ORIGINAL RESEARCH

Quality Evaluation of some Commercially Available Brands of Loratadine Tablets in Plateau State, Nigeria

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ABSTRACT

Background: Loratadine is a tricyclic, non-sedative histamine (H1)-receptor antagonist that is indicated for the treatment of allergic rhinitis and chronic idiopathic urticaria. Due to its high demand in Plateau State, Nigeria which has peculiar cold weather conditions, the drug is prone to falsification by unscrupulous individuals.
Objectives: This study was carried out to assess the chemical, physicochemical and biopharmaceutical quality of six brands of loratadine tablets marketed in the state.
Methods: Quality parameters such as uniformity of weight, crushing strength, friability, disintegration and dissolution were evaluated using standard Pharmacopoeial methods. The content of active pharmaceutical ingredients in the brands was also determined using a validated UV spectrophotometric method.
Results: The thickness (2.355 – 3.804 mm), diameter (7.195 -10.141 mm), uniformity of weight (0.0748 – 0.2462 g) and friability (0.10 – 0.28 %) of all the tested brands fell within acceptable limits. The crushing strength ranged between 3.10 – 8.80 KgF with four brands having values outside the acceptable range. Disintegration time for the brands ranged from 3.43 to 24.54 minutes. Two brands, LO2 and LO4, had content of active ingredient of 60 and 68% respectively which are below the Pharmacopoeial requirement. In the dissolution studies, three out of the six brands did not release up to 80% of active drug within one hour as required by official specification.
Conclusion: The study found that some of the tested brands of loratadine did not meet the Pharmacopoeial quality requirements hence there is an urgent need for continuous post-marketing surveillance of medicines.

Keywords: Loratadine; Quality control; GMP; Antihistamines; Tablets

INTRODUCTION

Allergic conditions such as rhinitis and urticaria are becoming increasingly prevalent[1] and have turned out to be diseases of global health concern due to the massive impact they have on the quality of life of the affected segments of the population[2]. The prevalence of allergic rhinitis varies according to demographic category and geographic location and in certain studies, has been found to be as high as 40 % in some areas[3]. A recent study in Nigeria similarly found high prevalence of rhinitis and asthma

across the country[4]. Allergic diseases are mainly caused by the release of histamine[5] and other mediators in response to a number of allergenic triggers such as pollen, cold weather, dust[6] *et cetera*. Antihistamines which inhibit H1-receptors constitute some of the first line treatments for these allergic conditions[7]. They may be classified into first, second and third generation H1-receptor antagonists[8].

Loratadine is a long-acting, tricyclic second-generation antihistamine with selective peripheral histamine H1-receptor antagonist activity[9]. It is categorized as a Biopharmaceutics Classification System (BCS) class 2b compound (weak base); that is, a solubility limited, poorly soluble and highly permeable drug[10]. The molecule has one major active metabolite (desloratadine), which is four times more active than the parent drug and showing a longer elimination half-life (20 versus 10 hours, respectively)[11]. It is indicated for the symptomatic relief of allergies such as hay fever/ allergic rhinitis[12], urticaria (hives), chronic idiopathic urticaria, skin and a host of others[13-14]. For allergic rhinitis, loratadine is indicated for both nasal and eye symptoms including sneezing, runny nose, and itchy or burning eyes[15]. Loratadine and other second generation H1-antagonists possess a greater degree of receptor selectivity and demonstrate reduced ability to cross the blood brain barrier (BBB) hence are considered non-sedative[16]. Loratadine is orally administered and is well absorbed from the gastrointestinal tract. It undergoes rapid first-pass metabolism in the liver and is metabolized by cytochrome P450 isoenzymes, including CYP3A4 and CYP2D6. Loratadine is almost totally (97–99 %) bound to plasma proteins. About 40 % is excreted as conjugated metabolites into the urine, and a similar amount is excreted into the faeces. Traces of unmetabolized loratadine can be found in the urine[17].

