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Statistical optimisation of diclofenac sustained release pellets coated with polymethacrylic films

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Abstract

The objective of the present study was to evaluate three formulation parameters for the application of polymethacrylic films from aqueous dispersions in order to obtain multiparticulate sustained release of diclofenac sodium. Film coating of pellet cores was performed in a laboratory fluid bed apparatus. The chosen independent variables, i.e. the concentration of plasticizer (triethyl citrate), methacrylate polymers ratio (Eudragit RS:Eudragit RL) and the quantity of coating dispersion were optimised with a three-factor, three-level Box-Behnken design. The chosen dependent variables were cumulative percentage values of diclofenac dissolved in 3, 4 and 6 h. Based on the experimental design, different diclofenac release profiles were obtained. Response surface plots were used to relate the dependent and the independent variables. The optimisation procedure generated an optimum of 40% release in 3 h. The levels of plasticizer concentration, quantity of coating dispersion and polymer to polymer ratio (Eudragit RS:Eudragit RL) were 25% w/w, 400 g and 3/1, respectively. The optimised formulation prepared according to computer-determined levels provided a release profile, which was close to the predicted values. We also studied thermal and surface characteristics of the polymethacrylic films to understand the influence of plasticizer concentration on the drug release from the pellets.
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Keywords: Sustained release; Pellet coating; Box-Behnken design; Diclofenac sodium; Eudragit RS; Eudragit RL; Dissolution

1. Introduction

The release of drug from a solid dosage form is often tailored by applying a polymeric coating. Nowadays, water-dispersed systems like aqueous dispersions of cellulosic (Lippold et al., 1999; Wesseling and Bodmeier, 1999) and acrylic (Lehmann, 1996; Petereit and Weisbrod, 1999) polymers, are extensively used for manufacturing sustained release oral dosage forms. Eudragit® RS30D and Eudragit® RL30D are copolymers of ammoniomethacrylate with a low content of positively charged quaternary ammonium groups. Eudragit® RL30D has higher water permeability and swellability than Eudragit® RS30D due to higher ratio of hydrophilic groups. The mixture of these two copolymers is often used for formulations of various controlled release drug delivery system (Lehmann, 1989; Harris and Ghebre-Sellassie, 1997).

Currently, much emphasis is laid on multiparticulate dosage forms because of their multiple advantages over single unit dosage forms demonstrated as flexibility during formulation development and therapeutic benefits for the patients. These include increased bioavailability, reduced risk of systemic toxicity due to dose dumping and reduced risk of local irritation and predictable gastric emptying (Follonier and Doelker, 1992; Daumesnil, 1994).

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Plasticizers are included in coating formulations to improve the mechanical and film-forming properties of the polymers. The effects of plasticizer type and concentration on the glass transition temperatures (T_g), on the mechanical and surface properties of polymeric films are described in the literature (Gutierrez-Roca and McGinity, 1994; Wang et al., 1997; Oh and Luner, 1999). It is known that plasticization results in a decrease in the intermolecular forces between polymer chains, generally causing a decrease in the glass transition temperatures and tensile strength. Plasticizers affect film formation from colloidal polymer dispersions and the mechanical properties of the resulting films, but their type and concentration can also affect the drug release from the coated dosage forms (Amighi and Moes, 1996).

Diclofenac sodium is a widely used non-steroidal anti-inflammatory drug (NSAID). It is rapidly absorbed after oral administration and has a half-life of 1–2 h (Mutscher and Derendorf, 1995). Its short half-life and increased need for patient compliance, especially in the management of chronic rheumatoid arthritis, require sustained drug release.

Optimisation with factorial designs and analysis of the response surfaces is a powerful, efficient and systematic tool that shortens the time required for the development of pharmaceutical dosage forms and improves research and development work (Schwartz and O'Connor, 1997). The Box-Behnken design is one of the experimental designs employed in optimisation techniques. The design was used to construct a second-order polynomial model to describe the reciprocal dependency of the studied parameters (Singh et al., 1995; Karnachi and Khan, 1996; Khan et al., 1996; Bodea and Leucuta, 1998).

The objective of our study was to evaluate the effect of three formulation parameters on cumulative percent of drug released, to statistically determine the levels of these factors and to optimise the product using mathematical equations and response surface plots. The optimisation procedure would enable preparation of sustained release pellets with predictable dissolution properties.

