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Insights on Analytical Methods for Determination of Risperidone, Levetiracetam, Sodium Valproate and Oxcarbazepine

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Abstract

In this literature review, we will introduce mode of action and most of up-to-date reported methods that have been developed for determination of certain antipsychotic drugs such as risperidone, levetiracetam, sodium valproate and oxcarbazepine in their pure form, combined form with other drugs, combined form with degradation products, and in biological samples. Most of reported methods include spectrophotometric and chromatographic methods in addition to some electrochemistry methods.

Keywords: Antipsychotic; Risperidone; Levetiracetam; Sodium valproate; Oxcarbazepine

Introduction

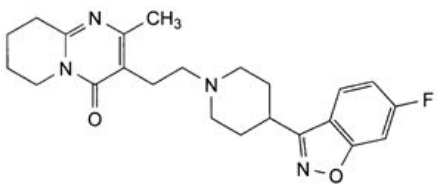
Epilepsy, which affects approximately 1% of the world's population, is a chronic disorder that usually persists for many years and often for a lifetime [1]. Antiepileptic Drugs (AEDs) are the mainstay of epilepsy treatment, and complete seizure control can be achieved in the majority (65%) of newly diagnosed patients by prescribing a single AED, and this is the ideal situation [2]. For the remaining 35% of patients, the prescribing of polytherapy regimens (the use primarily of two AEDs but often three or four AEDs), so as to achieve optimal seizure control, is a common practice.

However, for the majority of these patients, little additional benefit is achieved from the use of polytherapy AEDs as intolerable adverse effects commonly occur as a consequence of pharmacokinetic and/or pharmacodynamic interactions. Furthermore, for those patients that respond to monotherapy, they too may experience the consequences of AED interactions as AEDs are added and withdrawn during the optimization of their monotherapy drug regimen [3-5]. A further confounding factor is that since epilepsy is a chronic condition many patients will inevitably develop co-morbid diseases or other debilitating conditions and disorders, which will require the co-administration of non-AEDs. In this setting the potential for drug interactions is considerable [6]. A further source of potential clinically significant interactions that is being increasingly recognized relates to the increasing use of over-the-counter medications and supplements, many of which have unknown constituents and inconsistent quality [7]. Finally, AEDs are increasingly used to treat

Antipsychotic Drugs (APDs) can be separated into two classes: ''conventional'' APDs (CAPDs) and ''atypical'' APDs (AAPDs). The former includes 18 drugs developed between the 1950s and the 1970s. Their mechanism of action resides in their ability to block dopamine (DA-2) receptors, at the level of Meso-cortical, Nigrostriatal and Tuberoinfundibular DA pathways [8].

As such, in this review article, four antipsychotic drugs have been studied in respect of physical, chemical characters, mode of action and most reported analytical methods that have been developed for determination of these drugs in different matrices.

Risperidone (RSP)



- benzisoxazole derivatives and chemically, it is 3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one [9].

- $C_{23}H_{27}FN_4O_2$
- 410.5 gm/mol.
- It is White or almost white powder. It is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96 percent). It dissolves in dilute acid solutions. It shows polymorphism [9].
- 170°C.

Pharmacological action: RSP is a dopamine D2 receptor antagonist; serotonin 5HT2 receptor antagonist; neuroleptic [9]. RSP is mostly metabolized by alicyclic hydroxylation and oxidative N-dealkylation [10]. RSP is used to treat schizophrenia, symptoms of bipolar disorder (manic depression) and irritability in autistic children [11,12].

Methods of determination

Official methods

The BP [9] proposes a non-aqueous titration for the determination of RSP. The drug was dissolved in anhydrous acetic acid followed by addition of methyl ethyl ketone then titration with 0.1 M perchloric acid, determining the end-point potentiometrically [9].

