Journal of Research in Pharmacy

Research Article

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Formulation, characterization, and *in vitro* release studies of modified release multiple unit particulate system (MUPS) of venlafaxine hydrochloride

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Received: 03 October 2021 / Revised: 09 November 2021 / Accepted: 18 November 2021

ABSTRACT: Multiple unit particulate system (MUPS) is more recent, challenging, effective and attractive option for the pharmaceutical industries that gives an efficient way to deliver drugs in modified pattern. This study aimed to improve the release profile of venlafaxine hydrochloride by developing modified release MUPS using polyvinyl pyrrolidone K-30, ethyl cellulose 20 cps and Hypromellose E 5LV. Preliminary trials were carried out to select the inert carrier, binder, and viscosity grade of rate controlling polymers. Further, optimization of binder concentration and extended-release coating was carried out. The formulation development of MUPS was divided into two categories as (i) drug layering on inert carrier, i.e., sugar spheres and (ii) extended-release coating. Comparative multimedia dissolution study of venlafaxine hydrochloride extended-release capsules was carried out and compared with the marketed formulation to ascertain the *in vitro* drug release behavior. XRD study indicated conversion of monohydrate form of venlafaxine hydrochloride and remained unaffected during storage. SEM images confirmed smooth surface of MUPS without any pores. The coated spheres had more dense surface compared to the uncoated pellets. Hypromellose E 5 LV showed better binding properties. Ethyl cellulose (20 cps) showed sustained release profile. The blend containing ER – I spheres (10% coating) and ER – II spheres (11% coating) at 60: 40 ratio showed dissolution profile similar to that of the innovator product. The formulated venlafaxine hydrochloride loaded MUPS filled in hard gelatin capsule can open a new avenue for the delivery of therapeutics with improved potential.

KEYWORDS: Extended release; multiple unit particulate system; multimedia dissolution; polymorphism; sugar spheres.

1. INTRODUCTION

Oral solid dosage forms are the most preferred drug delivery systems due to their ease of administration, easy handling, and cost effectiveness [1]. Oral route provides maximum surface area for drug absorption [2]. Tablets and capsules are the most preferred and well-established pharmaceutical products. Oral drug delivery systems can be broadly classified into immediate release and modified release dosage forms. Immediate release oral dosage forms do not contain any specific polymers to modulate drug release profile and thus allow rapid release the drug after oral administration [3]. A conventional immediate release formulation fails to maintain plasma levels of drug over a prolonged period. These formulations have short duration of action and thus requires multiple daily dosing. This causes fluctuations in drug-plasma level. This is the major limitation associated with immediate release dosage forms. In addition to this, dose missing, and patient compliance are other limitations of immediate release dosage forms.

An ideal dosage form attains desired plasma drug concentration and maintains it for prolonged period [4]. Considering the drawbacks of the immediate release dosage forms, several modified release dosage forms have been developed. A modified-release dosage form improves the drug safety and efficacy due to prolonged and site-specific drug delivery [5, 6]. Modified-release dosage forms can increase drug selectivity and used in the treatment of new indications such as, neuropathic pain to severe or chronic pain management. A modified-

How to cite this article: Boyapati I, Awasthi R, Kulkarni GT. Formulation, characterization, and *in vitro* release studies of modified release multiple unit particulate system (MUPS) of venlafaxine hydrochloride. J Res Pharm. 2022; 26(1): 75-87.

https://dx.doi.org/10.29228/jrp.105
ISSN: 2630-6344

release system can protect the drug from degradation in gastric environment and minimize gastric irritation [7]. Modified-release dosage forms are classified as reservoir and matrix systems. A reservoir system follows zero-order kinetics (linear release as a function of time) whereas a matrix system shows a linear release profile as a function of square root of time [8].

Oral polymer-coated modified-release multiple unit particulate system (MUPS) is gaining significant interest of formulation scientist for oral drug delivery applications [9]. MUPS offers advantages, such as higher processing speed, lower cost of processing, rapid processing, and tamper-proof nature of the product in comparision to the conventional capsules and avoid dust problems during compression of conventional tablets. Oral administration of MUPS controls the release of bioactives and thus controls its absorption from the gastrointestinal tract. A MUPS effectively reduces adverse effects while maintaining the plasma level that needed to achieve therapeutic effect for a longer period. Due to the small size, MUPS has uniform and rapid transit in gastrointestinal tract. This reduces localized irritation; improves absorption and bioavailability of drugs. MUPS has various regulatory advantages, such as the extension of patent life and line extension of the product [10]. However, limited products (tablets) for example Antra® MUPS, Prevacid® SoluTab™ and Beloc® ZOK are available in the market which contains MUPS [11]. Therefore, this is the most flourishing field which needs to focus more on the development of such formulations.

Venlafaxine hydrochloride, freely water-soluble antidepressant molecule, is chemically designated as (R/S) - 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl cyclohexanol hydrochloride [12]. Venlafaxine and its active metabolite O-desmethylvenlafaxine are potent inhibitor of neuronal serotonin and nor-epinephrine reuptake and weak inhibitors of dopamine reuptake [13]. Oral bioavailability of Venlafaxine only 40-45% due to its extensive first-pass metabolism. Conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 h [14]. Thus, the intermittent drug intake becomes necessary to maintain desired drug concentration at target site. This may lead to the sub or supra therapeutic drug concentrations resulting in unpredicted side effects. Thus, the success of a conventional venlafaxine hydrochloride formulation is limited. Extended-release formulations of Venlafaxine has prolonged absorption profile, resulting in a lower maximum plasma concentration (C_{max}) when compared with that obtained after an immediate-release formulation. Venlafaxine extended-release formulation shows the peak plasma concentrations of Venlafaxine after 5.5 post-dose [15].

