Photometric Titration Methods for the Determination of Thiopentone Sodium in Injections

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Two simple photometric titration methods for the determination of thiopentone sodium in injections at milligram and sub-milligram levels have been developed. That the drug compound hydrolyses in aqueous *tert*-butanol to form sodium hydroxide which is instantaneously transformed into bright yellow sodium benzyl trithiocarbonate (λ_{max} 430 nm) through reaction with carbon disulphide and benzyl mercaptan has been made the basis of first method. For sub-milligram amounts, the method is based on the formation of yellowish green colour (λ_{max} 360 nm) on mixing the drug with cobalt (II) acetate in dimethylformamide.

Thiopentone sodium [sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate] (fig. 1) is a quick acting anticonvulsant and general anaesthetic drug. It is marketed as thiopentone sodium injection and is given intravenously for producing anaesthesia of short duration. In view of its wide clinical use, it has been determined by a number of methods and techniques[1-5]. Thiopentone sodium is assayed both for sodium and for thiopentone by IP method[1]. The method is tedious, time consuming and requiring large sample sizes for analysis. Other methods include UV spectrophotometry[2,3], TLC[4] and cathodic stripping voltammetry[5]. These methods have been developed primarily for the determination of this drug in biological materials but no efforts have been made to analyse commercial drug formulations. This prompted us to work out simple, rapid and sensitive methods for the determination of thiopentone sodium particularly for ensuring the quality of its drug formulations. Our efforts in this direction have led to the development of two such photometric titration methods.

Carbon disulphide AR, (Merck) was used as received. *tert*-butanol AR, (Extrapure) was used as such for preparing 80% solution by mixing *tert*-butanol with water in the ratio 4:1v/v. Benzyl mercaptan (Merck) was distilled before use. Standard benzyl mercaptan solution (0.01M) was prepared by dissolving a little more than the calculated amount in 80% *tert*-butanol and standardising the solution using a previously reported method[6]. Dimethylformamide (BDH) was purified before use. Cobalt (II) acetate tetrahydrate, standard solution (0.001M) in methanol, was prepared using a reported method[7]. Triethylamine (Fluka) was used as received. Thiopentone sodium supplied by Rhone-Poulenc India Ltd. Mumbai, was used. The purity of the drug compound was checked using the IP method[1]. A Bausch and Lomb spectrophotometer (Spectronic 20D) with 1 cm matched glass cells was used for all absorption measurements.

In method I, aliquots of solutions of thiopentone sodium in 80% aqueous *tert*-butanol were mixed with a drop (~100 µl) of carbon disulphide and the volume was made to 5 ml with the same solvent. Each solution was titrated photometrically at 430 nm at room temperature (~23°) with standard benzyl mercaptan (0.01M). Dilution corrections were applied and titration curves plotted in the usual way. An inverted L-shaped curve was obtained. The end point was found by extrapolation of two straight lines.

In method II, aliquots of solutions of pure drug compound in dimethylformamide were mixed with triethylamine

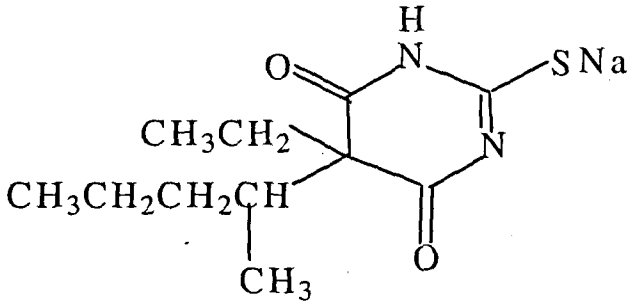

Fig. 1: Thiopentone sodium

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(1 ml, ~1M in dimethylformamide) and the volume was made to 5 ml with the same solvent. Each solution was titrated photometrically at 360 nm with the standard cobalt (II) acetate (0.001M). Dilution corrections were applied and titration curves plotted in the usual way. An inverted L-shaped titration curve was obtained. The end-point was found by extrapolation of two straight lines.

A single formulation of thiopentone sodium, Intraval sodium injection (Rhone-Poulenc India Ltd, Mumbai) containing 0.5 g of thiopentone sodium as active ingredient per vial was used. The contents of ten vials were weighed and mixed thoroughly for uniformity of weight. A single large sample of the mixed contents was weighed and dissolved in known volume of 80% *tert*-butanol (in case of method I) or dimethylformamide (in case of method II). Aliquots of this solution were taken and processed for the analysis by method I and method II, as described above. The results of analysis are recorded in Table 1.

