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In Vitro Pharmaceutical Quality Evaluation of Loratadine Tablets in Saudi Arabia

Hesham Alangari[1], Abdul Ahad[1], and Fahad I. Al-Jenoobi[1*]

[1]Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
**Corresponding author*

e-mail: aljenobi@ksu.edu.sa

ABSTRACT

Introduction: Loratadine (LOR) is a widely used second-generation antihistamine that blocks histamine H_1 receptors and relieves allergic symptoms. A variety of LOR brands are marketed in Saudi Arabia. The objective of this study was to compare the dissolution characteristics of various generic brands of LOR tablets with the innovator product available in Saudi Arabia. **Methods:** The dissolution study was conducted with four generic LOR products (LOR2, LOR3, LOR4, and LOR5) and the innovator product (LOR1) using the United States Pharmacopeia (USP) paddle apparatus in two different dissolution media, i.e., 0.1-N hydrochloric acid (HCl) and acetate buffer (pH 4.5). Samples were collected at specified time intervals and analyzed for in vitro drug release using ultraviolet (UV) spectrophotometry. **Results:** After 60 minutes in 0.1-N HCl, LOR1 (Ref), LOR2, LOR3, LOR4, and LOR5 presented cumulative mean ± SD drug release of 91.91% ± 1.67%, 90.88% ± 3.64%, 92.26% ± 2.77%, 96.08% ± 2.27%, and 94.15% ± 1.55%. In acetate buffer (pH 4.5), the cumulative drug release was 87.94% ± 5.05%,78.52% ± 4.04%, 105.35% ± 1.83%, 87.71% ± 2.53%, and 88.47% ± 2.07% for LOR1, LOR2, LOR3, LOR4, and LOR5 respectively after 1 h. The drug content of all studied tablet products was within the acceptable range. **Conclusion:** Rapid dissolution of LOR tablets was observed for all products in 0.1-N HCL; however, in acetate buffer (pH 4.5), one generic product (LOR2) exhibited a slightly lower release rate of LOR than the innovator product. This study highlights the importance of a comprehensive evaluation of generic products available in local market when considering the interchangeability between innovator and generic products.

Keywords: Antihistamine, dissolution, loratadine, solubility, drug assay

INTRODUCTION

Loratadine (LOR) is a widely used antihistamine medication that belongs to the class of second-generation H_1-receptor antagonists (Fig. 1). LOR is a Biopharmaceutics Classification System (BCS) class II drug, and the reported solubility of LOR in water is 3.27 µg/mL (*1*). As an antihistamine, LOR works by selectively blocking the H_1-receptors in the body (*2*). Histamine is a natural substance released by the immune system during an allergic reaction, triggering symptoms such as sneezing, itching, runny nose, and watery eyes. By blocking the action of histamine, LOR helps to relieve these symptoms and provides relief to individuals suffering from allergies.

LOR is available in various forms, including tablets, chewable tablets, fast melting, and oral suspensions. It is typically taken once daily, providing long-lasting relief from allergy symptoms (*3, 4*).

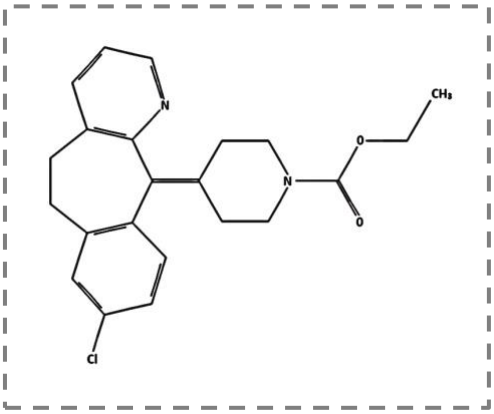

Figure 1. The chemical structure of loratadine.

The availability of quality generic drug products plays a critical role in enhancing cost-effectiveness and expanding access to healthcare services. These products offer affordable alternatives to their branded counterparts, making essential medications more accessible to a wider population. However, continuous evaluation and monitoring are essential to ensure that the desired level of quality is upheld throughout the post-marketing phase. Regular assessment of generic drug products is necessary to verify their adherence to quality standards and to identify any potential deviations or variations that may impact their efficacy and safety. The significance of post-marketing assessment lies in its ability to provide an evidence-based approach to decision-making. One of the major challenges in designing a solid dosage form formulation is to optimize tablet dissolution, specifically when it comes to a drug with low solubility like LOR. Dissolution analysis is essential to assess the quality of a pharmaceutical product (*5*–*7*). By conducting regular assessments of dissolution, regulatory agencies and healthcare providers can ensure the continued quality and efficacy of generic drug products. This proactive approach allows for timely identification of any dissolution-related issues and enables appropriate corrective actions to be taken. Ultimately, it helps to maintain confidence in the therapeutic equivalence of generic drug products, ensuring that patients receive the intended benefits of these cost-effective alternatives.

