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Determination of a cardiac antiarrhythmic, tricyclic antipsychotics and antidepressants in human and animal urine by micellar electrokinetic capillary chromatography using a bile salt

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Abstract

A micellar electrokinetic capillary chromatographic method based on the use of sodium taurodeoxycholate has been developed to detect and quantitate a total of 26 tricyclic drugs. Detection limits in urine down to 4 ng/ml have been obtained. The method uses a simple liquid–liquid extraction and recovery of analytes followed by ultraviolet detection.

1. Introduction

Phenothiazine, chlorpromazine (tricyclic antipsychotic agents) were the first tricyclics introduced in the 1950s for treatment of schizophrenia and depression, respectively [1]. These antipsychotic agents showed characteristic, sometimes severe and intolerable, neurologic side effects [1]. Patients who did not respond to antipsychotics such as chlorpromazine or haloperidol in the early 1970s were given clozapine [2,3]. The use of clozapine was limited in Europe and removed from the United States market due to the problem of agranulocytosis [2–4]. During 1990, clozapine was made available in the US through a monitoring system designed to minimise the risk of agranulocytosis [5]. In veterinary practice, tricyclic antipsychotics such as azaperone, chlorpromazine and acepromazine are used as tranquillisers to prevent mortality and loss of meat quality during transport of bulls and swine from the farm to the slaughterhouse [6]. Swine bred to give lean meat are especially prone to stress and this can result in tough meat [7]. Generally, tranquillisers are administered to the animal a few hours before transportation to the slaughterhouse. If time is not allowed for the drug to clear the animal's body, then drug residues can enter the food chain [7–9]. Drug metabolites can have similar chemical structure

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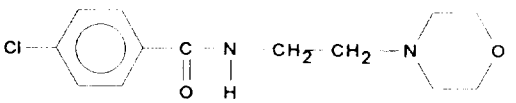

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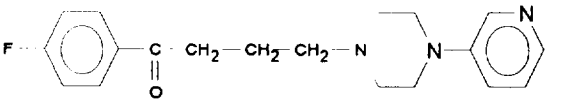

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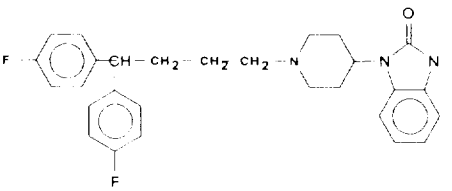

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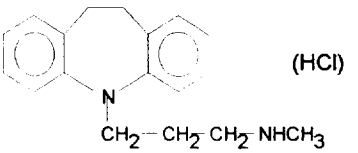

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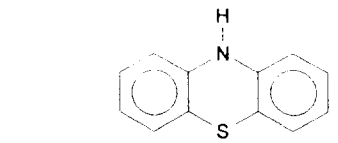

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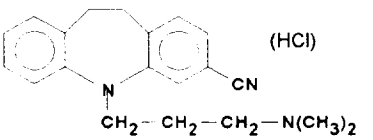

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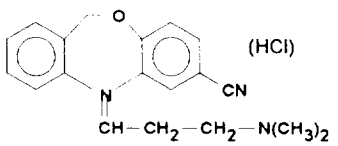

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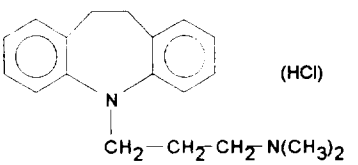

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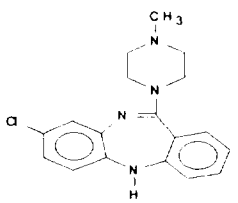

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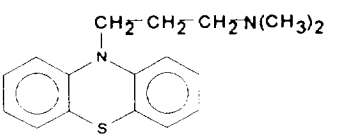

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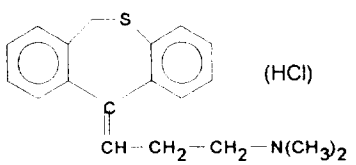

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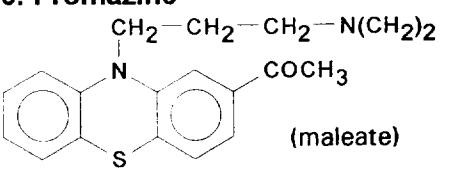

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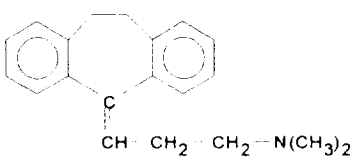

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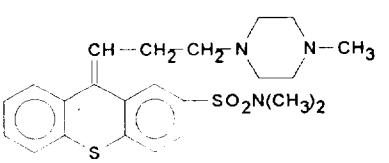
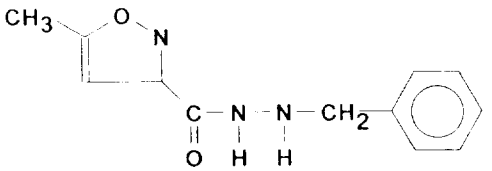


14. Thiothixene

Fig. 1. Structures of compounds studied with reference numbers.



