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Optimization of tamsulosin hydrochloride controlled release pellets coated with Surelease and neutralized HPMCP

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Abstract

This study was to optimize the coating level in the development of controlled release pellets coated with Surelease and neutralized hydroxypropyl methylcellulose phthalate (HPMCP) by a computer optimization technique based on a response surface methodology utilizing polynomial equation. A full factorial 3^2 design was used for the optimization procedure with coating level (X_1) and HPMCP content (X_2) as the independent variables. The drug release percent at 2, 3 and 5 h were the target responses, which were restricted to 12–39% (Y_1), 44–70% (Y_2) and 70–100% (Y_3), respectively. The quadratic model was well fitted to the data, and the resulting equation was used to predict the responses in the optimal region. It was shown that the optimized coating formulation was achieved at the ratio of 3:1 (Surelease: neutralized HPMCP) with 20% coating level. The optimized formulation showed release profiles and responses, which were close to predicted responses. Therefore, a full factorial 3^2 design and optimization technique can be successfully used in the development of optimized coating formulations based on Surelease and neutralized HPMCP to achieve a controlled release drug delivery system containing tamsulosin hydrochloride.

Introduction

Tamsulosin hydrochloride (TSH) is a highly selective alpha 1A-adrenoreceptor antagonist that has been used for treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). Moreover, following oral administration of 0.2–0.4 mg TSH, the drug is absorbed from the intestine and almost completely bioavailable (Wilde & McTavish 1996). Therefore, a controlled release delivery system is required to improve the absorption of drug in the intestinal tract.

In a previous study, we developed a controlled release delivery system containing TSH using sodium alginate and Surelease or alginate beads containing waxy materials (Kim et al 2005a, b). In addition, Lee et al (2004) and Seo et al (2006) reported on enteric coating systems such as hydroxypropyl methylcellulose phthalate (HPMCP) with triacetin and HPMCP with povidone K30 for the development of controlled release of TSH. Unfortunately, HPMCP as an enteric coating material has been traditionally applied as a film coating from a solution in organic solvents but environmental and health concerns with the use of organic solvents have led to an interest in the use of aqueous-based coating preparations (Ibekwe et al 2006).

A simple way to apply cellulose enteric polymers containing a free carboxylic group from water is by neutralization of the polymers with a base such as ammonia (Heinämäki et al 1994). In addition, Surelease aqueous ethylcellulose dispersions are stabilized by ammonium oleate (Colorcon 2006). Therefore, HPMCP as a cellulose enteric polymer was directly dissolved in Surelease via neutralization by ammonia without the use of organic solvents, such as ethanol and dichloromethane, to develop a controlled release delivery system of TSH, based on an aqueous coating system.

Here, we prepared TSH controlled release pellets with Surelease and neutralized HPMCP as coating materials. Moreover, to optimize the content of HPMCP and also the coating level, we applied a computer optimization technique based on a response surface methodology utilizing polynomial equation. The response surface method has been commonly used

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for the optimization of coating formulations with various kinds of drugs in the development of controlled release formulation design (Gupta et al 2001; Hamed & Sakr 2001; Nutan et al 2005).

Materials and Methods

Materials

Tamsulosin hydrochloride was purchased from Youn Sung Fine Chemicals Co., Ltd (99.6% purity, Korea). Poloxamer 407 (Lutrol F127; BASF, Germany), Carbopol 974P NF (Noveon, USA), microcrystalline cellulose (Avicel PH102; FMC, USA), sodium alginate (Duckalgin NSPH; Kibun Food Chemica, Japan), Surelease (E-7-19010; Colorcon, USA) and hydroxypropyl methylcellulose phthalate (HPMCP, HP-55; Shin-Etsu Chemical Co., Japan) were used. All organic solvents were of high-performance liquid chromatography (HPLC) grade. All other chemicals were of reagent grade.

Experimental design

A full factorial 3^2 design was used for the optimization procedure with the content of HPMCP (X_1) and coating level (X_2) as the independent variables. From the preliminary study, the content of HPMCP (based on total solid content of coating compositions) and coating level were determined in the range of 0–40% (w/w) and 15–35% (w/w), respectively. The % drug released at 2, 3 and 5 h was used as a dependent variable for desirable drug release, as described in literature (Food and Drug Administration; Lee et al 2004; Seo et al 2006). Experimental design, data analysis and desirability function calculations were performed by using Design-Expert software (V. 6.0; Stat-Ease Inc., Minneapolis, USA). A suitable polynomial equation involving the individual main effects and interaction factors was selected based on the estimation of several statistical parameters, such as the multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of square (PRESS), also provided by Design-Expert software.

