Journal of Population Therapeutics & Clinical Pharmacology

REVIEW ARTICLE
DOI: 10.53555/3ymhsq89

A COMPREHENSIVE REVIEW ON ANALYTICAL METHODS AND DRUG PROFILE OF ATOMOXETINE HYDROCHLORIDE AND OXYBUTYNIN CHLORIDE

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ABSTRACT:
Atomoxetine hydrochloride, a selective norepinephrine reuptake inhibitor, and oxybutynin chloride, a muscarinic antagonist, have recently gained attention not only for their primary therapeutic applications—attention-deficit/hyperactivity disorder (ADHD) and overactive bladder, respectively—but also for their synergistic role in managing obstructive sleep apnea (OSA). This review provides a comprehensive overview of their physicochemical properties, mechanisms of action, and clinical relevance in OSA. In addition, it summarizes official pharmacopeial methods (IP, USP, BP) and reported analytical techniques, including HPLC, RP-HPLC, HPTLC, spectrophotometry, and micellar liquid chromatography, for the estimation of both drugs individually and in combination with other agents. Critical evaluation of chromatographic parameters, detection wavelengths, and mobile phases highlights the advancements and challenges in method development and validation. This review underlines the significance of robust, sensitive, and stability-indicating methods for routine quality control and pharmacokinetic studies, offering a consolidated reference for researchers and analysts working on atomoxetine and oxybutynin.

Keywords: Atomoxetine hydrochloride; Oxybutynin chloride; Analytical method development; RP-HPLC; HPTLC; Obstructive sleep apnea (OSA); Drug profile; Validation; Pharmacopeial methods.

1.INTRODUCTION:

1.1 ANALYTICAL METHODS:

1.1.1 Definition:

Analytical chemistry is a subfield of chemistry that focuses on the quantitative and qualitative identification of the constituents of substances, samples, and mixtures. There are two different kinds of analysis: quantitative analysis and qualitative analysis. Identification of the mixture's or sample's constituent parts or analyte is done in qualitative analysis. Quantitative analysis involves determining the quantity of components or analytes in a mixture or sample.[1]

In addition to chemistry, other sciences like biology, zoology, the arts (such as painting and sculpture), archeology, space exploration, and clinical diagnostics also require analytical data. Analytical

chemistry is used extensively in clinical and biological research, geological tests, monitoring and controlling pollutants, quality control in industrial industries, and fundamental and applied research.[2]

1.1.2 Types of Analytical methods:[3]

Numerous methods are available for pharmaceutical analysis, and they are categorized based on the characteristics mentioned below.

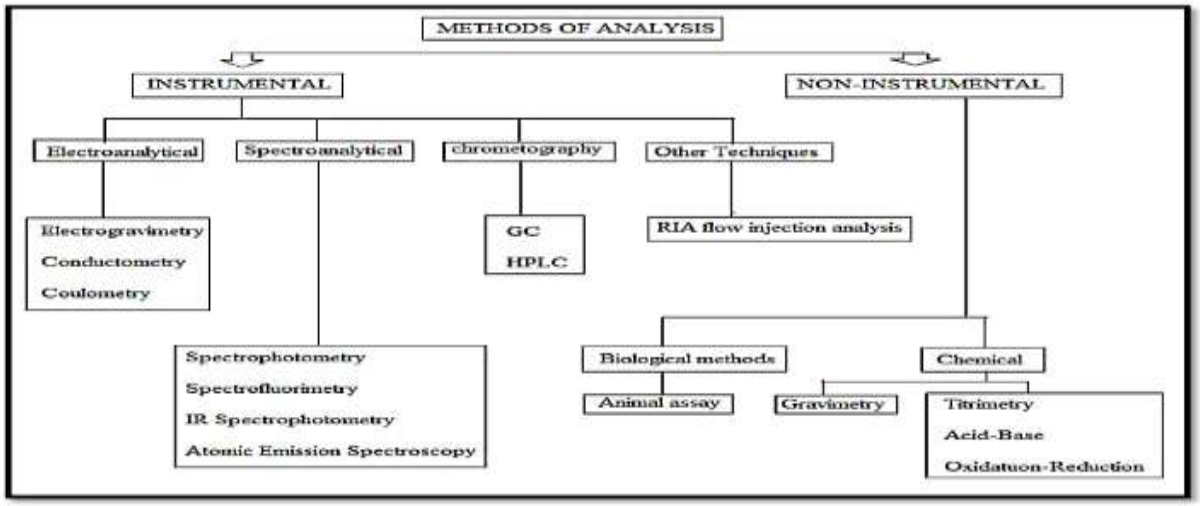
a) Qualitative analysis: This method entails figuring out a substance's nature as well as the nature of its constituent parts in the case of a mixture.

