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Statistical optimization of indomethacin pellets coated with pH-dependent methacrylic polymers for possible colonic drug delivery

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Abstract

The objective of this study was to evaluate the effect of two factors (ratio of Eudragit S100 and Eudragit L100 and the coating level) on indomethacin release from pellets in order to optimize coating formulations for colonic delivery. Coating formulations were designed based on the full factorial design. Two independent variables were the ratio of Eudragit S100:Eudragit L100 (1:4, 1:1 and 1:0) and the level of coating (10%, 15% and 20%, w/w), respectively. The evaluated responses were lag time prior to drug release at pH 6.8 (the time required for drug release up to 2%) and percent of drug release at pH 6.8 in 5 h. Polymers were coated onto the pellets containing 20% (w/w) indomethacin, using a fluidized bed coating apparatus. Dissolution test was carried out in media with different pH (1.2, 6.5, 6.8 and 7.2). The dissolution data revealed that the level of coating and the ratio of polymers are very important to achieve optimum formulation. Using responses and resulted statistical equations, optimum formulation consisted of Eudragit S100:L100 in 4:1 ratio and the level of coating (20%) was predicted. Practical results showed that the pellets prepared according to above formulation released no indomethacin at pH 1.2 (simulating stomach pH) and pH 6.5 (simulating proximal part of small intestine pH); drug release was slowly at pH 6.8 (simulating lower part of small intestine pH), but it was fast at pH 7.2 (simulating terminal ileum pH). The results of this study revealed that factorial design is a suitable tool for optimization of coating formulations to achieve colon delivery. It was shown that coating formulation consisted of Eudragit S100:Eudragit L100 in 4:1 ratio at 20% coating level has potential for colonic delivery of indomethacin loaded pellets. The optimized formulation produced dissolution profiles that were close to predicted values.

Keywords: Colonic delivery; Eudragit; Statistical optimization; Factorial design; Indomethacin

1. Introduction

In recent years, colon targeted delivery systems have been the focus point of formulation laboratories. Colonic drug delivery has gained increased importance

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not just for the delivery of drugs for the treatment of local diseases of colon but also for its potential for the delivery of proteins and peptides (Gupta et al., 2001). Over the last few years, different approaches have been reported in order to achieve specific colonic drug delivery. Most of the previous literature reports on colonic targeting have focused on the development of a colonic delivery system based on time-dependent delivery, pH-dependent systems and systems that utilize bacteria that colonize the colon or enzymes produced by these bacteria to affect drug release (Rodriguez et al., 1998; Khan et al., 1999). Among these approaches, the pH-dependent systems have found practical application. The pH of the GI tract gradually increases as one moves down the GI tract from stomach (pH 1.5–3) to terminal ileum (pH 7–8). On entry into the colon, the pH drops to 5.6–7.0 (Evans et al., 1988). Because the pH in the terminal ileum and colon is higher than in any other region of the gastrointestinal tract, the dosage forms which disintegrate at suitably high pH levels have the potential for site-specific delivery into this region.

Most commonly used pH-dependent coating polymers are methacrylic acid copolymers – Eudragit L100 and Eudragit S100 – which dissolve at pH 6.0 and 7.0, respectively. Since pH varies in the different parts of GI tract, if these two polymers are combined with each other at various ratios, it would be possible to manipulate drug release within the pH range of 6.0–7.0. Khan et al. (1999) developed a single coating system for mesalazine based on combination of these polymers. However, much emphasis is laid on multiparticulate dosage forms because of their advantages over single unit dosage forms. These benefits include increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying (Kramar et al., 2003). The coating thickness is also one important factor for the coating systems. Therefore, evaluation and optimization of two factors (coating composition and thickness) is useful to achieve the best pH-dependent colonic drug delivery.

Optimization with factorial designs is a powerful, efficient and systemic tool that shortens the time required for the development of pharmaceutical dosage forms and improves research and development work (Bodea and Leucuta, 1997; Kramar et al., 2003). The response surface method has been applied to dosage form design for various kinds of drugs by many researchers (Gohel and Amin, 1998).

