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# Analytical Methods for Estimation of Duloxetine: A Review

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## ABSTRACT

Determination of duloxetine by various methods from various matrices is reviewed in this paper. The methods used consist of spectrofluorimetry, ultraviolet (UV) spectroscopy, thin layer chromatography (TLC), and high-performance liquid chromatography (HPLC). These methods were used to determine the amount of duloxetine in bulk drugs, pharmaceutical dosage forms and biological matrix. HPLC with UV detector as well as mass spectrometric (MS) detector was used for evaluation of pharmacokinetics of duloxetine. It is concluded that HPLC-UV is the most reliable and applicable method for estimation in bulk drugs and formulations while LC-MS is widely employed in bioanalysis.

**Keywords:** duloxetine, analysis, estimation

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# INTRODUCTION

Duloxetine ((3S)-N-Methyl-3-naphthalen-1-yloxy-3-thiophen-2-ylpropan-1-amine) is an antidepressant[1] and a potent inhibitor of norepinephrine transporters and serotonin transporters[2]. Hence, duloxetine is categorized as selective serotonin and norepinephrine reuptake inhibitors (SSNRIs). The blockage of reuptake results in simultaneous increase in concentration of serotonin and norepinephrine at the synapse. This simultaneous increase of both these neurotransmitters potentiates serotonergic and noradrenergic activity in the CNS resulting into antidepressant and analgesic effect.

Duloxetine was initially licensed for treatment of urinary stress incontinence. Later its use was extended to acute and maintenance treatment of major depressive disorder and management of diabetic painful peripheral neuropathy (PPN)[3]. It has also been used for acute management of generalized anxiety disorder. It is also effective in treatment of fibromyalgia[4,5]

Duloxetine is rapidly absorbed following oral administration. Duloxetine is metabolized by the cytochrome P450 isoenzymes CYP2D6 and CYP1A2 to form multiple oxidative and conjugated inactive metabolites. CYP2D6 and CYP1A2, both, catalyze the oxidation of the napthol ring of duloxetine hydrochloride. Metabolites found in plasma include 4-hydroxyduloxetine glucuronide and 5- hydroxy-6-methoxyduloxetine sulfate[6]. These are largely excreted in the urine (72%) and to a lesser extent in faeces (18.5%). Half life of duloxetine is 12 hours. Duloxetine and its metabolites cross the placental barrier and are distributed into breast milk[6].

Duloxetine use in combination with CYP1A2 inhibitors such as quinolone antibiotics and selective serotonin reuptake inhibitors (SSRIs) is contraindicated as they will elevate the plasma concentration of duloxetine[3]. Duloxetine is a CYP2D6 inhibitor leading potential interaction with tricyclic antidepressants and type 1C antiarrhythmics, increasing their plasma levels as these drugs are metabolized by the same enzyme[3].

Mild or moderate nausea, somnolence, dizziness, constipation, dry mouth, sweating, decreased appetite, anorexia and weakness are the adverse effects most commonly observed in the patients using duloxetine[3]

# ANALYTICAL METHODS FOR DULOXETINE:

## I) For estimation in bulk and dosage forms

### A) Spectrometric methods

Prabu SL et al.[7], developed and validated a spectrofluorimetric method for estimation of duloxetine hydrochloride from bulk and dosage forms. Fluorimetric estimation of duloxetine

hydrochloride in 0.05M acetic acid was done using excitation and emission wavelength 225 nm and 340 nm, respectively. The method was linear over the concentration range of 0.020-0.400 µg/mL. The limit of detection and limit of quantitation were 0.003 µg/mL and 0.010 µg/mL, respectively. The percentage recovery ranged from 98.71% to 99.17%.

Kamila MM and coworkers[8] developed an UV spectrophotometric method for assay of duloxetine hydrochloride in raw material and capsules. Absorbance of drug solution was measured at 290nm. The method was accurate, precise and linear over the concentration range of 5-50 µg/mL.

**B) Chromatographic methods**

The high performance thin layer chromatograpy (HPTLC) as well as high performance liquid chromatography (HPLC) have been reported for analysis of duloxetine hydrochloride in bulk and dosage forms.

**i. HPTLC methods**

Patel SK et al.[9] developed simple, selective, precise, and stability-indicating HPTLC method for analysis of duloxetine hydrochloride in formulations. The compound was resolved on aluminum-backed silica gel 60 $F_{254}$ plates with toluene–methanol–10% (v/v) ammonia 3:1.3:0.05 (v/v) as mobile phase. Densitometric evaluation of the spots was carried out at 235 nm. The method was linear over the range of 60-480 ng/ band.

