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Research Article

Development and Optimization of Micro/Nanoporous Osmotic Pump Tablets

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Abstract. Micro/nanoporous osmotic pump tablets coated with cellulose acetate containing polyvinylpyrolidone (PVP) as pore formers were fabricated. Propranolol hydrochloride was used as a model drug in this study. Formulation optimization based on USP 31 requirements was conducted following a central composite design using a two-level factorial plan involving two membrane variables (pore former and coating levels). Effect of molecular weight of pore former (PVP K30 and PVP K90) was also evaluated. Responses of drug release to the variables were analyzed using statistical software (MINITAB 14). Scanning electron microscopy and atomic force microscopy showed that the pores formed by PVP. The drug release was dependent on the molecular weight and concentration of PVP and the level of coating. The results showed that acceptable 12-h profile could be achieved with only specific range of PVP K30-containing membrane at the defined membrane thickness. However, satisfactory 24-h profile could be accomplished by both PVP K30 and PVP K90-containing membrane at the range and membrane thickness tested. Preparation and testing of the optimized formulation showed a good correlation between predicted and observed values.

KEY WORDS: drug release; micro/nanoporous semipermeable membrane; osmotic pump tablet; PVP; response surface methodology.

INTRODUCTION

Osmotically controlled drug delivery system consists of an osmotic core containing drug and, as necessary, osmogent(s) surrounded by a semipermeable membrane with delivery orifice(s). When the osmotic system comes in contact with the aqueous environment, water will flow into the core due to an osmotic pressure differences. The drug solution will be pumped out of the system through the opening(s) at a constant rate (1,2). It has been shown that the drug release is independent of agitational intensity and pH of the release media (3–5). Therefore, theoretically the osmotic systems offer several advantages over conventional dosage forms including pH and gastric motility independence and predictable/programmable drug release. Consequently, it is possible to achieve and sustain drugs plasma concentrations within the therapeutic window of drug, thus reducing undesired side effects and the frequency of administration, and increasing patient compliance considerably. According to these benefits, the osmotic pump tablet is the system of choice for delivery of many drugs, e.g., an anti-hypertensive drug, of which the constant plasma profile is important and desirable.

Controlled-porosity osmotic pump (CPOP) is one type of osmotic tablets in which the delivery orifices are formed by incorporation of a leachable component into the coating solution. After coming into contact with water, this soluble additive dissolves resulting in an *in situ* formation of a microporous semipermeable membrane (6,7). The method to create the delivery orifice is relatively simple with the elimination of the common laser drilling technique. The mechanism of drug release from these systems was found to be primarily osmotic with simple diffusion playing a minor role (7). The release rate depends upon the solubility of the drug in the tablet core, the osmotic pressure gradient across the membrane, the coating thickness, and the level of leachable component in the coating (5,8,9).

Water-soluble additives that can be used for the purpose of formation of orifices in the membrane include sorbitol, urea, lactose, diols and polyols, e.g., PEG 4000, and other water-soluble polymeric materials, such as HPMC and PVP K30 (5,10–14). PVP K90 has not been studied so far as a pore former in coating applications. Erodible materials such as poly(glycolic), poly(lactic) acid or their combinations can also be used for this purpose (12). In this study, the application of PVP K30 and PVP K90 as pore-forming agents was investigated in order to develop both once and twice daily dosage forms, using propranolol hydrochloride as a model drug. A mixture of fructose:lactose (1:1) was used as an osmotic agent owing to its high osmotic pressure (12,15) instead of sodium

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chloride, which is commonly used as an osmogent in osmotic pump systems (3,16–18) as they are safe for patients with hypertension whose sodium chloride intake is restricted (19,20). In order to achieve the optimal dosage form formulations, statistical optimization designs have been employed. These designs are powerful and efficient, and have systemic features which can shorten the time required for the development of pharmaceutical dosage forms, improve research and development work, and enhance reliability of performance (21,22). A central composite design was employed for simultaneously determining the influences of membrane variables (pore former and coating levels) on drug release from micro/nanoporous osmotic pump tablets, in order to establish the optimum formulation based on USP 31 requirements. Consequently, it could provide useful information and a formulation that exhibited a satisfactory drug release for the development of controlled-porosity osmotic pump tablets, in particular, for industrial purposes.

MATERIALS AND METHODS

Materials

The following chemicals were obtained from commercial suppliers and used as received. Propranolol HCl was purchased from Sinochem (Shanghai, China). Fructose was obtained from Rama Production (Bangkok, Thailand). Lactose was supplied by Lactose of New Zealand (Taranaki, New Zealand). Cellulose acetate (39.8% acetyl content) was purchased from Aldrich Chemical (St. Louis, MO, USA). PVP K30 and PVP K90 were supplied by ISP (Wayne, NJ, USA) and BASF (Ludwigshafen, Germany), respectively. All other chemicals and reagents were either analytical or pharmaceutical grade.

Methods

Experimental Design

In this study, formulation optimization for the development of once and twice daily dosage forms of CPOP were conducted by a central composite design in order to assess the optimal drug release. Two factors of interest, i.e., PVP concentration and coating level, at two levels were observed for each PVP type. Eleven experiments of each type of PVP, i.e., PVP K30 and PVP K90, are summarized in Table I, including four factorial design runs, four axial runs, and three center runs. The values of the responses obtained, i.e., drug release at the predetermined time intervals, would allow the calculation of mathematical estimation models for each response, which were subsequently used to characterize the nature of the response surface. All statistical analyses were carried out using statistical software; MINITAB®14 (Minitab Inc., USA).

Preparation of Core Tablets

Each core tablet comprised 80 mg propranolol hydrochloride, 208 mg fructose and lactose mixture at 1:1 mass ratio as an osmogent, 1% PVP K30 in ethanol as a binder,

