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Enquiries:

The Editorial Office
International Journal of Health Research
236-202, St David Court, Cockeysville,
MD 21030, USA
E-mail: editor@ijhr.org
Tel: +1-614-535-7928

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Comparative Determination of Chlorpromazine Hydrochloride Content in Multi-sourced Chlorpromazine Tablets in Nigeria

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Abstract

Purpose: *Although different brands or unbranded chlorpromazine tablets from multiple sources are available in Nigeria today, they must all contain the same active principle and satisfy the standards of quality, efficacy and safety. This study is designed to check for possible faking and adulteration of chlorpromazine tablets and also establish the possibility of inter-brand substitution based on drug content (chemical equivalence).*

Method: *The determination of the chlorpromazine hydrochloride content was carried using non-aqueous titrimetric and spectrophotometric methods. Glacial acetic acid and acetone were used as the non-aqueous solvent and equivalence points were determined using visual indicators and potentiometer.*

Results: *The results obtained showed that all the brands analyzed met the specification of the British Pharmacopoeia and so contain acceptable amounts of chlorpromazine drug content thus enabling possible brand substitution.*

Statistical comparison showed no significant difference between the results obtained by determining end-point using visual indicators and the potentiometer.

Conclusion: *The use of the visual indicator method is recommended for fast and accurate routine laboratory analytical work especially in developing nations.*

Keywords: *Chlorpromazine, non-aqueous titration, spectrophotometric determination, potentiometry*

Henry A Okeri

Peter O Alonge

Emadoye Etareri

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

For Correspondence:

Tel: +234-802-311-2394
E-mail: hokeri1@yahoo.com

Introduction

Chlorpromazine (10-[3-dimethylaminopropyl] phenothiazine) belongs to the primary chemical group of antipsychotic agents known as the phenothiazines. It has an aliphatic side chain and is referred to as an atypical phenothiazine with a low to moderate-potency antipsychotic action. Apart from its antipsychotic activity where it is used as a tranquilizer and maintenance therapy to prevent acute relapse in chronic schizophrenic patients, chlorpromazine is also used for the treatment of vomiting and vertigo because of its sedative and extrapyramidal effects. [1, 2] Although chlorpromazine has been primarily replaced by newer generation of antipsychotic agents which have improved action and side effect profile, it is still used in the management of acute and chronic psychosis including schizophrenia and the manic phase of manic depression as well as amphetamine-induced psychosis, other serious psychiatric illnesses marked with agitation, and impaired reasoning. (2)

Chlorpromazine is highly lipophilic, membrane-bound, and protein-bound (especially albumin protein) and accumulate in the brain, lungs, and other tissues with a high blood supply. [3] The peak plasma concentration of chlorpromazine and other phenothiazines are attained within 2 – 4 hours and intramuscular administration helps to avoid much of the first-pass metabolism in the liver leading to increased bioavailability. [4] Chlorpromazine is mainly metabolized by oxidative processes mediated largely by the hepatic cytochrome-P450 microsomal oxidase and by conjugation processes. [5] Like all phenothiazine derivatives, chlorpromazine discolourizes under the influence of light and oxygen. Also it is readily oxidized in alkaline or neutral medium to the N-oxide derivative. [6]

Various analytical methods have been used for the analysis of the compound in both pharmaceutical dosage forms and biological fluids. Some of the analytical methods that have been employed include thin-layer chromatography [7], gas liquid chromatography [8], gas chromatography/mass spectrometry [9], high performance liquid chromatography [10 -12], spectroelectrochemical method [13], spectrophotometry [14], radioimmunoassay [15, 16] fluorimetry [17], voltammetry [18], chemiluminescence method [19], electron spin resonance spectroscopy [20], nuclear magnetic resonance (nmr) spectroscopy [21] and flow-injection potentiometric method. [22]

Presently, there is an increase in the number of generic drug products from multiple sources and this has placed the pharmacists and other health practitioners in a position of having to select one among several seemingly equivalent products. Most of the methods listed above employ expensive equipment not often available in poor countries. Non-aqueous titration is an approved assay method for chlorpromazine. The method was discontinued for the assay of the tablets because of interferences in the assay results due to formation of oxidation products in the presence of acetic acid. By overcoming this problem, non-aqueous titration is a reliable and cheap method for the assay of chlorpromazine tablets. Therefore the objective of this study is to develop a modified non-aqueous titrimetric method for the analysis of chlorpromazine tablets.

