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QUALITY EVALUATION OF THE COMMONLY PRESCRIBED ANTIPSYCHOTIC DRUGS (CHLORPROMAZINE & THIORIDAZINE TABLETS) MARKETED IN ETHIOPIA

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Keywords:

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ABSTRACT: The purpose of this study was to evaluate the quality of the commonly prescribed imported and locally manufactured antipsychotic drugs (chlorpromazine and thioridazine tablets) that are marketed in drug retail outlets in Ethiopia. Four different sources of Chlorpromazine and two thioridazine tablets were assessed in this investigation. The quality of the samples was examined in seven aspects: percent label amount (assay), weight variation, hardness, percent friability, purity, disintegration time and dissolution rate according to British pharmacopeia (2000) specification. The identity of the tablets was confirmed using FT-IR spectrophotometer. All chlorpromazine and thioridazine samples showed acceptable weight variation as none had percent deviation in weight greater than 5% as stipulated by BP (2000). The mean disintegration times of the products ranged from 4.50 ±0.84 (for chlorpromazine from Cyprus) to more than 60 min (for chlorpromazine Korea). All the tested samples showed active ingredient content with in the acceptable range (from 92.5%-107.5%). Thioridazine 25 mg showed high drug content (107±0.5) and the lowest amount was recorded for chlorpromazine from Cyprus (93.0 ±0.8). Most of the studied samples showed a good drug release pattern except Chlorpromazine tablets from Korea which did not pass the pharmacopeial specification for disintegration time and dissolution rate studies. So this specimen does not meet the quality requirements for tablets. This implies that the product may not release a significant amount of the drug on absorption in to the systemic circulation and thus leading to therapeutic failure. Chlorpromazine from Cyprus released the 50 and 70% of the active drugs with in 8.3 and 13.8 minutes respectively, showing a good drug release pattern than the others. Chlorpromazine (Ethiopia) took 19.0 and 31.1 minutes to release 50% and 70% of the drug respectively.

INTRODUCTION: Treatment with antipsychotic drugs has been a mainstay and management of psychotic patients internationally for nearly a half-century [1, 2].

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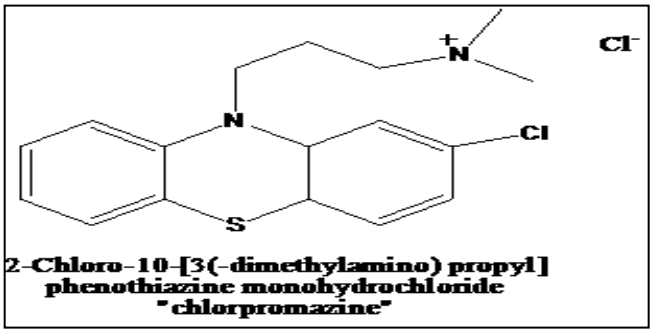
Psychotropic or psychoactive drugs are chemicals that affect the brain and the nervous system; alter feelings, emotions, and consciousness in various ways; and frequently are used therapeutically in the practice of psychiatry to treat a broad range of mental and emotional illness [3]. The phenothiazines have in common a three-ringed structure, with two benzene rings linked by S and N atoms [4]. 2, 10- di substituted phenothiazines are the best drugs in psychiatry characterized by a tricyclic ring with Sulphur and Nitrogen atoms at position 5 and 10 respectively [5].

The phenothiazines as a class especially chlorpromazine and thioridazine are the most commonly used drugs in these group [6]. None of the phenothiazines is superior in overall therapeutic efficacy to chlorpromazine [7]. Thioridazine is a very powerful neuroleptic agent used only as a last resort and needs to be very closely monitored [8]. Even though several dozen antipsychotic phenothiazines and several more isosteres had been introduced worldwide, chlorpromazine remains one of the most common drugs used for people with schizophrenia and a benchmark against which other treatments can be evaluated [9]. Hence the World Health Organization (WHO) have endorsed and included chlorpromazine in their list of essential drugs for use in schizophrenia. Thioridazine is now indicated only for the treatment of schizophrenia in patients who have failed treatment with at least two other antipsychotic drugs [10].



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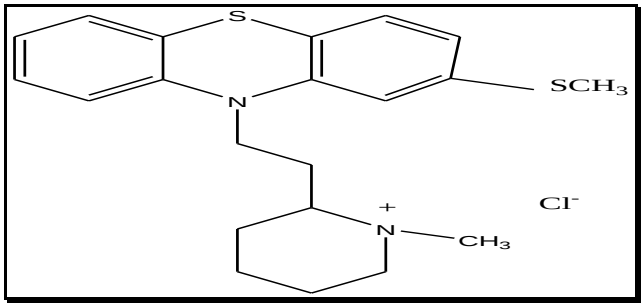

b. 2-methylmercapto-10-[2-(N-methyl-2-piperidyl) ethyl] phenothiazine hydrochloride