We also investigated thermal and surface characteristics of the polymethacrylic films. The results of these studies were used to explain the effect of the films on dissolution profiles of the coated pellets.

2. Materials and methods

2.1. Materials

The following chemicals were used as received: diclofenac sodium (Dinamite Dipharma, S.p.A, Milano, Italy), non-pareil beads (Nu-pareil PG Sugar Spheres NF, 710–850 μm, Hanns G. Werner, Tornesch, Germany), polymethacrylic aqueous dispersions Eudragit® RS30D and Eudragit® RL30D (Röhm Pharma GmbH, Darmstadt, Germany), triethyl citrate (Röhm Pharma GmbH), hydroxypropyl cellulose Klucel EF (Hercules GmbH, Düsseldorf, Germany) and talc (Luzenac, Torino, Italy).

2.2. Experimental design

A three-factor, three-level Box-Behnken design was used for optimisation procedure. It is suitable for investigating the quadratic response surfaces and for constructing a second-order polynomial model, thus enabling optimisation of a process with a small number of experimental runs (15 runs). Box-Behnken modelling, evaluation of the ability to fit to the model and response surface modelling were performed with SAS system (Version 8, 2000, SAS Institute, Cary). The design consists of replicated centre points and a set of points lying at the midpoints of each edge of the multidimensional cube that defines the interesting area. The model is of the form, where b_0–b_9 are the regression coefficients; X_1, X_2 and X_3 are the factors studied; Y is the measured response associated with each factor level combination; and E is a term used for error:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1X_2 + b_5X_2X_3 + b_6X_1X_3 + b_7X_1^2 + b_8X_2^2 + b_9X_3^2 + E \quad (1)$$

The preliminary studies provided a setting of the levels for each formulation variable. The studied factors were plasticizer concentration (X_1), polymethacrylate polymers ratio (Eudragit RS:Eudragit RL; X_2) and the quantity of coating dispersion (X_3). Table 1 summarises the factors and their levels. The chosen dependent variables were cumulative percentage values of diclofenac sodium dissolved in a chosen time (after 3, 4 and 6 h).

Table 1
Independent variables: factors and their levels for Box-Behnken design

Factors	Level		
	−1	0	1
X_1: plasticizer concentration (%)	10	20	30
X_2: polymers ratio (Eudragit RS/Eudragit RL)	2/1	4/1	6/1
X_3: quantity of coating dispersion (g)	300	500	700

2.3. Preparation of coated pellets

Diclofenac-loaded pellets (40% w/w drug loading) were prepared by layering a drug-binder solution onto non-pareil beads using a fluidised bed coater (GPCG3 Wurster insert, Glatt GmbH, Binzen, Germany). First, diclofenac sodium was mixed with aqueous hydroxypropyl cellulose solution (5% w/w), then suspension of talc was added. Drug-binder solution was sprayed onto non-pareil beads using the bottom spray mode. The layered pellets were dried at 40 °C overnight to evaporate residual water. The process parameters are listed in Table 2. Layering was not the objective of our research; hence all 15 experimental runs were the same.

Coating suspension was prepared from polymer (mixture of Eudragit RS and Eudragit RL), talc, plasticizer and water. Talc (10% w/w of the coating dispersion) was previously dispersed in water. Water dispersions of Eudragit RS (30% w/w) and Eudragit RL (30% w/w) were mixed in the desired ratio (6:1; 4:1 and 2:1, respectively) based on the experimental design (Table 3). The polymer content of the mixture was then adjusted to 20% w/w (related to the dry polymer) by dilution with water. With gentle stirring, suspension of talc was added to the prepared acrylic dispersion. At the end, aqueous polymer dispersion was plasticized with triethyl citrate (TEC). The amount of TEC was 10, 20 and 30%, respectively (related to the acrylic polymer) based on the experimental design (Table 3). Coating dispersion was blended for 1 h.

Known weights of diclofenac-loaded pellets (1500 g) were transferred into a fluidised bed coating apparatus (GPCG3 Wurster insert, Glatt GmbH) equipped with a bottom spray device and coated with the chosen formulation until the desired quantity of coating dispersion (300, 500 and 700 g, respectively) was used up. Based on the experimental design and the factors to be studied, 15 formulations were prepared. Table 2 summarised the coating conditions for the sustained release coating.

The coated pellets were cured at 40 °C for 18 h. The pellets were then stored in tightly closed containers, protected from light, until further experimentation.

