ORIGINAL ARTICLE

Statistical Optimization of Controlled Porosity Osmotic Tablet of Milnacipran HCl

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Abstract

Aim: The objective of this study was to identify critical formulation parameters affecting the drug release from controlled porosity osmotic tablet of milnacipran hydrochloride employing the concept of design of experiments. **Materials and Methods:** The optimized amount of ethocel (X_1) and mannitol (X_2) in core and percentage of sorbitol (X_3) in coat were determined employing a three-factor, three-level Box-Behnken design. A direct compression technique was employed for preparing the core tablets. The tablets were coated with cellulose acetate. The *in vitro* drug release study was carried out in an acidic medium (pH 1.2) for 2 h and thereafter the dissolution study was conducted in phosphate buffer (pH 6.8). **Results and Discussion:** The selected dependent variables were the cumulative percentage of milnacipran hydrochloride dissolved after 1 (Y_1), 8 (Y_2), 16 (Y_3), and 24 h (Y_4). Correlating the independent variables with dependent variables were evolved. Optimization was performed for the three independent variables using the decided target ranges; $Y_1 \leq 20\%$; $Y_2 = 45 \pm 5\%$; $Y_3 = 72 \pm 5\%$; $Y_4 = 100\%$. The optimized amounts of ethocel (X_1), mannitol (X_2), and percentage of sorbitol (X_3) were 30, 100, and 30, respectively. **Conclusion:** The optimized formulation showed a release profile that was close to the predicted values. The drug was released by anomalous diffusion from the optimized formulation.

Key words: Box-Behnken design, controlled porosity osmotic tablet, ethocel, mannitol, sorbitol, milnacipran hydrochloride

INTRODUCTION

Oral controlled release systems continue to be the most popular among all the drug delivery systems. Conventional oral drug delivery systems are known to provide an immediate release of drug. Hence, the effective concentration of the drug is not maintained for a long time at the target site. Therefore, a modulation of drug release rate is required.[1] The development of oral controlled-release delivery systems for highly water-soluble drugs exhibits a significant challenge to the formulation scientists.[2] Most of the highly water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce undesirable side effects on oral administration.[3] The majority of oral controlled release dosage forms of water-soluble drugs fall in the category of the matrix, reservoir, or osmotic systems. Drug release from matrix and reservoir systems is affected by pH, hydrodynamic conditions and the presence of food in the gastrointestinal tract.[4] Osmotic systems utilize the principle of osmotic pressure for controlled delivery of drugs.[5] Drug release from these systems is to a large extent independent of pH and other physiological conditions.[6] Oral osmotic systems have a large market potential, as evident from the available marketed products and number of patents granted in the last few years.[7,8]

The controlled porosity osmotic pump tablets are generally marketed as coated product with a semi-permeable membrane.[5] The drug solution is formed in the core, and subsequently, it is released from the osmotic tablet by hydrostatic pressure. The drug molecule passes through the

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pores created by the dissolution of pore formers present in the coating membrane. The hydrostatic pressure is created either by an osmotic agent or by the drug itself or by another component present in the tablet.[9] Release retardant polymers such as hydrophilic or hydrophobic could also be used at lower to moderate concentration to retard the release rate of highly soluble drug from controlled porosity osmotic tablet to get desired zero order drug release.[10]

Milnacipran hydrochloride is a cyclopropane derivative with the chemical name (±)-[1R(S),2S(R)]-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamidehydrochloride. It is a wonderful new weapon in the fight against both depression and pain. It has essentially equal potency for inhibiting the reuptake of both serotonin and noradrenaline, with no affinity for any neurotransmitter receptor. It is well absorbed following oral administration with an absolute bioavailability of 85%.[11] Milnacipran hydrochloride is a highly water soluble molecule (aqueous solubility 800 mg/mL). Milnacipran base is very unstable, and hence, it is unsuitable for pharmaceutical use. As milnacipran hydrochloride has a half-life of 8 h and hence its immediate release formulation may not be suitable for a once-a day dosing regimen.[12] Conventional milnacipran hydrochloride therapy is often associated with gastrointestinal side effects such as gastric discomfort, nausea, and diarrhea. Delivery of milnacipran hydrochloride in a modified-release (MR), once a day dosage form could reduce the dosing frequency and improve patient compliance.

