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REVIEW

APPLICATIONS OF THE EXTRACTIVE METHODS IN CHEMICAL ANALYSIS OF SOME PSYCHOTROPIC DRUGS

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Abstract: The review is devoted for the solid phase extraction and the extractive spectrophotometric methods for the determination of some psychotropic drugs, e.g. phenothiazines, thioxanthenes, dibenzothiazines, fluoxetine, fluvoxamine, trazodone.

Keywords: psychotropic drugs, solid phase extraction, extractive spectrophotometric methods

Psychotropic drugs are an important group of organic compounds. Some typical tricyclic psychotropic drugs and new generation psychotropic drugs, e.g. fluoxetine, fluvoxamine and trazodone are presented in Figure 1. These psychotropic drugs due to their characteristic structure – the presence chemically active nitrogen atoms and substituents, react with some organic reagents, e.g. flavianic and picramic acid, chrome azurol S, eriochrome cyanine R, triphenylmethane dyes (1-6) and thiocyanate complexes of metals (e.g. Co(II), Fe(III), Ti(IV), Nb(V)) with the formation of colored ion-association compounds (7). These reactions have been exploited in extractive spectrophotometric analysis of psychotropic drugs (8-11).

In recent years solid phase extraction (SPE) methods have found wide application in different fields of chemical analysis, including biological materials and pharmaceutical products. It is known that biological materials and pharmaceutical products often contain proteins, salts, acids, bases and organic compounds with similar properties to the analytes. In addition, the analytes often exist at low concentration in samples. Depending on the analytical objectives and origins of samples, drug analyses have been carried out using various analytical instruments in many circumstances such as clinical control for diagnostics and treatment of diseases, doping control, forensic analysis and toxicology. However, taking the advances in the development of highly efficient analytical instrumentation for the end point determination of analytes in pharmaceutical products and biological samples, sample pre-treatment is usually necessary in order to extract, isolate and concentrate the analytes of interest from complex matrices. Most of analytical instruments cannot handle the matrix directly. In general, during the analytical process, over 80% of analysis time is spent on the sampling and sample preparation steps. Furthermore, the quality of these steps is a key factor in determining the success of analysis from complex matrices, such as pharmaceutical products and biological samples.

Solid phase extraction

Among main extraction techniques for liquid and solid samples, solid phase extraction (SPE) can produce clean extracts for analysis very efficiently. This technique offers the unique advantages of high concentration of the final extract, selectivity and a wide choice of solid phases, enabling the extraction of virtually all compounds from aqueous or organic matrices.

SPE has been widely adopted for preparing samples in the analysis of pharmaceuticals and drugs of abuse in biological matrices. SPE offers the following advantages: high recovery, effective concentration, less organic solvent usage, no foaming or emulsion problems, shorter sample preparation time, easier operation and incorporation into an automated process. Various SPE products are now available, such as column cartridges, disks, well plates and microfibres. Recently, various applica-