Table I. Experimental Designs and the Percent Drug Release at Time *t*

		Variables		Responses For 24-h CPOP					Responses For 12 h-CPOP			
PVP type	Run	X_1	X_2	$Y_{1.5}$	Y_4	Y_8	Y_{14}	Y_{24}	Y_1	Y_3	Y_6	Y_{12}
K30	1	(−1) 12.5	(−1) 2	5.95	19.6	43.8	69.8	82.8	2.43	17.4	38.1	69.9
	2	(+1) 37.5	(−1) 2	32.2	78.4	96.4	90.0	99.6	26.8	71.4	84.2	87.9
	3	(−1) 12.5	(+1) 4	0.05	9.04	26.2	51.2	70.6	0.00	7.29	18.7	42.9
	4	(+1) 37.5	(+1) 4	18.5	59.7	81.8	92.5	96.5	11.2	49.9	74.0	84.4
	5	(−α) 7.33	(0) 3	0.50	5.20	15.5	31.7	54.0	0.45	5.87	13.3	29.6
	6	(+α) 42.7	(0) 3	31.6	76.4	91.3	96.7	96.8	12.5	49.1	71.3	81.2
	7	(0) 25	(−α) 1.59	31.1	81.1	92.8	99.2	102	22.5	69.5	84.3	88.4
	8	(0) 25	(+α) 4.41	4.48	21.9	48.8	72.5	82.9	1.87	16.9	39.0	68.8
	9	(0) 25	(0) 3	17.2	53.0	83.1	93.2	100	8.17	37.9	67.2	82.7
	10	(0) 25	(0) 3	18.1	54.4	84.5	95.6	102	8.13	39.4	69.1	84.4
	11	(0) 25	(0) 3	19.2	55.8	86.8	96.3	101	7.80	40.1	72.2	86.7
K90	1	(−1) 12.5	(−1) 2	7.52	26.5	55.4	76.0	84.4	4.98	27.4	50.8	69.1
	2	(+1) 37.5	(−1) 2	45.4	85.8	93.4	94.8	94.8	25.0	74.9	87.7	89.4
	3	(−1) 12.5	(+1) 4	0.30	10.6	29.1	56.2	70.9	0.07	7.47	19.7	46.6
	4	(+1) 37.5	(+1) 4	22.4	67.3	87.4	93.9	95.4	9.73	56.8	79.8	85.9
	5	(−α) 7.33	(0) 3	2.10	9.36	22.2	43.0	63.5	0.46	5.77	14.4	32.9
	6	(+α) 42.7	(0) 3	42.9	86.7	94.3	95.5	97.1	25.2	76.3	88.5	90.5
	7	(0) 25	(−α) 1.59	44.6	84.7	92.3	93.6	93.6	29.0	79.1	88.5	89.4
	8	(0) 25	(+α) 4.41	22.6	69.4	90.1	98.0	99.2	10.8	57.5	81.6	90.8
	9	(0) 25	(0) 3	29.2	73.7	91.7	94.1	95.1	16.9	68.7	88.8	93.1
	10	(0) 25	(0) 3	30.3	75.0	92.2	95.9	96.9	16.0	66.1	86.2	91.2
	11	(0) 25	(0) 3	31.1	75.1	93.6	96.7	97.7	12.4	61.6	84.7	91.6
Criteria of USP 31				≤30	35–60	55–80	70–95	81–110	≤20	20–45	45–80	80–100

X_1 PVP concentration, X_2 coating level, Y_t percent drug release at time t hour(s)

and 2% magnesium stearate, 0.75% talcum, and 0.25% colloidal silica as a lubricant system. To avoid batch-to-batch variation, a single batch of granulation was prepared. The tablets were prepared by wet granulation process using a 16-mesh sieve for wet-mass sieving and an 18-mesh for dry sieving to control the size of granules obtained. A single batch of tablets was prepared and compressed on a single punch press using 9 mm tooling to the weight of 300 mg and the hardness of 100 N. The compressed tablets were stored in well-closed containers prior to coating.

Coating of the Tablets

To determine the effects of PVP and the membrane weight on drug release, core tablets were coated with 3% *w/v* cellulose acetate in acetone/isopropanol (3:1) solution containing either PVP K30 or PVP K90 as a pore former at various concentrations of 7.33-42.7% by weight with respect to cellulose acetate to obtain 1.59-4.41% additional weight of the core tablets. All coatings were performed following experimental design (Table I) in a perforated pan coater (Thai Coater®, Model 15"(L), Pharmaceuticals and Medical Supply, Thailand).

Determination of Drug Release from the Tablets

Drug dissolution was evaluated using a dissolution station (Model SR8-plus Q-Pak™, Hanson Research, CA, USA) and a UV/visible spectrophotometer equipped with six 1-cm flow cells and a six-channel peristaltic pump at the wavelength of 318 nm. The procedure and criteria employed for the drug dissolution for both 24- and 12-h intervals were based on *Propranolol Hydrochloride Extended-Release Capsules USP 31*, *Dissolution Test 1* and *2*, respectively. According to *Dissolution Test 1*, the simulated gastric fluid (SGF, pH 1.2) and the simulated intestinal fluid (SIF, pH 6.8) without enzymes were used as dissolution media. The basket rotating speed was 100 rpm. The CPOP were placed in 900 mL of SGF and maintained at 37±0.5°C. After 1.5 h, the dissolution medium was changed to the SIF and then was run for a further 22.5 h. The samples were analyzed at appropriate intervals. *Dissolution Test 2* was performed in the SGF for first 1 h and then was changed to pH 7.5 buffer for the time specified at a rate of basket rotation of 50 rpm. The dissolution profiles were constructed by plotting the average percent release of six propranolol tablets against time.

Dissolution profiles of various formulations were compared using a model independent method, which is the calculation of 'similarity factor' f_2 defined by US FDA (23). The equation for calculating f_2 is as follows:

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

where R_t and T_t are percent drug dissolved at time t from the reference and test products, respectively. In this study, the evaluation of similarity was based on the conditions described earlier (24,25). The two release profiles were considered to be similar, if the f_2 value was between 50 and 100.

Characterization of Tablet Membrane

Surface morphology. In order to evaluate the surface morphology of osmotic pump tablets, the surface of the tablets both before and after the dissolution test was studied by scanning electron microscopy (Model S-2360 N, Hitachi, Tokyo, Japan) and atomic force microscopy (SPA 400, SII Nanotechnology, Chiba, Japan). Runs 1-9 of each PVP type were determined. Surface pore diameters were measured by visual inspection of scanning electron microscopy (SEM) pictures and of line profiles of atomic force microscopy (AFM) pictures which were generated by a nanoscope's image processing program. All line profiles created along selected lines in the images were helpful for the analysis of surface pore characteristics and of single pores. For each membrane, the diameters of 50 pores were measured. The smallest and largest diameters and the mean values, including their relative standard deviations of all 50 pores, were determined.

Membrane porosity. To determine the porosity of the semipermeable membrane, the weight of the membrane after dissolving away the core tablet was determined as follows. Fifty core tablets were weighed before (W_1) and after (W_2) coating with various formulations, at different PVP contents (7.33%, 25%, and 42.7%), in order to determine a weight of solely membrane (W_M; $W_M = W_2 - W_1$). Then, they were subjected to the dissolution test in water which was changed periodically until the core tablet and the soluble component in the membrane, i.e., PVP, were dissolved completely. In cases where part of the core remained, the membrane was then cut and placed in the dissolution medium in order to ensure complete dissolution of the core. All 50 membranes of tablets were pooled and dried at 50°C for 24 h before accurately determining the residual weight (W_R). Mean of membrane porosity (P_{mean}) was determined according to the following expression:

$$P_{\text{mean}} = \left(\frac{W_M - W_R}{W_M}\right)\times 100 \qquad (2)$$

where, W_M is the initial weight of the membrane, W_R is the residual weight of the membrane. Means of membrane porosity and their relative standard deviations were calculated from three determinations.

RESULTS AND DISCUSSION

Core Tablet Properties

Propranolol core tablets were evaluated for their physical properties. The results showed that the average weight, hardness, and friability of the core tablets were 303±7 mg (n=20), 100±9 N (n=10), and 0.14%, respectively. The disintegration test was carried out according to USP 31 test method. The average disintegration time in 37±2°C distilled water was 6.3±0.7 min (n=6) and the cumulative drug dissolved at 1 h was ranging from 84.0% to 89.9% with the average value of 86.3±2.3% (n=6). The drug content was 100.5% of the labeled amount. Tablet hardness and friability of core tablets are two important

parameters that indicate the appropriate characteristic of the core tablets to be able to withstand the tumbling motion of tablet beds in the pan coater. Disintegration time, drug dissolution, and content were also determined according to USP 31 to ascertain that they were appropriate for further study.

