Research Article

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Formulation, development and evaluation of duloxetin delayed released capsules

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ABSTRACT

The present aim of this work is to formulate and evaluate multiple unit particulate system of Duloxetine hydrochloride Capsules 60 mg, release profile of the dosage form and to compare with the innovator product, determine the best fit dissolution profile for dosage form and stability study. To know about innovator's product and gives an idea about the excipients to be used and what not to use, market value of the product and helps in identifying the generic companies. The work was carried out to delay the release of Duloxetine hydrochloride by using different enteric polymers like Acryl EZE, HPMC phthalate HP 55, HPMC phthalate HP 55 S, HPMC phthalate HP 50.With Acryl EZE only 5% drug release was observed in pH 5.5 phosphate buffer even after 90 minutes. The Enteric coating suspension was very viscous and the process was very slow when HPMC phthalate HP 55 S was used as enteric polymer. HPMC Phthalate (HP 55) showed poor drug release in pH 5.5 phosphate buffer, where as the drug release pattern with HPMC phthalate HP 50 was high when compared to innovator. So a combination of HPMC Phthalate (HP 55) and HPMC Phthalate (HP 50) were used. Here Different ratios of HPMC Phthalate (HP 55) and HPMC Phthalate (HP 50) were tried out. The release profile of E12 formulation matched with that of the innovator product (HP 55: HP 50=6:4).Different solvent systems like IPA/DCM-1:1, Acetone/water in the ratio 1:1 and 8:2 were tried out as enteric solvents. Acetone/water in the ratio 8:2 was optimized. The Different kinetic models were applied to optimized enteric coated formulation (E12) and observed that it follows zero order kinetics with Higuchi diffusion mechanism. Then the Stability studies were conducted at 40ºC / 75% RH (accelerated stability testing) for 2 months. Assay, acid resistance, dissolution release profile of optimized enteric coated formulation (E12) complies with that of innovator product and was found to be stable.

Keywords: Duloxetine, HPMC, Stability.

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INTRODUCTION

Oral Drug Delivery

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after complete absorption of the drug from the dosage form, plasma drug concentration decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms [6].

Modified Drug Delivery

The term modified-release drug productis used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined as "one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized". Several types of modified-release drug products are recognized [1-5].

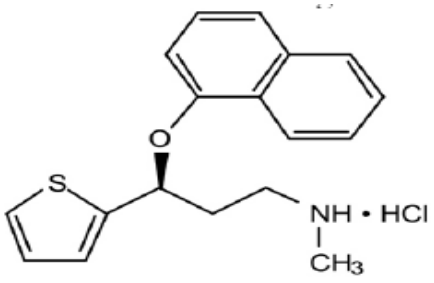
MATERIALS AND METHODS

Following are some of the important patents in relation to the present research work:

Patent study helps us to know about innovator's product and gives an idea about the excipients to be used and what not to use, market value of the product and helps in identifying the generic companies.

Physico Chemical Properties of Duloxetine Hydrochloride

Chemically Duloxetine Hydrochloride is (+)-(S)-N-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride



- **Empirical formula:** $C_{18}H_{19}NOS•HCl$
- **Molecular weight:**333.88
- **Melting point:**169-170°C
- **Organoleptic Characters:** Off-white to creamy crystalline solid, odorless & bitter in taste
- **Solubility**
- **Non-aqueous solvents - Soluble** in methanol and Chloroform
- **Isomers:** Due to the presence of asymmetric carbon, Duloxetine HCl occurs in two different isomer forms. The drug substance is manufactured as S-enantiomer and amount of R-isomer is controlled in the drug substance.

Pharmacokinetics

Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and steady-state plasma concentrations are typically achieved after 3 days of dosing. Elimination of Duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP1A2 [8].

Absorption and Distribution

Orally administered Duloxetine hydrochloride is **well absorbed**. There is a median 2-hour lag until absorption begins (T_{lag}), with maximal plasma concentrations **(C_{max})** of duloxetine occurring 6 hours post dose. Food does not affect the C_{max} of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%. There is a 3-hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose [7].

