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# Novel enantioselective synthesis and dissolution studies on enteric coated pellets of (*S*)-duloxetine hydrochloride

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The enantioselective hydrogenation of 2-bromo-1-(thiophen-2-yl)ethanone and further elaboration of the cyclic carbamate derived from γ-aminoalcohol to provide a facile synthesis of (*S*)-duloxetine, a potent dual inhibitor of serotonin and norepinephrine reuptake, is described. Enteric coated pellets with polymer load of 25% and 30% failed to provide the required acid resistance of the pellets. Very insignificant amount of drug was leached from the coated tablets with polymer load 35% and 40% in the acidic phase, whereas almost the whole amount of drug was released in the buffer phase. The results generated in this study showed that the proper selection of polymeric materials based on their physicochemical properties, as well as the polymer load is important in designing delayed release pellets dosage form with acceptable dissolution profile.

**Keywords**: Enantioselective synthesis, Eudragit L30 *D* 55, duloxetine hydrochloride, enteric coated pellets, powder layering.

## INTRODUCTION

Duloxetine, a medication with effects on both serotonin and noradrenaline transporter molecules, has recently been approved for the treatment of generalized anxiety disorder. Serotonin and norepinephrine neurotransmitters are intimately involved in a number of neurochemical and physiological processes, such as depression and pain disorders. Selective serotonin or norepinephrine reuptake inhibitors are currently an important class of antidepressants, which includes fluoxetine, nisoxetine, tomoxetine, and duloxetine [1]. They have been already approved as racemates, but some of them are since being redeveloped as 'chiral switches' derived from the established racemates [2]. While fluoxetine and nisoxetine are currently available as racemates, (*S*)-duloxetine [(*S*)-*N*-methyl-3-(1-naphthyloxy)-3-(2-thienyl)-1-propanamine] has gained acceptance in the market because it inhibited serotonin reuptake in rat synaptosomes two times more potently than the (*R*)-enantiomer [3]. The (*S*)-duloxetine, a dual inhibitor of both serotonin and norepinephrine reuptake, is effective for the treatment of major depressive disorders and is being considered for treatment of stress-related urinary incontinence. Several different approaches have been reviewed for the synthesis of duloxetine as a racemate or an enantiomerically enriched form [4]. However, there are only a few reports on the asymmetric and catalytic synthesis of duloxetine. One of the methods employs asymmetric reduction of β-aminoketone or α-cyanoketone/ β–chloroketone with a chirally-modified LAH complex [5] or an oxazaborolidine-catalyzed borane, respectively [6]. The other involves chemoenzymatic synthesis, for the most part, lipase-mediated resolution of β–cyano-, γ–chloro–, and γ–azidoalcohols [7].

Recently, the application of asymmetric-transfer hydrogenation has been extended to enantioselective hydrogenation of unsaturated carbonyl and imine groups [8]. The asymmetric-transfer hydrogenation, rather, offers operational simplicity, since the reaction does not involve molecular hydrogen and is insensitive to air oxidation, and thus is particularly valuable in scale-up syntheses of active pharmaceutical ingredients. In continuation of our earlier efforts towards the preparation of biologically important compounds, particularly possessing a chiral aminoalcohol unit [9] we herein report asymmetric-transfer hydrogenation of 2-tosyloxy-1-(2-thiophenyl) ethanone and further elaboration of a cyclic carbamate to access the facile synthesis of duloxetine.

The enteric film coat is a special film coat designed to resist gastric fluids and disrupt or dissolve in small intestine. The enteric coat is used to protect drug from degrading in stomach or to minimize the gastric distress caused by some drugs. Enteric coated pellets must empty from stomach