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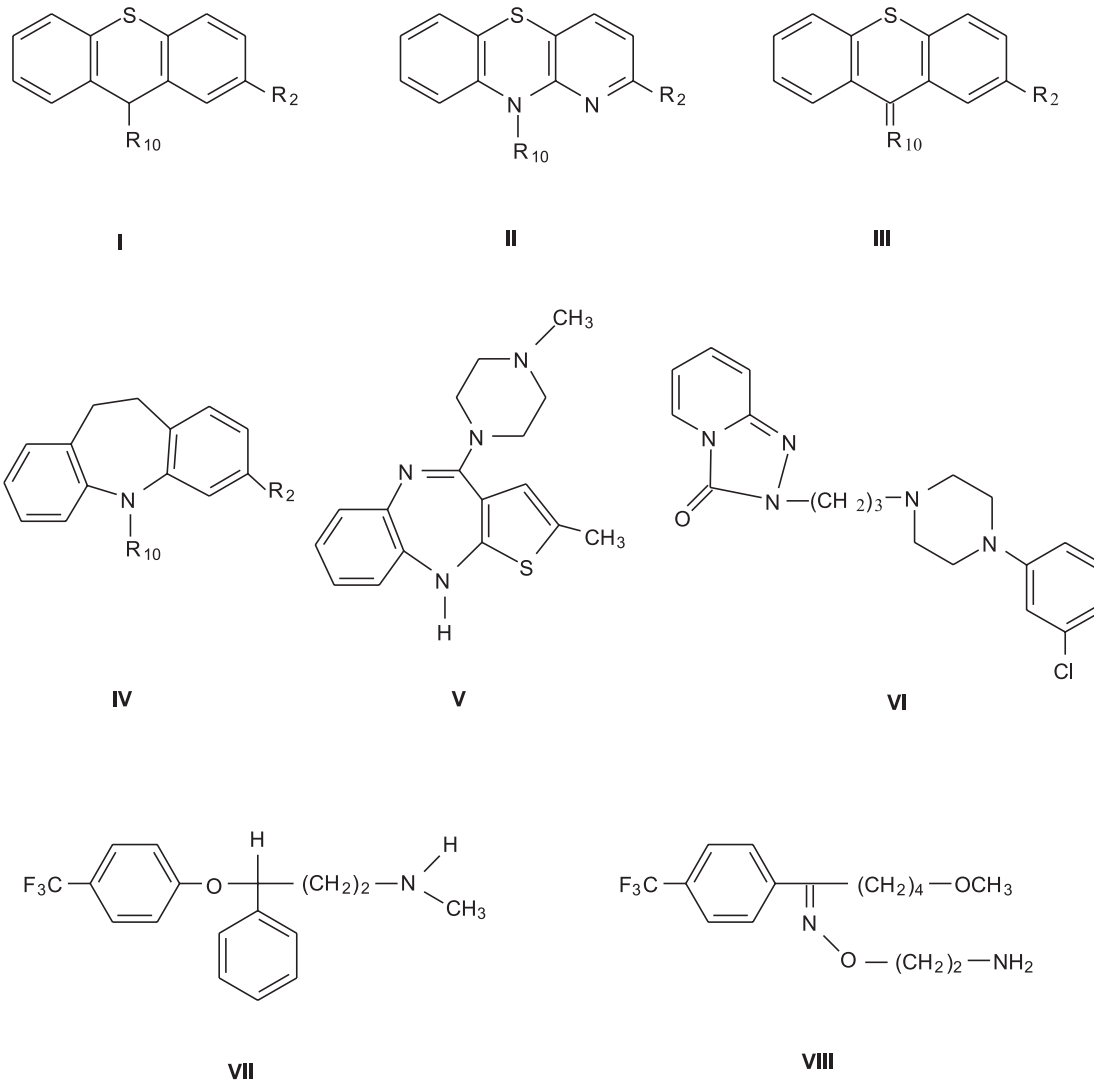


Figure 1. Formulae of phenothiazines **I**, azaphenothiazines **II**, thioxanthenes **III**, dibenzoazepines **IV**, olanzapine **V**, trazodone **VI**, fluoxetine **VII,** fluvoxamine **VIII**

tions of this technique have been reported for drug analysis. The detailed information about SPE techniques for clinical and pharmaceutical analysis were described by Kataoka et al. (12).

Jasińska et al. (13) proposed the SPE techniques for isolation of olanzapine from spiked albumin samples. The authors applied three types of SPE columns – C_{18}, C_6H_{11} and SDB-1. The best results were achieved with C_{18} cartridges The proposed SPE procedure was characterized by high analyte recovery, stability in the range of 98 – 104% and RSD values were less or close to 5%.

It was found (14) that SPE methods were applied to isolation of amitriptyline, imipramine and chlorprothixene from blood human serum. SPE was carried out using the C_{18} column for isolation of amitriptyline and CH column in the case of imipramine and chlorprothixene. The recoveries of SPE method using CH cartridge were 100.3 ± 1.63 % (n = 7), 99.7 ± 2.3 % (n = 9) for imipramine and chlorprothixene, respectively. The recovery of amitriptyline from C_{18} cartridge was 99.5 ± 1.5% (n = 8).

Olesen et al. (15) applied solid phase extraction apparatus in combination with high performance liquid chromatography for determination of nortriptyline in human serum. Solid phase extraction was performed on cyanopropyl cartridges. The extraction cartridge was an Isolute SPE column from International Sorbent Technology Ltd., which contains cyanopropyl-bonded silica gel.

