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Research paper

Modulating pH-independent release from coated pellets: Effect of coating composition on solubilization processes and drug release

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ABSTRACT

The aim of the study was to clarify the influences of three coating parameters on the drug release from chlorpheniramine maleate (CPM) pellets, coated with blends of poly(vinyl acetate) (PVAc) and poly(vinyl alcohol)–poly(ethylene glycol) (PVA–PEG) graft copolymer. A central composite design was implemented to investigate the effect of the polymer blend ratio, the film coat thickness and the plasticizer concentration on the drug release. The solubilization inside the pellets was monitored by EPR spectroscopy. The blending ratio of both the polymers and the film thickness were found to have a major influence on the drug release and the solubilization speed, in contrast to the plasticizer concentration. A pH-independent release profile was adjustable via modulating the polymer blend ratio and the coating thickness. A mathematical model was developed, providing a good predictability of the release profile, based on the film coat composition. This model offers the possibility to achieve a defined drug-release profile by selective adaptation of the film coat composition, in view of process times, feasibility or polymer costs.

1. Introduction

A multitude of different coating polymers are available today, each of them designed for customer needs, e.g. taste masking, moisture and gastric protection, sustained release or colon targeting [1,2]. In the case of sustained release, cellulose derivates (e.g. ethyl cellulose, EC), different polymethacrylates (e.g. Eudragit®) and polyvinyl derivates (e.g. Kollicoat®) are most frequently used for coating.

The influence of the coating composition on the drug release was investigated in a majority of publications, whereby blends of different functional polymers were in the main focus of interest. In most cases, the polymer blends consisted of an insoluble and a soluble polymer, e.g. blends of EC with hydroxypropyl methyl cellulose [3,4], EC with Eudragit® L [5–7] as well as Eudragit® NE with Eudragit® L [7,8].

The introduction of a new polyvinyl-based polymer for modified release, poly(vinyl acetate) (PVAc; trade name Kollicoat® SR 30D) offered new possibilities for polymer blends. Dashevsky et al. investigated the release from pellets, coated with blends of Kollicoat® SR and the enteric polymer Kollicoat® MAE [9]. Another approach was the blending of PVAc with poly(vinyl alcohol)–poly(ethylene glycol) (PVA–PEG; trade name Kollicoat® IR) graft copolymer, a soluble film polymer for immediate release. Film polymer blends of PVAc and PVA–PEG demonstrated several advantages, such as a pH-independent drug release, adjustable via the PVA–PEG ratio, and a high resistance to mechanical stress [10,11]. Detailed investigations by Strübing et al. described a pH-independent release from coated tablets, comprising a lag-time, depending strongly on the polymer blend ratio and the coating thickness. Interestingly, mechanistic release studies demonstrated a fast solvent penetration into the tablets and a fast dissolution of soluble components from the film coat surface, even during the lag-time [12,13]. In a previous study, a similar pH-independent release with an uncommon sigmoid-shaped release profile, including a lag-time with a fast release afterwards, was obtained from PVAc/PVA–PEG-coated chlorpheniramine pellets [14]. NMR studies also demonstrated a fast water influx with drug solubilization inside the pellets already during the lag-time.

In the current study, a central composite design (CCD) was implemented to determine the influences of three coating factors on the drug release and on the solubilization processes inside the pellets. The central composite design, a commonly used statistical approach for planning and optimization of experimental series, comprises a full 2^k factorial design with additional star points (Fig. 1), whereby k describes the number of investigated factors ($k = 3$ in this study). The CCD allows an estimation of all interactions, especially second order (quadratic) interactions between the factors and the responses [15,16]. The importance and worth of experimental designs have been reported frequently in the literature, especially for pellet coating processes [17–19]. A similar detailed study on PVAc/PVA–PEG-coated pellets was not published so far.

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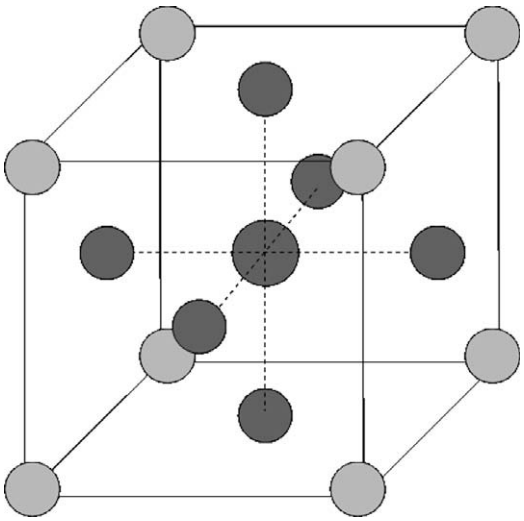

Fig. 1. Central composite design with eight vertices (grey) and seven star points (black).

The solubilization inside the coated pellets was investigated using Electron Paramagnetic Resonance spectroscopy (EPR), a powerful analytical tool to detect free radicals non-invasively. EPR spectroscopy is used today in many fields, e.g. analysis of free-radical drug intermediates, metabolism analysis and direct detection of NO radicals as critical physiological mediators [20,21]. In pharmaceutical technology, EPR-sensitive probes are incorporated into pharmaceutical systems to provide information about the internal structure, to optimize formulation development and to clarify drug delivery processes [22,23]. Further applications have been reported in the literature, e.g. analysis of distribution processes in two-phase systems and monitoring of solubilization processes into pharmaceutical systems [12,24]. The use of EPR-sensitive probes with functional groups allows the analysis of microenvironment pH and oxygen content [25,26]. Nevertheless, EPR spectroscopy was rarely applied on coated pellets.

