Pharmaceutical Sciences Asia

Pharm Sci Asia 2019; 46 (2), 98-107
DOI:10.29090/psa.2019.01.017.0057

Research Article

Formulation of controlled porosity osmotic pump tablets containing venlafaxine hydrochloride

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KEYWORDS:
Controlled porosity osmotic pump, Venlafaxine hydrochloride, Semipermeable membrane, Cellulose acetate.

ABSTRACT

Venlafaxine hydrochloride is an antidepressant agents, it has a short biological half-life (5 h) thereby requiring twice a day dosing to maintain adequate plasma levels of drug. The aim of this study was to formulate Controlled porosity osmotic pump (CPOP) tablets containing venlafaxine hydrochloride to be taken once daily. In this study, the core tablets consist of microcrystalline cellulose pH 101 and osmogents (sodium chloride, mannitol, lactose) were prepared by wet granulation method. The core tablets were coated semipermeable membrane of cellulose acetate containing polyethylene glycol 400 as a pore former and plasticizer, Tween 80 as a surfactant. The coating operation was performed using a pan coating machine. The formulation variables affecting on drug release *in vitro,* coating weight, concentration of pore former and surfactant were investigated using D-optimal design. The optimal tablet formulation has been proposed. An invention product, efexor® XR extended release capsules was used as reference for study *in vitro*. It was found that drug release rate was inversely proportional to coating weight and directly proportional to the concentration of pore former and surfactant in membrane. The drug release profile from the optimized formulation was similar to that from reference drug. CPOP tablets of venlafaxine hydrochloride were successfully prepared, the drug release from the tablets was extended for 24 hours. The CPOP tablets were prepared by coating the core tablets with a pore forming agent which is likely to be most cost-effective than laser drilling.

1. INTRODUCTION

Venlafaxine hydrochloride, (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol hydrochloride, is an antidepressant unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It has also been used for treatment of generalized anxiety disorder and social anxiety disorder. Hydrochloride salt of venlafaxine has high aqueous solubility (572 mg/ml) and short biological half-life (5 h), thereby requiring twice a day dosing to maintain adequate plasma levels of drug,

which often leads to patient non-compliance[1,2]. So, it is a suitable candidate for the development of one a day formulation.

Controlled porosity osmotic pump (CPOP) were introduced, the CPOP consists of (a) an osmotic core that contains the drug and along with an osmogent and (b) a semi-permeable membrane coating that contains a water-soluble pore-forming agent, instead of the delivery orifice created by laser drill[3]. Upon contact with the aqueous fluids, the pore forming agent was dissolved resulting an in situ formation of a microporous membrane that is substantially to both water and dissolved solutes. It was reported that the rate of drug release from these systems depends on the thickness of the semi-permeable membrane, level of the pore forming agent in membrane, the drug solubility in the core tablet, and the osmotic pressure difference across membrane[4].

In the current work, the ingredients of core tablets were selected suitably. For developing coating membrane formulation: D-optimal design in Modde 8.0 software was used to design of experiments. FormRules v2.0 software was used to evaluate the effects of in put variables on out put variables and optimized by INForm 3.1 software. An innovation drug, efoxor XR extended release capsules was a reference for *in vitro* dissolution study.

2. MATERIALS AND METHODS

2.1. Materials

Venlafaxine chloride was bought from Cipla Ltd. Lactose, talc, polyvinyl pyrrolidon K30, Tween 80, ethanol; aceton, sodium chloride, polyethylene glycol 400, mannitol, magnesium stearate, Avicel PH 101, Hydroxy propyl methyl cellulose K4M (HPMC K4M) were gifted by Department of pharmaceutics, Hanoi University of Pharmacy. Cellulose acetate (with 40% acetyl) was bought from Daejung Chemicals & Metals CO., LTD.

2.2. Methods

2.2.1. Drug-excipients compatibility study FTIR

The use of FTIR technique allows pointing out the implication of the different function groups of drug and excipients by analyzing the significant changes in the shape and position of the absorbance bands. The individual samples such as pure drug (venlafaxine hydrochloride), the mixture of drug and excipients were ground and mixed thoroughly with potassium bromide and compressed into disc. The mixture was kept in the sample holder and scanned from 2000 to 400 cm^{-1} in FTIR spectrophotometer. The peak characteristics of all samples were obtained.