The purpose of this study was to improve the release profile of venlafaxine hydrochloride for a prolonged period and to overcome above-mentioned limitations of conventional oral drug delivery systems. To achieve these goals the modified release MUPS was formulated using polyvinyl pyrrolidone K-30, ethyl cellulose 20 cps and Hypromellose E 5LV. Preliminary trials were carried out to select the inert carrier, binder, and viscosity grade of rate controlling polymer. Extended release MUPS was prepared using Hypromellose E 5 LV and ethyl cellulose 20 cps. Further, optimization of binder concentration and extended-release coating was carried out. The formulation development of MUPS was divided into two categories as (i) drug layering on inert carrier i.e., sugar spheres and (ii) extended-release coating. Comparative multimedia dissolution study of venlafaxine hydrochloride extended-release capsules was carried out and compared with the marketed formulation to ascertain the *in vitro* drug release behavior.

2. RESULTS AND DISCUSSION

An overlay of the X-ray powder diffraction pattern of venlafaxine hydrochloride (crystalline polymorph form I), venlafaxine hydrochloride monohydrate reference standard, venlafaxine hydrochloride extended-release capsules (initial), venlafaxine hydrochloride extended-release capsules (stored at 40 ± 2°C/75 ± 5% RH for 3 months) and placebo are presented in Figure 1. X-ray powder diffraction pattern of venlafaxine hydrochloride exhibited a crystalline polymorph form having characteristic intense peaks [16]. The X-ray powder diffraction pattern of venlafaxine hydrochloride extended-release capsules exhibited characteristic peaks of monohydrate form of venlafaxine hydrochloride, indicating the conversion of monohydrate form during formulation, and remained unaffected during storage.

DSC thermogram of pure venlafaxine hydrochloride exhibited an exothermic peak at 218.29°C representing its melting point (Figure 2) [17]. Drug loaded pellets containing Hypromellose and ethyl cellulose exhibited exothermic peaks at 215.18°C and 215.04 °C, respectively, indicating melting point of the drug. No thermal event in the examined temperature range was observed. Slight decrease in peak area suggesting partial conversion of the crystalline form of the drug to the amorphous state due to loading of the drug within the pellet matrix (Figure 2) [18, 19].

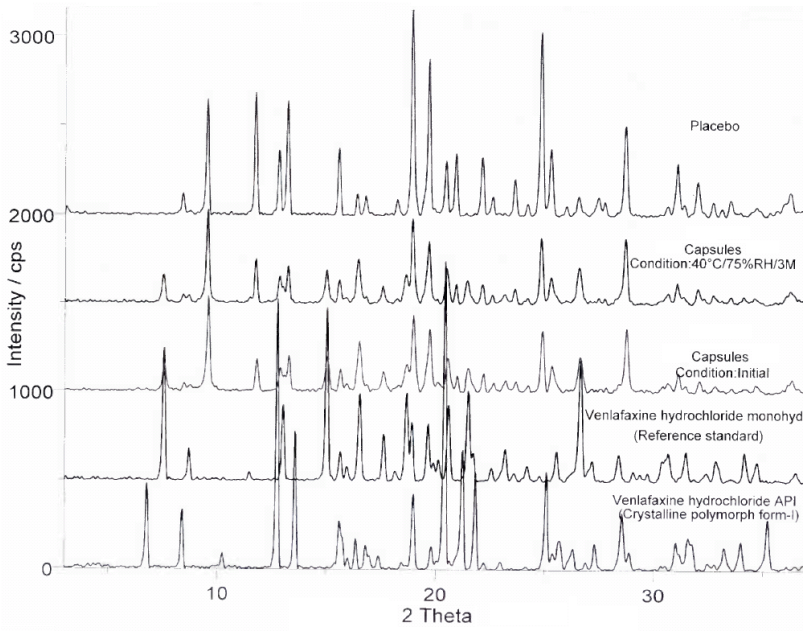

Figure 1. Results of X-ray powder diffraction analysis of venlafaxine hydrochloride API and standard, venlafaxine hydrochloride extended-release capsules (formulation $MUPS_1$) (initial and stored at 40 ± 2°C/75 ± 5% RH for 3 months) and placebo.

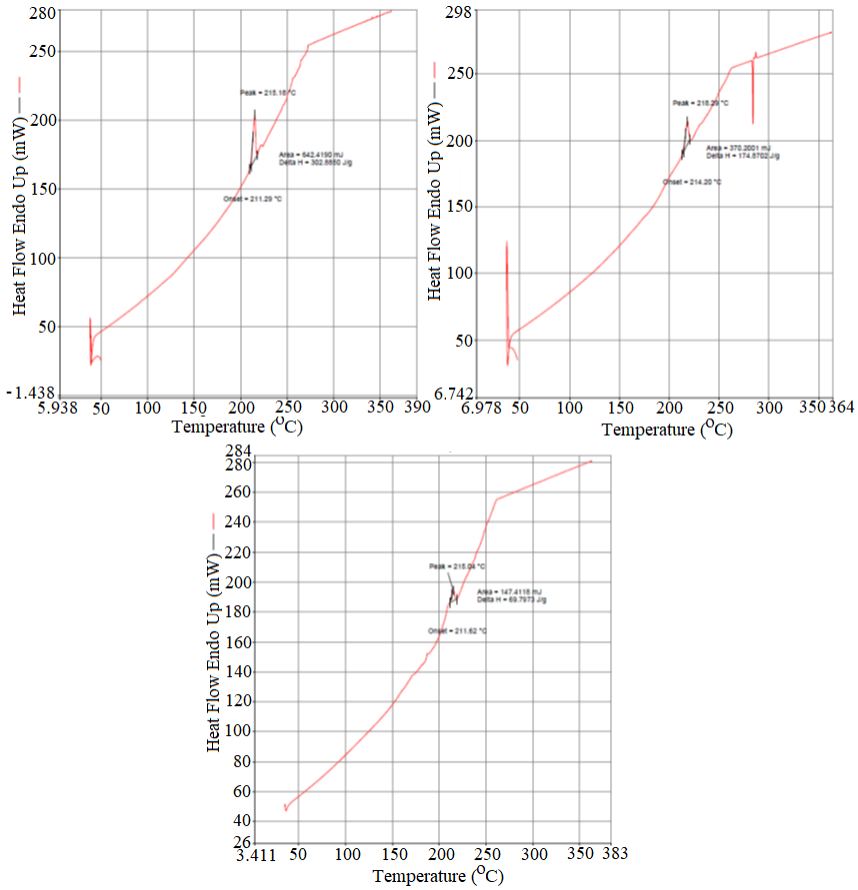

Figure 2. DSC thermogram of pure venlafaxine hydrochloride (A), drug loaded ER-I coated (formulation $MUPS_{13}$) (B), and drug loaded ER-II coated micro-pallets (formulation $MUPS_{16}$) (C).