Spectroscopic methods

Literature describes different spectroscopic methods for determination of RSP. A simple UV spectroscopic determination was carried out at an absorption maximum of 238 nm using 0.1 NHCl as solvent [13]. A simple, non-destructive, methodology based on FT-Raman spectroscopy was developed for the quantitative analysis of RSP in commercially available film-coated tablets. A simple linear regression model was constructed based on standard tablets, prepared using the same manufacturing process as the commercially available [14]. A simple, sensitive, specific, spectrophotometric method developed for the detection of RSP in bulk drug and Pharmaceutical formulation. The optimum conditions for the analysis of the drug were established. The λ max of the RSP was found to be 280 nm [15]. A simple, sensitive, specific, spectrophotometric using methanol as a solvent method has been developed for the detection of RSP in pure form and pharmaceutical dosage forms. The optimum condition for the analysis of the drug were established. RSP exhibiting absorption both at 240 and 280 nm [16].

Chromatographic methods

Several chromatographic methods were described for the determination of the proposed drug either in pure or in combination with other drugs summarized in Table 1.

Table 1: Chromatographic methods for the determination of RSP in pure form or in combination with other drugs.

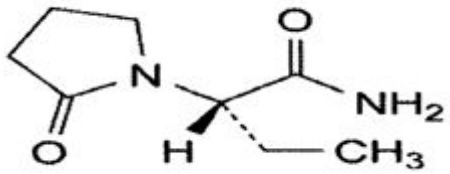
Drugs	Method	Column	Mobile phase	Detector	λ
RSP	HPLC	Waters Xterra RP C8 column (250* 4.6 mm, 5 µ)	Mixture of solution (10 mM potassium dihydrogen phosphate, pH 3.5 ± 0.05): acetonitrile: methanol (65:20:15)	UV	276 nm
RSP, paliperidone and olanzapine	HPLC-MS	Xbidge™ C18 column (3.5 µm, 100 × 2.1 mm)	70% acetonitrile and 30% ammonium hydroxide 1% solution	Mass spectrometry	Product ion 191.2 (m/z)
RSP	LC/DAD	Purosphere STAR RP-C18 250×4.5 mm (5 µ)	Mixture of water: glacial acetic acid 0.50%: triethylamine 0.80%: acetonitrile (65.00: 0.32: 0.52:34.16, v/v),	DAD	294 nm
RSP, Olanzapine, Quetiapine, Clozapine, Ziprasidone, Perospirone, Aripiprazole and Blonanserin	LC/MS/MS	Mightysil-RP-C18 MS column (2.0 mm × 150 mm, particle size 3 µm)	10 mM formic ammonium buffer (pH 6.0) and acetonitrile	Mass spectrometry	411 m/z →191 m/z
RSP and Benzoic acid	HPLC	Waters Xterra C18 column (150 mm × 4.6 mm, 5 µm pore size)	Methanol: water (50:50% v/v)	UV	275 nm
RSP	HPLC	C18 BDS Hypersil analytical column (3 µm, 100 × 4.6 mm I.D.)	Phosphate buffer (0.05 *M*, pH 3.7 with 25% H3PO4)–acetonitrile (70:30, v/v),	UV	278 nm
RSP	HPLC-MS/MS	Alltima-C18 column (2.1 mm × 100 mm, 3 µm)	0.1% formic acid-acetonitrile (40:60, v/v)	MS/MS	411.3→191.1 m/z
RSP, a benzisoxazole derivative	HPLC-MS/MS	Inertsil HPLC column (2.1 × 150 mm, 5-µm particle size)	Solvent A was water with 0.1% formic acid, and solvent B was in gradient ratio	MS/MS	411 to 191 m/z

			Acetonitrile with 0.1% formic acid.		
RSP, Citalopram, Clozapine, Quetiapine, Levomepromazine, Perazine and Aripiprazole	HPLC-DAD	AXselect CSH Phenyl-Hexyl	Ethanol, acetate buffer at pH 3.5 and 0.025 mL −1 diethylamine	DAD	200-400 nm range
	HPLC-MS	Phenyl-Hexyl analytical column	Methanol, acetate buffer at pH 3.5 and 0.025 mL $^{-1}$ mixed	MS/MS	50–1000 m/z
RSP	HPLC	Symmetry C18 column (5 µm size, 250 mm × 4.6 mm i.d.)	Methanol: acetonitrile (80: 20, v/v)	UV	280 nm
RSP	HPLC	Gemini analytical column(250 × 4.6 mm, particle size 5 µm)	acetonitrile-potassium dihydrogen phosphate (45:55, v/v, pH 6.5; 0.05 M)	PDA	237 nm
RSP	HPTLC	Silica gel 60 F254	Methanol-ethyl acetate 80:20 (v/v)	densitometry	285 nm