b) Quantitative analysis: The method of quantitative analysis involves determining the constituent constituents of a material and quantifying their quantity or distribution within the substance.

Furthermore, they fall under the following categories:

1) Instrumental methods

2) Non-instrumental methods



Diagrammatic representation of the analysis process

1.2 OBSTRUCTIVE SLEEP APNEA:

The condition known as obstructive sleep apnea (OSA) is brought on by partial or total obstruction of the upper airway while you sleep.[4] During sleep, the tone of the airway muscles changes, resulting in the collapse of the upper airways, which causes sporadic episodes of hypopnea and/or apnea (often during the inspiratory phase of breathing).[5,6] Autonomic dysregulation may result from these events, which cause a drop in arterial oxygen saturation.[6]

The most common and clinically relevant SDB at the moment is obstructive sleep apnea (OSA), which is linked to a number of illnesses, such as pulmonary hypertension, heart failure, atrial fibrillation, hypertension, and cerebrovascular accidents.[2,7]

1.2.1 Prevalence and risk factors:

Physical examinations can identify a number of risk factors linked to OSA.

• The strongest factors are obesity and a high body mass index. risk factors that make OSA more likely. The relationship between OSA and obesity is linear.[4,7]

• For males and women, the neck circumference should be greater than 17 inches (43 cm) and 15 inches (38 cm), respectively.[4]

• The gender of men.

• Over 50 years of age.

• Menopause, neuropathy or myopathy that may impact the genioglossus muscle and other upper airway muscles, the anatomy of the skull (especially in Asians), smoking, family history, and nasal congestion are additional risk factors.[5, 8]

1.2.2 CLINICAL SYMPTOMPS:

Patients typically report headaches, snoring, drooling, nocturnal gasping or choking, excessive daytime sleepiness, exhaustion, and/or dozing off while driving10. Motor vehicle collisions are more likely to involve patients with OSA.[9]

1.2.3 PATHOPHYSIOLOGY

One significant mechanism connecting obstructive sleep apnea with the pro-inflammatory transcription factor nuclear kappa factor B (NF-kB) is the activation of NF-kB by apnea-induced hypoxia.

inflammation of the system. Additionally, it may increase inflammatory indicators downstream, which could lead to end-organ cardiovascular disease. Patients with obstructive sleep apnea have higher levels of NF-kB activity in their circulating neutrophils and monocytes, and research has shown that people on continuous positive airway pressure therapy have lower levels of this protein.[10,11]

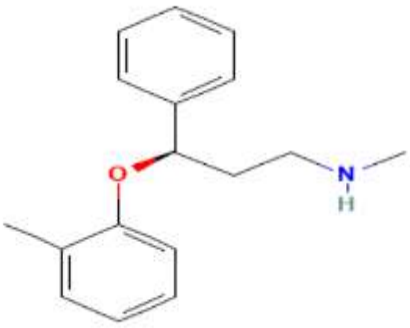
1.2.4 DIAGNOSIS:

Although there is no single sign or symptom that is particular to OSA, clinical signs are crucial in the diagnosing process. When there is a high level of suspicion, surveys and Using symptom-scoring scales can improve diagnosis precision. In the outpatient context, screening questionnaires are used to assess symptomatic patients and decide if polysomnography is necessary. The gold standard for diagnostic confirmation is polysomnography, but it's not always accessible and can be costly.[4]

