Available online at www.elixirpublishers.com (Elixir International Journal)

Pharmacy

Elixir Pharmacy 52 (2012) 11376-11380

ISSN: 2229-712X

Synthesis, formulation and characterization of physico-chemical property and dissolution of enteric coated pellets of (*s*)-duloxetine hydrochloride

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ARTICLE INFO

Article history:

Received: 14 September 2012;

Received in revised form:

30 October 2012;

Accepted: 8 November 2012;

Keywords

Duloxetine Hydrochloride,

Enteric Coated Pellets,

Solubility,

Dissolution, Stability.

ABSTRACT

Duloxetine, a medication with effects on both serotonin and noradrenaline transporter molecules, has recently been approved for the treatment of generalized anxiety disorder. Thus, the aim of the present study was to synthesis and formulates enteric coated pellets for delayed release and to characterise the physico-chemical property and dissolution. Duloxetin was prepared by photochemical reaction of n-bromo succinamide in carbon tetra chloride in the presence of catalytic amount of benzoyl peroxide. The prepared Duloxetine hydrochloride powder was then blended with mannitol and disodium hydrogen phosphate and sieved through 250 micron screen mesh to prepare dusting powder. It is then formulated as pellets which were seal coated by HPMC 5 cps. Further this seal coated pellets were enteric coated by using Eudragit L 30 D 55 (ammonio methacrylate copolymer dispersion), talc, triethyl citrate, titanium dioxide and purified water with the use of silversten stirrer (UK). The prepared formulations were characterized by scanning electron microscopy, differential scanning calorimeter, X-ray diffraction and Fourier transform infrared spectroscopy. Dissolution profile of the enteric coated pellets was compared with its recrystallized sample and pure sample. The samples were stored in stability chamber to investigate their physical stability. In stability test, the release profile of the pellets was almost unchanged as compared with the freshly prepared pellets stored at 40 ^{0}C and 75% relative humidity for 90 days. Hence these pellets can be formulated for giving Duloxetine hydrochloride as a delayed released formulation.

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]. The (*S*)-duloxetine, a dual inhibitor of both serotonin and norepinephrine reuptake, is effective for the treatment of major depressive disorder 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. However, there are only a few reports on the asymmetric and catalytic synthesis of duloxetine. One of the methods employs an asymmetric reduction of β-aminoketone or α-cyanoketone/ β-chloroketone with a chirally-modified LAH[2] complex or an oxazaborolidine-catalyzed borane[3] respectively. The other involves the chemoenzymatic synthesis, for the most part, lipase-mediated resolution of β-cyano-, γ-chloro-, and γ-azidoalcohols[4].

Duloxetine Hydrochloride is an anti-depressant drug. The degradation of this anti-depressant drug in the acidic environment of stomach leads to sub therapeutic levels. In order to avoid this degradation and to bypass the acidic pH of the stomach, one of the proven approaches is formulation of delayed release dosage forms (single unit or multiple units) by using different enteric polymers. The enteric coat film coat is a special film coat designed to resist gastric fluids and disrupt or dissolve in small intestine. Enteric coated pellets must empty from stomach 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 found to be large variability in absorption commonly found in this dosage form. The enteric coated tablets approximately require 0.8 to 5hrs to travel from stomach to duodenum but enteric coated pellets dispersed in the stomach and pass through pyloric sphincter after a mean residence time in the stomach similar to suspension dosage form[5]. The synthesized (*S*)-duloxetine hydrochloride was formulated as enteric pellets and evaluated for various characteristics including dissolution rate. Enteric-coated pellets get dispersed in the stomach and pass through the pyloric sphincter after a mean residence time in the stomach that is similar to a suspension dosage form hence they act faster than tablets which get released from stomach as such and get disintegrate only when it reach intestine and then get dissolved hence this usually take around 3 to 4 hours to get absorbed[6]. The possibility of increasing the dissolution rate of duloxetine through formulated enteric coated pellets was investigated.