Table 2
Process parameters for the diclofenac layering and the sustained release coating of layered pellets

Process parameter	Diclofenac layering	Sustained release coating
Inlet temperature (°C)	50–55	35–40
Product temperature (°C)	37–40	32–34
Outlet temperature (°C)	35–38	30–32
Nozzle diameter (mm)	1.0	1.0
Atomisation pressure (bar)	2.0	2.0
Spray rate (g min^{-1})	25–35	14–20

2.4. Dissolution test

In vitro dissolution studies were carried out using the USP XXIII dissolution apparatus I (basket method; ERWEKA DT6, ERWEKA, Heusenstamm, Germany).

In the first step, the beads were evaluated by dissolution testing in 1000 ml 0.1N HCl solution at 37 °C at a basket speed of 100 rpm. Accurately weighed samples ($n = 3$) containing the equivalent of about 100 mg of diclofenac sodium were introduced in the dissolution medium. After 1 and 2 h, the samples were taken from the vessel by a peristaltic pump, passed through a filter, then through multi-cell transport system on diode array spectrophotometer (Model HP 8452 A, Hewlett Packard Company, Wilmington), assayed at 276 nm and returned to the vessel. This continuous system is able to maintain the undiluted dissolution medium during the entire dissolution process.

In the second step, acidic medium was immediately replaced with the phosphate buffer (pH 6.8), then the dissolution testing was continued. Additional samples were taken in the same way as before at 3, 4 and 6 h and analysed at 276 nm.

Table 3
Experimental runs and observed values of responses for Box-Behnken design

Run	Variable factors			Measured responses		
	X_1	X_2	X_3	Y_1	Y_2	Y_3
1	30	6/1	500	20.0 ± 0.8	27.5 ± 1.1	38.0 ± 1.2
2	30	2/1	500	33.0 ± 1.0	45.4 ± 1.1	65.2 ± 1.1
3	10	6/1	500	42.4 ± 0.9	58.7 ± 1.5	80.5 ± 0.9
4	10	2/1	500	66.1 ± 1.3	85.6 ± 1.2	94.1 ± 2.0
5	30	4/1	700	15.4 ± 1.1	21.1 ± 1.6	29.5 ± 1.1
6	30	4/1	300	53.9 ± 1.4	71.7 ± 1.8	85.1 ± 1.0
7	10	4/1	700	32.9 ± 0.8	46.5 ± 1.3	68.5 ± 1.2
8	10	4/1	300	82.4 ± 2.0	91.0 ± 2.0	93.8 ± 2.0
9	20	6/1	700	10.8 ± 1.0	14.8 ± 1.1	20.3 ± 1.3
10	20	6/1	300	47.4 ± 1.1	62.7 ± 1.3	80.3 ± 1.5
11	20	2/1	700	22.1 ± 1.2	30.4 ± 1.2	42.8 ± 1.7
12	20	2/1	300	75.3 ± 0.9	87.1 ± 2.0	94.0 ± 1.9
13	20	4/1	500	26.5 ± 1.0	36.4 ± 1.5	50.8 ± 1.3
14	20	4/1	500	24.0 ± 1.5	32.9 ± 2.0	47.0 ± 2.0
15	20	4/1	500	25.0 ± 1.2	34.9 ± 1.5	49.3 ± 2.0

2.5. Preparation of dried water cast film from polymer dispersions

The polymethacrylic aqueous dispersion (the same formulations as used for coating) was also transferred into aluminium dishes (6 cm in diameter) and dried at 40 °C for 24 h. The films contained the same amount of polymethacrylic polymer (Eudragit RS30D:Eudragit RL30D) and 10, 20 or 30% of triethyl citrate as plasticizer.

2.6. Glass transition temperature measurement

A Perkin Elmer Pyris 1 Differential Scanning Calorimeter (Norwalk, CT) with the Dynamic DSC (DDSC) was used for T_g measurements of the polymethacrylic polymers MTDSC. Accurately weighed samples (3–5 mg) were non-hermetically encapsulated into Perkin Elmer standard aluminium pans and heated from 0 to 120 °C according to the dynamic heat–cool program. The single repetitive step of the program was a combination of heating for 30 s with a heating rate of 6 °C min^{-1}, and cooling for 30 s with a cooling rate of 4 °C min^{-1}. An empty pan was used as a reference pan, matching the sample pans by the mass of 0.1 mg. For each experiment, a new baseline was subtracted. The measuring cell was purged with dry nitrogen at a flow rate of 20 ml min^{-1}.