2. Materials and methods

2.1. Materials

Chlorpheniramine maleate (CPM) was delivered from SelectChemie AG, Zürich, Switzerland. Hydroxypropyl methyl cellulose (HPMC, grade: METHOCEL™ E3 Premium, 3 cps) was delivered from Dow Chemical Company; Midland, MI, USA. Cellulose starter cores (Cellets® 700–1000 μm) were received from PharmaTrans Sanaq AG, Basel, Switzerland. Talc was delivered from Luzenac val Chisone, Porte (TO), Italy. Titanium dioxide (TiO_2) was purchased from KRONOS TITAN GmbH & Co oHG, Leverkusen, Germany. 4-Hydroxy-2,2,6,6,-tetramethypiperidin-1-oxyl (4 Hydroxy-TEMPO, TEMPOL) and propylene glycol were delivered from Sigma–Aldrich Chemie GmbH, Steinheim, Germany. Poly(vinyl acetate) (PVAc; Kollicoat® SR 30D) and poly(vinyl alcohol)–poly(ethylene glycol) (PVA–PEG; Kollicoat® IR) graft copolymer were received from BASF AG, Ludwigshafen, Germany. All other used chemicals were of reagent grade.

2.2. Preparation of film-coated pellets

Chlorpheniramine maleate (CPM) was used as a highly soluble model compound. An aqueous drug-binder solution, containing 16% CPM (w/w), 1% HPMC (w/w) and 0.006% TEMPOL (w/w, corresponding to 1 mmol TEMPOL per kg high dosed CPM pellets), was sprayed onto cellulose starter cores using a fluidized bed coater (Mycrolab; OystarHüttlin GmbH, Schopfheim, Germany). A three-step pellet layering process with a batch size splitting after each step was implemented to achieve a high drug content. Subsequently, the high drug loaded CPM pellets were coated using the same fluid bed coater. The process parameters for the layering and coating processes are listed in Table 1.

For coating, PVAc and PVA–PEG (16% w/w total polymer) were blended in various ratios. Propylene glycol was added in different concentrations for plasticizing, according to the statistical design (Table 2). Furthermore, the coating dispersion contained talc as anti-tacking agent (4.8% w/w) and titanium dioxide as pigment (0.5% w/w), which were kept constant for all coating trials.

PVA–PEG (Kollicoat® IR) was dissolved in water, and propylene glycol was added. A 30% ready to use dispersion of PVAc (Kollicoat® SR 30D) was added, and the mixture was homogenized with an Ultra Turrax. Talc and titanium dioxide were separately dispersed in water, and both dispersions were blended afterwards. The final mixture was homogenized a second time, sieved and stirred during the coating process, to prevent settling. After coating, the pellets were dried in the fluid bed coater for 5 min at 50 °C.

2.3. Dissolution rate studies

The drug release from coated pellets was analyzed, using an USP rotating paddle method at 37 °C medium temperature and 50 rpm rotation speed over a 9–15 h period. Dissolution studies ($n = 5$) were carried out in 750 ml of hydrochloric acid/sodium chloride solution (pH 1.2). After 2 h, the media pH was changed from 1.2 to 6.8 to simulate the gastric transition, according to European pharmacopoeia [27]. The content of chlorpheniramine maleate was detected spectrophotometrically at 265 nm (HCl/NaCl pH 1.2) and 262 nm (phosphate buffer pH 6.8).

2.4. Statistical design

A central composite design (CCD) was chosen as experimental model, comprising eight "vertices" and eight "star points", whereby the center star point was repeated once to prove reproducibility and accuracy of the statistical model (Fig. 1). Three responses Y_1–Y_3 were individually investigated using the response surface model (1):

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2. \quad (1)$$

Using three parameters from the film coat composition as factors X_1–X_3, each at three levels, the CCD comprised 16 coating trials. The first factor (X_1) was the blend ratio of PVAc and PVA–PEG, which were blended in three different ratios at 8:2, 9:1 and 10:0 (PVAc/PVA–PEG). The film coat thickness was the second factor (X_2), whereby a film thickness of 10%, 20% and 30% (calculated as weight gain by PVAc and PVA–PEG, based on total pellet weight after coating) was defined as the range for the experimental series. The plasticizer concentration was chosen as the third factor (X_3) with propylene glycol as a suitable plasticizer, based on several publications [28,29]. In fact, due to its low minimum film forming temperature (MFT), an addition of plasticizer is not required for PVAc films [30]. Nevertheless, three different plasticizer levels of 10%, 5% and 0% plasticizer (calculated on dry mass of both polymers, PVAc and PVA–PEG) were investigated.

