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Research paper

Mechanistic analysis of drug release from tablets with membrane controlled drug delivery

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Abstract

The objective of this study was to receive detailed information on the mechanism of drug release from polyvinyl acetate (PVAc)/polyvinyl alcohol–polyethylene glycol graft copolymer (PVA–PEG) coated Propranolol HCl and Theophylline tablets. For this purpose the coating composition (PVAc/PVA–PEG: 90/10 and 80/20) and the amount of the coating layer have been varied. Due to its better solubility Propranolol HCl showed higher release rates than Theophylline. As expected, a higher percentage of the water soluble polymer accelerated drug release. Increased coating thickness led to amplified lag times of drug release. The water uptake of the tablets was quantified by gravimetric analysis. Furthermore, the microenvironment of the tablet core was monitored by EPR spectroscopy. For this purpose a hydrophilic EPR spin probe was incorporated into tablets. Surprisingly, despite a lag phase at the beginning and a controlled drug release over 24 h, the results of the EPR studies indicated an immediate water penetration through the coating layer into the tablet core. The water is able to solubilise the majority of water soluble compounds within minutes. The results obtained in this study demonstrate, that EPR is a powerful method to monitor the first steps of diffusion processes and the physicochemical state of coated dosage forms.

Keywords: EPR; ESR; Controlled release; Tablet; Film; Coated dosage forms

1. Introduction

Sustained release oral dosage forms play a very important role at the pharmaceutical market [1,2]. Principles for drug retardation include coating of tablets, capsules and pellets, matrix or hydrocolloid embedding, osmotic controlled release and multiparticulate dosage forms. Since many drugs like e.g. antihypertensives demand constant plasma levels, controlled drug delivery systems are used to avoid high fluctuations of drug plasma levels and decrease the frequency of administration. This leads to reduced side effects and a better compliance.

In this study two different coating compositions for diffusion controlled release were analysed. The main component of the coating was Kollicoat SR 30 D, which is a suspension of 27% polyvinyl acetate (PVAc) stabilized with 0.3% sodium lauryl sulphate and 2.7% povidone which is a soluble pore forming polymer. PVAc characteristics are water insolubility, a low minimum film forming temperature of 18 °C and a high tensile strength. Elongation at break is up to about 400% with an amount of 15% propylene glycol as a plasticizer [3]. We incorporated also Kollicoat® IR in two different ratios as a water soluble polymer in the film to accelerate the drug release. This polymer is a polyvinyl alcohol–polyethylene glycol copolymer (PVA–PEG), which entered the pharmaceutical market very recently. As a highly flexible film former it may be applied as the soluble part in a diffusion-controlled release coating for tablets and pellets. Combined with PVAc a pH independent sustained release coating is obtained that is characterised by a much lower risk of dose dumping due to its high flexibility.

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After contact with the dissolution medium, the polymers will first begin to swell and absorb water. Swelling will continue until an equilibrium state is reached between the ambition of hydration that will promote the diffusion and the elastic strength of the polymer network on the opposite. As a second process dissolution of the polymer occurs that is eroding the film coating [4,5]. For this step a linear polymer or a sufficient hydrophilicity of the polymer is required so it can be solvated by the water in the dissolution medium. The water which penetrated the film coating is reaching the tablet core and increases the polarity and molecular mobility inside the tablet so that dissolution of the drug and water soluble excipients occurs.

In addition to investigate the impact of drug characteristics, coating composition and coating film thickness on drug release we were interested to explore the drug release mechanisms in more detail. A detailed understanding of the release mechanisms is required for a rationale based improvement of the release characteristics. Therefore we quantified the water uptake by gravimetric measurements and analysed the microenvironment inside the tablet core by EPR spectroscopy. EPR spectroscopy (Electron Paramagnetic Resonance spectroscopy, syn. ESR spectroscopy) is a powerful tool to get unique information on drug delivery processes [6–11]. The EPR spectra of nitroxides are sensitive to the microviscosity and micropolarity (and using special probes also for pH). The spectral shape is determined by the hyperfine structure, which results from the anisotropic interaction between the unpaired electron and the nuclear spin of the nitrogen of the -NO moiety [11]. As a result, a broad and anisotropic spectrum is observed for highly viscous and solid samples. The anisotropy is averaged as the mobility of the nitroxide increases (e.g. the viscosity decreases). The EPR spectra of nitroxide solutions in low viscous media (e.g. water) are characterised by three lines of almost the same amplitude. The EPR spectrum will be a superposition of two spectra (e.g. anisotropic and isotropic), if nitroxide molecules are localized in two environments with different viscosities (e.g. in solid material and in water). Because of the small line width, the EPR signal amplitude of rapid tumbling nitroxides (e.g. water solubilised) will be high. In contrast, anisotropic EPR spectra (dry solids) have low amplitudes and broad lines. As a result, the spectral contribution of solubilised nitroxides is easily visible at a very low percentage (e.g. 95% immobilised, 5% solubilised). A quantitative assessment can be performed by simulation and fitting of the EPR spectra. In our experiments, the hydrophilic spin probe PCM (*N*-3-carbamoyl-2,2,5,5-tetramethylpyrrolidin-1-yloxy) (Fig. 1) was incorporated into tablets as a hydrophilic model drug.