In a study of LOR products in Pakistan, all investigated brands released greater than 80% within 45 minutes, and the authors concluded that most LOR products were in compliance with the quality control requirements for British Pharmacopeia (BP) and *United States Pharmacopeia* (USP) (*8*). Researchers in Bangladesh found that 10-mg LOR tablets produced and marketed by several Bangladeshi companies conformed to the quality standards required for effective therapy (*9*). In Africa, authors reported that among the brands evaluated, six generics products failed to meet pharmaceutical properties standards, and only two brands were pharmaceutically equivalent to the innovator brand (*10*). In the light of the above observation, the objective of the present study was to compare the dissolution performance of generic and innovator LOR tablet products marketed in Saudi Arabia.

LOR is rapidly absorbed and achieves peak plasma concentration in 1-2 h, while its main metabolite achieves peak plasma concentration in 3-4 h. LOR undergoes extensive first pass metabolism in the liver and is metabolized by CYP2D6, CYP1A1, CYP2C19 and primarily by CYP3A4. The bioavailability of LOR is reported to be approximately 40% (*11*–*14*).

METHODS

Materials

Hydrochloric acid (HCl) and potassium dihydrogen phosphate were procured from Riedel-De Haen AG, Germany. Sodium acetate and sodium hydroxide were provided by BDH laboratories and supplies, Poole, England, and Merck-Darmstadt, Germany, respectively. Acetonitrile and methanol were sourced from Sigma (USA) and Panreac (Spain), respectively. Purified water was sourced from Milli-QR purification system (Millipore, France).

Sample Collection

The LOR samples (four generic brands [LOR2, LOR2, LOR3, and LOR5] and one innovator brand [LOR1]) were collected from different community pharmacies. The pharmacies were chosen randomly, and for all brands, the batch number and expiry date were recorded. A strength of 10 mg was selected for the comparison.

Identification Test

A high-performance liquid chromatography (HPLC) system (Shimadzu, Japan) was employed to verify the actual pharmaceutical agent contained within the tablets. The experiment involved comparing peak retention times for the LOR1, LOR2, LOR3, LOR4 and LOR5 solutions and the LOR standard solution (*6*, *15*).

Preparation of Standard Curve

An accurately weighed amount of standard LOR powder (10 mg) was placed in a 10-mL volumetric flask. The volumetric flask was filled with methanol solution up to the 10-mL mark to prepare a solution with an LOR concentration of 1 mg/mL. Various concentrations of LOR solutions were prepared in 0.1-N HCL (1–15 µg/mL) and in acetate buffer (pH 4.5) (0.5–15 µg/mL). An ultraviolet (UV) spectrophotometer (V-530, Jasco, Japan) was used to measure absorbance at 280 nm against a blank, and the absorbance was plotted against the concentrations to obtain the standard curve.

In Vitro Dissolution Studies

According to the LOR *USP* monograph, 0.1-N HCl is the recommended dissolution medium for dissolution tests (*16*). In present investigation, in addition to 0.1-N HCl, LOR dissolution was also studied in acetate buffer (pH 4.5). The dissolution test was performed utilizing a USP dissolution apparatus 2 (paddle) (Sotax, Switzerland). The dissolution medium of pH 4.5 was prepared by using sodium acetate in purified water. The dissolution test was conducted separately in each media using 900 mL of 0.1 N HCL solution or 900 mL of sodium acetate buffer (pH 4.5) at 37 ± 0.5 °C. The paddle was set to rotate at 50 rpm. The sampling was performed by withdrawing and replacing 5 mL of the dissolution media using a pipette at specific time intervals up to 60 min. The pipetted samples were filtered using Whatman filter paper (grade 1). The amount of LOR released from the tablets was determined using UV spectrophotometer at 280 nm.