2.2.2. Preparation of core tablets

The formula of core tablets is listed in Table 1. The core tablets were prepared by wet granulation technique. Talc, magnesium stearate were passed through the 80 mesh sieve. The drug and other excipients were passed through the 60 mesh sieve. PVP K30 was dissolved in ethanol to obtain concentration of 10 % (w/v). The drug and other excipients except talc and magnesium stearate were blended homogeneously in a mortar. The mixture was moistened with PVP K30 solution, and granulated through 18 mesh sieve. The granulation was dried at 60^0C for 15 minutes. The dried granulation was passed through 20 mesh screen to break the lumps and to get uniform size of granules, the granulation was dried continuously at 60 ^{0}C till the moisture content of granules reached 2-3%. The granules was blended with lubricants (talc and magnesium stearate). The homogeneous blend was the compressed into tablets using 10 mm diameter, concave punches. The compression force was adjusted to give tablets with approximately 6-8 $kg.cm^2$ hardness.

2.2.3. Coating solution

Required quantity of cellulose acetate was accurately weighted and dissolved in a beaker containing acetone using mechanical stirrer. Required quantity of PEG 400 and Tween 80 were dissolved in ethanol in other beaker and was added to mixture of cellulose acetate with stirring for 2 hours.

2.2.4. Coating of tablets

Core tablets were placed in a coating pan with 30 g of core tablets. The coating pan was rotated at 20 rpm and heated air was passed through the tablets. Coating process was started when temperature pan reaches to 40±5^{0}C. The coating

solution was sprayed at the rate 3 ml/min. Coating was continued until desired coating weight was obtained. The coated tablets were dried at 40^0C for 3 hours in vacuum oven.

2.2.5. In-vitro drug release

Apparatus: USP I (basket type)
Medium: Water, 0.1N HCl pH 1.2; acetate buffer pH 4.5 and phosphate buffer pH 6.8.
Volume of medium: 900 ml
Sample volume: 10 ml
Replacement volume: 10 ml
The collected samples were analyzed by UV-spectrophotometer method at 235 nm using the medium as blank. The percentage drug release (%CDR) was calculated.

2.2.6. Scanning electron microscopy (SEM)

Scanning electron microscopy micrographs of the coating membrane of optimal CPOP tablets were taken, before and after conducting the dissolution studies in order to examine the effect of PEG 400 as a pore-forming agent. Membranes were dried at 45^0C for 12 hours and stored between sheets of wax paper in desiccator until examination. Scans were taken using a scanning electron microscope (S4800-NIKE Hitachi) at an excitation voltage of 10 KV.

3. RESULTS

3.1. Compatibility study

Figure 1, the images scanned by FT-IR method for the drug and mixture of drug-excipients of the core tablets (prepared by powdering the core tablets, N8) show that there is no significant change in the peaks of drug-excipient mixtures in comparison to pure drug. It means that there is no incompatibility of excipients with the drug.

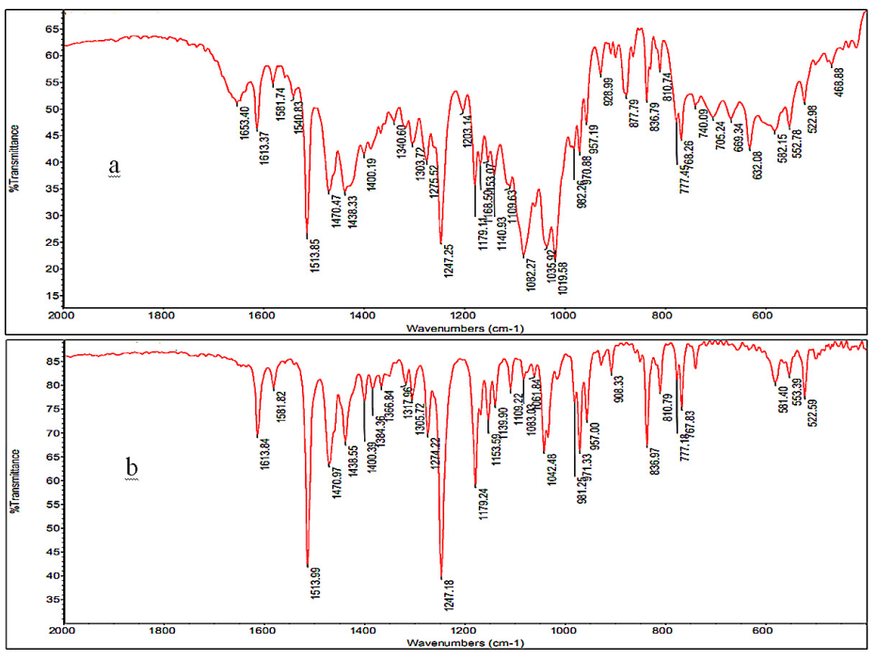

Figure 1. FTIR spectrum of mixture of drug-excipients of the core tablets N8 (a), pure drug (b)