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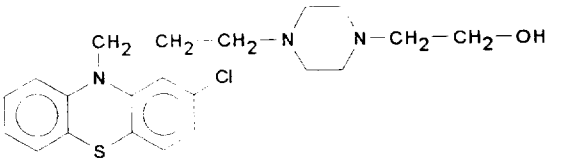

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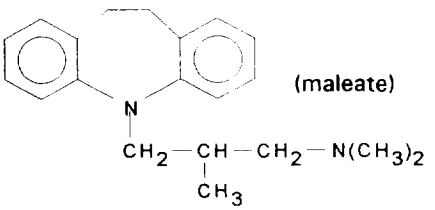

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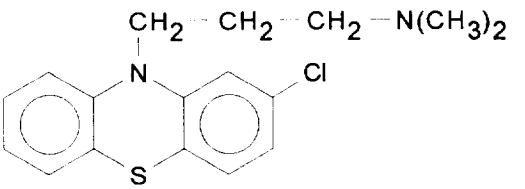

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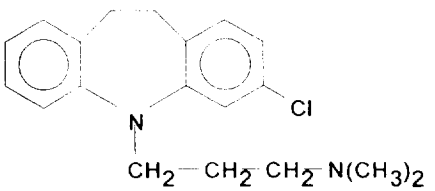
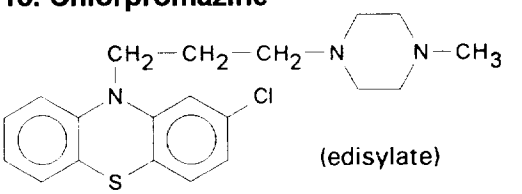


19. Clomipramine



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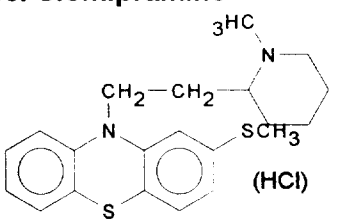

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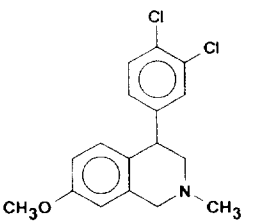

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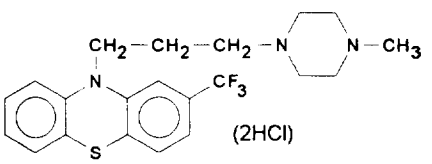
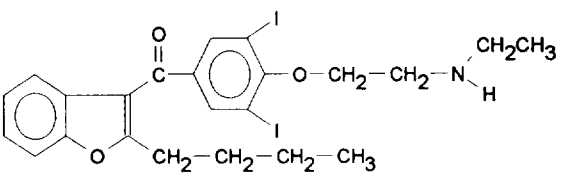


23. Trifluoperazine dihydrochloride



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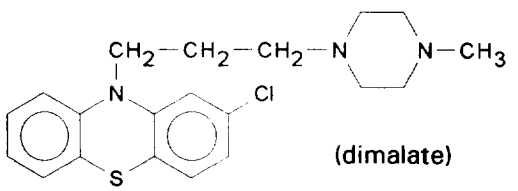
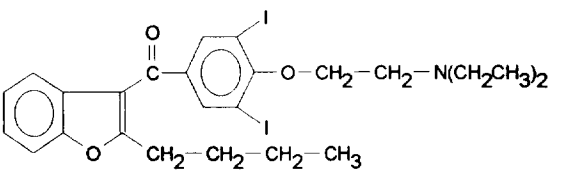


25. Prochlorperazine dimalate



26. Amiodarone

Fig. 1. (*Continued*).

to parent drug, but possess different pharmacological effects. For example, aminodarone has a chemical structure similar to tricyclic antipsychotic and antidepressant agents (tricyclics), as shown by Fig. 1, although aminodarone is used as a cardiac antiarrhythmic agent [10].

Capillary zone electrophoresis (CZE) is an efficient low-volume separation technique that has been applied in the analysis of small ions, peptides, carbohydrates, oligo-nucleotides and pharmaceutical drugs in biological fluids [10,11]. The separation principle of CZE is based on the different electrophoretic mobilities of solutes, which in turn, depend on charge densities [10].

Tricyclics are widely used and responsible for a disproportionate share of self-poisoning, requiring intensive care [12], and mortality when compared with other drug ingestions [13,14]. The development of fast and reliable techniques for toxicological screening of tricyclics in both human and animals constitutes a necessary task for laboratories dealing with veterinary drug residues, clinical and/or forensic toxicology.

Numerous methods have been proposed to identify tricyclics in emergency-room or forensic situations, including immunoassays [15], spectrophotometry [16], thin-layer chromatography [17], gas chromatography [18], high-performance liquid chromatography [19,20], and more recently, CZE [21–25]. In CZE, protonated tricyclics have been separated under the influence of an electroosmotic flow (EOF), based on the difference of electrophoretic mobilities [21,22]. Micellar electrokinetic capillary chromatography (MECC) —an interface between electrophoresis and chromatography— has been used to resolve tricyclics in serum by employing a cationic surfactant [24]. To date, tricyclic antidepressants, antipsychotics and cardiac antiarrhythmic agents have not been simultaneously resolved by MECC.

Reported in this paper is a MECC separation method using sodium taurodeoxycholate (STDC), a bile salt, to resolve cardiac antiarrhythmic [26] and metabolite [24], tricyclic antidepressant and antipsychotic agents (shown in Fig. 1), in urine to 0.1 μg/ml.

