

Comparative In Vitro Dissolution Testing of Hydrophilic Controlled-Release Venlafaxine Matrix Tablets and Effexor XR Using QbD

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ABSTRACT

A hydrophilic matrix-based, controlled-release formulation for venlafaxine HCl (Ven HCl) was developed using a combination of various forms of hydroxypropyl methylcellulose (HPMC K4M, K15M, and K100M). The aim of the development was to match the dissolution profile (similarity factor $f_2 > 50$) of Effexor XR capsules. The dissolution profile studies for the optimized formulation were performed as per the FDA guidelines for modified-release (MR) products using a QbD approach. The data show that the matrix-based formulation is statistically similar to Effexor XR in multimedia dissolution testing at different rpm, and the results between USP Apparatus 1 and 2 are similar. An alcohol-induced dose-dumping study was also performed, and the results are comparable. This indicates that the hydrophilic matrix tablet formulation is equivalent to Effexor XR, which is based on a coated-pellet platform.

KEYWORDS: Effexor XR; hydrophilic matrix tablets; dissolution; similarity factor.

INTRODUCTION

Venlafaxine (brand names Effexor, Effexor XR, Lanvexin, and Trevilor) is an antidepressant of the serotonin–norepinephrine reuptake inhibitor (SNRI) class (1–3). Venlafaxine is used primarily for the treatment of depression, general anxiety disorder, social phobia, panic disorder, and vasomotor symptoms (4). The extended-release (controlled-release) venlafaxine formulations give lower peak plasma concentrations over a longer period than the conventional formulations, and studies have indicated that the extended-release formulation has a lower incidence of nausea as a side effect and the resulting discontinuation of treatment (5).

The delivery system available for the controlled release of venlafaxine is a drug-loaded pellet with an ethyl cellulose coating contained in a capsule (4). Various patents (6–8) also disclose extended-release (once-a-day) venlafaxine formulations to be composed of spheroids of Ven HCl coated with either ethyl cellulose or a combination of ethyl cellulose and hydroxypropyl methylcellulose (HPMC). This multi-unit particulate system (MUPS) is extremely expensive and time-consuming to produce on the shop floor due to multiple coating stages, long coating times, capsule filling after testing, and evaluation of pellets at completion of each stage (9). In the present work, a

simple hydrophilic matrix-based tablet formulation was developed using a 33 full-factorial design with a target dissolution profile similar to that of Effexor XR capsules. The optimized formulation containing 75 mg venlafaxine was subjected to predictive dissolution testing as per FDA guidelines for QbD of modified-release (MR) tablets (10) and compared with the marketed Effexor XR capsule (containing 75 mg venlafaxine). The calculated similarity factor was used to statistically compare the dissolution profiles of Effexor XR and the matrix-controlled tablets.

MATERIALS AND METHODS

Materials

Ven HCl was purchased from EMCO industries (Hyderabad, India). Effexor XR (75-mg venlafaxine extended-release capsule, expiry date April 2016) was procured from the local market. Optimized hydrophilic matrix tablets prepared within the design space were formulated in the laboratory. Potassium dihydrogen orthophosphate, ammonium acetate, glacial acetic acid, ethanol, sodium hydroxide pellets (SD Fine Chemicals, India), hydrochloric acid (Merck India), and deionized water were used where required.

Formulation and Preparation of Hydrophilic Matrix within Design Space

The Ven HCl hydrophilic matrix tablets containing 75

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mg venlafaxine were prepared using different polymer concentrations of HPMC. Different viscosity grades of HPMC (i.e., K4M, K15M, and K100M) were used in combination to prepare the hydrophilic matrix tablets. A full 33 factorial design was applied, and 27 formulations of Ven HCl matrix tablets were prepared by varying the concentrations of HPMC K4M, K15M, and K100M. Design Expert 9.0.3.1 software (Stat-Ease, Minneapolis, MN, USA) was used to plot surface response and contour plots, and the design space was determined using these plots. The design space is shown in Table 1. The optimized hydrophilic matrix tablets of Ven HCl were then formulated within the obtained design space. The composition of the optimized formulation is listed in Table 2. To manufacture the tablets, weighed quantities of Ven HCl, HPMC K4M, K15M, K100M, and Avicel PH 102 were passed through a #30-mesh sieve and blended together for five minutes. Aerosil and magnesium stearate (passed through a #60-mesh sieve) were then mixed with the blend for three minutes. The blended mixture was compressed into 12.5-mm concave, circular tablets each having a weight of 500 mg and hardness in the range of 5–7 kg/cm².

