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Review article

Analysis of certain tranquilizers in biological fluids

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Abstract

A review with 282 references is presented that deals with the reported methods of analysis of phenothiazines, thioxanthenes, and benzodiazepine derivatives of pharmaceutical interest. The review includes the methods adapted in biological fluids. © 2002 Published by Elsevier Science B.V.

Keywords: Phenothiazine derivatives; Thioxanthene derivatives; Benzodiazepine derivatives; Biological fluids

1. Introduction

During the last half of the 20th century, a group of depressants of mental activity has been introduced into psychiatric practice, collectively referred to as tranquilizers. The term relates to their use in 'tranquilizing' patients with psychotic or neurotic illnesses. This group is usually subdivided into major and minor tranquilizers according to whether their main use is for the treatment of psychosis or neuroses [1,2]. Antipsychotic and antianxiety drugs are the newer terms for major and minor tranquilizers, respectively.

Before discussing the analysis of certain tranquilizers in biological fluids, it is worthy to give a spotlight on different types of tranquilizers and extraction of drugs from various biological fluids.

2. Types of tranquilizers

2.1. Major tranquilizers

The major tranquilizer drugs represented by the phenothiazines and thioxanthenes produce a specific improvement in the mood and behavior of psychotic patients without excessive sedation and without causing addiction.

Phenothiazine has a three-ring structure in which two benzene rings are linked by a sulfur and a nitrogen atom (Table 1). Substitution of an electron-withdrawing group at the position 2 increases the efficacy of phenothiazines (e.g., chlorpromazine). The nature of the substituent at position 10 influences pharmacological activity and the phenothiazine drugs can be divided into three groups on the basis of substitution at this site. Those with an aliphatic side chain include chlorpromazine and trifluprom azine are relatively

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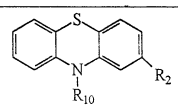
low in potency (but not in clinical efficacy). Those with a piperidine ring in the side chain include thioridazine and mesoridazine and appear to have a lower incidence of extrapyrimidal side effects. Several potent phenothiazine antipsychotic compounds have a piperazine (or piperazinyl) group in the side chain (e.g., fluphenazine and trifluoperazine) [3].

If the nitrogen at position 10 of phenothiazine nucleus is replaced by a carbon atom with a double bond to the side chain, the compound is a thioxanthene (Table 2). 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 *cis* (Z) isomers while the *trans* (E) isomers are practically inactive [2]. Although being closely related to the phenothiazine, the thioxanthenes have somewhat different metabolite pathways, especially being less liable to form phenolic metabolites, possibly because they are more resistant toward hydroxylation [3].

Thioxanthene have aliphatic or piperazine substituents in position 2 and can be divided into two groups on the basis of substitution at this site. Those with an aliphatic side chain include chlor-

Table 1
Phenothiazine derivatives used as major tranquilizers



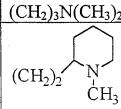
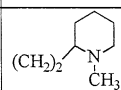
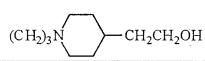
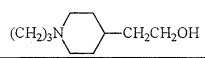
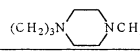
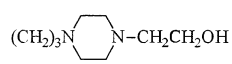
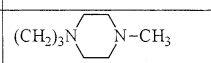
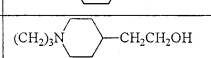
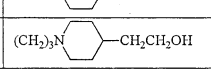
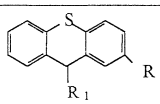
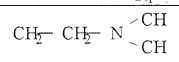
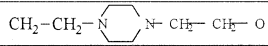
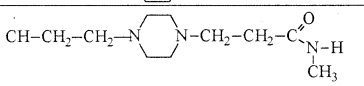
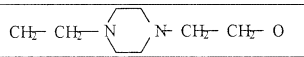
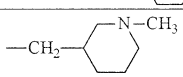
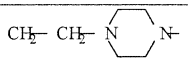
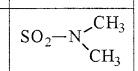
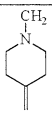
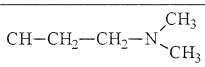
Compound	R_{10}	R_2
1- Chloropromazine	$(CH_2)_3N(CH_3)_2$.	Cl
2- Trifluopromazine	$(CH_2)_3N(CH_3)_2$.	CF_3
3- Promazine	$(CH_2)_3N(CH_3)_2$.	H
4- Thioridazine		SCH_3
5- Mesoridaine		
6- Piperacetazine		$COCH_3$
7- Perphenazine		Cl
8- Prochlorperazine		Cl
9- Fluphenazine		CF_3
10- Ttrifluoperazine		CF_3
11- Acetophenazine		$COCH_3$
12- Thiethylperazine		SCH_2CH_3

Table 2
Thioxanthene derivatives used as major tranquilizers



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

prothixene and prothixene. Thioxanthenes with a piperazine-substituted include clopenthixol, flupenthixol, and thiothixene; they are all potent and effective antipsychotic agents [3].

The thioxanthene derivatives have a more pronounced action than the phenothiazines, and have gradually replaced them. Owing to their relatively infrequent toxic effects with usual doses, thioxanthene derivatives may be preferred to phenothiazine derivatives.