2. Materials and methods

2.1. Materials

Kollicoat® IR, Kollicoat® SR 30 D, Kollidon® 30 and Theophylline monohydrate were a kind donation from BASF (Ludwigshafen, Germany). MicroceLac® 100 was a gift from Meggle GmbH and Co. KG (Wasserburg, Germany). Talc and Propranolol HCl were purchased from Sigma–Aldrich (Taufkirchen, Germany). Titanium dioxide was supplied by Kronos Titan GmbH (Leverkusen, Germany). The EPR spin probe PCM (*N*-3-carbamoyl-2,2,5,5-tetramethylpyrrolidin-1-yloxy) was obtained by Prof. V.V. Khramtsov, Institute of Chemical Kinetics and Combustion, Novosibirsk, Russia.

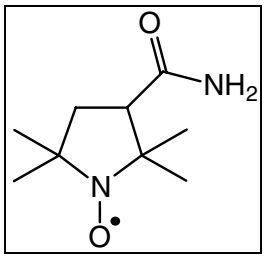

Fig. 1. Chemical structure of spin probe PCM.

2.2. Tablet preparation

The tablets had the following composition: 20% Propranolol HCl or Theophylline, respectively, 78.5% MicroceLac®100, 1% Aerosil®, 0.5% magnesium stearate. Propranolol HCl was chosen as a highly water soluble model drug (BCS I) whereas theophylline has poor water solubility characteristics (BCS IV) [12]. All formulation ingredients, except the magnesium stearate, were blended in a *z*-arm mixer (AR 400, Erweka, Germany) for 10 min. After addition of the magnesium stearate the powder mixture was blended for another 2 min. The tablets were compressed on a rotary tablet press (RL 12, Kilian GmbH and Co KG, Germany) with a compression force of 6 kN. Tablets weighed 310 mg (±15 mg) and measured 9 mm in diameter. For tablets containing EPR spin probe, 0.05 mmol PCM (Fig. 1), a hydrophilic spin probe with a log*P* value comparable to Theophylline, was dissolved in ethanol 70% and mixed in the *z*-arm mixer with 100 g of the powder mixture. The powder was dried at 40 °C in a drying oven for 48 h. This procedure was carried out to obtain a tablet powder with molecularly dispersed EPR spin probe PCM. The tablets were compressed on a rotary tablet press (Pharmapress 100, Korsch Pressen GmbH, Germany). Tablets weighed 500 mg (±25 mg) and measured 11 mm in diameter.

2.3. Film coating of tablets

Coating suspensions with two different PVAc/PVA–PEG ratios were prepared, modified according to [13]. Spray suspensions were containing triacetin (7.0 g), polyvinyl pyrrolidone (5.0 g), titanium dioxide (5.0 g), talcum (35.0 g) and distilled water (475.0 g). For formulation SR/IR-9/1 496.0 g Kollicoat® SR 30 D and 16.5 g Kollicoat® IR and for formulation SR/IR-8/2 435.0 g

Kollicoat® SR 30 D and 33.0 g Kollicoat® IR were added. Coating suspensions contained coating polymers in a 90%/10% and 80%/20% PVAc/PVA–PEG ratio, respectively, related to each other as dry mass. Triacetin, PVA–PEG and PVAc suspension were added to 300 ml distilled water and blended. Mixing was always carried out for 3 min using an Ultra Turrax (T 18 basic, Ika, Germany) at 18.000 rpm. Polyvinyl pyrrolidone (PVP) was diluted in 175 ml distilled water. After adding talc and titanium dioxide to the PVP solution the suspension was dispersed. Then the pigment suspension was incorporated into the polymer suspension and mixed again. The coating dispersion was stirred during the whole coating run to prevent settling using a blade stirrer (MR 25, MLW, Germany) at 100 rpm.

