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Research Article

Fabrication of Triple-Layer Matrix Tablets of Venlafaxine Hydrochloride Using Xanthan Gum

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Abstract. The objective of present investigation was to develop venlafaxine hydrochloride-layered tablets for obtaining sustained drug release. The tablets containing venlafaxine hydrochloride 150 mg were prepared by wet granulation technique using xanthan gum in the middle layer and barrier layers. The granules and tablets were characterized. The *in vitro* drug dissolution study was conducted in distilled water. The tablets containing two lower strengths were also developed using the same percentage composition of the middle layer. Kinetics of drug release was studied. The optimized batches were tested for water uptake study. Radar diagrams are provided to compare the performance of formulated tablets with the reference products, Effexor XR capsules. The granules ready for compression exhibited good flow and compressibility when xanthan gum was used in the intragranular and extragranular fractions. Monolayer tablets failed to give the release pattern similar to that of the reference product. The drug release was best explained by Weibull model. A unified Weibull equation was evolved to express drug release from the formulated tablets. Lactose facilitated drug release from barrier layers. Substantial water uptake and gelling of xanthan gum appears to be responsible for sustained drug release. The present study underlines the importance of formulation factors in achieving same drug release pattern from three strengths of venlafaxine hydrochloride tablets.

KEY WORDS: layered tablet; radar diagram; venlafaxine hydrochloride; weibull model; xanthan gum.

INTRODUCTION

An active pharmaceutical ingredient is uniformly distributed within a polymer matrix in hydrophilic matrix system (1). The drug release is extended over a much greater time from a matrix system as compared to immediate release dosage forms. In the recent years, preparation of matrix tablets has been demonstrated with the publication of numerous patents and research papers and their utilization in new products. The widespread and successful use of such polymeric systems could be attributed to their ease of manufacturing, relatively low cost, high biocompatibility, favorable *in vivo* performance, and versatility in controlling the release of drugs with a wide range of physicochemical properties (2,3).

Xanthan gum is a hydrophilic polymer, secreted from *Xanthomonas campestris* (a Gram-negative, yellow-pigmented bacterium) (4). It is used for the fabrication of matrices with uniform drug release characteristics (5–11). Xanthan gum is the only bacterial polysaccharide produced industrially on a large scale. It is a natural carbohydrate commercially produced by fermenting glucose with the appropriate microorganisms. Xanthan gum contains glucose 37%, mannose 43.4%, glucuronic acid 19.5%, acetate 4.5%, and pyruvate 4.4%. Xanthan gum swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug can slowly diffuse. This property makes xanthan gum a useful ingredient for controlled release and sustained release (SR) applications. Its compatibility with a wide variety of ingredients makes it particularly effective in these applications. Xanthan gum has been evaluated as a hydrophilic matrix for different model drugs including theophylline (12), cephalexin (13), prednisolone (14), indomethacin (15), and diclofenac sodium (16).

Venlafaxine imparts its antidepressant effects by inhibiting the neuronal uptake of norepinephrine, serotonin, and to a lesser extent, dopamine (17). The short biological half-life (5±2 h) and the fast clearance make the drug suitable candidate for the development of once-a-day formulation. Furthermore, it is an antidepressant, and so it is required to be taken for quite a long period. The recommended dose of venlafaxine hydrochloride is 75 to 450 mg/day. The use of extended release formulation is associated with less nausea and dizziness at the initiation of therapy (18). Effexor® XR capsules containing coated pellets were used as reference product. The major advantages of multiplayer approach over the coating method are higher productivity, shorter processing time, and minimum variation between and within batches.

US patents 7090867 and 6607751 and patent application 20030091634 covered the use of cellulose ether along with microbial polysaccharide for the development of modified

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release tablet of venlafaxine hydrochloride. US patents 6274171 and 6403120 employed coating of spheroids (pellets) with water insoluble excipients like ethyl cellulose. An effort was made in the present investigation to develop functional dosage forms of venlafaxine hydrochloride using a hybrid technique of direct compression and wet granulation. The objective of the present study was to obtain drug-release profile similar to that of the reference product using a simpler method.

