Chapter 3

Drug profiles

3. 1 DRUG PROFILE OF SALBUTAMOL SULPHATE

3. 1.1 NOMENCLATURE[1-9]

3.1.1.1 Chemical Name

(±) (alpha) $_1$ -[(*tert* -butylamino)methyl]-4-hydroxy- *m* -xylene-(alpha), (alpha)'-diol sulfate (2:1)

3.1.1.2 Formula

3.1.1.2.1 *Empirical formula*

$(C_{13}H_2NO_3)_2 \cdot H_2SO_4$

3.1.1.2.2 *Structural formula*

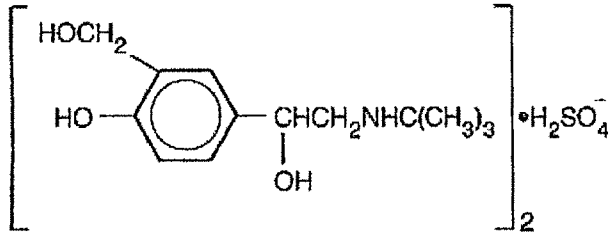

Figure 3.1. Structure formula of salbutamol sulphate

3.1.1.3 Molecular Weight

576.7

3.1.1.4 Element Composition of Salbutamol

C, 65.24 H, 8.85 N, 5.85 O, 20.06

3.1.1.5 Physicochemical Properties

3.1.1.5.1 *Appearance*

A white powder. It is odorless and almost tasteless.

3.1.1.5.2 *Solubility*

Soluble 1 in 4 of water; slightly soluble in ethanol, chloroform, and ether.

3.1.1.5.3 *Melting point*

M.p. 151° also reported as 157° to 158°.

3.1.1.5.4 *Dissociation Constant*

pK_a9.3, 10.3.

3.1.1.5.5 *Partition Coefficient*

Log *P*(octanol/water), 0.6.

3.1.1.5.6 *Storage*

Store in well-closed container protected from light.

3.1.2. PHARMACOLOGICAL PROPERTIES[1,8,9]

3.1.2.1 Stereoselectivity

The *R*(-)-enantiomer of salbutamol is preferentially metabolised and is therefore cleared from the body more rapidly than the *S*(+)-enantiomer, which lacks bronchodilator activity but may be implicated in some of the adverse effects of salbutamol.

3.1.2.2 Mechanism of Action[2,3]

Salbutamol sulphate is a selective β_2 adrenoceptor agonist. At therapeutic doses it acts on the β_2 adrenoceptors of bronchial muscle, with little or no action on the β_1 renoceptors of cardiac muscle.

The pharmacologic effects of it, is at least in part attributable to stimulation through beta-adrenergic receptors on intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

3.1.2.3 Pharmacokinetics

Salbutamol is readily absorbed from the gastrointestinal tract. It is subject to first-pass metabolism in the liver and possibly in the gut wall; the main metabolite is an inactive sulfate conjugate. Salbutamol is rapidly excreted in the urine as metabolites and unchanged drug; there is some excretion in the faeces. Salbutamol does not appear to be metabolised in the lung, therefore its ultimate metabolism and excretion following inhalation depends upon the delivery method used, which determines the proportion of inhaled salbutamol relative to the proportion inadvertently swallowed..

3.1.2.4 Bioavailability

After oral administration, about 50%.

3.1.2.5 Half-life

Plasma half–life, 4 to 6 h.

3.1.2.6 Protein Binding

In plasma, about 10%.

3.1.2.7 Therapeutic Indications

The therapeutic indication of salbutamol sulphate is the treatment of reversible airways obstruction of all types including bronchial asthma, chronic bronchitis and emphysema.

3.1.2.8 Adverse Effects

Salbutamol and other beta agonists may cause fine tremor of skeletal muscle (particularly the hands), palpitations, tachycardia, nervous tension, headaches, peripheral vasodilatation, and rarely muscle cramps. Potentially serious hypokalaemia has been reported after large doses.