The instrument was calibrated for temperature and enthalpy response using the standard indium reference. For heat capacity calibration, the response of a sapphire standard was compared to literature values in the scanning region. The calibration was performed using the same underlying heating rate and the same pan type as in the experiments.

2.7. Contact angle measurement

The films were cut and placed onto the adjustable platform of the contact angle goniometer (KRÜSS, Hamburg, Germany). The droplets of either 0.1 M HCl (pH 1.2), phosphate buffer (pH 6.8) or water were applied onto the film using a microsyringe equipment, after 1 min contact angles were measured. At least 12 measurements were carried out for each formulation.

3. Results and discussion

The experimental runs with independent variables and the observed responses for the 15 formulations are shown in Table 3. The dependent variables studied were cumulative percent released within 3, 4 and 6 h. Based on the Box-Behnken model, the factor combinations resulted in different diclofenac release rates. In acidic medium (0–2 h), dissolution profiles were

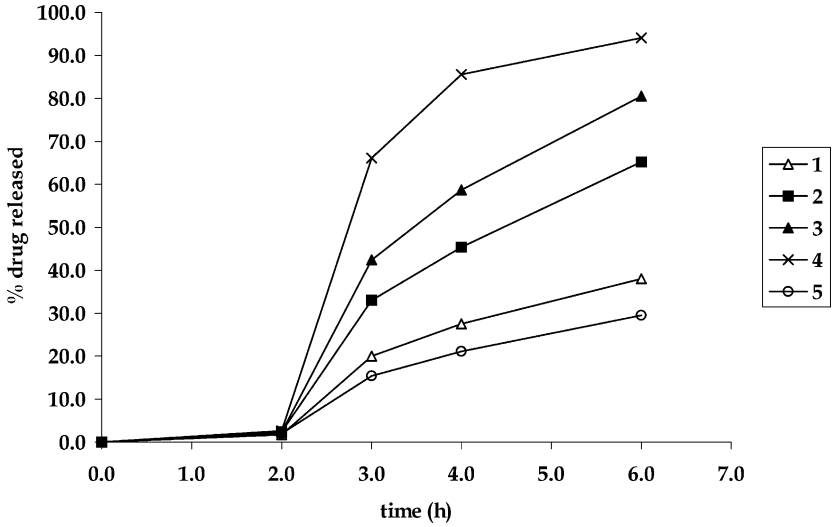

Fig. 1. Dissolution profiles of diclofenac sustained release pellets according to the Box-Behnken design runs 1–5.

very low (below 10%) and practically independent of composition and thickness of coating. In this medium, the main limiting factor was very poor solubility of diclofenac sodium. On the other hand, in phosphate buffer (pH 6.8, 2–6 h) dissolution rates were much higher and very sensitive to any changes in composition and thickness of the polymer film. The range of responses of Box-Behnken design was from low profile in run 9, to immediate dissolution in run 10 and very fast dissolution profile in run 8. Dissolution profiles of all 15 runs are shown in Figs. 1–3.

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 SAS. The resulted equations of all the responses

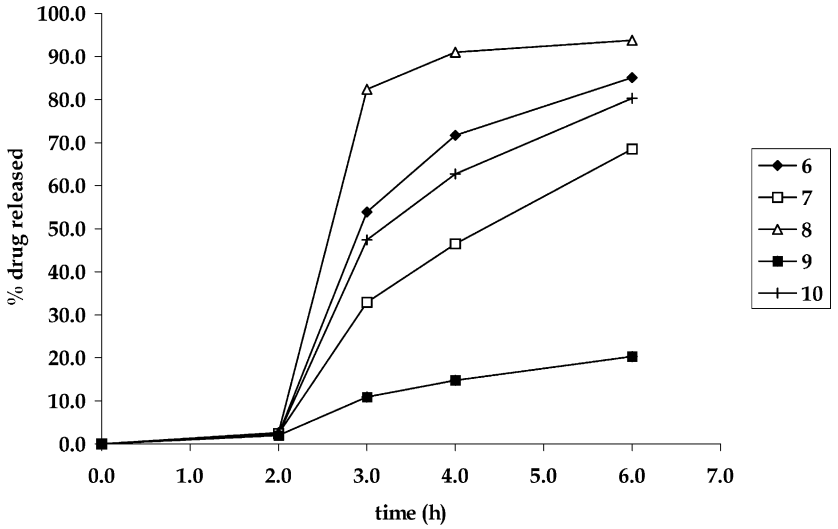

Fig. 2. Dissolution profiles of diclofenac sustained release pellets according to the Box-Behnken design runs 6–10.