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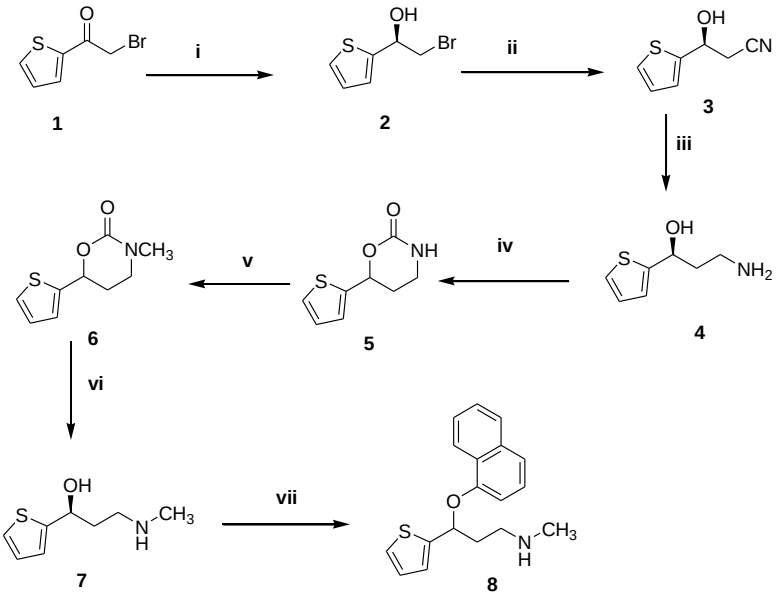
before absorption begins. The rate of appearance of blood after giving the enteric coated tablets is the function of gastric emptying. The differences in the gastric emptying from one patient to another or in the same patient with different administration were found to be largely variable in absorption commonly found in this dosage form. The enteric coated tablets approximately require 0.8 to 5 h to travel from stomach to duodenum but enteric coated pellets dispersed in the stomach pass through pyloric sphincter after a mean residence time in the stomach similar to that of a suspension dosage form [10]. The synthesized (*S*)-duloxetine hydrochloride was formulated as enteric tablets and was evaluated for various characteristics including dissolution rate. The possibility of increasing the dissolution rate of duloxetine through formulated enteric coated pellets was investigated.

## RESULTS AND DISCUSSION

The starting material, 2-bromo-1-(thiophen-2–yl) ethanone **1** was prepared by photochemical reaction of n-bromo succinamide in carbon tetrachloride in the presence of catalytic amount of benzoyl peroxide. The catalytic reaction of **1** (substrate/catalyst molar ratio 500) with Cp*RhCl[(*S*,*S*) –TsDPEN] [11] where Cp* = pentamethylcyclopentadienyl, was effectively performed with an azeotropic mixture of formic acid/triethylamine (molar ratio 5/2) in ethyl acetate to produce (*S*) –2–tosyloxy–1– (2-thiophenyl)ethanol **2**, $[\alpha]_D^{27}$ = –31.3 (*c* 1.08, $CHCl_3$), in 95% yield with 95% *ee*. It should be noted that the observed enantioselectivity was similar to that reported for the corresponding α-chloroketone [12] and thus represented a first successful application of α-tosyloxy heteroaryl ketone in transfer hydrogenation with high enantioselectivity. The *ee* value was measured by chiral HPLC analysis using Daicel Chiralcel OD-H column. The racemic alcohol (±)–**2** was prepared by sodium borohydride reduction of **1** in THF, and was used as a standard for *ee* determination.