Solid phase extraction with liquid chromatography (HPLC) were used for the assay of five anti-

Table 1. The extractive spectrophotometric determination of some psychotropic drugs in binary and ternary systems

Psychotropic drugs PS	Reagent or system	λ_{max} [nm]	ε [L×mol^{-1}cm^{-1}]	Range of determ. µg/mL	Ref.
Chlorpromazine Thioridazine Trifluopromazine Thioproperazine	Bromocresol green	420	$2.63\cdot10^4$ $2.13\cdot10^4$ $2.02\cdot10^4$ $2.65\cdot10^4$	2 – 8 2 -18 2 -10 2 -12	33
Chlorprothixene	Pyrocatechol violet	445	$1.40\cdot10^4$	3.5-32	34
Imipramine	Methyl orange	425	-	0.79-25.3	35
Fluoxetine Fluvoxamine	Chrome azurol S	500 502	$1.02\cdot10^4$ $9.05\cdot10^3$	5-50 7-100	36
Chlorprothixene	Eriochrome cyanine R	518	-	5-80	37
Fluoxetine Fluvoxamine	Eriochrome cyanine R	520 518	$1.7\cdot10^4$ $6.5\cdot10^3$	2-30 2-40	38
Trazodone	Bromophenol blue	414	-	3.75-14	39
Amitriptyline (AM) Desipramine (DE)	Ti(IV)-SCN^- – AM Ti(IV)-SCN^- – DE	360 355	$8.96\cdot10^3$ $5.85\cdot10^4$	3 – 60 5 – 200	40
Promazine (PM) Chlorprothixene (CX) Imipramine (IM) Doxepin (DX)	Nb(V)-SCN^- – PM Nb(V)-SCN^- – CX Nb(V)-SCN^- – IM Nb(V)-SCN^- – DX	400 362 350 400	- $8\cdot10^3$ $6.67\cdot10^4$ $7.12\cdot10^3$	20 – 200 9 – 50 0.8 – 8 5 – 50	41 42 43 44
Chlorpromazine (CPZ)	Ge(IV)-PCV-CPZ	580	$6.8\cdot10^3$	7-70	45
Chlorpromazine (CPZ)	Sn(IV)-PCV-CPZ	580	-	2-20	46

– no literature data

Table 2. Analytical characteristic of the extractive spectrophotometric determination of fluoxetine using eriochrome cyanine R

Parameters	Values
Analytical wavelength (nm)	520 nm
Beer's law range (mg×mL $^{-1}$)	2 – 30
Correlation coefficient (R)	0.9994
Regression equation (A^*)	
Slope (b)	0.0482
Intercept (a)	-0.0063
Relative Standard Deviation, RSD (%)	2,1 %

$A^* = a + bc$, where c is the concentration of analyte in mg × mL^{-1}.

depressant drugs (trazodone, doxepin, desipramine, maprotyline and imipramine) (16). The drugs were recovered from plasma buffered at a suitable pH using C_{18} Bond Elut cartridges as well as mixtures of methanol and aqueous buffer as washing and elution solvents. The recoveries of the antidepressants using other sorbent materials, e.g. C_8, C_2, cyclohexyl, cyanopropyl and phenyl Bond Elut and copolymer HLB cartridges were also examined. The selectivity of SPE was examined by using spiked plasma samples and the CH cartridge and gave rise to the cleanest extracts. The recoveries of trazodone, doxepin, desipramine, maprotiline and imipramine from spiked plasma samples using the CH cartridge were 58.2, 84.3, 83.3, 83.3 and 82.2%, respectively.

Pirola et al. (17) applied solid phase extraction for the isolation of clomipramine and its desmethyl and hydroxy metabolites in the plasma of patients. The SPE was efficient and rapid, allowing the extraction of several plasma samples on the same day and may therefore be usefully and realistically applied in the clinical outcome in a group of 15 patients with OCD (obsessive-compulsive disorders). A solid phase extraction was combined with HPLC technique to elaborate a new sensitive method of simultaneous determination of clomipramine and its N-desmethylated and hydroxylated metabolites in human plasma. The method was

applied to monitor the levels of clomipramine and its metabolites in a group of OCD patients.