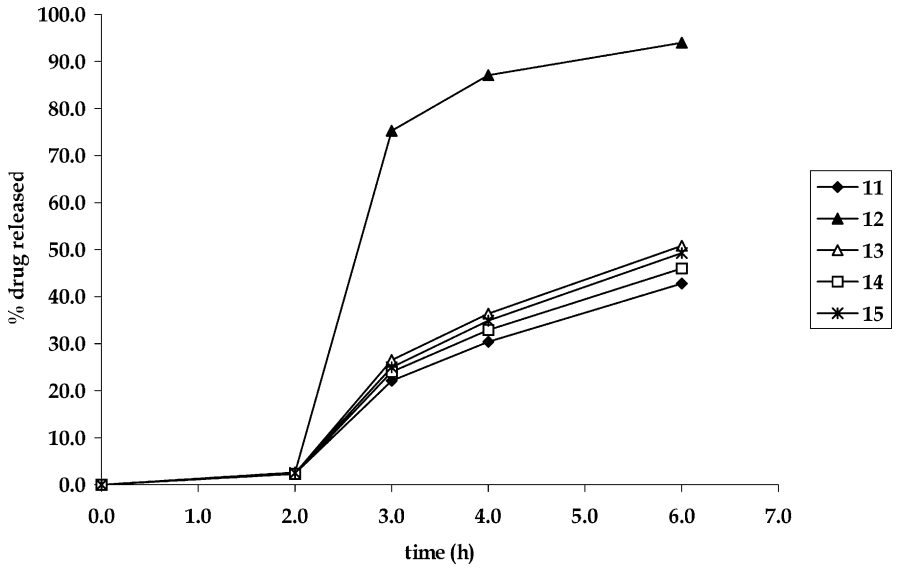

Fig. 3. Dissolution profiles of diclofenac sustained release pellets according to the Box-Behnken design runs 11–15.

are given below:

$$Y_1 = 292.076 - 6.9829X_1 - 20.5646X_2 - 0.4240X_3 + 0.13337X_1X_2 + 0.0104X_2X_3 + 0.0014X_1X_3 + 0.1123X_1^2 + 0.9948X_2^2 + 0.0002X_3^2 \quad (2)$$

$$Y_2 = 292.043 - 7.1983X_1 - 21.0417X_2 - 0.3477X_3 + 0.1125X_1X_2 + 0.0055X_2X_3 - 0.0008X_1X_3 + 0.1420X_1^2 + 1.3427X_2^2 + 0.0002X_3^2 \quad (3)$$

$$Y_3 = 208.818 - 4.9733X_1 - 9.2042X_2 - 0.1485X_3 - 0.1700X_1X_2 - 0.0055X_2X_3 - 0.0038X_1X_3 + 0.1515X_1^2 + 1.3177X_2^2 + 0.0001X_3^2 \quad (4)$$

Eqs. (2)–(4) represent the quantitative effect of the formulation variables on the three responses Y_1–Y_3, respectively. The values of the coefficients X_1–X_3 relate to the effects of these variables on the corresponding response. Coefficients with more than one-factor term represent the interaction terms and coefficients with higher order terms indicate the quadratic (non-linear) nature of the relationship. A positive sign indicates a synergistic effect while a negative sign represents an antagonistic effect. To justify the use of the polynomial equations, values of X_1–X_3 were substituted in Eqs. (2)–(4) to obtain the theoretical values of Y_1–Y_3. The theoretical (predicted) values were compared with the observed values and were found to be in good agreement. The observed, predicted and residual values for the dependent variable Y_1 are shown in Table 4.