FIGURE 1: A. STRUCTURE OF CHLORPROMAZINE AND ITS CHEMICAL NAME B. STRUCTURE OF THIORIDAZINE HYDROCHLORIDE AND ITS CHEMICAL NAME

Recently, chlorpromazine and thioridazine have been shown to have activity against multidrug-resistant strains of *Mycobacterium tuberculosis* [11], enhanced the activities of rifampicin and streptomycin against poly-drug resistant strains of *M. tuberculosis.* Thioridazine is used as an adjuvant for the four- and five-drug regimens used for the management of tuberculosis caused by multi- or poly-drug resistant organisms [12,13], had been implied in lower incidence of cancer by strongly inhibiting the effects on various enzymes those involved in carcinogenesis [14]. Chlorpromazine displayed a wide range of activity against viruses, bacteria (a wide range of *Salmonella* spp) and protozoa [15]. More over these groups of drugs have activity against *Schistosoma mansoni, Trypanosoma brucei, Trypanasoma gambiensi, Molinema dessetae, Leishmania spp., Plasmodium falciparum* and free-living *protozoa*.

These organisms and other parasitic infections are prevalent in HIV-infected humans and are becoming more frequently resistant to commonly employed antibiotics. Furthermore, their prevalence is known to be greatest in areas that have high rates of HIV infection [16]. Patients presenting with Acquired Immune Deficiency Syndrome (AIDS) are predisposed to co-infection with *Mycobacterium avium*. The management of such patients is problematic due to underlying immuno-incompetence and the high resistance of *M. avium* to most non-toxic compounds but thioridazine was the most active of the group against *M. avium* [17, 18]. So it would be necessary that these agents should receive close scrutiny.

Quality control must be administered in order to prevent the kind of product which is not suitable for the aims prescribed. Quality can be defined as the suitability of the goods or service to the determined qualifications [19]. Drug quality is a source of great concern worldwide, particularly in many developing countries [20]. The quality of medicines on the market in several countries has become a major cause for concern; surveys show that up to 20% or more of sampled medicines failed quality control tests. Failure of effective control mechanisms has led to the presence of fake or sub-standard drugs in many countries.

In several developing countries drug quality is a source of concern, because the quality of medicines available in these countries is inadequate and there is a general feeling that there is a high incidence of drug preparations which are not of acceptable quality [21, 22]. Reasons for the poor quality of drugs include widespread counterfeiting of medicines in less-developed countries, excessive decomposition of active ingredient (chemical instability) as a result of high temperature and humidity especially

in tropical climates and poor quality assurance during the manufacture of medicinal products [23]. Because consumers and prescribers are unable to assess their quality, safety and efficacy.

- One-third of the world's population has no guaranteed access to essential drugs, and
- Poor quality pharmaceutical raw materials and finished products continue to move in international trade [24].

During the past few decades, many pharmaceutical industries and distribution channels have flourished throughout the world, leading to an increase in the number of products circulating in national and international markets. At the same time, however, the presence of counterfeit and substandard drugs in those markets has increased substantially as a result of ineffective regulation of the manufacture of and trade in pharmaceutical products by both exporting and importing countries [20].

More over the import of pharmaceuticals to the 3rd World or their local production is oriented more to profit-making than to the satisfaction of the health needs of people. Among the problems in the field of marketing are the lack of qualified personnel in most 3rd World pharmacies, the common practice of many doctors to sell drugs they themselves prescribe and the lack of adequate information concerning the different drugs available on the market. This is due to economic reasons and to the lack of adequate quality control laboratory facilities [25].

The combination of market force, the low per capital spending on pharmaceuticals by most of the population in less developed countries and the lack of adequate resources for controlling and monitoring the quality of drug on the market creates an environment favorable for introducing low quality of drugs. Therefore, the quality of drugs must be guaranteed as in the opposite scenario counterfeit and substandard drugs could result an increase suffering and treatment costs [26].

Use of poor drug quality bears serious health implications such as treatment failure adverse reaction, drug resistance, increase morbidity and mortality; it can erode public confidence in a country's health program and wastes scarce resources. It can also severely affect the business of the manufacturer whose product are being copied through loss of confidence as well as revenue [27]. The phenothiazines; chlorpromazine and thioridazine, are used for long duration, so there is a chance for tolerance and hence relapse especially if the drug is substandard or counterfeited [14, 28]. This can be achieved by a preliminary physicochemical assessment of the product and *in vitro* dissolution testing which is a valuable predictor of the *in vivo* bioavailability and bioequivalence of oral solid dosage forms [26].

Based on such facts, this project is intended to evaluate the quality of the commonly prescribed either imported or locally manufactured antipsychotic drugs (chlorpromazine and thioridazine tablets) that are marketed in drug retail outlets in Ethiopia.