Dhaneshwear SS and coworkers[10] developed and validated HPTLC method for estimation of duloxetine hydrochloride in bulk drug and in tablet dosage form. The chromatographic separation was carried out on precoated silica gel 60 $F_{254}$ plated using chloroform: methanol (8:1) as mobile phase. Densitometric evaluation of the spots was carried out at 235 nm. The method was linear over the range of 600-2000 ng/spot.

Shahnawaz S and coworkers[11] developed and validated a simple, accurate, precise, sensitive, selective, and stability-indicating HPTLC method for determination of duloxetine hydrochloride in bulk drug as well as in tablet formulation. The stationary phase consisted of HPTLC aluminum plates pre-coated with silica gel 60F-254, while, chloroform: methanol (8 : 2, v/v) was used as binary mobile phase. . The method was linear over the range of 40-200 ng/spot.

**ii. HPLC methods**

Boopathy D et al.[12] developed a RP-HPLC method for the simultaneous estimation of duloxetine hydrochloride in enteric coated capsules. An X Terra RP, C-8 column (4.6x150mm) was used for the separation. The mobile phase was acetonitrile: phosphate

buffer (65:35%v/v) (Ph5.3) at a flow rate of 1.0 mL/min with detection at 230nm. Linearity curve was found to be linear over 20 to 120µg/mL.

Chhalotiya UK and coworkers[13] developed a stability-indicating RP-HPLC method for duloxetine hydrochloride in the presence of its degradation products generated from forced decomposition studies. Successful separation of the drug from the degradation products formed under acidic stress conditions was achieved on a Hypersil C-18 column (250 mm × 4.6 mm, 5µ) using acetonitrile: 0.01 M potassium dihydrogen phosphate buffer (pH 5.4 adjusted with orthophosphoric acid) (50:50, v/v) as the mobile phase at a flow rate of 1.0 mL/min. Quantification was achieved with photodiode array detection at 229 nm over the concentration range 1–25 µg/mL with range of recovery 99.8–101.3 % for DUL by the RP-HPLC method.

Bhimanadhuni CN and coworkers[14] developed a RP-HPLC method for determination of duloxetine hydrochloride in bulk and dosage form. The separation was effected on a Kromasil ODS C18 column (250mm × 4.6mm, 5µ) using a mobile phase mixture of buffer and methanol in a ratio of 85:15 v/v at a flow rate of 1.0mL/min. The detection was made at 230nm. Calibration curve was linear over the concentration range of 20-120 µg/mL of duloxetine hydrochloride.

Patel SK et al.[15] developed a RP-HPLC method for estimation of duloxetine hydrochloride in pharmaceutical formulations. Separation was achieved on Phenomax C-18 (250mm × 4.6 mm, 5 µ) using mobile phase containing 0.01 M phosphate buffer pH5.5: acetonitrile (60:40 v/v). The flow rate was 1.2 mL/min and effluent was monitored at 231 nm. The linearity curve was found to be linear over 0.25-4 µg/mL.

Srinivasulu P et al.[16] reported a reversed phase HPLC method for analysis duloxetine hydrochloride in presence of its impurities and degradation products generated from forced decomposition. Separation of the drug from the synthetic impurities and degradation products formed under stress conditions was achieved on Zorabax XDB C18 (50 mm x 4.6 mm, 5.0 µ) column using a mixture of aqueous 0.1% trifluroacetic acid, methanol, tetrahydrofuran (60:20:20 v/v/v) as mobile phase.

Sinha VR and coworkers[17] developed a stability indicating reversed phase HPLC method for duloxetine hydrochloride. Separation was achieved on C-8 column at $40^0$C using phosphate buffer (pH 2.5)-methanol-tetrahydrofuran (50:40:10 v/v/v) as mobile phase at a flow rate fo 1 mL/min. The detection wavelength was 232 nm. The method was linear over a concentration range of 1-100 µg/mL.

Reddy BP[18] developed a simple, selective, accurate reverse phase high performance liquid chromatography (RP-HPLC) for estimation of duloxetine hydrochloride in pharmaceutical formulations. Chromatographic separation achieved on a Kromasil C18 (250mm × 4.6 mm, 5µ) with mobile phase containing 0.5M TFA buffer: acetonitrile (65:35 v/v) and final pH adjust to 5.5±0.02 with phosphoric acid was used. The flow rate was 1mL/min and effluent was monitored at 232 nm. The method was validated in terms of linearity, accuracy and precision. The linearity curve was found to be linear over 0.25-4 µg/mL. The limit of detection and limit of quantification were found to be 2.44 and 8.16 ng/mL, respectively.