To determine whether tonsillar, uvular, and tongue enlargement are influencing the airway volume, the Mallampati classification—an assessment of the oropharyngeal inlet—is employed.[9]

1.3 DRUG PROFILE:

1.3.1 ATOMOXETINE HYDROCHLORIDE:[12]

IUPAC Name	N-methyl-3-(2-methylphenoxy)-3-phenyl-propan-1-amine hydrochloride
Molecular formula	$C_{17}H_{22}ClNO$
Chemical structure	
Molecular mass	291.82 g/mol
Description	White to off-white solid powder. Crystalline solid, odorless or almost odorless. Produces a clear solution when dissolved in ethanol; sparingly soluble in water, Slightly bitter.
Solubility	Sparingly soluble in water, soluble in anhydrous ethanol, practically insoluble in heptane.
pKa value	~10.13 (at 25 °c)
Melting point	167 °c – 169 °c
Cas no.	83015-26-3
Mechanism action	One type of selective norepinephrine reuptake inhibitor (nri) is atomoxetine. By inhibiting the norepinephrine transporter (net), it raises norepinephrine (ne) levels in the brain, which results in increased synaptic ne and improved activation of ne-sensitive neurons.

	Atomoxetine enhances upper airway dilator muscle tone via ne facilitation.

1.3.2 OXYBUTYNIN CHLORIDE:[13]

IUPAC Name	4-(diethylamino)-2-butynyl 2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride
Molecular formula	$C_{22}H_{32}ClNO_3$
Chemical structure	
Molecular mass	393.95 g/mol
Description	White crystalline powder. Slightly bitter. Odorless or nearly odorless, hygroscopic solid. When dissolved in water or ethanol, forms a clear solution.
Solubility	Freely soluble in water, ethanol, and chloroform; sparingly soluble in ether
pKa value	~10.2 (basic amine group)
Melting point	167 °c – 169 °c
Cas no.	1508-65-2
Mechanism action	Reduces detrusor overactivity by acting as a competitive antagonist at muscarinic acetylcholine receptors (m1–m5), particularly m3 receptors in the bladder. Oxybutynin decreases rem-related reduction of upper airway dilator muscle tone when paired with atomoxetine, which lowers the apnea–hypopnea index (ahi).

2. LITERATURE REVIEW:

2.1 ATOMOXETINE HYDROCHLORIDE:

2.1.1 Official Methods of Atomoxetine Hydrochloride:

Sr.no	Pharmacopeia	Method Description	Ref no.
1	IP 2022	**Assay by Liquid Chromatography** **Mobile phase:** a mixture of 70 volumes of a buffer solution prepared by dissolving 0.05M potassium dihydrogern orthophosphate in water, add 2 ml of triethylamine, adjusted to pH 2.5 with orthophosphoricacidaxdl30 volumes of acetonitrile, **Column**: a stainless-steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm). **Flow rate:** 1 ml/minute. **Detection Wavelength:** 220 nm, **Injection volume:** 20 µL.	14
2.	USP 2023	**Assay by Liquid Chromatography** **Mobile phase:** n-Propyl alcohol and Buffer (27:73). [NOTE—The ratio of n-propyl alcohol in Buffer can be varied between 26:74 and 29:71 to meet system suitability requirements.] **Column:**4.6-mm × 15-cm; 3.5-µm packing **Flow rate:**1 mL/min **Detection Wavelength:** UV 215 nm **Injection volume:**10 µL	15
3	BP 2023	**Assay by Liquid Chromatography**	16

		Mobile Phase: 1.5ml of diethylamine R, 2.0ml of trifluoroacetic and 150ml of 2 propanol and dilute in 1000ml with Heptane. **Column:** 0.25mm x 4.6mm (5 µm) **Flow rate:**1.0 mL/min. **Detection Wavelength**: Spectrophotometer at 273 nm. **Injection volume:**10 µL	

