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Development and Evaluation of Duloxetine HCl Delayed Release pellets and Absorption studies in Rats

Shashidhar Reddy Dodda[1*], Prakash Rao. B[2]

1. Department of Pharmacology, Bioneeds Preclinical Services, Bangalore, India.

2.Department of Pharmaceutics, Karnataka College of Pharmacy, Bangalore, India

ABSTRACT

This study describes the development and characterization of Enteric coated pellets of duloxetine hydrochloride that results to improve gastric stability and enhance oral systemic exposure of novel serotonin and nor-epinephrine reuptake inhibitor (SNRI), duloxetine. Duloxetine Pellets were prepared by coating drug solution on sugar sphere followed by various layering in fluidized bed Coater (FBC) with different polymers like hydroxy propyl methylcellulose (HPMC E5), Crospovidone, Hypermellose Acetate Succinate and polysorbate 80 in suitable proportion. In vitro Dissolution studies were carried out in 0.1N HCl (pH: 2) for two hours followed by Phosphate buffer (pH: 6.8) for 1.5 hours with USP (Type-II) dissolution method. Absorption studies for Optimized pellets were carried out in Rats at 5 mg/kg dose; pellets were filled in Capsule size 9 administered orally with modified gavage needle. The optimized formulation has better correlation in both In vitro and In vivo system. The systemic exposure (AUC) and maximum concentration in plasma (Cmax) of entiric coated pellets of duloxetine was significantly higher than conventional suspension formulation. Finally it can be concluded that multiparticulate approach can be used to improve the stability and systemic exposure of pH sensitive and poorly water-soluble drugs such as duloxetine.

Keywords: Duloxetine; Enteric coating; Pharmacokinetics; Capsule dose to rat

*Corresponding Author Email: sdodda@gmail.com

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INTRODUCTION

Mostly new chemical entities (NCEs) are unstable in gastric pH, poorly water-soluble and pose a challenge in developing an optimum solid oral dosage form. Oral route has been the major route of drug delivery for the treatment of various diseases. Delivery of pH sensitive and poorly water soluble molecule to oral route is difficult because, approximately 40% of the drug compounds are limited to low aqueous solubility and instability in gastric pH, which leads to limited oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality[1]. To increase the oral bioavailability of pH sensitive, poorly water soluble compounds and discussed drawbacks, various other formulation strategies have been adopted including the use of cyclodextrins, nanoparticles, solid dispersions and permeation enhancers[2,3]. In recent years, much attention has focused on delayed release formulations to improve the oral bioavailability of pH sensitive and poorly water-soluble compounds. In fact, the most popular approach is the incorporation of the drug compound into enteric-coated pellets, which delivers the drug to the small intestine they're by aiding for its better absorption.

Duloxetine hydrochloride [(+)-(S)-N-methyl-3- (1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride](Figure.1) is a novel serotonin (5-HT) and nor-epinephrine (NE) reuptake inhibitor (SNRI) that has been approved by USFDA for the treatment of major depressive disorder (MDD) and vasomotor symptoms associated with menopause. Duloxetine is also used for the treatment of stress urinary incontinence (SUI) and diabetic peripheral neuropathic pain[4-6].

MATERIALS AND METHODS

Chemicals/Reagents

Duloxetine hydrochloride and Telmisartan (IS) were procured from Dr Reddy laboratory Pvt Ltd (Hyderabad, India). HPLC-grade acetonitrile and methanol were purchased from Rankem (Ranbaxy Fine Chemicals Limited, New Delhi, India). Analytical grade formic acid was purchased from S.D. Fine Chemicals (Mumbai, India).

Preparation of core pellets

Drug core was prepared using a fluidized bed Equipment (Umang) under the following conditions: inlet temperature 38- 45 C; airflow rate 80–100 m^3/hr; atomizing air pressure 1.5 Bar; the drug was mixed with an Isopropyl alcohol with continuous stirring Then added methylene chloride to above drug dispersion under continuous stirring till to get the clear solution. Sugar spears were coated with the complete drug solution. The composition of Duloxetine with different polymers was stated in the Table1.