The observations that in aqueous *tert*-butanol, thiopentone sodium hydrolyses to form thiopentone and sodium hydroxide and the latter reacts with carbon disulphide and benzyl mercaptan in the same medium forming an intense yellow sodium benzyl trithiocarbonate(I), $NaOH+CS_2+C_6H_5SH \rightarrow C_6H_5S.CS.SNa(I)+H_2O$, have been made use of in developing method I. The method involves titrating drug solution in aqueous *tert*-butanol in the presence of carbon disulphide photometrically at 430 nm (λ_{max} of I) against standard benzyl mercaptan. The absorbance in these titrations goes on increasing till it attains a maximum value corresponding to the quantitative transformation of sodium hydroxide into yellow trithiocarbonate(I) and thereafter it attains a constant value. Thiopentone sodium is a mixture of sodium 5-ethyl-5-(1-methyl-butyl)-2-thiobarbiturate and sodium carbonate containing 10% of sodium. The sodium carbonate constituent of the drug is also transformed quantatively into above trithiocarbonate during the titration. That mercaptans react with carbon disulphide in the presence of bases (sodium hydroxide/carbonate) to form bright yellow sodium alkyl/aryl trithiocarbonates of the type (I), is already known[8,9]. The amount of drug is stoichiometrically related to the amount of yellow sodium benzyltrithiocarbonate (formed quantatively from sodium hydroxide and sodium carbonate, the constituents of drug). That drug compound indeed contains equivalent of 10% sodium, has been established by thermal studies carried out with a Shimadzu DT-40 (simultaneous TGA/DTA module) using Pt-Rh (10 %) crucible at a heating rate of 5° min^{-1}. The overall decomposition (two stage) of the drug compound from 161.8° to 720.9° corresponds to the above content of sodium in the drug. Thiopentone sodium in the range 1-3 mg could be determined with a maximum relative standard deviation (RSD) of 0.9%. When applied to a commercial drug formulation viz. injection, the recoveries were in the range 98.9-99.4% with RSD's in the range 0.6-0.8% (Table 1). The method is however, applicable when the drug sample is free from the basic impurities since latter could undergo colour reaction with the reagent and consequently causes interferences.

The drug can however be analysed without any interferences from the basic impurities by using method II involving cobalt (II) acetate reagent. The ease with which thiopentone sodium reacts with cobalt(II) in the presence of triethylamine in dimethylformamide medium in 2:1 molar ra-

TABLE 1: ANALYSIS THIOPENTONE SODIUM INJECTION

Method I		Method II	
Nominal amount taken (mg)	% Recovery*	Nominal amount taken (mg)	% Recovery*
1.0	99.4±0.8	0.1	99.0±0.7
1.5	98.9±0.6	0.2	99.2±0.5
2.0	99.0±0.8	0.3	99.5±0.6
2.5	99.0±0.7	0.4	99.0±0.3
3.0	99.2±0.8	0.5	99.6±0.7

Injection containing 0.5 g active ingredient per vial, the maker's specification established separately by IP Method[1]. *Values are mean of five determinations with standard deviation (±). Method I utilizes titration with benzyl mercaptan and method II is titration with cobalt(II) acetate.

tio to form an intense yellowish green complex (plausibly II) showing λ_{max} at 360 nm has been made basis of the method, $2C_{11}H_{17}N_2O_2S.Na+Co^{2+} \rightarrow [(C_{11}H_{17}N_2O_2S)_2Co](II)+2\ Na^+$ for the sub-milligram level determination of the drug compound. Photometric titration of the drug compound with cobalt(II) are marked by a well-defined intersection at drug to reagent molar ratio of 2:1 in the form of an inverted L-shaped titration curve. It may be mentioned that the formation of above type of complex (II), as a result of the reaction of thiobarbitueric acid and related compounds such as thioureas with metal ions like cobalt (II) and copper (II) through coordination with sulphur atoms, is well known[10-12]. Further, these compounds as such are weak nucleophiles and their complexes with metal ions are not formed readily, triethylamine (a base) activates them by abstracting hydrogen from thiol sulphur thus making them strong nucleophiles. With this method, thiopentone sodium in the range 0.1-0.5 mg could be determined with a maximum RSD of 0.7%. The Recoveries of active ingredient content from drug formulation were in the range 99.0-99.6% with RSD's in the range 0.3-0.7% (Table I).

The proposed photometric titration methods besides being simple, are more sensitive than pharmacopoeic method[1]. The excellent solution stability of the reagents and that of colour as well as well-established stoichiometries of the colour reactions involved are other attractive features of the proposed methods.

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Simultaneous Spectrophotometric Estimation of Ibuprofen and Methocarbamol in Tablet Dosage Form

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Two simple economical procedures for simultaneous estimation of ibuprofen and methocarbamol in two-component tablet formulation have been developed. The method employs Q-analysis and two-wavelength method. Ibuprofen has absorbance at 222 nm and methocarbamol has absorbance maxima at 224 nm and 272 nm. The isoabsorptive point of ibuprofen and methocarbamol was found to be 231.4 nm. Both

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