The tablets were coated in a drum coater (Lab-Coater GC-300, Glatt GmbH, Switzerland). The coating conditions were: inlet air temperature: 50 °C, air flow rate: 100 m^3/h, spray rate: 7.5 g/min, atomizing air pressure: 2.0 bar, drum speed: 10 rpm. During the coating process samples of 100 tablets were taken at 4, 6 and 8 mg polymer/cm^2, respectively.

2.4. Evaluation of the dissolved amount of Theophylline and Propranolol HCl

The dissolution tests were performed according to paddle method B in the USP 29 [14]. Therefore an automatic dissolution tester (PTWS 310, Pharmatest, Germany) was used. The dissolution conditions were set to 37 °C dissolution temperature and 50 rpm paddle speed. The first dissolution medium was hydrochloric acid with a pH of 1. After two hours the medium was changed to phosphate buffer with a pH of 6.8. The dissolved drug amount was determined by measuring the UV absorption at 290 nm (Propranolol HCl) and 272 nm (Theophylline), respectively, and calculated using the calibration equations of both drugs. Dissolution tests were carried out at least in triplicate.

2.5. Calculation of lag times

After extrapolating the approximately linear part of the dissolution slope to the abscissa it is possible to calculate the lag times at the initial phase of drug dissolution profiles.

2.6. EPR experiments

Propranolol HCl tablets containing EPR spin probe PCM in addition were used. Measurements were performed with an EPR spectrometer (Magnettech GmbH, Berlin, Germany) working at a microwave frequency of about 1.3 GHz. Measurements were carried out using the following parameters: B_0-field 49.0 mT, scan range 12 mT, scan time 60 s and modulation amplitude 0.21 mT.

Tablets were placed into a dissolution tester containing hydrochloric acid with a pH of 1. For EPR measurements, the tablets were removed from the dissolution medium and adhering water on the surface was removed using paper tissues (Carl Roth GmbH and Co., Karlsruhe, Germany). Each measurement was performed in triplicate.

For calculation of the mobile and immobile part of PCM ESR spectra, respectively, the software Nitroxide spectra simulation V. 4.99 from Biophysical laboratory EPR centre (Josef Stefan Institute, Ljubljana, Slovenia) was used (Fig. 8). For the immobile part of the spin probe the order parameter was set to 1.00 and the rotational correlation time to 3 ns. At first simplex optimisation was used followed by Monte Carlo optimisation. Spectra with an immobile part of nitroxide lower than about 15% could not be fitted with the used program with a high accuracy. Therefore in this study calculated amounts of mobile spin probe yield maximum values of about 80%.

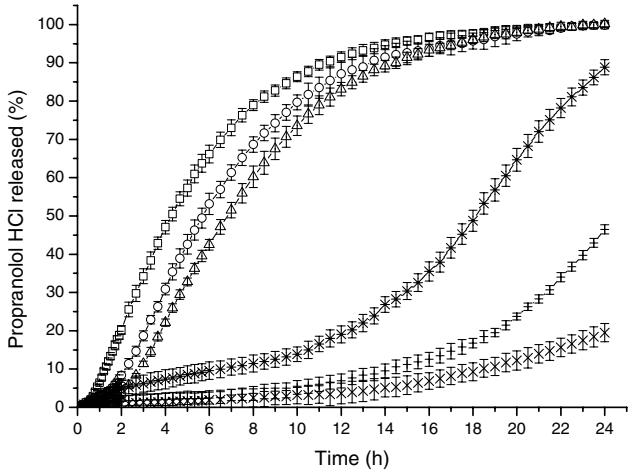

Fig. 2. Influence of coating level on Propranolol HCl release from tablets with coating formulation SR/IR-9/1 (*, 4 mg; +, 6 mg; ×, 8 mg polymer/cm^2) and formulation SR/IR-8/2 (□, 4 mg; ○, 6 mg; Δ, 8 mg polymer/cm^2).

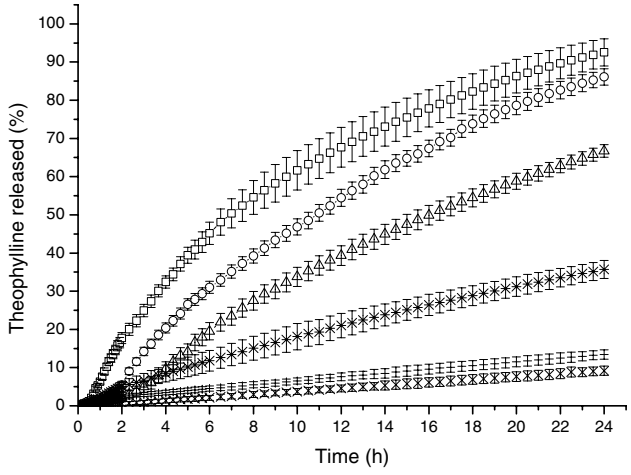

Fig. 3. Influence of coating level on Theophylline release from tablets with coating formulation SR/IR-9/1 (*, 4 mg; +, 6 mg; x, 8 mg polymer/cm^2) and formulation SR/IR-8/2 (□, 4 mg; ○, 6 mg; Δ, 8 mg polymer/cm^2).