In this study, controlled porosity osmotic tablet of milnacipran HCl was developed. Mannitol was selected as an osmotic agent as well as erosion-promoting agent. The major disadvantage of hydrophilic matrixing agent is high drug release in the initial phase (1st h). This is due to dissolution of the drug particles present near the surface of tablets. The second disadvantage is slow drug release duo to slow diffusion through the swollen gel layer especially in the terminal phase. To find a solution to these problems, we have used Ethocel Standard 45 The premium for the development of osmotic drug delivery system. The core tablet was coated with cellulose acetate. Sorbitol was added as a pore former for drug release in the coat. Based on preliminary studies, prospectively critical formulation parameters were found. The concept of design of experiment was used to identify critical parameters.

MATERIALS AND METHODS

Materials

Milnacipran hydrochloride and ethocel (Standard 45 Premium grade) were obtained as gift samples from Torrent Pharmaceuticals Ltd. (Ahmedabad, India). Hydroxypropylmethylcellulose (HPMC) (K4M grade), polyethylene oxide (PEO) (WSR 303 grade), and mannitol were obtained as gift sample from Zydus Ltd. (Ahmedabad, India). Sorbitol, cellulose acetate, and PEG 400 were purchased from SD fine Chem. Limited (Boisar, India). Dichloromethane and methanol were purchased from Finar Limited (Mumbai, India).

Experimental design

FDA and ICH guidelines put stress on the importance of systemic formulation development approach. Box-Behnken design (BBD) was used to ascribe the relationship between the independent variables and the dependent variables. A three-factor, three-level BBD with three replicates at the center point was selected to evolve mathematical models.[13] The amount of ethocel (X_1), mannitol (X_2), and concentration of sorbitol (X_3) were used as independent variables in the design, and the measured responses were the cumulative percent of the drug dissolved at 1, 8, 16 and 24 h. Table 1 summarize the levels of independent variables and arbitrarily decided target ranges for the four responses, respectively. Response surfaces were constructed using the Design Expert Software (Version 8.0, Stat-Ease Inc., Minneapolis, U.S.A.).

Preparation of milnacipran HCl controlled porosity osmotic tablet

The core tablets containing 100 mg milnacipran HCl and various proportion of ethocel and mannitol were prepared by direct compression technique. The ingredients were individually passed through mesh 30 # before use and blended for 15 min. The blend was lubricated with magnesium stearate (1%) and talc (2%). The tablets were prepared by compressing the lubricated blend using single punch tablet machine (Cadmach Machines Ltd.; India). The tablets were dedusted before use by applying vacuum. Cellulose acetate (film former, 2.5% W/V), PEG-400 (plasticizer, 15% W/V of cellulose acetate), and different concentrations of sorbitol

Table 1: Design layout for BBD

Independent variables	Low level (−1)	Medium level (0)	High level (1)
X_1, mg	20	30	40
X_2, mg	50	100	150
X_3, % w/w	15	30	45
Dependent variables		**Target ranges (%)**	
Y_1		≤20	
Y_2		45±5	
Y_3		72±5	
Y_4		100	

X_1=Amount of ethocel; X_2=Amount of mannitol; X_3=Concentration of sorbitol (%w/w of coating polymer-cellulose acetate, Y_1=Cumulative % drug release in 1 h, Y_2=Cumulative % drug release in 8 h, Y_3=Cumulative % drug release in 16 h, Y_4=Cumulative % drug release in 24 h. BBD: Box-Behnken design

(pore former, 15-45% W/W based on cellulose acetate) were dissolved in a blend of dichloromethane and methanol (80:20). The resultant solution was stirred at 80-100 RPM using Remi magnetic stirrer (1 MLH Remi Equipments; India) to achieve homogeneity. Finally, the fine dispersion of color (ferric oxide red) was mixed with the polymeric solution. At the end, the blend was passed through mesh 100 # to eliminate aggregated particles. Coating was applied in Gans coater (Gansons Ltd., Mumbai, India) at inlet air temperature 50°C, exhaust temperature 40°C, atomization air pressure 1.5-2 kg/cm^2; spray rate 4-6 mL/min, pan speed 5-10 RPM. The process of the coating was continued till the weight gain by tablets was 10%. The coated tablets were evaluated for *in vitro* drug release.

Evaluation of core tablets

Hardness and friability

The hardness of the tablets was measured using the Dr. Schleuniger Pharmatron Tablet Tester 8 m. The Roche friabilator (Friabilator USP XXIII by Electrolab) was used in the present study for friability testing. The tablets were dedusted carefully before testing. The accurately weighed tablets were placed in the drum, the drum was rotated 4 min at 25 rotation per minute and then the tablets were removed, dedusted and weighed and percentage weight loss (friability) was calculated.