Preparation of drug-loaded pellets

Pellets consisted of 0.17 w/w% tamsulosin hydrochloride, 0.42 w/w% Poloxamer 407, 0.42 w/w% Carbopol 974P NF, 47.21 w/w% microcrystalline cellulose, 5.20 w/w% sodium alginate, 31.61 w/w% magnesium trisilicate and 14.98 w/w% lactose. Briefly, tamsulosin hydrochloride (0.2 mg/capsule), Poloxamer 407 and Carbopol 974P NF were dissolved in 30% ethanolic solution. The drug solution was uniformly mixed with microcrystalline cellulose, sodium alginate, magnesium trisilicate and lactose. The mixture was then kneaded with drug solution in a mixer (Kitchen Aid Inc., MI). The wet mass was passed through a radial-basket extruder (Wooil Presicion Co. Ltd, Korea) with a 1-mm screen at 120 rev min^{-1}. The extrudates were processed in a spheronizer (Sejeong Pharmatech Co. Ltd, Korea) fitted with a cross-hatched plate rotated at 800 rev min^{-1} for 10 min. The spherical pellets were dried in a 60°C drying oven for 24 h.

Coating procedure

The drug-loaded pellets were coated with Surelease in the absence or presence of neutralized HPMCP. In each case, a calculated amount of HPMCP was dispersed in water and then added to Surelease. The final coating formulations were adjusted to obtain 12 w/w% for Surelease solid content and stirred throughout the coating processes. For coating, 1-kg quantities of drug-loaded pellets from the 1000–1190 μm sieve fraction were used. The drug-loaded pellets were coated using Glatt (GPCG908186) bottom spray fluidized-bed coater. Coating conditions were: inlet temperature = 47 ± 3°C, outlet temperature = 40 ± 3°C, air flow = 70 $m^3 h^{-1}$, nozzle diameter = 1.2 mm, and spray rate = 6 mL min^{-1}. Following coating solution application, the pellets were dried in a coater for an additional 30 min to keep the pellets from sticking. The coated pellets were spread onto paper trays and stored at 60°C for 24 h.

Dissolution studies

The release of tamsulosin hydrochloride from coated pellets was performed according to the USP XXV paddle method using a dissolution apparatus (Vankel VK7000; Cary, NC). The coated pellets containing 0.2 mg of drug were filled into hard gelatin capsules (capsule No. 3; Su-Heung Capsule Co. Ltd, Korea). The capsules were added into 500 mL of simulated gastric fluid without pepsin (adjusted to pH 1.2 with HCl) containing polysorbate 80 (0.003%, w/w) at 37 ± 0.1°C and with a paddle speed of 100 rev min^{-1}. A sinker was used to avoid capsule flotation. Each sample (5 mL) was withdrawn at defined time intervals, and the same volume of simulated gastric fluid was compensated. After 2 h, 500 mL of simulated intestinal fluids without pancreatin (pH 7.2, phosphate buffer according to the USP without enzyme) was replaced to adjust pH of dissolution medium from pH 1.2 to 7.2. The samples were analysed using HPLC as described in a previous study (Kim et al 2005a, b). Dissolution tests were repeated six times for all formulations and then the % drug released from the controlled release pellets was calculated.

Scanning electron microscopy

The morphology of pellets was examined by scanning electron microscopy (SEM; JSM-6300, Jeol Ltd, Japan). Pellets were coated with gold and palladium using a vacuum evaporator and examined using a scanning electron microscope at 20 kV accelerating voltage.

Results and Discussion

Statistical design experiments

Figure 1 shows different drug release profiles from pellets, depending on factor combinations such as the content of HPMCP and coating level using a full factorial 3^2 design. Among the different models, which are available in a full factorial 3^2 design of Design Expert software, the quadratic model was selected as a suitable statistics model for optimized coating formulations because of the smallest value of PRESS

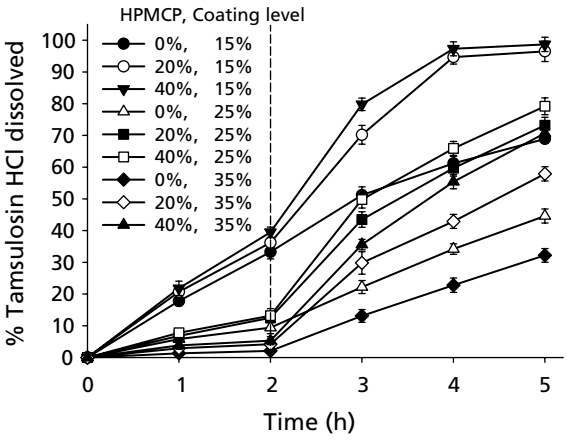

Figure 1 Dissolution profiles of all coating formulations (dashed line shows the change of medium pH from 1.2 to 7.2). Data are means ± s.d., n = 6.