2.1.2 Reported Methods of Atomoxetine Hydrochloride:

Sr.no	Title	Name of Journal with year of Publication	Summary	Ref
1	Prediction of the Trace Amounts of Atomoxetine in Biological Samples using Optimized Solvent Bar Microextraction Technique Coupled with HPLC-UV	*Journal of Applied Chemical Research,2019*	**Assay by HPLC** **Mobile Phase:** Phosphate buffer: acetonitrile (70:30, v/v) **Column Size:** (150 mm × 4.6mm, 5µm) **Flow rate:**1 ml/min **Injection volume:**10µL **Detection Wavelength:**224 nm	**17**
2	Development and Validation of RP-HPLC Method for the Determination of Atomoxetine Capsules	*The International Organization of Scientific Research (IOSR) journal of Pharmacy,2019*	**Assay by RP- HPLC** **Mobile phase:** Buffer and Methanol were mixed in the ratio of 40:60 v/v, **Column Size:** Symmetry-C8 column (4.6 mm x150 mm, 5 µm particle sizes) and with photodiode array detector**.** **Flow rate:** 1.0 ml/min **Detection wavelength:** 271 nm. **Injection volume**: 10µL	**18**
3	Analytical method development and validation of atomoxetine hydrochloride using rapid high-performance liquid chromatographic technique	*Asian Journal of Pharmaceutical and Clinical Research*,2018	**Assay By RP HPLC** **Mobile phase:** consisting of methanol: water 80:20 V/V. **Column Size:** column used as Xterra RP 18 (250 mm × 4.6 mm, 5 µ particle size) **Flow rate:** 1.0 mL/min **Detection Wavelength:**270 nm **Injection volume**: 10µL	**19**
4	Development and Validation of High Performance Thin-Layer Chromatographic Method for Determination of Atomoxetine Hydrochloride in Pharmaceutical Dosage Forms	*Der Pharma Chemica. 2012;4(1).*	**Assay by HPTLC** **Mobile Phase:** methanol-tritethylamine 10:0.5 **Flow rate:** 150nL S-1 **Injection Volume:** 10ml **Detection Wavelength:**270 nm	**20**
5	Development and Validation of a Stability-Indicating RP-HPLC Method for Determination of Atomoxetine Hydrochloride in Tablets	*Journal of AOAC INTERNATIONAL,2010*	**Assay by RP-HPLC** **Colum size:** Phenomenex C18 column (250 x 4.6 mm id, 5 m particle size) **Mobile phase**: acetonitrile–methanol–0.032 M ammonium acetate (55 + 5 + 40, v/v) **Flow rate:** of 1.0 mL/min. **Injection Volume:** 20 µL**.**	**21**
6	A quality by design approach to impurity method development for atomoxetine hydrochloride	*Journal of Pharmaceutical and Biomedical Analysis. 2008*	**Assay by HPLC** **Mobile Phase:** 27% n-propanol, 73% 25 mM o-phosphoric acid, **Column size:**15cm×4.6mm C8, 3.5 µm **Flow rate:** of 1.0 mL/min **Detection Wavelength:**270 nm **Injection Volume:** 10 µL.	**22**