Weight variation

About 20 tablets were selected randomly from each batch. Tablets were weighed individually, and the average weight was calculated. Deviation of each tablet from average weight was calculated.

In vitro drug release study

The milnacipran HCl drug release study was conducted using USP XXIII (paddle apparatus) at 37°C ± 0.5°C. 900 ml of 0.1 N HCl (pH 1.2) was used as a dissolution medium for first 2 h and thereafter 900 ml of phosphate buffer (pH 6.8) was used. The drug release study was carried out at the paddle rotation speed of 100 RPM. 10 ml sample was withdrawn after predetermined time interval and it was replaced by an equal volume of the respective dissolution medium. The samples were filtered through a 0.45 µm membrane filter (Whatman membrane filter). The drug content was measured using an ultraviolet (UV) spectrophotometer (model UV-1700 Pharmaspec, UV-visible spectrophotometer, Shimadzu, Japan) at a wavelength of 223 nm.

In vitro drug release study in presence of alcohol

The United States statistical data showed that around 50% of the American population routinely consumes alcoholic beverages. The potential effect of alcoholic drinks in significantly accelerating drug release from ER oral formulations has been of some concern in recent past. If the total amount of drugs is suddenly released from MR dosage forms in the body, untoward effects may be seen. *In vitro* dissolution profile of optimized formulation was taken in the presence of 40% v/v of ethanol.

Scanning electron microscopy (SEM)

The sample of coating membranes was obtained before commencing dissolution study and after complete drug dissolution from the optimized batch and then the membranes were examined in a SEM (ESEM EDAX XL-30, Philips).

RESULTS AND DISCUSSIONS

Experimental design

During preliminary study, hydrophilic polymers such as HPMC K4M and PEO WSR 303 were used for the preparation of core of the tablet. The tables were coated as describe in the experimental section. However, the desired drug release [Table 1] was not achieved due to rapid swelling and quick diffusion of the dissolved drug. For water soluble drugs, it becomes essential to include hydrophobic polymer such as ethocel in the core of the coated osmotic product.

The core tablets of all fifteen runs were evaluated for weight variation, hardness, and friability. The average weight of each batch is calculated and not more than two of the individual weights deviates from the average weight by more than 5% as per given in the Indian pharmacopeia and none deviates by more than twice of 5%. The hardness of all the tablets was between 6.2 ± 0.9 and 6.9 ± 0.6 kg/cm^2. The loss in total weight in friability test was in the range of 0.5 to 0.63%.

The experimental results of fifteen runs are presented in Table 2. Replication of center point batch (0, 0, 0) was done to determine the repeatability. The more an experiment is replicated, the greater is models reliability. The runs 4, 6 and 13 showed least experimental variation with a very low standard deviation. Hence, we can conclude that the dissolution procedure is precise in nature, and we can go for further data analysis (e.g., regression analysis of all the 15 data points) to evolve valid mathematical model with accurate predictive ability. The center point also assists us in investigating non-linear relationship between independent variables and dependent variables. Various models such as linear, two-factor interactions (2FI), quadratic, and cubic models were fitted to the data for three responses simultaneously using Design Expert® software. The multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2), and the predicted residual sum of square (PRESS) were used for selection of adequate models.

Table 2: Standardized main effects of the factors on the responses and their ranges

Batches	Independent variables			Dependent variables			
	X_1	X_2	X_3	Y_1	Y_2	Y_3	Y_4
B-1	−1	0	−1	9.54±0.23	47.32±2.18	80.4±1.95	101.5±1.48
B-2	1	0	1	27.56±1.87	37.132.07	64.35±0.77	92.53±1.88
B-3	−1	1	0	15.81±1.40	57.68±1.22	84.89±1.80	104.1±0.72
B-4	0	0	0	18.36±1.93	43.31±0.23	72.1±1.19	98.64±0.12
B-5	1	0	−1	11.23±0.30	39.74±1.58	58.21±2.06	88.2±0.59
B-6	0	0	0	18.54±2.50	43.69±3.31	72.19±2.16	98.6±1.73
B-7	−1	−1	0	14.11±1.01	40.87±2.90	82.36±2.96	103.4±0.70
B-8	1	−1	0	21.51±0.07	29.61±0.94	60.48±0.26	89.59±1.15
B-9	0	1	1	29.21±1.13	55.12±0.46	78.62±1.33	100.4±0.71
B-10	0	−1	−1	8.33±1.21	31.68±1.93	66.12±1.12	94.32±0.78
B-11	0	1	−1	20±0.37	53.9±0.79	68.3±2.49	95.5±1.07
B-12	−1	0	1	26.61±2.40	49.33±2.45	86.46±1.33	105.1±3.75
B-13	0	0	0	18.91±2.95	43.25±0.97	72.69±1.03	99.29±1.10
B-14	0	−1	1	24.51±1.22	33.61±0.12	76.71±0.17	99.51±0.62
B-15	1	1	0	23.11±0.77	51.32±0.33	62.52±0.42	91.82±0.67