MATERIALS AND METHODS:

Materials

Chlorpromazine and Thioridazine (25mg and 100mg) tablets produced by different manufacturers were collected from various drug retail outlets in Ethiopia. Details of the chlorpromazine and thioridazine tablets evaluated in the study are given in **Tables 1 a** and **b.**

TABLE 1 A: DETAILS OF CHLORPROMAZINE TABLETS SAMPLES EVALUATED IN THE STUDY

Product	Manufacturer	Bach Number	Manufacturing date	Expiration date
Chlorpromazine 100mg	Epharm (Ethiopia)	512234	12/2005	12/2008
Chlorpromazine 100mg	Kwang Myung (Korea)	402	12/2004	12/2007
Chlorpromazine 100mg	Remedica (Cyprus)	5104	5/2004	5/2009
Chlorpromazine 25 mg	Shangie (China)	031001	10/2003	10/2006

TABLE 1 B: DETAILS OF THIORIDAZINE TABLETS SAMPLES EVALUATED IN THE STUDY

Product	Manufacturer	Bach Number	Manufacturing date	Expiration date
Thioridazine 100mg	Ramedica (Cyprus)	19803	2/2003	2/2008
Thioridazine 25mg	Ramedica (Cyprus)	19277	11/2002	11/2007

Reagents and solvents

Hydrochloric acid GRG (Avondale Laboratory, Ban bury, Oxon, England), Ethanol absolute GRG (International Ltd, England), Diethyl amine (Scharlu Chamie S.A., Barcelona, Spain), Acetone (Fluka RiedeldeHain ChemieGmbh CH9471, Switzerland), Diethyl ether GPR (PROD, 281325F), Sodium hydroxide GR (MERK, C251395), Methanol (RiedelDeHaen 24229), Isopropyl alcohol Extra pure (Scharlau AL0311), Anhydrous sodium sulphate (Merck 2584333), cyclohexane (BDH, AnalaR K31785574), acetic acid (Fluka 4573133209), Potassium iodide (Evancs, medical Ltd, 7D550D),Chloroform (NATASO,CA120), Ammonia (BDH AnalaRB5O1007420).

Equipment's /Instruments

Analytical balance (Avery Berkel FA 214), Disintegration tester (PHAMA Test, PT 2E), Friability Tester (PHARMA test, GmbH, Heusetam Germany), Hardness tester (CALEVA) Dissolution test Apparatus (PHARMA Test PTW11), UV-Spectrophotometer (SPECTRONIC® GENESIS™ 5, spectronic instrument, U.S.A), FT-IR spectrophotometer (Perklin Elmer), Flask shaker SF1 (Stuart scientific, U.K).

Methods

The quality of the tablets was assessed according to the British pharmacopeia specifications BP, 2000 [29]. The quality of the samples was examined in seven aspects: percent label amount, weight variation, hardness, percent friability, purity, disintegration time and dissolution rate [30, 31]. All the samples analyzed during this study were within their shelf life at the time of the investigation.

Identification tests

Identification test for chlorpromazine tablets

To a quantity of the powdered tablets containing 40 mg of Chlorpromazine HCl, 10 ml of water and 2 ml of 10M sodium hydroxide was added. The mixture was agitated vigorously and extracted with 15 ml of ether. The ether layer was then washed with two 5-ml quantities of water, dried with anhydrous sodium sulphate and the ether was evaporated. The residue was dissolved in 0.4 ml of chloroform. Then the infrared absorption spectrum of the resulting solution was examined in the form of a thin film between two plates transparent to infrared radiation using Fourier transform infrared spectrophotometer. According to the British pharmacopeia the infrared spectrum of the test sample must be concordant with the reference spectrum of chlorpromazine found in the British pharmacopeia.

Identification test for thioridazine tablets

To a quantity of the powdered tablets containing 40 mg of Thioridazine HCl, 10 ml of water and 2 ml of 1M sodium hydroxide was added, shacked and extracted with 15 ml of ether. The ether was washed with 5 ml of water, dried with anhydrous sodium sulphate and evaporated to dryness. The residue was examined after dissolved in a suitable solvent (chloroform). The infrared absorption spectrum of the resulting solution was examined in the form of a thin film between two plates transparent to infrared radiation using Fourier transform infrared spectrophotometer to see whether the result was concordant with reference spectrum of thioridazine in the BP (2000) or not.

Tablet weight variation

Twenty tablets selected at random were weighed individually and the percentage weight variations and standard deviations were calculated to determine the weight uniformity. According to BP (2000) not more than two of the individual weights (masses) deviate from the average weight (mass) by 7.5% and none deviates by more than 15%.

Hardness and Diameter Tests

Ten tablets from each product were individually placed between the plates of integrated hardness and diameter tester. Values for tablet hardness and diameter were recorded simultaneously.