3.2. Development of the core tablet formulation

To develop formulation of core tablets, the formulas as in Table 1 were prepared and coated with coating membrane formulation containing CA 4%, PEG 400 20% and coating weight was 3%, 5%, 7%. The results of dissolution studies shown that the coating membrane did not remain intact till the end of dissolution study and ruptured after a short period for all levels of coating weight of formulas N1-N6. The coating membrane of tablets of formulas N7, N8 remains intact for 24 hours during dissolution testing. The formulas (N1-N6) containing HPLC K4M from 50 mg to 10 mg in core tablets, HPMC K4M is a swellable polymer

increase hydrostatic pressure inside the pump[5] due to their swelling nature that could lead to rupture of the system. An amount 5 mg of HPMC K4M incorporated in core tablets of formula N7 is small, so that it's hydrostatic pressure inside the pump could be not high enough to break the membrane. However, the drug dissolution profile from formulas N7 and N8 with 5% of coating weight was not difference significantly as showed in Figure 2, so formula N8 was used for further investigations.

Table 1. Formulations of core tablets

Ingredients	N1	N2	N3	N4	N5	N6	N7	N8
Venlafaxine.HCl (mg)	86.1	86.1	86.1	86.1	86.1	86.1	86.1	86.1
HPMC K4M (mg)	**50**	**30**	**30**	**15**	**15**	**10**	**5**	**0**
NaCl (mg)	10	10	10	10	10	10	10	10
Manitol (mg)	50	50	50	50	50	50	50	50
Lactose (mg)	75	75	75	75	75	75	75	75
Avicel PH101 (mg)	75	75	**20**	75	**20**	75	75	75
Magnesium stearate (mg)	2	2	2	2	2	2	2	2
Talc (mg)	2	2	2	2	2	2	2	2
PVP K30 (mg)	10	10	10	10	10	10	10	10

3.3. Development of coating membrane formulation

Preliminary studies

To select the range of input variables (formulation ingredients and coating weight of the coating membrane) that influences on response variables (percentage of released venlafaxine), preliminary studies were carried out. The tablets from formula N8 was coated with different membrane formulas and coating weight as listed in Table 2.

Table 2. Membrane formulas with difference ingredients and coating weight

Ingredients / Formulas	CA (w/v)	PEG 400 (w/w of CA)	Tween 80 (w/w of CA)	Coating weight
M1	4%	20%	-	3%
M2	4%	20%	-	5%
M3	4%	20%	-	7%
M4	4%	25%	-	5%
M5	4%	10%	-	3%
M6	4%	10%	5%	3%
M7	4%	10%	3%	3%

Coating weight: The core tablets was coated with coating weight 3% (M1), 5% (M2) and 7% (M3). The results of dissolution studies shown that the drug release rate was decreased with increasing in coating weight and lag time increases with increasing in coating weight, Figure 3. The percentage of drug dissolution from tablets with coating weight 7% (M3) is so low compared to the given requirement as shown in Table 3, base on dissolution data of the reference drug. So the range of coating weight from 3% to 5 % was used for experimental design.