Table 1. Optimized Range of Polymer Concentrations for Ven HCl Hydrophilic Matrix Tablets

HPMC Grade	Low Level (%)	High Level (%)
K4M	13	15.5
K15M	12.2	13.8
K100M	12.2	15.4

Table 2. Composition of Optimized Hydrophilic Matrix Ven HCl Tablets

Sr. No.	Ingredient	Amount/Tablet (% w/w)
1	venlafexine HCl ^a	16.98
2	Avicel PH102	40.57
3	HPMC K4M	14.25
4	HPMC K15M	13
5	HPMC K100M	13.8
6	Magnesium Stearate	1
7	Aerosil	5
Total weight		500 mg

^a venlafexine HCl 84.9 mg is equivalent to venlafexine 75mg.

Dissolution Testing

Dissolution testing of the optimized hydrophilic matrix tablets and Effexor XR was performed as per FDA guidelines for QbD of MR tablets (10). The comparative dissolution profile testing was carried out as per the scheme shown in Table 3.

Table 3. Parameters for Comparative Dissolution Profile Testing

Sr. No.	In Vitro Simulations of In Vivo Conditions	Dissolution Test Medium	Dissolution Test Conditions
1	pH of GIT	0.1 N HCl	900 mL, Apparatus 1, 50 rpm
		pH 4.5 acetate buffer	
		pH 6.8 phosphate buffer	
		Water	
2	Fasted gastric condition	0.1 N HCl	500 mL Apparatus 1, 50 rpm
3	Gastric motility	0.1 N HCl	900 mL, Apparatus 1, 25 rpm, 75 rpm, and 100 rpm
4	-----	0.1 N HCl	900 mL, Apparatus 2 v/s Apparatus 1
5	Alcohol ingestion	0.1 N HCl with 5%, 10%, 20%, and 40% alcohol	900 mL, Apparatus 1, 50 rpm

Validation of the Analytical Method in Different Dissolution Media

The UV spectrophotometric method was validated in different dissolution media (i.e., 0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, water, and 0.1 N HCl with different concentrations of alcohol). The method was validated by the analysis of specificity, linearity, precision, filter paper interference, placebo interference, and solution stability (11, 12) to demonstrate reproducibility and reliability.

Similarity Factor Determination

The in vitro drug release profiles of the hydrophilic matrix tablets were compared with the release profile of Effexor XR Capsules 75 mg by determining the similarity factor, f_2 (13–15) which can be calculated using the equation:

$$f_2 = 50 \cdot \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where n is the number of sampling points, R_t and T_t are the percentage dissolved of the reference and test products, respectively, at each time point t .

The similarity factor (f_2) is a logarithmic transformation of the sum-of-squared error of differences between the test T_t and the reference products R_t over all time points.

Statistical Analysis

The drug release profiles of optimized hydrophilic matrix tablets in the presence and absence of alcohol

in the dissolution medium (0.1 N HCl) were compared statistically with that of Effexor XR. The data were compared using Student's t-test using GraphPad Prism software Version 6.05 (San Diego, CA, USA). A statistically significant difference was indicated when $p < 0.05$.

RESULT AND DISCUSSION

Evaluation of Optimized Tablets

The hydrophilic matrix tablets formulated within the design space were compressed on a single-station tableting machine. The tablets were in compliance with the evaluation parameters. The average tablet weights were 500 ± 10 mg, and the friability of the tablets was 0.42%. The content uniformity results were 98.9–99.7%, assuring uniform distribution of drug in the matrix.

Validation of Analytical Method in Different Dissolution Media

A UV spectrophotometric method for the determination of Ven HCl was developed and validated. Calibration curves were plotted for different dissolution media (i.e., 0.1 N HCl, pH 4.5 buffer, pH 6.8 buffer, water, and 0.1 N HCl with alcohol concentrations of 5%, 10%, 20%, and 40%). The Ven HCl was determined in all the media at 274 nm, and linearity was determined. The linearity range of Ven HCl is 10–300 $\mu\text{g/mL}$ in 0.1 N HCl and water, whereas it is 50–350 $\mu\text{g/mL}$ and 20–350 $\mu\text{g/mL}$ in pH 4.5 and pH 6.8 buffers, respectively. The linearity range in 0.1 N HCl containing different concentrations of alcohol is 20–140 $\mu\text{g/mL}$ except for 0.1 N HCl containing 5% alcohol, for which the range is 20–120 $\mu\text{g/mL}$. The precision (interday and intraday) was determined in various dissolution media, and the %RSD did not exceed 5% for the repeatability and intermediate precision, indicating suitable precision. There was no interference from filter paper or placebo in different dissolution media, and the drug was stable for 9 h in solution.

