TECHNICAL NOTE

Nig. J. Pharm. Res. 2018, 14 (2) pp 197-202
ISSN 0189-8434, e-ISSN 2635-3555 **Available online at http://www.nigjpharmres.com**

Comparative Pharmaceutical and Physicochemical Equivalence of Some Brands of Chlorphenamine Maleate Tablets

O. M. ADEGBOLAGUN[*ACDEF], J. C. NWABUIFE[ABCDF]
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Ibadan, Nigeria

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Generic drugs has been accompanied by a variety of problems of which the most critical is the increasingly widespread of distribution of counterfeit, fake and substandard drug product. Chlorphenamine maleate tablet is a widely used antihistamine which is available as a multi-sourced drug compound globally and also subject to varied challenges of multi-sourced products.
Objectives: This study reports the biopharmaceutical and chemical inequivalence of nine brands of chlorphenamine maleate tablets.
Methods: Biopharmaceutical and chemical equivalence of nine brands of chlorpheniramine maleate tablets were assessed using the official quality control procedure for; uniformity of weight, thin layer chromatography, friability test, hardness, disintegration test, dissolution rate and chemical content determination.
Results: All the brands complied with the official specification for uniformity of weight, and disintegration test, while one brand failed the friability test. The thin layer chromatogram confirmed the presence of chlorphenamine in all the brands. All the brands complied with dissolution profile specification of >70%w/w at C_{45}. Chlorphenamine maleate contents for eight brands ranged from 94.31±0.64 to 107.36±8.56%w/w which was within the official specification, while one brand was lower than the specification.
Conclusion: Of the nine chlorphenamine maleate tablet brands investigated, only seven brands could be regarded as biopharmaceutical and chemical equivalents and therefore can be used interchangeably.

Keywords: Chlorpheniramine maleate tablets, Chemical equivalence, Biopharmaceutical equivalence

INTRODUCTION

The introduction of non-proprietary (generic) drug product from various manufacturers into the health systems of many countries in the world mostly the developing countries, was aimed at providing alternatives to a particular brand in areas where such brands are limited in supply or if such brands may be too expensive for the lower income earners in such country (Adegbolagun *et al.*, 2007). Generic drugs are thus aimed at improving the healthcare being delivered by the health systems of these countries. However, this has been accompanied by a variety of problems of which the most critical is the increasing widespread distribution of counterfeit, fake and substandard drug products (Soyinka *et al.*, 2008).

The need to select one product from among several generic drug products of the same active ingredients during the course of therapy is a cause of concern to healthcare practitioners and patients. The first stage in ascertaining the therapeutic equivalence of any drug product involves ascertaining the chemical and biopharmaceutical equivalency of such drug products. Drug products that are pharmaceutically equivalent must be identical in strength, quality, purity as well as content uniformity, disintegration and dissolution rates (Odunfa *et al.*, 2009).

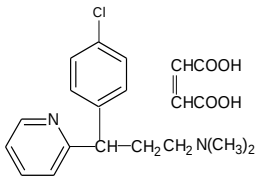
Ascertaining the quality of drug products involves the use of various procedures in form of biopharmaceutical and chemical assay techniques. A

variety of analytical techniques have been reported for drug products; instrumental and non-instrumental. Varied reports on biopharmaceutical and chemical equivalence of drugs exist in literature. Biopharmaceutical inequivalence has been reported for some brands of diclofenac tablet despite been chemically equivalent (Ayorinde *et al.*, 2012), while chemical inequivalence was reported for three brands of carbamazepin tablets (Malami *et al.*, 2015). Adegbolagun *et al.* in 2007 reported biopharmaceutical and chemical equivalence in six out of ten brands of ciprofloxacin investigated, while a recent study in Bangladesh reported chemical equivalence with ten brands out of which four were not pharmaceutical equivalent (Uddin *et al.*, 2017).

Antihistamines are drugs that inhibit the action of histamine in the body by competitively blocking the histamine receptors, thus they suppress symptoms associated with the release of histamine and subsequent interaction of histamine with H_1-receptors. Hence, they are widely used for symptomatic relief of common cold and allergic diseases either alone or as adjunct in pharmaceutical preparations (Rukshana *et al.*, 2014). They are classified into different generational and chemical groups of which diphenhydramine, chlorphenamine, clemastine, triprolidine, cyproheptadine, brompheniramine and hydroxyzine belong to the first-generation H_1 (Dalia, 2012; Kashif *et al.*, 2012), while loratidine, Fexofenadine and cetrizine are second generation antihistamines (Batra *et al.*, 2006).

