Structural Characteristics and Permeability of Ethyl Cellulose Films Containing Different Plasticizers

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Summary: The effect of different type of plasticizers was investigated in ethyl cellulose as coating polymer for manufacturing coated pellets of modified release containing a water soluble model drug. Scanning electron microscopic image analysis (SEM), differential scanning calorimetry (DSC), X-ray photoelectron spectroscopic chemical surface analysis (XPS) were used to study the films, and the dissolution profiles of coated pellets were evaluated. The effect of the different plasticizers and coating levels on the first order dissolution rate constant is determined by statistical experimental design. Correlation was found between the dissolution rate constant and the structural characteristics of the coating layer containing different plasticizers. Partial segregation of the plasticizers was detected especially on the surface of the films, which is in correlation with the differences in the glass transition temperatures. PEG 400 is found to be compatible enough to form continuous, durable EC coating at 5% concentration level, which gave the slowest dissolution.

Keywords: coated pellets; drug release; ethyl cellulose films; plasticizer; surface analysis

Introduction

The control of transport characteristics of polymeric systems has been introduced recently as a focus of research work not only in development of improved drug release systems, but also in other areas of polymer technology (packaging, stability, flame retardancy) [1-4]. Especially, it is important to understand the complex behavior of multicomponent systems [5-8]. Surface analytical studies demonstrated that the low molecular components of such systems, depending on their compatibility with the matrix polymer, tend to accumulate on the surface [9,10]. The compatibility of plasticizers with the polymer matrix determines their efficiency and the mechanism of the transport through the coating layer [11-13]. The objective of the work was to investigate the effect of different plasticizers on structure of ethyl cellulose films in connection with drug dissolution profile of the coated spherical multiunit dosage forms.

Experimental

Materials

The coating polymer was ethyl cellulose (EC; Ph.Eur.3, 45 mPas, Serva Feinbiochemica GmbH, Heidelberg, Germany). The applied plasticizers were: polyethylene glycol 400 (PEG 400), polyethylene glycol 1540 (PEG 1540; Ph. Hg.VII., Hungaropharma, Budapest, Hungary) and triacetin (Ph.Eur.3, Sigma-Aldrich Corporation, St. Louis, USA). The core of the multiunit dosage forms consisted of sotalol hydrochloride (Helm AG, Batch No.: 271924, Hamburg, Germany) as a model drug, microcrystalline cellulose (Avicel PH101, FMC Biopolymer, Brussels, Belgium),

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α-D-lactose monohydrate (Ph. Eur.3, Fluka Chemie AG, Buchs, Switzerland) and potato starch (Ph. Hg. VII., Hungaropharma, Busdapest, Hungary) as excipients.

Sample Preparation

Preparation of Free Films

Ethyl cellulose pseudolatex films were prepared by casting a 5% (w/w) colloid dispersion in water containing 0–30% (w/w) of various plasticizers based on the dry polymer weight. Dispersions were poured onto glass molds and dried for approximately 12 hours in a drying chamber (Heraeus Instruments, Hanau, Germany). The drying temperature was adjusted to 10 °C above the minimum film forming temperature, but at least to 40 °C and checked with a thermometer. The prepared free films were stored in a desiccator over silica gel expelling the humidity, kept in a closed glass container at room temperature for 1 week. The thickness of the films were between 300 and 350 μm. The obtained cast films were used for the DSC and XPS analysis.

Preparation of Pellets

The pelletisation was carried out in STEPHAN UMC 5 electronic apparatus (Stephan Maschinen GmbH, Wien, Austria) equipped with different choppers at 900 rpm revolution number. The batch size was 500 g. As granulating liquid, distilled water was atomized at 160 ml/min rate under 0.2 bar vacuum in the apparatus.

Coating procedure

500 g pellets of 800–1250 μm particle size range were coated in a conventional rotating pan (Erweka AR400, Erweka GmbH, Heusenstamm, Germany) with a pneumatic atomization technique (Wagner Everspray A, Wagner International AG, Altstätten, Switzerland) at 15 ml/min feeding, at 1.5 bar atomization pressure and at a bed temperature of 10 °C above the minimum film-forming temperature depending on the composition of the coating polymer system. The amount of coating material was determined by the mass increase of pellets.