Voltammetric methods

A voltammetry method has been reported for determination of RSP in pharmaceutical formulations using multiwalled carbon nanotube paste electrode as an easy, inexpensive and highly selective sensor [28]. Another adsorptive stripping differential pulse voltammetric determination of RSP with a multi walled carbon nanotube ionic liquid paste modified glassy carbon electrode was described [29].

Levetiracetam (LVT)



- (2S)-2-(2-Oxopyrrolidin-1-yl)butanamide [9]
- $C_8H_{14}N_2O_2$
- 170.2 gm/mol.
- It is White or almost white powder. It is Very soluble in water, soluble in acetonitrile, practically insoluble in hexane [9].
- 112-115°C [30].

Pharmacological action: LVT is a novel antiepileptic agent. It is used as an adjunctive therapy in the treatment of partial seizures [31]. LVT can prevent myoclonic jerks and generalizes epileptiform activity in patients with photosensitive epilepsy [32]. It is also used in veterinary medicine for similar purpose [33]. It is also used to treat neuropathic pain [34]. The bioavailability of LVT after oral administration is almost equal to 100% [35]. The biotransformation occurs by the enzymatic hydrolysis of acetamide group [36]. The metabolized drug is excreted through urine [35].

Methods of determination

Official methods

The BP proposes a HPLC-UV method using 0.25 m end-capped octadecyl silyl silica gel for chromatography column and mobile phase of 4:96 V/V 1.96 g/L solution of sulfuric acid, and acetonitrile, the retention time of LVT is about 10 minutes the detection was at 205 nm [9].

Spectroscopic methods

Literature describes different spectroscopic methods for determination of LVT, In the present study simple, precise, accurate, economical and reliable UV spectrophotometric method was developed for the estimation of LVT in tablet dosage form. The drug shows maximum absorption (maximum λmax) at 265.0 nm in distills water [37]. A simple UV spectrophotometric method has been developed for the estimation of LVT in tablet dosage form. The drug shows maximum absorption (maximum λmax) at 209.0 nm in triple distilled water [38]. Three simple, economical, precise, reliable and reproducible visible spectrophotometric methods (A, B and C) have been developed for the estimation of LVT in bulk as well as in Tablet formulation. The developed methods A, B and C are based on the formation of chloroform extractable complex of LVT with Bromocresol green (Method A), Bromophenol blue (Method B) and Bromothymol blue (method C) which shows absorbance maxima at 435 nm, 454 nm and 415 nm respectively [39]. Two simple, sensitive, reproducible, rapid and economical spectrophotometric methods are described for the determination of LVT in bulk and formulations. Both the methods are based on the formation of colored complexes of LVT with 2-chlorophenylhydrazine (Method-A) and anthranilic acid (Method-B) in alcoholic medium. Under the optimized conditions the complexes show an absorption maximum at 560 and 485 nm [40].

Chromatographic methods

Several chromatographic methods were described for the determination of the proposed drug either in pure or in combination with other drugs summarized in Table 2.

Table 2: Chromatographic methods for the determination of LVT in pure form or in combination with other drugs.