(predicted residual sum of squares). PRESS is a measure of the fitness of the model to the points in the design. The smaller the PRESS statistic, the better the model fits to the data points (Segurola et al 1999). The estimated statistical parameters of the quadratic model were obtained as follows: adjusted $R^2 = 0.9949$ and PRESS = 8.93 for Y_1; adjusted $R^2 = 0.9970$ and PRESS = 38.81 for Y_2; adjusted $R^2 = 0.9921$ and PRESS = 138.14 for Y_3. Besides, the residual plot tests of regression models confirmed the adequacy of the model fitting process. For estimation of significance of the model, the analysis of variance was applied. Using 5% significance level, a model is considered significant if $P < 0.05$. The equations of the responses are given below:

$$Y_1 = 12.03 + 2.20X_1 - 16.23X_2 + 8.40X_2^2 \quad (1)$$

$$Y_2 = 42.42 + 13.12X_1 - 20.45X_2 - 5.88X_1^2 + 8.12X_2^2 \quad (2)$$

$$Y_3 = 72.88 + 16.98X_1 - 17.55X_2 - 10.32X_1^2 + 4.48X_2^2 \quad (3)$$

The contour plots and three-dimensional response surfaces were drawn to estimate the effects of the independent variables on the each response (Figure 2). The values of the coefficients are related to the effect of these variables on the response. Positive or negative signs before a factor in polynomial equations represent that the response increases or decreases with the factor. The values of coefficient of X_1 and X_2 indicated that the drug release from coated pellets was mainly influenced by the coating level (X_2) (Kim et al 2005a; Lee et al 2005). However, it was found that the drug release was highly influenced by the content of HPMCP (X_1) at pH 7.2. In fact, drug release from coated pellets at pH 7.2 was increased with the content of HPMCP. Figure 3 shows SEM images of pellets with run 5 and run 7 formulations, which were taken at the end of dissolution and dried in an oven at 60°C. In coated pellets with Surelease at 25 w/w% level, there were cracks in the membrane structure during dissolution due to osmotic force induced by sodium alginate within core pellet (Kim et al 2005a). Moreover, there were bigger cracks and holes in the membrane in coated pellets with Surelease–HPMCP 80:20 at the same level. It was suggested that the cracks on the membrane were created by leaching of the HPMCP, which was dispersed within the continuous ethylcellulose membrane, resulting in faster drug release (Figure 3D). Previously, it was reported that the drug release rate was controlled by the leaching of enteric coating materials, such as Eudragit L, HPMCAS and Kollicoat MAE, from membrane composed of insoluble polymer and enteric polymer (Lecomte et al 2003, 2004, 2005; Siepmann et al 2005). It can be expected that the leaching of the enteric polymer out of the film coating at high pH plays an important role in the control of drug release (Lecomte et al 2005). In fact, the remaining ethylcellulose membranes, after partial or fully HPMCP leaching or hydration, are mechanically weak, enabling the formation of water-filled cracks though which the drug is rapidly released out. Therefore, the pH-dependent permeability of ethylcellulose membrane was controlled by incorporating HPMCP.

Optimization

As mentioned above, the percent of drug release after 2 h (pH 1.2), 3 h and 5 h (pH 7.2) was selected as the response variable (dependent variable). After generating the polynomial equations relating the dependent and independent variables, the process was optimized for the responses Y_1, Y_2 and Y_3. The range of these responses were restricted to $12\% \le Y_1 \le 39\%$; $44\% \le Y_2 \le 70\%$; $70\% \le Y_3 \le 100\%$, respectively, as descried in literature (Food and Drug Administration; Lee et al 2004; Seo et al 2006). The optimum values of the variables were obtained by the graphical and numerical analyses, using the Design-expert software, based on the criterion of desirability. The process is based on the methodology described by Myers and Montgomery (2002). It was found that a maximum level of desirability of 1.00 could be achieved, whereby the optimal calculated parameters were HPMCP content (25%) and coating level (20%). Predicted responses Y_1–Y_3 for optimal coating formulations were 22.8%, 57.8% and 86.2%, respectively. A new batch of pellets coated with the predicted levels of formulation factors was prepared to confirm the validity of the optimization procedure. Its observed responses Y_1–Y_3 were 23.8 ± 2.1%, 57.8 ± 2.5% and 86.2 ± 3.8%, respectively (Table 1). The coated pellets prepared at optimized coating formulations showed similar drug release profiles to those prepared at predicted values.