MATERIALS AND METHODS

Venlafaxine hydrochloride ($D(v,0.1)2.79\mu, D(v,0.5)10.04\mu$, and $D(v,0.9)43.98\mu$) was received as a gift sample from Cadila Healthcare Ltd., Ankleshwar. Xanthan gum was obtained from Alok International, Mumbai. Microcrystalline cellulose (Avicel PH 101, Avicel PH 102) and lactose monohydrate (Pharmatose DCL 21) were received from Colorcon Asia Pvt. Ltd., Goa. Magnesium stearate was purchased from Laser Chemicals, Ahmedabad. Effexor® XR Capsules (Wyeth Pharmaceuticals Inc.) containing 150, 75, and 37.5 mg of venlafaxine HCl with expiry dates 04/2011, 01/2011, and 04/2011, respectively, were used as reference products.

Preparation and Evaluation of Venlafaxine Hydrochloride Tablets

Modified release tablets of venlafaxine hydrochloride were prepared by hybrid wet granulation technique. Xanthan gum was used as a matrix forming material while Avicel PH 101 was used as a granulation facilitator and compression aid. The drug, intragranular fraction of xanthan gum (25% of total xanthan gum), and Avicel PH 101 were blended and granulated with water using rapid mixer granulator (Saral Engineering Company, Mumbai, India). The wet mass was dried in a tray dryer at 60°±5°C temperature until loss on drying was below 3%. The partially dried blend was sieved through mesh #24. The granules were blended using conta blender (Saral Engineering Company, Mumbai, India) for 10 min with the extragranular fraction of xanthan gum (batch A1 to A3) and Avicel PH 102 (batch A3). The formulation of monolayer tablets of venlafaxine hydrochloride (A1, A2, and A3) is shown in Table I. The blends were lubricated with magnesium stearate. The granules ready for compression were evaluated for angle of repose, Carr's index, and Hausner ratio. The batch size was 1,000 tablets for batches A1 to A3. The tablets were prepared by compressing the lubricated blend using 16 station rotary tablet press. Triple layer tablets were prepared by putting drug-free barrier layers on either side of the middle layer. The granules of middle layer were prepared as described above. Table I depicts the composition of batches A4 to A9. The core was made only of intragranular composition and the drug free barrier layer consisted of xanthan gum, Avicel PH 102 or pharmatose DCL 11, and magnesium stearate (extragranular composition, Table I). Each layer was sequentially filled in die cavity. Finally, the compression force was applied. The "Rimek" triple layer tablet compression machine (Karnavati Engineering Ltd., Mehsana, India) was used for compression of layered tablets. The batch size was 2,000 tablets for batches A4 to A9. The monolayer and triple layer tablets were examined for uniformity of weight, thickness, crushing strength, friability, and *in vitro* drug dissolution. The thickness and crushing strength were measured on hardness tester (Dr. Schleuniger Pharmatron AG, Switzerland). Friability was measured using Roche type friabilitor (Electrolab, Mumbai) by rotating the tablets for 4 min for 100 rotation.

Modified release tablets of venlafaxine hydrochloride with lower strengths were also formulated. From industrial point of view, it is always preferable to go for scale-up–scale-down for different strengths. The composition of granules for middle layer and barrier layers were kept same as that of batch A8, but the weight of barrier layer was changed to obtain release profile similar to that of reference product. Table II shows composition of tablets of lower strengths. The optimized formulation in each category was compared using similarity factor (f_2 value) (19). The amount of drug released from the three strengths were compared using surface area of the tablets. The tablet was assumed to be cylinder in shape; hence, the surface area was calculated using the following equation:

$$\text{Surface area} = 2\pi rh + 2\pi r^2 \quad (1)$$

Where r is radius of the tablet in centimeters and h is thickness of the tablet in centimeters. Round punches with 10 mm diameter were used for preparing batches A1 to A8. The batches B1 to B4 and C1, C2 were prepared using punches with 7.8 mm diameter. The thickness of the venlafaxine

Table I. Composition of Venlafaxine Hydrochloride Tablets

Ingredients (mg)	Batch code								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
Intragranular composition[a]									
Venlafaxine hydrochloride[b]	169.8	169.8	169.8	169.8	169.8	169.8	169.8	169.8	169.8
Xanthan gum	42.5	63.7	42.5	42.5	42.5	22.5	42.5	42.5	42.5
Avicel PH 101	53.0	53.0	53.0	53.0	53.0	53.0	53.0	53.0	53.0
Extragranular composition[a]									
Xanthan gum	127.4	191.0	127.4	127.4	127.4	127.4	85.0	75.0	65.0
Avicel PH 102	–	–	50.0	50.0	–	–	–	–	–
Pharmatose DCL 11	–	–	–	–	50.0	50.4	50.2	60.2	70.2
Magnesium stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5