Percentage drug loading and optimum amount of the polymer to be used may depends on the particle size. In the present study, more than 90% of the extended-release Effexor XR® spheres were found to pass through #14 (ASTM 1.4 mm) and completely retained on #25 mesh (Figure 3). Based on the results of size

distribution study results, it was decided to use sugar spheres in the size range of # 20 to #25 to achieve the product with a desired particle range of #14 pass and #25 retains.

The results show that the percentage yield of the formulation containing Hypromellose E5LV was higher (91%) than the formulation containing polyvinyl pyrrolidone K-30 (86%). The drug loading of formulation containing Hypromellose E 5LV (97.8%) was higher than the formulation containing polyvinyl pyrrolidone K-30 (94.3%). Higher percentage of drug loading in Hypromellose E5LV containing formulation might be due to the formation of a strong and tight gel consistency. Also, the binder type and binder amount had a strong effect on percentage yield. Thus, Hypromellose E 5LV was selected as binder for further studies.

Initial drug release rate was slow in formulations containing ethyl cellulose 10 and 20 cps. However, 57% of the drug was released from formulation containing ethyl cellulose 10 cps after 6 h of dissolution study. Only 48% of drug was released from the formulation containing ethyl cellulose 20 cps in 10 h (Figure 4). Hence, it was decided to use ethyl cellulose 20 cps to further optimize the percentage of coating required to achieve the desired release profile.

The dissolution profile of none of the particulate system exactly matched to that of the innovator product (Figure 5). It seemed difficult to achieve a comparable dissolution profile using spheres with any single ethyl cellulose USNF: Hypromellose E5 LV ratio. Hence, it was thought worthwhile to use a blend of spheres with different coatings to achieve the required dissolution profile. For this, the dissolution profile of 60: 40 blend of spheres containing 80: 20 and 90: 10 ethyl cellulose USNF: Hypromellose E5 LV coating was carried out.

The dissolution profile of venlafaxine hydrochloride spheres containing ER – I (EC: HPMC) 80:20 and ER – II (EC: HPMC) 90:10 (filled in size '0'capsules) matched with that of Effexor® XR capsules 150 mg (Figure 6). Hence, it was decided to blend ER – I and ER – II spheres in the ratio of 60: 40 using talc as lubricant. The spheres formed a loose cohesive mass at low concentration of binder leading to improper fluidization. With higher binder concentration, drug loading efficiency was not improved. Hence, 7% of the binder was selected as optimum for a satisfactory drug loading efficiency and percentage yield (Table 1).

Table 1. Effect of binder concentration on percentage yield and drug loading.

Formulation	$MUPS_9$	$MUPS_{10}$	$MUPS_{11}$
Yield (%)	94.00 ± 1.83	98.00 ± 1.91	94.00 ± 2.34
Drug loading (%)	86.00 ± 1.05	91.00 ± 0.97	90.00 ± 1.33

To optimize the coating level of ER – I and ER – II, the dissolution study of ER – I and ER – II coated spheres was carried out at 7, 10 and 13% and 8, 11 and 14% coating, respectively. The results show that none of the coating attained the dissolution profile as the innovator product (Figure 7).

The dissolution profile of the blends is presented in Figure 8 A. The dissolution profile of sphere blend containing ER – I spheres with 10% coating and ER – II spheres with 11% coating was identical to the innovator product. Hence, a weight buildup of 10% for ER – I spheres and 11% for ER – II spheres was finalized. The dissolution profile presented in Figure 8 B suggest that there is no significant difference between the dissolution profile of capsules containing three ratios of ER – I and ER – II coatings with respect to the innovator product. However, considering the standard deviation values throughout the time points, 60: 40 ratio of blend was finalized and further evaluated to access the comparative multimedia dissolution profiles.

Surface and cross-sectional morphological examination of the drug-loaded sugar pellets before and after ER-I and ER-II coating was carried out using a scanning electron microscope. The pellet surface before and after coatings had relatively smooth surface without any pores (Figure 9). The coated spheres had denser surface compared to the uncoated pellets. Figure 9A shows spherical shape of sugar sphere (749 µm) before drug loading and coating with rate controlling polymer. SEM image of cross-section of blank sugar sphere show a surface thickness of 16.2 µm (Figure 9B). The size of ER-I coated drug loaded sphere was 1.15 mm (Figure 9C) with a surface thickness of 19.8 µm (Figure 9D). The size of ER-II coated drug loaded sphere was 1.04 mm (Figure 9E) with a surface thickness of 20.5 µm (Figure 9F). In both, the ER-I and ER-II coatings, a clear distinction between the sugar sphere core and a coating layer was recorded with no visible deformation of the coating layer. Even after drug loading and coating of sugar spheres the original spherical shape of the pellets remained unchanged, without visible deformations or damages of the spheres.

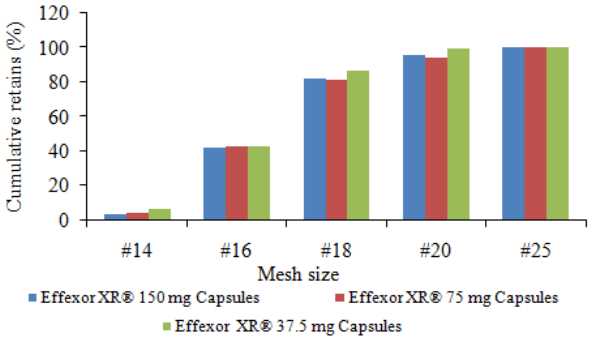

Figure 3. Results of particle size distribution study for the selection of inert carrier (sugar spheres).