2. Experimental

2.1. Reagents

The following compounds were donated by the indicated pharmaceutical companies:

1, **6**, **13**, **15**, **22**: F. Hoffmann–La Roche (Basel, Switzerland); **3**: Janssen Cilag (Sydney, NSW, Australia); **4**, **8**, **19**: Ciba-Geigy (Sydney, NSW, Australia); **7**: Alphapharm (Brisbane, Queensland, Australia); **7**, **14**: Pfizer (Sydney, NSW, Australia); **9**, **21**: Sandoz (Sydney, NSW, Australia); **11**: Boot's (Sydney, NSW, Australia); **16**: Schering-Plough (Sydney, NSW, Australia); **17**: Rhone-Poulenc Rorer (Melbourne, Victoria, Australia); **20**, **23**, **25**: Smith Kline Beecham (Melbourne, Victoria, Australia); **24**, **26**: Reckitt and Coleman (Sydney, NSW, Australia).

Compounds **2**, **10**, and **12** were supplied by the Curator of Standards, Australian Government Analytical Laboratories (Sydney, NSW, Australia). Compound **18** was donated by Dr. H. Keyzer (California State University, Los Angeles, CA, USA). Sodium taurodeoxycholate and **5** were supplied by Sigma (St. Louis, MO, USA). Chemicals and solvents were of AR or HPLC grade and were used without further purification.

2.2. Capillary electrophoresis

Apparatus

Qualitative work was performed with a 50 μm I.D. fused-silica capillary tube (Isco, Lincoln, NE, USA) with a length of 50 cm from injection end to the detector window (100 cm total capillary length). An Isco Model 3140 electropherograph was used for all analyses. The instrument was operated at 30 kV and at a temperature of 22°C with the detector placed on the cathode side. The sample solution was loaded into the capillary under vacuum (vacuum level 7.5 kPa/s for Isco 3140 electropherogram). The compounds were detected at 240 nm and 0.005 AUFS. Electropherograms were recorded and processed with the ICE Data Management and

Control Software supplied with the Model 3140 electropherograph.

Preparation of buffers

Stock buffer solutions of 0.100 *M* sodium tetraborate adjusted to pH 9.5 with 5.0 *M* sodium hydroxide and 0.100 *M* STDC were used to prepare CZE-buffers. The CZE-buffers were prepared by the appropriate volume of stock buffer and surfactant. The resulting CZE-buffer was degassed by sonication and filtered through a 0.2 μm PTFE filter (Micro Filtration Systems, Dublin, CA, USA) before use.

Procedure for capillary preparation and handling

Prior to extended use, the capillary was left filled for 1 h with 1 *M* sodium hydroxide and for another hour with 0.1 *M* sodium hydroxide. The capillary was rinsed with deionised water before filling with the CZE-buffer (between sample injections capillary was rinsed with 20 μl of CZE-buffer). The capillary was used for a maximum of 20 sample injections before rinsing with 1 *M* sodium hydroxide (200 μl), deionised water (200 μl), and CZE-buffer (200 μl); it was then left filled with CZE-buffer ready for sample injection.

Recoveries

Recoveries after sample treatment were determined by comparison of electropherogram peak height with peak height obtained by direct injection of standard drugs dissolved in 0.05 *M* STDC.

2.3. Sample preparation

Urine spiking

A pooled blank human urine sample obtained from six males had a specific gravity of 1.020 and pH 7.0. Urine samples from swine, bovine, cow and horse were obtained by catheter. Mixed standard solutions of all drugs were prepared in methanol at a concentration of 1 μg/ml. Volumes of 10 and 100 μl of drug standard solutions were added directly to a well-agitated aliquot of urine (100 ml) prior to workup giving 0.1 and 1.0 ppm spikes, respectively. Throughout spiking and extraction procedure the samples were covered with an aluminium foil to prevent any light-activated chemical reactions.

Extraction procedure

Urine or aqueous standard (10 ml) was mixed with 5 *M* sodium hydroxide (1 ml) in a 30-ml glass centrifuge tube. A solvent of 10 ml was added and the tube was vortex-mixed for 1 min, and centrifuged at 3000 *g*, 0°C for 5 min. The solvent layer was transferred into a 15-ml tapered centrifuge tube (silanized) and glacial acetic acid (50 μl) added, and evaporated to dryness under a slow stream of nitrogen (30°C). Finally, the residue was reconstituted in 50 μl of 0.05 *M* STDC, filtered through 0.2 μm PTFE filter (Micro Filtration Systems) and analysed by CZE.

3. Results and discussion

In a previous work [21], the optimum pH for resolving tricyclic antidepressants by CZE has been shown to be 9.5. Lee et al. [24] showed that MECC, employing sodium dodecylsulphate (SDS) buffered at pH 8 and also 11 did not resolve a mixture of **4**, **7**, **8**, **13**, and nortriptyline. However, **22**, a tricyclic antidepressant, was optically resolved by MECC using STDC and cyclodextrin at pH 9.5 [23]. In this work, STDC, a more polar surfactant than SDS, was employed in a MECC system buffered at pH 9.5 to attempt resolve the tricyclics shown in Fig. 1. In a series of experiments, varying amounts of buffer and surfactant were studied to separate examples of tricyclic standard solutions. Increases in buffer concentration from 30 to 60 m*M* increased solute migration times, as shown by Fig. 2. This was attributed to increases in