Dissolution Testing of Optimized Hydrophilic Matrix Tablets and Effexor XR Capsules

The in vitro dissolution studies of Effexor XR and optimized hydrophilic matrix tablets were initially carried out in 900 mL of different dissolution media (water, 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer) at 50 rpm in USP Apparatus 1. The dissolution studies were carried out for 24 h, and the drug release profiles are shown in Figure 1. The dissolution medium was selected on the basis that the drug, when ingested orally, goes into the stomach (pH 1.2) where it could reside for 3 h and then move to the duodenum, the upper part of small intestine. The pH of this part of GIT is in the range of 3.5–5.5 under fed conditions. Therefore, MR dosage forms given orally are typically exposed to this pH under

fed conditions in the stomach and upper part of the small intestine. Hence, dissolution studies carried out in 0.1 N HCl and pH 4.5 acetate buffer simulate the condition of the stomach and duodenum in fasted and fed conditions, and the dissolution medium of pH 6.8 simulates the pH of the large intestine. Water as a dissolution medium simulates the environment in the small intestine of the gastrointestinal tract (GIT) where the drug resides for a longer time during its absorption. The similarity factors between both products were calculated and are 71.90, 73.65, 61.22, and 62.55 for water, 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer, respectively. These results indicate that the optimized hydrophilic matrix tablets show statistically similar drug release to that of the reference product in all dissolution media.

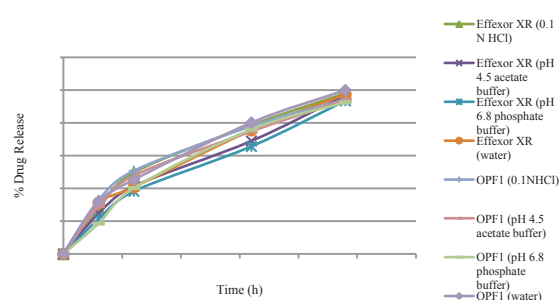


Figure 1. Comparative dissolution profiles of Effexor XR and optimized hydrophilic matrix tablets in different dissolution media.

The volume of the GIT is different in fed and fasted conditions, and dosage forms experience sink conditions in vivo. To mimic these physiologic conditions, the dissolution test was done in different volumes of dissolution medium. Dissolution testing of both Effexor XR and the optimized hydrophilic matrix tablets was performed in USP Apparatus 1 in several volumes of 0.1 N HCl (500 mL, 900 mL, and 1000 mL) at 50 rpm. The similarity factors are 74.104, 73.65, and 62.97 for 500 mL, 900 mL, and 1000 mL, respectively, of 0.1 N HCl. Optimized hydrophilic matrix tablets showed dissolution profiles similar to that of Effexor XR in different volumes of dissolution medium.

The in vitro dissolution method should mimic the physiological conditions of the human GIT. The least motility of the GIT is 25 rpm. The dissolution studies were carried out at 75 rpm, which is considered one of the possible motilities of the GIT that may affect drug bioavailability. The 100-rpm rotation speed of the dissolution apparatus is considered the highest possible motility of the GIT. The similarity factors of the optimized formulation in 900 mL compendial dissolution medium in

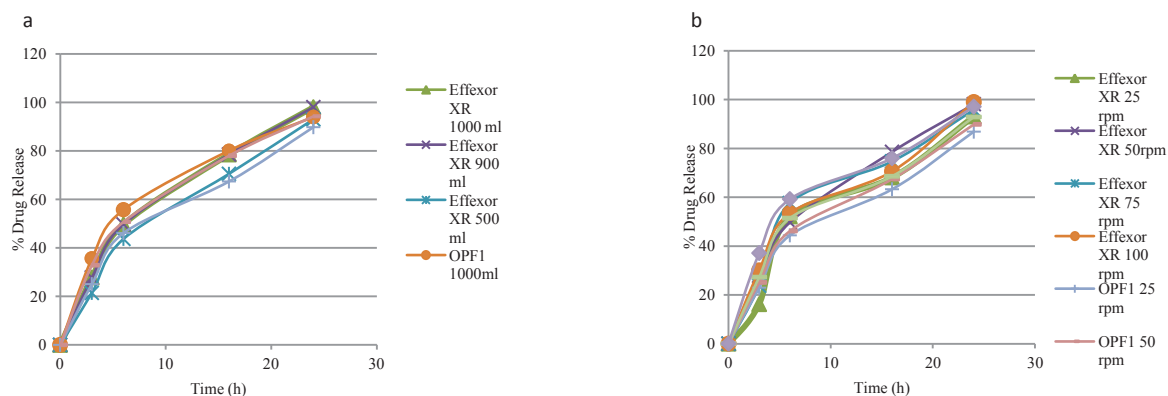


Figure 2. Comparative dissolution profiles of Effexor XR and optimized hydrophilic matrix tablets (a) in different volumes of 0.1 N HCl and (b) at different rpm of dissolution testing.

