with a RSD of 0.90 %, 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.

Fig. 4: UV spectrum of desloratadine and excipients solutions for specificity.
4 Conclusions
A discriminative dissolution method to evaluate desloratadine 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 280 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 desloratadine tablets since there is no official monograph using spectrophotometric method for this drug in the pharmacopoeias.

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6 Conflict of interests
No conflict of interest has been declared by the authors.

7 Author’s contributions
Research was designed by BRF and TRS. BRF carried out literature review and BRF, LMT and FZP carried out data acquisition/analysis/interpretation and manuscript preparation. BRF worked out the final draft of the manuscript and TRS, the corresponding author, review manuscript draft and all the authors approved the final manuscript.

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