ANALYSIS OF PROMAZINE AND CHLORPROMAZINE IN PHARMACEUTICAL PREPARATIONS

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The titration of promazine and chlorpromazine in acetone as the hydrochlorides or free bases has been applied to the assay of pharmaceutical products. The gravimetric procedure of Blazek and Stejskal has been used to verify the results.

Promazine and chlorpromazine are members of the phenothiazine nucleus type of antihistamines and tranquillising drugs for which several methods of analysis have been proposed. Durost and Pascal[1] estimated chlorpromazine in biological fluids by a colorimetric method using the carmine red colour produced by concentrated sulphuric acid. Blazek and Stejskal[2] used the precipitate formed in acid solution with silicotungstic acid as a gravimetric method. Sandri[3] used the oxidation of the phenothiazine nucleus with bromate and estimation of the excess bromate. This method has been used for determining chlorpromazine, promethazine and diethazine 10-(2-diethylamino-1-ethyl) phenothiazine). A non-aqueous titration of promethazine hydrochloride has been offered by Kleckner and Osol[4] and an aqueous back titration method is in commercial use. These methods were investigated and compared with non-aqueous methods developed in this laboratory, for the assay of pharmaceutical preparations.

Experimental

Reagents. Acetone, A.C.S. grade, hexane, B.D.H. certified reagent, glacial acetic acid, A.C.S. grade, chloroform, A.C.S. grade, 6 per cent mercuric acetate in glacial acetic acid, 0·05N perchloric acid in dioxane standardised against potassium acid phthalate, A.C.S. grade, 0·2N potassium hydroxide in water, 0·1 per cent methyl red in glacial acetic acid.

Apparatus. Fisher titrimeter model No. 9–311A with glass indicator electrode and fibre type calomel or silver-silver chloride electrodes; a semimicro-burette to measure 0·01 ml.

Non-aqueous procedures with Crystalline Promazine and Chlorpromazine Hydrochlorides

Method I. Accurately weigh and dissolve about 50 mg. of crystals in 40 ml. of acetone. Add 0·5 ml. of mercuric acetate solution, 3 drops of methyl-red indicator and titrate with perchloric acid in dioxane. The indicator colour change at the end point is from orange to salmon pink and it is preceded by a brilliant pink cone. The blank on 40 ml. of acetone is also estimated.

Method II. Accurately weigh about 50 mg. of crystals and transfer to a separating funnel containing 20 ml. of water. Add 4 ml. of potassium

hydroxide solution and extract four times with 20 ml. portions of hexane with vigorous shaking. Combine the hexane extracts, add 40 ml. of acetone, 3 drops methyl red indicator and titrate with perchloric acid in dioxane. The indicator colour change at the end point is the same as that in method I but all the colours are of a lighter shade. Estimate the blank on 80 ml. of hexane-40 ml. of acetone using the same end point.

Non-aqueous procedures with Pharmaceutical Preparations

Tablets. Weigh and powder 20 tablets. Extract an accurately weighed amount of the tablet mass containing 20 mg. of the active ingredient with 10 ml. acetone by stirring electromagnetically for 10 minutes. Filter out insoluble material using a fine sintered glass filter and suction. Wash the residue and container with 30 ml. acetone. Proceed by method I, beginning at "Add 0·5 ml. of mercuric acetate solution . . ." *Ampoules.* Take the contents of 5 ampoules and transfer an aliquot containing 25 mg. of the active ingredient to a separatory funnel. Add 2 ml. of 0:2 N potassium hydroxide solution and extract with 4 to 20 ml. portions of hexane with vigorous shaking. Proceed by method II, beginning at "Combine the hexane extracts . . ." *Suppositories.* Dissolve suppositories containing 25 mg. of chlorpromazine in 40 ml. of hot acetone. Titrate with perchloric acid in dioxane while hot using 3 drops of methyl red indicator. The end point is the same as that for ampoules. Determine the blank in 40 ml. of acetone as in procedure I.

Gravimetric procedures with Pharmaceutical Preparations

The gravimetric method of Blazek and Stejskal[2] was applied to a sample containing approximately 20 mg. of chlorpromazine or promazine with the following procedures to obtain the solution for precipitation and to wash the final precipitate.