Friability Test

Friability test was done only for one product of the tablets (chlorpromazine from Cyprus) because all the other products were coated tablets. Twenty tablets from the product were dedusted and weighed using an analytical balance (Avery Berkel FA 214). The tablets were then placed in the drum of friability tester (PHARMA Test, Gmbh, PTF10E, and Hainburg) and rotated at 25 rpm for four minutes (100 times). The tablets were re-dedusted, re-weighed and the difference between the weight of the tablets before and after the rotation was determined. Percentage weight loss was calculated. According to BP (2000) the tablets should not loss more than 1% of the total weight

Disintegration Test Disintegration test on the tablets was carried out using PHARMA Test PT2E,

disintegration apparatus. Six tablets from each product were put in to each tube of the disintegration basket maintained in distilled water at 37.5^0c as a media of disintegration. The British pharmacopeial specifications for maximum disintegration time for coated and uncoated tablets were used to evaluate the samples. Tablets were considered completely disintegrated when all the particles pass through the wire mesh except scratches of the coating material.

Purity (Related substance) test

Chlorpromazine tablets

Purity of the chlorpromazine tablets was tested according to British Pharmacopeia using pre-coated thin layer chromatography plates, silica gel GF_{254} as the stationary phase and a mobile phase containing a mixture of 10 volumes of acetone, 10 volumes of diethylamine and 80 volumes of cyclohexane. Two test solutions were freshly prepared as follows.

Solution 'A': a quantity of the powdered tablets containing 0.1 g of chlorpromazine HCl was extracted with 10 ml of a mixture of 95 volumes of methanol and 5 volumes of diethylamine and filtered.

Solution 'B': 1 volume of solution 'A' was diluted to 200 volumes with the same solvent mixture.

10 µl of each of the two test solutions of the substance being examined were spotted separately on the plates and developed in the above mentioned mobile phase. After removal of the developed plate, it was allowed to dry in air and examined under ultraviolet light (254 nm*)*. Any spot remaining on the line of application was disregarded. Any secondary spot in the chromatogram obtained with solution 'A' could not be more intense than the spot in the chromatogram obtained with solution 'B' (0.5%).

Thioridazine tablets

Purity test for thioridazine was done with the same kind of pre-coated TLC plate as in the test for chlorpromazine but with different mobile phase and method of sample preparation.

The mobile phase was a mixture of 74 volumes of chloroform, 25 volumes of propan-2-ol and 1 volume of 13.5M ammonia. 5 µl of each of the following sample solutions were applied separately to the plates.

The test solutions were prepared as follows. **Test solution 'A'**: a quantity of the powdered tablets containing 50 mg of Thioridazine HCl were extracted with 5 ml of a mixture of 2 volumes of 13.5M ammonia and 98 volumes of methanol, centrifuged and the supernatant liquid was used.

Test solution 'B': 1 volume of test solution 'A' was diluted to 200 volumes with the solvent similar to the one used in the preparation of test solution 'A'.

Test solution 'C': 1 volume of Test solution 'A' was diluted to 500 volumes with the solvent similar to the one used in the preparation of solution 'A'. The three test solutions were spotted on a silica gel plate and developed using the mobile phase given above for thioridazine. After removal of the developed chromatogram, it was allowed to dry in air and sprayed with a freshly prepared mixture of 1 volume of potassium iodobismuthate solution and 10 volumes of 2M acetic acid and then with freshly prepared hydrogen peroxide solution (10 vol).

The sprayed plate was immediately cover with a clear glass plate of the same size and examined under ultraviolet light (254 nm*)*. Any secondary spot in the chromatogram obtained with solution 'A' could not be more intense than the spot in the chromatogram obtained with solution 'B' and not more than one such spot was more intense than the spot in the chromatogram obtained with solution 'C'. Any spot with an R_F value lower than 0.1 was disregarded. The test was not valid unless the spot in the chromatogram obtained with solution 'C' was clearly visible.

Dissolution Test

The dissolution tests of chlorpromazine products were carried out according to BP (2000) specifications and the dissolution test for thioridazine tablets were carried out according to USP 1999 [32] specifications using a 6 Flask apparatus, paddle method or type II (PHARMA Test PTW11) apparatus.

Dissolution profile test for chlorpromazine HCl

The dissolution media contained 900ml of 0.1N HCl. The rotation speed of the apparatus was hold constant at 50 rpm and the temperature of the dissolution media was maintained throughout the test period at 37 ± 0.5 ^{0}c. Samples of 10 ml were withdrawn from the dissolution media and immediately substituted with equal volume of the

dissolution media maintained at 37^0c in a and 60 minutes. After the necessary dilution, solution from each flask was filtered using whatman No. 1 filter paper. The absorbance of the solutions was measured at 254 nm. The total content of chlorpromazine HCl was calculated by taking 914 as the value of A (1%, 1 cm) at the maximum at 254 nm using Beer-Lambert formula. Not less than 70% (Q) of the labeled amount of chlorpromazine HCl is expected to be dissolved in 45 minutes.