In vitro Dissolution Study

In the preliminary study, coating variables were PVP types (PVP K30 and PVP K90) and concentrations (12.5%, 25.0%, 50.0% *w*/*w* based on cellulose acetate). The coating level was set at 3% weight increase. All coating formulations formed clear solutions except the formulation containing 50% PVP K90 in which the coating solution became cloudy. As PVPs are soluble in isopropanol but not in acetone which is a solvent for cellulose acetate, the amount of 50% PVP K90 could exceed the solubility limit in this solvent mixture (26,27). Thus, the amount of 50% PVP K90 was excluded from the appropriate range of this variable. From the preliminary findings, it was found that in a range of 12.5–50.0% *w*/*w*, PVP K90 gave higher percent dissolution than did PVP K30. The effects of PVP K30 contents on drug release from CPOP are in agreement with an earlier report (5). The higher the content of pore formers in the membrane, the higher the drug release rate observed. This study revealed that the drug release was dependent on the molecular weight of PVP. Therefore, in this study, formulation optimization based on the dissolution criteria of USP 31 for propranolol extended-release capsules was conducted following the central composite design to establish the desired release profile.

Based on the central composite design, there were 11 coating conditions for each PVP *K* value. All the coating variables and the response, i.e., drug release, were presented in Table I. To illustrate the influence of the possible variables that could influence the drug release, the following factors would be discussed; the PVP content, PVP *K* value or molecular weight, and the coating level.

Effects of PVP Content on Drug Release

To study the effect of the content of pore former on drug release, the core tablets were coated with a coating solution containing various PVP contents, i.e., 7.33%, 25.0%, 42.7%, to obtain 3% weight increase of the tablets corresponding to runs 5, 6, and 9 in Table I. The results in Table I suggest, regardless of the PVP *K* value, that the higher the level of pore formers in the membrane, the higher the drug release was observed. This finding was consistent with the preliminary results previously discussed.

Dissolution profiles of CPOP, i.e., runs 5, 6, and 9 of both PVP K30 and PVP K90, were plotted for 24- and 12-h as shown in Fig. 1. The similarity of the releases of each PVP K value was evaluated and compared using a model independent method. The similarity factors (f_2) of the profiles were interpreted and summarized in Table II. The similarity factors of the profiles between the low level (7.33%) and the center point (25.0%) indicated much more dissimilarity than those of the profiles between the high level (42.7%) and the center point (25.0%). At the higher level of pore formers where large openings are provided (further discussed later), the PVP concentration did not substantially affect the drug release compared with the lower level. This finding was confirmed by the coefficients of the equation as listed in Tables III and IV, which PVP concentrations represented positive signs for all responses. Drug release significantly increased with increasing level of PVP in the membrane ($p<0.05$). Other investigators also reported similar results regarding the level of pore forming agents (6,7,13,28). The effect of PVP K30 level on the drug release from CPOP was in agreement with the previous works (5,14). It could be clearly seen that in this study PVP at the concentration of 7.33% created insufficient openings to deliver the drug to the desired level, whereas PVP at the concentration of 42.7% could be too high as reflected by the dissolution greater than the USP limit.

Effects of Molecular Weight of PVP on Drug Release

To study the effects of PVP molecular weight or K value, formulations with different types of PVP (PVP K30 and PVP K90) at a PVP concentration of 25.0% and coating level of 3% were prepared, corresponding to runs 9, 10, and 11. At a given PVP concentration and coating level, PVP K90 gave higher percent dissolution than did PVP K30. Since PVP is miscible in the mixture of acetone and isopropanol, yielding

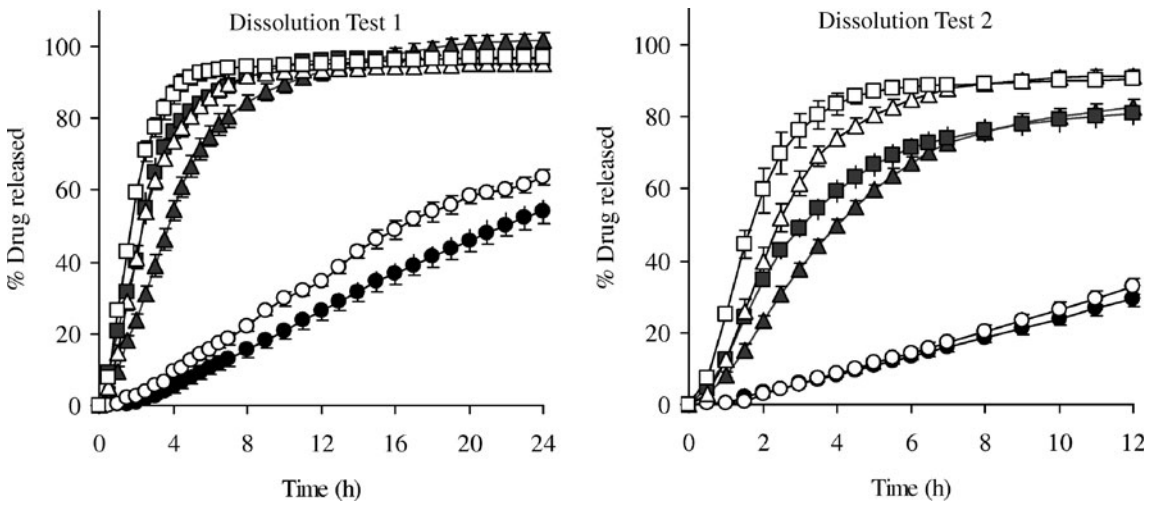

Fig. 1. Effect of PVP content on drug release (at 3% coating level; *filled circle* 7.33%, *filled triangle* 25%, *filled square* 42.7%, *closed symbol* PVP K30, *open symbol* PVP K90)

Table II. Similarity Factor (f_2) Compared Between Dissolution Profiles of the Different Formulations of CPOP at Various Amount of Pore Formers

		f_2			
		24-h profile		12-h profile	
Pore former	Concentration of pore former (%)	25.0	42.7	25.0	42.7
PVP K30	7.33	13.0	10.7	17.7	15.8
	25.0	-	46.4	-	57.9
PVP K90	7.33	13.8	11.5	11.6	9.49
	25.0	-	54.5	-	50.3

molecular dispersion of PVP in the coating solution. Theoretically, the PVP particle will distribute uniformly in the dried film. During dissolution process, the PVP particles at the film surface will dissolve and leave the holes on the film surface. The hole opening could reflect the molecular size of the PVP used. With different molecular weight of pore formers, the f_2 values of the 24- and 12-h release profiles of CPOP with the same PVP concentration and coating level were found to be 47.9 and 38.6, respectively. These observations may have been due to larger openings produced on the membrane containing higher molecular weight of PVP K90 (29).

Effects of Coating Level on Drug Release

To study the effects of coating level, core tablets were coated with cellulose acetate containing PVP to obtain different weight increases, i.e., 1.59%, 3.00%, 4.41%, corresponding to runs 7, 9, and 8. A decrease in drug release with increasing coating level was observed. The similarity factors (f_2) of the profiles were interpreted and summarized in Table V. The increase in the coat containing PVP K90 did not markedly affect the release profile whereas, the increased coat containing PVP K30 inhibited substantial influence on the percent drug release. These observations may have been due to the large openings obtained by dissolved PVP K90 (29) that yielded more effects on drug release than the effect of membrane thickness. In addition, the coefficients of the equation as listed in Tables III and IV indicated negative signs for some responses. It can be concluded that increasing membrane thickness decreased the drug release and resulted in a delayed profile.