Indomethacin is a widely used non-steroidal anti-inflammatory drug (NSAID). Studies showed that indomethacin can exhibit chemoprotective effects on tumors of the colon and reduce the risk of colon cancer (Fischer, 1997; Gallo et al., 2001). Also, the formulation of NSAIDs in the form of multiparticulate dosage form has been recommended (Sam and Rubinstein, 1985).

The objective of this study was to evaluate the effect of two factors (ratio of Eudragit S100:Eudragit L100 and coating level) on indomethacin release from pellets as a multiparticulate dosage form and optimize formulation using a full factorial design in order to obtain the best colonic drug delivery system for indomethacin.

2. Materials

Indomethacin (Darupakhsh, Tehran, Iran), non-pareil beads (NP Pharm, France), Eudragit® L100 and Eudragit® S100 (Rohm Pharma, GmbH, Germany), triethyl citrate (Merck, Germany), polyvinylpyrolidone K30 (Fluka, Switzerland) and talc (Merck) were obtained from the indicated sources.

3. Methods

3.1. Experimental design

A full factorial 3^2 design was used for optimization procedure. The studied factors (independent variables) were Eudragit S100:Eudragit L100 ratio (X_1) and coating level (X_2). The dependent variables were lag time (the time required for drug release up to 2%) at pH 6.8 (Y_1) and percent of drug release at pH 6.8 in 5 h (Y_2). Table 1 summarizes the independent and dependent variables. The resulted formulations are listed in Table 2.

3.2. Preparation of drug containing pellets

Drug containing pellets were produced by coating of indomethacin onto the non-pareil beads (850–1180 μm) using fluidized bed coater (Wurster insert, Werner Glatt, Germany). 30% (w/v) aqueous suspension of indomethacin (<90 μm) was prepared by dispersing indomethacin in 7% (w/v) PVP K30 solu-

Table 1
Experimental design: factors and responses

Factors (independent variables)	Levels used			Responses (dependent variables)
	−1	0	1	
X_1 = ratio of Eudragit S:Eudragit L	1:4	1:1	1:0	Y_1 = lag time at pH 6.8 (min)
X_2 = coating level (%)	10	15	20	Y_2 = percent drug released in 5 h at pH 6.8

Table 2
Composition of experimental formulations (runs)

	Variable factors	
	X_1 (Eudragit S:Eudragit L ratio)	X_2 (coating level) (%)
1	1:4	10
2	1:4	15
3	1:4	20
4	1:1	10
5	1:1	15
6	1:1	20
7	1:0	10
8	1:0	15
9	1:0	20

tion. This suspension was passed through a 140 mesh sieve. Drug-binder suspension was sprayed onto non-pareils using fluidized bed coater. Coating conditions are listed in Table 3. The suspension was stirred throughout layering process. The drug layering process was carried out to produce pellets with about 20% (w/w) drug load. After coating, the pellets were fluidized for about 5 min and then were kept in an oven for 2 h at 40 °C.

3.3. Content uniformity

Accurately weighed (500 mg) of drug loaded pellets were ground and transferred to 250 ml volumetric flasks containing phosphate buffer pH 7.2. The flasks were shaken in a shaking waterbath at 25 °C for 3 h. The indomethacin concentration was determined by spectrophotometry at 318 nm in filtered solutions. All assays were carried out in triplicate and the mean value was reported.

Table 3
Coating parameters for the indomethacin layering and polymer coating of non-pareils

Process parameter	Indomethacin layering	Polymer coating
Inlet temperature (°C)	60–65	40–45
Outlet temperature (°C)	45–50	30–35
Nozzle diameter (mm)	1.0	1.0
Atomization pressure (bar)	2.0	2.0
Spray rate (g min^{-1})	15	10

3.4. Coating of pellets

10% (w/w) solutions of polymethacrylates (Eudragit L100 and Eudragit S100) were prepared in isopropyl alcohol:water (9:1) mixture. The ratios of Eudragit S100:Eudragit L100 were 1:4, 1:1 and 1:0 based on the experimental design. The solution was plasticized with triethyl citrate (10%, w/w, with respect to dry polymer), and then talc was added as glidant (5%, w/w, related to dry polymer).

