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Formulation Development and Release Profile of Levomilnacipran Extended Release Capsules using Principles of Quality by Design

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Abstract

The study's goal was to use Quality By Design (QbD) principles to design an Extended Release dosage form of levomilnacipran and evaluate its *in vitro* release profile. Doses of levomilnacipran extended release capsules (LERC) ranging from 20 mg to 120 mg. QbD was employed in this work to design LERC capsule formulation and production, which ensures LERC safety and efficacy. To create the LERC, wurster coating was applied to non-pariel seeds, which were then filled with capsules. To provide prolonged absorption, a polymer derived from ethylcellulose was chosen. Extensive release capsules are made up of four main components: (1) Drug layering, (2) extended release coating, (3) lubricant application, and finally (4) capsule filling. Results revealed that there was no significant difference in release profile LERC in different doses; however, the highest release of drug was seen at 120 mg, that is, 93%. The present formulation may be used as an effective treatment therapy against major depressive disorder.

Keywords: Capsule, Ethylcellulose, Levomilnacipran, Pellet, Quality by design

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Introduction

Many people with major depressive disorder (MDD) can be benefited from antidepressant medication for acute, and long-term treatment (Cipriani *et al*., 2018).[1] Long-term antidepressant drug is related with a lower incidence of relapse and recurrence, while short-term therapy with antidepressants is beneficial for acute episodes. However, the antidepressants that are now on the market have significant drawbacks in terms of efficacy as well as tolerability. Tolerability remains an issue with antidepressants, and unpleasant effects are one of the top reasons for discontinuation in the first few months of treatment (Wilson and Lader, 2015).[2] Nausea, headaches, and sleep difficulties are all common side effects of this medication. Because of this, it is imperative that new antidepressants be created with discrete modes of action and better side effect profiles.

It has reported that most antidepressant drugs act by preventing the reuptake of serotonin (5-HT) and norepinephrine (NE) at the synapses in the brain (Yohn *et al*., 2017).[3] They include tricyclic antidepressants, serotonin NE retake inhibitors (SNRIs), and NE selective retake inhibitors as the most commonly prescribed therapies for depression. Tolerability and safety are better with selective reuptake inhibitors than with tricyclic antidepressants. As a result, there is some evidence that SNRIs may be superior to SSRIs or NRIs in the treatment of symptoms of MDD.

In July 2013, the US FDA approved Levomilnacipran hydrochloride (LVM) extended release (Fetzima, Forest Laboratories) for the treatment of MDD (Asnis and Henderson, 2015).[4] In Europe, it's also being studied to see if it might help people restore their functional abilities following an acute ischemic stroke. Only the first three in this family is available in the United States for use in treating MDD: Duloxetine, venlafaxine, desvenlafaxine, and milnacipran. Only in Europe and Japan is Milnacipran promoted as an antidepressant, but in the United States and Australia it is accessible for the treatment of fibromyalgia. Racemic milnacipran contains two enantiomers, one of which, levomilnacipran (1S, 2R-milnacipran), is more potent than the other, F2696 (1R, 2S-milnacipran) (Sambunaris *et al*., 2014).[5]

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In comparison to other SNRIs, this one is more effective at inhibiting NE reuptake than it is at inhibiting serotonin reuptake. LVM has been designed solely as an extended-release formulation to allow for once-daily dosage of the drug. Milnacipran, which is administered twice daily, has a lower rate of patient compliance. Over a period of 12–24 h, the active ingredients in extended-release drugs are progressively released into the body. Oral tablets and capsules are the most common dosage forms. Immediate-release drugs, on the other hand, take longer to take effect. Consequently, the study's procedure was devised to formulate Levomilnacipran extended release capsules (LERC) utilizing a Quality By Design (QbD) approach and evaluate their *in vitro* release profile.