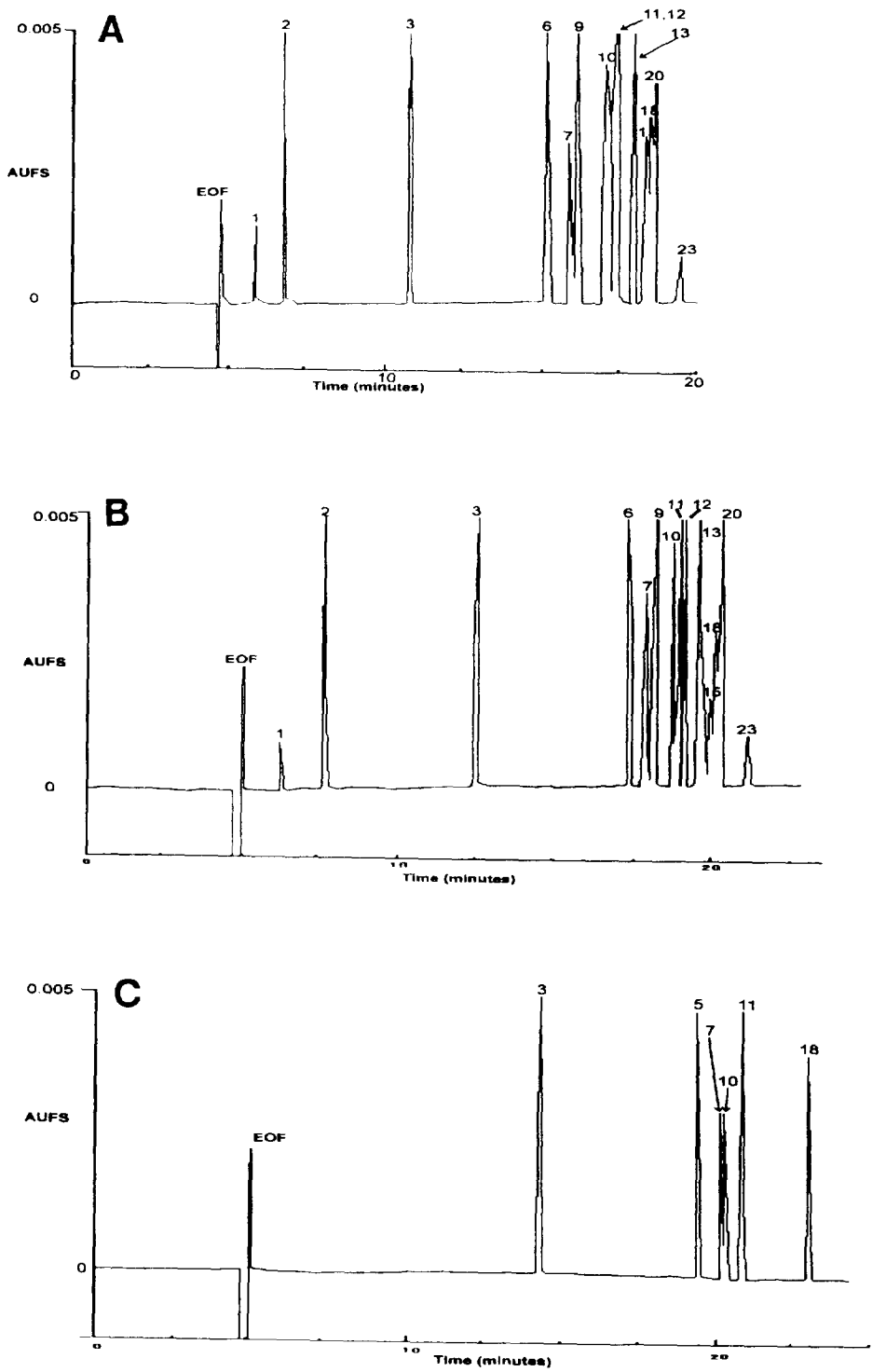


Fig. 2. MECC separation of tricyclics at pH 9.5 using CZE-buffer: (A) 30 m*M* borate, 50 m*M* STDC; (B) 40 m*M* borate, 50 m*M* STDC; and (C) 60 m*M* borate, 50 m*M* STDC.

buffer ionic strength, increasing the hydrophobic solute affinity for the slower migrating micellar pseudo-stationary phase. In Fig. 2A, **11** and **12** co-eluted with a 30 m*M* borate buffer. However, in the presence of 40 m*M* borate, **11** and **12** were satisfactorily resolved (Fig. 2B). Also, decreases in STDC concentration from 50 to 10 m*M* decreased solute migration times (Figs. 2B and 3), and co-eluted compound pairs **10**/**11** and **18**/**20** were resolved by reducing STDC from 30 to 10 m*M* (Fig. 3). Decreases in STDC concentration can decrease the hydrophobic solute affinity for the micellar phase, decreasing solute migration time. In Fig. 3B, **1–13**, **15**, **16**, **18**, **20**, and **23–26** were simultaneously resolved satisfactorily with 10 m*M* STDC. The corresponding migration order and retention factor (R_F = tricyclic migration time/methanol migration time) for the tricyclics resolved with 10 m*M* STDC is given in Table 1. The tricyclics studied appear to elute in order of increasing hydrophobicity, and decreases in buffer ionic strength and/or surfactant concentration decrease solute migration times, suggesting a reduction in solute residence time with the slower migrating micellar phase. The CZE-buffer consisting of 10 m*M* STDC and 40 m*M* borate was further investigated with urine samples.

