



## A COMPREHENSIV REVIEW ON ANALYTICAL METHODS FOR ESTIMATION OF DEXTROMETHORPHAN HYDROBROMIDE AND MEMANTINE HYDROCHLORIDE

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### ABSTRACT:

Dextromethorphan hydrobromide (DXM HBr) and memantine hydrochloride (MEM HCl) are two pharmacologically significant central nervous system (CNS) agents that have attracted considerable interest due to their neuroprotective potential. DXM, a dextrorotatory morphinan derivative, is primarily used as a non-opioid antitussive but also exhibits uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonism and sigma-1 receptor agonism, positioning it as a candidate in epilepsy, neuropathic pain, and neurodegenerative disorders. MEM HCl, a low-to-moderate affinity NMDA receptor antagonist, selectively blocks pathological glutamatergic excitotoxicity while preserving physiological neurotransmission, making it an approved therapy for moderate to severe Alzheimer's disease. The combination of DXM and MEM has been explored for synergistic neuroprotection, further emphasizing the need for reliable analytical methodologies. Over the past two decades, a variety of analytical approaches—including spectrophotometry, chromatography (TLC, HPLC, UPLC, GC), hyphenated techniques (LC-MS/MS, GC-MS), electrochemical methods, and capillary electrophoresis—have been developed for their individual and simultaneous quantification in pharmaceutical formulations and biological matrices. Among these, RP-HPLC and LC-MS/MS remain the most widely adopted, offering stability-indicating capability and ultra-sensitive detection, respectively. Method validation in line with ICH Q2(R1) ensures analytical reliability, covering accuracy, precision, linearity, specificity, and robustness. Emerging trends in green analytical chemistry, high-throughput analytical systems, and miniaturized lab-on-a-chip platforms are reshaping the field, focusing on sustainability, efficiency, and regulatory adaptability. This review provides a comprehensive overview of analytical strategies for DXM and MEM, highlighting their clinical importance, methodological challenges, and future perspectives in advanced pharmaceutical and bioanalytical sciences.

**KEYWORDS:** Dextromethorphan Hydrobromide (DXM HBr); Memantine Hydrochloride (MEM HCl); Neuroprotection; NMDA receptor antagonists; Spectrophotometry; RP-HPLC; LC-MS/MS; Analytical method development; Method validation (ICH Q2(R1)); Simultaneous estimation; Stability-indicating methods;

## 1. INTRODUCTION:

Dextromethorphan hydrobromide (DXM HBr) and Memantine hydrochloride (MEM HCl) are two therapeutically significant compounds that have gained substantial attention in pharmaceutical sciences due to their unique pharmacological actions on the central nervous system. Dextromethorphan, a dextrorotatory morphinan derivative, is widely used as a non-opioid antitussive agent. Beyond its well-established role in cough suppression, DXM is increasingly being investigated for its neuroprotective effects, attributed to its activity as an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist. These mechanisms contribute to its potential therapeutic role in neurological disorders, including epilepsy, neuropathic pain, and neurodegenerative conditions such as Alzheimer's and Parkinson's diseases.<sup>[1]</sup>

Memantine hydrochloride, on the other hand, is a low-to-moderate affinity NMDA receptor antagonist that selectively blocks excessive glutamatergic stimulation while preserving normal synaptic activity. This pharmacological profile has positioned memantine as a key therapeutic agent in the management of moderate to severe Alzheimer's disease, often improving cognitive function and slowing disease progression.<sup>[2]</sup> The combination of DXM and MEM has been explored in clinical settings due to their complementary neuroprotective effects, showing promise in the management of neurodegenerative disorders.<sup>[3]</sup>

The development and validation of these analytical procedures, guided by ICH Q2(R2) guidelines, ensure that the methods meet critical parameters such as linearity, precision, accuracy, limit of detection (LOD), limit of quantitation (LOQ), and robustness.<sup>[5]</sup> A comprehensive review of these analytical methods is essential for researchers, analytical scientists, and regulatory bodies to evaluate current advancements, compare methodologies, and identify future directions in the estimation of these clinically important compounds. This review aims to provide an in-depth overview of the analytical techniques employed for the estimation of dextromethorphan hydrobromide and memantine hydrochloride, highlighting their applications in pharmaceutical and biological matrices, validation aspects, comparative advantages, and emerging trends in green and advanced analytical chemistry.