Table 4
Observed and predicted values of the response Y_1

Run	Observed	Predicted	Residuals
1	20.0	20.9	−0.9
2	33.0	34.5	−1.5
3	42.4	40.9	1.5
4	66.1	65.2	0.9
5	15.4	14.0	1.4
6	53.9	52.9	1.0
7	32.9	33.9	−1.0
8	82.4	83.8	−1.4
9	10.8	11.3	−0.5
10	47.4	47.5	−0.1
11	22.1	22.0	0.1
12	75.3	74.8	0.5
13	26.5	25.2	1.3
14	24.0	25.2	−1.2
15	25.0	25.2	−0.2

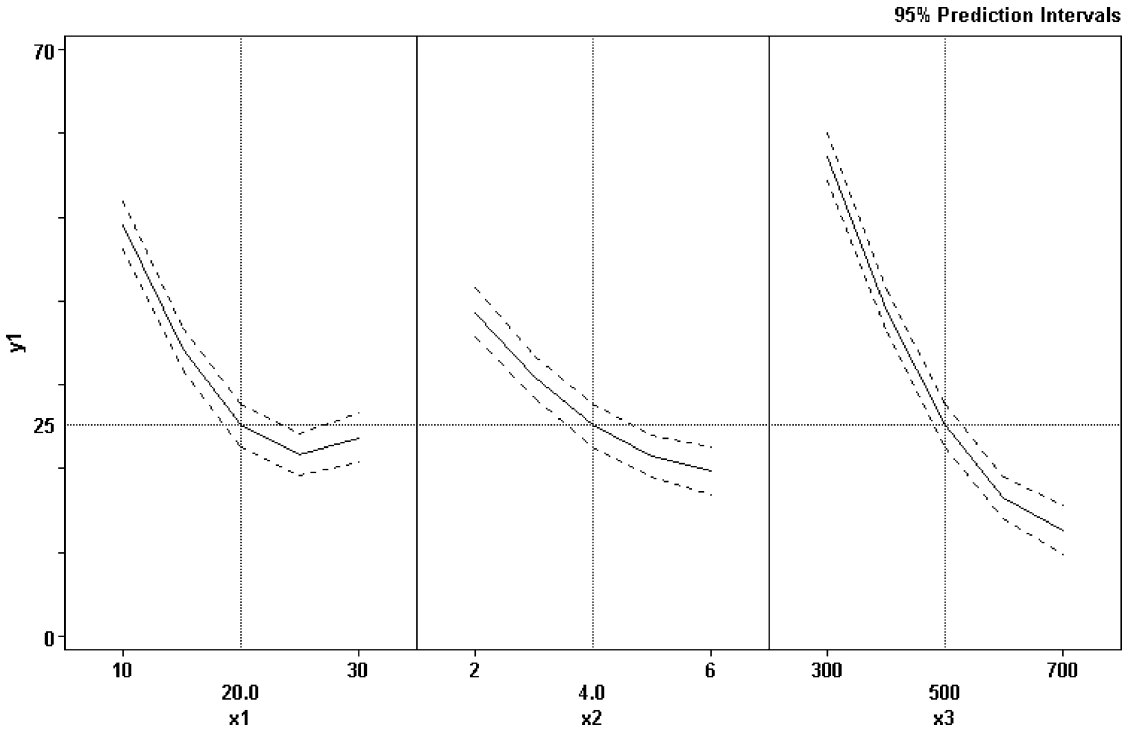

Fig. 4. The effect of formulation variables: % plasticizer (X_1), Eudragit RS:Eudragit RL ratio (X_2) and amount of coating (X_3) on the drug release after 3 h of dissolution (Y_1).

To compare the values of regression coefficients in Eq. (2), values of X_1–X_3 were substituted with code level (−1, 0, 1) to obtain the Eq. (5):

$$Y_1 = 25.167 - 12.6875X_1 - 9.4875X_2 - 22.225X_3 + 2.675X_1X_2 + 4.15X_2X_3 + 2.75X_1X_3 + 11.2292X_1^2 + 3.9792X_2^2 + 9.7542X_3^2 \quad (5)$$

As seen in Eq. (5), X_1, X_2 and X_3 have a negative, i.e. antagonistic effect on the response Y_1. The most important are X_3 then X_1 and X_2. In other words, by increasing the amount of coating (X_3) on pellet surfaces we obtained a remarkable effect in delaying the release of diclofenac. The same effect, yet somehow smaller, was obtained by increasing the amount of plasticizer (X_1). It can be also interpreted from the equation that higher Eudragit RS:Eudragit RL ratio (X_2) decreased the release profile to a smaller extent compared to that obtained by increasing the amount of plasticizer. On the contrary, positive synergistic effects are seen by the quadratic nature of responses, which were especially high in the X_1^2 and X_3^2 terms. The presented interactions have also positive synergistic effects but are less important.