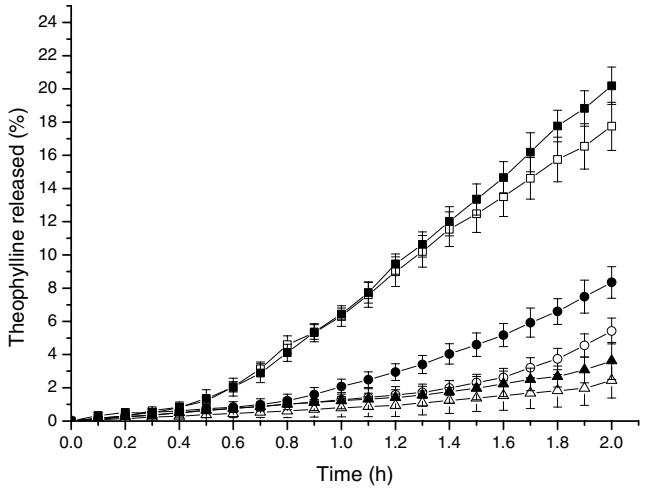

Fig. 4. Influence of coating level on lag time in Propranolol HCl (closed symbols) and Theophylline (open symbols) release from tablets with coating formulation SR/IR-8/2 (□, 4 mg; ○, 6 mg; Δ, 8 mg polymer/cm^2).

2.7. Evaluation of water uptake

Propranolol HCl tablets were placed into hydrochloric acid (pH 1) for the first 2 h and then transferred into phosphate buffer (pH 6.8). In predetermined intervals samples were taken and adhering water on the surface was removed using paper tissues. Then tablets were weighed and dried in a drying oven at 70 °C until constant mass. Water uptake was calculated as amount of penetrated water related to dry tablet mass. Measurements were carried out in triplicate.

3. Results and discussion

3.1. Dissolved amount of Theophylline and Propranolol HCl

In order to guarantee a reliable release, the amount of the coat was not lower than 4 mg polymer per cm^2. In all dissolution tests Theophylline tablets showed lower drug release rates compared to tablets with Propranolol HCl due to the poor water solubility of the drug (Figs. 2 and 3). Tablets with coating formulation SR/IR-9/1 exhibited no complete drug release for Theophylline and Propranolol HCl. Diffusibility of the film was too low due to a small amount of water soluble polymer PVA–PEG. Theophylline release behavior was approximately linear (Fig. 3) whereas Propranolol HCl delivery increased after an almost linear initial phase (Fig. 4). Due to a lower permeability an increasing coating thickness led to decreased drug release rates. As expected, drug delivery increased with a higher PVA–PEG concentration in coating formulation SR/IR-8/2 (Figs. 2 and 3). Dissolution profiles were characterised by an initial lag time with no drug release, followed by an increased permeability of the film coat (Fig. 4). Poor water solubility prevented complete theophylline release. Propranolol HCl tablets showed complete drug release within 24 h.