Apparatus 1 at 25, 50, 75, and 100 rpm are 59.15, 73.64, 64.14, and 62.83, respectively. The similarity factors for the hydrophilic matrix tablets at all speeds are greater than 50, indicating similarity between the reference and the test product in the performance of the delivery system. The comparative dissolution profiles of Effexor XR and the optimized hydrophilic matrix tablets in different dissolution volumes and at different rotation speeds are shown in Figure 2a,b.

In vitro dissolution studies of tablets are commonly performed using USP Apparatus 2. The official USP method for Ven HCl XR capsules calls for Apparatus 1. To evaluate the performance of the hydrophilic matrix tablet and to ensure that the dissolution profile does not change considerably with a change in the type of apparatus, dissolution testing of the reference and test products was done in both Apparatus 1 and Apparatus 2. The similarity factor calculated for dissolution done in Apparatus 2 was 71.645, which indicates that even if Apparatus 1 is replaced with Apparatus 2, the release profile of the drug from matrix tablets will not change, and both apparatus could be used to monitor the dissolution profiles of hydrophilic matrix tablets of Ven HCl.

Because FDA issued an alert (16) to healthcare professionals regarding an alcohol–Palladone interaction, alcohol-induced dose-dumping studies were conducted to ensure robustness of the prepared hydrophilic matrix tablets in the presence of alcohol. Dissolution profile testing was carried out over four hours in media consisting of 900 mL of 0.1 N HCl with varying concentrations of ethanol (5%, 10%, 20%, and 40%). According to the FDA guideline (17), up to 40% ethanol exposure should not induce dose-dumping for MR formulations. The release

profiles of drug from Effexor XR capsules and optimized hydrophilic matrix tablets at different concentrations of alcohol are shown in Figure 3. The results indicate that the release is faster with increasing concentrations of alcohol in the dissolution medium; the release is considerably faster with 40% ethanol than with no alcohol in the dissolution medium. The similarity factors between the reference listed drug and the generic MR optimized formulation were calculated. The f_2 values are 96.22 with no alcohol in the dissolution medium and 73.68, 76.71, 83.89, and 92.03 in the presence of 5%, 10%, 20%, and 40% alcohol, respectively. The results indicate that, in various concentrations of alcohol in the dissolution medium, the optimized formulation has a dissolution profile similar to that of the reference product and the difference in drug release for the generic MR formulation in the presence of alcohol was statistically insignificant ($p > 0.05$) in comparison with the reference product.

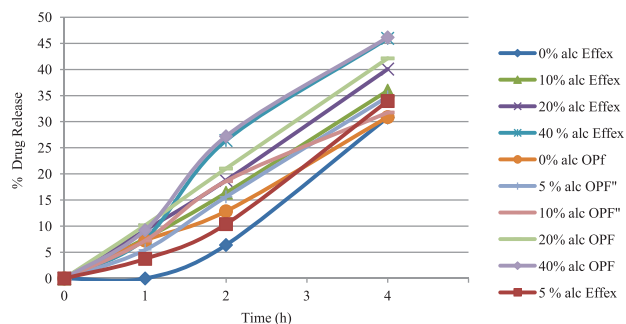


Figure 3. Comparative release profiles of Effexor XR and optimized hydrophilic matrix tablets in different concentrations of alcohol in 0.1 N HCl.

CONCLUSIONS

This study has shown that controlled-release Ven HCl tablets prepared using a hydrophilic-matrix platform instead of a coated-pellet technology (Effexor XR capsule) have *in vitro* drug release performance similar to that of Effexor XR in various dissolution testing conditions. In addition, the drug release profiles of the hydrophilic matrix tablets in dissolution media containing different concentrations of alcohol are similar, which is confirmed by the similarity factor. The formulated hydrophilic matrix tablets are robust in the presence of alcohol as they do not show dose-dumping.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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