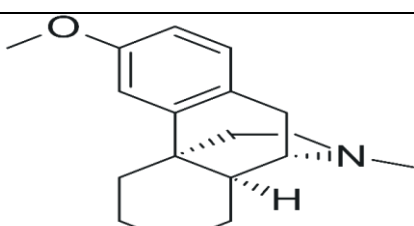
### 1.1. RP-HPLC Methods

Reverse Phase High-Performance Liquid Chromatography (RP-HPLC) is the most widely employed technique for simultaneous estimation because of its **sensitivity, reproducibility, selectivity, and stability-indicating capability**.

- RP-HPLC methods have been reported using **C18 columns** with mobile phases consisting of **acetonitrile, methanol, and phosphate buffers** at pH 3–6. Detection is generally performed using **UV or PDA detectors**.
- These methods provide high resolution and separation of DXM and MEM, even in the presence of degradation products or excipients, making them suitable for **routine quality control**.
- Some studies have also demonstrated forced degradation analysis, proving that the developed RP-HPLC methods are **stability-indicating**.<sup>[5]</sup>

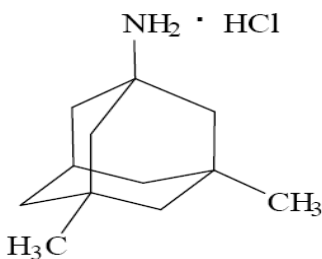
## 2. DRUG PROFILE:

### 2.1 Dextromethorphan Hydrobromide (DXM HBr) <sup>[1]</sup>

<b>IUPAC NAME</b>	(+)-3-methoxy-17-methyl-9 $\alpha$ ,13 $\alpha$ ,14 $\alpha$ morphinan
<b>MOLECULAR FORMULA</b>	C <sub>18</sub> H <sub>26</sub> BrNO
<b>CHEMICAL STRUCTURE</b>	

<b>MOLECULAR MASS</b>	352.32 g/mol
<b>DISCRIPTION</b>	White to off-white crystalline powder
<b>SOLUBILITY</b>	freely soluble in chloroform, soluble in ethanol, and sparingly soluble or slightly soluble in water
<b>pKa Value</b>	9.3-9.85
<b>MELTING POINT</b>	122-126 °C
<b>CAS No.</b>	6700-34-1
<b>MECHANISM OF ACTION</b>	Dextromethorphan is a low-affinity uncompetitive NMDA antagonist and sigma-1 receptor agonist. It is also an antagonist of $\alpha 3/\beta 4$ nicotinic receptors. However, the mechanism by which dextromethorphan's receptor agonism and antagonism translate to a clinical effect is not well understood.

## 2.2 Memantine Hydrochloride (MEM HCl) [2]

<b>IUPAC NAME</b>	1-amino-3,5-dimethyladamantane hydrochloride
<b>MOLECULAR FORMULA</b>	$C_{12}H_{21}N \cdot HCl$
<b>CHEMICAL STRUCTURE</b>	
<b>MOLECULAR MASS</b>	215.76 g/mol
<b>DISCRIPTION</b>	A fine White to off-white powder
<b>SOLUBILITY</b>	Soluble in water and ethanol
<b>MELTING POINT</b>	292-298 °C
<b>pKa Value</b>	10.3-10.4
<b>CAS No.</b>	41100-52-1
<b>MECHANISM OF ACTION</b>	Memantine hydrochloride mechanism of action (MOA) is primarily as a low to moderate affinity, uncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor.

## 3. ANALYTICAL METHODS FOR DXM HBr AND MEM HCl (SINGLE):

The quantitative determination of Dextromethorphan Hydrobromide (DXM HBr) and Memantine hydrochloride (MEM HCl) has been performed using a wide range of analytical techniques. These include spectroscopic and chromatographic methods, which are commonly employed in pharmaceutical quality control and bioanalytical studies. Each method varies in terms of sensitivity, selectivity, and applicability to different matrices such as bulk drug, pharmaceutical formulations, and biological fluids.

### 3.1 Spectroscopic Methods

#### UV–Visible Spectroscopy

UV–Vis spectrophotometry remains a simple, cost-effective, and widely employed method for the estimation of DXM HBr and MEM HCl in bulk and formulations.