3.1.2.9 Uses and Administration

Salbutamol and salbutamol sulfate are used as bronchodilators in the management of reversible airways obstruction, as in asthma and in some patients with chronic obstructive pulmonary disease. Salbutamol also decreases uterine contractility and may be given as the sulfate to arrest premature labour.

3.1.2.10 Dose

Usually the equivalent of 6 to 16 mg of salbutamol daily by mouth.

3.1.3 ANALYTICAL PROPERTIES[2,5]

3.1.3.1 Colour Tests

Liebermann's Test—black; Mandelin's Test—blue rim→brown rim; Marquis Test—yellow; Sulfuric Acid—yellow.

3.1.3.2 Thin-layer Chromatography

System TA—Rf 46; system TB—Rf 01; system TC—Rf 01; system TE—Rf 20; system TF—Rf 00; system TL—Rf 04; system TAE—Rf 16; system TAF—Rf 74. (Acidified potassium permanganate solution, positive.)

3.1.3.3 Gas Chromatography

System GA—salbutamol-AC_2 RI 2230, salbutamol-AC_3 RI 2250, salbutamol-H_2O RI 1850.

3.1.3.4 High Performance Liquid Chromatography

System HA—k 1.0; system HX—RI 220; system HY—RI 238.

3.1.3.5 Ultraviolet Spectrum

Aqueous acid—276 (A^1_1=71a); aqueous alkali—245 (A^1_1=510a), 295 nm (A^1_1=133a).

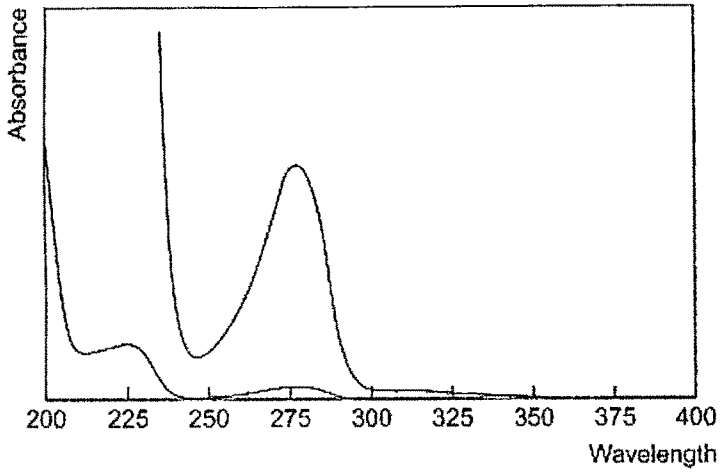

Figure 3.2. UV Spectrum of salbutamol sulphate.

3.1.3.6 Infra-red Spectrum

Principal peaks at wavenumbers 1075, 1038, 1263, 1228, 1213, 822 cm^{-1} (KBr disk).

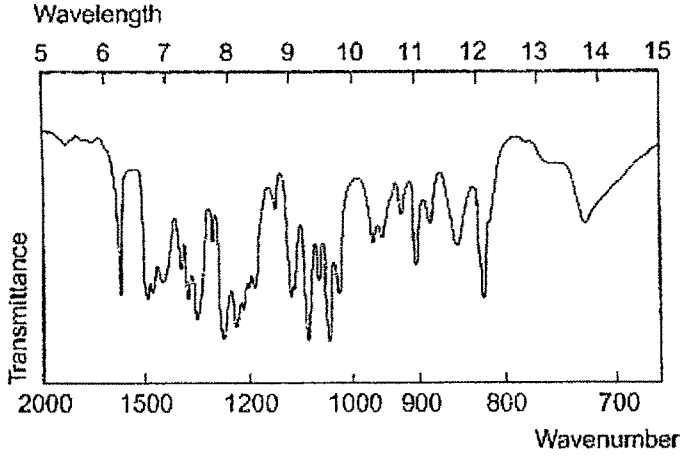

Figure 3.3. Infra-red spectrum of salbutamol sulphate.