2.2. Minor tranquilizers

The minor tranquilizer drugs include the benzodiazepines and related drugs; they decrease activity, moderate excitement, and calm the recipient. The term benzodiazepine refers to the portion of the structure composed of a benzene ring (A) fused to a seven-membered diazepine ring (B). However, since all the important benzodiazepines contain a 5-aryl substituent (ring C) and a 1,4-diazepine ring (Table 3) various modifications in the structure of the ring systems have yielded compounds with similar activities. These include 1,5-benzodiazepines (e.g., clobazam) and the replacement of the fused benzene ring (A) with heteroaromatic systems such as thiene (e.g., brotizolam).

The chemical nature of substituents at position 1–3 can vary widely and can include triazolo or imidazolo rings fused at position 1 and 2. Replacement of ring C with a keto function at position 5 and a methyl substituent at position 4 are important structure features of flumazenil.

3. Analysis of drugs in various biological fluids

Analysis or detection of a drug or its metabolite in biological fluids is usually complicated by the matrix [4]. In most cases, preliminary treatment of the sample is needed before the analyst can proceed to the measurement step. Each of the samples have their own set of factors that must be

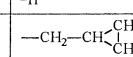
considered before an appropriate pre-treatment method can be selected. Such factors as the texture and chemical composition of the sample, the degree of drug–protein binding, the chemical stability of the drug and the types of interferences can affect the final measurement step. Because of this, various types of cleanup procedures involving techniques such as liquid–liquid extraction and liquid–solid extraction are used to separate drug components form endogenous biologic material. The solvent extraction techniques using a variety of solvents were still popular and offer acceptable recoveries and lack of significant interference from other substances.

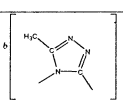
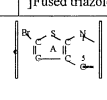
Other methods of cleanup involve a solid-phase extraction (SPE) and chromatography is employed to effectively separate drug components from endogenous biologic material [4]. The ultimate sensitivity and selectivity of the assay method may be limited by the efficiency of the cleanup methodology.

4. Analysis of phenothiazine derivatives in various biological fluids

Several methods and techniques have been reported for the determination of phenothiazine derivatives in different biological samples. A review of the literature reveals a variety of analytical methods applicable to the analysis of phenothiazine derivatives. A good guide to the work prior to 1967 can be found in the review written by Blazek [5]. Later on, in 1976, Blazek et

Table 3
Benzodiazepine derivatives used as minor tranquilizers

Benzodiazepine	R_1	R_2	R_3	R_7	$R_{2'}$
Alprazolam	]Fused triazolo ring[b		–H	–Cl	–H
Brotizolam	]Fused triazolo ring[b		–H	)Thieno ring A[c	–Cl
Chlordiazepoxide	(–)	$-NHCH_3$	–H	–Cl	–H
Clobazam	$-CH_3$	=O	–H	–Cl	–H
Clonazepam	–H	=O	–H	$-NO_2$	–Cl
Clorazepate	–H	=O	$-COO^-$	–Cl	–H
Demoxepam	–H	=O	–H	–Cl	–H
Diazepam	$-CH_3$	=O	–H	–Cl	–H
Estazolam	]Fused triazolo ring[d		–H	–Cl	–H
Flumazenil	]Fused imidazo ring[e		–H	–F	=]O at C_5]
Flurazepam	$-CH_2CH_2N(C_2H_5)_2$	=O	–H	–Cl	–F
Halazepam	$-CH_2CF_3$	=O	–H	–Cl	–H
Lorazepam	–H	=O	–OH	–Cl	–Cl
Midazolam	]Fused imadazo ring[f		–H	–Cl	–F
Nitrazepam	–H	=O	–H	$-NO_2$	–H
Nordazepam	–H	=O	–H	–Cl	–H
Oxazepam	–H	=O	–OH	–Cl	–H
Prazepam		=O	–H	–Cl	–H
Quazepam	$-CH_2CF_3$	=S	–H	–Cl	–F
Temazepam	$-CH_3$	=O	–OH	–Cl	–H
Triazolam	]Fused triazolo ring[b		–H	–Cl	–Cl

b 

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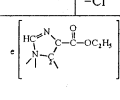
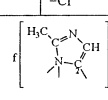
e 
f 

al. [6] published another review tabulating the bibliographical data on the methods of analysis of different phenothiazines. In 1979, Fairbrother [7] published an excellent review covering the published articles that appeared after 1976. In 1986, Belikov and Moiseeva [8] presented a review with 64 references covering the period from 1978 to 1984. Recently, in 1996, Karpinsk et al. [9] reported a good review with 81 references covering the published articles up to 1995. The recent published methods include the following.

4.1. Spectrophotometric methods

Several phenothiazine derivatives e.g., chlorpromazine, promazine and thioridazine were identified by their color product with $HClO_4$ and nitromethane after extraction from urine. All substances tested gave colored derivatives having absorption maxima between 505 and 635 nm [10]. A yellow orange color was developed through oxidation of thioridazine in urine samples by $NaNO_2$ and antimony potassium tartrate without interference [11].