[a] For batches A4 to A9, intragranular composition and extragranular composition represent core and barrier layer, respectively
[b] 169.8 mg venlafaxine hydrochloride is equivalent to 150 mg of venlafaxine base

Table II. Composition of Venlafaxine Hydrochloride Tablets

Ingredients (mg)	Batch code					
	B1	B2	B3	B4	C1	C2
Intragranular composition						
Venlafaxine hydrochloride	84.9	84.9	84.9	84.9	42.5	42.5
Xanthan gum	21.3	21.3	21.3	21.3	10.1	10.1
Avicel PH 101	26.5	26.5	26.5	26.5	13.8	13.8
Extragranular composition						
Xanthan gum	75.0	60.0	50.0	37.5	45.0	37.5
Pharmatose DCL 11	60.0	48.0	40.0	30.0	36.0	30.0
Magnesium stearate	7.5	6.0	5.0	3.8	4.5	3.8

hydrochloride tablets were 0.60, 0.45, and 0.39 cm, respectively, for batches A8, B3, and C1. Hence, the surface area of batches A8, B3, and C1 was 3.45, 2.11, and 1.91 cm^2, respectively. The drug release in milligrams per square centimeter was calculated and converted in percent value (Table III).

In Vitro Dissolution Studies

In vitro drug-release study (n=3) was carried out in USP apparatus I (Electrolab TDT 06-T, Mumbai, India) in 900 mL of distilled water at 37°±0.5C°. Five-milliliter samples were pulled at predetermined times. The drug solution was replaced with equal volume of distilled water. The samples were diluted with water and analyzed at 226 nm using UV visible spectrophotometer (Shimadzu-1700, Japan). The dissolution study was also performed for reference products (Effexor® XR Capsules 150, 75, and 37.5 mg). The optimized batch was also investigated for drug dissolution in distilled water containing 10% ethanol.

Drug-Release Kinetics

In order to investigate the kinetics of drug release from matrix tablets, the data of *in vitro* drug release were fitted to different models (20–24). The program was developed using FORTRAN language for zero order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, and Weibull models. The F value was employed to select the most appropriate kinetic model.

Water-Uptake Study

The swelling behavior of batches A8, B3, and C1 was studied (25). The tablets (n=3) were kept in beaker containing 100 mL distilled water at 37°±2°C. At selected time points, the tablets were withdrawn, wiped with tissue paper, and weighed. The percent water uptake by the tablet was calculated using the following formula:

$$\text{Percentage water uptake} = 100 \times \left[W_t - W_0 / W_0 \right] \quad (2)$$

Where W_t was weight of tablet at time t and W_0 was initial weight of the tablet.

The Radar Graphs

In the dissolution study, higher or lower % drug release than a target is permitted up to a certain limit. Shah *et al.* proposed that the maximum difference can be 10% (f_2=50) for establishing similarity (26). The reference products dissolution data were used as ideal release pattern. The ideal % drug release will get a score of 5 on a scale of 0 (ideal −10%) to 10 (ideal +10%). The lower and high permissible % of drug release will get a score of 0 and 10, respectively. The score of optimized batches (A8, B3, and C1) were calculated at each dissolution time point.

$$\text{Score} = 5 + \{(\%T_t - \%R_t)/2\} \quad (3)$$

Table III. Comparison of Drug Release Profile Per Unit Surface Area of All Strengths

Time (h)	Drug release per unit surface area (mg/cm^2)			Percent drug release		
	A8	B3	C1	A8	B3	C1
1	5.7	5.2	2.6	13.1	14.5	13.5
2	9.9	7.6	4.8	22.8	21.3	24.2
4	19.1	15.4	8.9	44.0	43.3	45.4
6	26.0	21.4	12.0	59.8	62.2	61.2
8	32.5	25.6	14.5	74.9	72.8	74.0
10	37.3	28.8	16.2	85.8	81.0	82.5
16	40.0	32.0	17.5	92.1	90.0	89.0
24	42.9	36.0	19.1	98.7	101.1	93.7

Where $\%T_t$ is percentage of drug released from test batch while $\%\ R_t$ is percentage of drug released from reference product at the same time.