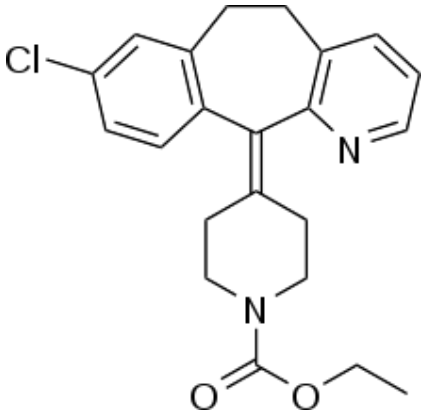

Figure 1: Structure of Loratadine

An Asian study evaluated five (5) brands of loratadine marketed in Pakistan and found that all the brands met all the Pharmacopoeial requirements and specifications for dissolution, disintegration, crushing strength and other parameters[18]. Another study on six different brands of loratadine in Bangladesh found that all the brands complied with the official specification for friability, uniformity of weight and disintegration time but four brands failed to comply with the official specification for crushing strength. Furthermore, assay of the brands in the same study revealed that all samples contained 86.65-95.02 % of labelled claim[19]. A recent study in Bangladesh also found that six brands of loratadine had varied physicochemical properties but the values all fell within allowed limits specified by official monographs[20]. A Sudanese study on three brands of loratadine marketed in the country also found that all the brands had satisfactory properties[21]. In contrast to the foregoing, a study in Nigeria comparing the equivalence of eight brands of the same drug found that one brand failed the friability test losing more than 1 % of its initial weight, while two brands failed the crushing strength test. One brand did not undergo complete disintegration within 15 minutes, while four brands released less than the stipulated amount of the active drug content within the specified time. Worse still, only two out of the eight brands tested had active drug content within the officially specified

range for loratadine tablets[22]. These alarming findings together with an extensive literature review which showed that there is no report on the quality of this essential medicine in Plateau State, Nigeria served as the motivation for this study which was aimed at evaluating the pharmaceutical and chemical characteristics of some commercially available brands of loratadine tablets in Jos, Nigeria.

MATERIALS AND METHODS

Materials

Six brands of loratadine (10 mg) tablets were purchased from different Pharmacy retail outlets across Plateau State, Nigeria. The samples were collected using simple random sampling technique. Pure loratadine reference powder was obtained from Hovid Nigeria Limited. Hydrochloric acid was obtained from Sigma-Aldrich (St. Louis, MO, USA).

Physical Examination

The samples were closely examined and details such as batch number, manufacturing and expiry dates were recorded and the brands coded as LO1, LO2, LO3, LO4, LO5 and LO6 (Table. 1). The shape, size and colour of the different brands were visually inspected at the start of the study.

Diameter and thickness inspection

Ten (10) tablets from each brand were randomly selected and their diameter and thickness determined using a digital slide calliper (Whitmore, USA). Mean thickness, diameter and their standard deviations (SD) were calculated.

Weight Variation test

To study the weight variation, twenty (20) randomly selected tablets of each brand were weighed individually using an analytical balance (Ohaus, USA). Then the weight of each tablet (wi) was compared with the average value (M) of the twenty tablets, and the weight variation was calculated according to the formula shown in equation 1.

$$Weight\ variation\ \% = \{(M - wi)|M\} \times 100\ \% \ldots\ldots\ldots equation\ 1$$

Friability test

Ten (10) tablets from each brand were weighed. The tablets were then rolled together (25 revolutions per minute (RPM) for 4 minutes) in the testing drum of the friability tester (Eagle Scientific, England), followed by de-dusting and then weighed again. The friability was calculated as the weight loss percent of the tablets.

Crushing Strength test

The crushing strength (KgF) was determined with a Monsanto hardness tester (Labappara, India). Ten (10) tablets were randomly selected from each brand and the pressures required to crush were recorded.

Disintegration test

Six (6) tablets from each brand were used for the disintegration test which was carried out in distilled water at 37 °C with the aid of a disintegration tester (Eagle Scientific, England), following the conditions specified by the United States Pharmacopeia[23]. The disintegration time (DT) which is the time taken for the entire tablet to disintegrate completely was recorded.

Assay/ Uniformity of content

Construction of Calibration Curve

A 100 mg quantity of loratadine reference powder was weighed and dissolved in some volume of 0.1 N HCl. The solution was then transferred into a 100 mL volumetric flask and the volume made up to mark. This stock solution was further diluted to give working solutions of loratadine of concentrations; 40 µg/mL, 30 µg/mL, 20 µg/mL, 10 µg/mL and 5 µg/mL. These were prepared in triplicates. The solution was then scanned between 200 – 400 nm with a UV-Visible Double beam spectrophotometer (Shimadzu, Japan) to determine the wavelength of maximum absorption which was found to be 280 nm.