Dissolution profile test for thioridazine HCl

The dissolution profile test of thioridazine tablets was done according to USP 1999 [32]. The dissolution media contained 1000ml of 0.1N HCl. The rotation speed of the apparatus was hold constant at 75 rpm and the temperature of the dissolution media was maintained throughout the test period at 37 ± 0.5 ^{0}c. Samples of 10 ml were withdrawn from the dissolution media and immediately substituted with 10 ml of the dissolution media maintained at 37^0c in a predetermined time interval, i.e., at 10, 20, 30, 40, 50, 60 and 70 minutes.

After the necessary dilution, solution from each flask was filtered using watman No 1 filter paper.The absorbance of the solutions was measured at 262 nm. The total content of thioridazine HCl was calculated by taking 987as the value of A (1%, 1 cm) at the maximum 262 nm using Beer-Lambert formula. Not less than 70% (Q) of the labeled amount of thioridazine HCl is expected to be dissolved in 60 minutes. Necessary corrections for dilution were made when calculating the amount of drug released at each sampling time.

Assay Methods

The content of chlorpromazine HCl and thioridazine HCl were determined using UV-spectrophotometer in accordance with an adopted method for each tablets of the BP 2000.

Method for assay of chlorpromazine HCl

10 tablets of chlorpromazine HCl were powdered without loss, triturated with 10 ml of absolute ethanol; about 300 ml of 0.1M hydrochloric acid was added and shaked for 15 minutes. Sufficient quantity of 0.1M hydrochloric acid was added to adjust volume to 500 ml, and filtered. A volume of the filtrate equivalent to 5 mg of chlorpromazine HCl was diluted to 100 ml with 0.1M hydrochloric acid and 10 ml of this solution was further diluted to 100 ml with the same solvent. The absorbance of the resulting solution was measured at a wave length of 254 nm. The content of chlorpromazine HCl was calculated taking 915 as the value of A (1%, 1 cm) at the maximum at 254 nm using Beer-Lambert formula.

Method for assay of thioridazine HCl

20 tablets were Weighed and powdered. 80 ml of ethanol (96%) was add to a quantity of the powder containing 50 mg of thioridazine HCl, shacked for 20 minutes and filtered through a sintered-glass filter. The residue was washed with ethanol (96%) and sufficient ethanol (96%) was added to the filtrate and washings to produce 100 ml. Then 10 ml this solution was further diluted to 100 ml with ethanol (96%) and 5 ml of this solution was again diluted to 50 ml with ethanol (96%). The absorbance of the resulting solution was measured at a wave length 264 nm. The content of thioridazine HCl was calculated taking 950 as the value of A (1%, 1 cm) at the maximum at 264 nm using Beer-Lambert formula.

RESULTS AND DISCUSSION:

Identification test

Infrared spectrums obtained for chlorpromazine HCl tablets were concordant with that of the reference spectrum of chlorpromazine HCl in the BP reference spectra. All chlorpromazine HCl tablets comply with the identification test. Also the IR spectrums obtained from thioridazine HCl tablets were concordant with that of the reference spectrum of thioridazine HCl in the BP. All thioridazine HCl products also comply the test as well.

Weight variation

The uniformity of dosage units can be demonstrated by either of two methods, weight variation or content uniformity [36]. In this work the weight variation method was used. As shown in the **Tables 2 a** and **b** below all chlorpromazine HCl and thioridazine HCl tablets agree well with the requirements set in BP (2000).

As shown in **Tables 2 a** and **b**, all products showed acceptable uniformity of weight as none had percentage deviation in weight for the pharmacopeial specification. The significance of this test is to ensure that the tablets in each lot are within the appropriate size range.

TABLE 2A: SUMMARIES OF PHYSICAL PARAMETERS OF THE STUDIED CHLORPROMAZINE TABLETS

Drug Product	Average weight(g) ±SD	Average diameter (mm) ±SD	Average Hardness (N)	Average Disintegration Time (Min)±SD
Chlorpromazine 100 mg (Epharm)	0.508 ± 0.025	8.1 ± 1.90	165.1	23.33 ± 2.34
Chlorpromazine100 mg (Korea)	0.413 ± 0.017	9.4 ± 1.10	120.3	> 60 min
Chlorpromazine100 mg (Cyprus)	0.412 ± 0.008	10.7 ± 0.02	121.0	4.50 ± 0.84
Chlorpromazine 25 mg (China)	0.111 ± 0.004	3.7 ± 0.34	94.1	13.70 ± 1.21

TABLE 2B: SUMMARIES OF PHYSICAL PARAMETERS OF THE STUDIED THIORIDAZINE TABLETS

Drug product	Average weight(g) ±SD	Averagediameter (mm) ±SD	Average hardness(N)	Mean disintegration time (Min) ±SD
Thioridazine 100 mg (Cyprus)	0.503 ± 0.011	6.33 ± 0.06	180.0	17.3 ± 1.86
Thioridazine 25 mg (Cyprus)	0.206 ± 0.005	4.53 ± 0.30	126.6	35.5 ±1.50

As shown in **Tables 2 a** and **b**, all products showed acceptable uniformity of weight as none had percentage deviation in weight for the pharmacopeial specification. The significance of this test is to ensure that the tablets in each lot are within the appropriate size range.