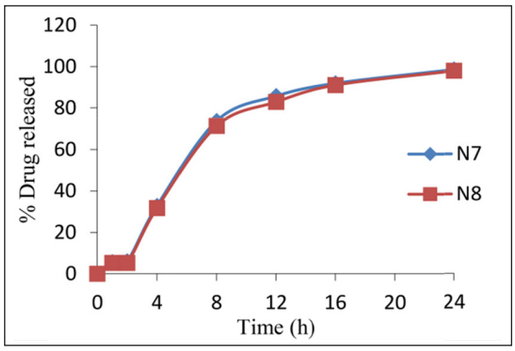

Figure 2. The dissolution profiles from formula containing 5 mg of HPMC K4M (N7) and without HPMC K4M (N8)

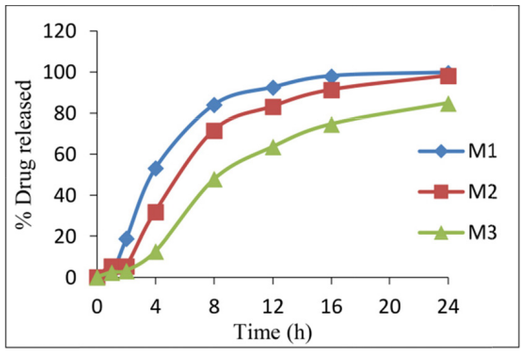

Figure 3. Dissolution profiles of CPOP tablets with difference coating weight, M1 (3%), M2 (5%), M3 (7%)

Coating membrane ingredients: The pore forming agents as PEG 400 was used individual or combination with Tween 80 in coating membrane formulations as shown in Table 2 to investigate their influences on the drug release rate. The results of dissolution studies showed that the drug release rate increases as ratio of PEG 400 in membrane increased as shown in Figure 4 (M1, M5). The drug release from from the CPOP tablets with coating membrane containing 25 % of PEG 400 is 90.8% in 12 hour that is higher than the given requirement (88%) as showed in Table 3. So, ratio of PEG 400 in range of 10% to 20% were used for experimental design.

For formulas containing PEG 400 combination with Tween 80, ratio of Tween 80 effects clearly on the drug release rate at early stage (2 h, 4 h) but it did not effect significantly at lately hours as shown in Figure 4 (M5, M6, M7). This effect of Tween 80 decrease lag-time that was usually observed for osmotic tablets, and it was suitable for developing the coating membrane formulation. The drug release rate from formula containing 5% of Tween 80 was high compared to the given requirement. So, the ratio of Tween 80 in the membrane is kept in range of 0% - 3% to experimental design of the coating membrane.

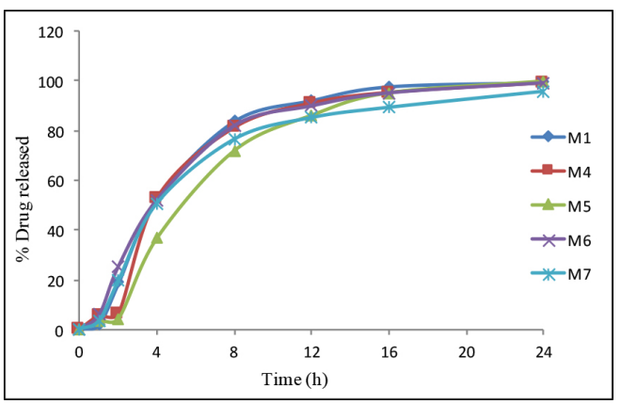

Figure 4. Effect of PEG 400, PEG 400 combination with tween 80 on the drug release rate in preliminary study.

Experimental design

D-optimal design in modde 8.0 software was used to design experimental formulas for the coating membrane and evaluation of the effects of the independent variables on dependent variables that is dissolution percentages as showed in Table 3.

Table 3. Independent and dependent variables

Independent variables	**Levels**	
	Low	Height
X1= amount of PEG 400 (%)	10	20
X2= amount of Tween 80 (%)	0	3
X3=coating weight (%)	3	5
Dependent variables	Requirements	
Y_{2h}= Percent of drug dissolved at 2 h	$10 \leq Y_{2h} \leq 30\%$	
Y_{4h}= Percent of drug dissolved at 4 h	$33 \leq Y_{4h} \leq 53\ \%$	
Y_{8h}= Percent of drug dissolved at 8 h	$58 \leq Y_{8h} \leq 78\ \%$	
Y_{12h}= Percent of drug dissolved at 12 h	$68 \leq Y_{12h} \leq 88\%$	
Y_{24h}= Percent of drug dissolved at 24 h	$Y_{24h} \geq 90\ \%$	

Table 4. Formulas and dissolution data of venlafaxine from CPOP tablets (n=6)