The so-called “prediction profiler” plots based on the Box-Behnken model can further explain the relationship between the dependent and independent variables when their values are shifted from lower to higher level.

The results presented in Fig. 4 comply with our expectations and previous studies as regards the influence of the Eudragit RS:Eudragit RL ratio (X_2) and amount of film (X_3) on the drug release after 3 h. Being less soluble than Eudragit RL, Eudragit RS provides less pores and channels for the effective drug diffusion resulting in lower drug release. Similarly, an increase in coating thickness is accompanied by a decrease in the release rate. The most significant effect responsible for such a relationship is the effective diffusional pathlength in the coating. In the absence of a tortuous path, thinner coating have shorter diffusional length and achieve faster release

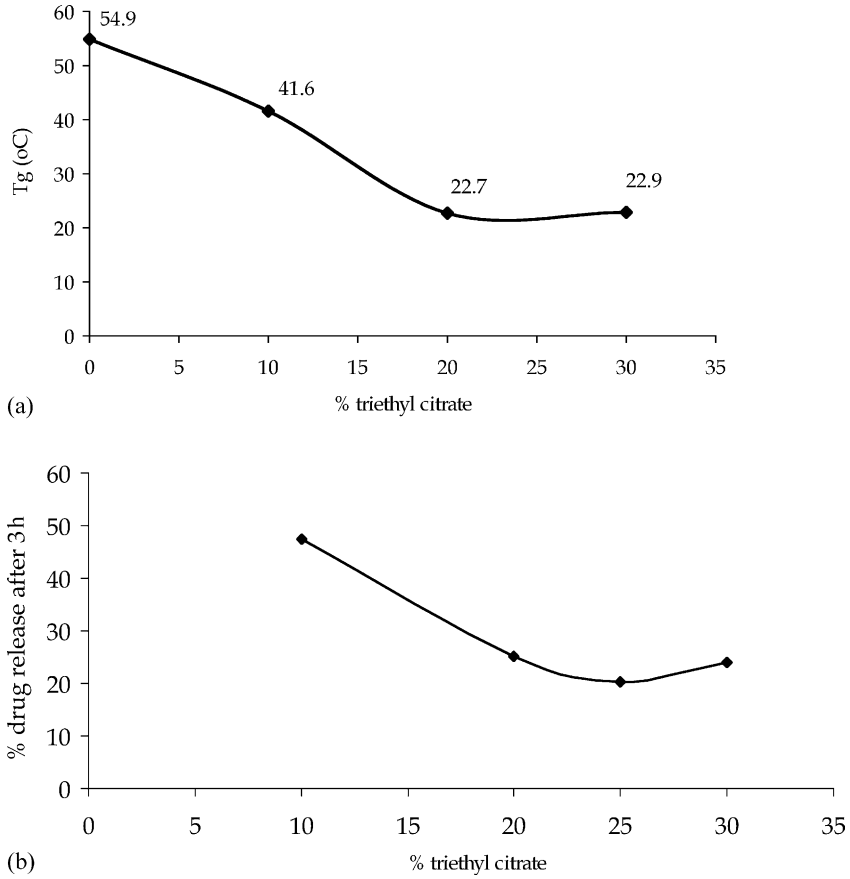

Fig. 5. Influence of plasticizer concentration on glass transition temperature (a) and drug release profile after 3 h of dissolution (b).

rates. However, an expressed impact of plasticizer triethyl citrate (TEC) concentration on the release rate was not expected. It can be seen from the left figure of "prediction profiler" (Fig. 4) that by increasing TEC concentration from 10 to 20%, diclofenac release is drastically decreased. Only slight changes in the response can be observed upon increasing its concentration to 30%. The possible explanation for this behaviour is that there is an incomplete formation of the polymer film with poor mechanical properties at low plasticizer concentration (below 20%), which results in faster drug release. The second possible reason may be found in TEC influence on hydrophobicity of the films. We also studied thermal and surface characteristics of the polymethacrylic films to understand the TEC influence on the drug release from the pellets.