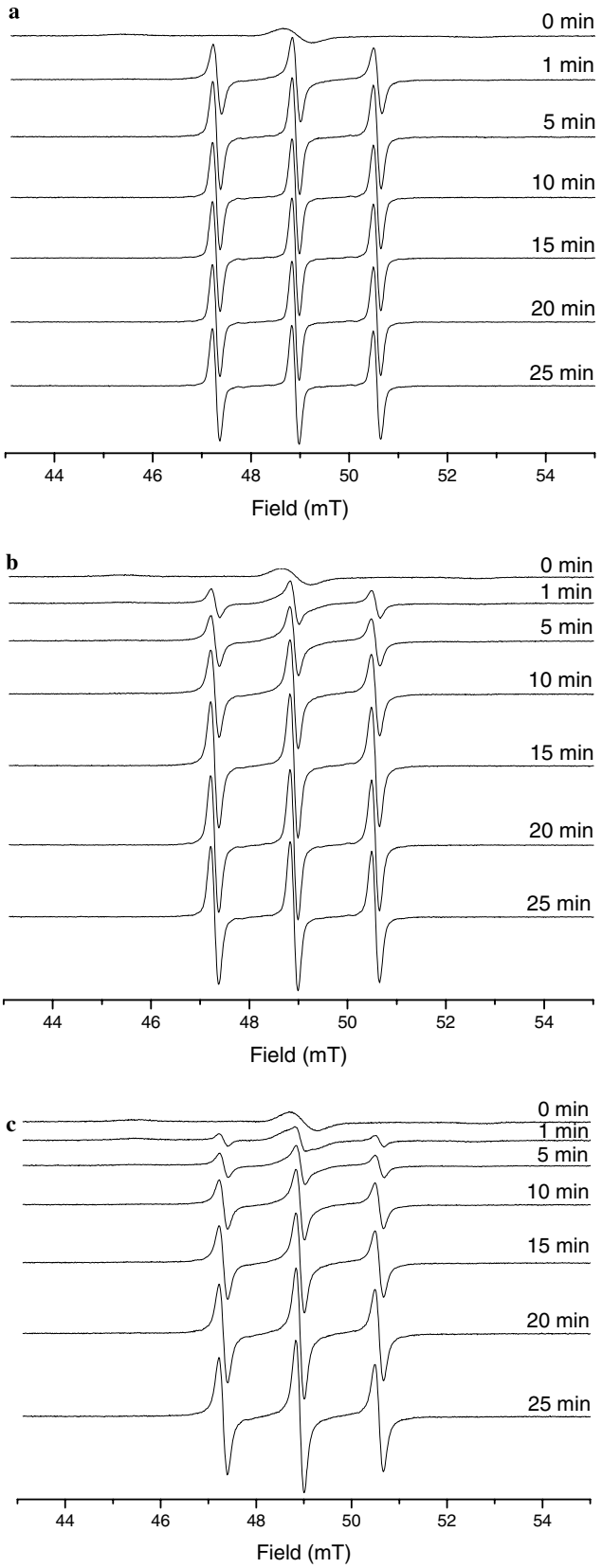

Fig. 5. (a) EPR spectra of PCM tablets with coating formulation SR/IR-9/1, 4 mg polymer/cm^2 after exposure to 0.1 N HCl. (b) EPR spectra of PCM tablets with coating formulation SR/IR-9/1, 6 mg polymer/cm^2 after exposure to 0.1 N HCl. (c) EPR spectra of PCM tablets with coating formulation SR/IR-9/1, 8 mg polymer/cm^2 after exposure to 0.1 N HCl.