Drugs	Method	Column	Mobile phase	Detector	λ
LVT and pyridoxine HCl	RP-HPLC	BDS Hypersil C8 (250 × 4.6 mm, 5 µm)	methanol and 25 mm KH2PO4 buffer pH 3 (38.4:61.6, v/v)	UV	214 nm
LVT, lamotrigine, oxcarbazepine and carbamazepine	HPLC	Nova pack C18 reversed-phase column (4.6 × 250 mm, 5 µm)	Methanol:acetonitrile:water (pH of the aqueous phase, adjusted to pH 5 with 0.2 M phosphoric acid) in a ratio of 30:10:60 (v/v)	DAD	230 nm
LVT, Methylparaben and propyl paraben	HPLC	RP C18 Hypersil BDS analytical column (150 mm × 4.6 mm ID)	0.05 M phosphate buffer pH 3.5: acetonitrile gradient elution	UV	240 nm
LVT	LC-ESI-MS	250×4.6 mm (i.d.) Discovery® (5 µm particle size) reversed-phase C18	0.1% formic acid in water–acetonitrile, in ratio of 85:15, v/v	UV for Quantification and Mass spectroscopy for Identification	210 nm & m/z 50–190
LVT	HPLC	Synergi 4-_m Hydro-RP, 150 mm × 4 mm I.D.	Mixture of potassium dihydrogen phosphate buffer (50 mM, pH 4.5) and acetonitrile (94:6, v/v)	UV-DAD	205 nm
LVT	GC	Rtx-5 capillary column (cross bond 5% diphenyl 95% dimethyl polysiloxane) with a length of 30 meters and an internal diameter of 0.25 mm	Nitrogen	Flame ionization detector at 250°C using Synthetic air (flow rate of 100 ml/min), hydrogen (25 ml/min)	
Gabapentin, Lamotrigine, LVT, Monohydroxy Derivative of Oxcarbazepine, and Zonisamide	U-HPLC-MS/MS	Waters ACQUITY UPLC BEH C18 Column (2.1 × 30 mm, 1.7 µm particle size),	Solvent A (2 mmol/ Lammonium acetate in Milli-Q filtered water with 0.1% formic acid) and solvent B (2 mmol/L ammonium acetate in MeOH with 0.1% formic acid) in gradient elution	Mass spectrometry	171 →69 m/z
LVT	UPLC-PDA	BEH C18 column (1.7 µm particle size and 100 × 2.1 mm i.d.)	Acetonitrile-phosphate buffer (pH=6.6; 0.01 M) (10/90 v/v)	UV-PDA	215 nm
Lamotrigine, Zonisamide and LVT	HPTLC	Silica gel 60 F254 plates	Ethylacetate: methanol:ammonia (91:10:15 v/v/v)	densitometry	312, 240 and 210 nm
LVT and oxcarbazepine	HPTLC	Silica gel 60 F 254 HPTLC plates	Toluene-acetone-methanol, 6:2:2 (v/v),	densitometry	200 and 261 nm

Miscellaneous methods

A voltammetry method have been reported for determination of LVT by screen-printed based biosensors [51], and based on a silver nanoparticle modified carbon ionic liquid electrode [52]. Another capillary electrophoresis method has been reported [53].

Sodium Valproate (VLP)

- Sodium 2-propylpentanoate [9].
- $C_8H_{15}NaO_2$
- 166.2 gm/mol.
- It is White or almost white, crystalline, hygroscopic powder. It is Very soluble in water, freely soluble in ethanol (96 percent). It shows polymorphism [9].
- 300°C.

Pharmacological action: VLP is the first line drug used for its unique anticonvulsant properties in the treatment of primary generalized seizures, partial seizures and myoclonic seizures. The mode of action is to stabilize the electrical activity in the brain by increasing the synthesis and decreasing the metabolism of gamma amino butyric acid [54].

Methods of determination

Official methods

The BP and USP proposes a Gas Chromatography (GC) and HPLC methods for quantitative analysis of VLP in formulation, respectively [9,55].