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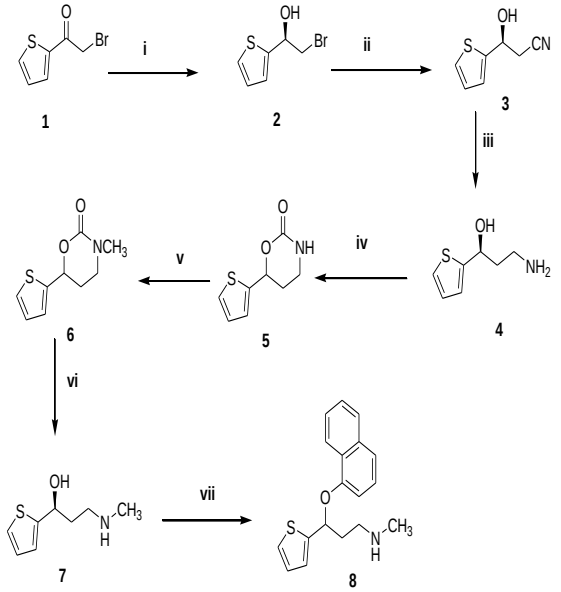
The objective of the present study was to synthesis duloxetine hydrochloride and to formulate enteric coated pellets of duloxetine hydrochloride which was evaluated for solvents residual and DSC, FT-IR, XRD, and SEM analysis to determine the physicochemical properties of the pellets and compare with recrystallized sample and pure drug and determined the solubility and dissolution characteristics of the duloxetine pellets and investigate their physical stability in a climate chamber at 40^0C and 75% relative humidity (RH) for 90 days.

Materials and Methods

Synthesis of (S)-Duloxetine hydrochloride powder

Doluxetine hydrochloride powder was synthesized by using 2-bromo-1-(thiophen-2-yl)ethanone as starting material. It was treated with Cp*RhCl[(*S*,*S*)-TsDPEN] [11] where Cp* = pentamethylcyclopentadienyl, in presence of an azeotropic mixture of formic acid/triethylamine (molar ratio 5/2) in ethyl acetate which finally gave enantioselectivity product that is (S)-Duloxetine hydrochloride. The following scheme represent the synthesis of (S)-Duloxetine hydrochloride.



Scheme 1. Asymmetric synthesis of (S)-duloxetine. Reagents and conditions: i) 10 mmol of 1 (S/C = 500), Cp*RhCl[(S,S)-TsDPEN], HCO2H/Et3N (molar ratio 5/2, 2 ml), EtOAc, 3h, 95%, 95% ee; ii) NaCN, DMSO, 20h, 88%; iii) BH3·SMe2, THF, reflux, 2h; iv) CDI, cat. DMAP, CH2Cl2, 8h, 71% (for 2 steps); v) MeI, NaH, THF, ice-bath, 6h, 89%; vi) LiOH, MeOH-H2O, reflux, 8h, 84%; vii) 1-fluoronaphthalene, NaH, DMSO, 8h, 78% .

Formulation of pellets

(S)-Duloxetine hydrochloride powder formed was blended with mannitol and disodium hydrogen phosphate and passed through sieve of 250 micron screen to form dusting powder. This was then coated with HPMC in coating pan to form seal coat and then with coated with Eudragit L 30 D 55 to form enteric coated pellets.

Differential scanning calorimetry (DSC)

A DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer.

Fourier transform infrared (FTIR) spectroscopy

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). About 2 pellets (which were crushed completely) , pure drug and only excipients were used separately. Pure drug, excipients and crushed pellet sample were dispersed in KBr powder and the pellets were made by applying 6000 kg/cm^2 pressure.

X-ray analysis

X-Ray powder diffraction patterns were used to detect possible polymorphic transition during the crystallization process. X-Ray powder diffraction patterns were obtained at room temperature using a Philips X' Pert MPD diffractometer, with Cu as anode material and graphite monochromator, operated at a voltage of 40 mA, 45 kV.