Raman NVVSS et al.[19] developed and validated a stability-indicating gradient reverse phase liquid chromatographic purity and assay method for duloxetine hydrochloride. Duloxetine hydrochloride was subjected to the stress conditions and it is sensitive towards oxidative, acid and hydrolytic degradation. Successful separation of duloxetine hydrochloride from its two process impurities and one degradation impurity formed under stress conditions was achieved on a Symmetry C18 (250mm × 4.6mm, 5µ) column using a gradient mixture of solvent A (0.01M potassium dihydrogen orthophosphate having 0.2% triethyl amine, pH adjusted to 2.5 with orthophosphoric acid) and solvent B (20:80 v/v mixture of acetonitrile and methanol). The flow rate was 1 mL/min and the detection wavelength is 230 nm.

Kumar Nand coworkers[20] developed a rapid, sensitive and specific reverse phase ultra-performance liquid chromatography (UPLC) method for quantitative determination of duloxetine in cleaning validation swab samples. Method was validated using an Acquity UPPLC HSS T3 (100mm × 2.1 mm, 1.8 µ) column with a mobile phase containing a mixture of 0.01M potassium dihydrogen orthophosphate pH 3.0 and acetonitrile (60:40 v/v). The flow rate of the mobile phase was 0.4 mL/min with a column temperature of $49^0$C and detection wavelength at 230 nm. Calibration curve was linear over the concentration range of 0.02-5.0 µg/mL.

Dahivelkar PP and coworkers[21] studied hydrolytic and oxidative behavior of duloxetine in aqueous solution using HPLC and developed a stability-indicating HPPLC method for use in drug development and testing laboratory for the quality control of duloxetine. The products formed under different stress conditions were separated on a Phenomenax C8 (250mm × 4.6 mm) chromatographic column with mobile phase composed of Methanol: 0.05M phosphate buffer pH 3.5 (60:40 v/v) pumped at 1 mL/min. The drug was

monitored at 289 nm. The proposed method was linear in the concentration range of 4-24 µg/mL with correlation coefficient of r=0.9996.

**II) For estimation from biological matrices**

Ma N et al.[22] developed and validated a rapid and sensitive liquid chromatography – mass spectrometric (LC/MS) method for determination of duloxetine in human plasma using flupenthixol as an internal standard. Sample preparation of the plasma involved deprotination with acetonitrile followed by high performance liquid chromatography using Thermo Hypersil–Hypurity C18 column (150 × 2.1 mm, 5 µ). Compounds were eluted up to a total retention time of 3 min using an isocratic mobile phase consisting of acetonitrile: methanol: 20 mmol/l ammonium acetate pH 3.5 (42:20:38, v/v/v) at 0.24 mL/min, and the injection volume was 10 µL. The single quadrupole mass spectrometer was operated in the positive ionization mode with single ion monitoring (SIM) m/z 298 for duloxetine and 435 for flupentixol.

Satonin DK et al.[23] reported a sensitive bioanalytical method for the determination of two major metabolites of duloxetine (4-hydroxy Duloxetine glucuronide (LY550408) and 5-hydroxy-4-methoxy Duloxetine sulphate (LY581920)) in plasma using liquid chromatography – tandem mass spectrometric method. HPLC separation for both analytes was achieved with an Aquasil C18 column (150mm × 2 mm, 5µ). The solvent system for the LY550408 analysis consisted of an isocratic flow with a mobile phase of water/acetonitrile/formic acid (80/20/0.1, v/v/v). For the analysis of LY581920, the mobile phase consisted of water/acetonitrile/acetic acid (70/30/0.05, v/v/v). For both analytes the flow rate was 0.3 mL/min and the column temperature was approximately 22 ◦C. For the LY550408 analyte and IS, selected reaction monitoring (M +H)+ transitions *m/z* 490→154 and *m/z* 494→158 were monitored, respectively.

Johnson JT et al.[24] developed and validated a high performance liquid chromatographic method for duloxetine and desmethyl duloxetine in human plasma. The human plasma was adjusted to pH 10 with 1.0 M sodium carbonate and extracted with hexane which contained 2% isopropylalcohol. The concentrated extract was derivatized with dansyl chloride (500 µg/mL) and was separated using Phenomenex Primesphere 5 $C_{18}$ HC column followed by fluorescence detection with excitation and emission wavelength at 285 nm and 525 nm respectively.

Selvan PS et al.[25] described a rapid, sensitive and accurate liquid chromatographic–tandem mass spectrometry (LC–MS–MS) method for the determination of duloxetine in human plasma. Duloxetine was extracted from plasma using methanol and separated on a C18 column. The mobile phase consisting of a mixture of acetonitrile and 5 mM ammonium acetate (45:55, v/v, pH 3.5) was delivered at a flow rate of 0.3 mL/min. Atmospheric pressure ionization (API)

source was operated in positive ion mode. Multiple reaction monitoring (MRM) mode using the transitions of *m*/*z* 298.1 → *m*/*z* 44.0 and *m*/*z* 376.2 → *m*/*z* 123.2 were used to quantify duloxetine and internal standard (I.S.), respectively. The linearity was obtained over the concentration range of 0.1–50.0 ng/mL and the lower limit of quantitation (LLOQ) was 0.1 ng/mL. This method was successfully applied to pharmacokinetic study of a duloxetine formulation product after oral administration to healthy human subjects.