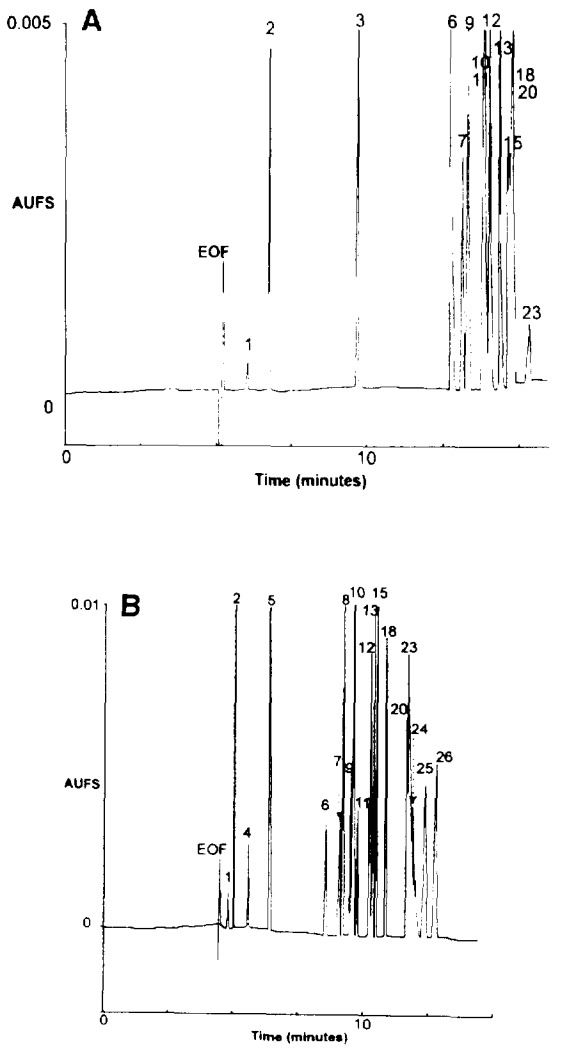


Fig. 3. MECC separation of tricyclics (each at 200 μg/ml) using CZE-buffer: (A) 40 m*M* borate buffer at pH 9.5, 30 m*M* STDC; and (B) 40 m*M* borate buffer at pH 9.5, 10 m*M* STDC.

3.1. Liquid–liquid extraction and analysis by MECC

A variety of extraction procedures have been proposed for tricyclics, including solid-phase [26–29] and single- or multiple-step liquid–liquid extractions [19,29,30]. Liquid–liquid extraction was chosen for this work in terms of convenience, simplicity and speed [29]. *n*-Hexane and diethyl ether were selected as extracting solvents because they are little prone to emulsion formation and allow good recoveries of tricyclics [19,29,30]. Drug recovery was determined by comparing the MECC analyte response of extracted spiked urine and water with analyte response of aqueous standards. A single liquid–liquid extraction using *n*-hexane and diethyl ether was performed with human urine samples (pooled sample) and water-spiked at 1 μg/ml with **1**, **2**, **4–13**, **15**, **18**, **20**, and **23–26**. Drug recoveries were higher for spiked water samples extracted with *n*-hexane (average recovery 92%, w/w) than diethyl ether (average recovery 48%, w/w) by MECC (Table 2, Figs. 4A and 5A). *n*-Hexane and diethyl ether extracts from spiked urine samples (Figs. 4B and 5B) analysed by MECC showed similar drug recoveries, as shown by Table 2. Urine matrix-interfering components

Table 1
Migration order of tricyclics by MECC (conditions given in Fig. 3B)

Compound	R_F	Compound	R_f	Compound	R_F
1	1.07	**11**	2.16	**21**	2.58
2	1.12	**12**	2.27	**22**	2.60
3	1.20	**13**	2.30	**23**	2.62
4	1.24	**14**	2.31	**24**	2.64
5	1.43	**15**	2.32	**25**	2.74
6	1.90	**16**	2.37	**26**	2.82
7	2.01	**17**	2.39	Methanol	1.00
8	2.04	**18**	2.41		
9	2.11	**19**	2.52		
10	2.12	**20**	2.58		

Table 2
Drug recovery (%, w/w) of tricyclics spiked at 1 μg/ml into human urine and water, solvent extracted (using *n*-hexane and diethyl ether), analysed by MECC

Compound	Drug recovery by MECC (%, w/w)			
	Extracted with *n*-hexane		Extracted with diethylether	
	Urine	Water	Urine[a]	Water
1	31	94	26	19
2	35	32	72	100
4	21	100	98	95
5	77	100	67	57
6	52	95	39	35
7	76	100	60	40
8	93	100	100	90
9	100	100	2	22
10	18	91	91	56
11	59	100	39	33
12	49	98	40	43
13	56	88	37	31
15	93	100	95	95
18	56	100	49	35
20	56	100	43	38
23	82	100	68	50
24	63	100	76	55
25	13	77	29	19
26	15	62	19	4
Mean recovery	55	92	55	48

MECC conditions given in Fig. 3B.
[a] Background subtracted using blank urine extract.