Drug Assay

For the drug content assay, the sample was prepared by dissolving 10 tablets of LOR in a 250-mL volumetric flask, with the addition of 100 mL of 0.1-N HCl and shaking for 40

minutes. A 75-mL mixture of methanol and acetonitrile was added in 1:1 ratio. Then a 20-mL water solution of dibasic potassium phosphate was added and mixed for 5 min. The sample was diluted to obtain a LOR concentration of 0.4 mg/mL. The drug was quantified using HPLC Nucleodur C_{18} (5 µm, 150 × 4.6 mm) column. The mobile phase was methanol, acetonitrile, and 0.01-M dibasic potassium phosphate (6:6:7). The flow rate of mobile phase was set at 1.5 mL/min. The drug was quantified by UV spectrophotometry at 254 nm.

RESULTS AND DISCUSSION

To reduce the risk of obtaining low-quality medications from the supply chain, it is important to assess the quality of available drugs in the market. In this study, the focus was on evaluating the consistency of different generics of LOR tablets in Saudi Arabia. Comprehensive quality control tests were conducted on all available LOR tablet brands to determine their dissolution rate and drug content.

The packaging and labeling details of LOR products are presented in Table 1. All tested products demonstrated acceptable physical characteristics with uniform color, size, and shape. No surface contamination or structural defects were observed.

Table 1. Packaging and Labeling Information for Loratadine (LOR) Tablets

Product	Uniformity of Tablets	Strength (mg/tablet)	Dosage Statement	Batch or Lot no.	Storage Condition	Expiry date
LOR1 (Ref)	✓	✓	✓	✓	✓	02/2025
LOR2	✓	✓	✓	✓	✓	01/2026
LOR3	✓	✓	✓	✓	✓	01/2027
LOR4	✓	✓	✓	✓	✓	07/2024
LOR5	✓	✓	✓	✓	✓	09/2025

✓*indicates presence of information.*

Identification Test

The peak retention time of LOR in samples prepared from tablets ranged from 9.927–10.007 min. The peak retention times for the standard sample, LOR1, LOR2, LOR3, LOR4, and LOR5 were 9.945, 10.007, 9.953, 9.953, 9.929, and 9.927 min, respectively. There was no difference between the peak retention times of samples prepared from LOR tablets (LOR1–LOR5) and those obtained from the LOR standard samples. This verified the identity of the LOR contained in the dosage form (*6, 16*).

In Vitro Dissolution Study

In vitro dissolution testing has become an essential tool in assessing the release properties and consistency of product batches. It plays a vital role in evaluating the dissolution behavior of solid dosage forms, particularly for drugs with low solubility such as LOR. According to reports, it is possible that poor dissolution of a dosage form restricts absorption of an active substance (*17, 18*). LOR is considered within the category of low solubility and high permeability. By conducting dissolution studies, we can gain insights into the amount of drug that is readily available for absorption.

For LOR analysis, calibration curves were prepared in 0.1-N HCL (1–15 µg/mL) and in acetate buffer pH 4.5 (0.5–15 µg/mL). A plot of absorbance versus concentration was produced for standard samples. LOR calibration curves in 0.1-N HCL (Fig. 2A) and

acetate buffer pH 4.5 (Fig. 2B) were linear in the calibration range, with R^2 values of 0.9994 and 0.9996, respectively, indicating a strong correlation. The quality control samples (low, medium, and high) revealed accuracy of 102.00%, 99.72%, and 99.34% in 0.1N HCL, and in acetate buffer (pH 4.5), accuracy was 101.79%, 101.32%, and 99.14%, respectively.

