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Polymer leaching from film coating: Effects on the coating transport properties

Mariagrazia Marucci[a,b,*], Gert Ragnarsson[c], Christian von Corswant[b], Anette Welinder[b], Annica Jarke[b], Frida Iselau[b], Anders Axelsson[a]

[a] Department of Chemical Engineering, Lund University, P.O. Box 124, SE-221 00 Lund, Sweden
[b] AstraZeneca R&D Mölndal, SE-431 83 Mölndal, Sweden
[c] Medical Products Agency, P.O. Box 26, SE-751 03 Uppsala, Sweden

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ABSTRACT

The release mechanism of metoprolol succinate pellets coated with a blend of a water-insoluble polymer, ethyl cellulose (EC), and a water-soluble polymer, hydroxypropyl cellulose (HPC), is mechanistically explained. The kinetics of drug release and HPC leaching were followed for drug doses. The coating was initially not permeable to the drug, and release started only after a critical amount of the HPC had been leached out. Drug release occurred mainly through pores created in the coating by the HPC dissolution. Single-pellet release experiments were also performed. The coating thickness and size of each pellet were measured. In order to quantitatively characterize the transport properties of the coating of the individual pellets, and to determine the effective diffusion coefficient (D_e) of the drug in the coating, a mechanistic model was used to fit the single-pellet release data. It was found that D_e increased with time due to an increase in the amount of HPC leached. It was also found that D_e was dependent on the coating thickness, and increased more slowly with a thicker coating. This agreed well with the finding that the HPC leaching rate decreased with increasing film thickness.

1. Introduction

The blending of water-insoluble and water-soluble polymers for the controlled release of drugs from coated formulations has been described many times in the literature (Donbrow and Samuelov, 1980; Lindstedt et al., 1989; Umprayn et al., 1999; Tang et al., 2000; Lecomte et al., 2005; Strubing et al., 2007). The existence of a critical concentration of the water-soluble polymer, above which the water permeability and/or the drug permeability of the film increases drastically, has been observed in several cases (Tang et al., 2000; Lecomte et al., 2005; Marucci et al., 2009). For films made of ethyl cellulose (a water-insoluble polymer) and hydroxypropyl cellulose (a water soluble polymer), we have previously shown for water-soluble drugs that below the critical concentration the release mechanism is mainly osmotic pumping (Marucci et al., 2009, 2010), while above it the diffusional contribution becomes increasingly more significant (Marucci et al., 2009). A sigmoid release profile, showing a lag phase with an initially slow release rate followed by a gradual increase in the release rate, has been observed in many cases. During the lag phase the solvent crosses the coating, mass accumulates inside the formulation (Ensslin et al., 2008) and a hydrostatic pressure builds up (Marucci et al., 2008, 2009). In systems where cracks are not developed in the coating due to the pressure build-up, the length of the lag phase depends on the time required for the water-soluble polymer to leach out, creating a pore system that connects the inside of the formulation with the release medium (Marucci et al., 2009).

During drug release, changes take place in the composition and structure of coating films composed of polymer blends due to leaching of the water-soluble polymer. We, recently, qualitatively studied the effects of the leaching of the water-soluble polymer on the properties of free films using a novel release cell. Free films of the water-insoluble ethyl cellulose (EC) and water-soluble hydroxypropyl cellulose (HPC) were investigated (Marucci et al., 2009). As HPC is not compatible with EC, phase separation occurs during the film formation process, resulting in regions very rich in HPC (Sakellariou et al., 1986, 1988; Sakellariou and Rowe, 1995). We have shown that the free films are initially not permeable to the drug, but films containing a high amount of HPC become permeable due to HPC leaching. However, the effects of the leaching of the water-soluble polymer on the transport properties of the EC/HPC films were not quantitatively characterized. Moreover, no coated formulations were used in that study.

Coated pellets can be compacted into a multiple-unit tablet or used to fill capsules, and are commonly used in oral modified release formulations. The overall release is determined by the

* Corresponding author at: AstraZeneca R&D Mölndal, SE-431 83 Mölndal, Sweden. Tel.: +46 31 7064532; fax: +46 31 7763729.
E-mail addresses: mariagrazia.marucci@astrazeneca.com, mariagrazia.marucci@gmail.com (M. Marucci).