X_1=Amount of Ethocel; X_2=Amount of Mannitol; X_3=Concentration of Sorbitol (%w/w of coating polymer-cellulose acetate, Y_1=Cumulative % drug release in 1 h, Y_2=Cumulative % drug release in 8 h, Y_3=Cumulative % drug release in 16 h, Y_4=Cumulative % drug release in 24 h

The quadratic model showed the smallest PRESS values. PRESS is a measure of the fit of the model to the points in design; the smaller PRESS the better the model fits to the data points. The general form of the quadratic model is shown below:

$$Y = A_0 + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_1X_2 + A_5X_1X_3 + A_6X_2X_3 + A_7X_1^2 + A_8X_2^2 + A_9X_3^2$$

Where, A_0 is an intercept and A_1-A_9 are the coefficients of respective factors. The coefficient of main effect (A_1, A_2, and A_3) represents the average result of changing one factor at a time from its low to high value. The coefficients of interaction terms (A_4-A_6) show how the response changes when two factors are changed simultaneously. The coefficients A_7 to A_9 show non-linearity. The reduced equations containing statistically valid terms are shown below:

$$Y_1 = 18.60+7.34X_3 \quad (1)$$

($R^2 = 0.91$, adjusted $R^2 = 0.57$, PRESS 540.33)

$$Y_2 = 43.41-4.67X_1+10.28X_2 \quad (2)$$

($R^2 = 0.99$, adjusted $R^2 = 0.78$, PRESS 1038.65)

$$Y_3 = 72.32-11.06X_1+4.13X_3 \quad (3)$$

($R^2 = 0.99$, adjusted $R^2 = 0.77$, PRESS 1126.75)

$$Y_4 = 98.84-6.49X_1+0.625X_2+2.25X_3-1.10X_1^2-0.902X_3^2 \quad (4)$$

($R^2 = 0.99$, adjusted $R^2 = 0.79$, PRESS 389.44)

A positive or a negative sign before a coefficient indicate a synergistic or an antagonistic effect for the factor respectively. The results of multiple regression analysis reveales that statistically significant coefficients ($P < 0.05$) were A_3 for Y_1; A_1 and A_2 for Y_2; and A_1, and A_3 for Y_3; and A_1, A_2, A_3, A_7 and A_9 for the response Y_4, respectively. The coefficients A_1 demonstrated the antagonistic effects for the responses Y_2, Y_3 and Y_4. The other coefficients A_2 and A_3 exhibited synergistic effects (Equations 1-4).

The drug solution is expelled from the dosage form due to hydrostatic pressure provided by mannitol solution and passage through the pores created by the dissolution of sorbitol present in the coating membrane.[14,15]

When the tablet contains a water-soluble drug and a water-insoluble polymer, drug release occur through the capillary generated by dissolution of the particles of active ingredient. As drug dissolution and release continues, the more porous network is available through which drug clusters present under the core can diffuse.[16-18]

Based on the evolved equations, contour and response surface plots were obtained for the description of the relationship between the independent variables and the responses and they are presented in Figure 1a-d.

Multiple regression analysis for percentage drug release at 1, 8, 16 and 24 h showed that amount of ethocel, mannitol and concentration of sorbitol had significant influence ($P < 0.05$). For the response Y_1 factor X_3 had a significant contribution on drug release at 1 h, which may be due to quick formation of