Hardness

Adequate tablet hardness and reasonable friability are among the quality parameters of conventional tablets. Tablets that have hardness greater than 50 N and that loss less than 1 % of their weight after friability tester are generally considered acceptable [29].

The results in **Table 2 a** and **b** showed that the samples examined had mean hardness within the range. All the tested products gave a hardness value greater than 50 N; hence all products pass the pharmacopeial requirement for hardness test but the average hardness of the products is different from each other i.e. higher (180 N thioridazine 100 mg) and lower (94.1 N, chlorpromazine of China) hardness values were registered because there are different factors that may alter tablet hardness such as alteration in machine speed, change in particle size distribution of granulation mix and lubricants. Dies filled with large particles of low density granules will produce softer tablet than dies filled with small particles of high density granules. Tablet hardens will be significantly affected if lubricants are used in too high concentration.

Friability

Crushing strength test may not be the best measure of potential tablet behavior during handling and packaging. The resistance to surface abrasion may be more relevant parameter. In this work the percentage friability of the tablet evaluated (chlorpromazine from Cyprus) was 0.12%; which is less than the maximum limit (1%) specified in the British pharmacopeia. The tablet is conformed to fulfill the required standard for friability.

Disintegration time

The mean disintegration times of the tested products are presented in **Tables 2 a** and **b** for chlorpromazine and thioridazine tablets respectively. The maximum disintegration time limit for coated tablets except film coated tablets in the British pharmacopeia in aqueous media is 60 minutes. All the tablets both chlorpromazine and thioridazine tablets disintegrate with in this range except chlorpromazine tablets from Korea. From the tablets that complied with the pharmacopeial specifications, the highest disintegration time were observed at 23.33 minutes for chlorpromazine of Epharm product and 35.5 minutes for thioridazine 25 mg tablets, whereas the shortest average disintegration time was 4.5 minutes for chlorpromazine from Cyprus. This is because chlorpromazine from Cyprus was uncoated but all the rest are sugar coated. More over these variations in disintegration time might be due to variation in the quality and quantity of the tablet excipients (binder and disintegrant) added and the variation in cohesive strength introduced into the mass by compression force used by different manufacturers.

Purity (Related substance) test

Related substances may be manufacturing impurities (intermediates or by-products) or degradation products or both.

It is usual for the Pharmacopoeia to require the absence of a visible spot in a thin-layer chromatogram or the absence of a peak in a liquid chromatogram. This may be done in a simple test by comparison with a spot or peak obtained with a

dilute solution of the substance being examined [29, 33].

Purity test of chlorpromazine tablets

In this work for all chlorpromazine tablets any secondary spot obtained with the concentrated solution (solution A) was less intense blue color than the spots obtained for the lower concentration (solution B); all chlorpromazine tablets fulfill the pharmacopeial requirement for related substances test.

Purity test of thioridazine tablets

In the purity test for thioridazine tablets, secondary spots were seen in all the three solutions (solution A, B, & C); and there were no difference in intensity of the spots produced in each solution. Secondary spot in the chromatogram obtained with solution (A) was not more intense than the spot in the chromatogram obtained with solution (B) (0.5%) and not more intense than the spot in the chromatogram obtained with solution (C) (0.1%), the tablets pass the pharmacopeial requirement for related substance test. The importance of this test is to control the quantity of specific impurities or group of impurities in the drug product.

Dissolution profile studies

In this work the dissolution profile study was carried out for all chlorpromazine and thioridazine products. Percent release of the active ingredients from each product is given in **Tables 3 a** and **b** and the dissolution profiles of chlorpromazine and thioridazine products are presented in **Figures 2 a** and **b**, respectively.

TABLE 3a: DISSOLUTION PROFILE RESULT OF CHLORPROMAZINE TABLET EVALUATED IN THE STUDY

	Percent Released			
Time in min.	Chlorpromazine Epharm (Ethiopia)	Chlorpromazine Kwang Myung (Korea)	Chlorpromazine Remedica (Cyprus)	Chlorpromazine Shangie (China)
10	28.00	1.75	60.00	7.70
20	52.00	5.90	87.80	47.10
30	68.60	9.45	89.35	76.25
45	83.54	66.00	90.00	87.30
60	85..45	87.00	89.70	86.50

TABLE 3b: DISSOLUTION PROFILE RESULT OF THIORIDAZINE TABLETS

TIME MIN	**PERCENT RELEASED**	
	Thioridazine 100 mg (Cyprus)	**Thioridazine 25 mg (Cyprus)**
10	7.50	4.00
20	83.80	86.13
30	92.00	85.80
40	98.08	84.82
50	95.40	80.00
60	88.70	80.00
70	83.10	80.00