Scanning Electron Microscopy

The surface morphology of coated pellets was examined by scanning electron microscopy (SEM). Samples were mounted onto the stages prior to coating for 70 seconds under argon atmosphere with platinum alloy (Jeol JFC-1300 auto film-coater, Tokyo, Japan) and then were observed with a scanning electron microscope (Jeol JSM-5600 LV, Tokyo, Japan). The applied magnifications of the examined samples were 500× and 5000×.

X-ray Photoelectron Spectroscopy

X-ray photoelectron spectroscopic (XPS or ESCA) characterization of the model films was performed by a Kratos XSAM 800 spectrometer (Kratos Analytical Ltd., Manchaster, UK) using Mg $K\alpha_{1,2}$ radiation (1253 eV). The spectra were referenced to the hydrocarbon type carbon at binding energy, BE = 285.0 eV.

Differential Scanning Calorimetry Studies

Differential Scanning Calorimetry (DSC) measurements were performed using Setaram DSC 92 (Setaram Scientific & Industrial Equipment, Caluire, France) with the following parameters. Sample weight: 10 mg of free films, heating rate: 10 °C/min, atmosphere: nitrogen. The samples were heated up to 180 °C in order to remove their thermal history (melting memory effect) and cooled down to 25 °C with a cooling rate of 20 °C/min, and then the second heating curves were determined.

Dissolution Studies

Dissolution was studied by the USP 23 paddle method at a stirring rate of 100 rpm in 250 ml of pH = 7.4 phosphate buffer solution. Dissolution tests were carried out in 6 parallels for all formulations containing 400 mg of sotalol HCl pellets from the sieve fraction of 800–1250 μm. The collected samples (5 ml) were analyzed by UV spectrophotometry (Shimadzu UV spectrophotometer type UV-160A, Shimadzu Corporation Spectroscopic Instruments, Kyoto, Japan) measuring the absorbance at 228 nm. The withdrawn samples of the

dissolution media were substituted with an equal volume of fresh buffer solution.

Minimal Film Forming Temperature (MFFT)

MFFT values of the different coating dispersions were determined by Haake Rheostress RS 80 apparatus. In the case of ethyl cellulose dispersion without plasticizer the MFFT value was 55 °C; in the case of plasticized dispersions with PEG 400 of 2.5% and 5% the MFFT values were 49 °C and 46 °C, with PEG 1540 of 2.5% and 5% the MFFT values were 53 °C and 51 °C; and with triacetin of 15% and 30% the MFFT values were 49 °C and 45 °C respectively.

Mathematical Model

The following first order mathematical model was used for evaluation of the dissolution profiles of the non-disintegrating coated pellets.

The drug quantity within the reservoir is assumed to decline exponentially and the release rate is proportional to the residual quantity:

$$M_t/M_\infty = 1 - \exp(-kt) \quad (1)$$

Where, M_t is the dissolved amount (%) at time 't' (min), M_∞ is the dissolved amount (%) at infinite time and k is the dissolution rate constant (min^{-1}).

Statistical Experimental Design

A 2-factor, 3-level face-centered central composite design [14-16] was applied to construct a second-order polynomial model describing the effect of formulation factors on the dissolution profile characterized by k dissolution rate constant after a significance test at the 95% confidence level. The two factors as well as their levels are shown in Table 1. The levels for each parameter are represented by a (−) symbol for the lower level, a (+) symbol for the higher level and by (0) for the base level.

A BASIC (Microsoft Visual Basic Professional Edition 3.0) language computer program was applied for the multiple regression analysis. The expected form of the polynomial equation is as follows:

$$y = b_0 + b_1x_1 + b_2x_2 + b_{11}x_1^2 + b_{22}x_2^2 + b_{12}x_1x_2 \quad (2)$$

where y is the response parameter which explains k in this experimental design, x_1, x_2 are the factors as independent variables detailed in Table 1, and b parameters denote the coefficients characterizing the main (b_1, b_2), the quadratic (b_{11}, b_{22}), and the interaction (b_{12}) effects.