- **Dextromethorphan HBr:** Exhibits  $\lambda_{max}$  around 278–282 nm in aqueous and acidic media.<sup>[4]</sup> Several methods have been reported for single estimation as well as in combination with other drugs.
- **Memantine HCl:** Being a non-chromophoric compound, direct UV detection is difficult. Derivatization techniques (e.g., with 1-fluoro-2,4-dinitrobenzene or o-phthalaldehyde) have been employed to enhance its UV absorbance and facilitate quantification.<sup>[6]</sup>

### Fluorescence Spectrometry

Due to its structural features, **DXM and its metabolites** exhibit intrinsic fluorescence, enabling sensitive quantification.

- Fluorescence spectrometric assays have been reported for **DXM in plasma and urine samples**, showing higher sensitivity than UV methods.<sup>[7]</sup>
- For MEM HCl, **derivatization with fluorogenic reagents** such as fluorescamine or o-phthalaldehyde allows sensitive fluorescence detection.<sup>[8]</sup>

### 3.2 Chromatographic Methods

#### Thin Layer Chromatography (TLC)

- TLC and HPTLC methods have been reported for DXM estimation in pharmaceutical preparations. Densitometric detection is used to improve quantification.
- For MEM HCl, TLC is less commonly applied due to poor sensitivity but has been explored in combination assays with derivatization.<sup>[9]</sup>

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#### High-Performance Liquid Chromatography (HPLC, RP-HPLC)

- **DXM HBr:** Several validated **RP-HPLC methods** have been developed for estimation in bulk drugs, dosage forms, and biological matrices. Commonly reported mobile phases include phosphate buffer–acetonitrile or methanol systems, with UV detection at ~278 nm.<sup>[4]</sup>
- **MEM HCl:** As a poorly chromophoric drug, RP-HPLC methods often involve **pre-column derivatization** with agents such as 2,4-dinitrofluorobenzene, yielding UV-absorbing derivatives for detection around 260–280 nm.
- **Simultaneous estimation:** RP-HPLC methods have been reported for **DXM HBr and MEM HCl in combination with other CNS-active agents**, ensuring selectivity and stability-indicating capability.<sup>[6]</sup>

#### Ultra-Performance Liquid Chromatography (UPLC)

- UPLC, offering higher resolution, shorter run time, and reduced solvent consumption, has been explored for DXM and MEM estimation.
- Reported UPLC-MS/MS assays achieve high sensitivity for pharmacokinetic and bioequivalence studies, detecting drug concentrations in the low ng/mL range.<sup>[10]</sup>

#### Gas Chromatography (GC)

- **DXM:** GC and GC-MS methods have been extensively used for DXM and its metabolites in toxicological screening and forensic applications due to high sensitivity and specificity.
- **MEM HCl:** GC is less common but has been applied following derivatization with silylating or acylating agents.<sup>[11]</sup>

### 3.3 Hyphenated Techniques

#### Liquid Chromatography–Mass Spectrometry (LC–MS / LC–MS/MS)

- **Dextromethorphan (DXM HBr):** LC–MS/MS is widely used for pharmacokinetic, bioequivalence, and drug–drug interaction studies. Highly sensitive assays have been developed to quantify DXM and its metabolite dextrorphan in human plasma, urine, and even dried blood spots. Detection limits reach the **pg/mL range**.<sup>[7]</sup>
- Applied in **CYP2D6 phenotyping**, since DXM is a probe substrate for cytochrome P450 2D6 activity.
- **Memantine (MEM HCl):** LC–MS/MS methods often require derivatization due to MEM's poor ionization. Derivatives with agents such as dansyl chloride improve sensitivity. Quantification in plasma and CSF has been reported with LLOQs as low as 0.05 ng/mL.<sup>[10,12]</sup> Widely applied in **therapeutic drug monitoring (TDM)** and clinical pharmacokinetic studies.