TABLE 4a: DISSOLUTION PARAMETERS ($T_{50\%}$ AND $T_{70\%}$) OF CHLORPROMAZINE TABLETS OF DIFFERENT MANUFACTURERS

Product	**Manufacturer**	**$T_{50\%}$ (min)**	**$T_{70\%}$(min)**
Chlorpromazine 100 mg	Epharm (Ethiopia)	19.0	31.1
Chlorpromazine 100 mg	Kwang Myung (Korea)	40.7	48.0
Chlorpromazine 100 mg	Remedica (Cyprus)	8.3	13.8
Chlorpromazine 25 mg	Shangie (China)	21.0	27.7

TABLE 4b: DISSOLUTION PARAMETERS ($T_{50\%}$ AND $T_{70\%}$) OF THIORIDAZINE TABLETS

Product	**Manufacturer**	**$T_{50\%}$ (min)**	**$T_{70\%}$(min)**
Thioridazine 100mg	Ramedica (Cyprus)	15.3	18.0
Thioridazine 25 mg	Ramedica (Cyprus)	15.3	18.0

As can be seen from **Tables 3a** and **Figures 2a,** different chlorpromazine tablets have different drug release patterns; all chlorpromazine tablets except the Korean product pass the single point dissolution test specified in BP 2000. High drug release pattern was seen by chlorpromazine from Cyprus, and the other product showed a good drug release pattern except chlorpromazine from Korea which show a delayed drug release pattern until the 40th minute. This may be due to the slow disintegration of the tablet and hence the nature of the excipients used or problem of the formulation or processing variables.

This implies that the product may not release a significant amount of the drug on absorption in to the systemic circulation and thus leading to therapeutic failure.

As can be seen from **Table 3b** and **Figure 2b**, both thioridazine tablets showed a good drug release pattern and both products passed the single point dissolution test specification of USP 1999.

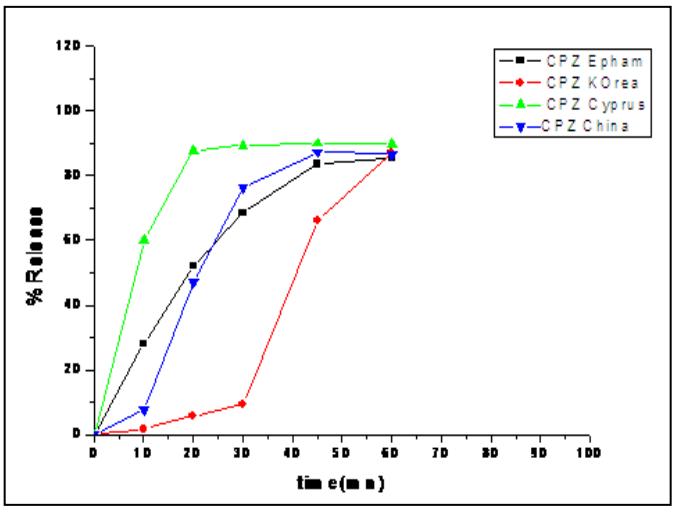

FIGURE 2a: DISSOLUTION PROFILE OF DIFFERENT CHLORPROMAZINE TABLETS

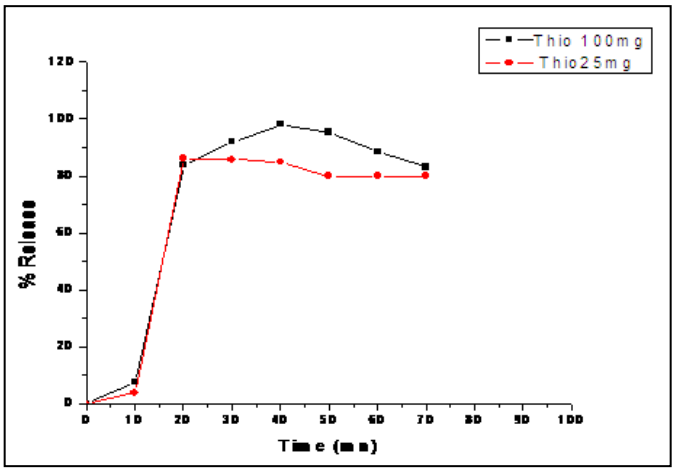

FIGURE 2b: DISSOLUTION PROFILES OF THIORIDAZINE TABLETS

Each chlorpromazine and thioridazine drug products showed different drug release pattern. From the $T_{50\%}$ and $T_{70\%}$ (the time elapsed for 50% and 70%of the drug to be released from the tablet) of chlorpromazine and thioridazine tablets shown in **Tables 4a** and **4b** each product was released 50% and 70 % of the drug at different time. The drug release pattern of all the tablets varies from one product to another; this shows that there may be a difference in the bioavailability of the drugs which will result in variation in therapeutic efficacy. Chlorpromazine sample from Remedica (Cyprus) released 70% of its content before 15 minutes.