Results and Discussion

Scanning electron microscopic photos taken from the cross section and from the surface of the coated particles are shown in Figure 1. Comparison of Figure 1A and 1B indicates that in contrast to the uniform and smooth fracture surface of the coating of unmodified ethyl cellulose (indicating a rigid fracture), fragments of different size was observed on the fracture surface of plasticized polymers. This structure, which was characteristic to all the plasticized samples, suggests a changed fracture mechanism in presence of plasticizer. However, comparing the surface of coatings (at lower magnification in order to see larger area) no significant differences was found. Figure 1C and 1D illustrate that

Table 1.
Experimental design with factors and their levels

Levels	x_1 Coating level (mg/cm^2)	x_2 Concentration of plasticizers (%w/w)		
		PEG 400	PEG 1540	Triacetin
lower (−)	0.85	0	0	0
base (0)	1.7	2.5	2.5	15
higher (+)	3.51	5.0	5.0	30

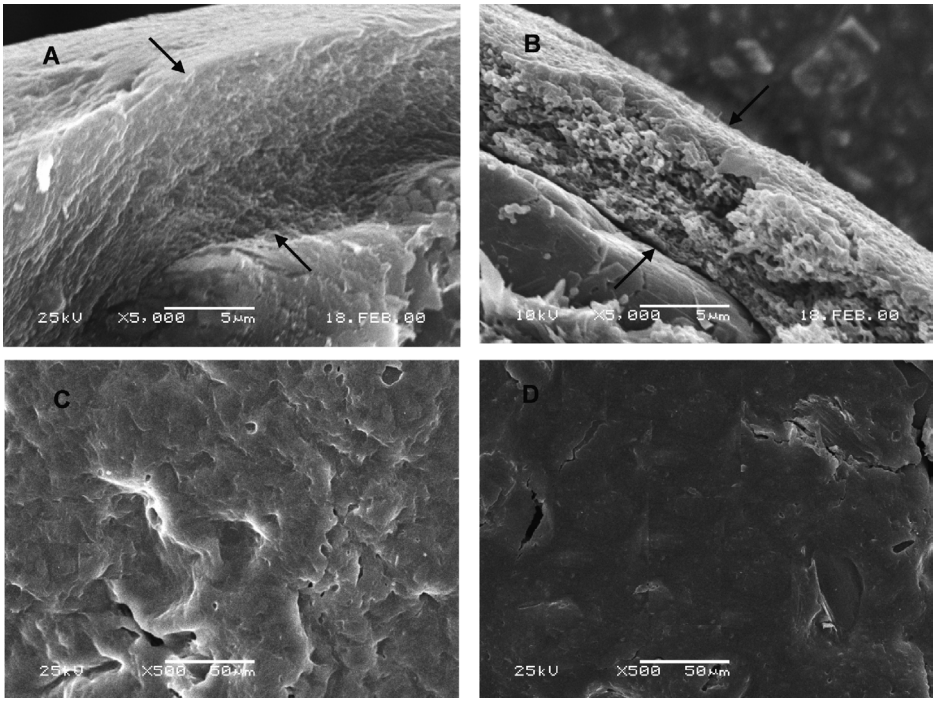

Figure 1.
Scanning electron microscopic photographs of 5 w/w% ethylcellulose coating containing of unplasticized 5 w/w% ethylcellulose coating (A), 2.5w/w% PEG 1540 (B), 2.5 w/w% PEG 400 (C) and 15 w/w% triacetin (D). Magnifications: 5000× (A, B) and 500× (C, D).

neither the type nor the amount of the plasticizer caused visible change and no separated plasticizer can be identified by this method on the surface.