Response Surface Methodology

All responses were established according to USP 31 criteria. Three-dimensional surface plots (Fig. 2) show the effects of the amount of PVP and coating level on drug release at various times. Drug release could be increased by increasing the level of PVP content in the semipermeable membrane or decreasing the coating level of the membrane.

The experimental tests with observed responses are shown in Table I. Based on the experimental design, the factor combinations yielded different responses. The responses of drug release at time t, Y_t, to the membrane variables were analyzed using MINITAB 14 software in order to provide a relationship between the variable factors and the responses. A second-order polynomial was fitted to the experimental data:

$$Y_t = a + bX_1 + cX_2 + dX_1^2 + eX_2^2 + fX_1X_2 \qquad (3)$$

where, Y_t is the response variables, drug release, at time t, X_1, and X_2 are the pore forming PVP concentrations (7.33–42.7% *w*/*w* based on cellulose acetate) and the coating levels (1.59–4.41% *w*/*w*), respectively, and a, b, c, d, e, and f are the equation constants. The coefficients of 24- and 12-h release equations are listed in Tables III and IV, respectively. The ANOVA shows significance of the models with a variance ratio of measurements residues compared to the model and the variance of all measured data (F value) with probability $>F$ less than 0.01 (which were lower than 0.05), which proved the model relevance (30). The multiple regression coefficient calculated for all responses indicated that more than approximately 90% (r^2>90%) of the experimental variance could be explained by the models. The high value of adjusted r^2, more than 80% for all responses, indicated that the model fitted the observed data quite well (31).

These equations represent the quantitative influence of membrane variables (X_1 and X_2) and their interaction on the response Y_t. Coefficients with more than one factor term and those with higher order terms correspond to interaction terms and quadratic relationship, respectively. A positive sign denotes a synergistic effect, whereas a negative sign indicates an antagonistic effect (32). Student's t test was employed for statistical analysis of the parameter estimates. As seen in Tables III and IV, PVP concentration had a significant positive effect on most responses. On the other hand, membrane thickness presented an antagonistic influence on the drug release.

Model Adequacy Checking

Typically, it is necessary to test the fitted model to guarantee that it presents an adequate approximation to the actual system. Unless the model shows an adequate fit, continuing on examination and optimization of the fitted response surface would provide poor or misleading results. The residual analysis is one technique for determining model adequacy. By constructing a normal probability plot of the residuals from the least squares fit, which is defined by the difference between observed and predicted data of each experimental run, a check of normality assumption can be confirmed. In this study, the normality was satisfied as all

Table III. Coefficients of the Equations Related to the Responses and the Independent Variables, p Values, r^2, and r^2 (adj) for 24-h CPOP

Variables		Coefficients									
		PVP K30					PVP K90				
		$Y_{1.5}$	Y_4	Y_8	Y_{14}	Y_{24}	$Y_{1.5}$	Y_4	Y_8	Y_{14}	Y_{24}
Constant	a	−9.00	−22.5	−55.1	3.36	26.7	−34.4	−75.7	−49.1	19.5	54.6[a]
PVP concentration (X_1)	b	1.91[a]	5.12[a]	7.00[a]	5.59[a]	4.26[a]	4.23[a]	8.48[a]	7.96[a]	5.12[a]	2.88[a]
Membrane increase (X_2)	c	1.94	5.20	28.8	8.89	10.5	5.36	16.3	13.6	−2.38	−2.59
PVP concentration×PVP concentration (X_1^2)	d	−0.0111	−0.0506	−0.101[a]	−0.0938[a]	−0.0756[a]	−0.0400	−0.112[a]	−0.128[a]	−0.0904[a]	−0.0559[a]
Membrane increase × membrane increase (X_2^2)	e	−0.867	−2.54	−7.02[a]	−3.80	−3.39	−0.692	−2.95	−3.48	−0.840	−0.681
PVP concentration× membrane increase (X_1X_2)	f	−0.156	−0.162	0.0604	0.243	0.184	−0.347	−0.189	0.173	0.256	0.251
p-value of model		0.002	0.003	<0.001	<0.001	0.001	0.006	0.005	0.001	0.001	0.003
r^2 (%)		96.1	94.7	98.6	98.0	96.6	93.1	93.8	96.3	97.2	94.8
r^2 (adj; %)		92.3	89.3	97.2	96.0	93.3	86.3	87.5	92.7	94.4	89.5

[a] Significant terms with $p<0.05$

residuals plots approximated along a straight line (22). The confidences that the regression equations would predict the observed values well fitted for most responses were more than 95% for all responses.

Formulation Optimization

To optimize the formulation for a satisfactory drug release profile, it is necessary to obtain response surfaces for all responses. Then, superimpose the contours for these responses in the PVP concentration–coating level plane, as illustrated in Fig. 3 for CPOP with PVP K30 and K90. In these figures, the contours for percent drug release are demonstrated. The non-shaded area in these figures represents the region containing acceptable drug releases that simultaneously satisfy all requirements of the USP 31 criteria. The results showed that satisfactory 24-h profile or once daily dosing could be accomplished by either PVP K30 or PVP K90-containing membrane. However, an acceptable 12-h drug release profile or twice daily dosage form could be achieved from only specific ranges of PVP K30-containing membrane at the defined membrane thickness.

After generating the polynomial equations relating the dependent and independent variables, the formulation was optimized for the responses $Y_{1.5}$, Y_4, Y_8, Y_{14}, and Y_{24}, and Y_1, Y_3, Y_6, and Y_{12}, in order to develop once and twice daily dosage forms, respectively. Optimization was performed to obtain the level of X_1 and X_2, which targeted or maximized all of the responses at constrained conditions of $Y_{1.5}$ through Y_{24} and Y_1 through Y_{12} as listed in Table I.

In this study, the optimized X_1 and X_2 in PVP K30-containing membrane were chosen at 35.0% and 4.2%,

Table IV. Coefficients of the Equations Related to the Responses and the Independent Variables, p Values, r^2, and r^2 (adj) for 12-h CPOP

Variables		Coefficients							
		PVP K30				PVP K90			
		Y_1	Y_3	Y_6	Y_{12}	Y_1	Y_3	Y_6	Y_{12}
Constant	a	10.9	21.1	−11.4	37.3	−10.8	−62.9	−53.4	17.6
PVP concentration (X_1)	b	1.50	4.04	5.49[a]	4.23[a]	2.38[a]	7.70[a]	8.08[a]	5.28[a]
Membrane increase (X_2)	c	−12.9	−21.5	4.59	−7.55	−2.69	11.5	12.5	−3.00
PVP concentration × PVP concentration (X_1^2)	d	−0.0037	−0.0355	−0.0841[a]	−0.0866[a]	−0.0186	−0.103[a]	−0.131[a]	−0.101[a]
Membrane increase × membrane increase (X_2^2)	e	2.26	2.32	−3.48	−1.92	0.621	−2.46	−3.72	−1.67
PVP concentration× membrane increase (X_1X_2)	f	−0.263	−0.228	0.183	0.473[a]	−0.258	0.163	0.211	0.397
p value		0.008	0.008	0.001	<0.001	0.022	0.006	0.001	0.002
r^2 (%)		92.2	92.5	96.7	98.2	88.3	93.4	96.2	95.6
r^2 (adj; %)		84.4	85.0	93.4	96.5	76.6	86.8	92.4	91.3