2.5. Evaluation of release data from DR

Using a fitting program (TableCurve 2D v5.01, SYSTAT Software Inc., San Jose, CA, USA), a model was fitted to the raw data from the dissolution rate studies. Due to the sigmoid shape of the release profiles, the data fits best to a sigmoid model. The major prerequi-

Table 1
Parameter setup for the stepwise fluid bed layering and the fluid bed coating process.

	Pellet layering I	Pellet layering II	Pellet layering III	Film coating
Starter cores	Cellulose cores	CPM pellets (step I)	CPM pellets (step II)	CPM pellets (step III)
Batch size	500 g	450 g	400 g	175 g
Product temp.	38–42 °C	43–47 °C	48–52 °C	38–42 °C
Spray rate	6–7 g/min	6–7 g/min	5–6 g/min	1–3 g/min
Inlet air temp.	55–60 °C	57–63 °C	60–65 °C	48–52 °C
Microclimate/spray pressure	0.5 bar/0.6–1.2 bar	0.5 bar/0.6–1.2 bar	0.5 bar/0.6–1.2 bar	0.4–0.5 bar/0.6–0.8 bar
Air flow	45–48 m^3/h	47–50 m^3/h	47–50 m^3/h	25–30 m^3/h
Applied layering liquid/coating dispersion	2750 g (to achieve 44% drug loading)	2700 g (to achieve 68% drug loading)	2620 g (to achieve 80% drug loading)	130, 300 and 550 g (to achieve 10%, 20% & 30% film thickness)

Table 2
Central composite design: results from pellet coating and dissolution rate analysis.

Run	Film thickness (%)[a]	PVAc/PVA–PEG ratio	Plasticizer conc. (%)[b]	Lag-time (h)	Median dissolution time (h)	Final release (h)	V_{max} (%/h)
01	30	9:1	5	6.7	9.9	13.3	23.1
02	20	9:1	5	2.3	3.7	5.0	52.8
03	19	8:2	5	0.5	1.5	2.9	59.6
04	20	9:1	10	2.4	3.7	5.0	57.5
05	10	9:1	5	0.4	1.1	2.1	77.3
06	29	10:0	0	15.6	20.1	24.0	16.6
07	20	10:0	5	5.1	7.2	9.7	34.3
08	29	8:2	0	0.6	1.9	3.6	45.5
09	9	8:2	0	0.1	0.4	0.8	208.2
10	29	8:2	10	0.7	2.2	4.4	37.9
11	10	10:0	10	0.8	1.7	2.7	72.2
12	19	9:1	0	2.5	3.7	4.9	63.2
13	19	9:1	5	2.5	3.8	5.0	60.7
14	10	10:0	0	0.9	1.8	2.8	73.5
15	10	8:2	10	0.1	0.6	1.3	129.7
16	30	10:0	10	12.0	16.3	20.1	17.2

[a] Film thickness calculated on weight gain by total polymer (PVAc and PVA–PEG).
[b] Plasticizer concentration calculated on total polymer concentration (PVAc and PVA–PEG).

sites for the applied fit were a sufficient matching with all release profiles from the experimental design and furthermore a simple formula with a minimum number of parameters as possible. Finally, the simplest and best matching sigmoid model, provided by the fitting program, was chosen. The sigmoid model comprised four parameters and is shown in the following equation.

$$y = a + \frac{b}{1 + \exp\left(-\frac{x-c}{d}\right)} \quad (2)$$

Average values for parameters *a–d* from all fittings were used to determine the effect of the different parameters on the sigmoid-shaped release curve. Furthermore, the time values for 5%, 50% (median dissolution time) and 95% drug release were calculated, using the fitting equation. Thereby, 5% drug release was defined as end of lag-time (response Y_1) and consequently, 95% drug release was defined as end of release (response Y_3). The median dissolution time was defined as response Y_2. Additionally, the maximum slope of the release profile, V_{max}, was determined in %/h.

JMP™ (SAS Institute Inc., NC, USA) was used to develop a mathematical model, providing predictions of the release profiles, based on the three film coating factors X_1–X_3 (polymer blend ratio, film thickness and plasticizer concentration).

2.6. EPR analysis

A small amount of coated pellets was filled into a flow through cell and was fixed with fiberglass. The flow cell was placed directly in the EPR spectrometer (EPR spectrometer with 2D-tomography-device, L-Band, magnettech GmbH, Berlin, Germany) and was floated with dissolution media at 1 ml/min media flow (HCl/NaCl, pH 1.2, and changed to phosphate buffer, pH 6.8, after 2 h). After predetermined time intervals, eight EPR spectra were recorded within 4–5 min measurement time and were subsequently accumulated to minimize the background noise. The EPR experiment was continued until the EPR signal did not change any more or disappeared, due to release of the EPR probe. Furthermore, an additional spectrum of dry pellets was recorded.

The EPR spectra were evaluated using a nitroxide spectra simulation software (V. 4.99F, Biophysical Laboratory, EPR Centre, Josef Stefan Institute, Ljubljana, Slovenia). The anisotropic domain parameters, obtained from the simulation of the dry pellet EPR spectra, were fixed and all other EPR spectra from release studies were evaluated by overlaying the anisotropic spectra with isotropic spectra in different ratios. A simplex optimization of the spectra was used, followed by a Genetic optimization until the best fitting was achieved.