3.1.3.7 Mass Spectrum

Principal ions at *m/z* 30, 86, 57, 41, 77, 135, 29, 206.

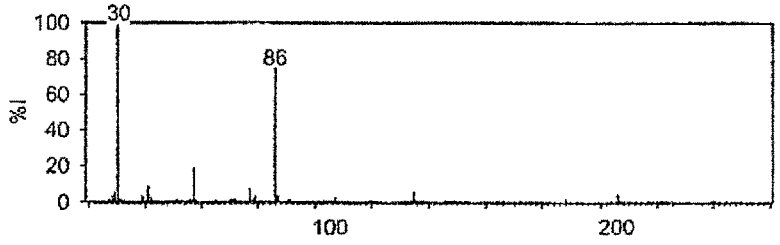

Figure 3.4. Mass spectrum of salbutamol sulphate.

3.1.3.8 Quantification

3.1.3.8.1 *Gas chromatography-massspectrometry*

In serum: limit of detection 1 μg/L—J. G. In postmortem blood: salbutamol and other *β*–agonists, limit of quantification 1 μg/L. In plasma: limit of quantification 50 ng/L. In postmortem blood or urine: salbutamol and other *β*-agonists. In serum: limit of detection 2 μg/L.

3.1.3.8.2 *High performance liquid chromatography*

In plasma: limit of detection 500 ng/L, electrochemical detection. In plasma: limit of detection 0.5 μg/L, amperometric detection. In serum: salbutamol enantiomers, limit of detection 1 μg/L, fluorescence detection. In plasma: salbutamol and terbutaline, limit of detection for salbutamol 1 μg/L, fluorescence detection. In plasma: salbutamol and terbutaline, limit of detection for salbutamol 1 μg/L, electrochemical detection. In plasma or urine: salbutamol enantiomers, limit of detection 250 ng/L, fluorescence detection. In plasma: salbutamol enantiomers, limit of detection 125 ng/L, fluorescence detection. In urine: salbutamol enantiomers, limit of detection 20 μg/L, electrochemical detection. In urine: salbutamol enantiomers, fluorescence detection.

3.1.3.8.3 *High performance liquid chromatography-mass spectrometry*

In plasma: limit of quantification 0.2 μg/L—K.

3.2 DRUG PROFILE OF ONDANSETRON HYDROCHLORIDE

3.2.1. NOMENCLATURE[10-18]

3.2.1.1 Chemical Name

1,2,3,9-Tetrahydro–9–methyl–3-[(2–methyl–1*H*-imidazol–1–yl)methyl]-4*H*-carbazol–4–one hydrochloride

3.2.1.2 Formula

3.2.1.2.1 *Empirical formula*

$C_{13}H_{19}N_3O \cdot HCl$

3.2.1.2.2 *Structural formula*

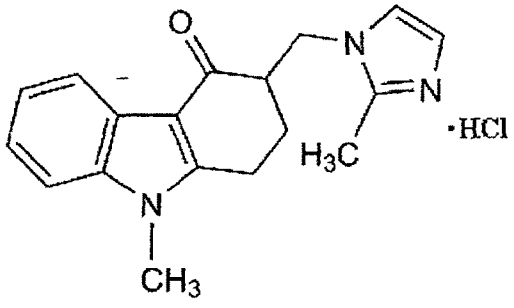

Figure 3.5. Structure formula of ondansetron hydrochloride.

3.2.1.3 Molecular Weight

329.9

3.2.1.4 Physicochemical Properties

3.2.1.4.1 *Appearance*

Ondansetron hydrochloride is obtained as a white or off-white powder.