Determination of the T_g was very important for us because it helped us estimate the optimal coating temperature and the amount of plasticizer needed. The effect of TEC concentrations (0, 10, 20 and 30%) on the T_g of polymethacrylic films was determined by MTDSC. The obtained results (Fig. 5a) show that TEC can be considered as a suitable plasticizer since it significantly decreases the T_g. Nevertheless, it is known that formation of the film from aqueous dispersion can occur at 10 °C above the T_g. In the technical report on the Eudragit RS30D and Eudragit RL30D (Röhm Pharma GmbH), it was pointed out that the suggested product temperature during coating in fluidised-bed machine is below 35 °C (higher temperatures may cause problems with adhesion). Fig. 5a shows that the suggested temperature was optimal only when more than 20% of TEC was used. In the case of 10% of TEC,

Table 5
Contact angles (degrees ± S.D.) of 0.1 M HCl, phosphate buffer and water on Eudragit films prepared with 10, 20 and 30% of TEC

TEC addition (%)[a]	0.1 M HCl (pH 1.2)	Phosphate buffer (pH 6.8)	Water (pH 6.2)
10	73.4 ± 4.3	81.5 ± 3.1	80.7 ± 3.0
20	81.5 ± 2.7	80.3 ± 1.5	81.8 ± 3.1
30	80.3 ± 4.2	81.7 ± 0.6	86.1 ± 3.1

Contact angles were measured after 1 min, $T = 20$–$22\,^{\circ}C$, RH < 25%, $n = 12$.
[a] Calculated according to the dry polymers.

our product temperature was too low. This caused incomplete coalescence of the polymer films and resulted in poor mechanical properties of the films, and consequently in rapid dissolution. This is probably the reason for good correlation between T_g and dissolution results depending on TEC (Fig. 5a and b).

No strong dependence of the contact angle on the pH of the medium was observed with Eudragit films (Table 5). The increase in TEC concentration did not affect the contact angle values, except in artificial gastric juice (0.1 M HCl) while the plasticizer concentration increased from 10 to 20% (Table 5). Although there is a statistically significant difference between the results of contact angle measurement at 10 and 20% of TEC ($P < 0.05$), this difference is not enough to conclude that increased TEC concentration increases film hydrophobicity.

The obtained results suggest that the increase in release profiles of diclofenac from pellets with decreasing plasticizer concentration can be attributed much more to poorer mechanical properties of the films than to the changes in hydrophobicity of coated pellets. According to T_g analyses and the product temperature used in the process of coating, it was concluded that concentration of TEC lower than 20% cannot be used. We continued our optimisation procedure by reducing our range of TEC concentrations from 10–30% (starting levels) to 20–30% (levels after T_g analyses).

After generating the polynomial equations to relate the dependent and independent variables, the process was optimised for response Y_1. In this study, optimisation was performed with limitation of the release profile, i.e. cumulative percentage released in 3 h was 40%. Two- and three-dimensional plots for the measured responses were formed based on the model to assess the change of response surface. This was done with the help of SAS package. The optimisation procedure generated optimum levels for 40% drug release after 3 h, where the levels of plasticizer concentration, quantity of coating dispersion and polymer to polymer ratio (Eudragit RS:Eudragit RL) attained 25% w/w, 400 g and 3/1, respectively.

Table 6
Response after optimisation procedure (maximising)

Responses	Predicted	Observed	Constraints (%)	Residuals
Y_1	40.6	41.3 ± 0.8	30–50	0.7
Y_2	52.7	56.4 ± 1.1	40–60	3.7
Y_3	69.0	72.6 ± 1.1	60–80	3.6

To check the validity of the optimisation procedure, a new batch of diclofenac pellets coated with the predicted levels of formulation factors was prepared. Table 6 illustrates the predicted and observed responses for the optimum formulation.

Table 6 shows that the optimised formulation prepared according to computer-determined levels ensured the release profile which was close to the predicted values.

4. Conclusions

Diclofenac sustained release pellets coated with polymethacrylic film with optimal release properties were prepared using the statistical model. A three-factor, three-level Box-Behnken design with plasticizer (triethyl citrate) concentration, methacrylate polymers ratio (Eudragit RS:Eudragit RL) and the quantity of coating dispersion was used. The quantitative effect of different levels of these factors on the release rates could be predicted by using polynomial equations. The levels of these factors were predicted to obtain optimal response. Observed responses were close to the predicted values for the optimised formulations.

MTDSC analyses showed the influence of TEC concentration on T_g values of polymethacrylic films. The complete formation of polymethacrylic films during the coating process was obtained with higher concentrations of TEC (above 20%), only.

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