Materials and Methods

Formulation of LERC

Briefly, 90 parts of purified water from dispensed quantity into suitable container with stirrer. Povidone was added to step 1 under

stirring into vortex to dissolve completely. LVM was added to step 2 under continuous stirring to dissolve completely. Talc was added to step 3 under stirring into vortex and stir for 15 min. Dispensed sugar spheres were loaded into FBP bowl and prewarmed the sugar spheres with low fluidization till bed temperature reached to 38 ± 5°C. Sprayed the dispersion of step 4 with continuous stirring onto sugar spheres of step 5 at bed temperature of 38 ± 5°C till to get target buildup is 170.44%w/w. The drug coated beads were dried as step 6 for NLT 15 min with low fluidization at bed temperature of 40 ± 5°C. The drug layered beads were shifted as step 7 through 1000 microns and discarded the retentions. Table 1 shows the composition of drug extended release beads for capsule filling. Extended release coating on drug layered beads extends the drug release. Based on the reference product characterization and package inset ethyl cellulose were selected as extended coating polymer, triethyl citrate as plasticizer, and talc as anti tackifier. These excipients dispersed impurified water and isopropyl alcohol (30:70 ratio, 5% w/w solids) to prepare the extended coating suspension (Siddique *et al*., 2010).[6] Figure 1 shows flow diagram of the manufacturing steps used during formulation development studies to manufacture the LERC.

In Vitro Release Profile of a LERC

Drug release studies of LERC were conducted using dialysis bag diffusion (Wani and Khan, 2019).[7] Dialysis bags were filled with LERC and placed in a beaker of pH 7.4 phosphate buffer, which was maintained at room temperature. For the duration of the experiment, the beaker and magnetic stirrer were kept at a constant 37 ± 1°C. A steady 100 rpm was maintained throughout the experiment. At predetermined intervals, 2 ml samples were taken out and replaced with fresh pH 7.4 phosphate buffer. The samples were tested using a UV-Visible spectrophotometer at 325 nm after appropriate dilutions.

Results

Formulation of multi-particulate delivery system (LERC 20, 40, 80, and 120 mg) comprised of extended release beads with contains drug layering and extended release coating on non-pariel seeds using wurster coating process followed by capsule filling. Figure 2 shows structure of extended release coated beads. Such a strategy minimizes the effects of diet and GI transit heterogeneity among individuals. The drug release profile showed that the dissolving profile of the medication in different strengths was not significantly different. The drug was highly soluble in water. Table 2 shows release profile of LERC in 24 h. It was observed that the release was increasing continuously with time up to 24 h, in which the highest release was noted for 120 mg dose, that is, 93%.

Discussion

The whole drug delivery market's largest and oldest sector is oral medication. It is the fastest-growing and most popular method of medication administration. LERC was synthesized utilizing the QbD method and its *in vitro* release profile was studied in this study. Upon testing, the produced LERC was found to be water soluble and to have a favorable release profile over a 24-h period.

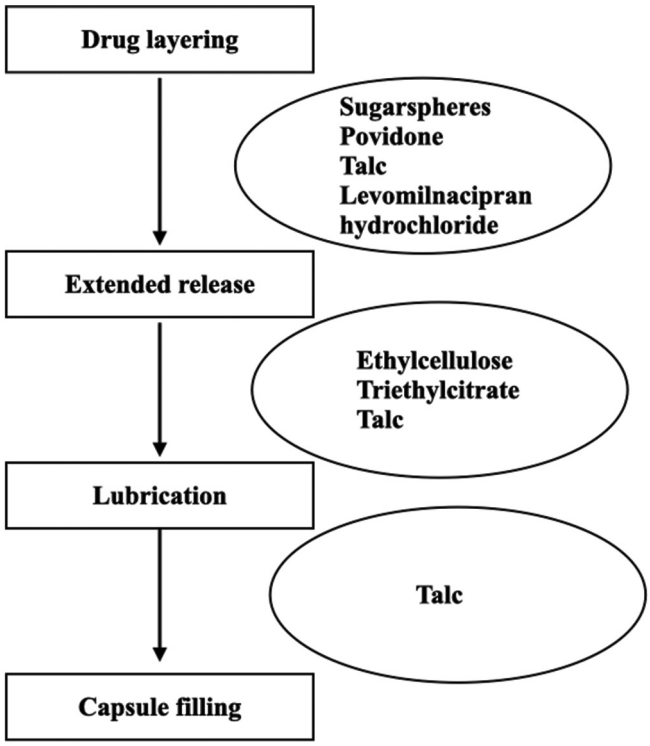

Figure 1: Flow diagram of the manufacturing steps used during formation development