Tablets. Extract the tablet mass with acetone and filter, washing the residue and container with sufficient acetone. Evaporate this solvent and replace with 20 ml. of water containing 1 ml. concentrated hydrochloric acid. Wash the final precipitate with 20 ml. of chloroform and 40 ml. of water. *Ampoules.* The ampoule solution previously basified with 2 ml. 0·2N potassium hydroxide solution is extracted four times with 20 ml. portions of hexane. Extract the combined hexane extracts twice with 10 ml. portions of water containing 0·5 ml. of concentrated hydrochloric acid per 10 ml. Wash the precipitate with 40 ml. of water. *Suppositories.* Dissolve suppositories in 15 ml. of hexane and extract twice with 10 ml. portions of water containing 0·5 ml. concentrated hydrochloric acid per 10 ml. of water. Combine the acid extracts and proceed with the precipitation. Wash precipitate with 20 ml. of hexane and 50 ml. of water.

Discussion

Promazine and chlorpromazine both contain two tertiary amino groups; one attached to an alkyl chain, the second incorporated in the central ring of the phenothiazine nucleus. Only the former can be titrated. These

drugs are present in pharmaceutical products as the hydrochloride or the free base and both forms can be titrated directly by non-aqueous methods. Titration of hydrochlorides by the use of mercuric acetate, was devised by Pifer and Wollish[5]. The titrant used in all instances was perchloric acid in dioxane.

Since the drugs are present as the hydrochlorides and estimation of the drug as free base took longer than as hydrochloride, the hydrochloride assay is preferred for tablets. Several solvents for the extraction of the hydrochloride from the tablet mass were investigated. Magnesium stearate, a common lubricant, created a major difficulty since it titrated as a

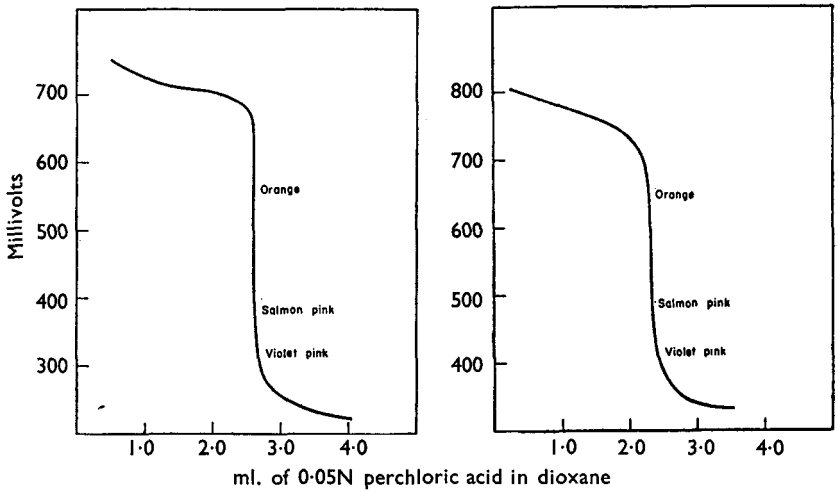

FIG. 1. Titration of chlorpromazine hydrochloride, extracted from tablet, in acetone using a glass: calomel electrode combination.

FIG. 2. Titration of promazine base, extracted from tablet, in hexane-acetone (2:1) using a glass: calomel electrode combination.

base with perchloric acid. Glacial acetic acid, the solvent used by Kleckner and Osol for titration of promethazine hydrochloride unfortunately dissolves this lubricant. But we found that magnesium stearate was practically insoluble in acetone giving a titration of only 0·005 ml. of 0·05N perchloric acid for 10 ml. of acetone saturated with the salt. Mercuric acetate was slightly basic in this solvent but the error caused by its presence was insignificant. The preferred solvent for mercuric acetate and the indicator was glacial acetic acid, since methanol gave a diffuse end point. Methyl red, bromcresol green, bromcresol purple and bromphenol blue can be used as indicators, but methyl red is superior. The colour change of methyl red at the end point was selected as being from orange to salmon pink. The colour at the true end point lies between orange and pink and may be described as the first change of the initial orange towards the pink. Although this colour change is distinct it is difficult to describe. For this reason the salmon pink end point was selected with full realisation that it was 0·005 ml. of titrant beyond the true end point.