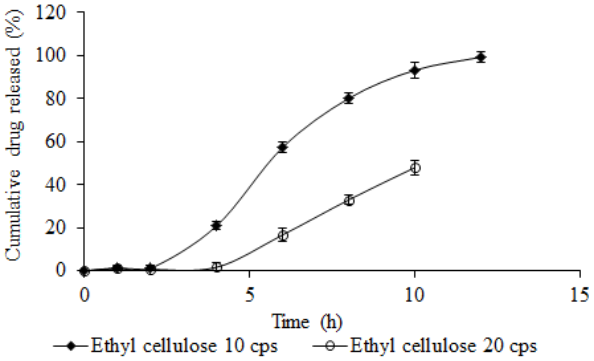

Figure 4. Effect of viscosity grade of rate controlling polymer on dissolution profile of drug in distilled water (filled diamonds: $MUPS_3$ and empty circles: $MUPS_4$). Data presents mean ± SD, n = 6.

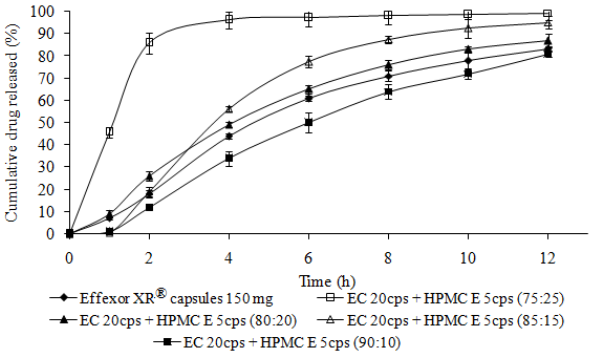

Figure 5. Comparative dissolution profile of venlafaxine hydrochloride from Effector XR® and extended release MUPS (ethyl cellulose in combination with Hypromellose E 5LV) (Filled diamond: Effexor XR® capsule 150 mg, blank squares: $MUPS_5$, filled triangles: $MUPS_6$, empty triangles: $MUPS_7$, filled squares: $MUPS_8$) in distilled water. Data presents mean ± SD, n = 6.

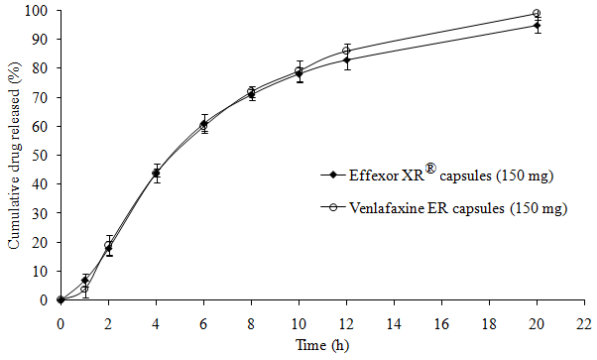

Figure 6. Dissolution profile of venlafaxine hydrochloride spheres formulation $MUPS_1$ (filled in size '0' capsule) and Effexor® XR capsule in distilled water. Data presents mean ± SD, n = 6.

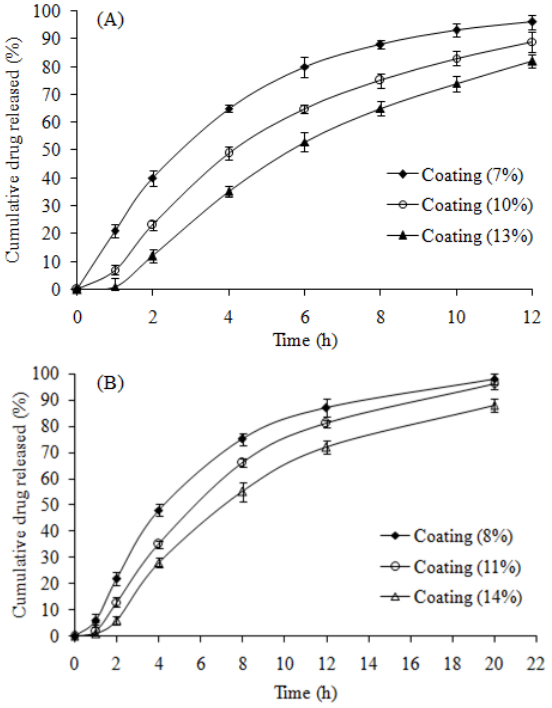

Figure 7. Dissolution profile of venlafaxine hydrochloride from extended-release coating – I (ER – I) (filled diamond $MUPS_{12}$, empty circle $MUPS_{13}$, filled triangle $MUPS_{14}$) (A), and extended-release coating – II (ER – II) (filled diamond $MUPS_{15}$, empty circle $MUPS_{16}$, empty triangle $MUPS_{17}$) (B) in distilled water. Data presents mean ± SD, n = 6.

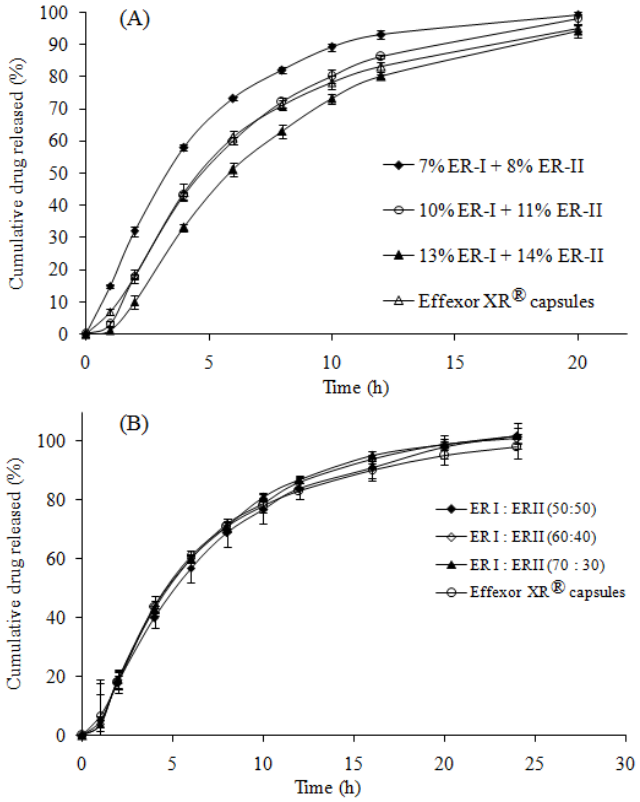

Figure 8. Dissolution profile of venlafaxine hydrochloride from spheres containing blends of ER – I and ER – II ratios (filled diamond: $MUPS_{12}$ + $MUPS_{15}$, empty circle: $MUPS_{13}$ + $MUPS_{16}$, filled triangle: $MUPS_{14}$ + $MUPS_{17}$, empty triangle: Effecxor XR® capsules) (A), and from different ratio of spheres containing blends of ER – I (10%) and ER – II (11%) (filled diamond: $MUPS_{18}$, empty diamond: $MUPS_{19}$, filled triangle: $MUPS_{20}$, empty circle: Effecxor XR® capsules) (B) in distilled water. Data presents mean ± SD, n = 6.