3. Results and discussion

3.1. Release experiments and statistical evaluation

The release profiles included a lag-time followed by a rapid and continuous drug release thereafter, which allows to describe them as a combination of delayed and sustained release. The release from the coated pellets was pH-independent, since the change of dissolution media after 2 h did not impact the release. A final drug release in mean of 100.8% ± 1.3 was obtained, demonstrating the complete release from the coated pellets. The dissolution data confirmed the previous results from a mechanistic study on high dosed pellets, coated with PVAc/PVA–PEG blends in 9:1 ratio [14].

The applied sigmoid fit (2) matched well with the release data, demonstrating a minimum r^2 of 0.99503 and a maximum r^2 of 0.99992. The statistical model demonstrated a r^2 of 0.98686 for the lag-time, a r^2 of 0.98806 for the median dissolution time and a r^2 of 0.99044 for the final release value. The accuracy of the CCD was proven by two identical coating trials with 9:1 PVAc/PVA–PEG ratio, 20% film thickness and 5% plasticizer (Table 2). Both coating trials demonstrated almost identical lag-times (2.3 vs. 2.5 h), median dissolution times (3.7 vs. 3.8 h) and final release values (both 5.0 h) as well as similar maximum slopes (52.8 vs. 60.7%/h).

A significant impact of the film coat thickness on the drug release was demonstrated. The lag-time as well as the median dissolution time was extended with the increasing coating thickness, and furthermore the slope of the drug-release profile was reduced with increasing coating thickness (Fig. 2A and Table 2). At 10% film thickness (9:1 blend ratio), a lag-time of 0.4 h and a median dissolution time of 1.1 h were obtained. Both, the lag-time and the median dissolution time were extended to 2.3 (2.5) and 3.7 (3.8) h at 20% film thickness and finally to 6.7 and 9.9 h at 30% film thickness. The maximum slope of the release profile decreased from 77.3 to 52.8 (60.8)%/h, and finally to 23.1%/h at 10%, 20% and 30% film thickness, respectively.

The blend ratio of PVAc/PVA–PEG also demonstrated a significant influence on the drug release. The lag-time as well as the median dissolution time were extended at higher PVAc ratios, but interestingly the maximum slope of release profile was hardly affected by the polymer ratio (Fig. 2B and Table 2). A blend ratio of 8:2 PVAc/PVA–PEG (20% film thickness) resulted in a lag-time of 0.5 h and a median dissolution time of 1.5 h. The lag-time as well as the median dissolution time were extended to 2.3 (2.5) and 3.7 (3.8) h at 9:1 polymer ratio and finally to 5.1 and 7.2 h at 10:0 polymer ratio. A maximum slope of 59.6%/h was detected at 8:2 ratio, which remained at a similar level at 9:1 ratio with 60.8 and 52.8%/h. A slight reduction of the slope to 34.3%/h was finally measured at 10:0 ratio. The maximum slope in summary did not show a clear tendency and was therefore not affected by the blend ratio of PVAc and PVA–PEG.

Interestingly, the plasticizer concentration did not show a significant influence neither on the lag-time nor on the release slope (Fig. 2C and Table 2). Lag-times and median dissolution rate times were almost similar at 9:1 polymer ratio and 20% film thickness (2.5 and 3.7 h vs. 2.3/2.5 and 3.7/3.8 h vs. 2.4 and 3.7 h). The slope of the drug-release profiles demonstrated a slight difference, a clear tendency was not observed (63.2%/h vs. 52.8(60.8)%/h vs. 57.5%/h). Also, at lower film thickness of 10%, the plasticizer concentration did not significantly affect the drug-release profile, regardless of the polymer blend ratio (data not shown). A slightly delayed release was observed at samples with 10% plasticizer at 8:2 polymer blends and high film thickness of 30%. Nevertheless, the lag-time remained unchanged. Solely at pure PVAc films (10:0 ratio) with a high film thickness of 30%, the samples without plasticizer showed a slightly extended lag-time (data not shown).

The results from statistical modeling indicated clearly that three factors and interactions had a significant influence on the three response signals (Table 3). The film coat thickness demonstrated the highest impact on the drug release, followed by the polymer blend ratio and by the second order interaction, film

