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Analysis of pharmaceutically-important thioxanthene derivatives

F. Belal *, M.M. Hefnawy, F.A. Aly

Department of analytical Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura 35516, Egypt

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Abstract

A review with 92 references is presented that deals with the reported methods of analysis of the thioxanthene derivatives of pharmaceutical interest. The review includes the methods adopted in dosage forms and biological fluids. A brief discussion of the metabolism and pharmacokinetics of this class of compounds is also reported. © 1997 Elsevier Science B.V.

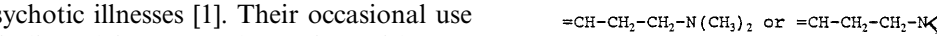
Keywords: Thioxanthene derivatives; dosage forms; biological fluids

1. Introduction

The thioxanthene class of drugs are effective in the systematic treatment of psychoses. They are most appropriately used in the therapy of schizophrenia, organic psychoses and other idiopathic psychotic illnesses [1]. Their occasional use may be indicated in severe depression with psychotic features and in the management of patients with organic psychotic disorders. However, these drugs have other clinically useful properties, including anti-emetic, anti-nausea and antihistamine effects, and the ability to potentiate analgesics, sedatives and general anaesthetic actions [1].

2. Pharmacokinetics

The chemical structure of the thioxanthene neuroleptic is based on the thioxanthene ring to which the side-chain is linked by a C=C double bone. The most frequently clinically used thioxanthenes, namely, chlorprothixene, clopenthixol, flupentixol and thiothixene, are all substituted in position 2 of the ring with $-Cl$, $-CF_3$ or $SO_2N(CH_3)_2$. The side-chain is either



as shown in Scheme 1.

Because of the double bond linking of the side-chain to the thioxanthene ring structure, the thioxanthenes exist as two geometric isomers, *cis* (*Z*)- and *trans* (*E*)-isomers. It is interesting that in pharmacological studies, the neuroleptic activity is associated with the *cis* (*Z*)-isomers, while the *trans* (*E*)-isomers are practically inactive [2]. Although being closely related to the phenothiazines, the thioxanthenes have somewhat different metabolic pathways, especially being less liable to form phenolic metabolites, possibly because they are more resistant towards hydroxylation [3].

The proposed main routes of metabolism of chlorprothixene—as a model example—in man

* Corresponding author.

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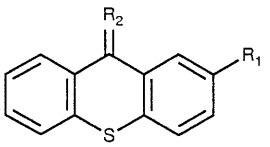
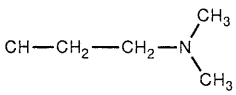
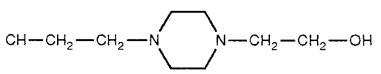
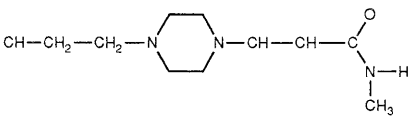
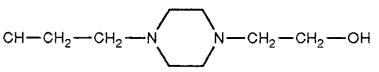
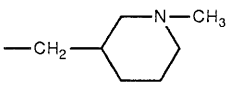
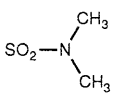
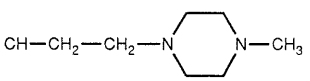
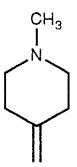
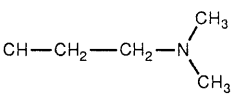