Derivative ultraviolet (UV) spectrophotometry has been applied for determination of some phenothiazines in spiked blood samples [12]. A second derivative spectrophotometry was utilized for chlorpromazine. Promazine, prochlorperazine, thioridazine, and trifluoperazine in spiked blood samples after treatment with phosphate buffer of pH 7.4. The second derivative spectra eliminated the effects of background signal caused by blood [13–15]. Whilst Tan et al. [16] measured second derivative spectra for chlorpromazine, trifluoperazine, and fluphenazine in H_2SO_4. The detection limits ranged from 0.52 to 0.94 μg/ml.

4.2. Electrochemical methods

Oelschlager [17] reviewed the polarographic methods reported for psychotropic drugs including phenothiazines. Chlorpromazine has been determined in patients urine samples by adsorptive stripping voltammetry in the presence of Triton X-100 [18].

Fluphenazine and trifluoperazine were determined by differential pulse voltammetry using acetate buffer pH 4 after pre-concentration at a wax-impregnated graphite electrode. For plasma, the electrode was covered with a membrane to prevent fouling by proteins [19]. Alternatively, chlorpromazine and promazine spiked in urine samples were oxidized by nitrous acid into the corresponding sulfoxides, which were polarographically active. They produce well-defined diffusion-controlled cathodic wave [20].

4.3. Radioimmunoassay methods

Only immunologically active drugs were determined by radioimmunoassay (RIA). Thioridazine was determined by RIA using an antiserum that was produced in rabbits, the detection limit was 80 pg/ml [21]. Similarly, Chakraborty et al. [22] measured mesoridazine by RIA with limit of detection 40 pg/ml. Perphenazine was determined by a specific RIA in human plasma [23]. Prochlorperazine was determined by sensitive RIA, the limit of detection was 31 pg/ml of plasma [24]. Fluphenazine and its metabolite 7-hydroxyfluphenazine were determined by using antiserum enabled measured in the range 20 pg/ml of drug and its metabolite [25–27].

4.4. Chromatographic methods

4.4.1. Gas chromatography

4.4.1.1. Gas chromatography with mass spectrometry. Phenothiazines in body fluids have been determined by gas chromatography with mass spectrometry (GC–MS) coupling techniques [28,29]. Fluphenazine and perphenazine by GC–MS, the limit of determination was 80 pg/ml of plasma [30,31]. McKay et al. [32] have analyzed chlorpromazine in plasma by using GC–mass spectrometric selected ion detection. Whilst Midha et al. [33] have determined trifluoperazine in plasma by GC–electron impact MS with a data system. Thiethylperazine, triflupromazine and their metabolites were analyzed by computerized GC–MS after acid hydrolysis of the conjugates [34]. Also, fluphenazine and chlorpromazine were determined by GC-mass-selective detection [35,36].

4.4.1.2. Gas chromatography with nitrogen detector. Chlorpromazine and its metabolites have been analyzed in serum by GC by using a nitrogen detector. The limit of detection was 5 and 20 ng/ml for the drug and its metabolite, respectively [37]. Favaid et al. [38] measured fluphenazine as its acetyl derivative by GC-nitrogen detector. Alternatively, trifluoperazine was analyzed directly without derivatization by GC-nitrogen detector [39]. Whilst Roscoe et al. [40] have determined trifluoperazine in plasma by a GLC-nitrogen–phosphorus detector. A wide-bore capillary GC with nitrogen phosphorus detection method has been applied for determination of thioridazine and chlorpromazine in cases of poisoning [41].

4.4.1.3. Gas chromatography with surface ionization detector. Thiethylperazine, chlorpromazine, and promazine were tested for their detection by gas chromatography with surface ionization detector (GC-SID) in blood and urine after isolation using Sep-Pak C18 cartridges SPE [42].

4.4.1.4. Gas chromatography with electron capture detector. Perphenazine and its main metabolites have been determined by gas chromatography with electron capture detector (GC-ECD), the limit of detection was 1 ng/ml of human plasma [43].

4.4.1.5. Capillary gas chromatography. Chlorpromazine and trifluoperazine have been analyzed by capillary GC in serum [44]. A similar gas chromatographic method has been applied for determination of chlorpromazine in blood sample [45].

4.4.2. High-performance liquid chromatography methods

4.4.2.1. High-performance liquid chromatography with fluorescence detector. Fluorescence detector offers many possibilities by sensitive and selective detection in liquid chromatography. If native fluorescence of the analyte is absent or weak, the analyte may be derivatized to a fluorescent product by a chemical reaction. It may be advantageous to use fluorescence detector with high-performance liquid chromatography (HPLC) for quantitation of many phenothiazine derivative. This method was reported for fluphenazine [46–48].

Similarly, thioridazine in human plasma was determined after deproteinization. The method involved post-column derivatization in which electrolytically generated bromine was applied as an oxidant to enhance the sensitivity of fluorescence of detector. The detection limit was 0.5 ng/ml of plasma [49].