Figure 2 illustrates the DSC curves of ethyl cellulose free films containing PEG of different types and concentrations. The PEG-type plasticizers preserved their sepa-

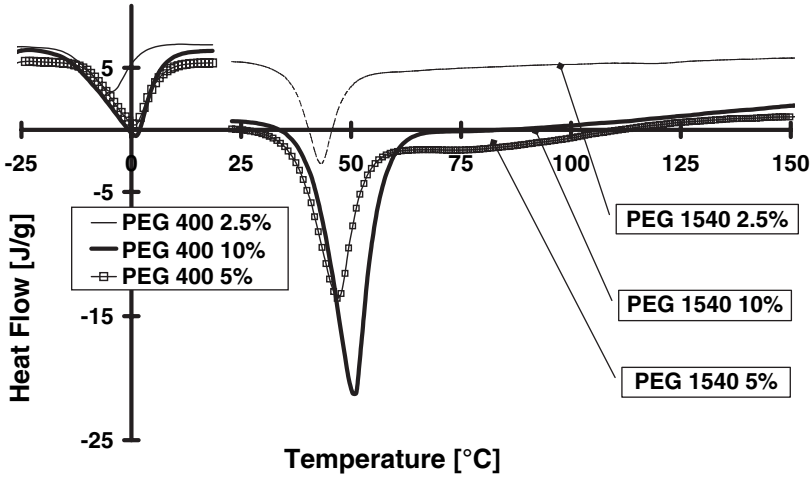

Figure 2.
DSC curves of free films containing different types and amounts of plasticizer.

rately crystalline phase in the mixture according to their melting peaks that appeared in the plot. It means that a part of the plasticizer molecules tends to form separate dispersed phase in EC instead of being entirely dissolved in the polymer phase. Since the melting temperature of PEG 400 is about 0 °C, while that of PEG 1540 is about 50 °C in the EC-plasticizer mixtures, the dispersed part of plasticizer is liquid in the former case, but it is crystalline in the last one at ambient temperature. In the case of triacetin no melting peak appeared in the given measuring range of DSC plots as its melting temperature is −78 °C.

Along with a decrease of PEG concentration in EC matrix, the melting temperature (T_m) slightly decreased suggesting the improving interaction with the polymer matrix. No characteristic differences were observed in this respect between the plasticizers.

The T_g transition of EC significantly changed with the concentration of the plasticizers. The position of T_g transition refers sensitively to the interaction of plasticizers and polymer matrix, consequently the higher the interaction, the lower the T_g . Table 2 summarizes the T_g values of various samples of free films. The T_g of EC without plasticizer (unmodified) was at 140 °C, which means that below this temperature the restricted movements of polymer segments do not support a quick migration through the film. The unmodified film is mechanically sensitive, too rigid to bear any deformation. Increasing the plasticizer content, the toughness of the film increases and the T_g decreases significantly. It means that, apart from the separately dispersed crystalline phase of plasticizers, a part of its molecules are dissolved in the polymer phase and initiate the segment movements at lower temperature. This effect is characteristic to all the investigated plasticizers but the extent is different. Applying 5–10% w/w of plasticizer the T_g can be lowered to 50–60 °C. The T_g value of EC free films without plasticizer is 140 °C.

The T_g modification is much more expressed by PEG 400, while the effects of PEG 1540 and triacetin are similar. PEG 400 at concentration of 0.5% caused a higher shift then PEG 1540 at 5% concentration. Considering the similar chemical structure of these two plasticizers, the explanation of the differences in their ability to build into the chain of the film coating polymer required the investigation of the third phase, where the plasticizer can be present without chemical binding. The third phase, that was the surface layer, was characterized by its chemical composition.

XPS method was selected to determine the relative amount of plasticizer on the surface of EC film. It is clear, that a part of the plasticizer is always present on the surface of the films, but the relative ratio of this segregated part depends on the compatibility between the matrix and the plasticizer.

Due to the chemical similarity of the EC and the plasticizers, it is difficult to distinguish them on the surface. XPS measurements of the 10 nm thick surface layer give accurate quantitative information about the different activity of the plasticizers to accumulate on the surface.