Two hundred grams of indomethacin pellets were coated in a fluidized bed coating apparatus (Wurster insert, Werner Glatt). Coating conditions are listed in Table 3. Samples of coated pellets were removed from the apparatus when the coating loads had reached 10, 15 and 20% (w/w). At each stage the pellets were fluidized for about 5 min and samples were kept in an oven for 2 h at 50 °C.

3.5. Dissolution studies

Dissolution studies were carried out in a USP XXIII dissolution apparatus I (Pharmatest, PTWS, Germany) in 900 ml medium at 37 °C at a rotation speed of 100 rpm.

Accurately weighed pellets containing the equivalent of 80 mg of indomethacin were transferred to the dissolution medium. At predetermined intervals, the samples were taken from the vessel by a peristaltic pump and passed through multi-cell system on the UV spectrophotometer (Shimadzu, UV-1204, Japan) and returned to the vessel ($n = 6$).

For simulating conditions of the GI tract, dissolution tests were carried out in media with pH 1.2 (HCl 0.1N),

pH 6.5, 6.8 and 7.2 (phosphate buffer). Samples were introduced into each medium, separately. Dissolution test was performed for 2 h for acidic stage (pH 1.2) and 10 h in the other media.

The most promising formulation, i.e., pellets coated with an Eudragit S100:Eudragit L100 ratio of 4:1 and coating level of 20% was tested under the continuous dissolution based on generally accepted GI transit times, i.e., 2, 1, 2 and 1 h for the stomach, proximal part of small intestine, lower part of small intestine and terminal ileum at the media with pH 1.2, 6.5, 6.8 and 7.2, respectively.

3.6. Scanning electron microscopy

At different time intervals some pellets with optimized formulation were taken from dissolution media with pH 6.8 and dried in oven at 40 °C. The surface characteristics of the coated pellets before and after dissolution test were observed by scanning electron microscopy (SEM) (LEO 1450 VP, UK). The pellets were sputter coated with platinum for 3 min in a sputter-coating machine (SC7620 sputter coater, Polaron, UK).

3.7. Statistical analysis of data

The effects of independent variables upon the responses were modeled using following second order polynomial equation:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2 \quad (1)$$

The modeling was performed using SPSS (Version 12.0) with a backward, stepwise linear regression technique and significant terms ($P < 0.05$) were chosen for final equations. Response surface plots and contour plots resulting from equations obtained by Statgraphics 5.1 Plus.

4. Results and discussion

Fig. 1 shows the release profile of uncoated drug pellet at pH 6.5, 6.8 and 7.2. There was no lag time prior to drug release in any pH value and more than 90% of drug released in less than 10 min. This demonstrates that despite the poor water solubility of indomethacin,

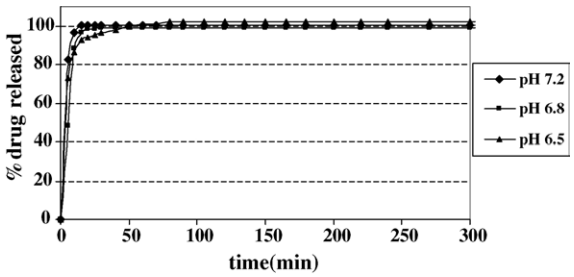

Fig. 1. Dissolution profile of uncoated drug pellet at pH 6.5, 6.8 and 7.2.

layering of the drug on the surface of pellets results in increase in dissolution rate of drug. This is one advantage of multiparticulate systems of poorly water soluble drugs compared to single unit systems.

According to the relatively constant transit time in the small intestine (approximately 3–5 h) (Leopold, 1999), we divided simulation of small intestine into three parts; proximal part of small intestine with pH 6.5 and residence time 1 h, lower part of small intestine with pH 6.8 and residence time 2 h, and finally terminal ileum with pH 7.2 and residence time 1 h. Thus, the dissolution tests were carried out in media with pH 1.2, 6.5, 6.8 and 7.2. The release profiles for coated indomethacin pellets at different pH media are shown in Fig. 2.