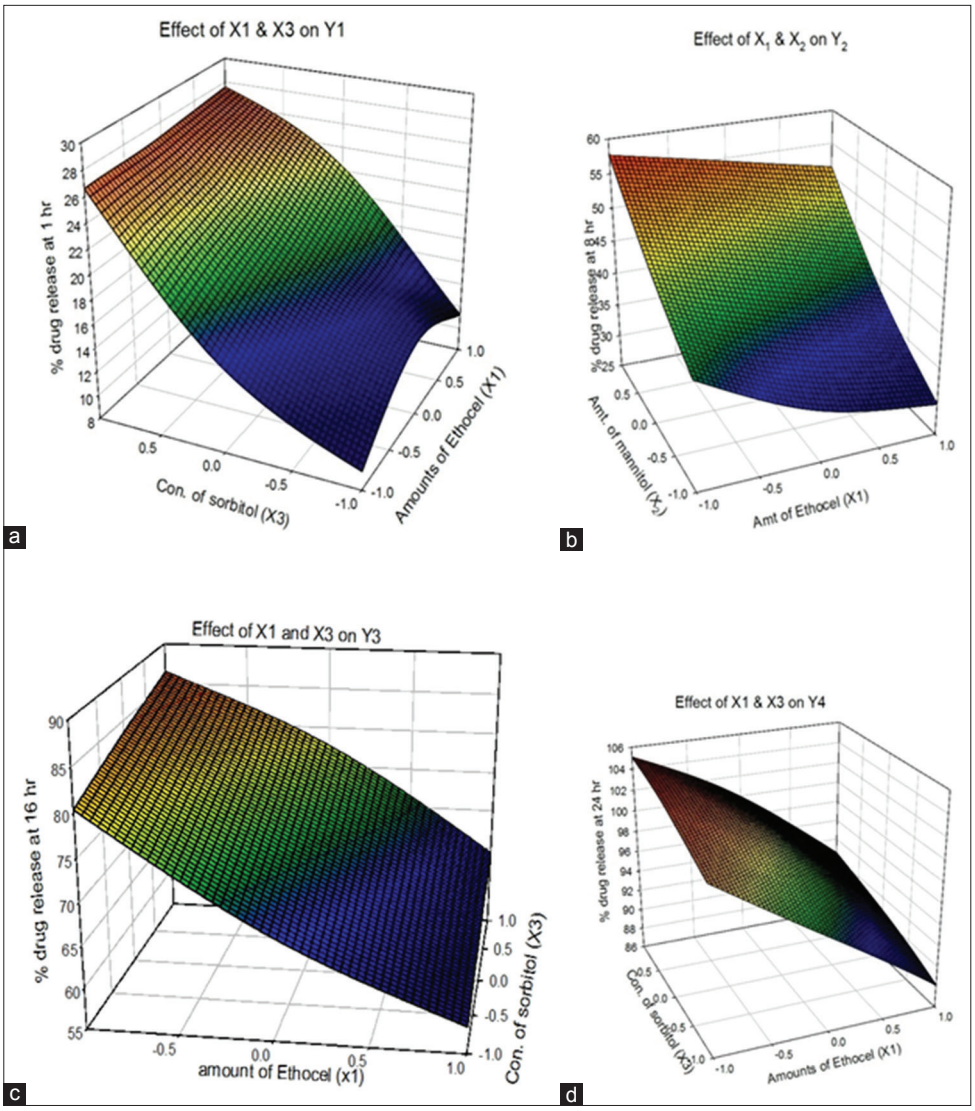

Figure 1: Response surface plot showing the cumulative % drug dissolved at, (a) 2 h, (b) 8 h, (c) 16 h, (d) 24 h

pores in the coating membrane and rapid release of drug. The amounts of ethocel (X_1) and amounts of mannitol (X_2) did not play a significant role in controlling drug release in 1 h.

The factors X_1 and X_2 exhibited antagonistic and synergistic effect respectively on drug release at 8 h (Y_2). The values of coefficients indicate that the drug release at 8 h was affected by a larger extent by the concentration of mannitol (A_2 = +10.28) because mannitol is a highly hydrophilic channeling agent and could enhance the in-flow of water from the external medium into the tablet. The rate of drug release from the tablet formulation may be enhanced due to availability of high amount of fluid.[19] Drug release at 8 h was affected comparatively lesser extent by amounts of ethocel (A_1 = −4.67) because ethocel has a tendency to erode slowly, which could become more prominent by the presence of the erosion-promoting ingredients such as mannitol. The erosion of the tablet could gradually reduce the distance between the diffusion boundary and the drug molecules to be diffused, thus attenuating the characteristic decrease of release rate.[20]

The factors X_1 and X_3 exhibited a significant effect on drug release at 16 h (Y_3). The values of coefficients indicate that the drug release at 16 h was affected by a larger extent by the amounts of ethocel (A_1 = −11.06) and comparatively to a lesser extent by the concentration of sorbitol (A_3 = +4.13). By manipulating concentration of pore forming agent in coating membrane, desired drug release could be achieved.