The absorbances of the solutions prepared above were then subsequently measured at 280 nm against a solvent blank. A Beer-lamberts plot of absorbance versus concentration was then constructed using the data obtained. The equation for the calibration curve was obtained using the least squares method of linear regression analysis. The method was also validated by conducting experiments to determine its accuracy, precision and other parameters.

Assay of Brands

Twenty (20) tablets of each brand were weighed individually and crushed with the aid of a mortar and pestle. An accurately weighed amount of the powdered sample equivalent to 100 mg of loratadine was dissolved in 0.1 N HCl and the volume made up to 100 mL in a volumetric flask. The solution was filtered and subsequently diluted, and the absorbance measured at the maximum of 280 nm with a UV-Visible Double beam spectrophotometer (Shimadzu, Japan). The drug content per tablet was calculated with the aid of the calibration curve.

Dissolution Studies

The rate of release of loratadine from the tablet brands was evaluated using the USP dissolution test apparatus Type II (paddle method); specifically the SRII 6-Flask Dissolution Test Station (Hanson Research, USA). The dissolution test was performed using 900 mL of 0.1 N HCl at 50 rpm. The temperature of the medium was maintained at 37±0.5 ºC and the study was carried out for 1 hour. Aliquots of 5 mL were withdrawn at time 5 minutes, 15 minutes, 30 minutes, 45 minutes and 60 minutes. The withdrawn samples were immediately replaced with fresh dissolution medium at the same temperature. The samples were filtered and subsequently analyzed at 280 nm. The actual drug content in the brands was then calculated using the calibration curve previously prepared with loratadine in 0.1 N HCl.

Data Analysis

After completion of the experiments, the data obtained were analysed using Microsoft Excel. Descriptive statistics were used including calculation of means, standard deviations, percentages. Results were presented as tables and charts.

RESULTS

Physical Examination

The results of assessment of the physicochemical and quality parameters of the commercial brands of loratadine tablets sampled in this study are presented in a tabular format. Table 1 shows the label information such as manufacturing and expiry date, batch number together with the code given to each brand to aid identification.

Table 1: Label information and codes for the six brands of loratadine tablets

S/N	Code	Manufacturing Date	Expiry Date	Batch number
1.	LO1	April 2020	March 2023	CA04560
2.	LO2	March 2019	February 2022	9115
3.	LO3	September 2020	August 2023	200953
4.	LO4	July 2020	June 2023	GT20303
5.	LO5	April 2020	March 2023	GT20039
6.	LO6	November 2020	October 2023	AF53001

Table 2 shows the average diameter, thickness and the results of the weight variation studies for all the loratadine brands and all the tablets are within the control limits specified by the British Pharmacopoeia[24]. The average thickness ranged between 2.355 – 3.804 mm for LO2 and LO6 respectively while the average diameter was between 7.195 - 10.141 mm for LO2 and LO6. In addition, LO2 and LO6 had the lowest and highest average weights of 0.0748 g and 0.2462 g respectively.

Mechanical Properties of the Tablets

Table 3 shows the percentage friability and average crushing strength of the tested brands in KgF. LO3 had the lowest % friability of 0.10 while LO1 and LO2 had the highest % friability of 0.28. It can be observed that all the brands had friability less than 1 % which is within the USP[23] specification. The average crushing strength ranged between 3.10 – 8.80 KgF for LO5 and LO3 respectively.

Release Properties and Assay of the Tablets

The disintegration time and results for assay of the brands are given in Table 4. LO2 and LO6 failed the disintegration test as they had average disintegration times above 15 minutes. The table also shows that the two brands had content of active ingredient of 60 and 68 % respectively which are below the Pharmacopoeial requirements for the drugs.