Table 2.
T_g values of EC free films containing plasticizer of different types and concentrations (average of three parallels ± 1.24 °C)

Plasticizer	T_g (°C)						
	Concentration of plasticizer (%)						
	0.25	0.5	1	2	2.5	5	10
PEG 400	–	92 °C	75 °C	–	65 °C	57 °C	53 °C
PEG 1540	133 °C	127 °C	124 °C	–	113 °C	102 °C	60 °C
Triacetin	–	–	124 °C	114 °C	–	–	–

Table 3.
Position binding energy, atomic concentration and O/C ratio of the coating systems containing plasticizer of different types and concentrations

Plasticizer	Position binding energy (eV)		Atomic concentration (%)		O/C
	C	O	C	O	
–	285.70	532.20	67.54	32.46	0.480
PEG 400	285.60	532.20	66.08	33.54	0.507
PEG 1540	285.70	532.10	64.68	34.12	0.527
Triacetin	285.80	532.20	62.89	34.22	0.544

Table 3 shows the theoretical and measured O/C ratios of samples containing different plasticizers. The presence of plasticizer on the surface increases this ratio as the O content of the plasticizer is somewhat higher than that of the matrix. The XPS results suggest that among the studied plasticizers PEG 400 has the lowest tendency to accumulate on the surface (O/C is the closest to that of the EC), which in turn caused the most significant shift of T_g. PEG 400 seemed to be the most compatible type of the three compared plasticizers.

The results of dissolution studies confirm the observations of SEM, DSC and XPS experiments. The effect of the plasticizers on the dissolution was compared using the pellets covered with 3.51 mg/cm^2 coating. The permeability of EC coating is influenced most significantly by 5% PEG 400 (Figure 3). The shape of this curve differs from the others that seem belonging to a group of similar behavior. Unmodified EC produced the highest rate of release. Probably this can be due to its rigid and brittle character causing discontinuities during processing. The two plasticizers of lower compatibility (PEG 1540 and triacetin) form highly water soluble inclusions that may act as channels enhancing the release rate. In contrast continuous, flexible coating can be formed using 5% PEG 400 which is efficient enough to bear the stresses during processing and does not contain high amount of inclusions. In this case, the release is only governed by the mobility of molecules. Further increase of the plasticizer concentration is not desirable as the too low T_g may cause processing problems.

The influence of independent variables on the dissolution kinetics was indicated by

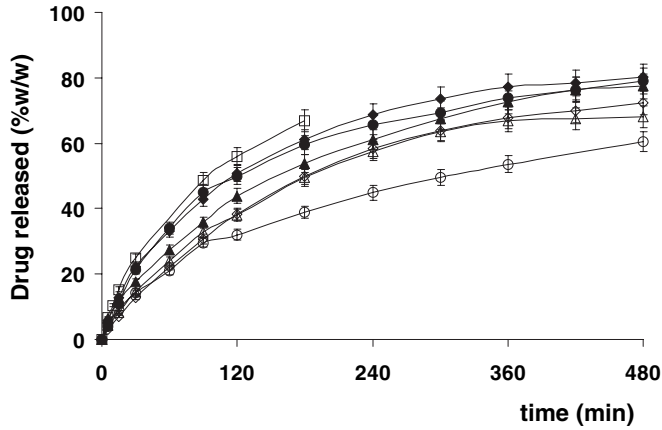

Figure 3.
Effect of the various plasticiser concentration on the drug release. Surface amount of the coating: 3.51 mg/cm^2 (n = 3) (□) EC; (△) 2,5% PEG 400; (○) 5% PEG 400; (▲) 2,5% PEG 1540; (●) 5% PEG 1540; (◇) 15% Triacetin; (◆) 30% Triacetin.

Table 4.
Randomized matrix of the two-factor, three-level face-centered central composite factorial design for k values (average of three parallels ± S.D.)