The factors X_1, X_2 and X_3 exhibited a significant effect on drug release at 24 h (Y_4). The drug release at 24 h was affected by a larger extent by the amounts of Ethocel (A_1 = −6.49) and to a lesser extent by the concentration of sorbitol (A_3 = +2.25) and amounts of mannitol (A_2 = +0.625).

Optimization

To find an acceptable formulation, the optimization process was performed for the factors X_1, X_2, and X_3 using the

following target ranges; $Y_1 \leq 20\%$; $Y_2 = 45 \pm 5\%$; $Y_3 = 72 \pm 5\%$; $Y_4 = 100\%$ in the Design Expert software.

The optimized levels of each independent variable were based on the criterion of desirability. The optimized coded levels of amounts of ethocel (X_1), amounts of mannitol (X_2) and concentration of sorbitol (X_3) as obtained from overlay plot [Figure 2a] were 0, 0 and 0 coded level, respectively. The optimized uncoded levels were 30 mg of ethocel, 100 mg of mannitol and 30% of sorbitol with a maximum value of desirability of one [Figure 2b] The predicted and observed responses for the optimized formulation indicates that the release profile of the milnacipran hydrochloride was close to each other.

The overlaid plot can be used for defining a design space and the normal operating range (NOR). FDA does not

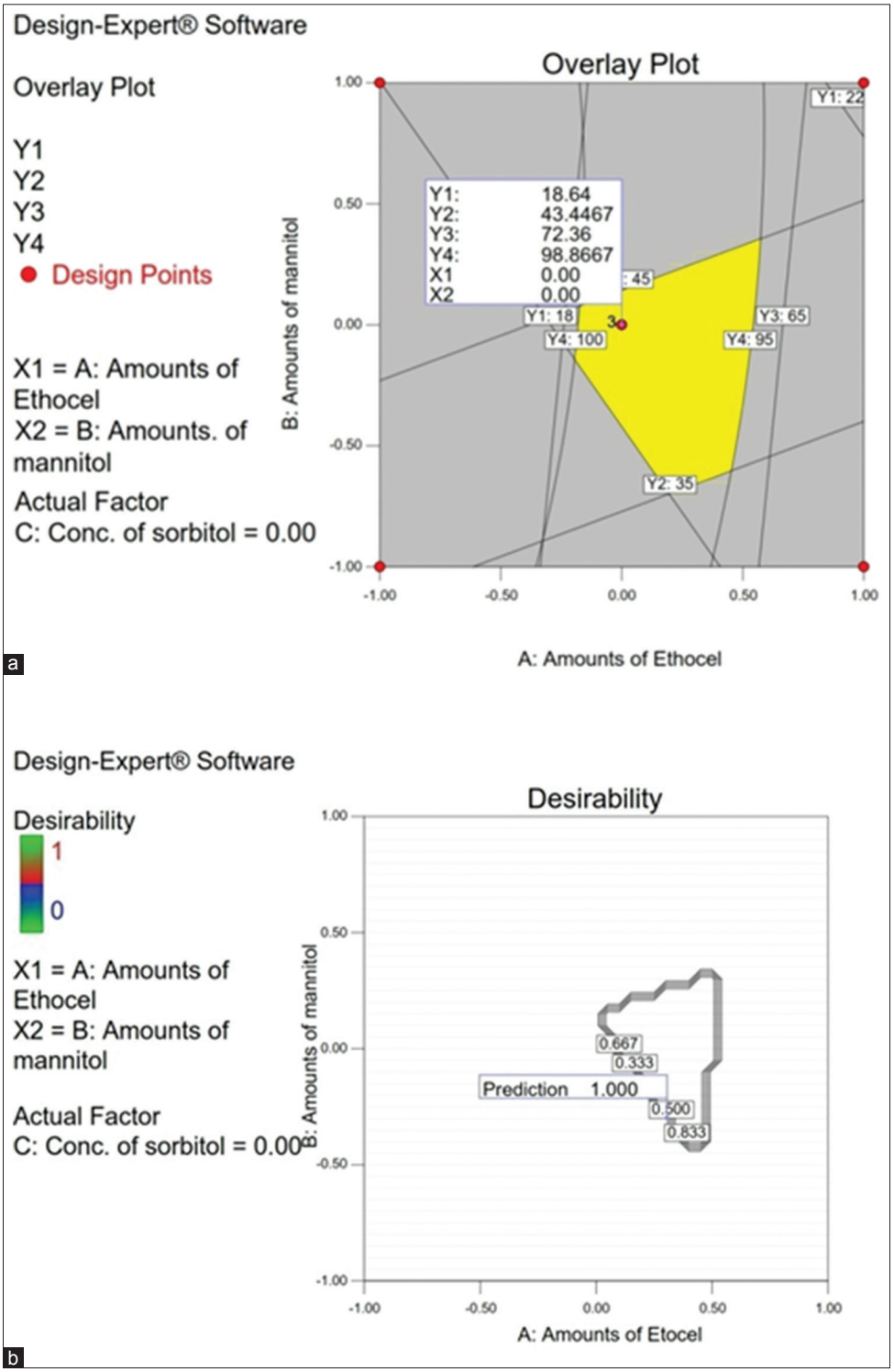

Figure 2: Overlay plot, (a) and desirability, (b) showing the optimized region

consider a change within the NOR as change for document resubmission. The area of NOR shall be kept in mind while scale up experiments is performed. Optimized formulation showed good linearity ($r^2 = 0.9864$), with the slope or exponential value (n) 0.688, indicating anomalous diffusion.

Spider graphs