Table 1: Various compositions of Duloxetine Pellet formulation

Ingredient	DUP3	DUP4	DUP5	DUP6	DUP7
Sugar Spheres (#20-#24)	31.95	34.95	39.35	31.5	42.62
Duloxetine HCl	20	20	20	20	20
Hypromellose 6cps (Pharmacoat 606)	4	4	4	4	4
Crospovidone (Polyplasdone XL)	0.35	0.35	0.35	-	-
Polysorbate 80 (Tween 80)	1	1	1	-	-
Isopropyl Alcohol	QS	QS	QS	QS	QS
Methylene Chloride	QS	QS	QS	QS	QS
Hypromellose 6cps (Pharmacoat 606)	11	8	8	10	7
Polysorbate 80 (Tween-80)	2	2	2	1	1
Sodium Lauryl sulphate (Stepanol WA 100)	-	-	-	3	3
Talc	1.5	1.5	1.5	1.5	1.5
Purified Water	QS	QS	QS	QS	QS
Hypromellose ASMG (AQOAT ASMG)	24	24	20	25	18
Triethyl Citrate	2.4	2.4	2	2.5	1.8
Talc (Talc Luzenac)	1.8	1.8	1.8	1.5	1.08
Isopropyl Alcohol	QS	QS	QS	QS	QS
Methylene Chloride	QS	QS	QS	QS	QS
Total	100	100	100	100	100

Barrier coating

After the drug layering, the cores were layered with clear solution of Hypermellose 6cps; tween 80 and talc under the condition of inlet temperature to 50°-60°C; atomizing air pressure of 3.0 – 5.0 Kg/cm^2. Dry the pellets for 15 min in FBD and The sub-coated pellets are sized (#16-#22) on a sifter and yield weight was recorded.

Enteric coating

Hypermellose acetate succinate was sprayed onto the sub layered drug cores from an organic dispersion containing the following ingredients: Hypermellose ASMF; try ethyl citrate; isopropyl alcohol; Methylene chloride and talc.

In Vitro Drug Release

The release characteristics of Duloxetine from the coated pellets were determined according to the USP dissolution II paddle method at a rotation speed of 50 rpm in 900 mL of simulated gastric (pH 1.2) and intestinal (pH 6.8) fluids at 37 ± 0.5 ◦C, using a D-800 LS dissolution tester The core of the coated pellets equivalent to 20 mg Duloxetine was exposed to dissolution medium for 2h in acidic medium. The dissolution samples (5 mL) were collected at given intervals and the same volume of fresh dissolution medium was replenished. The collected samples were filtered through 0.45 _m Millipore filters. The concentration of Duloxetien in the dissolution samples was determined by a HPLC. Dissolution profiles for Developed Duloxetine pellets were shown in Figure 1.

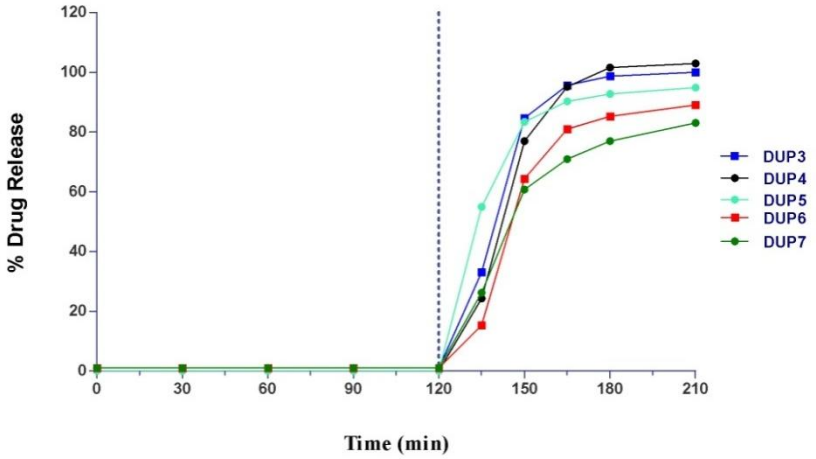

Figure 1: In-vitro release of Duloxitine enteric coated pellets

In vivo Studies in Rats

Six male SD rats weighing 250-300 g were randomly divided into two treatment groups, each containing three rats. The rats were fasted over 12 h prior to the experiments. A polyethylene Cannula (inner diameter, 0.58 mm; outer diameter 0.96 mm; dural plastics) was surgically introduced into the right Jugular vein of rat under ether anesthesia to obtain blood samples at the various sampling times. The Duloxetine powder was suspended in the distilled