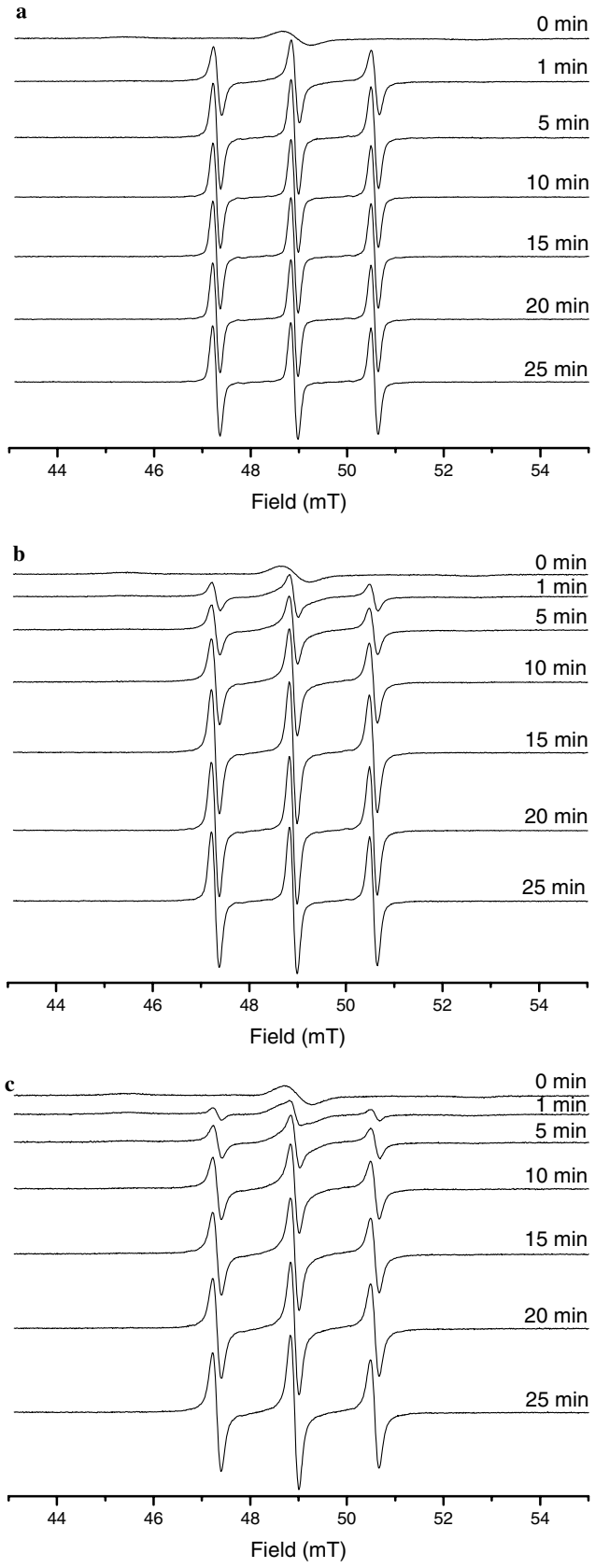

Fig. 6. (a) EPR spectra of PCM tablets with coating formulation SR/IR-8/2, 4 mg polymer/cm^2 after exposure to 0.1 N HCl. (b) EPR spectra of PCM tablets with coating formulation SR/IR-8/2, 6 mg polymer/cm^2 after exposure to 0.1 N HCl. (c) EPR spectra of PCM tablets with coating formulation SR/IR-8/2, 8 mg polymer/cm^2 after exposure to 0.1 N HCl.

3.2. Calculation of lag times

During the lag time at the beginning of the dissolution test the concentration of permeant in the film is building up. After water penetration of the film the drug inside the tablet is dissolved. It begins to diffuse through the film as permeability increases. The lag times for coating formulation SR/IR-8/2 were calculated. Propranolol HCl tablets showed the following lag times: 28 ± 4 min (4 mg/cm^2), 82 ± 2 min (6 mg/cm^2) and 104 ± 2 min (8 mg/cm^2). Lag times of Theophylline tablets were as follows: 28 ± 1 min (4 mg/cm^2), 84 ± 2 min (6 mg/cm^2) and 124 ± 4 min (8 mg/cm^2). Higher coating thickness led to slower water diffusion and increased lag times (Fig. 4). Differences in lag times were caused by the low water solubility of Theophylline. Due to its low permeability lag times for tablets with coating formulation SR/IR-9/1 were not calculated.

3.3. EPR experiments

EPR spectra of dry tablets are strong anisotropic and indicate a high immobilisation of the spin probe (Figs. 5 and 6a–c, 0 min). These are expected for randomly orientated nitroxides in solid samples. Positioning tablets into 0.1 N HCl led in all cases to changes in spectral shape and signal intensity. Surprisingly, already after 1 min exposure to the dissolution medium, the EPR spectra of all tablets were characterised by three narrow lines, which indicate a solubilisation of a certain percentage of the spin probe PCM by water molecules as a result of water penetration into the tablet. At this point neither Theophylline nor Propranolol HCl is released from the tablet core. The almost equal amplitude of the three EPR lines indicates the formation of a low viscous environment within the tablet core. The nitroxide PCM is now localized. A quantitative assessment of the percentage of solubilised/immobilized nitroxide molecules can be done by spectral simulation (Figs. 7–9). The contribution of the mobile part to the whole spectrum of the nitroxide increased steadily with time, indicating continuation of water penetration into the tablet core. Changes in spectral shape were more rapid for tablets with a lower coating thickness (Figs. 5 and 6a) than compared to ones with a higher coating amount (Figs. 5 and 6b–c), indicating that changes in molecular mobility were dependent on coating thickness showing lower permeability with increased coating amounts. After 10 min (4 mg polymer/cm^2), 20 min (6 mg polymer/cm^2) and 25 min (8 mg polymer/cm^2), respectively, the maximum detectable amount of mobile EPR spin probe is reached (Figs. 8 and 9). Similar spectral changes were detected for tablets with both coating formulations. As film coating SR/IR-9/1 shows a significantly lower permeability for Theophylline and Propranolol HCl than formulation SR/IR-8/2, it was interesting to see that the EPR spectra were quite similar. Only for tablets with a coating application of 8 mg polymer/cm^2 a slightly