3.2.1.4.2 *Solubility*

It is soluble in aqueous solutions but solubility decreases with pH >5.7. It weak base and under the acidic conditions is water-soluble. The natural pH of ondansetron hydrochloride is about 4.5 to 4.6. The solubility is markedly reduced in solutions for which the pH greater than or equal to 6. Precipitation of ondansetron (as free base) occurs in solutions with a pH of 5.7 or more. Resolution of the ondansetron precipitate occurs at pH 6.2 when titrated with hydrochloric acid, and precipitation by combintion with alkaline drug been observed.

3.2.1.4.3 *Melting Point*

178.5° to 179.5°C

3.21.4.4 *Dissociation Constant*

pK_a 7.4.

3.2.1.4.5 *Storage*

Store in well-closed container protected from light.

3.2.2 PHARMACOLOGICAL PROPERTIES[10, 11, 15-18]

3.2.2.1 Mechanism of Action

It is a potent, highly selective, competitive antagonist at the 5-HT3 receptor, and thus inhibits the symptoms of nausea and vomiting. Compared with metoclopramide, ondansetron hydrochloride demonstrates equal or superior efficacy, but has no dopamine-receptor antagonist activity, and thus does not induce extrapyramidal side effects.

3.2.2.3 Pharmacokinetics

Following oral administration, ondansetron hydrochloride is rapidly absorbed with peak plasma concentrations being reported about 1.5 to 2 hours after an oral dose of 8 mg. The absolute bioavailability is about 60%, due mainly to hepatic first-pass metabolism. It is extensively distributed in the body; results *in vitro* suggest that about 70 to 75% of the drug in plasma is protein bound. It is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways, with less than 5% of a dose being excreted in urine unchanged: clearances of around 6 mL/minute per kg have been reported in young, healthy subjects. In elderly subjects, bioavailability may be somewhat higher (65%) and clearance lower (4 to 5 mL/minute per kg), presumably due to reduced hepatic metabolism.

3.2.2.4 Bioavailability

60% (young healthy subjects), 65% (elderly); 85% (patients with cancer) and 100% (severe hepatic impairment).

3.2.2.5 Half-life

3 h (young healthy subjects), 5 h (elderly) and 15 to 32 h (severe hepatic impairment).

3.2.2.6 Volume of Distribution

Approx. 140 to 160 L; also reported as 1.3 to 2.9 L/kg. 3.05 L/kg (mild liver disease); 3.36 L/kg (moderate); 3.86 L/kg (severe); 2.5 L/kg (healthy individuals).

3.2.2.7 Clearance

16.6 L/h (patients with mild liver disease); 15.9 L/h (moderate liver disease); 11.6 L/h (severe); 28.3 L/h (healthy volunteers).

3.2.2.8 Distribution in Blood

Blood:plasma ratio is 0.83. It distributes into erythrocytes and circulates bound within.

3.2.2.9 Protein Binding

70 to 75%.

3.2.2.10 Adverse Effects and Precautions

Ondansetron and other 5-HT_3 antagonists may cause headache, a sensation of flushing or warmth, and constipation. There have been rare reports of immediate hypersensitivity reactions, including anaphylaxis, chest pain, hypotension, tachycardia, and bradycardia have been reprted rarely.

3.3.2.11 Uses and Administration

It is used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. It is also used for the prevention and treatment of postoperative nausea and vomiting. Ondansetron hydrochloride is given by intramuscular or slow intravenous injection as the hydrochloride, by mouth as the hydrochloride or base, or rectally as the base.

3.2.2.12 Dose

Doses are expressed in terms of the base. Adult: 8 mg (orally) before treatment followed by 8 mg every 12 h. 16 mg daily (by rectum administration) or 32 mg (intravenously). Children: 5 mg/ml (intravenously) immediately before treatment and then 4 mg orally every 12 h. Alternatively, 100 μg/kg (maximum 4 mg) (over 2 years old).

3.2.3 ANALYTICAL PROPERTIES[11-13]

3.2.3.1 High Performance Liquid Chromatography

System HZ—retention time 2.9 min.