Formulations	PEG 400 (%)	Tween 80 (%)	Coating weight(%)	Y_{2h} (±SD)	Y_{4h} (±SD)	Y_{8h} (±SD)	Y_{12h} (±SD)	Y_{24h} (±SD)
CT1	20	0	3	18.8 ± 1.9	53.1 ± 2.0	83.9 ± 1.4	92.3 ± 2.3	99.5 ± 1.9
CT2	10	3	3	19.6 ± 0.5	50.7 ± 1.4	76.4 ± 1.0	85.0 ± 0.8	95.5 ± 0.7
CT3	20	3	3	39.3 ± 0.8	75.6 ± 1.7	86.6± 2.2	95.7 ± 2.4	100.8 ± 2.7
CT4	10	0	5	4.7 ± 1.8	15.5 ± 4.0	58.8 ± 3.1	73.1 ± 1.1	90.9 ± 1.9
CT5	20	0	5	5.3 ± 0.6	31.7 ± 4.4	71.4 ± 4.9	83.0 ± 3.6	98.0 ± 1.3
CT6	10	3	5	4.2 ± 0.6	30.0 ± 1.9	61.2 ± 0.4	77.2 ± 0.3	93.8 ± 1.2
CT7	20	3	5	5.8 ± 0.1	41.5 ± 4.8	72.6 ± 4.4	85.0 ± 5.1	95.3 ± 1.1
CT8	10	0	3.7	10.4 ± 2.7	42.8 ± 0.9	75.8 ± 1.4	84.2 ± 1.6	94.4 ± 1.4
CT9	10	1	3	11.5 ± 3.4	47.0 ± 2.4	76.6 ± 2.4	84.5 ± 1.5	93.7 ± 1.5
CT10	13.3	0	3	22.1 ± 1.2	51.2 ± 1.8	75.7 ± 2.9	86.6 ± 0.9	99.0 ± 1.1
CT11	16.7	0	3	18.2 ± 2.4	52.3 ± 2.3	79.7 ± 1.8	88.3 ± 2.2	98.8 ± 1.0
CT12	20	1.5	4	7.9 ± 0.5	49.1 ± 0.9	79.8 ± 0.1	87.7 ± 0.8	97.5 ± 0.4
CT13	15	3	4	17.8 ± 2.8	58.6 ± 1.8	83.0 ± 2.4	91.2 ± 2.9	100.2 ± 1.4
CT14	15	1.5	5	4.7 ± 1.5	37.3 ± 3.2	73.2 ± 0.7	85.6 ± 0.3	97.7 ± 0.5
CT15	15	1.5	4	9.8 ± 2.1	40.5 ± 0.9	72.2 ± 1.0	83.7 ± 2.3	96.0 ± 1.1
CT16	15	1.5	4	11.7 ± 3.4	42.1 ± 1.9	74.3 ± 1.3	87.6 ± 2.4	98.1 ± 1.2
CT17	15	1.5	4	8.7 ± 2.9	38.6 ± 0.9	75.8 ± 0.8	84.2 ± 2.2	94.4 ± 2.0

Effects of independent variables on dependent variables

Base on the results of dissolution of 17 experimental formulations in Table 4, analyzing ANOVA statistical data and evaluating the effect of the input variables on out put variables was analyzed by FormRules v2.0 software. R^2-values and effect of the input variables on out put variables shown in Table 5 and Table 6.

Table 5. R^2-values

Parameter	Y_2 (2 h)	Y_4 (4 h)	Y_8 (8 h)	Y_{12} (12 h)	Y_{24} (24 h)
R^2	97.8	98.8	98.1	97.6	93.5

Table 6. The effects of independent variables of dependent variables

Parameters	Y_2 (2 h) (%)	Y_4 (4 h) (%)	Y_8 (8 h) (%)	Y_{12} (12 h) (%)	Y_{24} (24 h) (%)
X1	+	+	+	+	+
X2	+	+	+	+	-
X3	+	+	+	+	+
Where: + Effect, - Not effect					