Comparative study on six brands of loratidine a non-sedative antihistamine from Nigeria reported large variations in the pharmaceutical properties with only two out of the six brands investigated to be pharmaceutically equivalent with innovator brand (Adetunji *et al.*, 2015). A similar study in Bangladesh on six brands reported low loratidine content of 86.65 – 95.02% of the labelled potency though the drug release was satisfactory across the brands (Oishi *et al.*, 2017). Another study on Fexofenadine hydrochloride tablets reported compliance with quality control specification for all the brands investigated (Khan *et al.*, 2016).

Chlorphenamine maleate (CPM), (3*RS*)-3-(4-Chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl) propan-1- amine hydrogen (*Z*)- butenedioate (B.P. 2013), is about the most widely used antihistamine, which is available in different dosage forms; oral solution, tablets, injectable etc, as a multi-sourced drug compound globally.



It is also subject to varied challenges of multi-sourced products including therapeutic failure as a result of fake and substandard products. However, there is no previous report on the equivalence of chlorphenamine maleate tablets despite its wide use in allergic diseases in Nigeria.

Hence, this study was aimed at evaluating the biopharmaceutical and chemical equivalency of nine brands of chlorphenamine maleate tablets distributed within the South-western part of Nigeria.

MATERIALS AND METHODS

Materials

Chlorphenamine maleate (CPM) pure compound was a gift from Bond Chemical Industry Awe, Oyo State, Nigeria (Batch Number: SU/C/04/4067, Expiry Date: March 2019). Nine brands of chlorphenamine maleate tablets including the innovator brand which were also available within the Southwestern states of Nigeria with labelled content of 4mg were obtained from retail pharmacies in Ibadan Oyo State, Nigeria.

Analytical grade reagents used include hydrochloric acid, glacial acetic acid, potassium hydrogen phthalate, crystal violet indicator, ethylacetate, sodium hydroxide, perchloric acid, methanol, tetraoxosulphate (VI) acid, diethylether and chloroform.

Identification and assay of Chlorphenamine maleate pure powder

The melting point and thin layer chromatography analysis of the pure chlorphenamine hydrochloride were determined, while a modified BP 2013 method using crystal violet as indicator was used for the chemical content determination.

Into a conical flask containing neutralised 25mL of anhydrous acetic acid was dissolved 0.150g. The solution was titrated against 0.1M perchloric acid VS to blue-green end point using two drops of crystal violet as indicator. The procedure was carried out in triplicate.

Biopharmaceutical evaluation of the tablet dosage forms

The biopharmaceutical evaluation on the nine brands was carried out using the official method as follows (B.P. 2013).

Tablet description: The colour and physical characteristics of the tablets were recorded.

Thin Layer Chromatography: a solution of the CPM in chloroform using a mixture of 1M acetic acid, methanol and ethyl acetate (20:30:50) as mobile phase on Silica gel GF254 pre–coated plates. The plates were allowed to air-dry followed by visualisation under ultraviolet light at 254 nm.

Uniformity of weight test: The average weight and percentage deviation were determined using official method by weighing twenty tablets from each of the three brands individually using weighing balance (Mettler 1180 weighing balance).

Thickness and Diameter test: the thickness and diameter of five tablets for each brand was determined using a Veneer calliper, after which the mean and standard deviation was recorded.

Hardness test/Crushing test: crushing strength of five tablets for each brand was determined using tablet hardness tester (D. B. K. Instruments, Mumbai – 400 060 Model EH01).

Friability test: The weight of ten tablets of each brand was determined before and after subjection to abrasion using a friability tester (D.B K. friability tester, England) at 25 rpm.

Disintegration test: This was determined at 37 ± 0.5^0C using disintegration testing apparatus (Copley DTG 4000) until no particle remained on the basket of the system for six tablets from each brand. The time taking for each tablet from each of the brand was recorded.

Dissolution profile determination:

The obtained absorbance of aliquots of pure CPM solutions in 0.01M HCl at 0.58–4.4mg/ml determined at 265nm using UV spectrophotometer (Spectrumlab®, England) was used to generate a calibration curve.

One tablet was placed in a dry basket of the dissolution rate apparatus (Copley DIS 6000) and lowered into the vessel containing 900ml dissolution medium (0.01M HCl) maintained at 37 ± 0.5^oC, the basket was rotated at 100 rpm. Samples (5ml) were withdrawn at 0, 10, 20, 30, 40, 50 and 60minutes, replaced with 5ml fresh dissolution medium after each sampling. The samples were cooled to room temperature, filtered and diluted appropriately before the absorbances were determined at 265 nm. The determination was done in triplicate for each brand.