In turn, most approaches to the synthesis of *N*-methylamine **7** routinely adopted lithium aluminum hydride reduction in refluxing THF of the ethyl carbamate derived from the aminoalcohol **4** with ethyl chloroformate, or mono-demethylation of the reduced Mannich product with 2,2,2-trichloroethyl formate with Zn in toluene. In order to circumvent these harsh conditions, we supposed that the formation of a cyclic carbamate [13] would offer a facile route to the introduction of an *N*-methyl group into the γ-aminoalcohol, as shown in Scheme 1. It was ambitioned that the required aminoalcohol **4** can be easily prepared from the tosylate **2**, a versatile chiral building block. Thus, the tosylate (*S*)-**2** was readily converted into the nitrile **3** without loss of chirality, $[\alpha]_D^{20}$ = –39.7 (*c* 0.45, $CHCl_3$); lit.[7b] $[\alpha]_D^{30}$ = -33.5 (*c* 1 , $CHCl_3$), by the treatment of sodium cyanide in DMSO. Subsequently, the nitrile **3** was reduced with borane-dimethyl sulfide in refluxing THF to give the γ-aminoalcohol which was directly cyclized using *N*,*N*-carbonyldiimidazole (CDI) in the presence of catalytic amount of DMAP to obtain the corresponding cyclic carbamate **5** in 71% yield for the two steps. Indeed, this allowed a facile introduction of the *N*-methyl group, by the treatment of methyl iodide with sodium hydride in THF to give the *N*-methyl oxazinanone **6**. Hydrolysis of the oxazinanone **6** by refluxing with lithium hydroxide in aqueous methanol afforded the aminoalcohol **7**. The final installation was then carried out by nucleophilic aromatic substitution with 1-fluoronaphthalene by means of sodium hydride in DMSO to afford (*S*)-duloxetine **8** in 78% yield with 95% *ee* [14]. Duloxetine hydrochloride powder, mannitol and disodium hydrogen phosphate were blended and sieved through 250 micron screen mesh to prepare dusting powder. Disodium hydrogen phosphate and sodium hydroxide were dissolved in purified water. HPMC 5 cps was then dispersed using a stirrer to prepare the binding solution. NPS (710 micron – 1.0 mm) was taken in a conventional coating pan and dusting powder was applied on it. The pan rotated at 40 rpm and simultaneously binding solution was sprayed onto the NPS. After completion of drug loading, the nuclei were dried in an oven at 100ºC for 5 h. The dried nuclei were sieved in a 1.18 mm screen mesh followed by 850 mm screen mesh to get the desired size (850 micron to 1.18 mm). The under- and oversized nuclei were discarded. Seal coating suspension was prepared containing HPMC 5 cps, PEG–6000, titanium dioxide, sodium hydroxide pellets with the use of a Silverson stirrer (UK). The dried uncoated nuclei were taken in a fluid bed coater and seal coating suspension was sprayed onto it. The sealed coated pellets were dried at 600ºC for 3 h. Dried seal coated pellets were sieved through 1.18 mm and 850 micron to get 850 micron to 1.18 mm seal coated pellets. Under- and oversized nuclei were discarded. Enteric coated suspension was prepared by Eudragit L 30 D 55 (ammonium methacrylate




**Scheme 1**. Asymmetric synthesis of (S)-duloxetine. Reagents and conditions: i) 10 mmol of 1 (S/C=500), Cp*RhCl[(S,S)-TsDPEN], $HCO_2H/Et_3N$ (molar ratio 5/2, 2 ml), EtOAc, 3h, 95%, 95%ee; ii) NaCN, DMSO, 20h, 88%; iii) $BH_3SMe_2$, THF, reflux, 2h; iv) CDI, cat. DMAP, $CH_2Cl_2$, 8h, 71% (for 2 steps); v) MeI, NaH, THF, ice-bath, 6h, 89%; vi) LiOH, MeOH-$H_2O$, relux, 8h, 84%; vii) 1-fluoronaphtalene, Nah, DMSO, 8h, 78%.

copolymer dispersion), talc, triethyl citrate, titanium dioxide and purified water with the use of a Silverson stirrer. The seal coated pellets were coated using lab coater with Eudragit L 30 D 55 to a thickness equivalent to a theoretical polymer load of 25%, 30%, 35% and 40% w/w on dry basis.

**Table 1.** Composition of nuclei and seal coated pellets (weights are expressed in grams)

| Nuclei | Quantity | Seal coating | Quantity |
|---|---|---|---|
| Duloxetine hydrochloride | 256.24 | Nuclei | 800.00 |
| Disodium hydrogen phosphate | 5.53 | HMPC | 50.42 |
| HMPC | 38.30 | PEG-6000 | 6.824 |
| Mannitol | 21.56 | Sodium hydroxide pellets | 0.060 |
| Sodium hydroxide pellets | 0.452 | Titanium dioxide | 10.48 |
| NPS | 677.90 | Weight of seal coated pellets | 836.00 |
| Weight of nuclei | 920.00 | Potency of seal coated nuclei | 23.00 |
| Potency of nuclei | 25.30 | | |

The enteric coated pellets were dried in a fluid bed coater at 600ºC for 5 h and then sieved through 1.40 mm and 850 micron mesh to get 850 micron - 1.40 mm size enteric coated pellets by discarding under- and oversized pellets. In this way all lots of pellets were coated according to the formula for F-1 to F–4 (Table 2). The compositions of nuclei and seal pellets are shown in Tables 1 and 2. Machine parameters during fluid coating are shown in Table 3.