Conclusions

It was shown that the optimized coating formulation was achieved at the ratio of 3:1 (Surelease–neutralized HPMCP) with coating level (20%) and the observed responses were close to the predicted values for the optimized coating formulations. Therefore, a full factorial 3^2 design and optimization technique can be successfully used in the development of optimized coating formulations based on Surelease and neutralized HPMCP to achieve a controlled release drug delivery system containing tamsulosin hydrochloride.

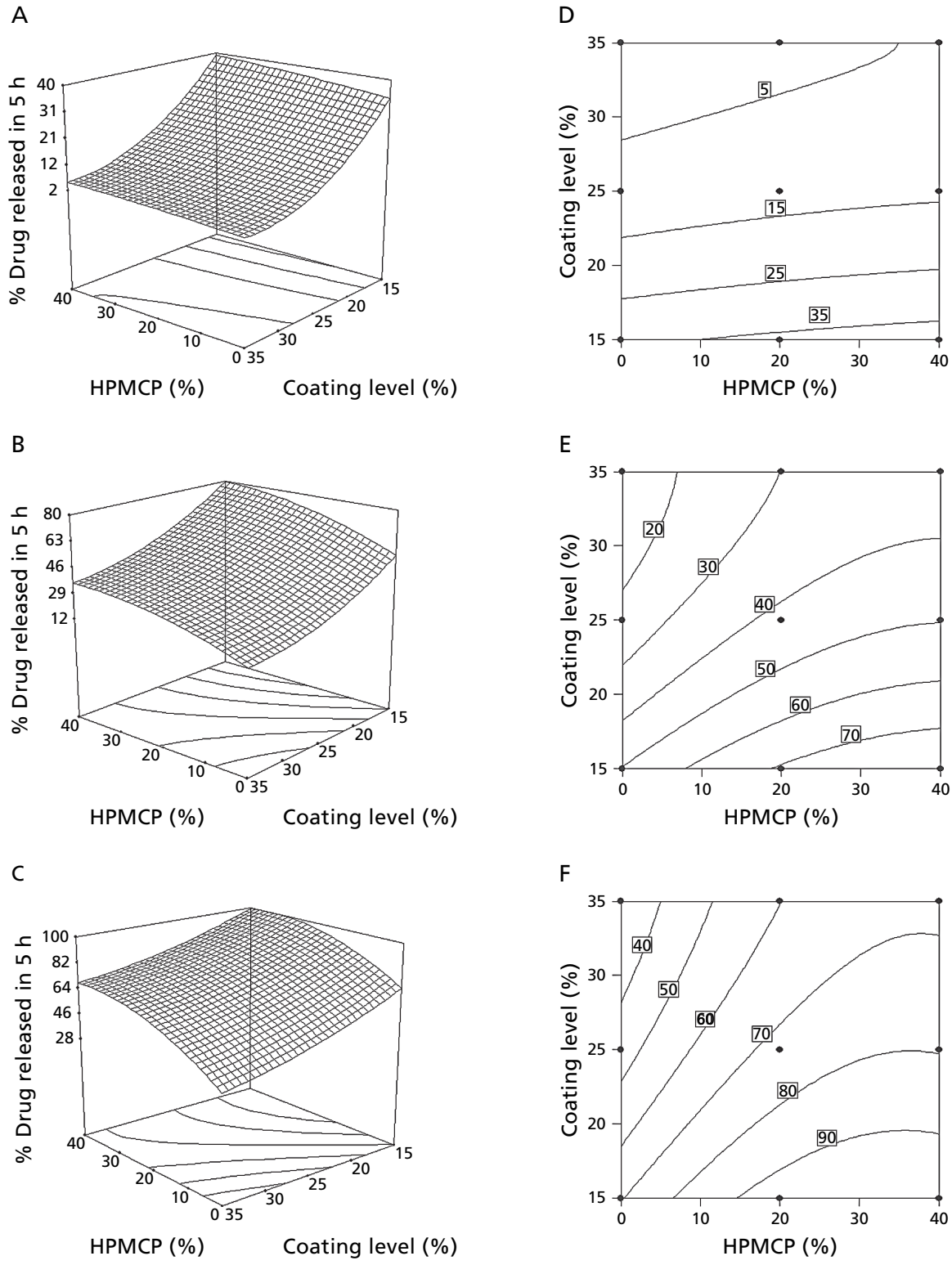

Figure 2 Effect of the content of HPMCP and coating level (%) on response using response surface plot (A, B and C) and its contour plot (D, E and F).