The active ingredient in ampoules was measured as the base. Extraction was with hexane in preference to ethyl ether to reduce the carry over of water and basic substances. The active ingredient could not be titrated successfully as the free base in glacial acetic acid. Hexane-acetone (2 : 1) was found to be a good solvent and not only permitted potentiometric measurements but also eliminated the necessity to replace the hexane. Methyl red dissolved in glacial acetic acid proved to be a good indicator for this titration also. Procedure II for the pure drug and the recoveries by this procedure have been included to indicate that the hexane extraction was complete and the assay procedure for ampoules is reliable.

All indicator end points were checked potentiometrically with a glass electrode in combination with a fibre type calomel or a silver-silver chloride electrode. Figures 1 and 2 show the titration curve of the hydrochloride in acetone and the free base in hexane : acetone (2 : 1) respectively using the glass-calomel electrode combination and a burette measuring 0·05 ml. Figure 3 illustrates the titration curve of the hydrochloride in acetone using the glass silver-silver chloride electrode combination and a burette calibrated to 0·01 ml. With the calomel electrode if the flow of potassium chloride became excessive the end point could not be observed and for this reason the silver-silver chloride electrode was preferred.

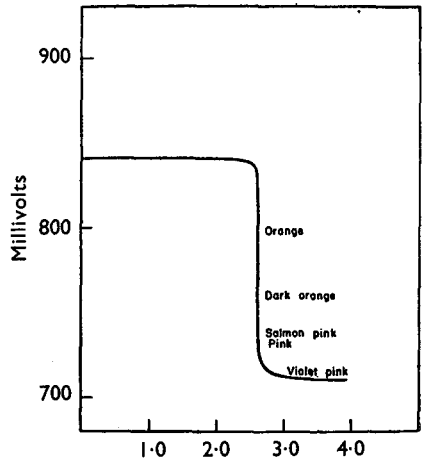

FIG. 3. Titration of crystalline promazine hydrochloride in acetone using a glass : silver-silver chloride electrode combination.

The recoveries of the pure active ingredient by either method I or II were 1 per cent high. The partial titration of the second amino group may provide a possible explanation but other than this no answer can be given.

In Durost and Pascal's colorimetric method[1], some dependence of optical density on concentration of chlorpromazine was found. However, the optical density was so sensitive to time of colour development and age of initial aqueous chlorpromazine solutions that this method was considered unsatisfactory. A second reagent used for colour development, ferric chloride in dilute hydrochloric acid was also found unsuitable. Several difficulties were inherent in the back titration procedure. A large quantity of product was needed for accurate analysis, and the extraction of the tablet mass with water was found to be unsatisfactory. Ethyl ether was used to extract the drug from basic solution but this step was also objectionable since undesirable basic substances could be carried over into the ether layer by the water which is slightly soluble in ethyl ether.

TABLE I

COMPARATIVE RECOVERIES OF NON-AQUEOUS AND GRAVIMETRIC METHODS

Form	Non-aqueous methods			Gravimetric method
	No. of estimations	Mean recovery per cent	Standard deviation	Mean recovery per cent
Pure chlorpromazine hydrochloride by method I	6	101·4	0·130	—
Pure promazine hydrochloride by method I	6	101·05	0·150	—
Pure chlorpromazine hydrochloride by method II	6	101·3	0·225	—
Chlorpromazine tablets	10	106·02	0·812	105·4
Promazine tablets	5	96·23	0·472	96·15
Chlorpromazine ampoules	5	110·06	0·689	110·8
Promazine ampoules	5	97·92	0·502	100·1
Chlorpromazine suppositories	5	102·2	*	102·2

* Single suppositories analysed and therefore standard deviation not representative of method itself.

Although the recoveries obtained by the oxidation method were in closer agreement with those of the gravimetric and non-aqueous methods (Table I), we found that they were not reproducible. Blazek and Stejskal's gravimetric assay[2] was found to be reliable and accurate but like all gravimetric methods it was time-consuming.

REFERENCES

1. Durost and Pascal, *Ann. pharm. franc.*, 1953, **11**, 615.
2. Blazek and Stejskal, *Analyt., Abstr.*, 1956, Feb., No. 530.
3. Sandri, *II Farmaco, Ed. Sci.*, 1955, **10**, 444.
4. Kleckner and Osol, *J. Amer. pharm. Ass., Sci. Ed.*, 1952, **41**, 573.
5. Pifer and Wollish, *Analyt. Chem.*, 1952, **24**, 300.