Also, Wells et al. [50] analyzed thioridazine and its major metabolite in plasma at single dose level, the method involved extraction of the materials from plasma and used post-column oxidation and fluorometric detection. The sensitivity of the method to thioridazine and its metabolites is 2 ng/ml. Prochlorperazine was quantitated in the presence of plasma doxorubicin. The method consists of extraction through a conditioned C18, SPE cartridge followed by detection with electrochemical and fluorescence detector [51].

4.4.2.2. High-performance liquid chromatography with electrochemical detector. Promazine was determined by HPLC in human plasma. The assay involved a single-step liquid–liquid extraction system and electrochemical detector at potential + 750 mV [52]. An accurate method has been developed for the therapeutic monitoring of perphenazine and its major metabolites in human plasma. The method involved extraction and separation on a nucleosil 5 μm C18 column and coulometric detection [53]. Louo et al. [54] developed a sensitive method for the measurement of fluphenazine decanoate and fluphenazine in plasma with coulometric detector. The detection limits for both fluphenazine decanoate and fluphenazine were 0.1 ng/ml plasma and the limit of quantitation was 0.25 ng/ml plasma. Similarly, an ultrasensitive method for the measurement of fluphenazine in plasma was described. The drug was isolated by a simple one step extraction technique and analyzed by HPLC with coulometric detection. The limit of detection was 10 pg/ml plasma [55]. Also, Hoffman et al. [56] determined fluphenazine and its metabolite in human plasma by HPLC-ECD at + 850 mV vs. silver–AgCl. An anodic electrochemical detector at a glassy car-

boelectrode was used in combination with HPLC for the determination of fluphenazine and perphenazine in blood [57]. Prochlorperazine was determined in plasma by HPLC with amperometric detection at 0.851 V [58]. Subnanogram quantitation of chlorpromazine in plasma by HPLC-ECD. The use of oxidative thin-layer amperometric detection allows the quantitation of 0.25 ng of chlorpromazine of human plasma [59].

4.4.2.3. High-performance liquid chromatography with mass spectrometry. Thiethylperazine have analyzed with other phenothiazine derivatives in human blood by HPLC/electrospray (ES) tandem MS. The HPLC/ES tandem MS showed much higher sensitivity than HPLC–MS for phenothiazines spiked to whole blood [60]. Promazine and their metabolites were extracted from acidified urine or plasma and determined by HPLC–MS [61] or by thermospray GC–MS [62].

4.4.2.4. High-performance liquid chromatography with ultraviolet spectrometry. Thioridazine and its main metabolites were determined in human serum by HPLC using UV detection after SPE [63–66]. Enantioselective separation and determination of thioridazine enantiomers in plasma after isolation using HPLC with UV spectrometry (HPLC–UV) were reported [67,68].

Mou et al. [69] have determined prochlorperazine in plasma by HPLC–UV. The same method was reported for perphenazine [70] and chlorpromazine [71,72].

4.4.3. Capillary electrophoresis methods

A capillary electrophoresis method for the simultaneous determination of thioridazine [73] in human urine using amperometric detector was described. A tenfold dilution of the urine sample with water was enough for the quenching effect of endogenous component of urine.

5. Analysis of thioxanthene derivatives in various biological fluids

Several methods and techniques have been reported for the determination of thioxanthene derivatives in various biological fluids. A review of the literature reveals a variety of analytical methods applicable to the analysis of thioxanthene derivatives. A good guide to the work published for thioxanthene derivatives is found in the review with 92 references covering the published articles up to 1996 written by Belal et al. [74]. The recent published method concerning the analysis of thioxanthene derivatives in biological fluids include the following.

5.1. Spectrophotometric methods

A UV spectrophotometric method for the determination of chlorprothixene and its metabolites in blood and urine from poisoning cases following thin-layer chromatography (TLC) separation was reported. The limited detection was 0.1 μg/ml of blood sample [75].

5.2. Mass spectroscopy methods

The advantageous use of chemical ionization of mass fragmentography using quadropole mass spectroscopy over magnetic sector instruments was discussed. Unlimited range of ion monitoring and cost of apparatus were discussed in detail during the analysis of chlorprothixene in urine [76].

5.3. Radioimmunoassay methods

The pharmacological active *cis* (Z)-flupenthixol was determined in human serum by specific RIA. The developed RIA method can measure as low as 60 pg of the drug [77].

5.4. Electrochemical methods

The thioxanthene derivatives, chlorprothixene, and clopenthixol 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 [78]. Peng and Yang [79] reported an adsorptive pre-concentration method for the

voltammetric measurement of trace levels of chlorprothixene. The method was applied for urine analysis.

5.5. Fluorimetric methods

Fluorometric analysis has proven to be a valuable method for the analysis of thioxanthenes. Shehata et al. [80] used the fluorescence obtained in nitrous acid to assay chlorprothixene, clopenthixol, flupenthixol, and thiothixene in human urine and plasma. The minimum detectability of the method was 2 mg/ml. A similar method but in 60% sulfuric acid was reported for chlorprothixenes, clopenthixol and flupenthixol in blood and urine after TLC separation [81]. Thiothixene in Britton Robinson buffer pH 8, where exposed to irradiation of mercury lamp produced fluorescence measured in human serum [82]. Jorndal and Oreland [83] 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 achieved with 0.1% hydrogen peroxide.