The CPM content at each sampling time obtained from the calibration curve was used to determine the dissolution profiles with calculation of T_{70} (time for 70% of the active drug to be dissolved) and C_{45} (amount dissolved at 45min).

Chemical content determination of Chlorpheniramine maleate (CPM) tablets

The CPM content of the samples was determined using the official method (B.P. 2013).

Powdered tablet equivalent to 3mg of chlorpheniramine maleate was transferred into a separating funnel containing 0.05M sulphuric acid (20mL) and mixed by shaking for 5mins. Diethyl ether (20mL) was added to the mixture, shaken carefully, the acid layer was then filtered into a second separating funnel. The ether layer was further extracted with 0.05M sulphuric acid (2 x 10mL), each acid layer obtained was filtered into the second separating funnel after which the filter was washed with 0.05M sulphuric acid. The combined acid layer was made just alkaline to litmus paper using 1M sodium hydroxide with addition of 2mL in excess. The alkaline solution obtained was extracted with diethyl ether (2 x 50mL), with each ether extract obtained washed with the same 20 mL of water.

The washed ether layer was then extracted with successive quantities of 0.25M sulphuric acid (20, 20 and 5 mL), the combined acid extracts made up to 50 mL with 0.25M sulphuric acid in a volumetric flask. Aliquot of 10ml was diluted to 25 mL with 0.25M sulphuric acid and the absorbance of the resulting solution determined at 265nm. The CPM content was determined using 212 as A (1%, 1 cm). The determination was done in triplicate for each brand.

STATISTICAL ANALYSIS

Student t-test and one-way analysis of variance (ANOVA) was used for the statistical analysis at $p<0.05$ level of significance.

RESULTS AND DISCUSSION

Post market surveillance is a critical component of drug quality control system globally. The introduction of multisource products in form of non-proprietary (generic) drug products globally was aimed at providing alternatives to specific brands in areas where such brands are limited in supply or too expensive in economically deficient population. The increasing prevalence of fake, sub-standard and counterfeit drug products has been associated with multi-sourcing of drug compounds. Hence regular

quality evaluation of multi-sourced drugs within the drug distribution system is important to the success of such system.

Chlorpheniramine maleate which is available in almost all possible dosage forms is a widely prescribed antihistamine for varied clinical conditions probably because of its low cost. It is available as a multi-sourced product globally of which Nigeria is not an exception. This study comparatively evaluated biopharmaceutical and chemical equivalence of nine brands of chlorphenamine maleate tablets obtained from retail pharmacies within Ibadan metropolis. All the brands were duly registered with NAFDAC and were within their shelf life as at the time of the study.

The pure chlorphenamine maleate (CPM) powder used as reference was confirmed to be of good quality based on the melting point (132 – 134ºC) and TLC (R_f 0.52) with chemical content of 100.79±7.46%w/w which complied with official specification (BP 2013).

The CPM content was confirmed in all the brands investigated with R_f ranging from 0.51 – 0.55 which compares favourably with that of the pure reference compound (Table 1).

The investigated brands had round shape with colours varying from off-white, white and various shades of yellow. All the brands had score line except P_1, P_3 and P_9 with brand name and labelled content embossed except brand P_8. The nine brands complied with the official specification for uniformity of weight as none of the brands deviated by a value greater than twice of 10% from their mean (Table 1).

Thickness and diameter though not official methods of assessing tablet quality are still useful in assessing the integrity of the tablet dosage form in terms of batch to batch tablet consistency as the shape and size of the tablet can be influenced by the choice of particle size and particle size distribution.

Table 1: R_f and Biopharmaceutical parameters (Mean ± SD) obtained for the nine brands of chlorphenamine maleate tablets

Code	Uniformity of weight (g)	TLC R_f	Friability (%)	Hardness (KgF)	Thickness (mm)	Diameter (mm)
P_1	0.141±0.08	0.55	0.48	2.83±0.35	3.54±0.24	7.23±0.01
P_2	0.134±0.12	0.54	0.30	2.54±0.32	3.30±0.11	7.18±0.03
P_3	0.146±0.07	0.55	0.36	1.24±0.21	3.46±0.15	7.35±0.01
P_4	0.190±0.06	0.53	0.13	3.30±0.24	2.64±0.04	8.60±0.01
P_5	0.203±0.09	0.54	0.53	5.07±0.40	2.50±0.10	8.13±0.01
P_6	0.117±0.09	0.54	0.12	2.24±0.27	2.58±0.13	7.18±0.03
P_7	0.147±0.06	0.52	4.55	1.63±0.28	2.79±0.08	7.24±0.02
P_8	0.146±0.10	0.53	0.09	7.88±0.57	2.41±0.02	7.07±0.02
P_9	0.135±0.04	0.51	0.26	3.61±0.29	2.74±0.05	7.15±0.01

Consistent thickness and diameter were observed within each brand as the deviations from the mean were less than 0.5 (Table 1).