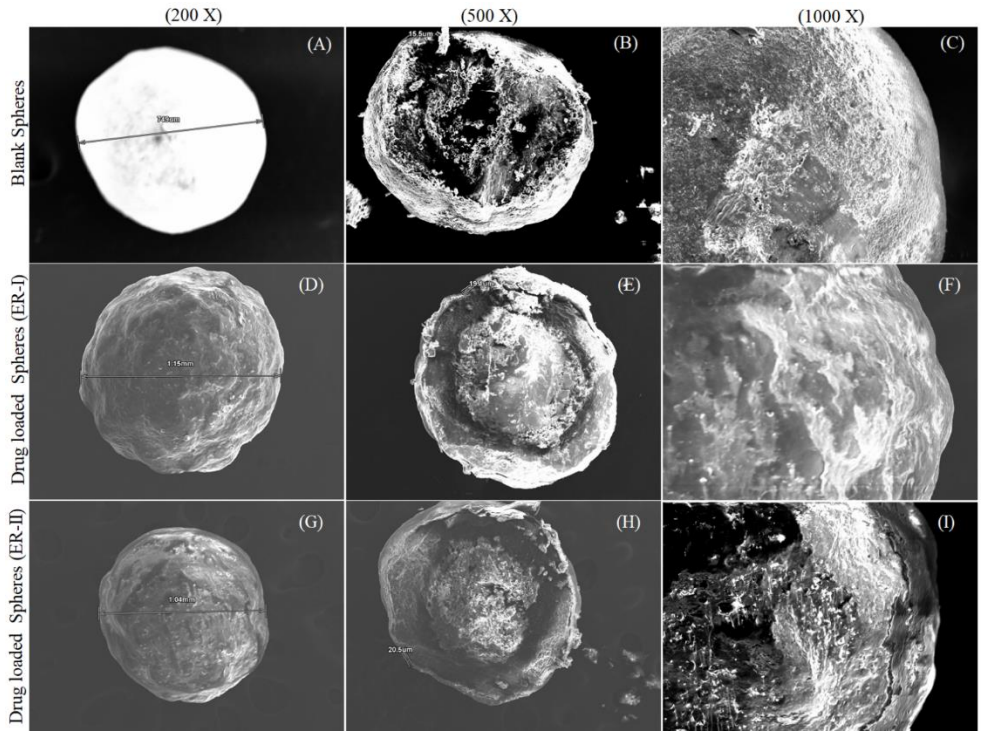

Figure 9. Scanning electron microscopic (SEM) photomicrographs of blank sugar spheres (A, B, C), drug loaded ER-I coated (formulation $MUPS_{13}$) (D, E, F), and drug loaded ER-II coated (formulation $MUPS_{16}$) micro-pallets (G, H, I) at 200, 500, and 1000 nm scales, respectively.

The comparative dissolution study results suggested consistency in the release profiles from the capsules containing prepared MUPS (Figure 10). The drug release from the optimized formulation was identical to the innovator product in all the tested dissolution media. US-FDA suggests that if the value of similarity factor lies within 50-100, the two formulations have similar release profiles. If the value of dissimilarity factor (f_2) is 0 and similarity factor (f_1) is 100 then the two formulations are considered as identical with respect to their dissolution profiles [20]. In the present study, the dissimilarity factor (f_2) values were less than 50 and similarity (f_1) factor values were greater than 50 in all tested dissolution media, indicating that the formulated MUPS and innovators product had similar release profiles (Table 2).

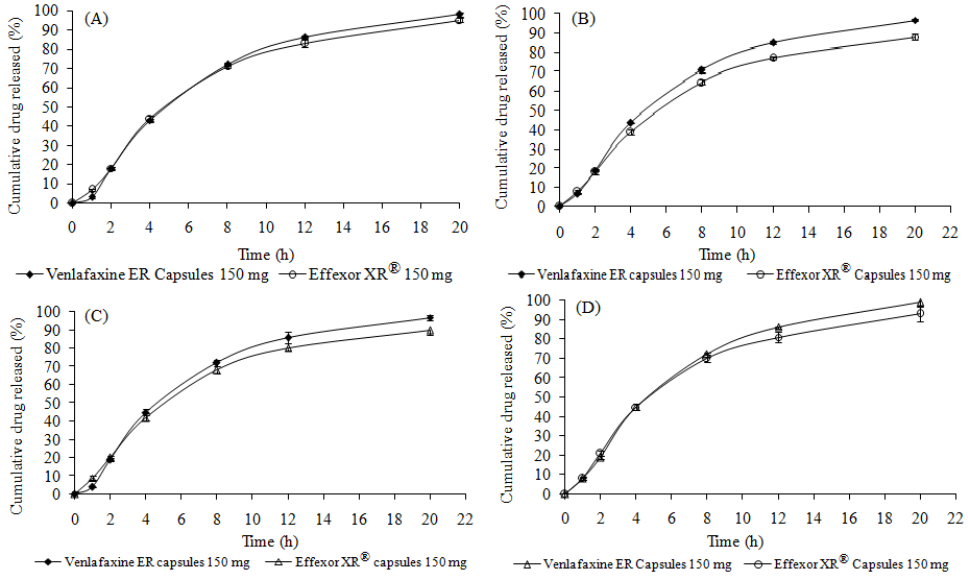

Figure 10. Results of comparative dissolution study of venlafaxine hydrochloride extended-release capsules containing MUPS (batch $MUPS_1$) coated with ER – I (10%) and ER – II (11%) and Effexor XR® 150 mg in distilled water (A), 0.1 N HCl (pH 1.2) (B), acetate buffer (pH 4.5) (C), and phosphate buffer (pH 6.8) (D). Data presents mean ± SD, n = 6.