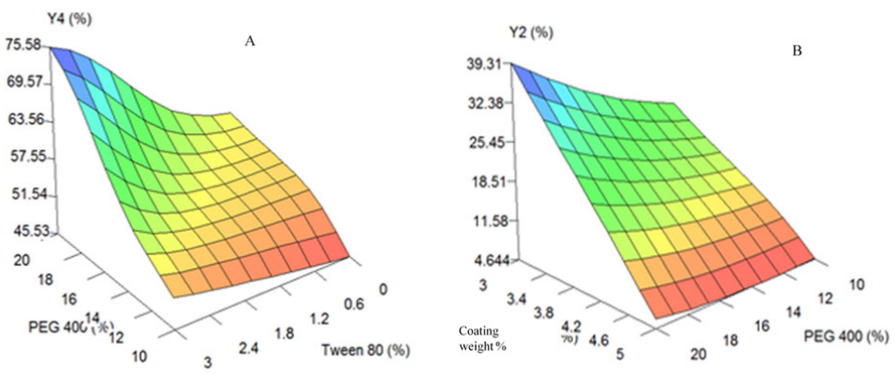

Figure 5. Response surface plot (A) showing effects of PEG 400 and Tween 80 on drug release at 4h, and (B) showing effects of PEG 400 and coating weight on drug release at 2h.

Optimization of coating membrane

Base on the data from the experimental results in Table 4 and requirement of dissolution for dependent variables (Y_2, Y_4, Y_8, Y_{12}, Y_{24}) as presented in Table 3, INForm 3.1 software was used for optimizing the coating membrane. The optimized parameters of coating membrane was presented in Table 7.

Optimal tablet formulation

The CPOP tablets containing a core tablets of N8 with optimized coating membrane as showed in Table 7 was proposed as the optimal CPOP tablets. Dissolution profile of venlafaxine from the optimal CPOP tablets was similar to that from invention tablets (exfexor) as shown in Figure 6, and f2-value was 64.2.

Table 7. The optimized coating membrane formulation

Parameters	Ratio
PEG 400	12.2%
Tween 80	1.2%
Coating weight	3.8%

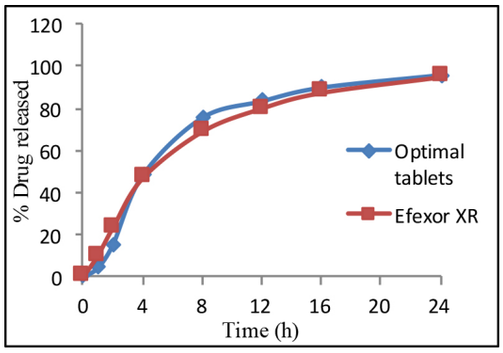

Figure 6. Dissolution profile of reference (efexor XR) and optimal CPOP tablets in water, (n=12)

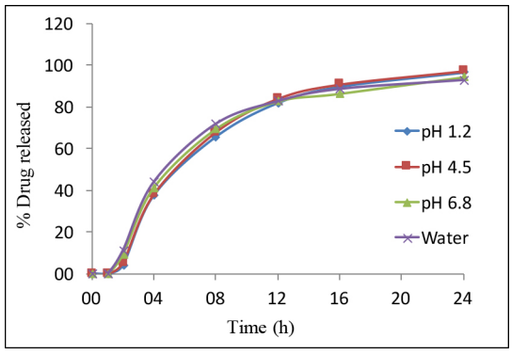

Figure 7. Effect of pH of dissolution on the drug release rate, (n=6)

3.4. Effect of pH on the drug release rate

The dissolution profile of the drug from optimal CPOP tablets in water and different pH media was shown in Figure 7. The drug release rate in different media was almost similar. The pH of dissolution media has not significant effect on the drug release. So, the drug release from the osmotic pump tablet was independent from pH.

3.5. SEM micrographs

Figure 8 compares SEM micrographs of the optimized coating membrane before and after the dissolution studies. Before contact with the dissolution medium, SEM micrographs revealed that the membrane has a rough surface and no pores were observed (Figure 8a). After 24 hours of dissolution, SEM micrographs revealed pores formed, possibly, due to the dissolution of PEG 400, a pore-forming agent, upon contact of the tablets with dissolution medium (Figure 8b). Base on observation it could be suggested that release of the drug from CPOP tablets passes through the following steps: dissolution of fore forming agents upon contact with the dissolution medium, penetration of the tablet by the dissolution medium through the formed pores, dissolution the drug particles within the tablet and release of the drug through the pores.