Trial	Controlled factors		k (1/min) Response parameters		
	x_1	x_2	PEG400	PEG1540	Triacetin
1	+	0	0.0057 ± 2.67e-4	0.0068 ± 2.99e-4	0.0058 ± 2.74e-4
2	−	−	0.0222 ± 4.26e-4	0.0222 ± 2.13e-5	0.0222 ± 4.00e-5
3	0	−	0.0165 ± 5.11e-4	0.0165 ± 4.65e-5	0.0165 ± 1.07e-4
4	−	+	0.0078 ± 2.83e-4	0.0154 ± 1.07e-4	0.0142 ± 3.24e-5
5	0	0	0.0082 ± 8.23e-4	0.0084 ± 6.69e-4	0.0078 ± 6.22e-5
6	+	−	0.0117 ± 8.53e-5	0.0117 ± 6.78e-5	0.0117 ± 1.47e-4
7	0	+	0.0055 ± 2.95e-4	0.0099 ± 3.41e-4	0.0108 ± 3.71e-4
8	+	+	0.0059 ± 1.13e-5	0.0105 ± 2.34e-4	0.0082 ± 4.03e-4
9	−	0	0.0112 ± 5.57e-4	0.0129 ± 3.69e-4	0.0128 ± 2.12e-4

the k dissolution rate constant. Table 4 summarizes the measured and the estimated dissolution kinetic parameter of various coating polymer systems and Figure 4 shows the effect of coating level and plasticizer. The effect of formulation factors (x_1,x_2) on the dissolution rate constant (k) in the case of different plasticizers can be demonstrated by the following model equations:

$$Y_{\mathrm{PEG\,400}} = 0.02796 - 0.00812x_1 - 0.00583x_2 + 0.00099x_1^2 + 0.0050x_2^2 + 0.00066x_1x_2 \quad (3)$$

$$Y_{\mathrm{PEG\,1540}} = 0.03016 - 0.01071x_1 - 0.00560x_2 + 0.00156x_1^2 + 0.00072x_2^2 + 0.00050x_1x_2 \quad (4)$$

$$Y_{\mathrm{triacetin}} = 0.03025 - 0.01088x_1 - 0.01471x_2 + 0.00161x_1^2 + 0.00481x_2^2 + 0.0011x_1x_2 \quad (5)$$

The positive sign of the coefficients refers to an increasing effect, while the negative sign indicates a decreasing effect on the corresponding response. Increasing the amount of coating polymer and the plasticizer concentration reduced the dissolution rate constant. Due to the positive sign of the quadratic coefficients (b_{11}, b_{22}), the decreasing power of the coating level and the plasticizer content becomes less effective (Eq. 3,4,5).

The surface plot of the estimated dissolution kinetic parameters and the randomized matrix of the factorial design has a minimum value on the base (0) and higher (+) level in the case of PEG 400 and on the higher (+) and base (0) level in the case of PEG 1540 and triacetin (Table 4, Figure 4).

The effect of concentration on the dissolution rate constant is significant in the case of PEG 400, while the effect of coating thickness is more pronounced when PEG 1540 or triacetin are used, which can be clearly due to the higher tendency of these plasticizers to form separate phase.

Conclusion

The selection of type and concentration of the plasticizer has decisive impact on the properties of ethyl cellulose film coating and thus the processing, dissolution and storage of coated dosage forms. Complex investigation of the structure could help to interpret the results of dissolution experiments. SEM images demonstrate change of the structure and fracture mechanism owing to the introduction of plasticizers.