Table 2. Values of similarity factor (f_2) and dissimilarity factor (f_1) for the multimedia release profile of capsule containing MUPS (batch $MUPS_1$) coated with ER – I (10%) and ER – II (11%) and innovator product (Effexor XR®, Wyeth Pharmaceuticals, USA).

Dissolution media	Similarity factor (f_2)	Dissimilarity factor (f_1)
Water	79	4
0.1 N HCl	61	9
Acetate buffer, pH 4.5	66	8
Phosphate buffer, pH 6.8	73	5

3. CONCLUSION

Venlafaxine hydrochloride loaded MUPS filled in hard gelatin capsule was produced by using polyvinyl pyrrolidone K-30, ethyl cellulose 20 cps and Hypromellose E 5LV. The influence of various binders, sphere size, viscosity grade of rate controlling polymer and coating ratios on the drug release profiles was systematically assessed. All these parameters had tremendous influence on the dissolution behavior of venlafaxine hydrochloride. Apart from the high percentage drug loading, binder showed prolonged drug release effect. The release profile of the best selected formulation matched with the marketed formulation (Effexor XR®). Overall, the formulated venlafaxine hydrochloride loaded MUPS filled in hard gelatin capsule can open a new avenue for the delivery of therapeutics with improved potential.

4. MATERIAL AND METHODS

4.1. Materials

Venlafaxine hydrochloride was purchased from Amoli Organics Pvt. Ltd., Vadodara, India. Sugar spheres USNF (Pharma - spheres™ pellets neutral, 710-850 µm) were obtained from Wilhelm Werner GmbH, Leverkusen, Germany. Hypromellose USP (Methocel E5LV premium) and Ethyl cellulose USNF were purchased from Colorcon, Goa, India. Polyvinyl pyrrolidone K-30 was received from BASF Ludwigshafen, Germany, India. Talc USP was obtained as a generous gift sample from Luzenac Val Chisone S.P.A., Torino, Italy. Empty hard gelatin capsule shell (Size '0' and '1') were procured from Associated Capsules Pvt. Ltd., India. All other chemicals used were of analytical grade.

4.2. Methods

4.2.1. Preliminary trials to select formulation and process parameters

Determination of polymorphism by X – ray diffraction study: To study the effect of processing parameters on the physical state of drug (*i.e.*, crystalline of amorphous), X-ray diffraction study of venlafaxine hydrochloride standard, venlafaxine hydrochloride API, venlafaxine hydrochloride extended-release particles (initial and stored at 40±2°C/75±5% RH for 3 months) filled in hard gelatin capsules was carried out using X-ray powder diffractometer (D8 Advance Davinci, Bruker, Germany) [21].

Analysis of thermal behavior: The DSC thermograms of pure venlafaxine hydrochloride, and drug loaded extended-release particles (ER-I and ER-II) were recorded using a differential scanning calorimeter (DSC 8000, PerkinElmer, Inc, Massachusetts, United States). The instrument was calibrated using zinc (419.5 ^{o}C), tin (232 ^{o}C), and indium (156 ^{o}C), as internal standards. The samples were accurately weighed (5 mg) and sealed into an aluminum pan. The probes were heated from 5 to 390^{o}C at a rate of 10 K/min under nitrogen atmosphere.

Selection of inert carrier (sugar spheres): The size of sugar spheres can influence the rate of drug release. Hence, it was decided to study the particle size distribution of spheres in Effexor XR® capsules (Wyeth Pharmaceuticals, USA). Spheres were separated into different fractions using an electromagnetic sieve shaker (EMS-8, Electrolab Pvt. Ltd., Mumbai, India). The British Standard Sieves # 14, # 16, # 18, # 20 and # 25 were arranged in ascending order *i.e.*, from sieve no. The nest of sieves was shaken for 15 min (at 1.5 amplitude). Percentage cumulative retains was calculated for all the fractions.

Selection of binder and drug loading: Binder type has a significant effect on drug release profile from a pharmaceutical dosage form [22]. In the present study, we evaluated the effect of two different binders i.e., Hypromellose E 5LV and polyvinyl pyrrolidone K-30 for their binding efficiency (Table 3). Briefly, an accurately weighed quantity of venlafaxine hydrochloride was dissolved into the required quantity of purified water (60% of total quantity) in a suitable vessel to get a clear solution. Accurately weighed quantity of binders

were added separately to the remaining quantity of purified water (i.e., 40% of total quantity) with continuous stirring to form a clear solution without foaming and any lump formation. Drug solution was added to the binder solution under continuous stirring. The resulting solution was passed through 250 µm sieve (ASTM mesh # 60) to remove the undissolved particles, if any. Required quantity of talc was added with continuous stirring to form a clear suspension of 45% w/w solid. The resulting drug suspension was sprayed over the sugar spheres. The actual quantity of venlafaxine hydrochloride was calculated based on actual assay and loss on drying (LOD) using following equation 1 where 313.86 and 277.40 are the molecular weights of Venlafaxine hydrochloride and Venlafaxine, respectively.

$$\text{Quantity required (mg/ capsule)} = \text{Label claim} \times 313.86/277.40 \times 100/ (\%\ \text{w/w assay on dried basis}) \times 100/ (100 - \%\ \text{w/w LOD}). \quad \text{(Eq. 1)}$$

Table 3. Composition of drug loaded spheres for screening of binder type in the formulation of extended-release venlafaxine hydrochloride particulate system.