Spectroscopic methods

Literature describes different spectroscopic methods for determination of VLP. Four simple and direct spectrophotometric methods for determination of VLP were developed through charge transfer complexation reactions. The first method was based on the reaction of the drug with p-chloranilic acid in acetone to give a purple colored product with maximum absorbance at 524 nm. The second method was depending on the reaction of VLP with dichlone in dimethylformamide forming a reddish orange product measured at 490 nm. The third method was based upon the interaction of VLP and picric acid in chloroform resulting in the formation of a yellow complex measured at 415 nm. The fourth method involved the formation of a yellow complex peaking at 361 nm upon the reaction of the drug with iodine in chloroform. Experimental conditions affecting the color development were studied and optimized. Stoichiometry of the reactions was determined [56].

Chromatographic methods

Several chromatographic methods were described for the determination of the proposed drug either in pure or in combination with other drugs summarized in Table 3.

Table 3: Chromatographic methods for the determination of VLP in pure form or in combination with other drugs.

Drugs	Method	Column	Mobile phase	Detector	λ
VLP and its five metabolites	HPLC–MS/MS	Hypersil GOLD C18	Acetonitrile: 10 mm ammonium acetate solution (90:10, v/v)	Mass spectroscopy	m/z 143.183 → 143.183
VLP and 2-propyl-4-pentenoic acid	HPLC-UV	Waters Xterra MS C18 column (5 µm, 4.6 mm × 150 mm, Waters, Milford, USA)	Methanol/water (76:24, v/v)	UV	254 nm
Phenobarbital, VLP, phenytoin sodium and carbamazepine	HPLC-MS	XDB-C18 (2.1mm × 150.0 mm, 3.5 µm)	0.05% ammonium acetate in water methanol (47:53)	Mass spectroscopy	
9-Fluorenylmethyl chloroformate as a fluorescence-labeling reagent for derivatization of carboxylic acid moiety of VLP	HPLC	Shim pack CLC-ODS (Shimadzu, Kyoto, Japan), 150 mm×4.6 mm I.D., 5 _m particle size, which was protected by a Shim-pack G-ODS guard column (1 cm×4.0 mm I.D., 5 _m particle size).	A mixture of acetonitrile and distilled water (78:22)	Spectro- fluorometric	265 and 315 nm
VLP and two metabolites	GC-MS	HP-I cross-linked methyl siloxane, 60 mx O.25 mm i.d.,	Helium	Mass spectroscopy	m/z 199
VLP	GC-FID	30 m × 0.32 mm i.d. × 0.25 µm film thickness BP-10	Carrier (Helium, 99.999%) 2.0 mL/min, make-up (Nitrogen, 99.999%) 30 mL/min	Flame ionization	Temperatures were set at 250°C and 280°C respectively using hydrogen and air (for FID) 40 and 300 mL/min, respectively.

Miscellaneous methods

A potentiometric method for quantitative analysis of VLP in pharmaceutical preparations by a Valproate-Selective Electrode [63] and by ion selective sensor based on conducting polypyrrole films [64].

A direct method for determination of VLP acid in biological fluids by capillary electrophoresis with contactless conductivity detection has been reported [65].

Oxcarbazepine (OXZ)

- 10,11-dihydro-10-oxo-5H-dibenz [b,f]azepine-5-carboxamide [9].
- $C_{15}H_{12}N_2O_2$
- 252.3 gm/mol.
- It is White to faintly orange crystalline powder. It is Slightly soluble in chloroform, dichloromethane, acetone, and methanol and practically insoluble in ethanol, ether, and water [9].
- 215.5°C.

Pharmacological action: OXZ is a new antiepileptic drug that has been registered in more than 50 countries worldwide since 1990 and recently received approval in the United States and the European Union. OXZ has a more favorable pharmacokinetic pro ile than carbamazepine [66]. It is rapidly absorbed a ter oral administration and undergoes rapid and almost complete reductive metabolism to form the pharmacologically active 10-monohydroxy derivative [66].

Methods of determination

Official methods

The BP and USP proposes a HPLC method for quantitative analysis of OXZ [9][67].