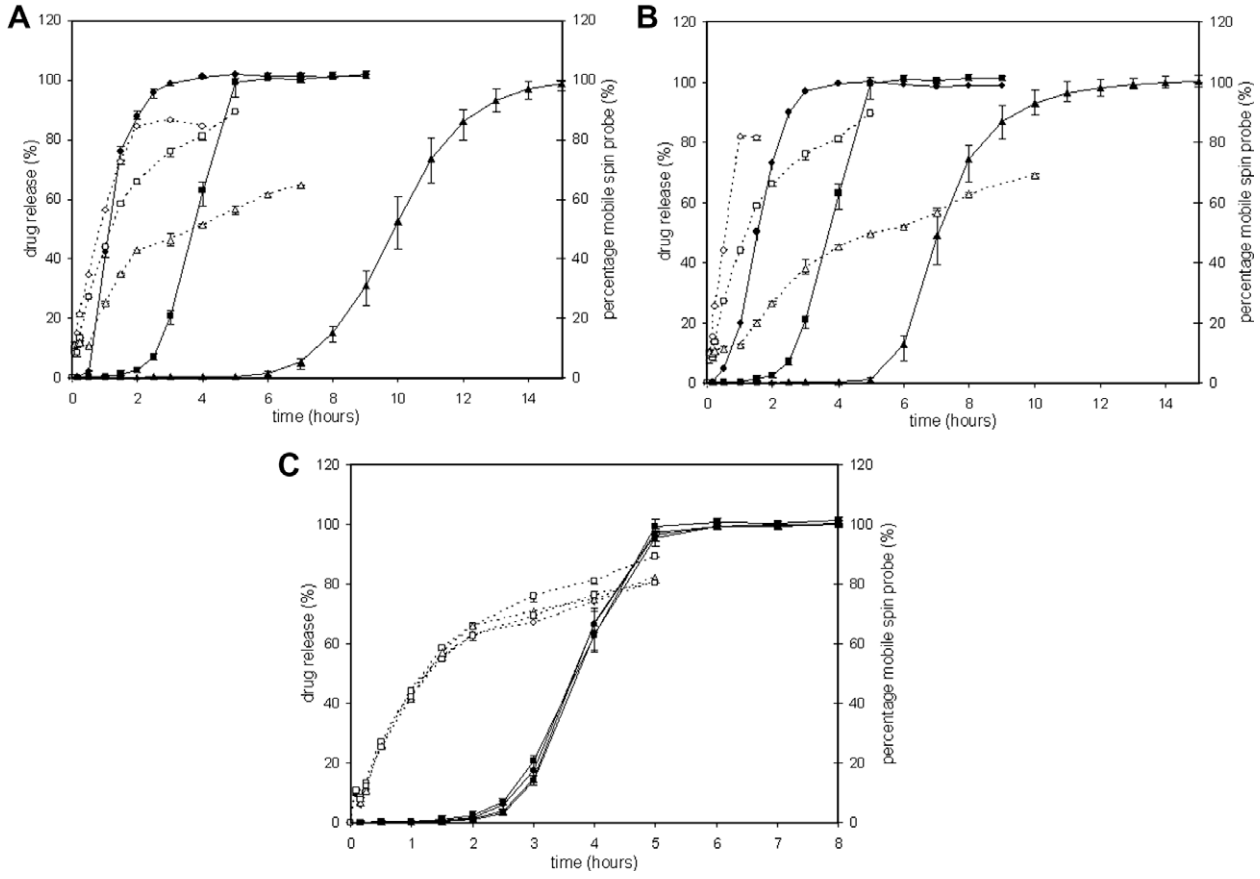

Fig. 2. Solubilization of TEMPOL inside coated pellets (open symbols), in relation to drug release (closed symbols) (A) at 10% (●), 20% (■) and 30% (▲) film coat thickness, 9:1 PVAc/PVA–PEG ratio and 5% plasticizer; (B) at 8:2 (●), 9:1 (■) and 10:0 (▲) PVAc/PVA–PEG blend ratio, 20% coating thickness and 5% plasticizer; (C) at 0% (▲), 5% (■) and 10% (●) plasticizer, 9:1 PVAc/PVA–PEG ratio and 20% coating thickness.

Table 3
Statistical impact of the coating parameters on three response values.

Response	Lag-time (Y_1)		Median dissolution time (Y_2)		Final release (Y_3)	
Term	Plot and scaled estimate	*p*-values	Plot and scaled estimate	*p*-values	Plot and scaled estimate	*p*-values
Film coat thickness	3.3264414	<.0001	4.4827454	<.0001	5.5851849	<.0001
Polymer blend ratio	3.2341619	<.0001	4.0438492	<.0001	4.6200243	<.0001
(Film coat thickness 20) × (Polymer blend ratio 90)	3.1057156	<.0001	3.717952	<.0001	4.0951185	<.0001
(Film coat thickness 20) × (Film coat thickness 20)	1.0889136	0.0745	1.586653	0.0412	2.1124697	0.0170
(Polymer blend ratio 90) × (Polymer blend ratio 90)	0.307573	0.5650	0.4167891	0.5217	0.6847482	0.3299
(Plasticizer concentration 5) × (Plasticizer concentration 5)	−0.004652	0.9930	−0.225267	0.7257	−0.67989	0.3331
Plasticizer concentration	−0.378511	0.1948	−0.352858	0.3048	−0.267891	0.4501
(Film coat thickness 20) × (Plasticizer concentration 5)	−0.430721	0.1880	−0.440417	0.2571	−0.434043	0.2862
(Polymer blend ratio 90) × (Plasticizer concentration 5)	−0.475114	0.1525	−0.544868	0.1723	−0.653066	0.1287

thickness × polymer blend ratio. All other parameters and interactions, especially the plasticizer concentration, did not demonstrate a statistical significant impact on the drug-release profile.