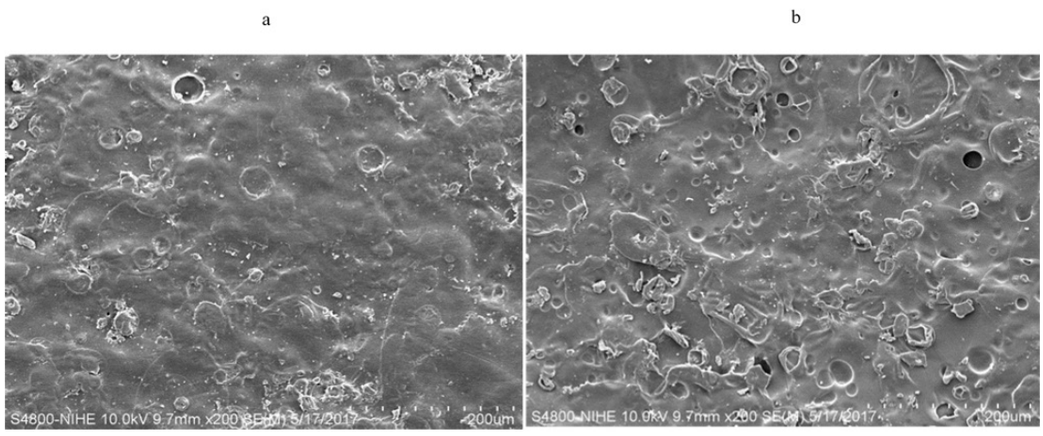

Figure 8. SEM micrographs of optimized coating membrane, (a) taken before dissolution study and (b) taken after dissolution study for 24 h

4. DISCUSSION

The results in Table 5 and Table 6 shown that, the R^2-value at all time points was higher than 80, so there was good regression between input variables (coating membrane formulation and coating weight) and out put variable (percentage of the drug release). All input variables (X1= PEG 400, X2 = Tween, X3 =Coating weight) affect the out put variables at all time points except a time point 24 h, Tween does not affect on. Base on analyzing response surface as in the Figure 5 **(B),** the drug release rate decreased as coating weight increases, the effects of PEG 400 on the drug release rate from coating weight 3% was higher than that at 5% Figure 5 **(A)**. In a previous study, *Shokri et al.*[6] proved that thickening the semipermeable membrane can decrease the rate of water penetration through the membrane resulting in a decrease in the drug release rate. It can be seen from equation (1), that release rate from osmotic system is inversely proportional to membrane thickness.

$$dM/dt = (A/h)*k*\Pi*C \quad (1)$$

Where, *dM/dt* is drug delivery rate, *A* an *h* are the membrane area and thickness, respectively. *C* is the soluble fraction of the drug, Π is the osmotic pressure of the system and *k* is the equation constant[6].

PEG 400 had a direct effect on the drug release rate, the higher the PEG 400 concentration, the faster the drug release rate, specially at the time after 4 h. Similar results were reported by *Ahmed Abd-Elbary et al*[3] . This behavior could be related to the hydrophilic nature of PEG 400. After coming into contact with the aqueous environment, the higher PEG 400 levels would leach out the membrane easily, resulting in more porous structure and faster drug release rate.

The results of dissolution test in Table 4 and Figure 4 showed that the drug release rate from formulas incorporated Tween 80 was faster at early hours. In previous study[6], an initial lag-time of 1 h is necessary to moisten the device and penetration of water into the core. This time may be reduced by the addition of a surface-active agent to the coating material. Surfactants are useful when added to wall forming material also. They produce an integral composite that is useful for making the wall of device operative[7]. The surfactant act by regulating the surface energy of material to improve their blending into the composite and maintain its integrity in environment of use during the dug release period[7].

5. CONCLUSIONS

Extended release tablets of venlafaxine HCl were developed based on CPOP technology, the drug release from the tablets was extended for 24 hours. The drug release rate was inversely proportional to coating weight of membrane and directly proportional to the concentration of pore former. The surfactant in membrane improves the drug release rate at early time. The drug release profile from the optimized formulation was similar to that from reference drug (efexor XR).

The CPOP tablets were prepared simply by coating the core tablets with the a pore forming agent which is likely to be most cost-effective than laser drilling.

6. ACKOWLEDGEMENT

The authors acknowledge Department of pharmaceutics, Hanoi University of Pharmacy, Vietnam and National Institute of Drug Quality Control, Vietnam for their support to conduct this research.

Conflict of interest

None to declare

Funding

None to declare

Ethical approval

None to declare

Article info:
Received October 15, 2017
Received in revised form March 29, 2018
Accepted April 15, 2018

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