Ingredients (mg/unit)	Formulation code	
	$MUPS_1$	**$MUPS_2$**
Venlafaxine hydrochloride*	169.715	169.715
Sugar spheres	174.285	174.285
Hypromellose E 5LV	16.000	-
Polyvinyl pyrrolidone K-30	-	16.000
Talc USP	42.000	42.000
Purified water	q.s	q.s
Total	402.000	402.000

*equivalent to 150 mg of venlafaxine

Selection of viscosity grade of rate controlling polymer: As per the developmental plan, the drug loaded sugar spheres were coated with different viscosity grades of rate controlling polymer (ethyl cellulose) to examine the effect on dissolution profile at a level of 12% weight gain (Table 4). Briefly, required quantities of methanol and methylene chloride in the ratio of 40: 60 were transferred into a suitable vessel. Different viscosity grades of ethyl cellulose (10 cps and 20 cps) were added separately to the organic phase under continuous stirring to dissolve completely without formation of lumps. The resulting solution was passed through 250 µm sieve (ASTM mesh # 60) and sprayed over drug loaded spheres prepared using Hypromellose E 5LV. The final weight of the coated drug loaded sugar spheres was maintained at 450 mg.

4.2.2. Preliminary trials to select formulation and process parameters

To achieve the dissolution profile comparable to that of innovator product (Effexor XR® 150 mg, Wyeth Pharmaceuticals, USA), it was decided to use Hypromellose E 5 LV as a channeling agent along with the rate controlling polymer (ethyl cellulose 20 cps) (Table 5). Initially for extended-release coating, Talc was not used in $MUPS_3$ and $MUPS_4$ trials. During the extended-release coating process charge development was observed and pellets were found to have tendency to adhere to the walls of the Wurster chamber (GFB Pro 30, M/s. Glatt, India). Hence to improve this behavior, talc was added in all the subsequent trials of extended-release coating. Talc was used as anti-tacking agent in drug loading and extended-release coating. Drug loading and extended-release coating were carried out as per the procedure described in section 4.2.1. Extended-release coating was applied to the drug loaded sugar spheres (formulation $MUPS_1$).

4.2.3. Preliminary trials to select formulation and process parameters

Optimization of binder concentration in drug loading: Based on the results of preliminary batches, three levels of Hypromellose E 5LV (4%, 7% and 10%) (Table 6) were further used to study the percentage yield and drug loading efficiency. The procedure used to prepare drug loaded spheres was similar as mentioned under selection of binder and drug loading.

Table 4. Screening of rate controlling coating polymer in the formulation of extended-release venlafaxine hydrochloride particulate system ($MUPS_1$).

Ingredients (mg/unit)	Formulation code	
	$MUPS_3$	$MUPS_4$
Ethyl cellulose 10 cps	48.000	-
Ethyl cellulose 20 cps	-	48.000
Methanol	q.s.	q.s.
Methylene chloride	q.s.	q.s.

Table 5. Composition of extended-release coating applied to the drug loaded sugar spheres (formulation $MUPS_1$).

Ingredients (mg/unit)	Formulation code			
	$MUPS_5$	$MUPS_6$	$MUPS_7$	$MUPS_8$
Percentage coating	10%	10%	10%	10.5%
Ethyl cellulose 20 cps: Hypromellose E 5LV	75:25	80:20	85:15	90:10
Ethyl cellulose 20 cps	27.30	29.10	30.94	29.59
Hypromellose E 5LV	9.20	7.30	5.46	3.44
Talc USP	3.60	3.60	3.60	8.97
Methanol	q.s.	q.s.	q.s.	q.s.
Methylene chloride	q.s.	q.s.	q.s.	q.s.
Total weight of the coated $MUPS_1$	442.00	442.00	442.00	444.00

Table 6. Composition for the optimization of level of selected binder in venlafaxine hydrochloride extended-release multiple unit particulate system.

Ingredients (mg/unit)	Formulation code		
	$MUPS_9$	$MUPS_{10}$	$MUPS_{11}$
Venlafaxine hydrochloride*	169.715	169.715	169.715
Sugar spheres (20/25)	174.285	174.285	174.285
Hypromellose E 5LV	9.100 (4%)	16.000 (7%)	22.770 (10%)
Talc USP	48.900	42.000	35.230
Purified water	q.s	q.s	q.s.
Total	402.000	402.000	402.000

*equivalent to 150 mg of venlafaxine

Optimization of extended-release coating (ER – I and ER – II): To optimize the percentage buildup of extended-release coating, spheres were prepared with 7, 10 and 13% buildup using Ethyl cellulose 20 cps and Hypromellose E 5LV at 80: 20 (ER – I). Similarly, three batches were prepared with 8, 11 and 14% buildup using Ethyl cellulose 20 cps and Hypromellose E 5LV at 90: 10 (ER – II) (Table 7). The procedure used to prepare drug loaded spheres was similar as mentioned in section 4.2.1. Dissolution study was carried out in 900 mL of distilled water using USP tablet dissolution type I (TDT 08L, Electrolab, Mumbai, India). The temperature was maintained at 37°C and the basket was rotated at 100 rpm. Samples were withdrawn at predetermined time interval of 1, 2, 4, 6, 8, 10 and 12 h for ER – I and 1, 2, 4, 8, 12 and 20 h for ER – II. Same volume of dissolution media (maintained at 37°C) was added after each sampling to maintain sink condition. Sampling was carried out in six replicated for each time point. The samples were analyzed using UV spectrophotometer (UV 3000+, Lab India Instruments, Mumbai, India) at 225 nm to estimate the cumulative percentage of drug released.

Optimization of blending ratio of ER – I and ER – II: Three different blending ratios (50:50, 60:40 and 70:30) of ER – I (10% coated) and ER – II (11% coated) were used to select best coating to achieve desired release profile of venlafaxine hydrochloride. Talc USP was used as a lubricant for the blending of the ERI and ER – II spheres (Table 8).

Morphological characterization of sugar based blank, and drug loaded ER coated MUPS: The morphological characterization of blank and drug loaded coated MUPS was carried out using a scanning electron microscope (SEM) (SU1510, Hitachi, Marunouchi, Japan). The samples for SEM analysis were attached on the stubs by

adhesive carbon tape and coated with silver under argon atmosphere using a high-vacuum evaporator before observation. Coated samples were scanned, and photomicrographs were taken.