Studies of Strübing et al. on tablets, coated with blends of PVAc and PVA–PEG, had also demonstrated a significant impact of the polymer blend ratio and the film coat thickness on the release of two model compounds, propranolol and theophylline [12,13]. Within those studies on tablets, the release profile included also a lag-time, which was followed by a sustained slow release. In contrast to the clearly sigmoid s-shaped release profiles from coated CPM pellets, the release from PVAc/PVA–PEG-coated propranolol and theophylline tablets was much slower with about 20% and 10% drug release after 24 h, respectively. The slower release can be partially explained by the lower solubility of theophylline and propranolol, compared to chlorpheniramine maleate. Furthermore, the CPM pellets comprised a much higher drug content, compared with the coated theophylline and propranolol tablets. Finally, the surface of coated pellets, used for dissolution rate analysis (about 100 mg = 30–40 pellets), was much larger than the film coat surface of a single tablet.

Independently from the difference shape of the release profile, the same influence of the polymer blend ratio and film coat thickness was observed for coated pellets and coated tablets. At both systems, the lag-time was extended at higher film coat thickness and higher PVAc content in the film coat. The occurrence of a lag-time was not dependent on the dosage form, on the dosage surface or on the different drug substances. The lag-time was only dependent on the composition of the film coat as well on the thickness of the film coat layer, suggesting to be an important characteristic for film coats from PVAc/PVA–PEG polymer blends.

3.2. EPR experiments

In this study, EPR analysis was applied to determine the mobility of the EPR probe inside the pellets. This mobility increases with an processing solubilization of the probe. A hydrophilic probe, TEMPOL, with a low molecular weight was used, to simulate the solubilization behavior of the hydrophilic drug, CPM. Finally, the increasing solubilization was considered as an indicator for a proceeding water penetration into the pellet core, giving important information of the underlying release mechanism.

Primarily, coated CPM pellets were analyzed in dry state. An anisotropic spectrum with low amplitudes and broad lines was observed (Fig. 3A), typical for highly viscous and solid samples. A second spectrum was recorded from an aqueous TEMPOL solution, resulting in an isotropic spectrum with three lines of a similar high amplitude (Fig. 3B), typical for low viscous and liquid samples. In the case of a proceeding solubilization, the shape of the EPR spectra is formed by a superposition of the two spectra types, based on the spectral contribution of solubilized and still immobile probe. In the current study, the spectra shape changed from immobile to mobile within 30 min, demonstrating a fast solubilization of TEMPOL inside the coated pellets (Fig. 4). This fast solubilization inside the coated pellets confirmed results from previously NMR experiments [14] on coated pellets as well as EPR measurement on coated tablets [12].

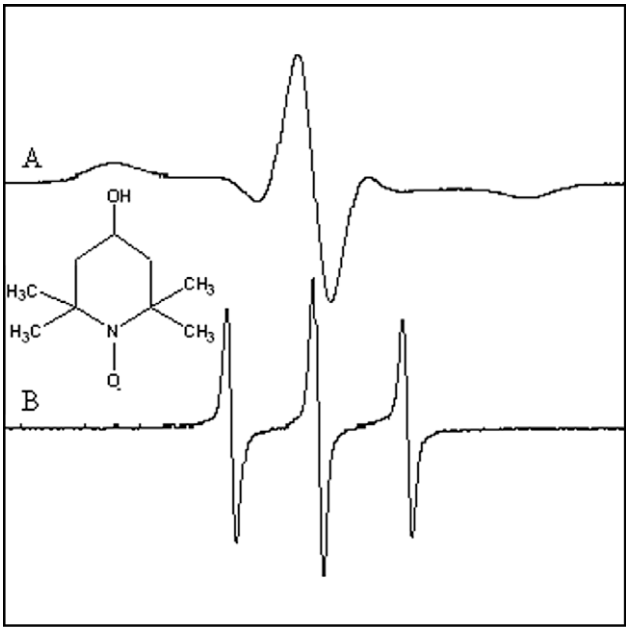

Fig. 3. Chemical structure and EPR spectra of TEMPOL in solid state (A) and dissolved in water (B).

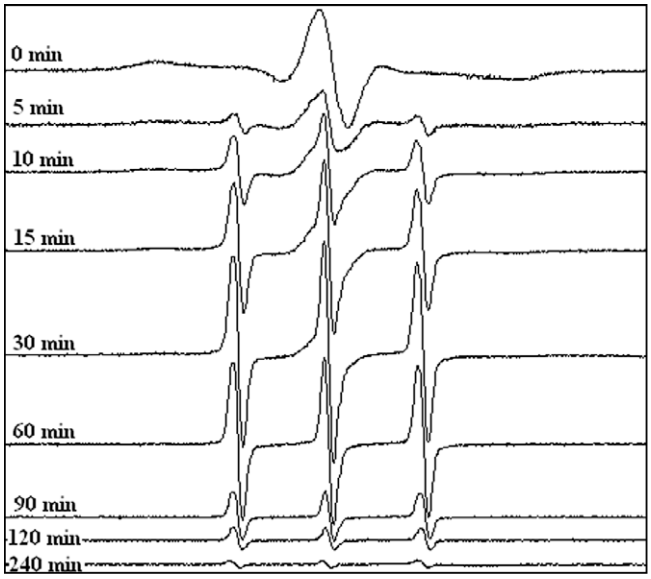

Fig. 4. EPR spectra from coated CPM pellets containing TEMPOL, recorded during DR at predetermined time intervals.

