Chapter 2

DRUG PROFILE &

LITERATURE REVIEW
Drug Profile

2.1. MILNACIPRAN HYDROCHLORIDE (MIL) [1-3]

Structure:

![Chemical structure of MIL](image)

FIGURE 2.1 Chemical structure of MIL

Synonyms: (-)-milnacipran, Midalcipran, Milnacipranum (Latin)

Chemical names:
- (1R, 2S) -2-(amino methyl)-N,N-diethyl-1-phenylcyclopropane-1-carboxamide hydrochloride;
- (±)-cis-2-(Aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride;
- 1-phenyl-1-(diethylaminocarbonyl)-2-(aminomethyl)-cyclopropane.

Empirical formula: C₁₅H₂₃ClN₂O

Molecular weight: 282.8

CAS No.: 101152-94-7

Appearance: A white crystalline powder

Melting point: 179-181°C

Solubility: It is freely soluble in water, methanol, ethanol, chloroform, and methylene chloride and sparingly soluble in diethyl ether.

pKa value: 9.65

Log P/ Lipophilicity: 1.7

Indications: MIL is indicated to treat moderate to severe clinical depression and chronic pain.

Pharmacological class: Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)
Chapter 2: Drug profile and literature review

Pharmacokinetics:

Absorption: Absorption of MIL is rapid and at least 90 % is absorbed. First-pass metabolism is low. The drug shows linear pharmacokinetics and peak plasma concentrations are reached within 3 h of dosing. Steady state concentrations are rapidly achieved within 2 to 3 days of administration and the drug does not accumulate after multiple doses.

Metabolism: The major metabolite is the glucuronide conjugate of the parent drug and no active metabolite has been identified.

Distribution: The protein binding of MIL is low and non-saturable binding to plasma protein is approximately 13 %.

Excretion: Urine is the main route of elimination with more than 90 % of the dose is recovered in this way and 5 % in faeces over 96 h 50 to 60 % of drug is excreted unchanged; 20 to 30 % as the glucono-conjugated drug and less than 20 % as the glucorono-conjugated phase I metabolites including N-dealkylated MIL. Elimination is rapid and over 85 % of the initial dose is recovered within first 24 h. The metabolites are not pharmacologically active at clinically relevant doses. The liver and the kidneys are both involved in the elimination of the drug.

Pharmacodynamics: MIL inhibits norepinephrine and serotonin reuptake in a 3:1 ratio, in practical use this means a balanced (equal) action upon both transmitters. The serotonin reuptake inhibition is likely to improve depression, while the norepinephrine reuptake inhibition probably improves chronic pain. MIL exerts no significant actions on postsynaptic H1, alpha-1, D1, D2, and muscarinic receptors, as well as on benzodiazepine/opiate binding sites.

Bioavailability: 85 %.

Half life: 6.1 h to 8.1 h

Dosage and administration: The recommended dose of MIL is 100 mg/day (50 mg twice daily). Based on efficacy and tolerability dosing may be titrated.

MIL is available in India for oral administration as immediate release capsules having strength of 12.5 mg, 25 mg, 50 mg, and 100 mg.
Review of Literature of MIL

MIL is not official in any of the Pharmacopoeias till now. The published reports focusing on analytical methodologies of MIL are summarized in Table 2.1.

**TABLE 2.1 Summary of reports published on analytical methods of MIL**

<table>
<thead>
<tr>
<th>Author/s</th>
<th>Details of publication</th>
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<tbody>
<tr>
<td>Patti, A. et al.</td>
<td>Chiral HPLC analysis of milnacipran and its FMOC-derivative on cellulose-based stationary phases. <em>Chirality</em> <strong>2008</strong>, 23, 63-68.</td>
<td>6</td>
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2.2. DROTAVERINE HYDROCHLORIDE (DRT) [11-12]

Structure:

![Chemical structure of DRT](image)

**FIGURE 2.2** Chemical structure of DRT

*Synonyms:* Drotaverin HCl; Drotaverinium chloride; Isodihydroperparine hydrochloride

*Chemical names:*
- (1Z)-1-[(3,4-diethoxyphenyl)methylidene]-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline;
- 1-(3,4-Diethoxybenzylidene)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride;
- (1Z)-1-((3,4-diethoxyphenyl)methylidene)-6,7-diethoxy-3,4-dihydro-2H-isoquinoline hydrochloride;