2.1.3 Reported Methods of Atomoxetine Hydrochloride in combination with other drugs:

Sr.no	Title	Name of Journal with year of Publication	Summary	Ref
1	Development and Validation of (HPLC) Method for Simultaneous Determination of Atomoxetine HCl & Fluoxetine HCl in their Pharmaceutical Dosage Form	*Biomedical Journal of Scientific & Technical Research. 2021*	**Assay by HPLC** **Mobile Phase:** 375ml of distilled water containing 0.1ml tetra-n-butylammonium hydroxide + 0.4ml triethylamine (adjust pH to 3.5 with phosphoric acid) & 625ml Acetonitril (375: 625, v/v) **Column:** Thermo BDS Hypersil C18 column (250mm x 4.6mm, 5µm particle size) **Flow Rate:** 1ml/min Injection **Injection Volume:** 20µL. **Detection Wavelength :**220nm	23
2	Determination of Atomoxetine or Escitalopram in human plasma by HPLC. Applications in Neuroscience Research Studies	*International journal of clinical pharmacology and therapeutics. 2020*	**Assay by HPLC** **Mobile Phase:** a mixture of acetonitrile and aqueous 30 mM potassium dihydrogen phosphate (34:66 (v/v), pH 5.1). **Colum size:** 2.1 x 150 mm (3.5-Micron). **Flow rate:**0.225 mL/min **Injection Volume:** 10µL.	24
3	An Assay to Quantify Methylphenidate and Atomoxetine in Pharmaceutical Preparations by Micellar Liquid Chromatography	*Separation Science Plus,2025*	**Assay by Micellar Liquid Chromatography** **Mobile Phase:** aqueous solution of 0.10 mol/L SDS—6% 1-pentanol, buffered at pH 7 with 0.01 mol/L sodium dihydrogen phosphate **Column size:** C18 (150 × 4.6 mm; particle size,5 µm; pore size, 10 nm). **Flow rate:** 1 mL/min **Injection Volume:** 20µL. **Detection Wavelength:**220nm	25

2.2 OXYBUTYNIN CHLORIDE:

2.2.1 Official Methods of Oxybutynin Chloride:

Sr.no	Pharmacopeia	Method Description	Ref no.
1	**IP 2022**	**Assay by Liquid Chromatography** **Mobile phase:** a mixture of 49 volumes of a buffer solution prepared by dissolving 3.4 g of potassium dihydrogen phosphate and 446 g of di potassium hydrogen phosphate in 1000 ml of wafer and 51 volumes of acetonitrile, **Column Size:** a stainless steel column 15 cm x 3.9 mm, packed with octylsilane bonded to silica gel (5-µm), **Flow rate:** 1 ml/minute**,** **Detection Wavelength:** 210 nm, **Injection volume:** 10 µL.	26
2	**USP 2021**	**Assay by Liquid Chromatography** **Mobile Phase:** Acetonitrile and Solution A (1:4) Solution A = Methanol, water, and triethylamine (800:3200:0.9), adjusted to pH 3.5 ± 0.05 with phosphoric acid **Column:** 4-mm × 30-cm; **Detection Wavelength**: UV 203 nm **Flow rate:** 2 mL/min **Injection size:** 20 µL.	27
3	**BP 2025**	**Assay by Liquid Chromatography** **Mobile phase:** 49 volumes of phosphate buffer (3.4 g/L KH_2PO_4 + 4.36 g/L K_2HPO_4) and 51 volumes of acetonitrile **Column:** Length = 0.15 m (150 mm)	28

		Internal diameter = 3.9 mm **Flow rate:** 1 mL/min **Detection Wavelength:** UV spectrophotometer at 210 nm **Injection volume:** 10 µL.	

