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Review

The determination of chlorpromazine, related impurities and degradation products in pharmaceutical dosage forms

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Abstract The literature relating to the determination of chlorpromazine, related impurities and degradation products in pharmaceutical preparations is reviewed Related impurities and degradation products are defined and official methods of analysis are described Analytical methods including gravimetric, titrimetric ultraviolet-visible spectrophotometric, chromatographic and electrochemical techniques are discussed

Keywords *Chlorpromazine, related impurities, degradation products, pharmaceutical dosage forms, review*

Introduction

The 10-substituted phenothiazine derivatives constitute one of the largest drug classes in the official monographs in the *British Pharmacopoeia* 1980 [1] and the *United States Pharmacopeia* XXI 1985 [2] Chlorpromazine, 2-chloro-10-[3-dimethylaminopropyl]-phenothiazine (**1**), is an important member of this group and has wide clinical application in psychiatry as an anti-psychotic drug [3] It is medicinally presented as an elixir, tablet, injection, suppository or syrup The widespread use of chlorpromazine has led to the development of analytical methods for the determination of

(a) chlorpromazine in the pure drug state or in the various pharmaceutical dosage forms,
(b) related impurities in chlorpromazine samples,
(c) chlorpromazine degradation products in pharmaceutical dosage forms,
(d) chlorpromazine and its metabolites in biological samples following clinical administration of chlorpromazine

This review will concentrate only on the analytical methods that have been applied to the determination of chlorpromazine, related substances and degradation products in pharmaceutical dosage forms, i e (a) to (c) above

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Before elaborating the analytical methodologies, it will be necessary to define the degradation products and the "related impurities" found in formulated products Chlorpromazine is known to degrade to chlorpromazine sulphoxide (**2**) and eventually to chlorpromazine sulphone (**3**) through aerial oxidation, this degradation being promoted by the presence of moisture and exposure to light [4] The oxidative degradation of chlorpromazine proceeds via a semi-quinone free radical, and many dosage forms incorporate anti-oxidants (e g ascorbic acid and sodium metabisulphite) capable of reducing these free radicals back to chlorpromazine [5] Chlorpromazine sulphoxide, like chlorpromazine itself, is pharmacologically active and has also been implicated in the phototoxic side-effects associated with chronic administration of chlorpromazine [6–10] (Fig 1)

The *British Pharmacopoeia* 1980 [1] and the *United States Pharmacopeia* XXI 1985 [2] specify limits for impurities in chlorpromazine The *British Pharmacopoeia* 1980 [1] refers to these impurities as "related impurities" whilst the *United States Pharmacopeia* XXI 1985 [2] uses the phrase, "other alkylated impurities" These two terms are used to indicate compounds which are essentially substituted phenothiazines formed during the manufacture of chlorpromazine and include such compounds as 2-chloro-10-[3-methylaminopropyl]-phenothiazine (**4**), 2-chloro-10-[3-methyl-3-(3-dimethylaminopropyl)-aminopropyl]-phenothiazine (**5**), 2-chlorophenothiazine (**6**), 2-chloro-10-[3-dimethylaminopropyl]-phenothiazine N-oxide (**7**) and 2-chloro-10-[3-dimethylaminopropyl]-phenothiazine sulphoxide (**2**, chlorpromazine sulphoxide)

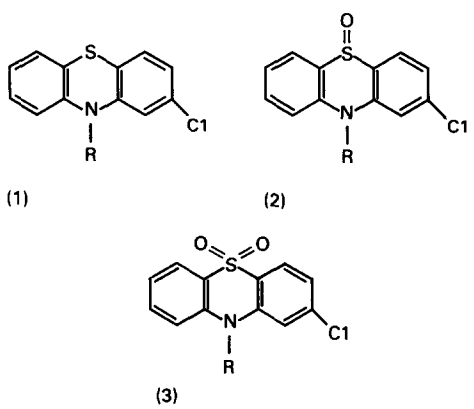

Figure 1
Chlorpromazine (**1**) and its degradation products chlorpromazine sulphoxide (**2**) and sulphone (**3**)

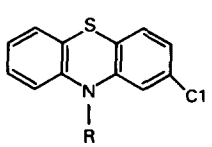

Figure 2
Common related impurities in chlorpromazine

(4) R = $CH_2CH_2CH_2NHCH_3$
(5) R = $CH_2CH_2CH_2NCH_3(CH_2CH_2CH_2N(CH_3)_2)$
(6) R = H
(7) R = $CH_2CH_2CH_2N(O)(CH_3)_2$