Table 7. Selection of extended-release coating (ER – I and ER – II) for venlafaxine hydrochloride extended-release multiple unit particulate system (formulation $MUPS_1$).

Ingredients (mg/unit)	ER – I			ER – II		
	$MUPS_{12}$	$MUPS_{13}$	$MUPS_{14}$	$MUPS_{15}$	$MUPS_{16}$	$MUPS_{17}$
Extended-release coating	7%	10%	13%	8%	11%	14%
Ethyl cellulose USNF (20 cps)	20.400	29.100	37.830	22.500	31.000	39.500
Hypromellose E5LV	5.200	7.300	9.490	2.600	3.600	4.600
Talc USP	2.400	3.60	4.680	6.800	9.400	11.820
Methyl alcohol USNF	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Methylene chloride USNF	q.s.	q.s.	q.s.	q.s	q.s.	q.s.
Total weight of the coated $MUPS_1$	430.000	442.000	454.000	434.000	446.000	458.000

Table 8. Optimization of blending ratio of extended-release coatings (ER – I and ER - II).

Ingredients (mg/capsule)	$MUPS_{18}$	$MUPS_{19}$	$MUPS_{20}$
Blending ratio (ER I: ER II)	50: 50	60: 40	70: 30
ER – I spheres (10% coated)	223.58	268.30	313.00
ER – II spheres (11% coated)	229.12	183.30	137.47
Talc USP	1.13	1.13	1.13
Weight of blended spheres*	453.58	452.73	451.6

The weights of ER-I and ER-II spheres are based on assay value of respective coated spheres, *weight of the coated $MUPS_1$

4.3. Optimized method for preparation of extended-release system

4.3.1. Drug loading

For drug loading, weighed quantity of venlafaxine hydrochloride was dissolved in required quantity of purified water (60% of total quantity) to get a clear solution. Hypromellose E 5LV was dissolved in the remaining quantity of purified water (40% of total quantity). Both the solutions were mixed under continuous stirring to form a clear solution without any lump formation and foaming. The resultant solution was passed through 250 µm sieve (ASTM mesh #60). Talc was added with continuous stirring to form a clear suspension of 45% w/w solids. The sugar spheres were sifted through 850 µm sieve (ASTM mesh no # 20). The under sized sugar spheres were passed through 710 µm sieve (ASTM mesh no # 25). The under-size spheres were discarded, and the required quantity of oversize spheres was loaded into Wurster chamber (GFB Pro 30, M/s. Glatt, India). The bed temperature was maintained at 35°C ± 10°C. The drug suspension containing talc was sprayed to achieve desired weight gain. The dried drug coated spheres were passed through 1.18 µm sieve (ASTM mesh no # 16).

4.3.2. Extended-release coating

The drug loaded spheres were used for ER – I (ethyl cellulose 20 cps and Hypromellose E 5LV at 80: 20) coating or ER – II (ethyl cellulose 20 cps 10 % and Hypromellose E 5LV at 90: 10) coating. To prepare coating solutions, required quantity of ethyl cellulose and Hypromellose E 5LV were dissolved in a methanol and methylene chloride solvent system (40:60 ratio). The solutions were passed through 250 µm sieve (ASTM mesh #60). Talc was added under stirring to form uniform suspension of 6.53% w/w and 7.54% w/w solids, respectively for ER – I and ER – II coating. The coating of the spheres was carried out in a Wurster chamber (GFB Pro 30, M/s. Glatt, India) at 37°C ± 5°C. The percentage of coating was 10% and 11%, respectively for ER – I and ER – II coating. The coated spheres were dried to obtain the LOD as NMT 3.0%. The dried coated

spheres were sifted through 1.4 µm sieve (ASTM mesh no # 14). Oversized spheres were removed, and undersize spheres further passes through 710 µm sieve (ASTM mesh no # 25).

4.3.3. Blending of ER – I and ER – II

The ER I and ER II coated spheres were blended in the ratio of 60% (ER – I spheres) and 40% (ER – II spheres) for 10 min. Talc was shifted through 150 µm sieve (ASTM mesh no # 100) and mixed to the ER – I and ER – II blend.

4.3.4. Filling in hard gelatin capsule

The blended/lubricated extended-release drug coated spheres were filled in empty hard gelatin capsules (size 0).

4.4. Comparative multimedia dissolution study

Being an extended-release product, a comparative dissolution data was generated with the optimized composition across the physiological pH (pH 1.2 to pH 6.8). This is done to ensure that the proposed formulation has similar release behavior in comparison to the innovator product across the physiological pH. The comparative dissolution study of formulated extended release MUPS of venlafaxine hydrochloride filled in hard gelatin capsule (Size 0, No. 1) and innovator product (Effexor XR® 150 mg, Wyeth Pharmaceuticals, USA) was carried out in 900 mL of different dissolution media (distilled water, 0.1N HCl, acetate buffer (pH 4.5) and phosphate buffer (pH 6.8) using type I dissolution apparatus (Basket) at 100 rpm. The temperature of dissolution media was maintained at 37±0.5°C. Sampling was carried out in six replicates at predetermined time intervals. The same volume of fresh dissolution media (maintained at 37°C) was replaced after each sampling to maintain the sink condition. The samples were analyzed at 225 nm using UV spectrophotometer (UV 3000+, Lab India Instruments, Mumbai, India).

The release data of extended release MUPS (formulation $MUPS_1$) coated with ER-I (10%) and ER-II (11%) filled in hard gelatin capsule was analyzed for similarity factor (f_2) and dissimilarity factor (f_1) to find out the degree of closeness between the release profiles of different formulations.

Author contributions: Concept – I.B., R.A., G.T.K.; Design – R.A., G.T.K.; Supervision – R.A., G.T.K.; Resources – I.B.; Materials – I.B.; Data Collection and/or Processing – I.B.; Analysis and/or Interpretation – R.A., G.T.K.; Literature Search – I.B., R.A.; Writing – R.A..; Critical Reviews – I.B., R.A., G.T.K.

Conflict of interest statement: The authors declared no conflict of interest in the manuscript.

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