In the dissolution study, higher or lower % drug release, than target value is permitted up to a certain limit. Shah *et al*. proposed that the maximum difference can be 10% ($f_2 = 50$) for establishing similarity in dissolution.[21] The dissolution profile of reference was considered as ideal release pattern.[22] The percent drug release of reference product will get a score of five (ideal) on a scale of 0 to 10. The lower and high permissible % of drug release will get a score of 0 and 10, respectively. The scores of optimized batches were calculated at each dissolution time point using the following equation:

Score = 5+{(%Tt−%Rt)/2}

Where % Tt is percentage drug released from test batch while % Rt is percentage drug released from reference product at the same time.

The calculated scores of optimized batch are shown in Table 3 and as radar diagram is shown in Figure 3. The dissolution pull times are shown on the periphery of radar diagrams (1-24 h). The outer surface of radar graphs shows the highest score (10) while the center shows lowest score (zero). Ideally, all the data points should fall on score line of five, i.e., in the middle of radar diagram. The low values of computed difference quantitatively show the similarity. The value of sum can vary between 0 (ideal) and 40 (borderline case). The diagram can be used to present the dissolution data in such a way that data interpretation is easy.

Figure 4 shows that the cumulative drug release has almost identical in dissolution media containing up to 40% v/v alcohol. Hence, dose dumping is not expected even if the dosage is taken with alcohol.

SEM

Figure 5a and b show SEM of cellulose acetate membranes of optimized formulation, obtained before and after dissolution, respectively. Membranes obtained before dissolution showed nonporous characteristics. After 24-h of conducting the dissolution study, the membrane clearly shows pores in the range of 1-50 µm owing to dissolution of sorbitol.

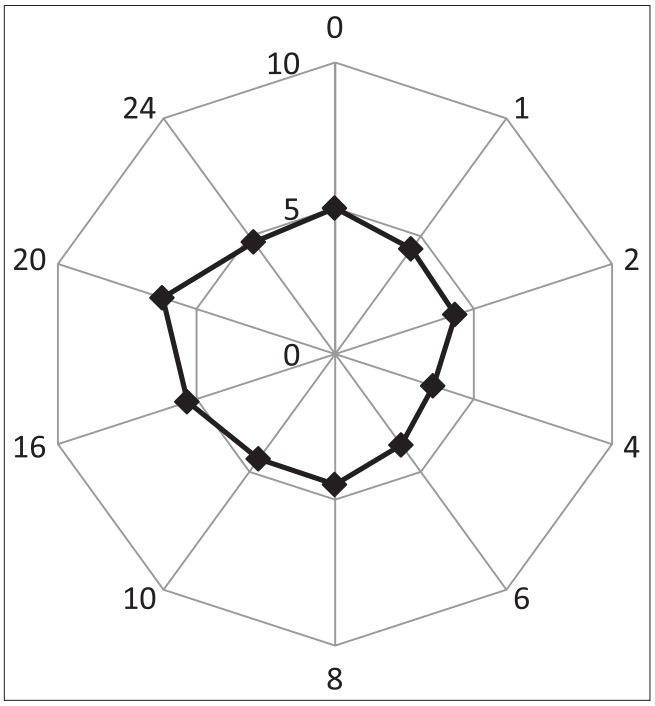

Figure 3: Comparative drug release profiles of optimized batch with reference using spider diagram