Chlorpromazine tablet form Korea took longer time to release 50% and 70% of their active ingredient. Very long $T_{50\%}$ and $T_{70\%}$ recorded for chlorpromazine from Korea (45 and 48 minutes respectively) indicates that this could result in lower rate and extent of bioavailability in the body and hence result in therapeutic failure. This difference in drug release pattern is due to difference in processing and formulation variables. Processing and formulation variables which influence dissolution includes; nature of the diluents, granule size, distribution nature and concentration of the lubricant physical property of the drug and compression force used in production[34]. Quite a number of formulation variables are reported to have a significant effect on the dissolution rate of solid dosage forms e.g. increase in binder concentration results in a decrease in dissolution rate of tablets [35].

The dissolution rates of tablets were found to increase with decreasing granule size and decreasing disintegrant concentration. Hydrophilic lubricants (magnesium stearate) retard dissolution, while a water soluble lubricant was found to enhance the dissolution rate [36-38].

A decrease in drug release pattern of each tablet was seen which could be because of the fact that these drugs can decompose easily in exposure to air and light [39]. In addition the solubility of chlorpromazine HCl and thioridazine HCl decreased with the increase in pH which was too low to dissolve the whole amount of drug contained in a tablet at pH 8. The elevation or change of pH seemed to be mainly brought about by dissolution of some alkaline excipient like calcium carbonate.

After the 40th minute a large decrease in dissolution profile of thioridazine tablets at 75 rpm may be due to the dissolution of some alkaline excipients which remained in the mass at 50 rpm under the high agitation condition (75 rpm) and hence increase the pH of water which decrease drug solubility. As the alkaline excipient, calcium carbonate was deduced, since it is popularly used for sugar-coated tablets and, because of the low solubility and heavy specific gravity, the excipient will not disperse and hence not dissolve well in the test fluid at 50 rpm, a low speed. Also there may be

other excipients that might increase the pH of water and decrease the drug solubility[40].

Chemical Assay

Arguably the most important criterion in establishing the quality of a given drug preparation is its content of active ingredients [33]. The most obvious benchmark quality in this respect is the compliance of the preparation with pharmacopeial limits [21]. In this work the limits specified in the BP (2000) were used.

The result obtained from the assay of the four chlorpromazine products and the two thioridazine tablets evaluated in this study is presented in **Tables 5a** and **5b.**

According to BP (2000) chlorpromazine HCl and thioridazine HCl tablets are expected to contain not less than 92.5 percent and not more than the l07.5 percent of labelled amount of chlorpromazine HCl and thioridazine HCl.

TABLE 5a: DATA FOR ASSAY OF CHLORPROMAZINE HCL TABLETS OF FOUR DIFFERENT MANUFACTURERS

Name of product	Assay result (%) ± SD
Chlorpromazine Epharm (Ethiopia)	96.00 ± 2.3
Chlorpromazine Kwang Myung (Korea)	95.50 ± 0.4
Chlorpromazine Remedica (Cyprus)	93.30 ± 0.8
Chlorpromazine Shangie (China)	94.00 ± 0.7

TABLE 5b: DATA FOR ASSAY OF THIORIDAZINE HCL TABLETS

Name of product	Assay result (%) ±SD
Thioridazine 100 mg (Cyprus)	93.50 ± 3.8
Thioridazine 25 mg (Cyprus)	107.00 ± 0.5

As can be observed from data presented in **Tables 5a** and **5b** all the tested chlorpromazine and thioridazine tablets meet the British pharmacopeial requirements for content of active ingredient for chlorpromazine HCl and thioridazine HCl tablets respectively. One chlorpromazine tablet gave near the minimum requirement point 93.3 percent. This could be due to poor preparation techniques during formulation and subsequent manufacturing. An important characteristic of powder during mixing is segregation, which occurs due to difference in particle size which will result in non-uniformity of content.

CONCLUSION: This study attempted to evaluate the quality of different products of chlorpromazine and thioridazine tablets marketed in Ethiopia. The quality of the samples was examined in seven aspects: percent label amount, weight variation, hardness, percent friability, purity, disintegration time and dissolution rate. All tablets analyzed except chlorpromazine tablets from Korea passed all the BP quality specifications. Chlorpromazine from Korea did not pass the pharmacopeial specification for disintegration time and dissolution rate studies. This implies that the product may not release a significant amount of the drug for absorption in to the systemic circulation and thus leading to therapeutic failure.

However, further *in vivo* studies should be conducted to obtain complete picture of the bioavailability of tablets originated from different manufacturers. In developing countries like Ethiopia where the Drug control might be weak, the quality of marketed drug products cannot be guaranteed always so evaluation of the marketed products could give an insight as to the quality of many drug products sold and consumed and could lay bases for future corrective measures. Moreover, regulatory mechanisms must be strengthened and enforced to improve the quality of drugs available in the country.

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