2.2.2 Reported Methods Oxybutynin Chloride:

Sr.no	Title	Name of Journal with year of Publication	Summary	Ref
1	Analytical Method Development and Validation for the Estimation of Related Substances in Oxybutynin HCl Prolonged Release Tablets by Reverse-Phase High-Performance Liquid Chromatography.	*International Journal of Pharmaceutical & Biological Archives (IJPBA). 2018*	**Assay by RP - HPLC** **Mobile phase:** Water: Acetonitrile: Triethylamine =690:310:2 (v/v/v) **Column:**C18 (150 × 4.6 mm, 3.5 µm SS **Flow rate:** 1.0 mL/min (isocratic) **Injection volume:** 25 µL **Detection wavelength:** 210 nm (UV)	**29**
2	Method Development and Validation of Oxybutynin Chloride by RP-HPLC Analytical Technique	*International Journal of Advances in Science Engineering and Technology. 2017*	**Assay by HPLC** **Mobile Phase:** Phosphate buffer: Acetonitrile (51:49, v/v) (degassed) **Column:** Symmetry C8 (75 × 4.6 mm, 3.5 µm SS) **Flow rate:** 1.0 mL/min (isocratic) **Injection volume:** 10 µL **Detection wavelength:** 210 nm (UV)	**30**
3	Validated RP - HPLC method for the estimation of oxybutynin in formulation	*Pharmacophore. 2011.*	**Assay by RP HPLC** **Mobile phase** :1% orthophosphoric acid: acetonitrile: methanol (40:45:15, v/v/v). **Column:** Symmetry C18, 250 × 4.6 mm, 5µm. **Flow rate**: 1.0 mL/min**.** **Detection Wavelength:** UV at 205 nm. **Injection volume:** 20 µL	**31**
4	Rapid and selective UV spectrophotometric and RP-HPLC methods for dissolution studies of oxybutynin immediate-release and controlled-release formulations	*Journal of Pharmaceutical and Biomedical Analysis,2004*	**Assay by RP HPLC** **Mobile phase:** phosphate buffer (pH ~3.0–4.0): acetonitrile (approx. 50:50 v/v) — adjust to match retention and peak shape. **Column:** C18, 150–250 × 4.6 mm, 3–5 µm. **Flow rate**: 1.0 mL/min**,** **Detection Wavelength:**205–210 nm	**32**
5	High performance liquid chromatographic determination of oxeladin citrate and oxybutynin hydrochloride and their degradation products.	*Il Farmaco. 2005*	**Assay by HPLC** **Mobile phase:** Acetonitrile:0.01 M potassium dihydrogen phosphate: diethylamine (60: 40:0.2,v/v/v). **Column:** VP-ODS (Shim-pack) C18, 250 × 4.6 mm i.d., (particle size reported in paper ~4–4.6 µm). **Flow rate:** 1.5 mL·min^{-1}. **Injection volume:** 20 µL. **Detection:** UV at 220 nm**.**	**33**

2.2.3 Reported Methods of Oxybutynin Chloride in combination with other drugs:

Sr.no	Title	Name of Journal with year of Publication	Summary	Ref
1	Simultaneous determination of selective drugs, fluoxetine, ketoprofen, oxybutynin and clonidine in human plasma.	*Jordan Journal of Pharmaceutical Sciences,2011*	**Assay by RP HPLC** **Column:** Octadecyl ODS (C18) YMC column (3 µm, 150 mm × 4.6 mm), with a guard column**. Mobile phase:** Gradient elution combining acetonitrile (organic phase A) with 10 mM potassium dihydrogen phosphate buffer **Flow rate:** 1.0 mL/min. **Detection Wavelength:** UV detection (specifically 220 nm)	34

CONCLUSION:

Official methods: Pharmacopoeias (IP 2022, USP 2021–2023, BP 2023–2025) recommend liquid chromatography with specific mobile phases and detection wavelengths for assay of both drugs.
Reported analytical methods:

- Atomoxetine has been quantified using RP-HPLC, HPTLC, and stability-indicating assays with high sensitivity (detection at ~220–270 nm). Combination assays include co-estimation with fluoxetine, escitalopram, and methylphenidate.
- Oxybutynin has been analyzed using RP-HPLC, UV spectrophotometry, and validated stability-indicating methods. Combination assays include co-determination with fluoxetine, ketoprofen, and clonidine.

These findings emphasize the availability of robust, reproducible, and validated analytical methods, while also pointing to the need for further simultaneous estimation methods in complex biological matrices.

Atomoxetine hydrochloride and oxybutynin chloride are clinically important drugs with expanding therapeutic relevance in obstructive sleep apnea. Numerous validated analytical methods, particularly RP-HPLC and spectrophotometric techniques, are available for their assay, ensuring quality control and reliability in pharmaceutical formulations. This review highlights the evolution of analytical methodologies, demonstrating their importance in drug development, regulatory compliance, and clinical pharmacology. Future research should focus on developing advanced hyphenated techniques (LC–MS/MS, UPLC) and bioanalytical methods for simultaneous multi-drug quantification, thereby supporting pharmacokinetic and bioequivalence studies.

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