Furthermore, the percentage friability of all the brands was less than the official specification of 1%w/w except brand P_7 with 4.55% (Table 1).

This shows that the brand could not resist chipping and breaking resulting from shock and abrasion during distribution and may result in reduction in the active drug content by the time of consumption by the patient. Although, crushing strength is not an official method of assessing tablet quality, it is still useful in assessing the integrity of tablet dosage forms. The mean crushing strength which is a measure of the degree of hardness of the tablets was highest for P_5 and P_8 at 5.07 and 7.88kgf respectively, while the other brands ranged from 1.24 to 3.61KgF (Table 1). Generally, there was no direct correlation between the % friability and the crushing strength, but brand P_8 with highest crushing strength (7.88±0.57KgF) was

observed to have the least friability (0.09%), while brand P_7 with high friability (4.55%) had very low crushing strength (1.63KgF).

All the brands complied with the disintegration rate specification for uncoated tablets as they all disintegrated within 15minutes, although brand P_5 gave 9.97 minutes which was significantly higher than the others (Table 2) (B. P. 2013).

Table 2: Disintegration time and dissolution profiles (T_{70} and C_{45}) in 0.1M HCl at 37±0.5ºC and chemical content of nine brands of chlorphenamine maleate tablets

Brand	Disintegration time (mins)	Dissolution profile		Chemical content (%w/w)
		C_{45} (%w/w)	T_{70} (mins)	
P_I	0.68	82.5± 12.86	7.2± 0.40	107.4 ± 8.56
P_2	3.24	87.2± 10.29	8.0± 0.20	96.3 ± 10.23
P_3	0.64	80.8± 1.28	8.4 ± 0.14	92.1 ± 3.82
P_4	1.64	80.6± 3.39	7.7± 0.21	96.4 ± 9.99
P_5	9.97	108.7± 7.63	6.3± 0.75	95.8 ± 1.67
P_6	0.59	73.3± 10.85	9.1± 0.89	98.5 ± 6.32
P_7	1.18	81.4± 0.82	6.8± 0.15	94.3 ± 0.64
P_8	0.47	78.1±7.07	8.9± 0.81	96.0 ± 1.47
P_9	3.50	95.4± 6.35	8.1± 1.03	94.6 ± 2.73

The lack of significant difference in the time to obtain 70% dissolution for six brands (P_2, P_3, P_4, P_6, P_8 and P_9) compared to the remaining three brands (P_1, P_5 and P_7) (p= 0.0003) is an indication of possible difference in the time for onset of action between the two sets. The three brands with the lower T_{70} may have faster onset of action than the remaining six brands. The official specification for tablets is that not less than 70%w/w labelled content of CPM should be dissolved at 45minutes. All the nine brands investigated had values ranging from 73.25±10.85 to 108.7±7.63 % w/w at 45minutes (Table 2). The obvious implication of this is that all the brands will exhibit good *in vivo* bioavailability profile.

However, despite the brands complying with the dissolution specification, statistically significant difference was observed with the C_{45} values between seven brands and the remaining two (P_5 and P_6) ($p = 0.0012$). No significant difference was observed within the seven brands with values ranging from 78.1 to 95.4 ($p>0.05$). This proposes possible similar bioavailability profiles within the seven brands translating to similarity in their efficacies, which may be different from the remaining two brands P_5 and P_6 with C_{45} values of 108.7 and 73.3 %w/w respectively.

CONCLUSION

It can be concluded from this study that seven of the investigated brand which constitute 77.8% of the Brand P_8 though with the highest crushing strength had the least disintegration time, friability and good dissolution profile; this indicates the importance of good formulation. Also, the low percentage release at 45minutes observed with brand P_6 (73.3%w/w) is reflected in the highest time to achieve 70% release (9.1minutes); its good friability and disintegration time could be adduced to formulation issues. Similar study on formulation issues reported low C_{45} values for two brands of ascorbic acid tablets despite complying with official content specification (Soyinka *et al.*, 2008).