*Empirical formula:* $C_{24}H_{33}NO_4Cl$

*Molecular weight:* 433.97

*CAS No.:* 985-12-6

*Appearance:* Light yellow or greenish yellow crystalline powder

*Melting point:* 208-210 °C

*Solubility:* Moderately soluble in water, soluble in alcohol (96 %) easily soluble in chloroform

*pKa Value:* 6.3

*Log P/ Lipophilicity:* 5.35


*Pharmacological class:* Selective phosphodiesterase IV inhibitor.
Pharmacokinetics:

Absorption: Although therapeutic serum levels have not been established, peak concentrations occur approximately 1 to 3 h after an oral dose. Oral bioavailability of DRT ranges from 25% to 91%.

Distribution: DRT and its metabolites are 80% to 95% protein bound and it has a volume of distribution of 193 to 195 liters.

Metabolism: DRT appears to undergo extensive first-pass metabolism. It is readily metabolized in the liver by O-deethylation to mono- and di-phenolic compounds and their corresponding glucorono acid derivatives.

Excretion: DRT is extensively metabolized in the liver and it is excreted in the urine and faeces. The half-life of DRT ranges from 7 to 12 h.

Pharmacodynamics: DRT is a spasmolytic agent by inhibiting PDE4 in smooth muscle cells. It causes smooth muscle relaxation by increasing intracellular levels of cyclic adenosine monophosphate (cAMP) secondary to inhibition of phosphodiesterase. It acts to correct cyclic AMP and Ca imbalance at the spastic site, thereby relieving smooth muscle spasm and pain.

Bioavailability: Highly variable

Half life: 7-12 h

Protein binding: 80-90%

Dosage and administration:
Adult: 40-80 mg tid (three times a day) Child: 1-6 yr: 20 mg 3-4 times daily; > 6 yr: 40 mg tid may be taken with or without food.
Review of literature on DRT

DRT is also not official in any of the pharmacopoeias till now. The published reports focusing on analytical methodologies of DRT are summarized in Table 2.2.

**TABLE 2.2** Summary of reports published on analytical methods of DRT

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2.3. **TOLTERODINE TARTRATE (TOL)** [27-29]

**Structure:**

![Chemical Structure of TOL](image)

**FIGURE 2.3** Chemical Structure of TOL


**Chemical names:**
- 2-[(1S)-3-[bis(propan-2-yl)amino]-1-phenylpropyl]-4-methylphenol;
- (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen Tartrate.

**Empirical formula:** C_{26}H_{37}NO_{7}

**Molecular weight:** 475.6

**CAS No.** : 124937-51-5

**Appearance:** TOL is a white, crystalline powder.

**Solubility:** Solubility in water is 12.0 mg/mL. It is soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene.

**pKa value:** 9.87

**Log P/ Lipophilicity:** 5.6

**Indications:** TOL is indicated for the treatment of overactive bladder (with symptoms of urinary frequency, urgency, or urge incontinence).

**Pharmacological class:** Competitive muscarinic receptor antagonist
**Pharmacokinetics:**

**Absorption:** TOL immediate release capsules are rapidly absorbed and maximum serum concentrations (Cmax) typically occur within 1 to 2 h after dose administration. Cmax and area under the concentration-time curve (AUC) determined after dosage of TOL immediate release are dose-proportional over the range of 1 to 4 mg. Food intake increases the bioavailability of TOL (average increase 53 %), but does not affect the levels of the 5-hydroxymethyl metabolite in extensive metabolizers.

**Distribution:** TOL is highly bound to plasma proteins, primarily α1-acid glycoprotein. The blood to serum ratio of TOL and the 5-hydroxymethyl metabolite averages 0.6 and 0.8, respectively, indicating that these compounds do not distribute extensively into erythrocytes. The volume of distribution of TOL following administration of a 1.28 mg intravenous dose is 113 ± 26.7 L.

**Metabolism:** TOL is extensively metabolized by the liver following oral dosing. The primary metabolic route involves the oxidation of the 5-methyl group and is mediated by the cytochrome P450 2D6 (CYP2D6) and leads to the formation of a pharmacologically active 5-hydroxymethyl metabolite. Further metabolism leads to formation of the 5-carboxylic acid and N-dealkylated 5-carboxylic acid metabolites, which account for 51 % ± 14 % and 29 % ± 6.3 % of the metabolites recovered in the urine, respectively.