RESULTS AND DISCUSSION

Xanthan gum has ability to take up water when it comes in contact with aqueous environment. The processing of xanthan gum becomes difficult due to its sticky nature on wetting, especially when it is used in higher amount. The concept of adding a part of xanthan gum intragranularly and a part extragranularly was adopted to achieve ease in processibility and flexibility in achieving the desired drug-release profile. Use of xanthan gum both intra- and extra-granularly permits addition of higher amount of xanthan gum compared with the classical wet granulation technique. The concept can be adopted only for those excipients that show good flow and compression behavior like xanthan gum. The drug release pattern can be tailored by adjusting the proportion of intra- and extragranular fraction. The process can be considered as a hybrid process between wet granulation and direct compression.

The reference product, Effexor® XR capsules contained coated pellets. The dissolution of the reference product was performed in distilled water and was targeted for the formulated venlafaxine hydrochloride matrix tablets. The reason for choosing distilled water as a dissolution medium is that the Food and Drug Administration (FDA) endorses the use of it as a dissolution medium for the generic version of venlafaxine hydrochloride. The reference product exhibited sustained drug release. The result shown in Fig. 1 reveals that the drug release was less than 25% in first 2 h. The pellets of reference product might be coated with water insoluble coating agent.

The granules of batches (A1 to A9) showed good flow and compressibility as the value of the angle of repose, Carr's index, and Hausner ratio were in the range of 22° to 26°, 15% to 18%, and 1.17 to 1.22, respectively. The developed tablets fulfilled the requirements of crushing strength (>6 kp) and friability (<1%). The problems of weight variation and content variation were not observed. Moreover, high speed tablet press can be used for manufacturing of tablets. It is well known that preparation of pellets and subsequent coating requires expertise and time.

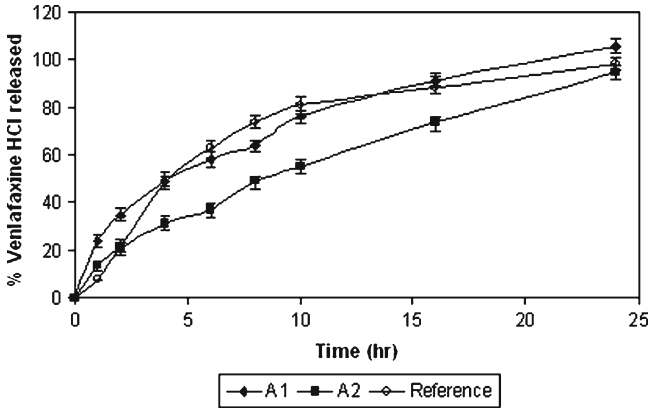

Fig. 1. Comparative release profiles of monolayer matrix tablets

The batches A1, A2, and A3 were compressed as monolayer matrix tablets while batches A4 to A9 were compressed as three-layer matrix tablets. In the batches A1 and A2, xanthan gum to venlafaxine hydrochloride ratio was 1:1 and 1.5:1, respectively. The data for *in vitro* dissolution show that with increase in the amount of xanthan gum, the drug release was decreased (Fig. 1). Neither batch A1 nor batch A2 showed release profile similar to that of the reference product. The two most important challenges in the development of matrix tablets are slow drug release in the earlier phase and complete drug release in the terminal phase with a fairly uniform drug release in between. The batch A1 showed faster drug release until 4 h and comparable drug release with the reference product thereafter while batch A2 showed comparable drug release up to 2 h and slow drug release thereafter. The high aqueous solubility of venlafaxine hydrochloride and high gel viscosity appears to be responsible for the behavior of batches A1 and A2. Thus, it can be concluded that by varying the amount of xanthan gum in uncoated monolayer tablets, the required release profile could not be achieved. Our objective was to avoid the use of time consuming two stage procedures, i.e., compression and subsequent solvent coating or pelletization and coating for the development of sustained release venlafaxine HCl formulation.