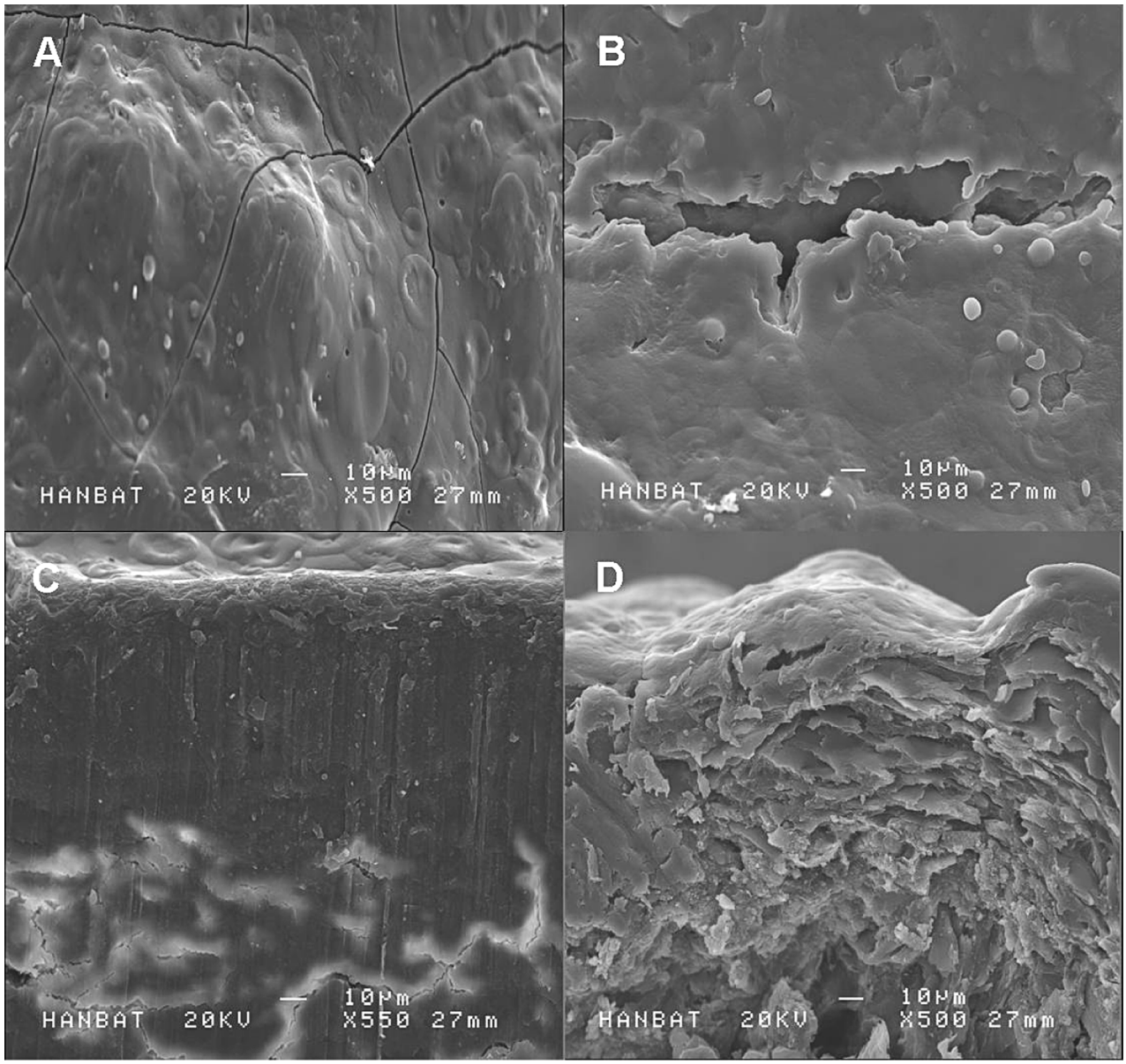

Figure 3 Surface (A and B) and cross-section (C and D) of coated pellets with Surelease (left) or Surelease–HPMCP 80:20 (right) at 25% w/w coating level.

Table 1 Comparative levels of predicted and observed responses for optimized coating formulations

Responses		Predicted error[a] (%)
Predicted (%)	Observed (%)	
Y_1 (22.8)	23.8 ± 2.1	4.39
Y_2 (57.8)	55.3 ± 2.5	–4.33
Y_3 (86.2)	83.5 ± 3.8	–3.13

[a]Predicted error (%) = (observed value – predicted value)/predicted value × 100%.

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