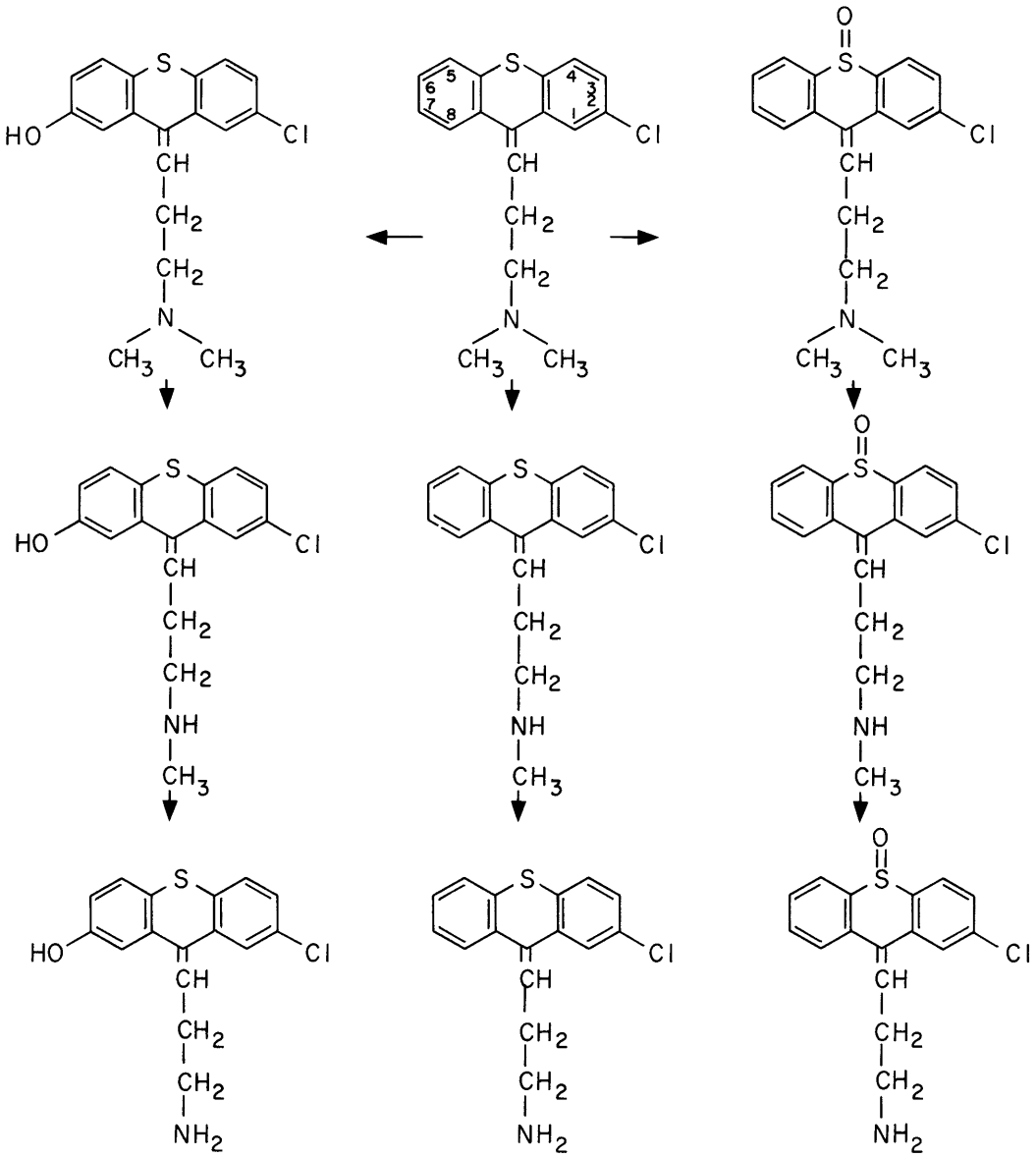
Compound	R_1	R_2
1 - Chlorprothixene	Cl	
2 - Clopenthixol	Cl	
3-Clotixamide dimaleate	Cl	
4 - Flupenthix	CF_3	
5 - Methixene	H	
6 - Thiothixene		
7 - Pimethixene	H	
8 - Prothixene	H	

Scheme 1.

and animals based on the metabolites found in urine and faeces [4–6] are shown in Scheme 2.

3. Methods of analysis

Exhaustive monographs covering the physical, chemical and spectral characteristics of thioxanthenes, in addition to a description of their methods of synthesis, their stability, pharmacokinetics and methods of analysis were published for each of chlorprothioxene [7], thiothixene [8] and methixene [9].



Scheme 2.

3.1. Gravimetric and precipitimetric analysis

Complex chromium thiocyanate (K^+ or NH_4^+) salt were used to precipitate chlorprothixene, clopenthioxol and flupentioxol in acid or neutral media. The excess precipitation agent was bromometrically determined after hydrolysis. Composition of the complex salts was reported in [10].