Table 2: Average diameter, thickness and weight variation for the six brands of loratadine tablets

S/N	Code	Average Diameter (mm)	Average Thickness (mm)	Average Weight (g)
1.	LO1	8.195 ± 0.0800	3.079 ± 0.0303	0.1053 ± 0.0014
2.	LO2	7.763 ± 0.0738	2.355 ± 0.0460	0.0748 ± 0.0028
3.	LO3	8.207 ± 0.0312	3.212 ± 0.0839	0.1108 ± 0.0036
4.	LO4	8.073 ± 0.0306	3.07 ± 0.0383	0.1000 ± 0.0037
5.	LO5	7.195 ± 0.0836	3.556 ± 0.0826	0.1586 ± 0.0031
6.	LO6	10.141 ± 0.0178	3.804 ± 0.0347	0.2462 ± 0.0016

Data are presented as mean ± standard deviation

Table 3: Percentage friability and crushing strength variation for the six brands of loratadine tablets

S/N	Code	% Friability	Average Hardness (KgF)
1.	LO1	0.28	5.50 ± 0.7071
2.	LO2	0.28	3.50 ± 0.9428
3.	LO3	0.10	8.80 ± 1.8135
4.	LO4	0.27	7.29 ± 0.4909
5.	LO5	0.23	3.10 ± 0.4595
6.	LO6	0.15	6.38 ± 0.9542

Table 4: Disintegration time and assay results for the six brands of loratadine tablets

S/N	Code	Average Disintegration Time (Min)	% Drug Content
1.	LO1	3.43 ± 0.6834	90.64 ± 0.037
2.	LO2	24.54 ± 7.6109	60.78 ± 0.010
3.	LO3	6.58 ± 1.2072	98.17 ± 0.024
4.	LO4	11.42 ± 8.3044	68.61 ± 0.014
5.	LO5	4.56 ± 2.2621	94.12 ± 0.019
6.	LO6	23.25 ± 7.6476	107.16 ± 0.045

The calibration curve of absorbance versus concentration for loratadine in 0.1 N HCl at 280 nm is shown in Figure 2. The curve had an excellent correlation coefficient (r^2) of 0.9938. Figure 3 displays the dissolution profile of the brands of loratadine tested showing the percentage of drug released at various time sampling points. Three brands; LO2, LO4 and LO6 were only able to release 72.35, 78.22 and 45.74 % of active drug within one hour and these values are below the 80 % release required by official specification.