Mercolini L et al.[26] developed a rapid and sensitive high-performance liquid chromatographic method for duloxetine analysis in human plasma. The assays were carried out using a C8 reversed-phase column and a mobile phase composed of 60% aqueous phosphate buffer containing triethylamine at pH 3.0 and 40% acetonitrile. The UV detector was set at 230 nm and loxapine was used as the internal standard. Pre-treatment of plasma samples was done using solid-phase extraction (SPE) with mixed-mode reversed phase—strong cation exchange cartridges (30 mg, 1 mL). The extraction yields values were higher than 90%. Linearity was found in the 2–200 ng/mL duloxetine concentration range; the limit of quantitation was 2.0 ng/mL and the limit of detection was 0.7 ng/mL.

Malfara WR et al.[27] reported a high-performance liquid chromatographic method for the determination of 10 frequently prescribed tricyclic and nontricyclic antidepressants: imipramine, amitriptyline, clomipramine, fluoxetine, sertraline, Paroxetine, citalopram, mirtazapine, moclobemide and duloxetine. The simple and accurate sample preparation step consisted of liquid: liquid extraction with recoveries ranging between 72% and 86%, except for moclobemide (59%). Separation was obtained using a reverse phase Select B column under isocratic conditions with UV detection (230 nm). The mobile phase consisted of 35% of a mixture of acetonitrile/ methanol (92:8, v/v) and 65% of 0.25M sodium acetate buffer, pH 4.5. The standard curves were linear over a working range of 2.5–1000 ng/mL for moclobemide, 5–2000 ng/mL for citalopram, duloxetine, fluoxetine, 10–2000 ng/mL for sertraline, imipramine, paroxetine, mirtazapine and clomipramine.

Choong E et al.[28] developed and validated a simple and sensitive LC–MS method for the simultaneous quantification of aripiprazole, atomoxetine, duloxetine, clozapine, olanzapine, sertindole, venlafaxine and their active metabolites dehydroaripiprazole, norclozapine, dehydrosertindole and O-desmethylvenlafaxine in human plasma. The above mentioned compounds and the internal standard (remoxipride) were extracted from 0.5mL plasma by solid-phase extraction (mix mode support). The analytical separation was carried out on a reverse phase liquid chromatography at basic pH (pH 8.1) in gradient mode. All analytes were monitored

by MS detection in the single ion monitoring mode and the method was validated covering the corresponding therapeutic range.

Musenga A et al.[29] developed a method based on capillary electrophoresis for the analysis of the novel antidepressant drug duloxetine in human plasma. The method used laser-induced fluorescence detection after derivatisation of the analyte with 5-(4,6-dichlorotriazinyl)amino fluorescein at pH 11. A single step liquid/liquid extraction procedure with a mixture of hexane/2-propanol allowed the sample clean-up with extraction yields always ≥84% and interference removal. The electrophoretic separation was achieved using uncoated fused silica capillaries (60.0cm effective length, 75.0cm total length, 50µm internal diameter) and a background electrolyte composed of borate buffer (40mM, pH 10.3), tetrabutylammonium bromide (10 mM), and acetone (10%, v/v). The applied voltage was 20 kV and the samples were injected by pressure (50 mbar × 8 s).

Samanidou VF and a co-scientist[30] developed a simple and rapid HPLC method for the determination of two serotonin–norepinephrine-reuptake inhibitors (duloxetine and venlaflaxine) and two selective serotonin-reuptake inhibitors (fluoxetine and paroxetine) in human biofluids. Separation was performed on an Inertsil ODS-3 column (250 x 4.0 mm, 5 µm) with acetonitrile–ammonium acetate (0.05 M, 41:59 v/v) at 235 nm, within 7 min. SPE on Oasis® HLB cartridges was applied for the isolation of analytes from biofluids. Limit of detection was 0.2–0.6 ng/µL in blood plasma and 0.1–0.8 ng/µL in urine.

## CONCLUSION

It has been found that HPLC-UV is the most used and reliable method for the determination of duloxetine hydrochloride in bulk as well as dosage forms while LC-MS and LC-MS/MS are the widely used techniques for estimation of duloxetine from plasma and other biological fluids to determine its pharmacokinetics as well as for bioavailability and bioequivalence studies.

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