Ammonium reineckate was used for precipitating chlorprothixene. The precipitate was filtered off, and the chromium content in the filtrate was measured by atomic absorption spectroscopy [11]. Thiothixene was gravimetrically determined after precipitation using tetraphenylborate [12].

3.2. Titrimetric methods

Titrimetric procedures are useful for assaying dosage forms known to be free from all degraded products. Non-aqueous titrations were described for the analysis of chlorprothixene [13] and thiothixene [12]. The drug is dissolved in glacial acetic acid then titrated with acetous perchloric acid. The end point is detected either visually or potentiometrically.

Beltagy et al. [14] determined chlorprothixene through oxidation with iodine monochloride, the liberated iodine being titrated with potassium iodate. Chlorprothixene could be determined by titration with potassium bromate in a mixture of hydrochloric and acetic acids. The end point was detected either potentiometrically, amperometrically or coulometrically [15].

An indirect titrimetric method was recommended for the determination of chlorprothixene, clopenthixol and flupenthixol. The method depends on precipitating the stated compounds with chromium thiocyanate complex in acid medium, and the excess reagent is determined bromometrically [11]. Other two indirect titrimetric methods were described for the determination of chlorprothixene, thiothixene and methixene hydrochloride. The first method involves the use of 1,3-dibromodimethylhydantoin, *N*-bromosuccimide or *N*-bromophthalimide as titrants [16]. The second method involves the use of 2-iodoxybenzoate as titrant [17]. A known excess volume of either of these reagents is added, and after a specified time, the residual reagent is determined iodometrically [16,17].

Similarly, hexa-amminecobalt(III)-tricarbonatocobaltate (III), (HCTC) has been reported as a redox titrant for the determination of chlorprothixene, methixene and thiothixene, the detection of the end point was accomplished visually, using ferroin indicator in case of chlorprothixene and thiothixene. Methixene, on the other hand, was a self-indicator [18]. An automatic potentiometric two-phase titration was described for methixene [19].

3.3. Ultraviolet and visible spectrophotometric methods

Direct spectrophotometry of the compounds in the ultraviolet region either in alcohols [20] or in acids [21,22] was described. The chlorprothixene content in tablets was determined spectrophotometrically in 0.5 M HCl after extraction.

Thioxanthene derivatives were determined colorimetrically by dissolving in concentrated sulphuric acid and measuring the color produced at 520 nm [23]. Chlorprothixene could be estimated colorimetrically via its reaction with nitazine yellow [24], aconitic anhydride [25], tropaeolin 000 [26], chloranil [27], 2,3-dichloro-5,6-dicyano-*p*-benzoquinone [28] and methyl orange [29]. Also, chlorprothixene and flupentixol were precipitated as picrates, redissolved in ethanol or acetone and then measured spectrophotometrically [30].

Ibrahim et al. [31] reported on the determination of chlorprothixene using different oxidising agents viz; sodium nitroprusside, 2,6-dibromoquinone chlorimide and sodium arsenate. The developed colors in phosphoric acid medium were measured spectrophotometrically.

Similarly, simple sectrophotometric methods based upon formation of charge transfer complexes with the π-acceptor tetracyano-ethylene [32] and the σ-acceptor iodine [33] were described. A difference–spectrophotometric method was reported for the determination of chlorprothixene, thiothixene, clopenthixol and flupenthixol [34]. These drugs were oxidized with peroxyacetic acid and the first derivative ultraviolet spectrum of the oxidized drugs were recorded from 200–400 nm versus a solution of the unoxidised drugs.

3.4. Mass spectroscopy methods

The advantageous use of chemical ionization of mass fragmantography using quadropole mass spectroscopy over magnetic sector instruments with respect to use of operation, unlimited range of ion monitoring and cost of apparatus were discussed during the analysis of chlorprothioxane in urine [35].

3.5. Polarographic methods

The thioxanthene derivatives chlorprothixene, clopenthixol, flupentixol and methixene were identified adopting square-wave polarography by measuring their half-wave potentials, and determined quantitatively by measuring the height of the polarographic peaks. Acetic acid (50%) was the solvent and Britton Robinson buffers of pH 6–6.5 was the supporting electrolyte [36].