Mellinger et al. [84] 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 clopenthixol decanoate injections was reported [85].

Two fluorimetric methods were described for determination of thioxanthenes in biological fluids without prior separation of the drug and its metabolites [86,87]. The methods are based on the unique property of thioxanthenes in acidic medium, they form thioxan thyllum ions, which are strongly fluorescent.

5.6. Chromatographic methods

5.6.1. Thin-layer chromatography methods

A TLC method was described for the identification of psychotropic drugs (including thioxanthenes) in blood, urine, saliva, and hair after extraction using isopropanol and chloroform mixture. Four different developing systems were attempted. The sensitivity was 0.01–5 μg% [88]. A quantitative HPTLC method was described for thiothixene in blood. The method involved in situ fluorimetric detection; the sensitivity was 0.1 μg/ml of plasma [89]. Quantitative analysis of *cis* and *trans* chlorprothixene and its metabolites, chlorprothixene sulfoxide and 2-chlorothioxanthene using HPTLC for the separation under suitable conditions was also described [90].

5.6.2. Gas chromatographic methods

Gas chromatography with mass spectroscopy combined technique was utilized by Cailleux et al. [91] for identification and quantitation of drugs acting on the CNS of patients suspected of poisoning (including thioxanthene derivatives). Flupenthixol in plasma was measured using GC-with a nitrogen–phosphorus detector. The minimum detectability of the flupenthixol found was 0.5 mg/ml [92]. A capillary GC–MS method was used for the routine toxicological analysis of chlorprothixene and its metabolites in human plasma including its sulfoxide, hydroxide, and hydroxylated sulfoxide using a genetic EISTA Kit [93]. A sensitive GLC method was described for *cis* (Z) flupenthixol in serum after extraction. The working range is 1–10 mg/ml [94].

5.6.3. High-performance liquid chromatographic methods

A quantitative LC thermospray tandem mass spectroscopic method was described for thioxanthenes in whole blood [95,96]. Several HPLC methods were reported for each member of the class. Chlorprothixene was determined in human plasma by using a unique HPLC coupled with electrochemical detection at the glassy carbon electrode at 0.65 V [97]. Also, Brooks et al. [98] determined chlorprothixene and its sulfoxide metabolite in plasma by HPLC with UV and amperometric detection. HPLC was also used for the determination of chlorprothixene and clopenthixol in plasma [99]. Zuclopenthixol (the *cis* isomer of clopenthixol) was determined by HPLC–MS in biological fluids [100]. Also zuclopenthixol and its metabolites were determined by HPLC with post-column photochemical derivatization and fluorimetric detection [101].

Clopenthixol was determined by ion pairing HPLC [102]. Similarly, Tas et al. [103] determined clopenthixol with bromazepam, respectively LC–MS.

A specific HPLC method was reported for the estimation of *cis* (Z) and *trans* (E) isomers of clopenthixol and its *N*-dealkyl metabolite [104]. Zuclopenthixol (among various medications and drugs of abuse for toxicological screening) has been extracted through uniform SPE procedure in serum and urine by HPLC with photodiode-array detection [105]. Flupenthixol was determined in human serum in the presence of haloperidol by HPLC–UV detection [106]. Several HPLC methodologies have been described for the determination of thiothixene in human plasma [107–111].

Pinethixene was determined in human plasma and milk by SPE and HPLC. The detection limit of the drug was 15 ng/ml in both plasma and milk [112]. Also, pinethixene was measured in human plasma and urine by HPLC with detection limit 20 ng/ml [113].

6. Analysis of benzodiazepine derivatives in various biological fluids

Several methods and techniques have been reported for the analysis of benzodiazepine derivatives in different biological fluids. A review of the literature reveals a variety of analytical methods applied to the analysis of benzodiazepine derivatives. A good guide to the work prior to 1982 can be found in the book written by Schutz [114]. Later on, in 1989, Schutz [115] published another book covering the published articles from 1982 to 1989. Recently, in 1998, Drummer [116] reported an excellent review with 136 references dealing with methods for the measurement of benzodiazepines in biological samples. The recent published method includes the following.

6.1. Ultraviolet and visible spectrophotometric methods

A difference spectrophotometric method was reported for the determination of clonazepam and nitrazepam in biological fluids [117]. The use of fifth-order derivative spectrophotometry enabled the direct determination of nitrazepam in urine at 388 nm with a limit of detection of 1 μg/ml, but in plasma was carried out directly by fourth-order derivative spectrometry at 402 nm with a limit of detection of 1.5 μg/ml. Clonazepam was determined directly in urine by sixth-order derivative spectrometry at 384 nm with a limit of detection 1 μg/ml and in plasma by fourth-order derivative spectrometry at 384 nm with a limit of detection at 0.5 ppm. Similarly, chlordiazepoxide, diazepam, nordiazepam and oxazepam were determined in urine sample containing all these compounds by zero, first and second order derivative with spectra between 300 and 500 nm. The recoveries were 92–97% [118]. Also, Randez-Gil et al. [119] reported a third-order derivative UV spectrum of clonazepam in urine with detection limit of 150 ppb. An automatic kinetics spectrophotometry determination of oxazepam in urine was reported by continuous addition of $NaNO_2$ and α-naphthol to oxazepam after hydrolysis with 6 M HCl and measured the colored at 530 nm [120].