At pH 1.2 (simulating stomach) none of the formulations released their drug content and after 2 h pellets were completely intact (data are not shown). As shown in Fig. 2a and b, pellets coated with Eudragit S alone (formulations 7–9) are not completely resistant to pHs below 7.0. This is due to this fact that pH-sensitive Eudragits are ionized and solubilized in a range of pH not at a definite pH. The release rate was slower at higher coating levels because of the increased diffusion path length and tortuosity at higher coating levels (Gupta et al., 2001). However, coating levels more than 20% was not used because the formulation with lower coating level has advantages such as lower cost, reduction in processing time and lower weight and smaller size of the final dosage form (Gupta et al., 2001). Polymers used for colon targeting should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral to slightly alkaline pH of the terminal ileum (Chourasia and Jain, 2003). Concern to this fact the lag time prior to drug release

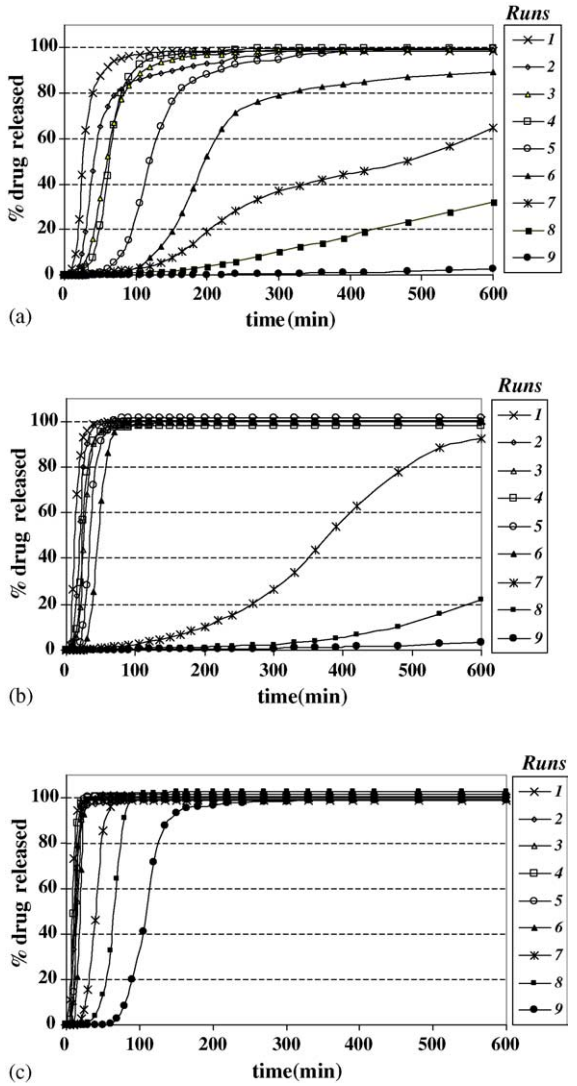

Fig. 2. Dissolution profiles of all formulations (1–9) (Table 2) at (a) pH 6.5, (b) pH 6.8 and (c) pH 7.2.

in different pHs of the small intestine was important. It is also possible in some cases that the pH value of small intestine does not approach to 7.0; therefore, it is important for a drug formulated for colonic delivery to be released at pH 6.8 after a suitable lag time. This is a pH at which the formulation contacts most of the time in small intestine. Thus, among the different release parameters utilized as response variables to describe and optimize drug release behavior, the following were selected as the most representative:

Table 4
Experimental runs and observed results

Run	Responses	
	Y_1	Y_2
1	5.0 ± 0	100.0 ± 0
2	8.3 ± 0.6	100.0 ± 0
3	12.7 ± 0.6	100.0 ± 0
4	10.0 ± 0	100.0 ± 0
5	19.3 ± 1.2	100.0 ± 0
6	27.3 ± 1.2	100.0 ± 0
7	73.3 ± 5.8	26.7 ± 2.1
8	106.7 ± 11.6	4.0 ± 0
9	206.7 ± 23.1	2.7 ± 0.6

Y_1: lag time (the time required for drug release up to 2%) at pH 6.8;
Y_2: percent of drug release at pH 6.8 in 5 h.

Lag times at pH 6.5 and 7.2 were not considered as dependent variables, because all formulations with a lag time of more than 60 min at pH 6.8 did not release drug at pH 6.5 during the first hour of dissolution test. All formulations had also a lag time lower than 70 min at pH 7.2 which met suitable response.