Table 1: Composition of drug extended release beads for capsule filling

Components	*120 mg/cap*	*80 mg/cap*	*40 mg/cap*	*20 mg/cap*
Sugar spheres (500–600 µm)	94.29	62.86	31.43	15.71
Levomilnacipran hydrochloride	137.76	91.84	45.92	22.96
Povidone K-30	15.30	10.20	5.10	2.55
Talc	7.65	5.1	2.55	1.27
Purified water	482.13	321.42	160.71	80.35
Weight of drug loaded beads	255	170	85	42.50
Extended release coating				
Ethylcellulose	30	20	10	5
Triethyl citrate	6	4	2	1
Talc	9	6	3	1.5
Isopropyl alcohol	598.50	399.00	199.50	99.75
Purified water	256.50	171.00	85.50	42.75
Weight of extended release coated beads	300	200	100	50
Lubricants				
Talc	3	2	1	0.5
Total weight of lubricated beads	303	202	101	50.50

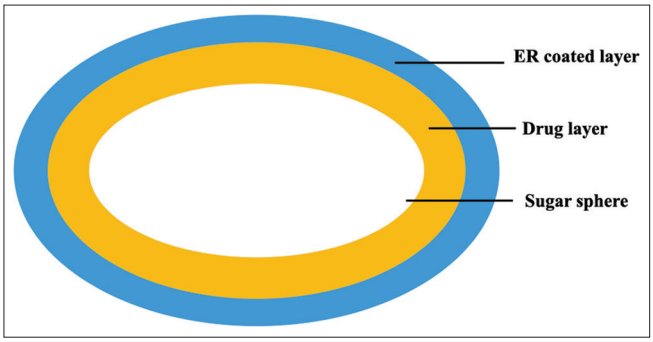

Figure 2: Structural representation of extended release coated beads

Table 2: Release profile of Levomilnacipran extended release capsule

Time (hr)	*120 mg*	*80 mg*	*40 mg*	*20 mg*
1	5	4	3	7
2	30	29	27	28
4	53	51	51	50
6	64	62	62	61
8	72	69	70	68
12	81	78	79	77
16	87	84	85	82
20	91	88	88	85
24	93	90	91	88

Diazepam's extended-release formulation has many advantages over standard dosing formulations. Taking the extended-release capsule of Levomilnacipran once a day eliminates the need for any additional dosages for 24 h. With an extended-release formulation, patients avoid having to take multiple dosages throughout the day, allowing them to achieve their desired effects more quickly and easily. Frequent dosing with normal bioavailability results in unavoidable peak concentrations above the optimum level, followed by decreases to low or inactive levels, such that the active chemical is only present in optimum concentration for a short time. This composition avoids both the excessively high and the excessively low dosages.

According to the findings of Siddique *et al*., 2010 our investigation found that the medicine was released for a lengthy period of time when packaged into an extended-release capsule. We used the QbD approach to establish a formulation and manufacturing process that ensures the quality, safety, and efficacy of capsules. As a starting point, the quality target product profile (QTPP) was defined by taking into account the RLD product's label and intended patient demographic as well as the drug substance's features. LERC 20/40/80/120 mg were developed to meet all of the QTPP's characteristics. However, our analysis throughout pharmaceutical development focused on the important quality features that could be impacted by a realistic adjustment to the therapeutic product composition or manufacturing method.

Conclusion

Extended release dosage forms comprise a wide range of prolonged action preparations that continuously release their active ingredients for a set time period. Ethylcellulose was used as a polymer to successfully prepare LERC. It can be deduced from these data that the drug release could be extended further if the polymers are combined because of their probable interaction and cross-linking. LERC may be used to treat MDD following pre-clinical and clinical research.

References

1. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, *et al.* Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. Lancet 2018;391:1357-66.
2. Wilson E, Lader M. A review of the management of antidepressant discontinuation symptoms. Ther Adv Psychopharmacol 2015;5:357-68.
3. Yohn CN, Gergues MM, Samuels BA. The role of 5-HT receptors in depression. Mol Brain 2017;10:28.
4. Asnis GM, Henderson MA. Levomilnacipran for the treatment of major depressive disorder: A review. Neuropsychiatr Dis Treat 2015;11:125-35.
5. Sambunaris A, Bose A, Gommoll CP, Chen C, Greenberg WM, Sheehan DV. A phase III, double-blind, placebo-controlled, flexible-dose study of levomilnacipran extended-release in patients with major depressive disorder. J Clin Psychopharmacol 2014;34:47-56.
6. Siddique S, Khanam J, Bigoniya P. Development of sustained release capsules containing "coated matrix granules of metoprolol tartrate". AAPS PharmSciTech 2010;11:1306-14.
7. Wani TU, Khan NA. Formulation of carbopol capsules for sustained release of losartan potassium. J Drug Deliv Ther 2019;9:92-7.