**Excretion:** Following administration, 77 % is recovered in urine and 17 % in feces in 7 days. Less than 1 % (<2.5 % in poor metabolizers) of the dose was recovered as intact TOL, and 5 % to 14 % (<1 % in poor metabolizers) was recovered as the active 5-hydroxymethyl metabolite.

**Pharmacodynamics:** TOL is a competitive muscarinic receptor antagonist. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors. After oral administration, TOL is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of TOL, contributes significantly to the therapeutic effect. Both TOL and the 5-hydroxymethyl metabolite exhibit a high specificity for muscarinic receptors, since both show negligible activity and affinity for other neurotransmitter receptors and other potential cellular targets, such as calcium channels. TOL has a pronounced effect on bladder function. The main effects of TOL are an increase in residual urine, reflecting an incomplete emptying of the bladder, and a decrease in detrusor pressure, consistent with an antimuscarinic action on the lower urinary tract. Following
administration of a 5-mg oral dose of 14C-tolterodine solution to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in feces in 7 days.

**Half life:** 1.9-3.7 h

**Protein binding:** Approximately 96.3%.

**Dosage and administration:** The recommended dose of TOL is 4 mg daily. And the formulations of TOL are taken once daily with liquids and swallowed whole. The dose may be lowered to 2 mg daily based on individual response and tolerability 2-4 mg depending upon the need of the patient.
Review of literature on TOL

TOL is available in for public comment in USP as Pending Monograph since 2010 [30]. The published reports focusing on analytical methodologies of TOL are summarized in Table 2.3

**TABLE 2.3** Summary of reports published on analytical methods of TOL

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<td>Basaveswara, Rao M.V. et al.</td>
<td>Drug release method by HPLC for tamsulosin hydrochloride 0.2 % and tolterodine tartrate 0.2% combination pillets. International Journal of Chemical Engineering Research 2009, 1 (2), 155-159.</td>
<td>37</td>
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<tr>
<td>Xia, et al.</td>
<td>An enantiospecific HPLC method for the determination of (S)-</td>
<td>39</td>
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<td>Reference</td>
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2.4. Rationale for selection of the drug candidates

MIL is antidepressant drug belonging to class of SNRI, approved by US FDA in year 2009. Chemically MIL has carboxamide functional group and can undergo cleavage of amide functional group in presence of acid. The literature survey reveals that reports available for estimation of MIL in biological fluids [5, 8-10]. The study about chiral analysis of MIL is also reported [6-7]. One report is published regarding comparative study of estimation of MIL by HPLC and derivative spectroscopy methods. This published report lacks systematic approach for development of stability Indicating Assay method as well as characterization of degradation products of MIL [4]. Hence, MIL was selected for complete degradation study and its correlation with any impurity found in formulations.

DRT is isoquinoline derivative, analogue of papaverine, approved by FDA in India since long time (2002). It acts as an antispasmodic agent by inhibiting phosphodiesterase IV enzyme. Analytical methods like spectrophotometric and HPLC are reported for DRT alone and also in combination with other drugs [13-16, 19-23, 25-26]. Reports for analysis of DRT are also available in presence of other drugs in biological fluid [15]. Pulse voltammetry study and analysis using membrane selective electrodes is also carried out [17, 24]. But so far extensive stability study of DRT, along with nature and origin of degradation products, presence of known and unknown impurities in API, and its formulations of DRT is not reported.

TOL is phenylpropylamine derivative, used in the management of urinary frequency, urgency and incontinence in detrusor instability, approved by USFDA in 1999, and TOL is available as pending monograph for public comment in USP in year 2010 [30]. The reported USP method involves use of gradient programming with cyano column as stationary phase. Other spectroscopic and chromatographic methods are also available for estimation of TOL in combination with other drugs [32, 36-37]. Few reports are also available for stability indicating assay methods of TOL [31, 35, 38-41], but no reports explain the degradation behavior of TOL and characterization of degradation products formed. The nature of origin of listed USP impurities are also not reported for TOL.
Considering lack of information available on systematic study, correlating chemistry of drugs, its degradation behavior, and impurity found in marketed formulations, it was thought to select above mentioned three drugs for detailed stability studies. This data are supposed to be available with the manufactures of drugs (originators) and formulators but are not available in form of scientific publication. As per the regulation and guidelines suggested by WHO [45], by conducting these studies and subsequently providing complete information through scientific publications, the repetitive studies can be avoided by generic manufacturers of same drugs.
2.5. References