Column: Spherisorb silica (S3W, 100 × 4.6 mm i.d., 3 μm). Column temperature: 35°. Mobile phase: sodium acetate buffer (25 mM, pH 4.2 with glacial acetic acid):acetonitrile (6:4), flow rate 1 mL/min. UV detection (λ=305 nm). Retention time: 4–5 min.

Column: (analytical) Chiralcel OD (250 × 4.6 mm i.d., 10 μm); (guard) Chiralcel OD (50 × 4.6 mm i.d., 10 μm). Mobile phase: hexane:95% ethanol:2–propanol:acetonitrile (65:25:10:1), flow rate 1 mL/min. Internal standard: prazosin. UV detection (λ=216 nm). Retention times: R(−)-ondansetron, 10.0 min; S(+)-ondansetron, 11.6 min; I. S., 8.0 min.

Column: RP C_{18} (Spherisorb, 100 × 4.6 mm i.d., 10 μm). Mobile phase: acetonitrile:sodium phosphate monobasic buffer (20 mM, pH 3 with phosphoric acid) (60:40), flow rate 1.5 mL/min. Internal standard: loxapine. UV detection (λ=305 nm). Retention time: ondansetron, 3.9 min; I. S., 5.5 min.

3.2.3.2 Ultraviolet Spectrum

Aqueous acid (pH 2.8)—210, 248, 266, 310 nm.

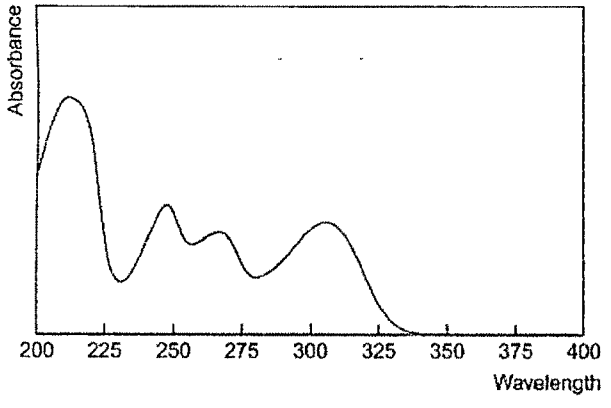

Figure 3.6. UV spectrum of ondansetron hydrochloride.

3.2.3.3 Mass Spectrum

Principal ions at *m/z*: 96, 293, 198, 211, 143, 183, 55, 115.

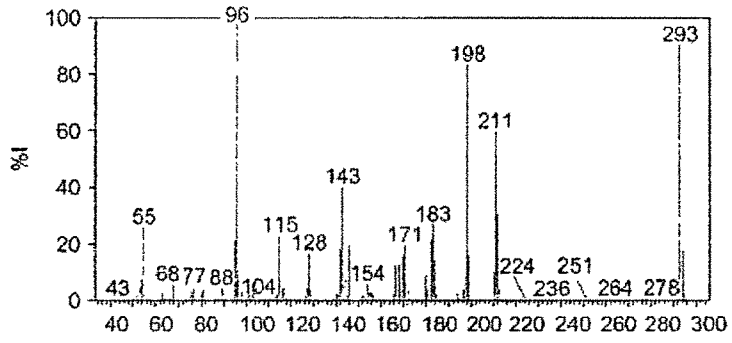

Figure 3.7. Mass spectrum of ondansetron hydrochloride.

3.2.3.4 Quantification

3.2.3.4.1 *High performance liquid chromatography*

In serum: limit of detection 0.25 μg/L. MS detection. In plasma: limit of detection, 1 μg/L. UV detection (λ=305 nm. In serum: limit of quantification, 15 μg/L for each enantiomer and limit of detection, 7 μg/L, UV detection (λ=210 nm). In serum: limit of quantification, 10 μg/L for each enantiomer and limit of detection, 2.5 μg/L, UV detection (λ=216 nm. In plasma: limit of quantification 0.5 μg/L. UV detection (λ=305 nm).