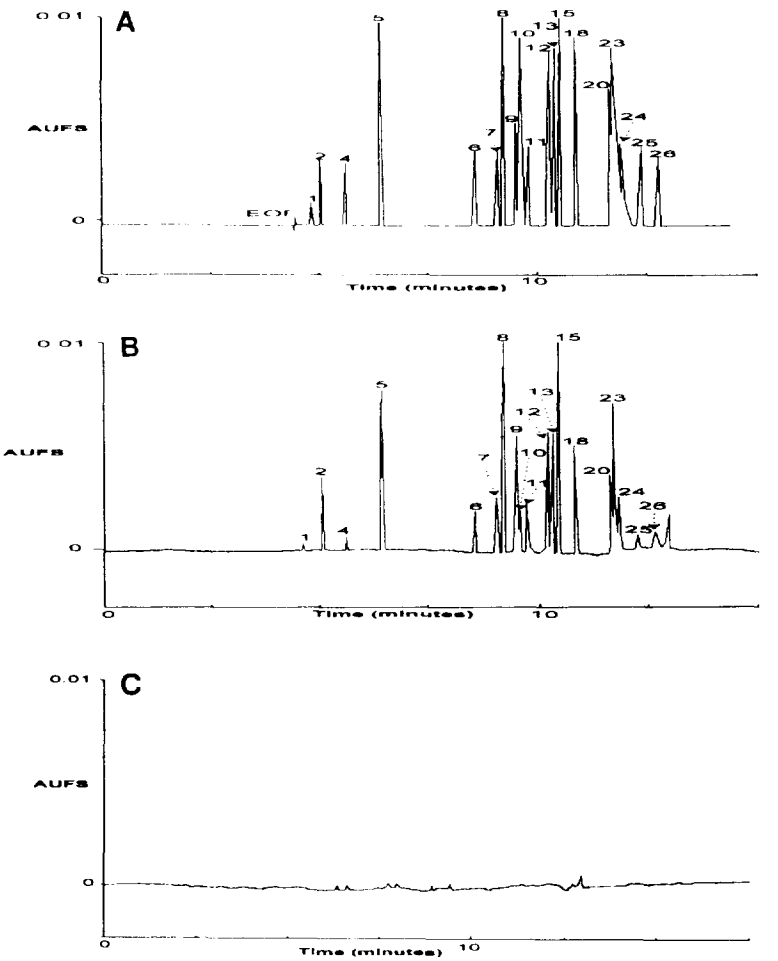


Fig. 4. Electropherogram of *n*-hexane extracts from: (A) 1 μg/ml spiked water; (B) 1 μg/ml spiked human urine; and (C) blank human urine (spiking solution contains **1**, **2**, **4–13**, **15**, **18**, **20**, **23–26**; MECC conditions given in Fig. 3B).

were determined by extracting blank human urine with each solvent and comparing the electropherogram of extract to the tricyclic standards. Blank urine extracted with diethyl ether gave more matrix-interfering peaks than *n*-hexane, reflected by MECC traces (Figs. 4C and 5C).

Drug recovery determined by MECC from spiked urine using single liquid–liquid extraction with *n*-hexane was low (Table 2). However, drug recovery can be improved by multiple liquid–liquid extraction with *n*-hexane. Triplicate liquid–liquid extraction of urine was studied by spiking a pooled human urine at 0.1 μg/ml with tricyclics (**1**, **3**, **5**, **8**, **9**, **12**, **22**, and **23**), and analysing the *n*-hexane extract by MECC. Higher drug recoveries were obtained with a negligible increase in background noise, (Table 3 and Fig. 6). This extraction method was further studied with blank urines from horse, cow, bovine, porcine and human. These urine extracts appear to show no interfering endogenous com-

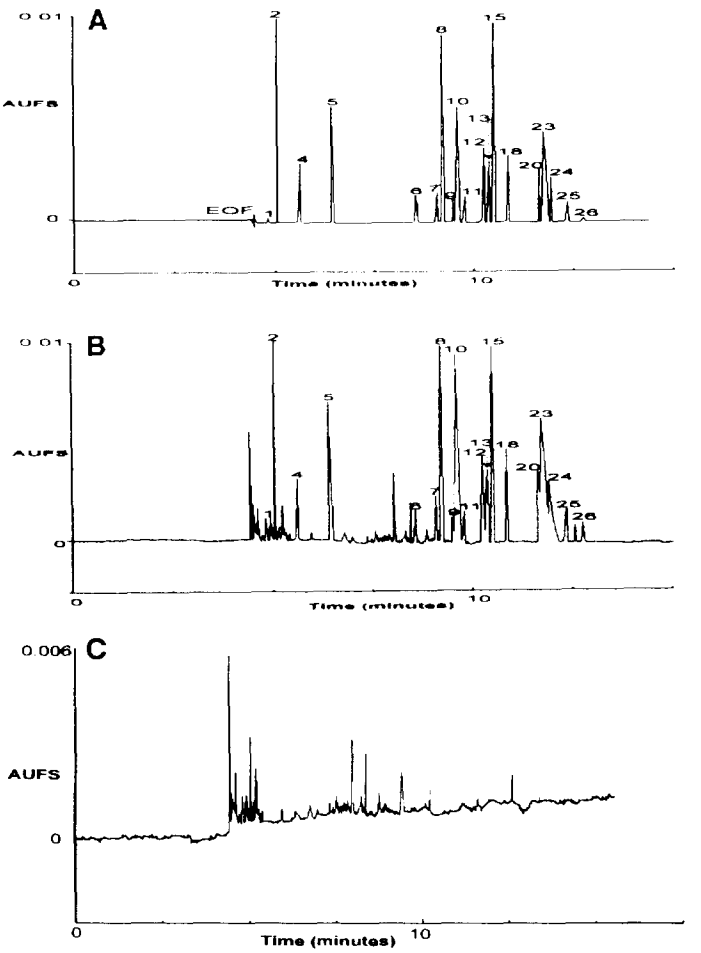


Fig. 5. Electropherogram of diethyl ether extracts from: (A) 1 μg/ml spiked water; (B) 1 μg/ml spiked human urine; and (C) blank human urine (spiking solution contains **1**, **2**, **4–13**, **15**, **18**, **20**, **23–26**; MECC conditions given in Fig. 3B).