The multilayered matrix system overcomes inherent disadvantages of nonlinearity associated with diffusion controlled matrix devices by providing adequate drug-release rate with time (27). Few researchers developed multilayer tablets for modulating release of active pharmaceutical ingredient (API) from hydrophilic polymeric system (17,28–31). The use of xanthan gum has not been explored in layered tablets. Geomatrix® technology was used to reduce the active surface area to engineer the API release at the initial time points. Directly compressible microcrystalline cellulose (Avicel PH 102) was added to the xanthan gum to augment compressibility and increase weight of barrier layer. It is very important to remember that the middle layer and barrier layers should maintain their integrity in the layered tablets during manufacturing, storage, and drug-release study. The excipients were selected considering the stated objectives. The middle layer was formulated using 25% of the total xanthan gum present in the formulation to prevent quick drug release. The gelled particles of xanthan gum provide the required hindrance to drug release. Figure 2 represents the comparative release profile of monolayer matrix tablet (A3) and triple-layer matrix tablet (A4) of same composition. The release rate is reduced in batch A4 compared to batch A3. The probable reason could be availability of limited surface area in batch A4. However, the drug release from batch A4 was slower than the release shown by the reference.

The release rate of API can be increased by incorporation of soluble pore forming material in the barrier layers (Batch A5), by reducing the percent of polymer in core layer (Batch A6), or by reducing the percent of polymer in the barrier layers (Batch A7). Figure 3 shows that incorporation of water soluble excipients such as lactose monohydrate (Pharmatose DCL 11) facilitated the API release rate after 2 h as desired. Batch A6 showed higher drug release than the required release due to quick tablet erosion. Batch A7 showed drug-release profile very close to the reference product. Batches A8 and A9 were prepared to fine-tune the

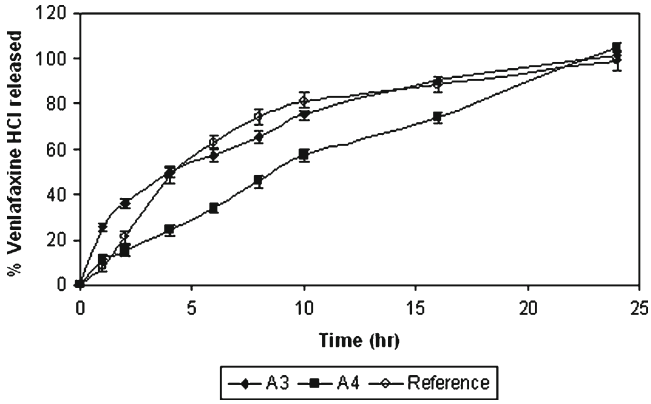

Fig. 2. Comparative release profiles of monolayer matrix tablets (Batch *A3*) with three-layer matrix tablets (Batch *A4*)

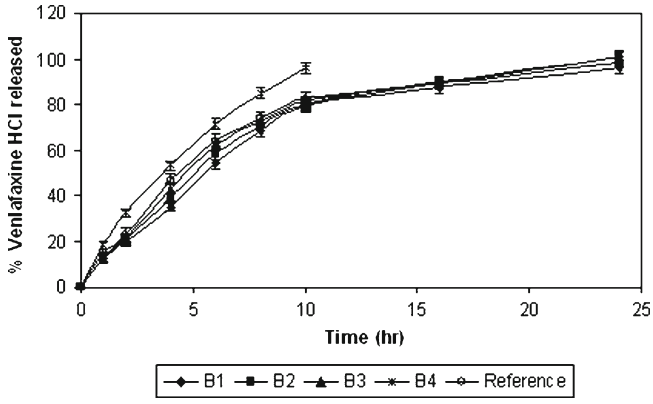

Fig. 4. Comparative release profiles of three-layer matrix tablets of venlafaxine hydrochloride 84.9 mg

drug release (Fig. 3). The batches A7, A8, and A9 showed similarity factor f_2 values of 62, 74, and 70, respectively.

The FDA has recently enforced the testing of modified release dosage forms in dissolution media containing ethanol. The FDA mentioned that the potentially fatal interaction of a modified release system might be observed on consumption with alcohol which resulted in impairment of the formulation and dose dumping (32). Hence, effect of ethanol on release of venlafaxine hydrochloride was studied. Ten percent concentration of ethanol typical of those found in alcoholic beverages was included in dissolution medium (distilled water). The dissolution study of batch A8 was performed using same dissolution conditions with and without ethanol. Batch A8 showed similarity factor (f_2) 92 with and without ethanol. The matrix of xanthan gum will not collapse in presence of alcohol since it is insoluble in alcohol (33). Thus, we can conclude that the developed formulation is robust and is safe to take with alcohol. Batch A8 was selected for development of tablets with other strengths, i.e., 75 and 37.5 mg.