Therefore, constraints used for the responses were:

$90\ \text{min} < Y_1 < 130\ \text{min}$;
$50\% < Y_2 < 70\%$.

At these constraints, optimum formulation releases drug in the terminal ileum and even if the pH of terminal ileum is below 7.0, it does not prevent drug release.

The experimental runs with the observed responses are shown in Table 4.

In order to determine the levels of factors which yield optimum dissolution responses, mathematical relationships were generated between the dependent and independent variables using the statistical package SPSS. The equations of the responses are given below:

$$Y_1 = 178.074 - 3.757X_1 - 17.323X_2 + 0.02324X_1^2 + 0.442X_2^2 + 0.165X_1X_2 \quad (2)$$

$$Y_2 = 92.346 + 2.033X_1 - 3.263X_2 - 0.0222X_1^2 + 0.142X_2^2 - 0.0318\ X_1X_2 \quad (3)$$

The equations represent the quantitative effect of independent variables (X_1 and X_2) upon the responses (Y_1 and Y_2). Coefficients with more than one factor represent the interaction between factors while coefficients

Table 5
Observed and predicted values for the Y_2 response

Run	Observed	Predicted	Residual
1	100.0	99.3	0.7
2	100.0	97.6	2.4
3	100.0	102.9	−2.9
4	100.0	104.2	−4.2
5	100.0	97.7	2.3
6	100.0	98.2	1.8
7	26.7	23.4	3.3
8	4.0	8.9	−4.9
9	2.7	1.6	1.1

with second order terms indicate the quadratic nature of the phenomena. To justify the validity of the equations, values of X_1 and X_2 (Table 2) were substituted in Eqs. (2) and (3) to obtain the predicted values of Y_1 and Y_2. The predicted and observed values were found to be in good agreement. Table 5 shows the observed and predicted values for the Y_2 response.

Analysis of variance (ANOVA) (Table 6) indicated that the assumed regression models were significant and valid for each considered response.

The three-dimensional response surfaces were drawn to estimate the effects of the independent variables on each response (Figs. 3 and 4).

Fig. 3 shows the effect of two formulation factors on lag time at pH 6.8. This figure indicates that increase in ratio of Eudragit S rises lag time significantly. This is in agreement with this fact that Eudragit L and Eudragit S are copolymers of methacrylic acid and methyl methacrylate and the ratio of carboxyl to ester group is approximately 1:1 in Eudragit L and 1:2 in Eudragit S (Chourasia and Jain, 2003). Lower ratio of carboxyl group in Eudragit S causes less ionization

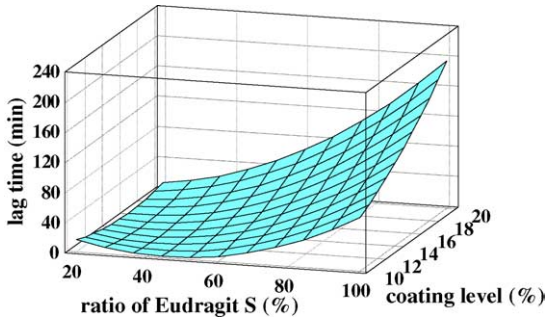

Fig. 3. Response surface plot for Y_1 response (lag time).

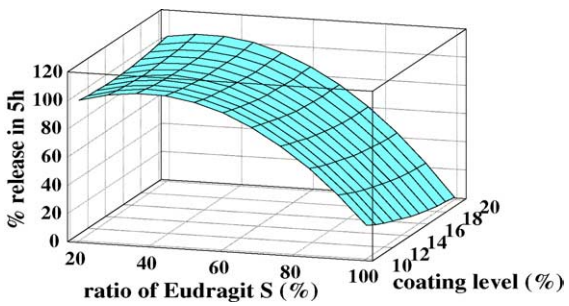

Fig. 4. Response surface plot for Y_2 response (percent release in 5 h).

in neutral to alkaline media than Eudragit L, and hence slower solubilization of this anionic polymer. Fig. 3 shows that the effect of coating thickness on lag time is smaller at low levels of Eudragit S, but it rises lag time at higher ratio of this polymer. These results indicate that when coating material is completely soluble in medium, the thickness of coating is not an effective factor for resistance to dissolution. This is in agreement with other study which showed that lag time is a func-