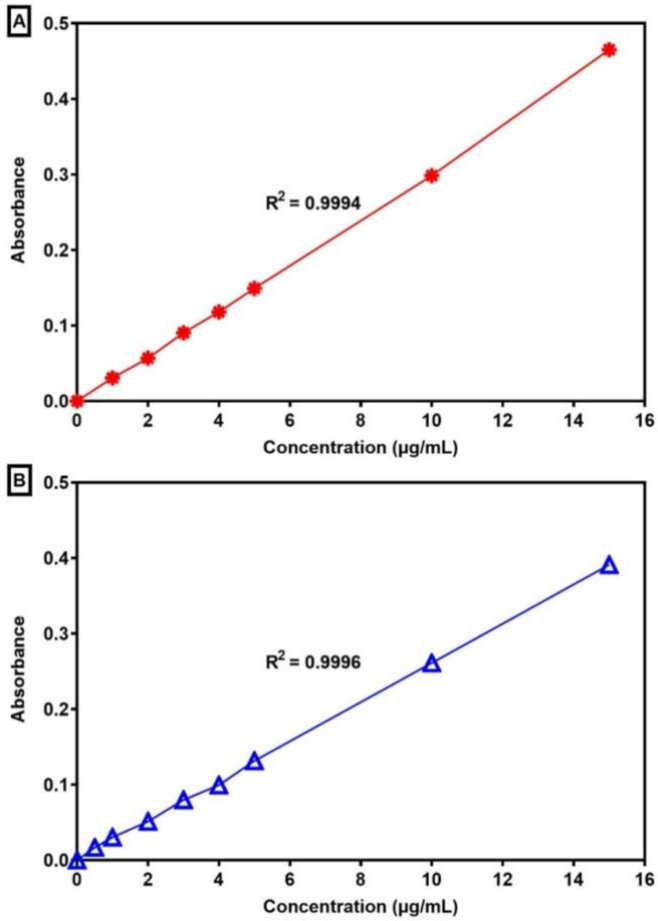

*Figure 2. Calibration curve of loratadine (LOR) in (**A**) 0.1-N hydrochloric acid and (**B**) acetate buffer (pH 4.5).*

In Vitro Dissolution in 0.1 N HCl

All tested tablet formulations (LOR1–LOR 5) exhibited extremely quick dissolution, releasing at least 85% of LOR content within 15 min in 0.1-N HCL (Fig. 3). For LOR1, LOR2, LOR3, LOR4, and LOR5, the mean ± SD cumulative drug release values were 86.86% ± 2.91%, 89.04% ± 3.16%, 95.35% ± 11.79%, 94.36% ± 2.50%, and 91.34% ± 1.62% at 15 min in 0.1N HCl media. The USP monograph recommends that at least 80% of the drug is released within 1 hour (Ref). After 60 minutes, the cumulative drug release values for LOR1–LOR5 were 91.91% ± 1.67%, 90.88% ± 3.64%, 92.26% ± 2.77%, 96.08% ± 2.27%, and 94.15 ± 1.55% in 0.1N HCl.

Numerous generic drugs are seen as more cost-effective in comparison to their innovator owing to a range of price differences between them. However, it is necessary for a generic product to demonstrate that it is similar to the innovator product to be approved for marketing (*19–21*). In our study, the investigated generic LOR products were equivalent to the innovator in terms of drug released in 0.1 N HCL media.

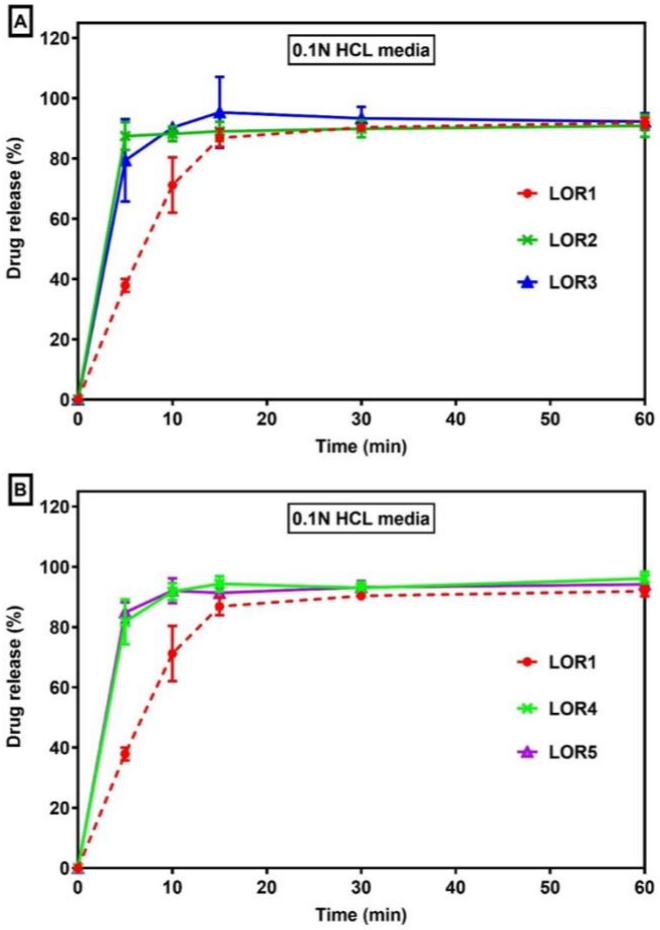

*Figure 3**.** Comparative drug release of loratadine (LOR) from tablets in 0.1-N hydrochloric acid. (**A**) LOR1 (Ref), LOR2, and LOR3. (**B**) LOR1 (same as in A), LOR4, and LOR5.*

In Vitro Dissolution in pH 4.5 Buffer

Dissolution studies of various drugs are commonly conducted using a pH 4.5 buffer. Acetate buffer (pH 4.5) was used in this study because it simulates the small intestine condition, providing valuable insight into drug availability variations and influencing an in vitro-in vivo correlation (*22*). Hence, in addition to the official dissolution media (0.1-N HCL), we conducted LOR dissolution studies in the acetate buffer (pH 4.5).