Scanning electron microscopy (SEM)

Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 100x) photographs were obtained to identify and confirm spherical nature and morphological characters of the crystals.

Solubility studies of Pellets

The solubility of pellets in water and pH 7.2 Phosphate buffer was determined by taking known number of pellets and adding to screw- capped 50 ml glass vials filled with water. The vials were shaken for 24 hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and the drug concentration was determined spectrophotometrically at 218 nm[7].

Dissolution studies of crystals

The dissolution of Duloxetine hydrochloride pure sample and pellets was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium (900ml) consisted of 7.2 Phosphate buffer was used and 10 ml of dissolution medium was withdrawn at every 10 min interval for 1 h. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 218 nm[7].

Determination the physical stability

To determine the physical stability pellets were placed in a climate chamber of 40^0C and 75% relative humidity (RH). After 90 days, the % drug release of Duloxetine hydrochloride in the pellets was determined by dissolution study and compare with freshly prepared pellets.

Result and discussion:

The starting material, 2-bromo-1-(thiophen-2-yl)ethanone 1 was prepared by photochemical reaction of n-bromo succinamide in carbon tetra chloride 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, 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 the observed enantioselectivity was similar to this reported in 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 used as standard for *ee* determination.

In turn, most approaches to synthesis of the *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 an introduction of *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, $[\alpha]_{D20}$ = -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*[7].

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 stirrer to prepare binding solution. NPS (710 micron- 1.0 mm) was taken in conventional coating pan and dusting powder was applied on it. The pan rotated at 40 rpm and simultaneously binding solution was sprayed on to the NPS. After completion of drug loading, the nuclei were dried in oven at 100 cc for 5 hrs. The dried nuclei was sieved in 1.18 mm screen mesh followed by 850 mm screen mesh to get the desired size (850 micron to 1.18 mm) and discard under and over sized nuclei. Seal coating suspension was prepared containing HPMC 5 cps, PEG-6000, titanium dioxide, sodium hydroxide pellets with the use of silverson stirrer (UK). The dried uncoated nuclei were taken in fluid bed coater and seal coating suspension was sprayed on to it. The sealed coated pellets were dried at 600 C for three hours. Dried seal coated pellets were sieved through 1.18 mm and 850 micron to get 850 micron to 1.18 mm seal coated pellets and discard under and oversized nuclei. Enteric coated suspension was prepared by Eudragit L 30 D 55 (ammonio methacrylate copolymer dispersion), talc, triethyl citrate, titanium dioxide and purified water with the use of silversten stirrer (UK). The seal coated pellets were coated using lab coater with Eudragit L 30 D 55 to different thickness equivalent to theoretical polymer load 25%, 30%, 35% and 40% w/w on dry basis.

The enteric coated pellets were dried in the fluid bed coater at 600C for 5 hours and then sieved through 1.40 mm and 850 micron mesh to get 850 micron 1.40 mm size enteric coated pellets and to discard the under and over sized pellets. In this way all lots of pellets were coated according to the formula for F-1 to F-4 (Table 1). The composition of nuclei, seal pellets are shown in Table 2. Machine parameters during fluid coating are shown in Table 3.

The DSC thermograms showed a sharp endothermic peak for all the pellets prepared. This one step melt might be due to only one crystal form of duloxetine hydrochloride, thus indicating that duloxetine hydrochloride did not undergo any crystal modification. The temperature range of the endothermic peak of all the duloxetine hydrochloride pellets lies in the range of 177.9^0 C to 160.8 ^{0}C (Fig. 1). In DSC curve, pure duloxetine hydrochloride powder had a sharp endothermic peak at 172.7°C ; ΔH= -10.73 J/gm that corresponded to the melting point of duloxetine hydrochloride .