Pharmacopoeial Methods

Official methods [1, 2] for the assay of the pure drug substance, as the free base or as the hydrochloride salt, involve non-aqueous titration techniques with perchloric acid as the titrant In the *British Pharmacopoeia* [1] both substances are determined using potentiometric end-point detection In the *United States Pharmacopeia* [2] the assay of chlorpromazine hydrochloride also incorporates potentiometric end-point detection, whereas the free base is determined using an indicator (crystal violet)

The *United States Pharmacopeia* [2] utilises UV difference spectrophotometry for the determination of chlorpromazine or chlorpromazine hydrochloride in suppositories, injections, syrups or tablets Measurements at both 254 and 277 nm, on standard and sample solutions, are used in these assays The *British Pharmacopoeia* [1] also makes use of UV spectrophotometry for the assay of chlorpromazine and chlorpromazine hydrochloride in dosage forms However, measurement at a single wavelength (258 nm for chlorpromazine in suppositories and 254 nm for chlorpromazine hydrochloride in tablets, injections and elixirs) is used and results are calculated on the basis of stated absorptivity (A1%, 1 cm) values Both the *British Pharmacopoeia* and the *United States Pharmacopeia* describe thin-layer chromatography (TLC) methods for the semi-quantitative estimation of impurities in chlorpromazine dosage forms as well as in the pure drug substances The estimation of impurities by these TLC methods is based on a comparison of spot intensities and a maximum limit of 0 5% is specified The *United States Pharmacopeia* monograph for chlorpromazine hydrochloride injection also specifies a limit of 5% for chlorpromazine sulphoxide This is also measured semi-quantitatively by a TLC procedure

Gravimetric and Titrimetric Methods

Blazek and Stejskal [11] reported a gravimetric method, involving precipitation with tungstosilicic acid, for the analysis of chlorpromazine hydrochloride in pharmaceutical preparations Milne and Chatten [12] described a non-aqueous titrimetric method for the determination of promazine and chlorpromazine (free bases or hydrochlorides) as the pure substance or in pharmaceutical preparations The titration was carried out in acetone using perchloric acid with methyl orange as the indicator The endpoint was also determined potentiometrically The stated recoveries were 101% for both substances and the assay results obtained were reported to be comparable with the gravimetric method of Blazek and Stejskal [11] Soliman *et al* [5] also reported a non-aqueous titrimetric method for the determination of chlorpromazine The titration was carried out with acetous perchloric acid in glacial acetic acid containing ascorbic acid Visual end-point detection involved the use of crystal violet as the indicator, and this was checked potentiometrically During the non-aqueous titration of chlorpromazine in glacial acetic acid, the oxidizing effect of perchloric acid produces a red colouration due to the formation of semi-quinone free radicals which obscures the visual end-point determination For this reason, the official methods employ potentiometric rather than visual end-point detection In the work by Soliman *et al* [5] it was shown that the addition of ascorbic acid reduces the radicals back to chlorpromazine and enables a visual end-point determination to be made Deleo and Stern [13] investigated an aqueous thermometric titration method for the determination of chlorpromazine in pharmaceutical preparations However, the enthalpograms of test substances failed to give

distinctive end-points Agarwal and Blake [14] analysed chlorpromazine and other phenothiazine derivatives in dosage forms by an aqueous photometric titration method using cerium(IV) sulphate as the titrant The titration was monitored at 420 nm and the end-point was obtained from a plot of absorbance versus volume of titrant Initially, the addition of cerium(IV) sulphate produces the red coloured semi-quinone free radical which represents the first stage of oxidation Further oxidation results in the formation of chlorpromazine sulphoxide which is colourless On completion of the oxidation, further addition of cerium(IV) sulphate results in an increase in cerium(IV) ion concentration and consequently the absorbance at 420 nm increases