The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α1-acid glycoprotein. The interaction between duloxetine and other highly protein bound drugs has not been fully evaluated. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

Metabolism and Elimination

Biotransformation and disposition of duloxetine have been determined following oral administration of 14C-labeled duloxetine. Duloxetine comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation [6-10].

Both CYP2D6 and CYP1A2 catalyze the oxidation of the naphthyl ring in vitro. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the feces.

Primary metabolites – Hydroxy duloxetine with hydroxylation at 4,5 or 6 positions, N-desmethyl duloxetine, Dihydrodiol duloxetine, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate [11-14].

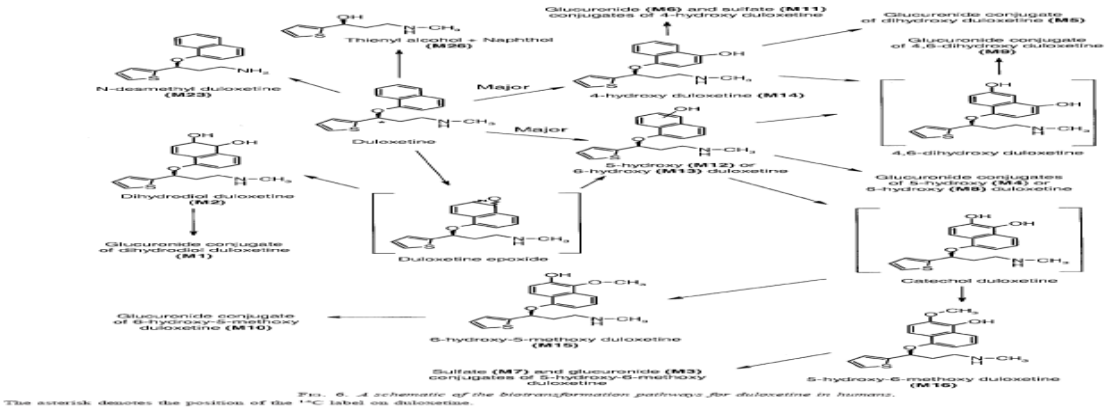


Fig. 6. A schematic of the biotransformation pathways for duloxetine in humans.
The asterisk denotes the position of the ^{14}C label on duloxetine.

PHARMACODYNAMICS

Mechanism of action

Duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors in vitro. Duloxetine does not inhibit monoamine oxidase (MAO).

Fig 4.1 b: Mode of action of Duloxetine

Indications

Treatment of major depressive disorder (MDD) Management of neuropathic pain associated with diabetic peripheral neuropathy Generalized Anxiety Disorder.

CHARACTERIZATION OF INNOVATOR PRODUCT

Innovator Product Details

Details of the innovator tablets are retrieved from the relevant literature including patient information leaflet (PIL), summary basis of approval (SBOA), and publications. The pharmaceutical details of the reference product are given below [12].

a) **Brand Name:** Cymbalta®
b) **Generic Name:** Duloxetine hydrochloride Delayed Release capsules
c) **Company:** Eli-Lilly & Co, USA
d) **Market:** USA
e) **Approval date:** Aug 3, 2004
f) **NDA number:** NDA No.021427
g) **Strengths &Label Claim**
20 mg strength
Each capsules contains 22.4 mg of Duloxetine Hydrochloride equivalent to 20 mg Duloxetine
30 mg strength:
Each capsules contains 33.7 mg of Duloxetine Hydrochloride equivalent to 30 mg Duloxetine
60 mg strength :
Each capsules contains 67.3 mg of Duloxetine Hydrochloride equivalent to 60 mg Duloxetine
h) **Route of administration:** Oral
i) **Indication:** For major depressive disorder
j) **Packs Available**