3.3 DRUG PROFILE OF LAMOTRIGINE[19-24]

3.3.1 NOMENCLATURE

3.3.1.1 Chemical Name

6-(2,3-Dichlorophenyl)-1,2,4–triazine–3,5–diamine

3.3.1.2 Formula

3.3.1.2.1 *Empirical formula*

$C_9H_7Cl_2N_5$

3.3.1.2.2 *Structural formula*

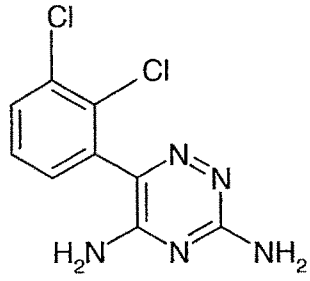

Figure 3.8. Structural formula of lamotrigine.

3.3.1.3 Molecular Weight

256.1

3.3.1.4 Physicochemical Properties

3.3.1.4.1 *Appearance*

White to pale cream crystals from isopropanol

3.31.4.2 *Solubility*

Solubility at 25° (mg/mL); water, 0.17; HCl (0.1 M), 4.1. It is practically insoluble in ethanol.

3.31.4.3 *Melting point*

M.P. 216° to 218°.

3.3.1.4.4 *Dissociation Constant*

pK_a5.7.

3.3.1.5 Storage

Store in well-closed container protected from light.

3.3.2. PHARMACOLOGICAL PROPERTIES[19,22,23]

3.3.2.1 Mechanism of Action

The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests for antiepileptic activity. The relevance of these models to human epilepsy, however, is not known. One proposed mechanism of action of lamotrigine, the relevance of which remains to be established in humans, involves an effect on sodium channels. In vitro pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g.,

glutamate and aspartate). The mechanisms by which lamotrigine exerts its therapeutic action in Bipolar Disorder have not been established.

3.3.2.2 Pharmacokinetics

Lamotrigine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur approximately 2.5 hours after oral administration. It is widely distributed in the body and is reported to be about 55% bound to plasma protein. It is extensively metabolised in the liver and excreted almost entirely in urine, principally as a glucuronide conjugate.

3.3.2.3 Bioavailability

Oral formulation, 98%.

3.3.2.4 Half-life

Mean range (administration with no other medication) is 25 ± 10 h. Single dose, healthy volunteers is 24.1 ± 5.7 h.

3.3.2.5 Volume of Distribution

1 to 1.4 L/kg for healthy volunteers administered with a single 120 mg dose. 0.77 to 1.04 L/kg for healthy males administered with a weekly doubling dose of 30 to 240 mg.

3.3.2.6 Clearance

20.7 to 52.3 (mean, 41.7) mL/min for healthy volunteers receiving a 120 mg single dose. 22.4 to 37.7 (mean 29.6) mL/min for those administered with a weekly doubling dose between 30 and 240 mg.

3.3.2.7 Protein Binding

Plasma, 56%.

3.3.2.8 Dose

50 to 400 mg per day.

3.3.2.9 Adverse Effects

Skin rashes may occur during therapy with lamotrigine; severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

3.3.2.10 Uses and Administration

Lamotrigine, a phenyltriazine compound, is an antiepileptic used as monotherapy and as an adjunct to treatment with other antiepileptics for partial seizures and primary and secondarily generalised tonic-clonic seizures. It is also used for seizures associated with the Lennox-Gastaut syndrome.

3.3.3 ANALYTICAL PROPERTIES[20]

3.3 3.1 Gas Chromatography

System GB—RI 2562; system GAJ—RRT 1.941 (relative to methylphenobarbital).

3.3.3.2 High Performance Liquid Chromatography

System HY—RI 272; system HZ—Retention time 2.3 min.

3.3.3.3 Ultraviolet Spectrum

Aqueous acid (0.025 M sulfuric acid)—208, 265 nm; (0.1 M $HCOONH_4$, pH 3)—267 nm; ethanol—307.5 nm.