**Table 2**. Codes and formulation of duloxetine enteric coated tablets

| Materials | Formulation codes | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| Seal coated pellets | 200.00 | 200.00 | 200.00 | |
| Sodium hydroxide pellets | 0.590 | 0.702 | 0.826 | 0.942 |
| Titanium dioxide | 2.250 | 3.024 | 3.524 | 4.212 |
| Methacrylic acid copolymer dispersion | 166.67 | 200.00 | 233.23 | 265.65 |
| Purified talc | 1.889 | 2.645 | 2.657 | 3.021 |
| Triethyl dispersion | 8.062 | 9.673 | 11.28 | 12.900 |
| Weight of the enteric coated pellets | 237.00 | 240.00 | 256.34 | 266.43 |
| Potency of enteric coated pellets | 17.52 | 16.72 | 15.75 | 15.23 |

**Table 3**. Machine parameters during fluid bed coating

| Parameters | Fluid bed coating | |
|---|---|---|
| | Seal coating | Enteric coating |
| Batch size | 800 g | 200 g |
| Inlet air temperature | 40-45ºC | 40-45ºC |
| Outlet air temperature | 30-35$^0$C | 30-35$^0$C |
| Product temperature | 37-40ºC | 37-40ºC |
| Chamber humidity | 55%-60% | 55%-60% |
| Air flow | 90m$^3$/h | 90m$^3$/h |
| Spraying pressure | 1.20 bar | 1.20 bar |
| Spraying rate | 2.0 g/min | 3.0 g/min |
| Secondary drying | 60$^0$C /180 min | 60$^0$C /300 min |

## EXPERIMENTAL

The dissolution of duloxetine hydrochloride enteric coated pellets was studied in a dissolution tester (En/veka, Germany) using USP apparatus ll

(Paddle method). An appropriate amount of duloxetine hydrochloride enteric coated pellets containing 20 mg of duloxetine in total was used in 900 ml of dissolution medium (0.1 N hydrochloric acid) at 370ºC and 100 rpm for 2 h. After 1 h 25 ml sample was withdrawn from each vessel and was replaced with fresh medium so that the volume remains constant. At the end of the 2nd h 25 ml sample was withdrawn from each vessel. The drug content of the sample solution, i.e., the quantity of drug release was determined by high-performance liquid chromatography (HPLC) method. Then by replacing the acid medium after the 2nd h, 900 ml of dissolution medium ($KH_2PO_4$ buffer, pH 6.8) was added in each vessel. Then again the machine was operated at a rotation of 100 rpm at 370ºC for the next 1 h. Thereafter 25 ml sample was withdrawn from each vessel. After appropriate dilution, the drug content of the collected samples, i.e., the quantity of drug release was determined by HPLC method. The HPLC system consisted of a pump (Waters, USA), an auto sampler (Waters), and a UV detector (Waters). The reverse-phase column (C18) O(terra, 5 pm, 4.6 mm × 25 cm, Waters) was used at ambient temperature. The mobile phase consisted of acetonitrile (40%) and the flow rate was 1 ml/min. The injection volume was 20 pl and the signal was observed at 218 nm.

The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (230–400 mesh). Melting points were measured on an Electrothermal apparatus and were uncorrected. NMR spectra were recorded at 300 MHz for $^1$H and at 75 MHz for $^{13}$C. Mass spectra were recorded on a GC/MS operating system at an ionization potential of 70 eV. Optical rotations were measured on a high resolution digital polarimeter. The *ee* values of the samples were determined by HPLC analysis using Daicel Chiralcel OD–H chiral column.