SUMMARY AND CONCLUSION

The work was carried out to delay the release of Duloxetine hydrochloride by using different enteric polymers like Acryl EZE, HPMC phthalate HP 55, HPMC phthalate HP 55 S, HPMC phthalate HP 50.With Acryl EZE only 5% drug release was observed in pH 5.5 phosphate buffer even after 90 minutes. The Enteric coating suspension was very viscous and the process was very slow when HPMC phthalate HP 55 S was used as enteric polymer. HPMC Phthalate (HP 55) showed poor drug release in pH 5.5 phosphate buffer , where as the drug release pattern with HPMC phthalate HP 50 was high when compared to innovator. So a combination of HPMC Phthalate (HP 55) and HPMC Phthalate (HP 50) were used. Here Different ratios of HPMC Phthalate (HP 55) and HPMC Phthalate (HP 50) were tried out.

The release profile of E12 formulation matched with that of the innovator product(HP 55:HP 50=6:4).Different solvent systems like IPA/DCM-1:1, Acetone/water in the ratio 1:1 and 8:2 were tried out as enteric solvents. Acetone/water in the ratio 8:2 was optimized. The Different kinetic models were applied to optimized enteric coated formulation (E12) and observed that it follows zero order kinetics with Higuchi diffusion mechanism. Then the Stability studies were conducted at 40ºC / 75% RH (accelerated stability testing) for 2 months. Assay, acid resistance, dissolution release profile of optimized enteric coated formulation (E12) complies with that of innovator product and was found to be stable [11].

REFERENCES

[1]. Martindale, The Complete Drug Reference', edited by Kathleen Parfitt, Pharmaceutical Press, London, UK.
[2]. Ansel, H.C., LoydV.Allen Jr.,Nicholoas G. Popovich. Ansel's Pharmaceutical Dosage forms and Drug Delivery Systems, 9, 2011, 258-259
[3]. Peck, G.E., Baley, G.J., McCurdy, V.E., Banker, G.S, Tablet Formulation Design. In: chwartz, B. J. (ed) Pharmaceutical Dosage Forms: Tablets. Marcel Decker, New York, 1989, 75-130.
[4]. Ansel, H.C., LoydV.Allen Jr.,Nicholoas G. Popovic. Ansel's Pharmaceutical Dosage forms and Drug Delivery Systems, 6, 1995, 213.
[5]. Ojantakanen, S, Effect of viscosity grade of polymer additive and compression force on release of ibuprofen from hard gelatin capsules. Eur J Pharm Sci. 1(2), 1993, 109-114.
[6]. Follonier, N., Doelker, E. Biopharmaceutical comparison of oral multiple unit and single unit sustained release dosage forms. STP Pharma Sciences. pp.2, 1992, 141-5.
[7]. Vial-Bernasconi, Doelker E., P. Prolonged release capsules divided and monolithic forms. STP Pharma Sciences. 4, 1988, 397-409.
[8]. Ghebre-Sellassie, I., Mechanism of pellet formation and growth, in Ghebre-Sellassie, Pharmaceutical pelletization technology, Marcel Dekker, Inc., New York and Basel. 1, 1989, 123 – 143.
[9]. Sherrington, P. J., Oliver, R. Globulation processes, in granulation, Heyden and Son ltd., London. 1981, 118 – 140.
[10]. Jalal, M., Malinowski, H.J., Smith, W.E. Tablet granulations composed of spherical-shaped particles, Journal of Pharmaceutical Science. 1972, 1466-790.
[11]. Bechgaard,H., and Hegermann-Nielsen, G. Drug Development and Industrial Pharmacy, 4, 1978, 53–67.
[12]. Parikh, B.M. Alternatives for Processing Spherical Granules, paper presented at Interphex ,USA. New York 1990.
[13]. Reynolds, Manuf,A.D. Chem.Aerosol News. 41, 1970, 40–43.
[14]. Bechgaard,H., and Hegermann-Nielsen, G. Drug Development and Industrial Pharmacy, 4, 1983, 55–68.