Chlorprothixene and flupentixol were precipitated as their picrates, redissolved in ethanol or acetone then determined polarographically [37]. Also chlorprothixene was oxidized with dilute nitric acid to 2-chloro-9-thioxanthone and 1-nitro-3-dimethylaminopropane. Each product was determined polarographically after separation on a basic alumina column [38].

Alternatively chlorprothioxene and thiothixene were determined polarographically through the formation of their bromo-derivatives which manifest well defined cathodic waves in 0.1 M hydrochloric acid or Britton Robinson buffers of pH 10.13 [39].

Pen and Yang [40] reported an adsorptive preconcentration method for the voltammetric measurement of trace levels of chlorprothxene. The method was applied for urine analysis.

3.6. Fluorimetric methods

Fluorimetric analysis has proven to be a valuable method for the analysis of thixanthens. Dell et al. [41] used the fluorescence obtained in 60% sulphuric acid to assay chlorprothixene, prothixene, clopenthixol, flupentixol, meprothixol and their sulphoxides in blood and urine after TLC separation. Also Dell et al. [42] used ceric sulphate to oxidize flupentixol, chlorprothixene, prothixene and clopenthixol. The thioxanthones—thus obtained—were fluorimetrically measured in 60% sulphuric acid.

Mjorndal and Oreland [43] developed a method for measuring thioxanthenes at therapeutic levels in plasma, based on measurement of the fluorescence of the oxidized drugs. The oxidation is performed with 0.1% potassium permanganate and reduction of the excess potassium permanganate was reported to oxidize chlorprothixene to 2-chloro-10-thioxanthone [44] and thiothixene to thioxanthone sulphoxide [45].

Thomas and Dryon [46] reported on the intense orange fluorescence given by chlorprothixene after treatment with Marquis reagent. Mellinger et al. [47] described a fluorescence identification test for chlorprothixene in urine using phosphoric acid (85%). A specific fluorimetric method for assay of drug levels in serum of patients treated with clopentixol decanoate injections was reported [48].

Hexamminecobalt(III) tricarbonatecobaltate (III) was used as an oxidant in aqueous sulphuric acid medium to induce fluorescence to 5 thioxanthenes [49]. Another fluorimetric determination of clopenthixol through treatment with orthophosphoric acid was reported [50], both methods were applied successfully to their dosage forms.

Two fluorimetric methods were described for thioxanthes in biological fluid without prior separation of the drug and its metabolites [51,52]. The methods are based on the unique property of thioxanthenes in acidic medium, they form thioxanthylium ions which are strongly fluorescent.

3.7. Chromatographic methods

3.7.1. Thin-layer chromatographic methods

Stead et al. [53] described a general TLC method for the detection of nitrogenous organic bases (including thioxanthenes). The developing system is methanol: strong ammonia (100:1.5) and the spray reagent is acidified platinate solution. A TLC screening test was described for the qualitative analysis of illicit drugs and/or their metabolites [54]. The developing system is toluene–isopropanol–strong ammonia solution (3:6:1). The spray reagent is a mixture of bismuth nitrate and potassium iodide. Zingales [55] described a systematic TLC method for the identification of psychotropic drugs on patients who were given various drugs, e.g. chlorprothixene and clopenthixol.

A similar TLC method was described for the identification of psychotropic drugs in blood, urine, saliva and hair after extraction using an isopropanol and chloroform mixture. Four differ-

ent developing systems were attempted. The sensitivity was 0.01–5 μg% [56]. A quantitative HPTLC method was described for thiothixene in blood. The method involves in-situ fluorometric detection. The sensitivity was 0.1 μg ml^{-1} of plasma [57]. Li Win Po and Irwin [58] used HPTLC for the separation of *cis* and *trans* isomers of thioxanthenes under suitable conditions. The same technique was used for the quantitative analysis of *cis* and *trans* chlorprothixene, chlorprothixene sluphoxide and 2-chlorothixanthone [59].