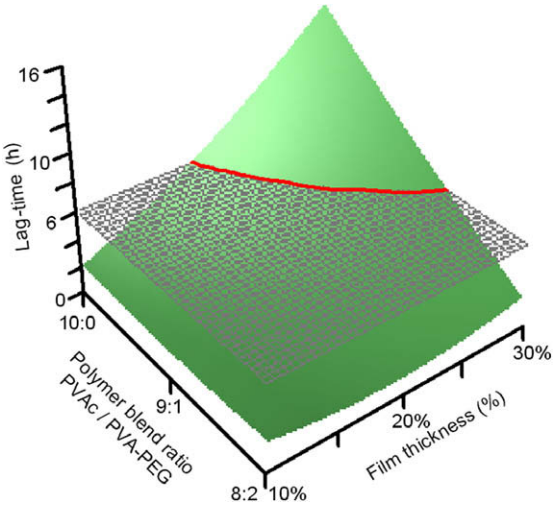

Fig. 6. Prediction plot for lag-time, comprising the aimed lag-time of 6 h (black shaded area) and the provided film compositions (black line).

The blend ratio of PVAc and PVA–PEG as well as the film coat thickness demonstrated a significant influence on solubilization inside the pellets (Fig. 2A and B). About 50–60% of the EPR probe had changed from immobile to mobile (= solubilized) state at the end of the lag-time.

The speed of solubilization was reduced at higher PVAc ratios and at thicker film coats, whereby the reduction of solubilization speed was much more obvious at higher PVAc ratios than at thicker film coats. Analogous to the release analysis, the plasticizer concentration did not have a significant influence on the solubilization (Fig. 2C). The speed of solubilization inside the pellets was almost similar with 60–70% mobile probe after end of the lag-time.

EPR spectra with more than 80% mobile probe could not be fitted with a sufficient high accuracy with the used program. Therefore, the calculated ratios yield maximum values of 80%. Even though, some EPR spectra could not be fitted sufficiently, an analysis of the first derivation verified the further progress of solubilization by decrease of immobile EPR probe ratio in the sample.

Finally, it was demonstrated that all three investigated coating parameters had a similar influence on the solubilization speed just like on the drug release. It was shown that about 50–70% of the EPR probe inside the pellet drug layer was solubilized, when the drug release was initiated. One can conclude that the progress of solvent penetration is directly affecting the drug release and is therefore the initial mechanistic and essential step in drug-release mechanism from PVAc/PVA–PEG-coated CPM pellets.

3.3. Development of a mathematical model

The sigmoid fit (2), comprising four parameters *a*–*d*, was used to create a mathematical connection between the film coat composition and the drug release. The average values for all four parameters, received from the fitted release profiles, were used to determine the effect of the parameters on the release profile. Parameter "*a*" described the intersection between the release profile and the *y*-axis, defined as start value (0% by definition). Parameter "*b*" determined the height of the release profile, which represents the final drug release and was set to 100% by definition. The parameter "*c*" shifted the release profile on the *x*-axis and therefore influenced the lag-time, the median dissolution time as well as the final release. Finally, parameter "*d*" described mainly the slope of the release profile, affecting also the lag-time, the median dissolution time and the final release value. Only parameter "*c*"

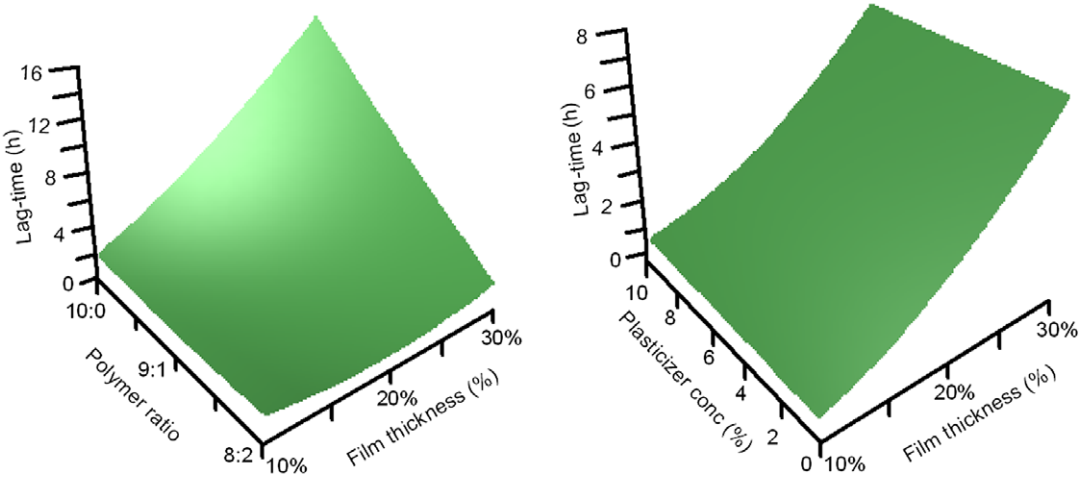

Fig. 5. Prediction plot for lag-time, calculated on polymer blend ratio vs. film coat thickness (left) and plasticizer concentration vs. film coat thickness (right).

Table 4
Predictability of the mathematical model. Comparison of prediction and measured release.