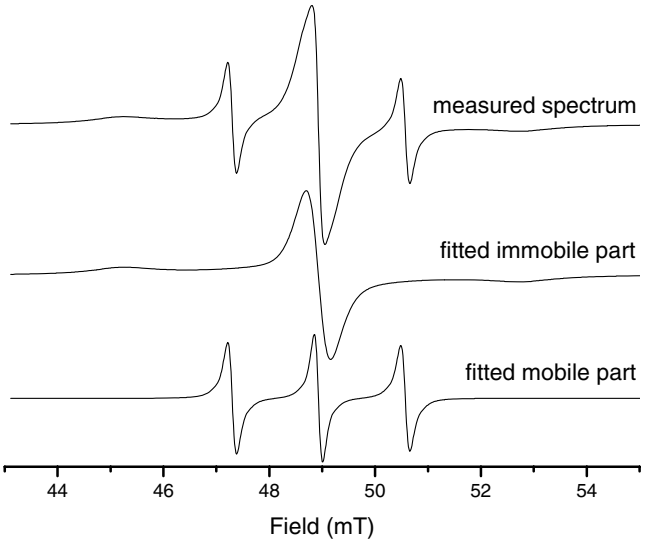

Fig. 7. EPR spectrum of PCM tablet with coating formulation SR/IR-8/2, 8 mg polymer/cm^2, 5 min after 0.1 N HCl exposure and fits for immobile and mobile part of spin probe by nitroxide spectra simulation.

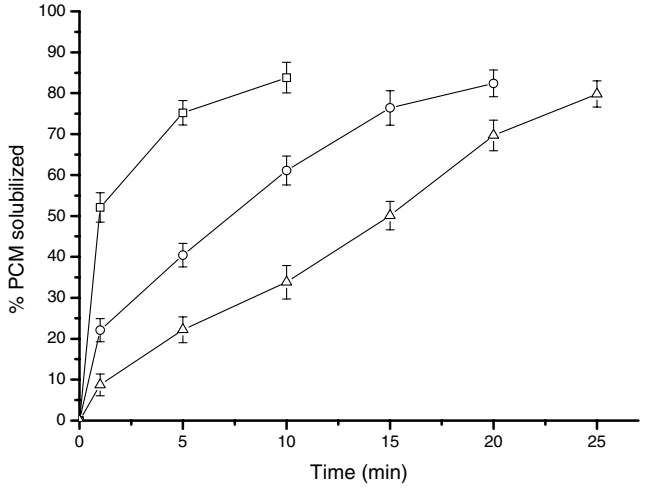

Fig. 8. Influence of the coating level on the solubilisation of the nitroxide PCM in the tablet core with coating formulation SR/IR-9/1 (□, 4 mg; ○, 6 mg; Δ, 8 mg polymer/cm^2).

decreased contribution of the mobile part to the whole nitroxide spectrum could be detected.

3.4. Evaluation of water uptake

In addition to the EPR experiments, the water uptake into tablets was determined gravimetrically. It could be shown once again that water penetration was dependent on coating thickness (Figs. 10 and 11). Tablets with a low coating thickness demonstrated fast water penetration behavior, whereas higher coating film thickness led to initially reduced water permeability with a subsequent rise. Due to the beginning dissolution of the water soluble polymer diffusibility of the film increases. These results agree

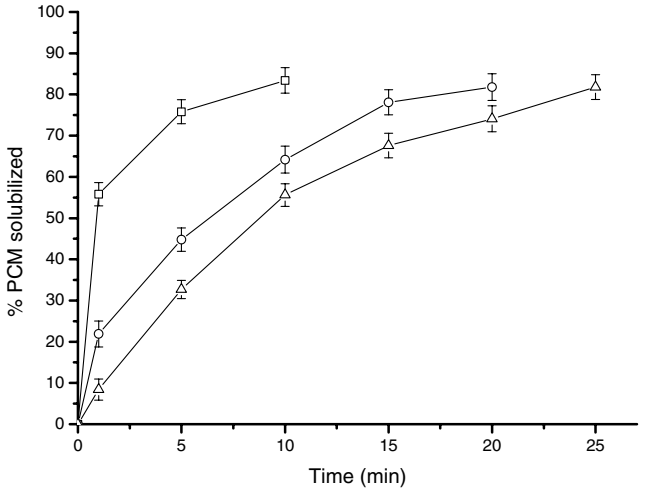

Fig. 9. Influence of coating level on the solubilisation of the nitroxide PCM in the tablet core with coating formulation SR/IR-8/2 (□, 4 mg; ○, 6 mg; Δ, 8 mg polymer/cm^2).