Materials and Methods

Sample selection and storage

Six different brands of chlorpromazine tablets labeled as DAL and CPE (with a label claim of 50mg of chlorpromazine HCl), as well as CPM, CPK, CPH and CPZ (with a label claim of 100mg of chlorpromazine HCl) were randomly purchased from pharmacies in Benin City, Nigeria. All the tablets were stored in air-tight, amber-coloured

containers kept in a dry cool place prior to the assay. Sampling and assay of chlorpromazine HCl in all the brands were done one and half years before the expiry dates.

Materials

Glacial acetic acid, acetic anhydride, acetone, perchloric acid (70%) and hydrochloric acid all of Sigma-Aldrich (Germany); mercuric acetate, methyl orange powder and crystal violet crystals all of BDH (Poole, England), ascorbic acid was obtained from Merck (Germany), pH meter (Jenway, England, model 3020) and a Spectronic 21D UV/Visible spectrophotometer (Milton Roy Ltd., USA).

Preparation of solutions

Perchloric acid (0.1M) that was standardized with potassium hydrogen phthalate, 2M and 1M HCl, crystal violet solution (0.2% w/v in acetic acid), mercuric acetate solution (5%w/v in acetic acid) and a saturated methyl orange solution in acetone were all prepared prior to the assay.

Assay methods

Non-aqueous titration using acetic acid: Twenty tablets of each brand were accurately weighed and reduced to fine powder. From the powdered drug, an amount equivalent to 0.35g of chlorpromazine HCl were taken and transferred into a 250ml conical flask containing 50ml of glacial acetic acid. The mixture was shaken and 10ml of 5% w/v mercuric acetate, 2g of ascorbic acid and 2 drops of 0.2% w/v crystal violet indicator were added. The solution was stirred for 15 min with a magnetic stirrer and then titrated with 0.1M acetous perchloric acid to a blue end-point. For the potentiometric method, the crystal violet indicator was omitted and the end-point was determined potentiometically. [23] All the determinations were done in triplicates.

Non-aqueous titration using acetone: A modification of the International Pharmacopoeia method [24] was used. Twenty tablets of each brand were accurately weighed and reduced to fine powder. From the powdered drug, an amount equivalent to 0.35g of chlorpromazine HCl was transferred into a 250ml conical flask containing 100ml of acetone. The mixture was shaken and 10ml of 5% w/v mercuric acetate and 3ml of methyl orange/acetone solution were added. The solution was stirred for 15 min with a magnetic stirrer and then titrated with 0.1M acetous perchloric acid to a blue end-point. For the potentiometric method, the methyl orange indicator was omitted and the end-point was determined potentiometically. All the determinations were done in triplicates. [24]

Spectrophotometric determination:
Twenty tablets of each brand were accurately weighed and reduced to fine powder. From the powdered drug, an amount equivalent to 0.05g of chlorpromazine HCl was taken and transferred into a 500ml volumetric flask containing 5ml of 2M HCl and 200ml of distilled water. The mixture was shaken for 15 min with a magnetic stirrer and then diluted to the 500ml with distilled water. The mixture (50ml) was centrifuged at 1000 rpm for 15 min and 5ml of a clear supernatant was pipetted into a 100ml volumetric flask. Hydrochloric acid (10ml of 1M) was added to this solution and made up to the 100ml with distilled water. The absorbance of the resulting solution was then taken at 254nm against a reagent blank of 10ml 1M hydrochloric acid solution diluted to 100ml with distilled water. The content of chlorpromazine HCl was calculated and all the determinations were done in triplicates. [25]