6.2. Electrochemical methods

Stripping voltammetric determination of some benzodiazepine derivatives at a hanging-mercury-drop electrode has been reported. Chlordiazepoxide has been determined in serum samples by cathodic-stripping voltammetry with detection limit of 0.5 nm [121]. Similarly, halazapam has been determined by adsorptive stripping voltammetry with detection limit of 25 ng/ml [122]. Zapardiel et al. [123] determined clonazepam in urine sample with adsorptive stripping voltammetry. Also, lorazepam was determined by adsorptive stripping voltammetry in urine sample [124,125].

Clobazam and diazepam were identified by measuring their half-wave potentials and determined quantitatively by measuring the height of the polarographic peaks. Acetate buffer of pH 4.6 and 10% dimethyl formamide was the supporting electrolyte [126]. The same method was reported for alprazolam, but used phosphate buffer pH 5.5

as supporting electrolyte [127], triazolam has been determined by linear-sweep chronoamperometry using dimethyl formamide–acetate buffer pH 4.7 (1:9) as supporting electrolyte [128].

6.3. Flow injection analysis

The inherent absorption properties of clonazepam, chlordiazepoxide, and lorazepam were used in their determination in urine sample by flow injection analysis and spectrophotometric detection [129,130].

6.4. Fluorimetric methods

Walash et al. [131] described a selective spectrofluorimetric method for the determination of lorazepam, oxazepam, and temazepam in biological fluids. The target compound reduced by Zn/HCl at room temperature with the formation of highly fluorescent derivative product with limit of detection 4 ng/ml.

6.5. Immunoassay methods

A range of immunoassay procedures using RIA, enzyme multiplied immunoassay (EMIT), fluorescence polarization immunoassay (FPIA), substrate labeled fluorescent immunoassay (SLFIA) and cloned enzyme donor immunoassay (CEDIA) methods have been published for analysis of benzodiazepine-derivatives [116]. Improved detection limits for many benzodiazepines in urine were achieved by spiking the enzyme β-glucuronidase to convert glucuronide metabolites to immunoreactive substances. This is because each immunoassay uses antibodies directed towards free drug not the glucuronide conjugate, which must be hydrolyzed to achieve a positive result [132]. Ropero-Miller et al. [133] used CEDIA immunoassay for determination of benzodiazepine derivatives, lorazepam, nordiazepam, oxazepam, and temazepam in urine. Urinary benzodiazepines, oxazepam, diazepam, nordiazepam, temazepam, lorazepam, and metabolites of nitrazepam, alprazolam, triazolam were detected with EMIT and FPIA immunoassay methods and comprised with GC–MS as the reference method. The cutoff limits for quantitation were between 50 and 72 ng/ml [134]. Similarly, Meatherall [135] used EMIT immunoassay method to detect diazepam, oxazepam, tempepam, lorazepam, alprazolam, and chlordiazepoxide in urine sample. Nordiazepam, triazolam, lorazepam, and alprazolam in blood were analyzed by RIA, EMIT and FPIA method [136]. AFPIA immunoassays on an Abbott Adx system after acetone precipitation of serum and pre-treatment of urine were used for the measurement of triazolam, brotizolam, clobazam, and diazepam. The serum assay was more sensitive than the urine assay [137].

Several immunoassay methods were reported for each member of the class of lorazepam in urine and were determined by CEDIA and compared with EMIT and FPIA methods [138]. Alprazolam in serum in the presence of nordiazepam were detected by EMIT method [139]. Also, Fraser and Bryan [140] determined alprazolam by EMIT method and compared it with FPIA immunoassay method. The immunoreactivity towards alpha OH triazolam by CEDIA method was assessed in urine after a single oral dose of triazolam [141]. Similarly, Bellet [142] detected alprazolam and triazolam metabolites by five immunoassay systems. Oxazepam in urine was determined by FPIA with the Adx analyzer, the sensitivity of the method was improved tenfold with detection limit of 0.1 μg/ml [143]. Brotizolam was evaluated by RIA in plasma; the sensitivity of the assay was 10 pg/ml [144]. Also, prozepam and flurazepam were determined by RIA method [145,146].

6.6. Chromatographic methods

6.6.1. Thin-layer chromatographic methods

Kastmer and Klimes [147] described a general TLC method for the detection of benzodiazepine derivatives in plasma after extraction with CH_2Cl_2. The TLC separation on RP-18 plates were used, various solvent mixture-developing systems were attempted and fluorescence detection after acid hydrolysis was used. A TLC detection was described for nitrazepam and oxazepam in biological fluids [148]. The developing system

was hexane–acetone (3:2); the spray reagents were stannous chloride in HCl, NH_4Cl solution, $NaNO_2$ solution, and Griess reagent. The detection limits were 0.1 and 1 μg/ml for nitrazepam and oxazepam, respectively.