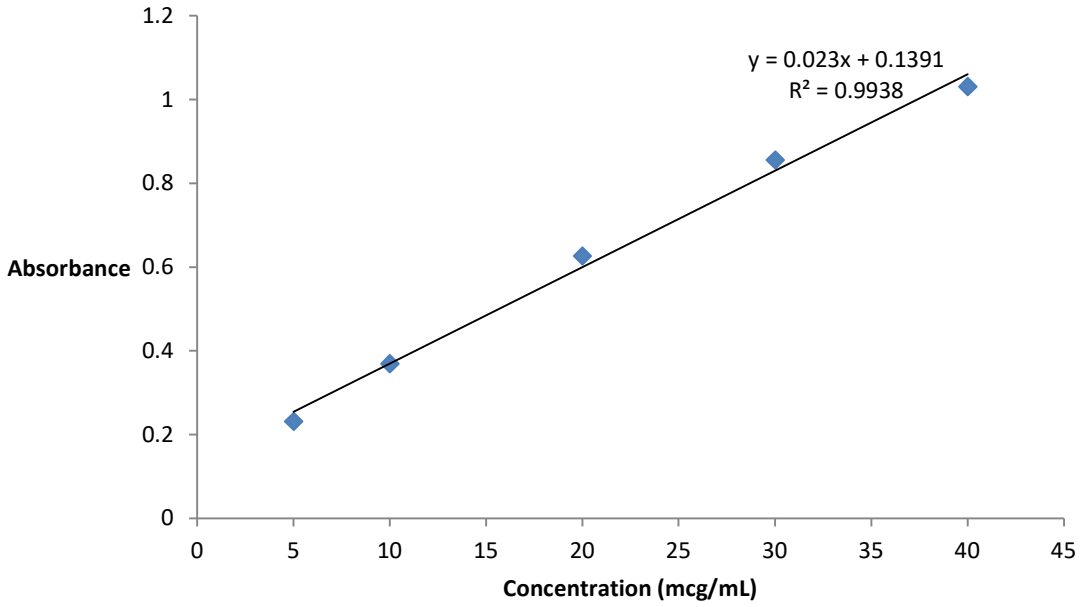

Figure 2: Calibration Curve for Loratadine in 0.1 N HCl at 280 nm

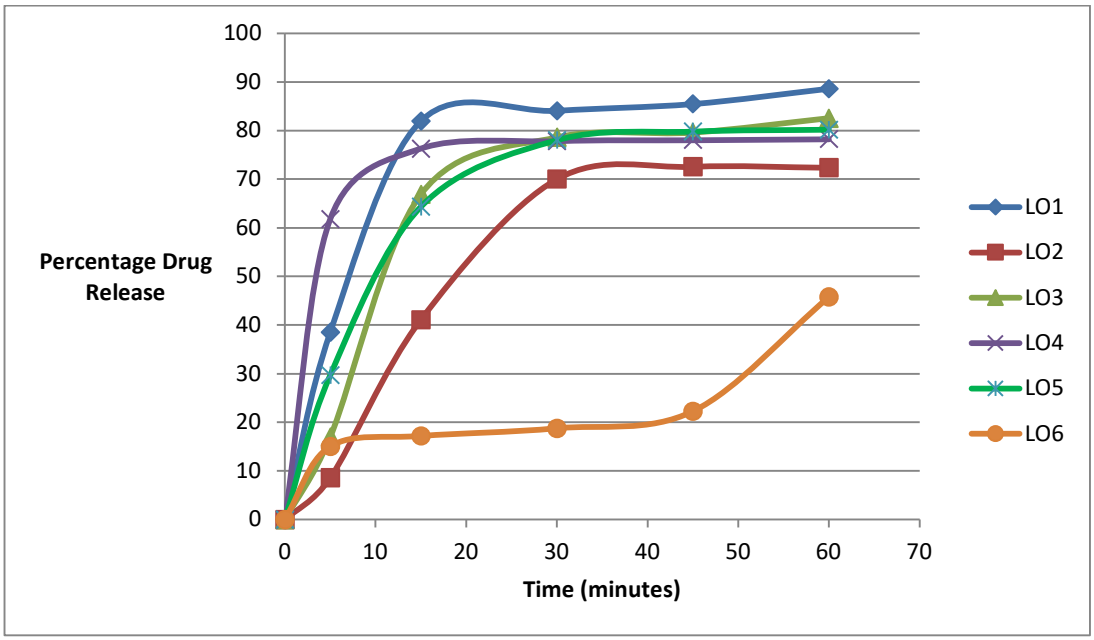

Figure 3: Dissolution Profile for the six brands of loratadine tablets

DISCUSSION

Physical Examination

All the brands of the loratadine tablets were in good physical condition and no abnormalities were found in their appearance throughout the duration of the study. They were also all within the valid period with respect to their shelf life and had all required dates and documentation as required by the Nigerian drug regulatory agency (NAFDAC).

Diameter and Thickness

During the production of tablets, it is important to monitor the diameter and thickness of the tablets at regular intervals in order to prevent potential problems linked to differences in tablet weight and also to ensure that the tablets are all uniform in appearance. This is particularly important as it can affect the fit of the tablets in the packs during the packaging process. Among the six brands evaluated, it was observed that there was very little variation in the average diameter and average thickness within the same brand and this is a good attribute. The values obtained are quite similar to the values obtained in another study where the six brands evaluated had average diameter in the range of 6.06-8.03 mm and average thickness of 2.57-3.18 mm[19].

Weight variation

The average weight of the tablets for each brand was found to be relatively uniform. This is suggestive of uniform weighing of the granules during the tableting process. Weight uniformity is one of the indicators that good manufacturing practice (GMP) was employed in the production process. The USP[23] specifies the limit of deviation of ± 10 % for tablets weighing 130 mg or less, not more than two tablets should cross the single limit and none of them should go beyond twice that limit. The weight variation for all the tablets used in this study complied with the official specifications mentioned above. Furthermore, this result is in agreement with other studies[18-22] where the brands evaluated all showed conformance with Pharmacopoeial requirements for this parameter.

Friability

Abrasion, friction and mechanical shocks can lead to breakage and other damage to tablets. Friability test measures the ability of tablets to withstand abrasion that may occur during packing, storage, and transport and is usually expressed as a percentage. The USP[23] specifies friability of less than 1 %. Friability is closely linked to hardness as the harder the tablet, the lower the friability and vice versa[25]. For the six brands of loratadine tablets investigated in the study, all were found to have percentage friability less than one percent thereby complying with the compendial guidelines. This is in contrast to the study in Southwest Nigeria where one out of eight brands tested lost more than 1 % of the initial weight thereby failing the friability test[22].