pounds co-eluting with the tricyclics studied by MECC (Fig. 7). A blank porcine urine was spiked at 0.1 and 1.0 μg/ml with **2**, **7**, **12**, **14**, and **18**, and subjected to the extraction and MECC method, (Figs. 8 and 9). Drug recoveries from 0.1 and 1.0 μg/ml spiked porcine urine ranged from 29 to 71% (w/w) and from 58 to 101% (w/w), respectively (Table 4). The limit of detection (LOD) and reporting (LOR) in human and porcine urine was determined by estimating the minium concentration equivalent to or greater than three and six times the background noise for MECC. Lower detection limits for all analytes were between 4 and 86 ng/ml, and LOR between 8 and 171 ng/ml (Table 5).

Table 3
Absolute average recovery (%, w/w) of three human urine samples spiked at 0.1 μg/ml and analysed by MECC

Compound	Recovery (mean ± S.D.) (%)	C.V. (%)
1	35.3 ± 0.9	2.7
3	82.7 ± 17.4	21.1
5	53.7 ± 2.9	5.3
8	74.3 ± 15.0	20.1
9	75.0 ± 15.0	20.0
12	47.3 ± 4.0	8.5
22	82.7 ± 8.7	10.5
23	18.0 ± 1.4	7.9

MECC conditions given in Fig. 3B. S.D. = standard deviation; C.V. (%) = percent coefficient of variation.

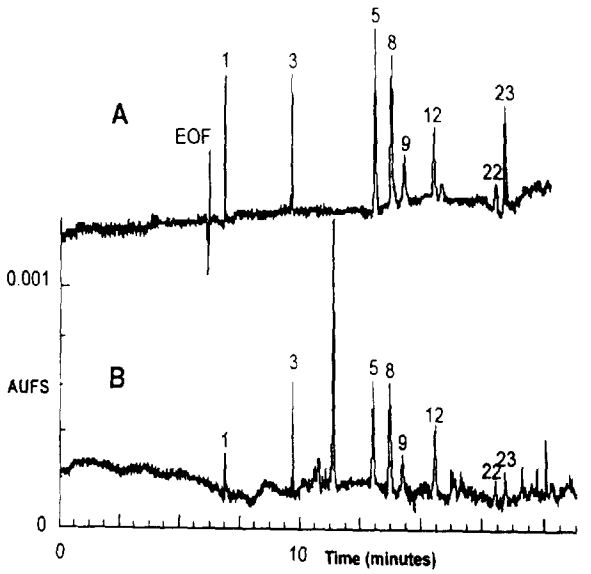


Fig. 6. Electropherograms of: (A) tricyclic standard mixture of 0.1 μg/ml; and (B) 0.1 μg/ml spiked human urine extracted with *n*-hexane (standard mixture and spiking solution contains **1**, **2**, **4–13**, **15**, **18**, **20**, **23–26**; MECC conditions given in Fig. 3B).

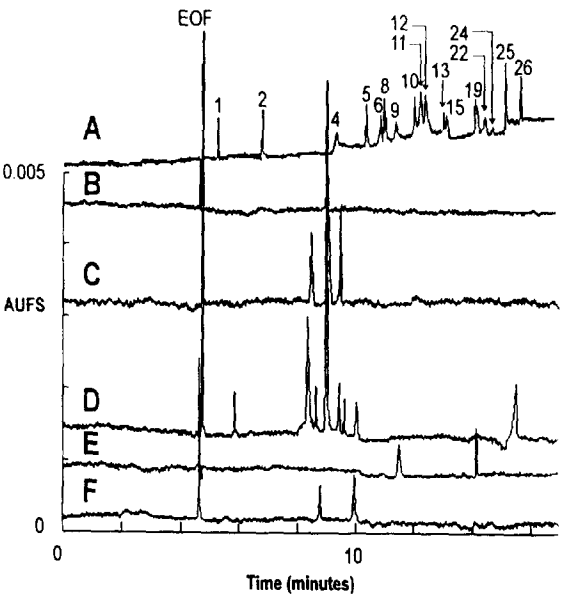


Fig. 7. Electropherograms of: (A) standard mixture of **1**, **2**, **4–6**, **8–13**, **15**, **19**, **22**, and **24–26** each at 0.1 μg/ml, and *n*-hexane extracts from blank; (B) horse urine; (C) cow urine; (D) bovine urine; (E) porcine urine; and (F) human urine (MECC conditions given in Fig. 3B).

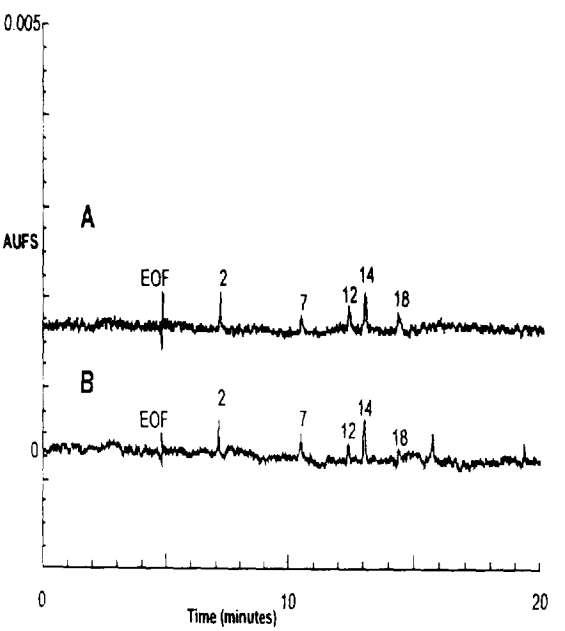


Fig. 8. Electropherograms of: (A) 0.1 μg/ml tricyclic standard mixture; and (B) 0.1 μg/ml spiked porcine urine extract (standard mixture and spiking solution contains **2**, **7**, **12**, **14**, **18**; MECC conditions given in Fig. 3B).