Table 3: Score of optimized batch for spider graph

Time	Cumulative percentage release of optimized batch (%Tt)	Reference release (%Rt)	Score A	5-Score A
0	0	0	5	0
1	18.91	20	4.455	0.545
2	22.15	23.47	4.34	0.66
4	27.51	30.41	3.55	1.45
6	35.08	37.35	3.865	1.135
8	43.25	44.29	4.48	0.52
10	50.14	51.23	4.455	0.545
16	72.69	72.05	5.32	−0.32
20	88.37	85.93	6.22	−1.22
24	99.29	99.81	4.74	0.26

Prediction of *in vitro* profile

The pharmacokinetic parameters for milnacipran HCl were collected from literature.[23] The dissolution data of optimized batch were used for predicting the *in vitro* as per method adopted by Qureshi.[24] The results are shown in Figure 6; which clearly shows that the drug release is extended. This exercise can be helpful at industry for the selection of bio batch by overlapping the plasma concentration profile of reference and test batches.

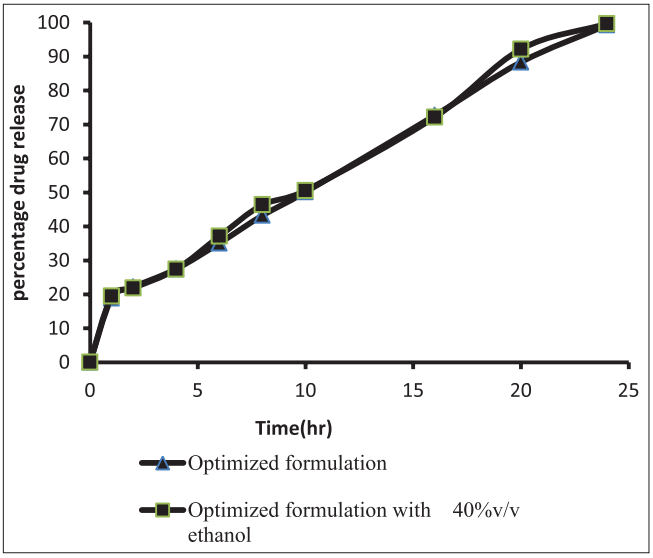

Figure 4: Drug release profile of optimized batch in 40% vv ethanol

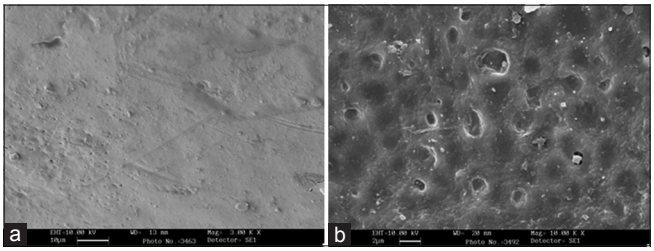

Figure 5: Scanning electron microscopy of membrane structure of optimized formulation, (a) before dissolution studies, (b) after dissolution studies

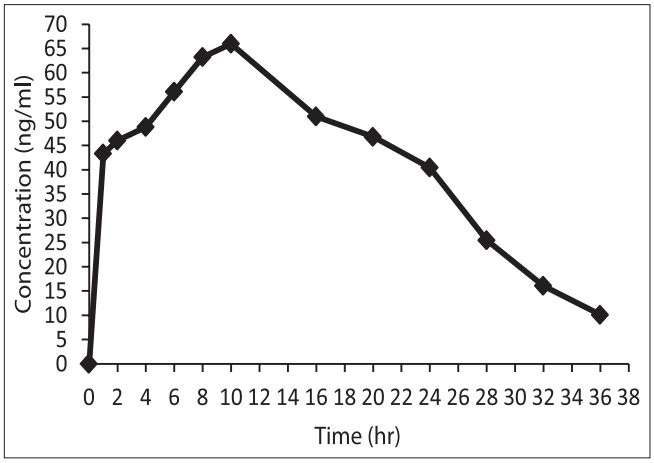

Figure 6: Drug concentration profile derived from dissolution profile of optimized formulation

CONCLUSION

In this study, milnacipran hydrochloride controlled porosity osmotic tablets were prepared and evaluated. The presence of insoluble excipients such as Ethocel is desirable in the core for modulation of drug release. The amount of mannitol played a dominant role in controlling the drug release in the initial phase. Sorbitol created pores in the coat for smooth passage of drug solution. These can be considered as critical formulation parameters while going for scale-up operations. Statistical optimization can help the formulator to identify an optimized formulation.

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