Crushing Strength

As mentioned earlier, tablet hardness has a great influence on friability and the ability of the tablets to withstand mechanical stress during handling. Conversely, excessive hardness can lead to increased disintegration time and reduced dissolution rate, both of which can negatively impact bioavailability. Crushing strength is a non-compendial test and does not have any official limit but a crushing strength of between 4-6 kilogram of Force (KgF) (which is roughly equivalent to 40-60 N) is considered to be the minimum requirement for a satisfactory tablet[20]. In this study, the average crushing strength of two of the brands were slightly below this range, two brands fell within the range and the final two brands had values slightly above the range and these variations may have implications for release of the API from the tablets. In contrast, a Sudanese study evaluating the quality of loratadine tablets found crushing strength values of between 4–12 KgF[21] while a study in Pakistan found crushing strength values of 22 – 73 Newton[18]. In yet another study, four out of the six brands tested did not possess the minimum crushing strength required[19].

Disintegration

The test for tablet disintegration is a measure of the time it would take a group of tablets to disintegrate into particles that will pass through a 10 mesh screen under a given set of conditions. Before a drug can be absorbed from the GIT, it has to first disintegrate into smaller particles, then it dissolves in gastric fluids prior to absorption into systemic circulation. Disintegration is therefore a crucial aspect that can influence a drugs therapeutic action. In this study, four out of the six brands tested passed the disintegration test by meeting the USP[23] criteria of complete disintegration within 15 minutes. However, two brands; LO2 and LO6 failed this test and even contained several tablets that did not disintegrate until after 30 minutes. This indicates that there may be a problem with these brands due to the inconsistent performance of the tablets in this quality control test. Usually, a tablet which fails disintegration test will likely also fail dissolution criteria since these two parameters are intricately linked. Furthermore, this result is similar to that obtained in a study conducted to evaluate and compare the quality of different brands of loratadine tablets collected from pharmacy outlets in Addis Ababa city, Ethiopia where one product failed the disintegration time test[26].

Assay

For four out of the six brands evaluated, the values of drug content were found to meet the USP[23] requirement for loratadine tablets which specifies an acceptance criterion of between 90 – 110 % of the stated label claim. However, two brands LO2 and LO4 had drug content values of 60 % and 68 % and these values fall below the USP requirement. Drugs having active ingredient content below the Pharmacopoeial specifications can lead to therapeutic failure when administered to patients and this underscores the importance of ensuring that drug formulations contain the requisite content of active ingredient. This assay result is similar to that obtained in a previous study[22] where six (6) out of eight (8) brands assayed had loratadine API content less than the specified Pharmacopoeial range.

Dissolution

Dissolution can be defined as "the rate of mass transfer from a drug substance to the dissolution medium or solvent under standardized conditions"[27]. It is a complex property that changes over time and describes the process of obtaining a homogeneous mixture of a solid or a liquid in a solvent and is used to measure the rate of drug release from solid dosage forms. It also gives the knowledge of bioavailability of drugs by correlating dissolving pattern in the gastrointestinal tract before reaching the systemic circulation. In the dissolution study of the six (6) brands of loratadine tablets, it can be observed that three brands LO1, LO3 and LO5 met the USP requirement which mandates that not less than 80 % of the labelled amount of loratadine is released in 60 minutes while LO2, LO4 and LO6 did not meet this criterion. These results are also in tandem with the results of the disintegration test as LO2 and LO4 did not pass the disintegration test and invariably also did not meet the USP[23] dissolution criteria. In some previous dissolution studies[18-21] on loratadine tablets, all the tested brands released not less than 80 % of the labelled amount in line with Pharmacopoeial requirements while four out of eight brands tested in an earlier Nigerian study failed the dissolution test[22].

CONCLUSION

Despite the slight variation in the test results, most of the brands of loratadine evaluated had results that were within the official limits provided by the pharmacopoeia. This indicates that these brands are likely to produce the required antihistamine effects when administered to patients. However, two of the brands are not acceptable as they had API content below the stated claim. In addition, the same two brands and another failed to release up to 80 % of the active ingredient within one hour as required by the USP. It can therefore be concluded that some

of the tested brands of loratadine do not meet up to the Pharmacopoeial quality requirements and this may be linked to deliberate counterfeiting, poor compliance of the manufacturers to good manufacturing practices (GMP) or inappropriate handling and storage in the drug supply chain. There is therefore the need for continuous post-marketing surveillance of these medicines in addition to rigorous enforcement of good manufacturing practice by drug regulatory bodies in the country.

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