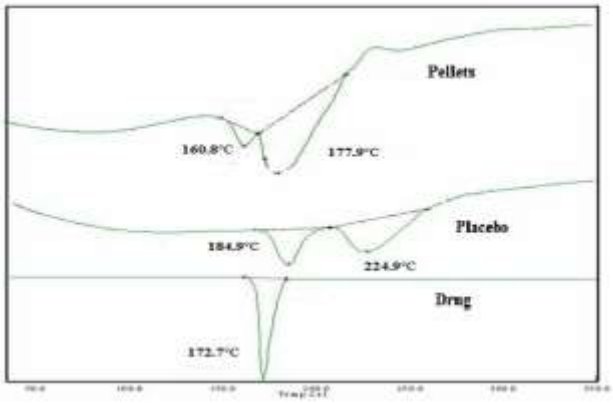


Fig. 1. Shows DSC Spectrum of different samples of duloxetine hydrochloride

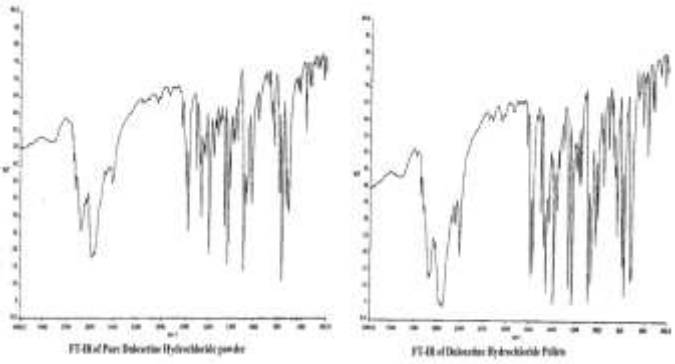


Fig. 2. Shows FT-IR Spectrum of different samples of Duloxetine hydrochloride

Infrared spectra of duloxetine powder commercial, synthesized and duloxetine showed pellets showed characteristic peaks at 1490 cm^{-1} (thiophene ring) 3000-3001 cm^{-1} (aromatic alkene proton, C=C-H) 1400-1600 cm^{-1} (aromatic alkene, C=C) 1000-1300 cm^{-1} (ether, C-O) and 1080-1360 cm^{-1} (C-N bond) (Fig. 2). Specific changes in IR spectra are not very clear, could be due to variations in the resonance structure, rotation of a part of a molecule or certain bonds. Alteration could be due to minor distortion of bond angles, or even a result of the presence of solvents of used in synthesis.

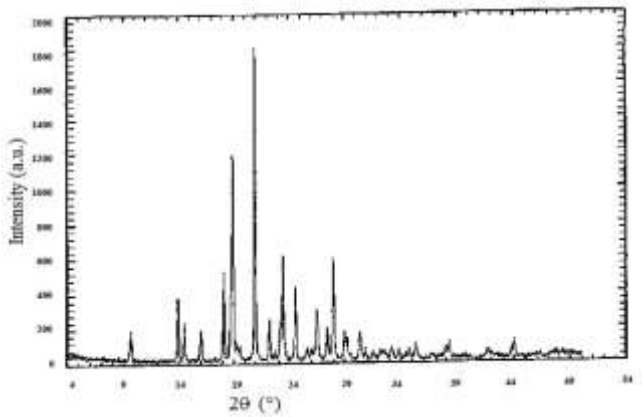


Fig. 3. Shows XRD Spectrum of duloxetine hydrochloride

X-Ray diffraction was used to analyze potential changes in the inner structure of duloxetine hydrochloride during the formulation of pellets. The characteristic peak of the duloxetine hydrochloride appeared in the 2θ range of 9–50°(Fig. 3).