Spectroscopic methods

Literature describes different spectroscopic methods for determination of OXZ. A Simple, accurate, rapid and sensitive method was reported for the estimation of OXZ in tablets. The estimation is based on the reduction of ferric ions in its salt form to ferrous ions by the drug, which in presence of potassium ferricyanide produces green colored chromogen measured at 770 nm against reagent blank [68]. Two simple, selective and stability indicating UV-spectrophotometric methods have been developed and validated for assay of OXZ in bulk drug and in its dosage forms. Proposed methods were based on measurement of absorbance of OXZ either in methanol (Method A) or in acetonitrile (Method B) at 254 nm [69]. Spectrophotometric methods were described for the determination of OXZ in bulk drug and in tablets. The methods used N-bromosuccinimide and bromopyrogallol red as reagents. The method involved the addition of known excess of N-bromosuccinimide to an acidi ied solution of OXZ followed by the determination of the unreacted N-bromosuccinimide by reacting with bromopyrogallol red and measuring the absorbance of the unreacted dye at 460 nm [70].

Chromatographic methods

Several chromatographic methods were described for the determination of the proposed drug either in pure or in combination with other drugs summarized in Table 4.

Table 4: Chromatographic methods for the determination of OXZ in pure form or in combination with other drugs.

Drugs	Method	Column	Mobile phase	Detector	λ
OXZ	HPLC	Hypersil BDS C18 column (250 mm × 4.6 mm, 5 µ)	Mixture of Acetonitrile, methanol And pH adjusted by Triethylamine	215 nm	UV
OXZ	HPLC	Diamonsil C18 column	acetonitrile, potassium phosphate monobasic buffer (pH 6.8) and water (36:8:56, v/v)	UV	255 nm
OXZ and its main metabolites	HPLC-UV	a X-TERRA C18 column	20 mM KH2PO4, acetonitrile, and *n*-octylamine (76:24:0.05, v/v/v)	UV	237 nm
Carbamazepine, OXZ, and Eslicarbazepine	HPLC-UV	Lichrocart®Purospher® Star (C18, 3 µm, 55 mm × 4 mm)	Water, methanol, and acetonitrile in the ratio 64:30:6	UV	235 nm
OXZ	HPTLC	20 cm × 20 cm aluminum foil plates coated with silica gel G60F254	Ethyl acetate-toluene-methanol 7.0:2.0:1.0 (v/v)	densitometry	254 nm
OXZ	HPTLC	Precoated silica gel aluminum plate 60 F254, (20 × 10 cm with 250 mm thickness;	Ethyl Acetate: Methanol (6:4 v/v)	Densitometryin the fluorescence mode	366 nm
Carbamazepine, OXZ, and Eslicarbazepine acetate	UPLC-MS/MS	Intersil® ODS column (250 x 4.6 mm, 5 µm)	acetonitrile, methanol, 0.5% formic acid in water (5:40:55, v/v/v) (i.e. 45% organic: 55% aqueous)	Tandem mass spectrometry	208.14 m/z

Miscellaneous methods

Titrimetric method was described for the determination of OXZ in bulk drug and in tablets. The methods use N-bromosuccinimide and bromopyrogallol red as reagents. An acidified solution of OXC was titrated directly with N-bromosuccinimide using methyl orange as indicator [70]. The catalytic effect of silver nanoparticles in the development of disposable screen-printed sensors for the analysis of the drug OXZ has been demonstrated. Mercury film and metallic nanoparticles modified screen-printed carbon electrodes have been tested for the analysis of OXZ using differential pulse adsorptive stripping voltammetry. Mercury coated screen-printed electrodes were obtained by means of electrodeposition at a fixed potential from a Hg(II) solution. Nanoparticle modified electrodes were obtained also by electrode position on the screen-printed carbon surface of silver and gold nanoparticles. Among the electrodes tested only silver nanoparticle modified screen-printed carbon electrodes gave rise to an analytical signal viable for the determination of OXZ [71-77].

Conclusion

This literature review represents an up to date survey about all reported methods that have been developed for determination of certain antipsychotic drugs such as risperidone, levetiracetam, sodium valproate and oxcarbazepine in their pure form, combined form with other drugs, combined form with degradation products, and in biological samples such as liquid chromatography, spectrophotometry, and voltammetry.

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