Wille et al. (18) described reproducible SPE procedure for new generation antidepressants, e.g. fluvoxamine, sertraline, maprotiline, fluoxetine, trazodone and some of their metabolites. The method was developed for GC-MS analysis, a HPLC–DAD was used as monitoring system.

A bioanalytical method based on on-line SPE using turbulent flow chromatography has been developed by Song and Putcha (19) for the simultaneous determination of promethazine and its three metabolites in plasma, saliva, and urine. The results obtained demonstrated that this on-line SPE coupled with HPLC by column-switching is an ideal technique for quantitative analysis of promethazine and its metabolites and is suitable for clinical research applications.

The review shows that solid phase extraction methods are very useful for the preconcentration of psychotropic substances in biological samples and body fluids.

The extractive spectrophotometric methods

Psychotropic substances (PS), e.g. phenothiazines, thioxantenes, dibenzocycloheptadienes react with some organic substances or thiocyanate complexes of metals forming colored ion-association binary compounds (7, 20):

$$PS \cdot HCl \Leftrightarrow (PS \cdot H)^+ + Cl^-$$

or base

$$PS + H^+ \Leftrightarrow (PS \cdot H)^+$$

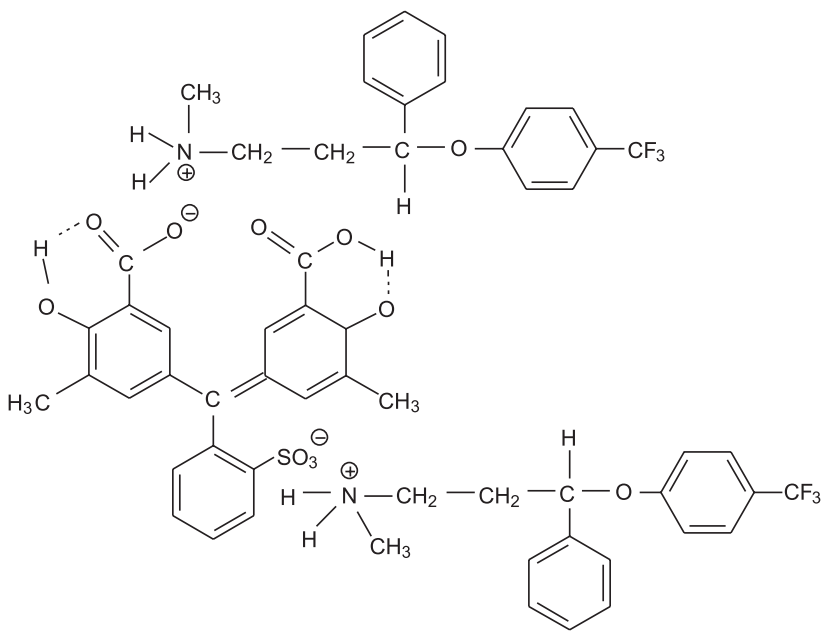
$$(m - n)(PS \cdot H)^+ + [MeX_n]^{(m-n)} \Leftrightarrow$$

$$\Leftrightarrow (PS\ \ H)_{(m-n)}[MeX_n]$$

where: Me = Co(II), Pd(II), Fe(III), Cr(III), Ti(IV), Nb(V), Mo(V), W(V), U(VI); X = SCN^-.

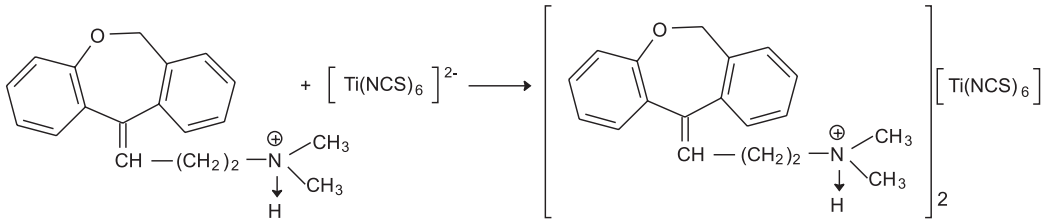
The compounds are insoluble in water, but fairly soluble in organic solvents. These properties were applied successfully in chemical analysis of psychotropic drugs (21-47). Some of the extractive spectrophotometric methods are given in Table 1.