Results and Discussion

The results of the non-aqueous titration using acetic acid with mercuric acetate, acetone and spectrophotometry are given

Table: Assay of different brands of chlorpromazine HCl using non-aqueous titration and spectrophometry

Brand	Label claim/ Manufacturer	Non-aqueous Titration using acetic acid		Non-aqueous Titration using acetone		Spectrophotometric determination (%)
		Visual Indicators (%)	Potentiometer (%)	Visual Indicators (%)	Potentiometer (%)	
DAL	50mg, Ernest Chemist ltd, Ghana	97.87 ± 0.23	98.12 ± 0.16	98.52 ± 0.31	99.07 ± 0.23	97.74 ± 0.34
CPE	50mg, England	99.83 ± 0.37	100.28 ± 0.29	100.67 ± 0.27	99.85 ± 0.18	98.33 ± 0.26
CPM	100mg, Kinapharma ltd, Ghana	94.97 ± 0.22	95.31 ± 0.17	95.33 ± 0.15	95.08 ± 0.20	94.71 ± 0.29
CPK	100mg, XL-Laboratory PVT ltd, India	98.75 ± 0.31	97.82 ± 0.24	99.45 ± 0.36	98.84 ± 0.28	97.17 ± 0.30
CPH	100mg, Medopharm malur-India	96.53 ± 0.21	95.88 ± 0.19	96.37 ± 0.23	96.05 ± 0.19	95.29 ± 0.25
CPZ	100mg, Hans-E-lembcke, Germany	99.67 ± 0.27	100.28 ± 0.15	99.48 ± 0.25	99.71 ± 0.34	98.89 ± 0.21

in the Table. Some of the official monographs ((International Pharmacopeia [24], British Pharmacopoeia [25] and United States Pharmacopoeia [26]) specified perchloric acid titration for the assay of chlorpromazine HCl. Results of the assay using acetic acid with mercuric acetate was not significantly different from those of the spectrophotometric assay method (2-tailed $p<0.05$; 95% confidence interval). All the brands passed the different assay tests since they were all within the acceptable range of 92.5 – 107.5%. [25]

The addition of mercuric acetate in the non-aqueous titrimetric method is based on the principle of removing the chloride counter ion so as to prevent the interference of the halide ion released by the titrant (acetous perchloric acid). The addition of mercuric acetate (which is undissociated in acetic acid) replaces the halide ion in chlorpromazine with a quantitative acetate ion which is a strong base in acetic acid. An intense red coloured oxidation product was formed when ascorbic acid was not added. This made end-point detection with visual indicators to be difficult. The addition of ascorbic acid solution prevents the formation of the red colouration due to the reduction of ascorbic acid to dehydroascorbic acid. It has been shown that ascorbic acid and its oxidation product (dehydroascorbic acid) are neutral to acetous perchloric acid and do no interfere with the titration. [23] Thus, the addition of ascorbic acid allows titrations using a visual indicator and also sharpens the potentiometric end-point. When acetone was employed as the solvent in the place of glacial acetic acid, there was no colour formation which means that the oxidation of chlorpromazine does not occur in acetone. However, because of the questionability of the non-aqueous titrimetric method resulting from the catalyses of oxidation by the necessary addition of mercuric acetate, the British Pharmacopoeia (BP) later adopted the spectrophotometric method for the determination of chlorpromazine and other phenothiazines. This method we are reporting has overcome the problem for which non-aqueous titration was discontinued in the BP.

Conclusion

A non-aqueous titrimetric method for the assay of chlorpromazine tablet, using glacial acetic acid or acetone as solvents, has been successfully developed. The method is simple, cheap and reliable, and produced assay results that are not significantly different from those of the official monographs assay methods. It can easily be used in the quality control of chlorpromazine dosage forms.

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