The Effexor® XR capsules are available in three strengths, 150, 75, and 37.5 mg. Respective strengths were used as reference for development of venlafaxine hydrochloride tablets. Four batches of venlafaxine hydrochloride with 75-mg drug content and two batches of venlafaxine hydrochloride with 37.5-mg drug content were prepared and evaluated (Table II). The comparative release profiles are shown in Figs. 4 and 5. The batch B1 showed slower drug release as the thickness of barrier layer was higher compared to that of batch A8. The batches B1, B2, B3, B4, C1, and C2 showed f_2 values of 60, 70, 83, 51, 89, and 79, respectively. Hence, the tablets of batches B3 and C1 were selected and evaluated for swelling behavior.

It is well known that the drug-release profile from the SR tablet changes with the surface area of tablet. To correlate the drug-release rate from tablets of different strength, the surface area of optimized batches was calculated followed by normalization of drug release in milligrams per unit area. For batches A8, B3, and C1, the complete release corresponded to 43.43, 35.61, and 19.63 mg/cm^2. The drug release was expressed in terms of percentage considering the three computed values. The results shown in Table III reveals that the percentage of drug release from the three optimized batches, using calculated normalized amount of drug release (mg/cm^2), was almost identical. The percentage composition of core layer of the three batches was identical. However, the barrier layer composition was different. Formulation development time can be shortened in industry simply by focusing on barrier layer composition.

The goodness-of-fit test was used to determine the mechanism of drug release. The *in vitro* dissolution data of batches A7, A8, and A9 were fitted to different mathematical models using software developed in FORTRAN language.

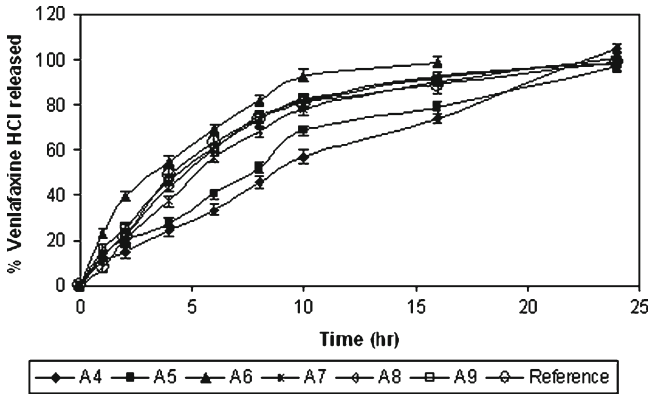

Fig. 3. Comparative release profiles of three-layer matrix tablets of venlafaxine hydrochloride

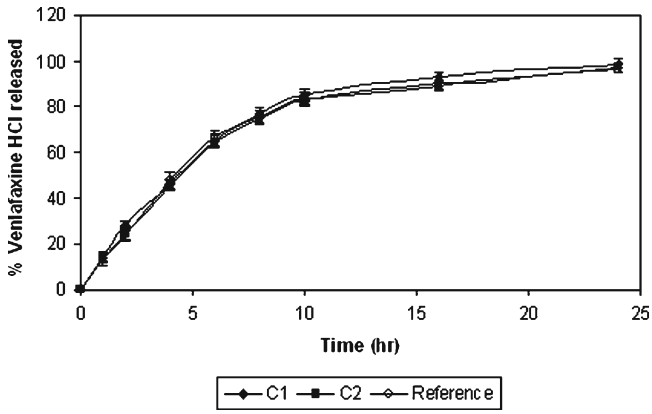

Fig. 5. Comparative release profiles of three-layer matrix tablets venlafaxine hydrochloride 42.5 mg

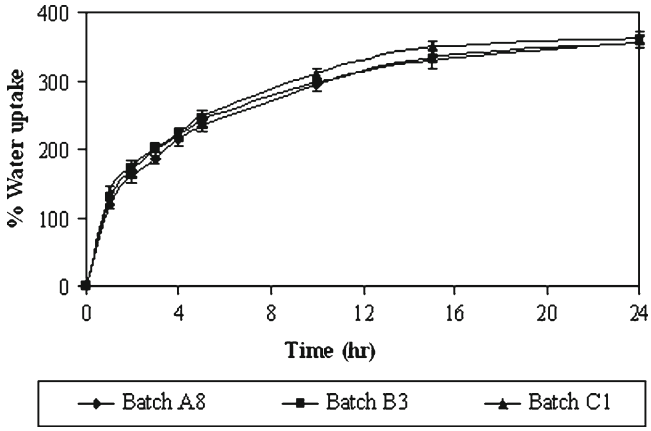

Fig. 6. Water uptake of optimized batches of venlafaxine hydrochloride tablets of all strength