Table 1: Codes And Formulation Of Duloxetine Enteric Coated Tablet

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 2: 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		

Table 3: Machine Parameters during Fluid Bed Coating

Parameters	Fluid bed coating	
	Seal coating	Enteric coating
Batch size	800 gm	200 gm
Inlet air temperature	40-45^{0}C	40-45^{0}C
Outlet air temperature	30-35^{0}C	30-35^{0}C
Product temperature	37-40^{0}C	37-40^{0}C
Chamber humidity	55%-60%	55%-60%
Air flow	90m^3/hr	90m^3/hr
Spraying pressure	1.20 bar	1.20 bar
Spraying rate	2.0 g/minute	3.0 g/minute
Secondary drying	60^{0}C /180mins.	60^{0}C /300mins.

All the samples showed similar peak positions (2θ) in X-ray diffraction, formation of different polymorphs of duloxetine hydrochloride was ruled out. The relative abundance of the planes exposed to the X-ray source would have been altered, producing the variations in the relative intensities of the peak or may be due to differences in crystal sizes [8,9]. The pure drug exhibits its characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity.

SEM study showed that the coated pellets appeared to exist as spherical discrete units whilst the surface morphology of the pellets was compact, continuous and uniform and is porous in nature. SEM demonstrated the spherical nature of the pellets. The average size of the pellets was found to be 1080±5 µm (Fig. 4).

Drug enclosed in pellets showed increased solubility than the pure sample in water and increased nearly to (0.00437 mg/ml) than pure Duloxetine hydrochloride (0.00296 mg/ml). The higher solubility of Duloxetine hydrochloride from pellets may be due to the reduction in particle size of drug powder and increased wettability [10, 11].

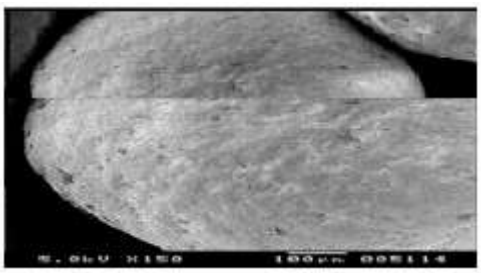


Fig. 4. Shows SEM photographs of Duloxetine hydrochloride pellet

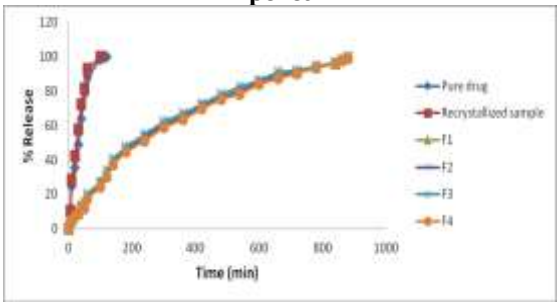


Fig. 6. Invitro dissolution profiles of Duloxetine powder, recrystallized powder and pellets formulation

The dissolution profiles of Duloxetine hydrochloride pellet (fig. 6) exhibited improved dissolution behavior for pellet than synthesized sample. The pellets took 14 hour to completely release the drug.

The result of physical stability shown that prepared pellets were stable at 40^0C and 75% relative humidity (RH) for After 90 days, the % drug release of Duloxetine hydrochloride in the pellets was almost same as with freshly prepared pellets.

Conclusion

Duloxetine hydrochloride powder was synthesized and then formulated in enteric coated pellets which result in delayed release of drug. On pellets various studies were carried out to confirm compatibility with excipients used. DSC, FT-IR and XRD studies showed that there is no change in the crystal structure of Duloxetine hydrochloride hence found to be compatible with excipients used. SEM showed that pellets were spherical discrete uniform and is porous in nature. The dissolution of the pellets was improved compared with pure Duloxetine hydrochloride sample. It completely released drug after around 14 hours. Hence it can be concluded that for delayed release of Duloxetine hydrochloride, pellets are suitable dosage form.

Acknowledgements

The authors thank department of studies in industrial chemistry for the laboratory support, and Principal, J.S.S.College of Pharmacy, Mysore for providing facilities to carry out this work.

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