	Film coat thickness (%)	Polymer blend (PVAc/PVA–PEG)	Plasticizer conc. (%)	Lag-time (h)	Difference
Prediction sample C_1	13.6	9.5/0.5	5	1.5	0.3 h (20%)
Manufactured sample C_1	12.8	9.5/0.5	5	1.2	
Prediction sample C_2	22.9	8.5/1.5	5	1.5	0.2 h (13%)
Manufactured sample C_2	22.6	8.5/1.5	5	1.3	

and "*d*" showed a significant impact on the release profile. Especially, parameter "*c*" could be assigned to the factor "polymer blend ratio", since those both demonstrated a clear impact on the lag-time, without affecting the slope of drug release (see Supplementary Information). A relation of factor "film coat thickness" to parameter "*d*" was likely, but was not provable sufficiently by the release results.

In a second step, the responses values (Y_1–Y_3) from the fitted release profiles were transferred into a statistical program, which provides different prediction plots of the coating parameters for each response. Two prediction plots were obtained for the lag-time (Y_1), whereby a significant impact of the film coat thickness and polymer blend ratio on the drug release was demonstrated (Fig. 5). The second plot underlined clearly that the plasticizer concentration was without an influence on the drug release (Fig. 5). The same impacts were reported for the other responses, Y_2 and Y_3 (data not shown).

The plots were used to predict the film coat compositions, based on an aimed drug-release profile. Since the plasticizer concentration did not influence the drug release, only one plot with two film coat parameters was necessary for the mathematical model. An example with an aimed lag-time of 6 h is shown, whereby the lag-time is demonstrated by a black shaded area (Fig. 6). The mathematical model provided all the possible film coat compositions, resulting in the aimed values for the lag-time, symbolized by a line at the intersection of the prediction graph and the black shaded area. A suitable film coat composition, comprising the film coat thickness and the polymer blend ratio could be chosen easily from the prediction plot. This choice could be founded on several individual preconditions, which are explained in the next section.

3.4. Possible applications for the mathematical model

The developed mathematical model could be useful and valuable for several purposes within pharmaceutical development. Implementing the mathematical model, a suitable film coat composition for different needs could be chosen, using an optimized level for polymer blend ratio and film coat thickness (e.g. a minimum film coat thickness for a short process time or a specific polymer blend ratio, to reduce costs and viscosity or avoid incompatibilities). The mathematical model could also be used for reverse prediction of the drug-release profile, based on a given film coat composition, which might help to simplify and accelerate pharmaceutical development.

The developed model is only valid for the given system of CPM pellets with a defined drug load and pellet size. A transfer of the mathematical model to pellets with alternative drugs, to smaller starter cores (different surface areas) and to pellets with different drug loadings will be the next logical step. A uniform application of the model would be likely, but has to be proven by further investigations.

3.5. Predictability of the mathematical model

The predictability of the mathematical model was verified within two coating trials. A lag-time of 1.5 h was defined as aimed response value. Based on the model, two film coat compositions (C_1 and C_2) were chosen. Since the addition of plasticizer did not influence the drug-release profile, the plasticizer concentration in the composition was fixed to 5% (calculated on dry mass of both polymers, PVAc and PVA–PEG). Pellets were coated with the chosen film coat dispersion to the defined coating thickness, and the release profile was analyzed using dissolution rate studies (Table 4). The sigmoid fit was applied to the release profiles, and the lag-times were determined.

A lag-time of 1.2 h for sample C_1 and 1.3 h for sample C_2 was measured, demonstrating that the aimed lag-time of 1.5 h was almost achieved. The small difference between aimed and measured lag-times (0.3 and 0.2 h) was caused by the small difference between setpoint coating thickness and actual coating thickness (Table 4). The aimed coating thicknesses, from the predicted compositions, were missed during the coating process and the resulting thickness was marginally thinner than predicted (12.8% vs. 13.6% and 22.6% vs. 22.9%). Nevertheless, the prediction was successful, the aimed lag-time was achieved, the accuracy was acceptable and the mathematical model has thoroughly demonstrated its usefulness.

4. Conclusion

A three-level central composite design was implemented to investigate the influences of film coat thickness, PVAc/PVA–PEG blend ratio and plasticizer concentration on the drug release from film-coated CPM pellets. The film coat thickness as well as the PVAc/PVA–PEG blend ratio demonstrated a significant influence on the drug release, which resulted in an extended lag-time at thicker film coats and at higher PVAc ratios. In contrast, the plasticizer concentration did not affect the drug release. Analogous to drug release, the film coat thickness and the PVAc/PVA–PEG ratio demonstrate a significant influence on the solubilization speed inside the coated pellets, measured by EPR spectroscopy. The speed of solubilization was reduced with increasing coating thickness and higher PVAc ratio, emphasizing the solvent penetration into the pellets as the initial mechanistic step before drug release.

A mathematical model was developed connecting the important coating factors, film coat thickness and PVAc/PVA–PEG blend ratio, with the drug-release profile. The model provides predictions of usable film coat compositions, based on an aimed drug-release profile. Furthermore, the model allows predictions vice versa of drug-release profiles, based on a given film coat composition. The predictability was proven successfully, demonstrating the importance and worth of the mathematical model to simplify and increase flexibility in pellet coating within pharmaceutical development.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejpb.2008.11.005.

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