Ultraviolet-visible Spectrophotometric Methods

Ryan [15] reported an indirect colorimetric method for the determination of unoxidized phenothiazine derivatives The determination involved the reaction between a palladium–phenothiazine complex and magnesium lauryl sulphate which results in a complex salt whose concentration was measured colorimetrically The complex did not form with the oxidized phenothiazines and thus the method provided an indirect measurement of oxidative decomposition at the sulphur atom of these compounds This method was used for the assay of injections and was reported to be suitable for routine evaluation of raw materials and for accelerated storage trials Ramappa *et al* [16] described a colorimetric method for the analysis of chlorpromazine and three other phenothiazines based on the coloured compounds formed between the phenothiazines and molybdoarsenic acid The presence of anti-oxidants in formulated products interfered with the analysis, and required extraction of the phenothiazines prior to determination Ramappa and Nayak [17] have also determined chlorpromazine spectrophotometrically in tablets, syrups and injection solutions, following oxidation with vanadophosphoric acid Recoveries were 98 4–100 6% and, whilst common excipients did not interfere, ascorbic acid and bisulphite did cause difficulties Tarasiewicz *et al* have reported the estimation of chlorpromazine in dosage forms following complexation with flavianic acid [18] and Alizarin S [19] The reaction products are poorly soluble in aqueous solutions However, following extraction into organic solvents these products can be estimated spectrophotometrically Sane *et al* [20] have reported a colorimetric method for the assay of chlorpromazine following treatment with sodium nitrite in strongly acidic solution

Smith [21] reported a spectrophotometric method for the determination of phenothiazines (and other drugs) in pharmaceutical formulations The nitrogenous bases were separated from their excipients by retention on a sulphonated polystyrene resin column and subsequently eluted with an appropriate concentration of hydrochloric acid The concentration of the drugs in the eluates was then measured spectrophotometrically Recoveries of 100 and 96% were obtained for pure chlorpromazine hydrochloride and a 25 mg tablet sample, respectively

Davidson [22] reported a difference spectrophotometric method for the determination of chlorpromazine and other phenothiazine drugs in a variety of pharmaceutical formulations The technique, based on the measurement of the difference in the absorbance of the sulphoxide derivative of the drug, relative to that of the parent drug, was considered specific for that particular intact drug The sulphoxide was obtained by the action of peroxyacetic acid on the drug The measured absorbance difference (at 343 nm for chlorpromazine) was proportional to the intact drug and was unaffected by

excipients, decomposition products or co-formulated drugs Gurka *et al* [23] have also investigated the use of the difference UV assay for a range of phenothiazines including chlorpromazine In this procedure, standard and sample solutions were passed through a short column of siliceous earth prior to the oxidation step with peracetic acid This method is reported to be superior to official UV methods These authors also discuss a difference fluorescence method for the assay of samples with lower formulation strengths Davidson [24] extended the difference UV method to the assay of chlorpromazine sulphoxide in degraded formulations The method was based on the measurement of the difference in the absorbance of a degraded solution relative to a corresponding solution reduced with zinc dust in hydrochloric acid Interfering colouring matter and other breakdown products were removed by solvent extraction

Derivative UV spectrophotometry has been applied to the determination of chlorpromazine and chlorpromazine sulphoxide in dosage forms Fell and Davidson [25] determined chlorpromazine sulphoxide in degraded chlorpromazine formulations by second derivative UV spectrophotometry In a series of constituted binary mixtures of chlorpromazine and chlorpromazine sulphoxide, the sulphoxide level was varied to give a calibration curve which simulated oxidative degradation of chlorpromazine of up to 30% The method was applied to the investigation of formulated products and the results were compared with those given by the method of Davidson [24] The recovery of chlorpromazine sulphoxide in two samples of degraded chlorpromazine syrup were 97 5 and 99 1% In one case, a high sulphoxide level (17 5%) was found to be present in a syrup sample Fasanmade and Fell [26] reported the determination of chlorpromazine and chlorpromazine sulphoxide in pharmaceutical dosage forms by third-order derivative UV spectrophotometry By using this method, chlorpromazine sulphoxide levels as low as 0 13% were measured in degraded chlorpromazine dosage forms

Chlorpromazine hydrochloride in tablets has been determined by molecular emission cavity analysis (MECA) [27] The sulphur atom in the chlorpromazine hydrochloride is oxidized by dichromate in condensed phosphoric acid (CPA) to sulphate which is subsequently converted to hydrogen sulphide by heating with tin dissolved in CPA The generated hydrogen sulphide is then determined by MECA using the S_2 emission at 384 nm

Chromatographic Methods

French *et al* [28] assayed the alkylated and non-alkylated impurities in tablet formulations of chlorpromazine, promazine and promethazine by TLC and gas–liquid chromatography (GLC) In the TLC method, solutions of formulation samples and anticipated impurities were investigated and the chromatograms were visualized using short-wave UV light or by use of a spray reagent (1% selenious acid in concentrated sulphuric acid) The authors reported that official TLC methods for impurities in phenothiazines were unable to resolve certain impurities, and the estimation of the levels of the impurities was difficult due to the tailing of the main spot in the chromatogram New solvent systems were developed for investigation of the various phenothiazines including chlorpromazine Cyclohexane/dioxane/ethanol/concentrated ammonium hydroxide (70 20 15 0 5) was recommended By using this system, chlorpromazine tablet formulations and bulk drug samples were examined and found to contain promazine, 4-chloropromazine and 2-chlorophenothiazine In an extension of this work, a semi-quantitative survey of tablet samples was carried out to determine the frequency of