#### Gas Chromatography–Mass Spectrometry (GC–MS)

- **DXM HBr:** Extensively used in **forensic toxicology** and **clinical toxicology** to detect DXM and dextrophan in serum, plasma, and urine. Sample preparation often involves **liquid–liquid extraction** followed by derivatization to enhance volatility.<sup>[13]</sup>
- **MEM HCl:** GC–MS is less common but has been applied using derivatization with **silylating reagents** such as N, O-bis(trimethylsilyl)trifluoroacetamide (BSTFA). It provides high sensitivity in biological matrices.<sup>[11]</sup>

### 3.4 Electrochemical & Other Methods

- **Potentiometric Methods** Potentiometric sensors and ion-selective electrodes (ISEs) have been reported for direct estimation of DXM HBr and MEM HCl in pharmaceutical formulations.
- For DXM HBr, **PVC membrane electrodes** modified with ion-association complexes provide rapid and selective determination.<sup>[14]</sup>
- For MEM HCl, potentiometric sensors using **molecularly imprinted polymers (MIPs)** as recognition elements have been developed, enabling sensitive estimation in dosage forms.<sup>[15]</sup>

#### Capillary Electrophoresis (CE)

- CE offers **high separation efficiency** with minimal solvent consumption.
- **DXM HBr:** Capillary electrophoresis with UV detection has been reported for simultaneous estimation of DXM and its metabolites in biological samples.<sup>[11]</sup>
- **MEM HCl:** CE methods with derivatization (e.g., o-phthalaldehyde) allow detection in plasma and pharmaceutical dosage forms.<sup>[16]</sup>

## 4. LITERATURE REVIEW:

### 4.1 Dextromethorphan Hydrochloride:

- **official method of Dextromethorphan Hydrobromide**

Sr. No	TITLE	CHROMATOGRAPHY PARAMETERS	REF No.
1.	IP	<b>Mobile phase:</b> Dissolve 3.11 of docusate sodium in a mixture of 400 ml of water and 600 ml of acetonitrile. Add 0.56 g of sodium nitrate, adjust to pH 2.0 with glacial acetic acid, <b>Flow rate:</b> 1ml/min <b>Wavelength:</b> 280nm <b>Column:</b> 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous, silica (5 µm) <b>Retention time:</b> 22min	17
2.	EP	<b>Mobile phase:</b> dissolve 3.11 g of docusate sodium R in a mixture of 400 mL of water R and 600 mL of acetonitrile R, add 0.56 g of sodium nitrate R and adjust to apparent pH 2.0 with glacial acetic acid R. <b>Flow rate:</b> 1ml/min. <b>Wavelength:</b> 280 nm. <b>Column size:</b> l = 0.25 m, Ø = 4.6 mm; <b>Retention time:</b> 22 min	18

- **Reported method for Dextromethorphan Hydrobromide**

Sr. no	TITLE	METHOD	DESCRIPTION	REF No.
1.	Development and Validation of Simple UV Spectrophotometric Method for the Estimation of Dextromethorphan Hydrobromide in Bulk and Marketed Dosage Formulations	UV Spectrophotometric	<b>Solvent:</b> Hcl and water <b>λ<sub>max</sub> :</b> 250 nm <b>Linearity range:</b> 5.0-30.0 µg/ml <b>R<sup>2</sup>:</b> 0.9993	19
2.	Development and validation of stability indicating HPTLC method for estimation of dextromethorphan hydrobromide	HPTLC	<b>Solvent:</b> Toluene: Methanol: Triethylamine (8.5:1:0.5 v/v/v) <b>λ<sub>max</sub> :</b> 225 nm. <b>Linearity range:</b> 10-60 µg/mL <b>R<sup>2</sup>:</b> 0.991	20

3.	Spectrophotometric Determination of Pipazethate HCl and Dextromethorphan HBr using Potassium Permanganate	HPLC	<b>Solvent:</b> potassium permanganate in acidic medium <b><math>\lambda_{max}</math> :</b> =521 nm <b>Linearity range:</b> <b>PiCl:</b> 2.0-16 $\mu\text{g/ml}$ & <b>DEX:</b> 2.0 -15 $\mu\text{g/ml}$ <b>R<sup>2</sup>:</b> 0.9993	21
4.	Simultaneous determination of dextromethorphan HBr and bromhexine HCl in tablets by first-derivative spectrophotometry	UV Spectrophotometric	<b>Solvent:</b> methanol and phosphate buffer <b><math>\lambda_{max}</math> :</b> 234 and 324 nm, <b>Linearity range:</b> <b>DEX:</b> 0.033 $\mu\text{g/ml}$ <b>BMX:</b> 0.103 $\mu\text{g/ml}$ <b>R<sup>2</sup> :</b> 0.9999	22