### *(*S*)-Duloxetine (8)*

To a solution of **7** (171 mg, 1 mmol) in DMSO (5 ml), were added sodium hydride (36 mg 1.5 mmol) and then 1-fluoronaphthalene (190 mg, 1.3 mmol). After stirring for 8 h, the reaction mixture was partitioned with ethyl acetate and water. After extractive workup, the combined organic layers were dried over sodium sulfate and then concentrated *in vacuo*. The residue was purified by flash chromatography (ammonium hydroxide/ methanol/ dichloromethane, 0.1/1/4) to yield 232 mg (78%) of **8**: $^1$H NMR (300 MHz, $CDCl_3$) δ 8.37-8.33 (m, 1H), 7.79-7.74 (m, 1H), 7.50-7.44 (m, 2H), 7.39-7.37 (m, 1H), 7.28-7.18 (m, 2H), 7.05-7.04 (m, 1H), 6.93-6.90 (m, 1H), 6.86-6.84 (m, 1H), 5.78 (dd, 1H, *J* 7.6 and 5.3 Hz ), 2.86–2.78 (m, 2H), 2.50–2.39 (m, 4H), 2.27–2.16 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 153.3, 145.2, 134.5, 127.4, 126.5, 126.2, 126.1, 125.7, 125.2, 124.6, 124.5, 122.1, 120.5, 106.9, 74.7, 48.3, 39.0, 36.5; EIMS (70eV) *m/z* (rel. intensity) 297 ($M^+$, 4), 187 (80), 153 (69), 144 (100); $[\alpha]^{20}_D$ = +110.5 (*c* 1.1, MeOH); lit. [7b] $[\alpha]^{30}_D$ = +114 (*c* 1, MeOH); lit.[15b] $[\alpha]^{20}_D$ = +112 (*c* 1, MeOH); HPLC analysis: 95% *ee* (Chiralcel OD-H, hexane/Pr$^i$OH, 85/15, 0.5 ml/min; $t_R$ (*S*) 18 min, $t_R$ (*R*) 25 min.

## CONCLUSION

The (*S*)-duloxetine hydrochloride was successfully synthesized using enantioselective hydrogenation of 2-bromo-1-(thiophen-2-yl)ethanone and further elaboration of cyclic carbamate derived from γ-aminoalcohol. Duloxetine hydrochloride loaded pellets were prepared by powder-layering technology. Acid resistant coating with acrylic polymer was done using fluid bed coater at different coating loads and the *in vitro* release of drug was investigated. The release of drug was found to be a function of polymer load. The results indicated that it is possible to prevent the release of drug in the upper GI tract where the environment is acidic and the release of drug in the intestinal region by developing a multiparticulate system coated with suitable pH dependent polymer.

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# НОВА ЕНАНТИОСЕЛЕКТИВНА СИНТЕЗА И РАЗТВАРЯНЕ НА ФИЛМОВИ ТАБЛЕТКИ ОТ (*S*)-ДУЛОКСЕТИН ХИДРОХЛОРИД С ЕНТЕРО-ПРИЛОЖЕНИЕ

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(Резюме)

Описано е енантиоселективното хидриране на 2-бромо-1-(тиофен-2-ил)етанон и следващото третиране с цикличен карбамат, получен от γ-аминоалкохол за получаването на (*S*)-дулоксетин. Последният е потенциален двоен инхибитор за резорбцията на серотонин и норепинефрин. Таблетките с ентеро-приложение и филмово покритие от 25 и 30% полимер нямат нужната устойчивост в кисела среда. Незначително количество от лекарството се освобождава от таблетките при съдържание на полимера от 35% до 40% в кисела среда, докато почти цялото количество лекарство се освобождава в среда на буфер. Получените резултати показват, че подходящият избор на полимерния материал, основан на физико-химичните му свойства, както и количеството му са важни за създаването на таблетки със забавено освобождаване с приемлив профил на разтваряне.