Several TLC methods were reported for each member of the class: alprazolam in plasma was detected on silica gel GF 254 plate with cyclohexane–$CHCl_3$–diethylamine (50:40:1) and measured at 246 nm [149]. Diazepam and its metabolites in urine were extracted into toluene–heptane (4:1). The extract was subjected to TLC on silica gel 60 GE 254 with various mobile phases and detection by UV densitometry with a fluorescent-quenching technique [150]. Also, quazepam and its metabolites were extracted into toluene on TLC plate diazotization and coupling with Bratton-Marshall reagent to produce a violet azo-dye [151]. The detection limit was 0.05 mg/ml. Similarly, halazepam and its major metabolites in blood, urine, and stomach content were extracted into ethyl ether that was developed on TLC silica gel F 254 with toluene as mobile phase. Diazotization on TLC plate was achieved to form an azo-dye [152]. The detection limit was 0.05 mg/ml. Also, Schuetz and Suphachearabhan [153] screened flurazepam and its metabolites in urine and detected the spots by diazotization and treatment with Bratton-Marshall reagent. A quantitative HPTLC method was described for midazolam in serum. The method involved a fast atom-bombardment MS detection [154].

6.6.2. High-performance liquid chromatographic methods

HPLC methods of benzodiazepine derivatives in biological fluids were reported for separation, detection, and determination. The determination of benzodiazepines in urine or plasma depended upon the complete extraction of the medicaments [155]. HPLC method was described for benzodiazepines, the detection was accomplished spectrophotometrically for concentration of about 1–2 ng/ml using 1–5 ml/urine or serum [156–162]. A quantitative HPLC methods with photodiode array detection were described for benzodiazepines in whole blood [163,164]. A quantitative LC tandem mass spectroscopic method was described for benzodiazepines in serum and urine [165,166]. Lioyd and Parry [167] described HPLC method with coulometric detector fitted with porous carbon electrodes maintained at OV for benzodiazepines. The detection limits of benzodiazepine derivatives were in the range 1–5 mg/ml. A micellar electrokinetic capillary chromatography (MEKC) method was reported for benzodiazepines in serum [168,169].

Several HPLC methods were reported for each member of the class: alprazolam was determined in human plasma using reversed HPLC-switching techniques [170]. Adams et al. [171] described a normal HPLC for prazadam with 94% acetonitrile as a mobile phase and UV detection. Alprazolam has been determined simultaneously with its metabolites in plasma by HPLC assay with UV detection [172–178].

Clobazam has been determined with its metabolites by HPLC and UV detection with limit/detection of 2.5 ng/ml [179–182]. HPLC method with electrochemical detection at 300 mV was reported for chlordiazepoxide in plasma after UV irradiation [183]. Simultaneous determination methods of chlordiazepoxide with its metabolites in blood were published [184–186].

Clonazepam has been determined in human serum using HPLC methods coupled with UV detection [187–190]. Li et al. [191] described normal HPLC method for clonazepam with *n*-hexane–ethanol (9:8) as mobile phase and UV detection. Diazepam was determined in plasma using HPLC accomplished with UV detection [192]. HPLC method with chiralcel OD-R column was reported for simultaneous separation of diazepam and its chiral and achiral metabolites.

Several HPLC methods were published for determination of diazepam and its major metabolites in plasma and urine [193–198]. Flurazepam and its metabolites were determined in plasma with reversed HPLC with UV detection [199,200].

Fitos et al. [201] reported HPLC method for enantioseparation of flurazepam in serum with UV detection. Similarly, Kanazawa et al. [202] published a stereospecific method for the separation of racemic lorazepam using UV detector. Lorazepam and its metabolites were determined by HPLC with UV detection [203].

Flumazenil and its metabolites were determined by LC [204,205]. Several HPLC methodologies have been described for the determination of midazolam in biological fluids [206–209].

Portier et al. [210] determined midazolam in the presence of fentanyl in plasma by HPLC with UV detection. Alternatively, Eeckhoudt et al. [211] used capillary HPLC for separation of midazolam and its metabolites. Also, several HPLC methodologies have been described for the determination of midazolam and its metabolites in plasma [212–216]. Nitrazepam was determined in plasma using HPLC with limit of detection 200 ng/ml [217]. MEKC was reported for the estimation of nitrazepam and its metabolites in urine sample [218]. Oxazepam was determined by HPLC with post-column derivatization and fluorimetric detection [219]. Also, oxazepam and its metabolites were estimated by HPLC coupling with UV detection [220,221].

Chopineau et al. [222] determined temazepam and its active metabolites in plasma and urine using SPE and HPLC. Quazepam and its metabolites were determined by LC following sublingual administration of quazepam [223]. Komatsu et al. [224] determined triazolam in biological fluids by HPLC with UV detection. A specific HPLC method was reported for the estimation of triazolam and its metabolites. The limit of detection was 20 pg/ml [225]. Estazolam was determined simultaneously with triazolam in serum by HPLC assay and detection limits were 8.35 and 20 μg/ml, respectively [226].