## 5.2 Memantine Hydrochloride

### • Official Method of Memantine Hydrochloride

Sr no	Title	CHROMATOGRAPHY PARAMETERS	REF no:
1	IP	<b>Mobile phase:</b> 15 ml of 1 M sodium hydroxide and mix. Add 25.0 ml of internal standard solution, and shake for 15 minutes. Allow the layers to separate, and filter upper hexane layer through anhydrous sodium sulphate. <b>Flow rate:</b> 4ml/min. <b>Wavelength:</b> 210 nm <b>Column:</b> a capillary column 50 m x 0.32 mm, coated with 5 per cent phenyl and 95 per cent methylpoly siloxane (film thickness 0.52 $\mu\text{m}$ ) <b>Retention time:</b> 3.37min	23
2	USP	<b>Mobile phase:</b> Methanol and water <b>Flow rate:</b> $4.0 \pm 0.4$ mL/min <b>Wavelength:</b> 205nm. <b>Column:</b> 50-m $\times$ 0.32-mm; 0.52- $\mu\text{m}$ packing G27 <b>Retention time:</b> 3.9 min	24

### • Reported Methods of Memantine Hydrochloride

Sr. No.	TITLE	METHOD	DESCRIPTION	REF No.
1	To Develop HPLC Method For the Assay of Memantine Hydrochloride Tablets Using Refractive Index (RI) Detector,	RP-HPLC	<b>M.P:</b> buffer (pH-6.0): Methanol (45:55 v/v) <b>Column:</b> C18 column (250 $\times$ 4.6 mm, id, 5 $\mu$ ) <b>F.R:</b> 1.0 ml/min Linearity :50-150 $\mu\text{g/ml}$ <b>R.T. :</b> 7 min	25
2	High-Performance Liquid Chromatographic Ultraviolet Determination of Memantine Hydrochloride after In Vitro Transdermal Diffusion Studies	HPLC	<b>M.P:</b> hydrochloric acid water solution (0.01 M; pH 2.4)-methanol (15: 85, v/v) <b>Column:</b> Kromasil C-18, 4.5 $\mu\text{m}$ column (250mm x 4.6 mm, 5m) <b>F.R:</b> 1.2 ml/min <b>Linearity:</b> 0.5-50 $\mu\text{g/ml}$ <b>R.T.:</b> 5.5 min	26
3	Estimation of Memantine Hydrochloride using ultraviolet visible spectrophotometry in bulk drug and formulation	UV Spectrophotometric	<b>Solvent:</b> Distilled water <b><math>\lambda_{max}</math> :</b> 291nm <b>Linearity range:</b> 10-30 $\mu\text{g/mL}$ <b>R<sup>2</sup>:</b> 0.9999	27
4.	Development and validation of memantine hydrochloride by RP-HPLC method.	RP-HPLC	<b>M.P:</b> potassium di-hydrogen phosphate, acetonitrile and methanol <b>Column:</b> 250x4.6mm packed with particle size of 5 $\mu\text{m}$ <b><math>\lambda_{max}</math> :</b> 260nm <b>F.R.:</b> 1ml/min at 25°C <b>Linearity range:</b> 60-140 $\mu\text{g/mL}$	28

## 6. CONCLUSION:

Analytical methods play a pivotal role in ensuring the therapeutic quality, safety, and efficacy of dextromethorphan hydrobromide (DXM HBr) and memantine hydrochloride (MEM HCl), both individually and in combination. Their clinical relevance in managing neurological disorders necessitates highly accurate, sensitive, and validated methods for routine quality control, pharmacokinetic studies, and therapeutic monitoring. Traditional techniques such as UV spectroscopy and RP-HPLC remain widely used due to their simplicity and reliability, while advanced hyphenated methods like LC–MS/MS and UPLC–MS/MS provide superior sensitivity and selectivity in complex biological matrices. Stability-indicating approaches further ensure robustness against degradation, supporting regulatory compliance. Looking ahead, the integration of green analytical chemistry principles, high-throughput platforms, and miniaturized lab-on-a-chip systems offers exciting opportunities to reduce environmental impact, increase efficiency, and enable real-time monitoring. Thus, the future of analytical development for DXM and MEM will not only address regulatory and scientific requirements but also align with sustainable and innovative pharmaceutical practices.

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