Water and the resulting suspension were administered orally at a dose equivalent to 5 mg/kg body weight using oral gavages to one group. Meanwhile, the mini capsules containing

Coated (DUP5) pellets were also administered orally at the same dose using an intragastric capsule administering gavages to other group, respectively. Approximately 0.2 mL heparinized blood samples were collected using an indwelling cannula at 0.25, 0.5, 1, 2, 3, 4, 6,8hr and 24 hr, and then centrifuged at 4000 rpm for 10 min to collect the plasma samples. The plasma samples were stored in a freezer at −70 ◦C until analyzed by LSMS/MS.

Pharmacokinetic and statistical analysis

Pharmacokinetic parameters of Duloxetine were calculated using non-compartmental Methods. The maximum plasma concentration (Cmax) and the time to reach the Cmax (Tmax) were read directly from the plasma concentration–time profiles of Duloxetine. The areas under the plasma concentration–time curve from zero to 24 h (AUC0–24 h) were calculated using the classical trapezoidal method. All data are presented as mean ± standard deviation.

Scanning Electron Microscopy

The morphology of coated pellets were studied by scanning electron microscopy (SEM) (JEOL JSM 6360A, IISC, Bangalore) was performed to characterize the surface of formed pellets. The

coated pellets were loaded on studs and applied fine gold coating for 5 min at 10 mA ion current under pressure of 0.1 torr using ion sputter.

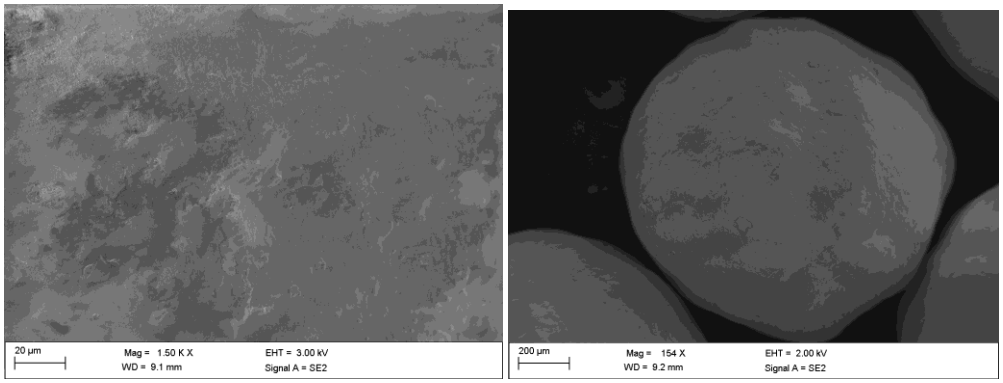

Figure 2: SEM images of Duloxetine coated pellets (DUP5).

RESULTS AND DISCUSSIONS

In-vitro evaluation

Duloxetine resistance to acidic media is 99.80% for 2 hr in 0.1N Hcl dissolution media. These indicated that release of duloxetine was delayed greatly (Figure 3), suggesting that duloxetine delayed release pellets are stable at gastric pH and which will help to enhance the bioavailability.