6.6.3. Gas chromatographic methods

GC-ECD combined technique was utilized by Guan et al. [227] for detection of benzodiazepine derivatives in urine sample after solid-phase microextraction (SPME). The detection limit for the benzodiazepines were 2–20 ng/ml. Also, GC coupled with ion-trap mass spectroscopy was utilized by Luo et al. [228] for determination of benzodiazepines in serum and urine after SPE. The detection limit was 20 ng/ml. Similarly, SPME and GC were used for the determination of benzodiazepines in urine plasma [229]. A GC coupled with negative ion chemical ionization mass spectroscopy was used for the detection of benzodiazepines in human hair [230]. An automated online SPE–GC with nitrogen–phosphorus detection was used for the determination of benzodiazepines in human plasma [231]. Similarly, an automated online SPE–GC was used for determination of benzodiazepines in plasma [232]. Several GC–MS methodologies have been described for the determination of benzodiazepines in human urine [233–235].

GC on two parallel fused-silica columns with temperature programming and ECD and N–P detection was used for analysis of benzodiazepines in plasma [236].

Several GC methods were reported for each member of the class: alprazolam was determined in human urine using GC–MS combined technique with the detection limit 0.3–13.5 ng/ml [237]. Alprazolam and its hydroxy metabolites were determined in plasma by GC-negative ion chemical-ionization mass spectroscopy [238] and dual capillary column, dual nitrogen detector GC [239]. A sensitive GLC method was described for determination of brotizolam and its main hydroxy-metabolite in plasma with double internal standardization [240]. An isothermal GLC with nitrogen detector was described for clobazam in serum. The detection limit was 2–5 ng/ml [241].

Clobazam and norclobazam were quantitated in serum by GLC-ECD. The detection limit was 0.3 ng/ml for both analytes [242]. Clobazam and its *N*-demethyl metabolites were determined in serum by GC-nitrogen detector [243]. Chlordiazepoxide was determined in mouse plasma by GC–CIMS at 230 eV with methane as reagent gas. The working range was 5–50 ng/ml and detection limit was 0.1 ng/ml, respectively [244]. Similarly, clonazepam was determined in plasma by GC–SIMS [245]. Whilst Miller et al. [246] utilized GC-ECD for determination of clonazepam in serum. A sensitive GLC method was described for diazepam in plasma after SPME [247]. Alternatively, Brathen et al. [248] described GLC coupled with atomic emission detection (AES) for determination of diazepam in plasma. GC–MS methods were used for the analysis of diazepam and *N*-demethyl diazepam in human plasma [249,250].

Flumazenil in human plasma has been analyzed by GC–MS methods [251,252]. A similar GC method has been applied for determination of flumazenil and midazolam in blood samples [253]. Kelly and Greenblatt [254] described a sensitive GC-ECD for determination of estazolam in plasma. Flurazepam and its major metabolites in plasma have been determined by GC with SIMS [255] or with ECD [256]. GC–MS combined technique was utilized by De-Vries et al. [257] for determination of midazolam in plasma. Whilst Ha et al. [258] utilized the GLC-ECD for measuring midazolam in plasma. Midazolam have been determined in the presence of flumazenil in plasma by GC after SPE [259,260]. Midazolam and its metabolites has been measured by GC–MS in plasma [261]. Also De-Kroon et al. [262] utilized GC-ECD for determination midazolam and its metabolites without derivatization. Nitrazepam has been determined in serum and saliva by GC–MS coupling technique [263]. Whilst Lin and Beck [264] utilized GC–MS technique for measuring nitrazepam and flunitrazepam in urine. Sensitive GLC methods were described for determination of quazepam and its major metabolites in plasma after extraction [265,266].

Triazolam has been determined in serum either by deactivated metal GLC-ECD [267] or by GC-ECD [268] or GC-nitrogen–phosphorus detection with SPE [269]. Escoriaza et al. [270] had quantitated temazepam in plasma by GLC and UV detection.

7. Capillary electrophoresis methods

MEKC assay of benzodiazepine derivatives was reported for separation and quantitation of this isomer. Jinno et al. [271] described MEKC method for benzodiazepines in urine; the detection was accomplished spectrophotometrically for concentration of about 1 ppm. Similarly, Tomita and Okuyama [272] have quantitated benzodiazepines in serum by capillary zone electrophoresis (CZE).

Benzodiazepines and their metabolites have been determined by CE with UV detection [273]. CZE-tandem MS was utilized for determination of midazolam and three of its metabolites in body fluids [274]. Similarly, flurazepam and its metabolites were determined by CE–UV detection in urine samples [275].

8. Miscellaneous methods

Radioreceptor assays of benzodiazepine derivatives were reported for determination of these derivatives in urine [276–278]. Benzodiazepines have been analyzed by desorption chemical ionization tandem MS [279]. Also, estazolam and its major metabolites were identified by ES ion-trap MS [280].

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