[a] Significant terms with $p<0.05$

Table V. Similarity Factor (f_2) Compared Between Dissolution Profiles of the Different Formulations of CPOP at Various Membrane Thickness

		f_2			
		24-h profile		12-h profile	
Pore former	Membrane weight increase (%)	3.00	4.41	3.00	4.41
PVP K30	1.59	43.5	21.0	34.7	19.7
	3.00	-	28.7	-	33.6
PVP K90	1.59	55.3	46.5	46.0	19.7
	3.00	-	66.9	-	76.1

respectively. For PVP K90, X_1 and X_2 were 23.0% and 4.2%, respectively. The weight increase of the two formulations was kept constant for comparison between each formula. Propranolol release profiles of the optimized formulations were illustrated in Figs. 4 and 5. An important consideration for the *in vivo* use of this type of delivery system is the mechanical stability and resistance of the film coating to rupture during passage through the GI tract. None of the optimized formulations ruptured during the dissolution studies, as observed visually, and as indicated by the absence of a burst in drug release initially. Empty polymeric shells retained their original shape and floated on the dissolution medium after completion of drug release. Under the hand pressure, the fluid-filled polymeric shells were flexible and the fluid was squeezed out from the shells.

Preparation and testing of the optimized formulation showed a good correlation between predicted and observed values. The observed *versus* predicted values of $Y_{1.5}$ to Y_{24}

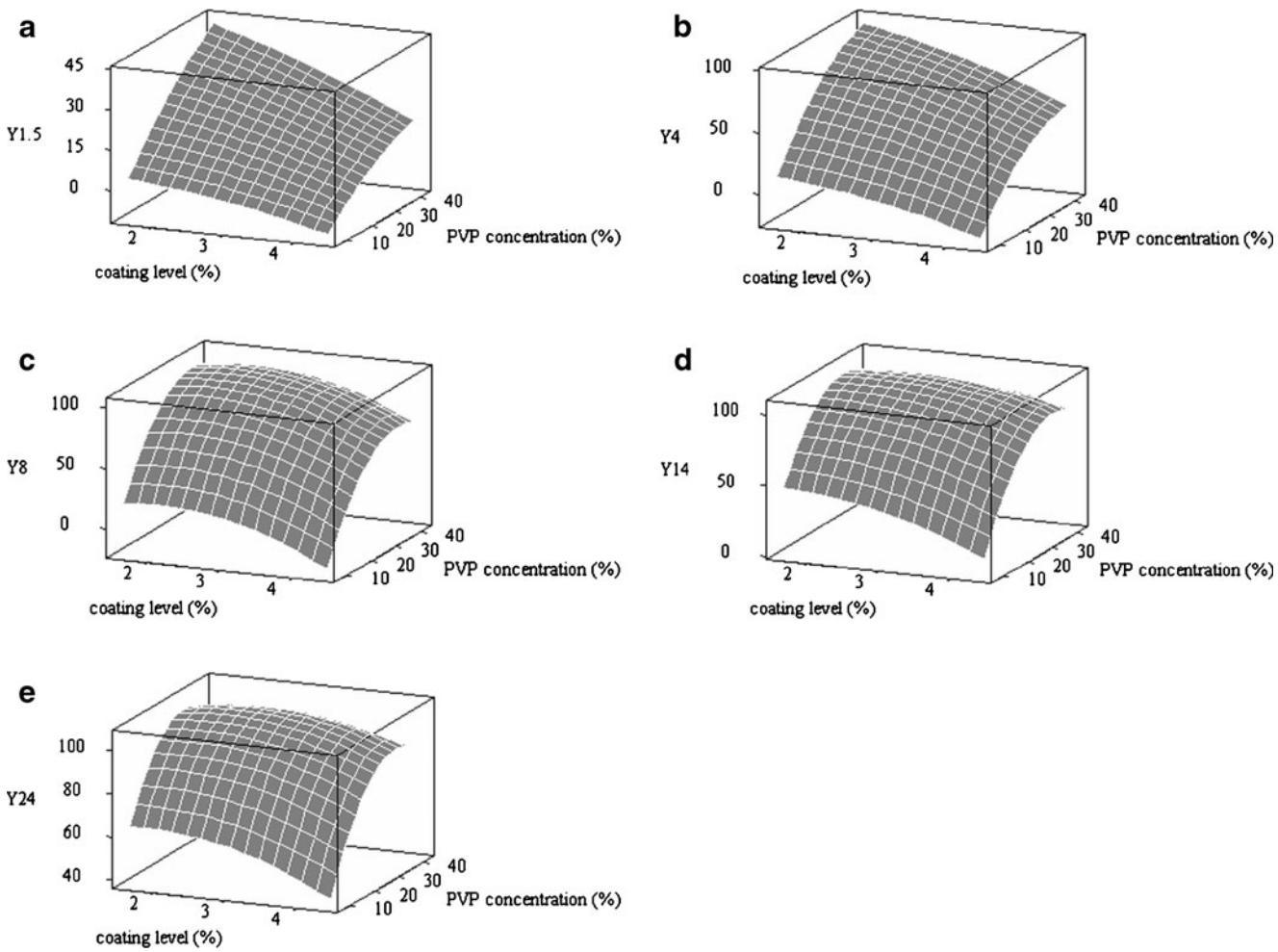

Fig. 2. Response surface plots showing the effect of the PVP concentration and coating level on the drug release of CPOP with membrane containing PVP K30 at various times according to *Dissolution Test 1* (**a** 1.5 h, **b** 4 h, **c** 8 h, **d**14 h, **e** 24 h)