Chlorpheniramine maleate content in all the brands except brands P_3 complied with the 92.5 to 107.5%w/w official specification for tablets (BP 2013) (Table 2), thus the remaining eight brands could be regarded as chemical equivalents. The low chlorphenamine maleate content in brand P_3 may actually suggest substandard product as a result of formulation or production error, rather than fake or counterfeit product. The overall outcome of this study showed that only seven brands (P_1, P_2, P_4, P_5, P_6, P_8 and P_9) may be regarded as biopharmaceutical and chemical equivalents indicating the possibility of their use interchangeably with expected similar efficacy.

multi-sourced chlorpheniramine maleate tablet brands investigated are interchangeable. This affirms the need for caution in substituting brands and regular post

market surveillance of drug products including chlorphenamine maleate tablets

ACKNOWLEDGEMENTS

The authors appreciate Bond Chemical Industry, Aawe, Oyo State for supplying the pure chlorphenamine maleate powder used in the study. We are also grateful to the Department of Pharmaceutics and Industrial Pharmacy, University of Ibadan for releasing their equipment and facilities for the study.

REFERENCES

Adegbolagun, O.A., Olalade, O.A., and Osumah, S.E. (2007). Comparative evaluation of the biopharmaceutical and chemical equivalence of some commercially available brands of ciprofloxacin hydrochloride tablets. Trop. J. Pharm Res. 6 (3): 737-745.

Adetunji OA, Adigun NF, Odeniyi MA. (2015). Pharmaceutical equivalent studies of some commercially available brands of Loratadine hydrochloride tablets. Afr. J. Med. Med. Sci. 44(3): 269-276.

Ayorinde, J. O., Odeniyi M.A. and Itiola, A.O. (2012). Evaluation of pharmaceutical and chemical equivalence of selected brands of diclofenac sodium tablets. East and Central Afr. J. Pharm. Sci. 15: 3-9.

Bartra, J., Velero, A.L., del Curvillo, A., Davila, I., Jauregui, I., Montoro, J., et al. 2006. Interactions of the H1 antihistamines. J. Investig. Allergy Clin. Immunol. 16(1): 29-36.

British Pharmacopoeia (2013). Her Majesty Stationary Office.

Dalia, H. E. (2012). Antihistamines in pediatric allergy. Egypt J Pediatr Allergy Immunol. 10(1): 3-12.

Khan M.N, Naveed S, Dilshad H, Ayub M (2016). Pharmaceutical equivalent dissertation of fexofenadine hydrochloride brands. Bull. Env. Pharmacol. Life Sci., 5(9): 21-27.

Maroof K., Zafar F., Huma, A., Ubaidullah, K., Huma, S. 2012. Chlorpheniramine maleate: an effective antiallergic agent. Baqai J. Health Sci. 15(2): 35 – 38.

Malami, S., Usman, A.M., Shehu, M.A. and Yerima, M. (2015). Chemical equivalence assessment of three brands of carbamazepine tablets and their anticonvulsant outcome on electrically-induced seizures in chicks. Bayero J. Pure Applied Sci. 8(2): 192 – 195.

Odunfa, O. O., Adegoke, O.A. and Onaga, I.C. (2009). Pharmaceutical equivalence of some commercial samples of artesunate and amodiaquine tablets. Trop. J. Pharm. Res. 8 (6): 491-499.

Oishi, T.M., Munna, S., Noor, Z., Das, S., Akhter, R., Huque, S. and Shahriar, M. (2017). Comparative in vitro equivalence evaluation of some loratadine generic tablets marketed in Bangladesh. IOSR J. Pharm. Biol. Sci. (IOSR-JPBS). 12(2): 76-81.

Rukshana, B. (2014). H1 Antihistamines as antiallergy drugs. Am. J. Med. Med. Sci. 4(6): 236-240.

Soyinka, J.O., Faleye, F.J., Adetogun, G.E. (2008). Quality evaluation of some brands of Vitamin C preparations. Nig. J. Pharm. Res. 7(1): 12 – 17.

Uddin, M.S., Mamun, A.A., Hossain, M.S., Asaduzzaman, M., Sarwar, M.S., Rashid, M., Herrera-Calderon, O. (2017). In vitro quality evaluation of leading brands of ciprofloxacin tablets available in Bangladesh. BMC Res. Notes. 10(1): 185-187.

World Health Organization (2005). Guidelines for registration of fixed-dose combination medicinal products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report. Geneva, World Health Organization, (WHO Technical Report Series, No. 929), Annex 5:94–142.

.

*Address for correspondence: Adegbolagun, Olayemi M.

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Ibadan, Nigeria.

Telephone: +2348023451393

E-mails: duplag03@yahoo.com

Conflict of Interest: None declared

Received: September 14, 2018

Accepted: November 26, 2018