Table 6
Analysis of variance (ANOVA) of dependent variables

Source of variation	Sum of squares	Degree of freedom	Mean square	F ratio	P-value
Y_1					
Regression	106537.99	5	21307.598	104.757	0.000
Residuals	4271.417	21	203.401		
Total	110809.41	26			
$R^2 = 0.961$					
Y_2					
Regression	48267.912	5	9653.582	843.339	0.000
Residuals	240.384	21	11.447		
Total	48508.296	26			
$R^2 = 0.995$					

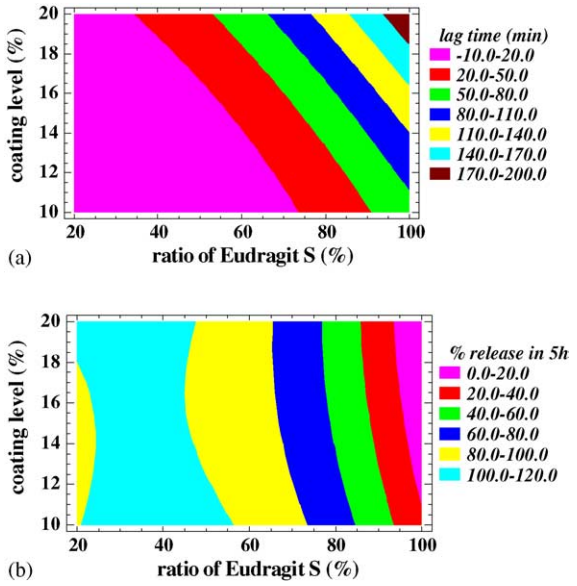

Fig. 5. Contour plots for responses Y_1 (a) and Y_2 (b).

tion of the thickness when polymer used for coating is not completely soluble (Kao et al., 1997).

Fig. 4 shows the effect of two formulation factors on percent of drug release in 5 h at pH 6.8. The effect of Eudragit S ratio on the percent of drug release is more predominant than coating thickness. In other words, coating thickness did not significantly affect the percent of drug release in 5 h at pH 6.8. This was in agreement with finding of Marvola et al. (1999) who reported that coating thickness above a critical value did not retard drug release or increase lag time to more extent.

According to response surfaces (Figs. 3 and 4) and constraints for favor responses, it is obvious that Eudragit S alone is not suitable for colonic delivery. However, by using proper combinations of Eudragit S100 and Eudragit L100 and coating level, the release of drug from formulation after an optimum lag time will be ensured especially when the pH value of GI tract does not reach more than 6.8. This is an advantage for using the combination of polymers against using single polymer (Eudragit S) which sometimes does not release drug at all, as it has already been reported (Watts and Illum, 1997).

According to contour plots (Fig. 5) the best area for formulation to obtain desired responses was found. The best conditions to optimize drug release corresponded to a Eudragit S:Eudragit L ratio of 4:1 and a coating level of 20%. By substituting X_1 and X_2 by the amounts of optimized formulation in Eqs. (2) and (3) predicted responses were obtained. In order to check the validity of the optimization procedure, a new batch of pellets with the predicted levels was prepared. The results in Table 7 show that observed responses were inside the constraints and close to predicted responses, and therefore factorial design is valid for predicting the optimum formulation.

Table 7
Predicted and observed responses of optimum formulation

Responses	Predicted	Observed	Constraints
Y_1	120.6	104.7 ± 4.5	90–130
Y_2	53.6	59.7 ± 6.6	50–70

The optimum formulation also was tested under continuous dissolution based on accepted GI transit time. Fig. 6 shows the release profile of optimum formulation in media with different pH. The pellets prepared according to optimum formulation released no indomethacin at pH 1.2 (simulating stomach pH) and pH 6.5 (simulating proximal part of small intestine pH); drug release was slow at pH 6.8 (simulating lower part of small intestine), but it was fast at pH 7.2 (simulating terminal ileum pH).

During dissolution test at pH 6.8, some pellets coated with optimized formulation were taken from medium at different time intervals. Fig. 7 shows the scanning electron micrographs of the surface characteristics of the pellets before (Fig. 7a) and after dissolution (Fig. 7b–d). These pictures clearly show that pore formation is the most important mechanism of release.