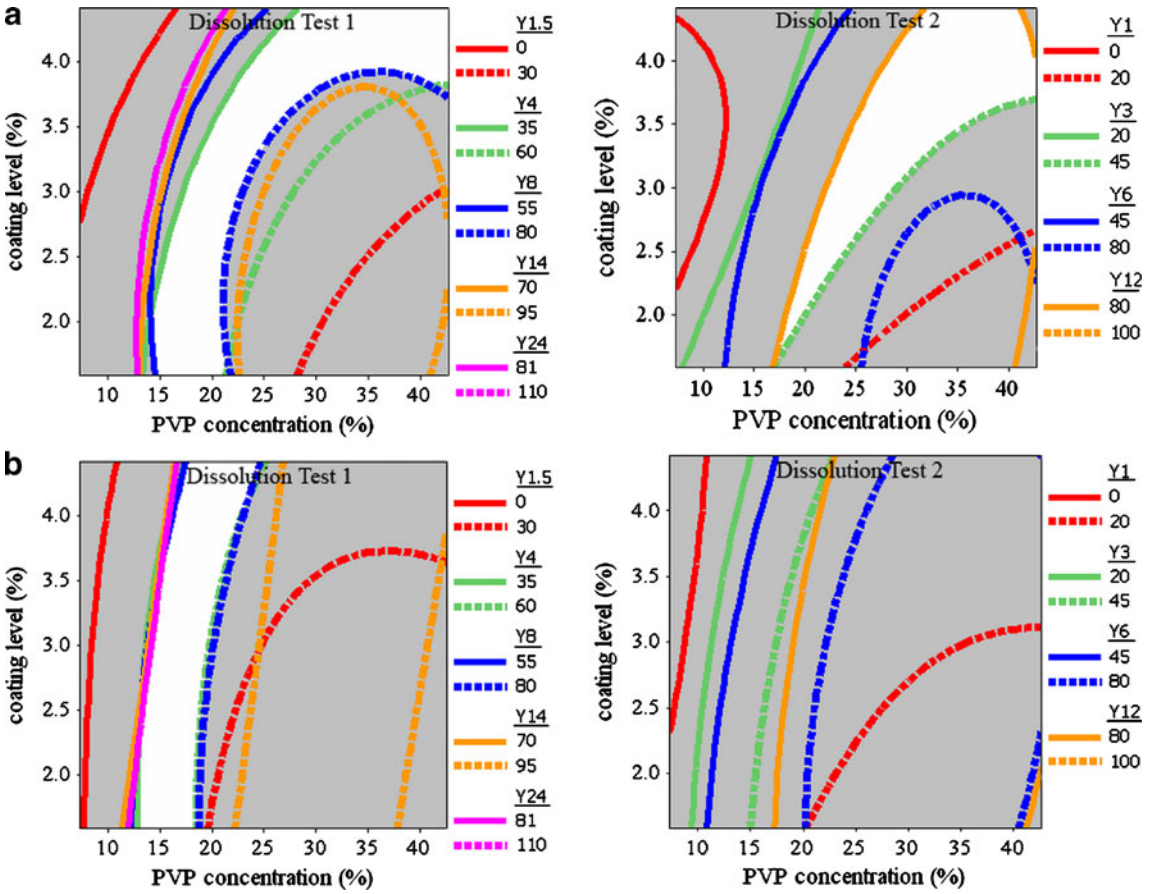

Fig. 3. Overlaid contour plots of CPOP with membrane containing **a** PVP K30 and **b** PVP K90 (*solid line* lower limit of USP criteria, *dash line* upper limit of USP criteria)

and Y_1 to Y_{12} of PVP K30-containing membrane are shown in Fig. 6. The observed *versus* predicted data of $Y_{1.5}$ to Y_{24} of PVP K90-containing membrane are illustrated in Fig. 7. These figures show that the predicted data of all responses from the polynomial equations are in agreement with the observed ones in the range of the operating variables, which were confirmed by the high correlation coefficient value of each figure, i.e., 0.9971, 0.9994, and 0.9655.

Membrane Characterization Study

In membrane sciences, surfaces of microfiltration and ultrafiltration membranes were extensively and profitably investigated by SEM and AFM to understand the characteristics of pore structure for determining their filtration properties (33–35). Therefore, it was expected that the study of the surface morphology of membrane of osmotic pump tablets could facilitate the identification of the influences of membrane variables on drug release from the tablets.

Surface Pore Diameter

Runs 1-9 of each PVP type were studied. Runs 9-11 were the center points; therefore, these three runs had the same coating formulation. Most surfaces of micro/nanoporous membranes containing PVP as pore formers were found to have a network-like fine structure when examined by SEM and AFM as illustrated in Figs. 8 and 9. Differences in number of pores between those membranes at different PVP contents are clearly visible. The higher level of PVP, the more crowded pores were observed. Surface pore diameters were measured by visual inspection of SEM images and by line profiles of AFM images. Each membrane was measured for 50 pores (34). The smallest and largest diameters and the mean values, including their relative standard deviations of all 50 pores are listed in Table VI.

The result shows that pores formed by PVP ranged from nanometers to micrometers in size. The average pore sizes of membrane containing PVP K30 which were measured by SEM and AFM were approximately 400 and 200 nm, respectively. Whereas, PVP K90 gives larger pore size of around 500 and 300 nm measured by SEM and AFM, respectively. It was also observed that at the higher level of PVP concentration, significantly larger pore size was created on the micro/nanoporous membrane ($p<0.05$).

The molecular weight (M_r) of PVP K90 and PVP K30 are 1,000,000 and 50,000, respectively (27). As such, the molecular size of PVP K90 is drastically larger than PVP K30. It is expected that when PVP K90 leached from the semipermeable membrane, the larger pore was formed. This finding is in agreement with publications in the area of membrane sciences (29,36) since PVP has been used as a pore

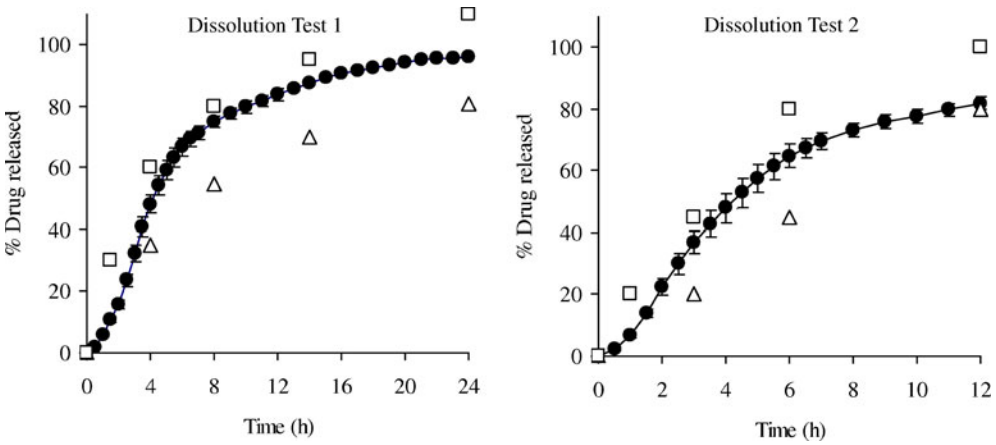

Fig. 4. Drug release from CPOP with membrane containing 35% of PVP K30 at 4.2% weight gain (USP 31 criteria at various times; *triangle* lower limit, *square* upper limit, $n=6$)

forming agent for ultrafiltration membranes (29,36–38). It was clearly evident that the addition of PVP changed the membrane porosity, resulting in the increase of permeability without changing the membrane selectivity (36). Gas permeability through the ultrafiltration membranes was observed to be increased remarkably with incremental PVP contents (38) and molecular weight (29). It was also reported that the micropore volume was increased by increasing molecular weight of PVP (29).

The variety in pore diameters was observed within each membrane, indicating broad size distribution of the pores. The deviation was between ±30–50% from the average values in most cases. Two possible assumptions could be explained as follows. (1) PVP stays in various configurations of its side chain in the membrane. Once it dissolves, various pore sizes are generated in the membrane. The long-chain polymers give larger openings while the short-chain polymers give smaller openings. (2) Some of the large entries were not single pores, but were composed of two or more small pores (34). So an overestimation could occur from this cause that multiple pores could not be resolved within one observed large opening.