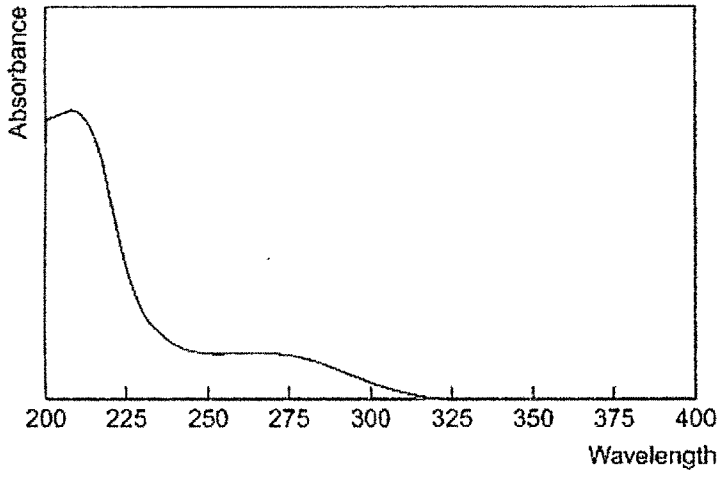

Figure 3.9. UV spectrum of lamotrigine.

3.3.3.4 Infra-red Spectrum

Principal peaks at wavenumbers 1614, 1488, 1429, 1404 cm^{-1}.

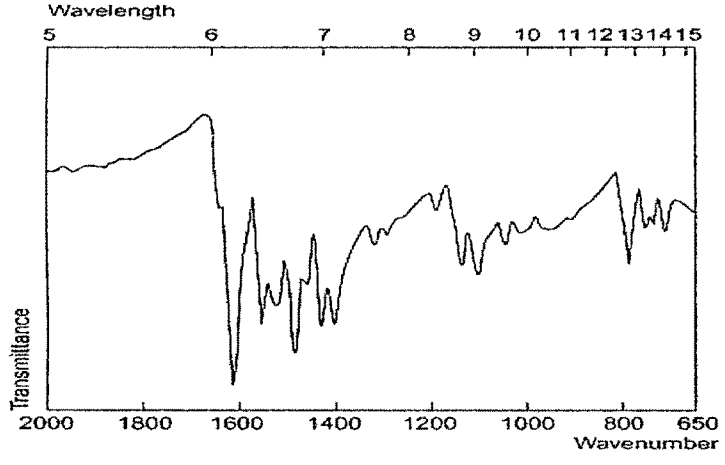

Figure 3.10. Infra-red spectrum of lamotrigine.

3.3.3.5 Mass Spectrum

Principal ions at *m/z* 185, 187, 255, 257, 123, 115, 157, 150.

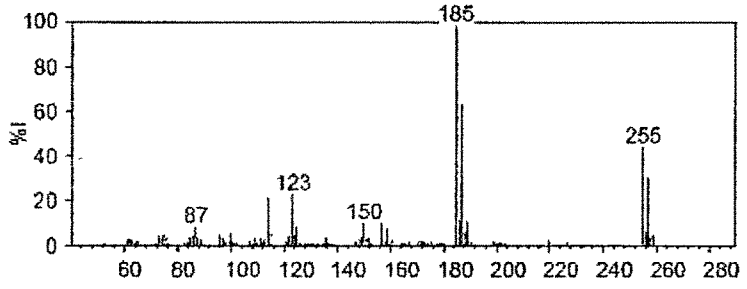

Figure 3.11. Mass spectrum of lamotrigine.

3.3.3.6 Quantification

3.3.3.6.1 *High performance liquid chromatography*

In plasma: limit of detection 0.05 mg/L, UV detection (λ=306 nm). In plasma: the limit of quantification 0.5 mg/L, limit of detection 0.1 mg/L, UV detection (λ=280 nm, In urine: limit of detection (for full spectra) 100 ng. MS detection.

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