3.7.2. High-performance liquid chromatographic methods

A high-performance liquid chromatography (HPLC) assay of *cis* and *trans* isomers of tricyclic neuroleptics was reported for separation, detection and quantification of these isomers. The determination of the isomer ratio in formulations was found to rely upon the complete extraction of the medicament [60]. Curry et al. [61] described a HPLC method for thioxanthens; the detection was accomplished spectrophotometrically for concentrations of ~ 10 ug ml^{-1}, and amperometrically for lower concentrations. A quantitative LC thermospray Tandem mass spectroscopic method was described for thioxanthens in whole blood [62]. HPLC was also used for the determination of chlorprothixene and clopenthixol in plasma [63].

Several HPLC methods were reported for each member of the class. Chlorprothixene was determined in human plasma using HPLC coupled with electrochemical detection at the glassy carbon electrode at $+0.85$ V [64]. Clopenthioxol was determined by ion-pairing HPLC [65]. Zuclopenthixol (the *cis* isomer of clopenthioxol) and its metabolites were determined by HPLC with post-column photochemical derivatization and fluorometric detection [66]. A specific HPLC method was reported for the estimation of *cis* (*Z*) and *trans* (*E*) isomers of clopenthioxol and *N*-dealkyl metabolite was described [67]. Flupenthioxol was determined in commercial tablets after extraction with 0.001 M HCl. The detection was effected spectrophotometrically at 254 nm [68].

Bomgema et al. [69] succeeded in separating the *cis* and *trans* isomers of methixene by HPLC. Several HPLC methodologies have been described for the determination of thiothixene in bulk drug, finished products [70,71] and plasma [71–73].

3.7.3. Gas-chromatographic methods

A gas-chromatography-mass spectrocsopy (GC-MS) combined technique was utilized by Hobbs et al. [74] and Bombardt et al. [75] for the determination of thioxanthenes. Cailleux et al. [76] described a GC-MS method for the identification and quantitation of drugs acting on the CNS (including thioxanthenes) of patients suspected of poisoning. A temperature-programmed method using a fused silica column was utilized for the identification of psychotropic drugs (including thioxanthenes), hypnotics and narcotics [77].

A GC method was described for the determination of antidepressants (including chlorprothixene) and their metabolites in serum [78]. A comprehensive screening and quantitation of 49 basic drugs (including thiothixene) and their metabolites was accomplished using capillary gas chromatography after liquid–liquid extraction [79]. A capillary GC method was used for the routine toxicological analysis of thioxanthenes [80]. Chlorprothixene and its metabolites including its sulphoxide, hydroxide and hydroxylated sulphoxide were determined by a GC-MS method using a commercially available generic EISTA Kit [81]. A sensitive GLC method was described for *cis* (*Z*) flupenthioxol in serum after extraction. The working range is 1–10 ng [82].

3.8. Radioimmunoassy

Radioimmunoassay (RIA) was used for the pharmacokinetic studies of flupenthioxol at a time when the assay of drugs by GC was unsuccessful. The method has the advantage of only measuring the active *cis* (*Z*) isomer [83]. A similar radioimmunoassay was described for flupenthioxol in blood [84]. A radioimmunoassay capable of detecting as little as 6 ng of flupenthioxol per ml of plasma following ethylacetate extraction was reported [85].

Jorgensen et al. [86] compared RIA and chromatographic methods for flupenthixol; they preferred the latter methods as they were less susceptible to interference from other described drugs.

3.9. Miscellaneous methods

The isotachephoresis behavior of chlorprothixene was studied on a paper support. The determination could be done by the internal standard method [87]. Capillary isotachephoresis was also described for chlorprothioxene [88].

The degree of purity of chlorprothixene was determined by differential calorimetry. The molar fraction of the impurity was determined from a Vant Hoff equation obtained from the melting enthalpy determined graphically [89]. Methixene was identified by discrimination analysis using fragment molecule connection value [90]. Thiothixene, on the other hand, was determined by thermomicroscopic analysis. The data (m.p., eutectic temperature, refractive index, polymorphism and crystal form) were used as diagnostic acids [91].

Nuclear magnetic resonance (NMR) spectroscopy was successfully applied to the determination of the isomeric content in chlorprothixene [92].

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