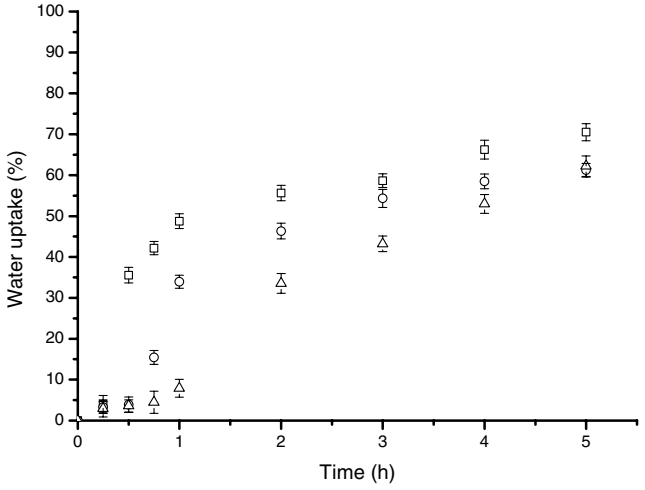

Fig. 10. Influence of coating level on water uptake into tablets with coating formulation SR/IR-9/1 (□, 4 mg; ○, 6 mg; Δ, 8 mg polymer/cm^2).

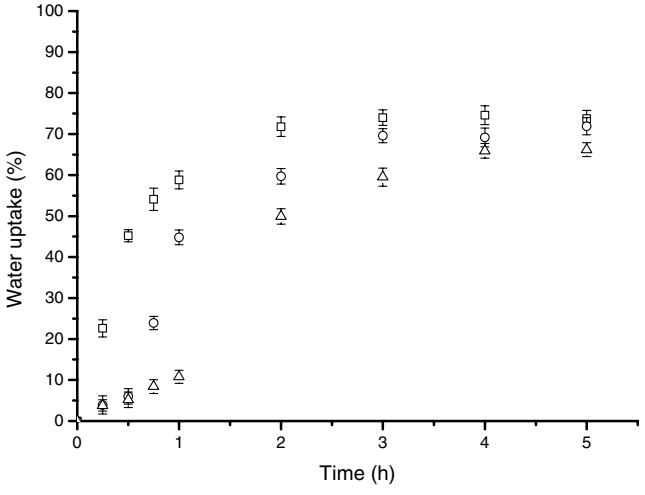

Fig. 11. Influence of coating level on water uptake into tablets with coating formulation SR/IR-8/2 (□, 4 mg; ○, 6 mg; Δ, 8 mg polymer/cm^2).

with the determined lag times at the beginning of drug release for coating formulation SR/IR-8/2.

Comparing the kinetics of water uptake (Figs. 10 and 11) with the kinetics of PCM solubilisation (Figs. 8 and 9) it becomes clear that even few percentage of water are sufficient to solubilise large amounts of the hydrophilic model drug PCM within the tablet core.

The coating composition had only a small influence on water diffusion into tablets as can be seen in only little differences in water uptake for both coating formulations. After 5 h water uptake values for all samples are similar. Water uptake of 80% is not leading to a macroscopically damaged coating surface, which demonstrates a high flexibility of the film that might reduce the danger of dose dumping.

4. Conclusion

The present work contributes to a more profound understanding of permeation processes through polymer film coatings using noninvasive methods. The findings of this study demonstrate that for Propranolol HCl tablets with a coating formulation containing 20% PVA–PEG and 80% PVAc (related to each other as dry mass) a complete and sustained drug delivery is achieved within 24 h with different release profiles. Water penetration into tablets occurs very rapidly as can be seen in a fast change in molecular mobility for all tablet samples. In contrast to drug release, water permeation is only marginally dependent on PVA–PEG content, as changes in the molecular mobility of the micro environment of the spin probe PCM are detected within one minute for both coating formulations and show similar characteristics in further water permeation process. These findings were also underlined by the results of the characterisation of water uptake behavior. For the first time the initial steps of diffusion processes through film coatings were monitored noninvasively and continuously by using EPR spectroscopy.

In summary, the release rates depend on drug solubility, coating composition and coating level. Water penetration through the Kollicoat films occurs within few minutes. The penetrated water is able to solubilise water soluble molecules inside the tablet core efficiently. Water uptake continues in most cases for 1–2 h at a high rate and slows down thereafter. Drug release rates increase after the water penetration slows down. We conclude that the lag time of drug release does not contradict the observed rapid water uptake, because water transport is one way directed from outside to inside for the first 1–2 h. Drug release becomes only efficient after the tablet core is water saturated and the transport processes through the membrane become diffusion controlled in both directions.

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