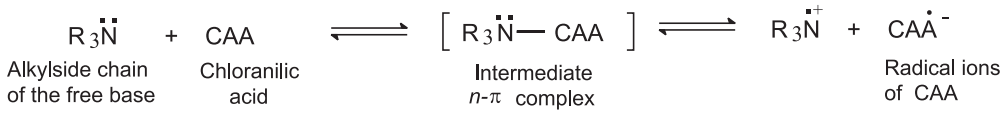
The extractive spectrophotometric methods for the determination of psychotropic drugs are based on the binary or ternary systems. The composition and character of the formed compounds was confirmed by UV-VIS, IR and NMR spectroscopy (4, 38, 44). For example, the structure of ion-association compound of fluoxetine (FXT) with eriochrome cyanine (ECR) can be given as follows:



This suggests that compound is formed with participation of the nitrogen atom from the tertiary amine group in aliphatic chain of the FXT and the eriochrome cyanine R form ECR^{2-} (which occurs at pH 3,5 – 6,0).

From the analysis of the spectroscopic studies (44) it results that the reaction of doxepin with thiocyanate complex of Ti(IV) can be expressed as:





There are a few reports on the extractive spectrophotometric assay of some psychotropic drugs based on charge-transfer complexes (48-51). For example, the reaction scheme between phenothiazine free base and chloranilic acid with the formation of charge transfer complex of *n*-π type can be given as follows:

It was found that ion-association and charge-transfer compounds of psychotropic drugs with some organic reagents are precipitated from aqueous solutions as colored sediments. These compounds are sparingly soluble in water but fairly soluble in organic solvents.

The extraction constants (K_{ex}) of some these compounds were determined spectrophotometrically by the Likussar's method and other methods (52) (e.g. log K_{ex} = 6.9 for imipramine-methyl orange system (35), log K_{ex} = 4.83 for amitriptyline-eriochrome system (38)).

These values of log K_{ex} indicate that compounds studied are quantitatively extracted from aqueous phase with organic solvents, e.g. chloroform, benzene, butanol, dichloroethane. The colored extracts are stable about 1-3 days (33, 35, 38) and are basis for the extractive spectrophotometric methods of the determination of some psychotropic drugs (21-46). The methods are general, simple, rapid and do not require special working conditions. They can be applied successfully to determine active substances in pharmaceutical preparations and biological fluids. The methods are characterized by good precision and reproducibility (Table 2) (38).

CONCLUSIONS

Reviews of the solid phase extraction (SPE) methods show that these methods have been widely adopted for preparation of samples in the analysis of pharmaceuticals and drugs in biological matrices. SPE offers high recovery, effective concentration and lesser organic solvent usage.

It was found that psychotropic drugs, e.g. dibenzoazepines, dibenzocycloheptadienes, thioxanthenes, phenothiazines and new generation drugs, e.g. fluoxetine, fluvoxamine, and trazodone form cations which react with some organic substances (e.g. picramic acid, bromocresol green, methyl orange, triphenylamine dyes) and thiocyanate anionic complexes (e.g. Co(II), Fe(III), Cr(III), Ti(IV), Nb(V)) with formation of ion-association compounds. The compounds precipitated from aqueous solutions and can be quantitativelly extracted into organic solvents (e.g. chloroform, dichloroethane, butanol). The extracts are intensely colored and stable for 1-3 days. These properties have been applied for the determination of above mentioned and some other psychotropic drugs in pharmaceutical preparations.

The official compendia (53, 54) recommend for the determination of psychotropic active substances in bulk or in pharmaceutical forms the measurement of absorbance in the UV region at selected wavelengths, or the titration in a non-aqueous medium with potentiometric or visual indication at the end-point. The proposed pharmacopoeial procedures require intensive isolation and purification steps in the case of the assay of the studied psychotropic substances in their pharmaceutical dosage forms. The main disadvantage of direct UV spectrophotometry is the sensitivity to excipients usually present in pharmaceutical formulations. Commonly encountered excipients and additives do not interfere in the extractive spectrophotometric methods.

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