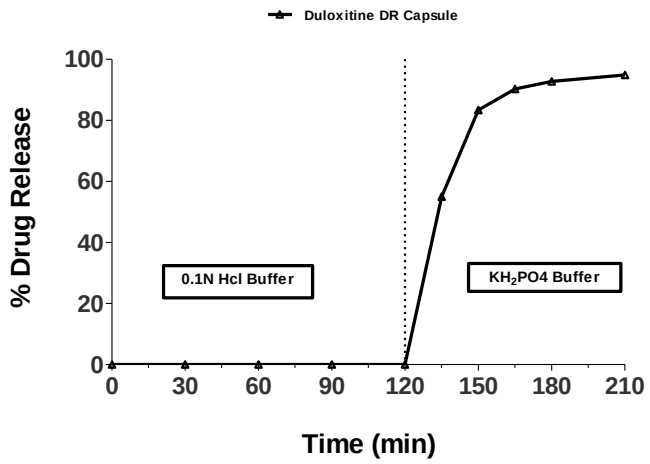

Figure 3: In-vitro stability of Duloxitine enteric coated pellets at gastric pH

In vivo Studies

The sensitivity and specificity of the assay were found to be sufficient for accurately characterizing the plasma pharmacokinetics of duloxetine in rats. Profiles of the mean plasma concentration vs time were shown in (Figure 4). Pharmacokinetic parameters were tabulated in (Table 2). Maximum concentration in plasma (Cmax 74.3 ± 6.31ng/mL, 116 ± 5.15ng/mL) was achieved at (0.5 h, 3.0h) Tmax respectively for duloxetine suspension and duloxetine enteric-coated pellets. The $AUC_{(0-t)}$ was (256 ± 8.1 h*ng /mL, 1030 ± 11.2 h*ng /mL) respectively for

duloxetine suspension and duloxetine delayed release pellets. The higher sensitivity of this method compared with the current existing methods in literature facilitates the quantification of duloxetine at lower concentrations with high turnover.

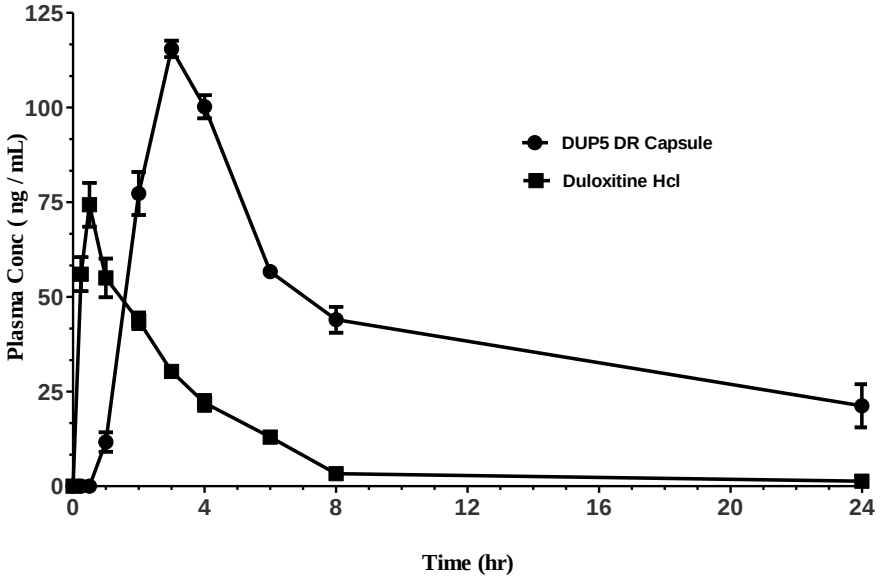

Figure 4: Mean ± SD plasma concentration–time profile of Duloxetine suspension (5mg/kg) and DRP (delayed release pellets containing Duloxitine Hcl equivelent to 5mg/kg) in rat plasma following oral dosing of duloxitine to rats

Table 2: Mean ± SD pharmacokinetic parameters of Duloxitine (5mg/kg) and Duloxitine delayed release pellets containing Duloxitine equivalent to 5mg following oral dosing to rats

Group	Dose	Cmax (ng/mL)	Tmax (Hr)	AUClast (hr*ng/mL)
DUP 5 Pellets	5	116 ± 5.15	3	1030 ± 11.2
Duloxetine solution	5	74.3 ± 6.31	0.5	256 ± 8.1

Scanning Electron Microscopy

Coated pellets have smooth surface and porous in nature and polymers are uniformly distributed on to pellets. SEM images for optimized pellets (DUP5) were shown in Figure 2.

CONCLUSION

An optimized delayed release pellet system for Duloxetine was successfully developed with an increased acidic stability, dissolution rate and solubility, which ultimately increased the systemic exposure of Duloxetine in rats.

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