The dissolution test data revealed that in buffer pH 4.5, the innovator product (LOR1) released 87.94% ± 5.05% in 1 h, and the generic products (LOR2–LOR5) released of 78.52% ± 4.04%, 105.35% ± 1.83%, 87.71% ± 2.53%, 88.47% ± 2.07%, respectively, after 1 h (Fig. 4). Brands LOR1, LOR4, and LOR5 showed nearly identical drug release in buffer pH 4.5 media, whereas LOR2 and LOR3 differed (Fig. 4). The dissolution study at pH 4.5 revealed that one out of the four generic products (LOR2) struggled to release LOR at a similar rate as the reference product. The observed deviation in generic drug release percentages emphasizes the importance of evaluating generic formulation dissolution behavior.

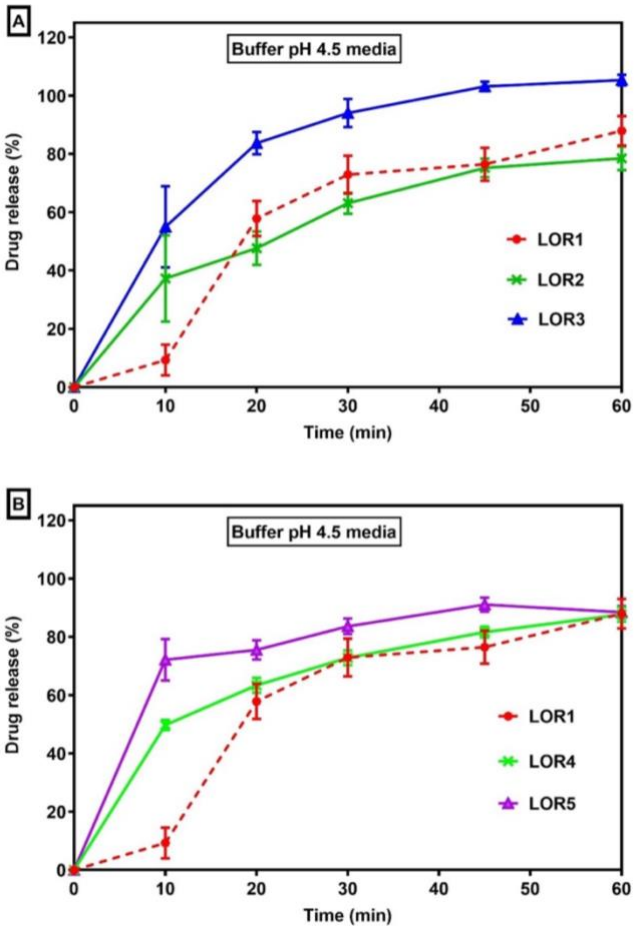

*Figure 4. Comparative drug released loratadine (LOR) from tablets in acetate buffer pH 4.5. (**A**) LOR1 (Ref), LOR2, and LOR3. (**B**) LOR1 (same as in A), LOR4, and LOR5.*

Drug Assay

Analyzing the drug content versus the label claim is an important quality control parameter for tablets. Furthermore, precise drug content testing is essential for patient care because it ensures that patients are receiving safe and effective medication. Drug content variations can have a serious impact on clinical outcomes (*23–25*).

In the present study, products LOR1, LOR2, LOR3, LOR4, and LOR5 presented drug content values of 99.79% ± 0.26%, 101.31% ± 0.38%, 100.77% ± 0.41%, 105.42% ± 1.96%, and 109.00% ± 0.07%, respectively. All studied tablet products were within the acceptable range (90–110%) as specified in the USP monograph for LOR tablets.

CONCLUSION

This study provides valuable insight into the dissolution and drug content properties of the various LOR products available in Saudi Arabia. Rapid dissolution and acceptable LOR release were observed for all products in 0.1-N HCL media. When tested in acetate buffer (pH 4.5), one generic product (LOR2) showed a slightly lower release as compared to the innovator product. All products had acceptable levels of drug content. The results of this study confirm the importance of comprehensive quality assessment for ensuring the safety and effectiveness of generic drug alternatives.

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DISCLOSURES

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