Considering pore sizes observed by SEM and AFM, the AFM results were approximately 200 nm lower than those estimated with SEM. In AFM, the opening that is composed of two or more pores could be identified and excluded. Thus, the overestimation of the pore size could be diminished. Another possibility is that the samples for AFM imaging do not need to be dried during the sample preparation, thus changes in the surface were less likely to occur (34,39). On the other hand, the samples for SEM imaging need to be dried and exposed to vacuum, then treated for increasing conductivity. Thus, the surfaces were prone to being altered (39), causing the enlargement of the pore. However, the values obtained from both PVP types were correlated in their pattern. Regarding SEM and AFM results, the average surface pore size on the membrane with PVP K90 was significantly larger than that with PVP K30 ($p<0.05$).

At a given PVP concentration, PVP K90 generally gave higher drug release than did PVP K30 as previously discussed. These surface morphology studies confirmed the *in vitro* release observations that for higher molecular weight PVP, the pore size of the micro/nanoporous membrane is larger which leads to higher drug release.

Membrane Porosity

To determine the porosity of the membrane, the formulations with various PVP concentrations (7.33%, 25%, 42.7%) at 3% weight increase were selected and the porosities of 50 membranes after the dissolution test were determined. The results are shown in Table VII. Despite the fact that porosity would not be equal to PVP concentration in the membrane at any time, it was clearly shown that the porosity increased with increasing PVP concentration. From the visual inspection of the membrane after dissolution, it was observed that the more PVP content in the membrane, the more hazy and brittle the membrane was, and this behavior increased with PVP K90. It could be due to incomplete solubilization of PVP in the coating solution, resulting in the

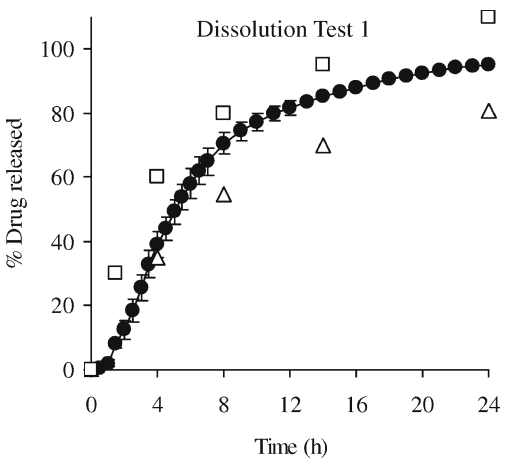

Fig. 5. Drug release from CPOP with membrane containing 23% of PVP K90 at 4.2% weight gain (USP 31 criteria at various times; *triangle* lower limit, *square* upper limit, $n=6$)

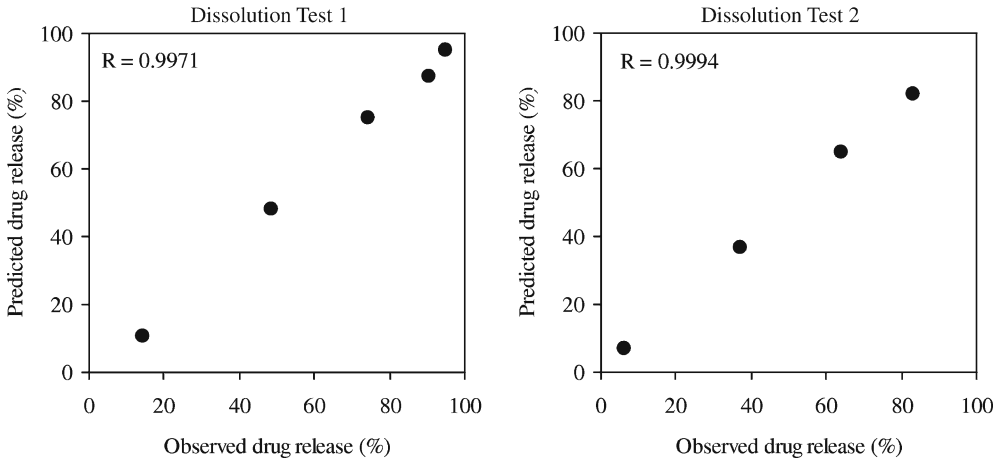

Fig. 6. Relationship between the observed drug release and the predicted values of the optimized formulation of CPOP with membrane containing PVP K30 (35% PVP K30, 4.2% weight gain; n=6)

non-uniform membrane. The deviations of porosity were small, even though the pore size distributions were broad. This result supports the understanding of surface pore size and drug release of the CPOP, the higher the level of pore forming PVP, the higher the porosity of the membrane and the higher the drug release.

CONCLUSIONS

In this study, the application of PVP K30 and K90 as the pore-forming agents was investigated. The central composite design was employed for simultaneously determining the influences of membrane variables (PVP type, PVP concentration, and coating level) on the characteristics of propranolol micro/nanoporous osmotic pump tablets, in order to establish the optimum formulation based on the criteria of USP 31. Drug release was dependent on the molecular weight and concentration of PVP, and the level of coating. The CPOP formulation that gave the desired release profile for both once and twice daily dosing interval employed PVP K30 as pore formers. In this study, it was found that the optimized formulation was CPOP with cellulose acetate coating con-

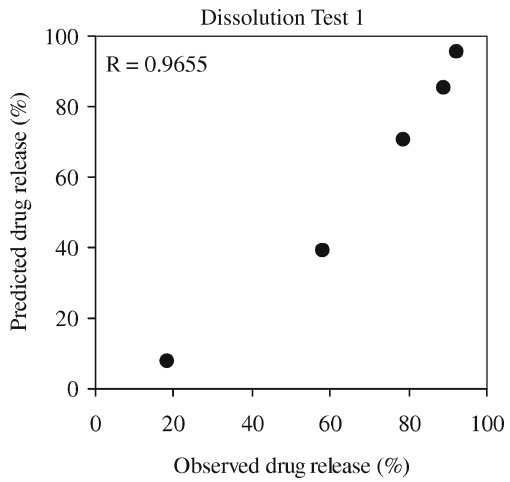

Fig. 7. Relationship between the observed drug release and the predicted values of the optimized formulation of CPOP with membrane containing PVP K90 (23% PVP K90, 4.2% weight gain; n=6)