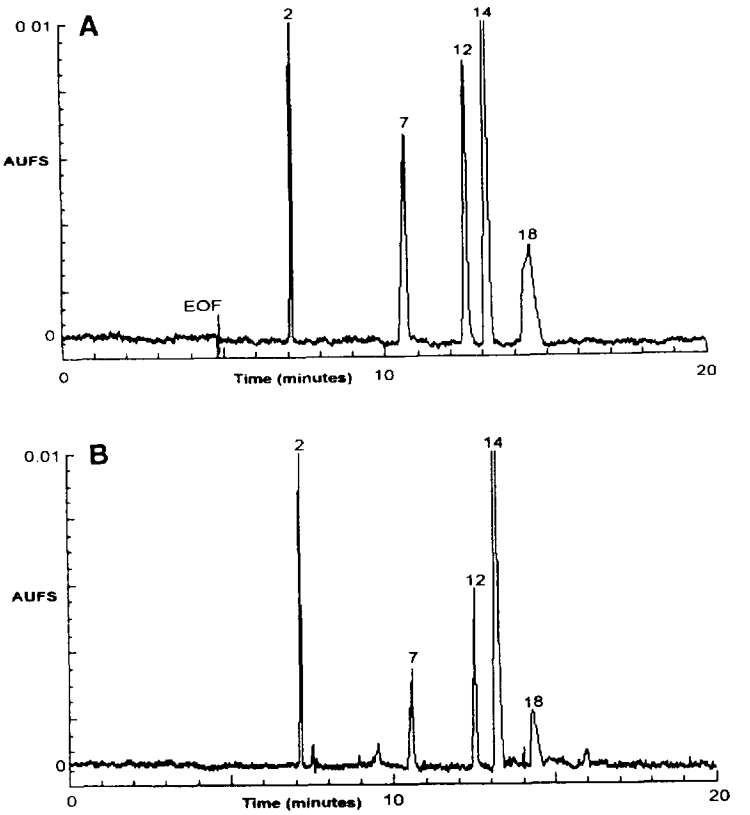


Fig. 9. Electropherograms of: (A) 1 μg/ml tricyclic standard mixture; and (B) 1 μg/ml spiked porcine urine extract (standard mixture and spiking solution contains **2**, **7**, **12**, **14**, **18**; MECC conditions given in Fig. 3B).

Table 4
Absolute average recovery (%, w/w) of eight porcine urine samples spiked at 0.1 μg/ml and 1.0 μg/ml and analysed by MECC

Compound	Recovery (Mean ± S.D.) (%)	C.V. (%)
Spiked at 0.1 μg/ml		
2	57.0 ± 6.4	11.1
7	58.1 ± 6.9	11.8
12	52.5 ± 5.7	10.9
14	71.3 ± 5.9	8.3
18	28.6 ± 5.0	17.5
Spiked at 1.0 μg/ml		
2	85.0 ± 7.2	8.5
7	57.6 ± 5.2	9.0
12	67.9 ± 6.1	8.9
14	101.0 ± 3.6	3.6
18	64.9 ± 7.8	1.5

MECC conditions given in Fig. 3B.

Table 5
The lowest order of detection (ng/ml) and lowest order of reporting (ng/ml) based on extraction of eight human and porcine blank urine samples analysed by MECC

Compound	Porcine urine			Human urine		
	S.D.	LOD	LOR	S.D.	LOD	LOR
1	1.4	4	8	1.4	4	8
3	1.9	6	12	1.9	6	12
4	2.1	6	13	2.1	6	13
5	3.1	9	19	3.1	9	19
6	4.3	13	26	4.3	13	26
7	1.4	4	8	1.4	4	8
8	2.2	7	13	2.2	7	13
9	3.1	9	19	3.1	9	19
10	2.5	7	15	2.5	7	15
11	3.4	10	20	3.4	10	20
12	3.2	10	19	3.2	10	19
13	3.2	10	19	3.2	10	19
14	5.4	16	32	5.4	16	32
15	28.6	86	171	28.6	86	171
16	1.8	5	11	1.8	5	11
17	1.9	6	12	1.9	6	12
18	2.0	6	12	2.0	6	12
19	4.4	13	27	4.4	13	27
21	12.5	38	75	12.5	38	75
22	6.1	18	36	6.1	18	36
23	14.3	43	86	14.3	43	86
24	1.8	5	11	1.8	5	11
25	1.6	5	9	1.6	5	9
26	3.2	10	19	3.2	10	19

MECC conditions given in Fig. 3B.

4. Conclusions

Tricyclic drugs (Tables 1–4) were recovered from human and animal urine using a simple liquid–liquid extraction method. Detection and quantification of tricyclic drugs in human and animal urine was obtained by MECC using sodium taurodeoxycholate as a surfactant buffered at pH 9.5.

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