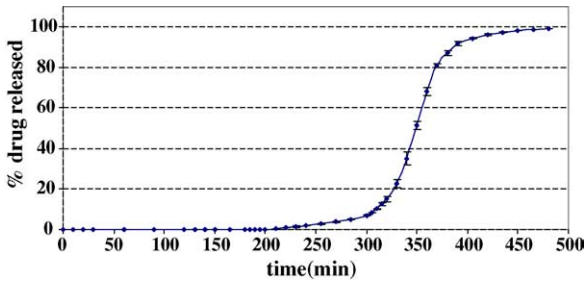

Fig. 6. Dissolution profile of optimized formulation under continuous dissolution based on accepted GI transit time (0–120 min at pH 1.2, 120–180 min at pH 6.5, 180–300 min at pH 6.8 and 300–500 min at pH 7.2).

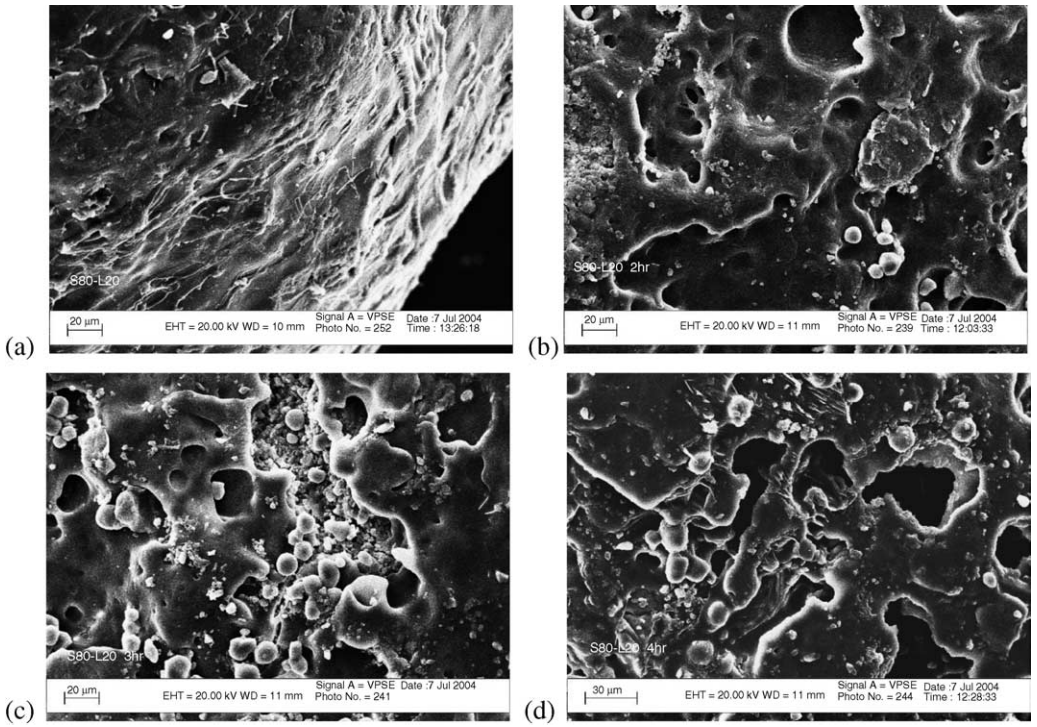

Fig. 7. Scanning electron micrograph of pellets coated with Eudragit S:Eudragit L in 4:1 ratio and coating level of 20% (a) before dissolution, (b) after 2 h, (c) after 3 h and (d) after 4 h dissolution in pH 6.8 medium (magnification 400×).

5. Conclusions

It was shown that appropriate factorial design and optimization technique can be successfully used in the development of coating formulations based on Eudragit S and Eudragit L to achieve colon delivery. Response surface plots and optimization enabled formulation of indomethacin pellets coated with combination of pH-sensitive polymethacrylates with the desired release profile. It was shown that coating formulation consisted of Eudragit S100:Eudragit L100 in ratio of 4:1 at 20% coating level has potential for colonic delivery of indomethacin pellets. The optimized formulation showed release profiles and responses which were close to predicted responses.

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