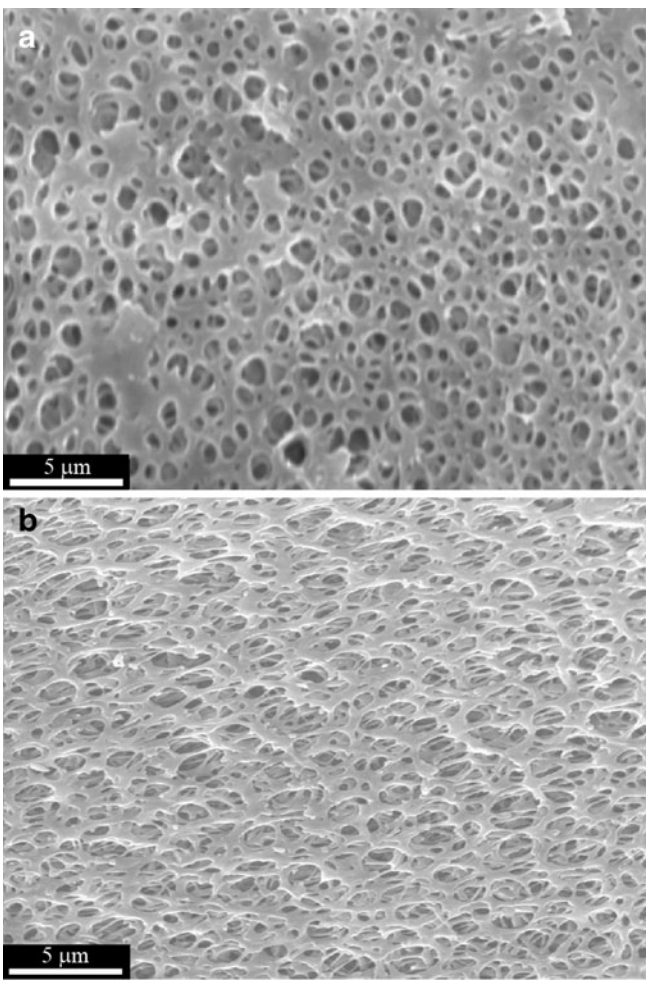

Fig. 8. SEM images of CPOPs at PVP concentration of 42.7% *w*/*w* (of cellulose acetate) and 3% membrane weight gain after dissolution (**a** PVP K30, **b** PVP K90)

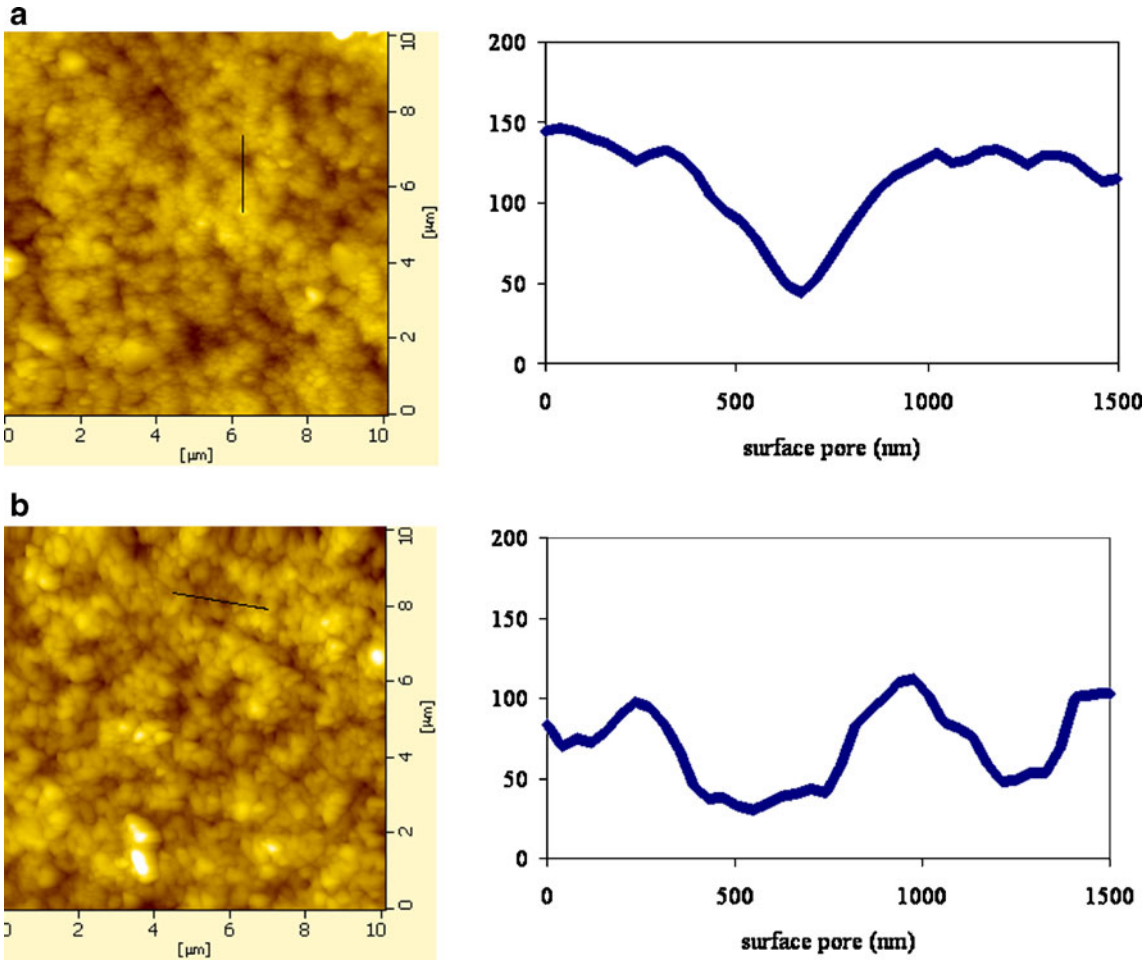

Fig. 9. AFM images of CPOPs at PVP concentration of 42.7% *w/w* (of cellulose acetate) and 3% membrane weight gain after dissolution. The right graphs show 1,500 nm long line profiles across typical pore openings (**a** PVP K30, **b** PVP K90)

Table VI. Pore Characteristics of Osmotic Pump Tablet Membranes

		Surface pore diameter (nm±RSD%)					
		SEM			AFM		
PVP type	Run	Min	Max	Mean	Min	Max	Mean
K30	1	108	974	416±59.1	76	400	194±43.3[a]
	2	153	971	472±50.2	100	497	222±33.3[a]
	3	72	1,048	363±69.1	98	409	208±35.1
	4	72	1,063	449±61.9	104	448	225±41.8[a]
	5	81	776	249±41.0[a]	100	332	174±28.2[a]
	6	149	1,154	585±54.0	153	562	322±24.8
	7	161	1,195	482±58.7	167	409	243±23.9
	8	80	1,125	374±71.1[a]	173	606	254±29.5[a]
	9	81	896	425±56.9	80	429	225±37.3[a]
K90	1	144	1,299	507±50.3	120	496	243±32.9[a]
	2	180	1,414	536±55.6	188	605	360±28.3[a]
	3	144	904	446±38.6	110	482	219±43.8
	4	180	1,046	535±51.4	172	556	319±28.5[a]
	5	72	844	415±48.4[a]	88	365	202±36.1[a]
	6	130	1,250	602±47.3	200	499	343±25.1
	7	144	974	484±54.1	99	551	255±42.4
	8	108	1,209	576±48.8[a]	108	660	322±39.8[a]
	9	108	1,181	508±60.8	107	553	286±31.5[a]

[a] Significant difference with $p<0.05$ (comparing between different molecular weight of PVP)

taining 35% of PVP K30 at 4.2% coating level. For CPOP with cellulose acetate coating containing PVP K90, the desired release profile for the once daily dose was achieved at a PVP concentration of 23% and coating level of 4.2%. The advantages of these formulations are that they are simple in design, manufacture without the need of specific equipment, are economical and lend themselves to mass production. Consequently, the general method of incorporating drug into the described osmotic system has great potential for commercial production.

Table VII. Porosity (%) of the Membrane Containing Various PVP Concentrations (SD in Parentheses, $n=3$)

	Porosity (%)		
	PVP Concentration (%)		
PVP type	7.33	25	42.7
K30	7.21 (0.26)	21.43 (0.42)	30.57 (0.63)
K90	2.00 (0.05)	18.74 (0.29)	22.19 (0.44)

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