Weibull model showed best fit. The dissolution data of Effexor XR capsule was also subjected to model fitting. The Fisher's ratio (F) was 20 for the Weibull model. The next objective was to develop unified equation to correlates drug release from different batches within the area of interest with time. Weibull equation is given below (34):

$$M = 1 - e^{-(t^{\beta})/\alpha} \tag{4}$$

Where M is the cumulative amount of drug released at time t, β is slope parameter (slope), and α is the scale parameter (intercept). The term α was replaced by term T_d (time necessary to dissolve 63.2% of drug) using the relationship $\alpha=(T_d)^{\beta}$. The unified Weibull model was:

$$M = 1 - e^{-\left[t/T_d\right]^{\beta}} \tag{5}$$

As β is equal to equation of slope, the Eq. 5 can be written as shown below:

$$M = 1 - e^{-\left[t/T_d\right]^{0.033*X+0.475}} \tag{6}$$

The linear equation of slope (r=0.99) was evolved by the method reported by Kirilmaz using the dissolution data of batches A7 to A9. The values of T_d for batches A7, A8, and A9 were 6.54, 6.41, and 6.13, respectively. The evolved model was validated by comparing calculated and predicted release profiles. The calculated percent drug release and experimental percent drug release of the optimized batch A8 can be considered as comparable since f_2 is equal to 88. Thus, by using the unified weibull equation (Eq. 6), we can modulate the drug-release pattern. This investigation demonstrates that the release of venlafaxine hydrochloride can be modified by changing the amount of xanthan gum and using the triple-layer concept. The optimized batches B3 of venlafaxine hydrochloride 75 mg and C1 of venlafaxine hydrochloride 37.5 mg also followed the Weibull model and the calculated F values were 9 and 6, respectively.

Figure 6 shows the average value of water uptake of the optimum batches (A8, B3, and C1). The study showed that all three batches showed almost identical and substantial water uptake. The water taken up by the tablet is responsible for gelling of xanthan gum.

The radar diagrams of batches A8, B3, and C1 are shown in Fig. 7. The dissolution pull times are shown on the periphery of radar diagrams. The outer surface of radar graphs shows highest score (10) while the centre shows lowest score (0). Ideally, all the data points should fall on score line of 5, i.e., in the middle of radar diagram. The radar diagrams of batches A8, B3, and C1 show that the formulated batches and reference products show almost similar dissolution at all the time points. The sums of absolute value of difference between reference and test at all time points were 8.7, 8.9, and 5.9, respectively, for batches A8, B3, and C1. The low values of computed difference quantitatively show the difference.

CONCLUSION

The drug-release rate was found to be dependent on the percentage of xanthan gum, pore-forming agent-like pharmatose DCL 11, and surface area of the formulation exposed to the dissolution medium. The optimized formulation showed media-independent drug release in distilled water and in 10% aqueous ethyl alcohol solution. The drug release was explained by Weibull model. The use of unified Weibull model is demonstrated to investigate the influence of minor changes in the formulation. A drug-release profile similar to that of the reference product (Effexor® XR Capsule) was achieved by adopting systemic formulation approach. The use of radar diagram is demonstrated.

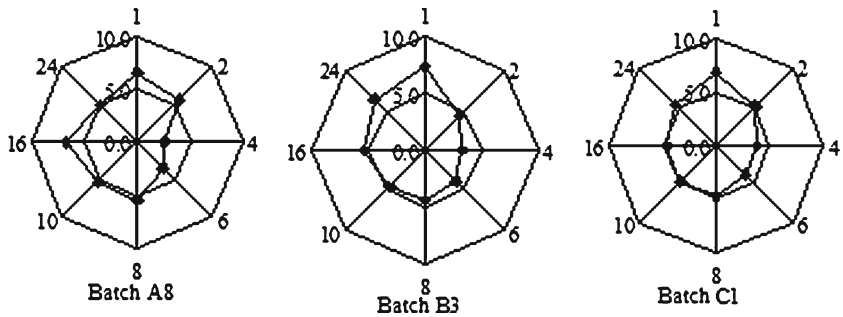

Fig. 7. Comparison of release profiles of optimized batches of all strengths of venlafaxine hydrochloride with respective reference product using radar graphs

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