impurities present This was done using a GLC method utilizing a column packed with 5% OV-7 on 100–120 mesh GasChrom Q and a FID detector For chlorpromazine, 126 batches (19 formulations) were investigated and 45% of the batches were shown to contain >0 5% of alkylated impurities (i e levels greater than permitted in the monographs) The authors concluded that this widespread occurrence of impurities required careful monitoring during quality control procedures, and that the reported TLC method was suitable for such monitoring TLC followed by densitometry has been utilized for the determination of chlorpromazine, promazine, promethazine and thioridazine in tablets, pills and injection solutions [29] The TLC system involved the use of silica gel plates and a mobile phase consisting of propan-1-ol/water (17 3)

A number of papers have investigated various aspects of the separation of chlorpromazine and related substances by high-performance liquid chromatography (HPLC) Rodgers [30] investigated the HPLC separation of a number of classes of tranquilizing drugs by using silica gel and bonded pellicular ion-exchange packing materials and spectrophotometric detection at 254 nm This study was essentially qualitative as was that of Twitchett and Moffat [31] who investigated the chromatographic behaviour of a series of drugs, including chlorpromazine, on an ODS column These authors reported that the chromatographic elution was highly correlated with the partition coefficient and pK_a of the compounds Further qualitative HPLC studies have been reported on chlorpromazine and possible impurities involving the use of Spherosil XOA 600 [32, 33] The use of isohydric solvents in the liquid–solid chromatography of phenothiazines has also been investigated [34, 35]

Smith [36] reported the separation and determination of chlorpromazine and its related compounds in tablet formulations and biological matrices using a reversed-phase HPLC column (dimethylsilyl silica, RP-2) The mobile phase consisted of acetonitrile/water/ammonium carbonate and detection was at 254 nm Peak height/area quantitation and external standardization was employed, and the assay of a sample of chlorpromazine tablets (200 mg) gave 104% of the label claim The same batch was found to contain 1 3% of chlorpromazine sulphoxide The HPLC determination of chlorpromazine and thioridazine in pharmaceutical formulations by using a reversed-phase Hypersil ODS column has been reported [37] The mobile phase was methanol/water, and spectrophotometric detection at 254 nm was used Internal standardization using cinchocaine was employed, and the results obtained were comparable with those obtained by using official methods

Takahashi [38] reported an HPLC method in which an amino-bonded stationary phase with fluorescence detection was used for the determination of chlorpromazine and oxidation products in pharmaceutical preparations The mobile phase used was acetonitrile/benzene/water For chlorpromazine, the fluorescence detection utilized excitation at 280 nm with emission at 450 nm For chlorpromazine sulphoxide and sulphone, the excitation was also at 280 nm but the emission monochromator was set at 385 nm By using these conditions, the quantitation of these two compounds in the presence of a 100-fold excess of chlorpromazine was possible The use of spectrophotometric detection under similar chromatographic conditions resulted in interference from chlorpromazine Chagonda and Millership [39] reported a modification of this method in which a mobile phase of acetonitrile/0 1 mM hydrochloric acid and internal standardization were employed By using this method degraded samples of chlorpromazine injection were investigated and a comparison was made with the official BP spectrophotometric method [40] The selectivity of the HPLC method (for chlorpro-

mazine and chlorpromazine sulphoxide) was contrasted with the non-specific official method

Electrochemical Methods

Chlorpromazine in tablets and injections has been determined polarographically at the rotating platinum electrode [41] The determination was carried out by using 0 1 M universal buffer (various pHs) and the authors reported that at neutral or alkaline pH the polarographic wave was not observed The rotating platinum electrode was superior to a stationary electrode Faith *et al* [42] have described the use of square-wave polarography for the determination of a variety of phenothiazines in dosage forms and also in urine samples Kross *et al* [43] have utilized a combination of TLC and polarography for the development of a stability-indicating assay The phenothiazines were separated from the possible decomposition products by TLC The TLC zones containing the phenothiazines were subsequently extracted and the compounds quantified by polarography following bromination Teare *et al* [44] have employed a bromination step prior to the polarographic determination of phenothiazines in dosage forms These workers used differential pulse polarography with 0 5 M hydrochloric acid as the supporting electrolyte The authors reported that there was no interference from tablet excipients or additives in oral and injection formulations

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