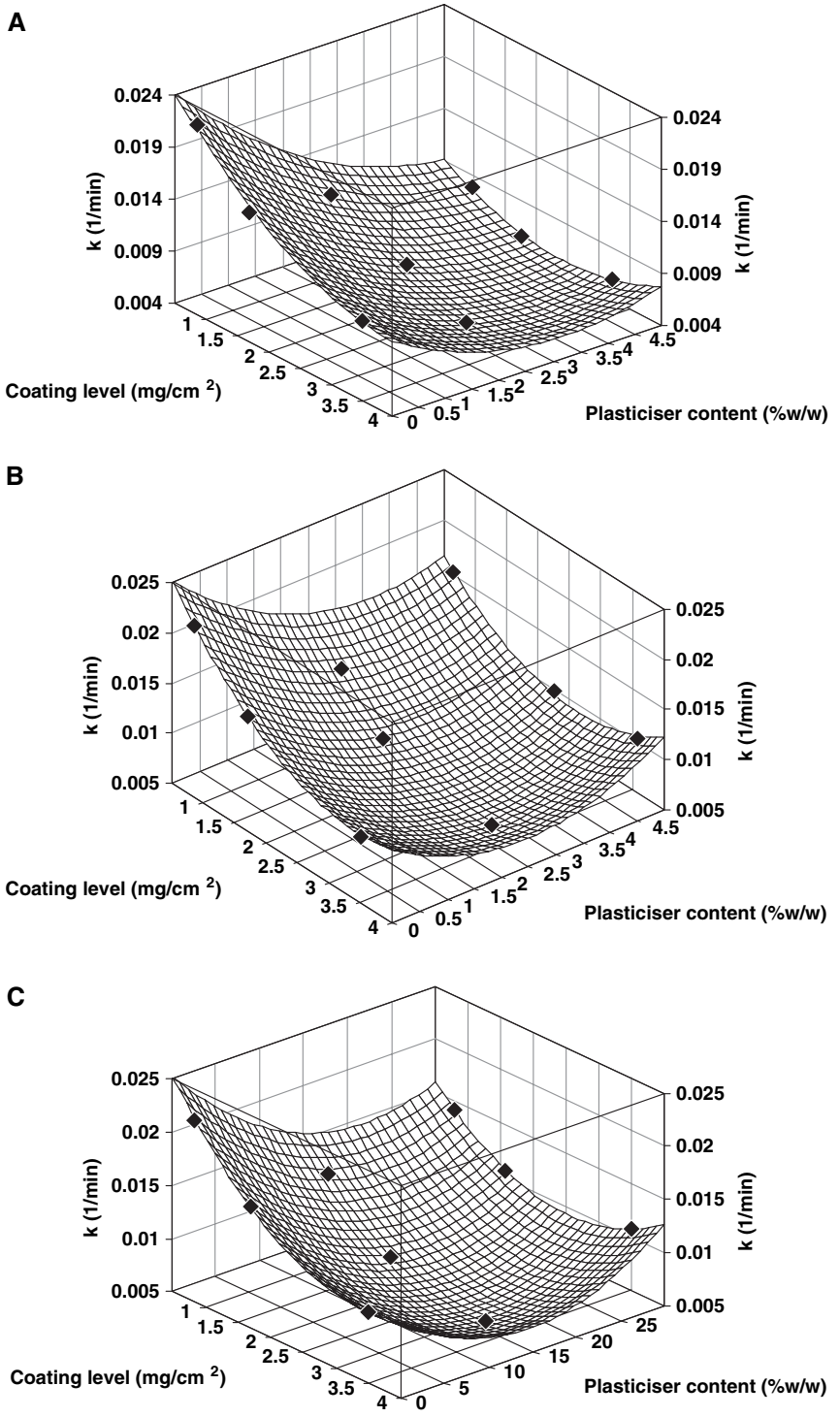

Figure 4.
Surface plot for the influence of coating level and plasticizer content on the release rate. (A = PEG 400, B = PEG 1540 and C = triacetin)

The unmodified EC is too rigid, causing discontinuities in the coating layer. Plasticizers do not dissolve entirely in the EC matrix according to DSC and XPS measurements. A part of the plasticizers is accumulated on the surface of the films. The lowest level of surface separation and thus the highest level of compatibility is found in case at PEG of lower molecular mass.

PEG 400 is found to be compatible enough to form continuous, durable EC coating at 5% concentration level, which gave the slowest dissolution. Above the 5% plasticizer concentration, the T_g of the polymer decreases to the processing temperature and the dispersed plasticizer phase may cause disadvantageous migration of the drug through the coating layer. PEG 1540 and triacetin have shown lower compatibility with EC, which could be seen from the T_g results and from the increased concentration of the plasticizers in the surface layer of the coating. Due to lower compatibility level inclusions of high water solubility are formed, which may act as channels enhancing the release rate.

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