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release from each single pellet, thus in order to fully understand the overall release, a mechanistic understanding of single-pellet release is required (Hoffman et al., 1986). When the drug release occurs by diffusion, the main factors that affect the release profile of a single pellet are: pellet size, drug load, coating thickness, D_e of the drug in the coating and drug solubility. A large number of studies have been devoted to mathematically describe the diffusional drug release from multiparticulate matrix systems and multiparticulate film-coated reservoir systems (Watano et al., 1995; Frenning et al., 2003; Haddish-Berhane et al., 2006). The aim of these studies was often to calculate D_e by tuning the model to fit the experimental data. However, the majority of these studies do not take into account the differences between pellets, dose release data are used and the calculations are based on an ideal "average" pellet. Thus, the calculated D_e is an averaged parameter. This is acceptable if the differences between the release profiles of the individual pellets are small. However, as the differences become larger, the results may be misleading and the calculated D_e may not have a physical meaning. The heterogeneity in pellet size and film coating thickness of the pellets is considered in some more complete models (Sirotti et al., 2002; Manca and Rovaglio, 2003). However, the film coating of each pellet is assumed to have the same D_e, and the value of D_e calculated from the whole dose release should still be regarded as an average value of the parameter. Borgquist et al. (2004) used single-pellet release data to determine the D_e for a single pellet, but their calculations were based on the dose average diameter and average coating thickness, which compromises the accuracy of the calculations. To the best of our knowledge, the values of D_e reported so far in the literature should be regarded as averaged values, as the calculations are based on the average values of some important parameters.

The aims of this study were: (a) to characterize the release mechanism of a water-soluble drug from pellets coated with a film consisting of a blend of a water-insoluble (EC) and a water-soluble (HPC) polymer; (b) to characterize the leaching of the water-soluble polymer from the coating; and (c) to quantitatively investigate the effects of the leaching of the water soluble polymer on the transport properties of the film. The last-mentioned effects were studied by using a validated mechanistic model to calculate the D_e of the drug in the coating of single pellets. The drug contained in the pellets was metoprolol succinate, which is a water-soluble drug.

The combination of the many experiments presented in this study and of the mathematical modelling is novel for pellets coated with polymer blends and consented the accurate determination of D_e. Single-pellet release data were used in the calculations and, uniquely, the pellet size and coating thickness of the pellets used in the single-pellet release experiments were measured. Thus, the value of D_e was not an average value but was truly characteristic of the coating of each individual pellet. The most important advantages of this are: (1) the possibility of accurately studying the homogeneity of the transport properties of the coating on different pellets, and (2) the possibility of relating D_e to the coating thickness for each pellet.

2. Theory

The type of pellet considered in this study consists of a solid core coated with a polymer film, in which the release is drug-diffusion controlled. The following assumptions were made:

- the pellets are spherical,
- each pellet has a coating of a uniform thickness and
- the drug concentration in the solution inside the pellet is homogeneous and not dependent on the position inside the core.

The model used has been validated in previous studies (Grassi et al., 2007).

2.1. Drug dissolution

The dissolution process is described by the Noyes-Whitney equation (Noyes and Whitney, 1897):

$$\frac{dV_c}{dt} = -4\pi r_c^2 k_{diss}\left(\frac{c_{sat} - c_s}{\rho_c}\right) \quad (1)$$

where V_c is the volume of the solid core, r_c is the radius of the core, ρ_c is the density of the solid phase of the drug, k_{diss} is the dissolution rate constant, which describes the mass transfer rate from the solid core into the internal dissolved phase, c_s is the drug concentration in the dissolved phase within the pellet, and c_{sat} is the drug concentration at the solid surface, and is assumed to be at saturation. The dissolution rate constant can be estimated using a mass transfer equation:

$$k_{diss} = \frac{D}{r_c}(1 + 0.3Re^{0.5}Sc^{0.33}) \quad (2)$$

where D is the diffusion coefficient of the drug in an aqueous solution, Re is the Reynolds number and Sc is the Schmidt number. Manca and Rovaglio (2003) showed that the product $Re^{0.5}Sc^{0.33}$ is very small, and that k_{diss} could therefore be written as:

$$k_{diss} = \frac{D}{r_c} \quad (3)$$

2.2. Mass balance in the dissolved phase within the pellet

Assuming the internal dissolved phase to be well mixed, the mass balance in this phase can be written as:

$$\frac{d(c_s V_s)}{dt} = 4\pi r_c^2 k_{diss}(c_{sat} - c_s) - k_T 4\pi r_e^2 (c_s - c_{rel}) \quad (4)$$

where V_s is the volume of the dissolved phase, r_e is the radius of the coated pellet and c_{rel} is the drug concentration in the release medium. The overall mass transport coefficient, k_T, depends on the mass transfer coefficient in the boundary layer near the internal coating surface, k_{ic}, the mass transfer coefficient of the coating, k_c, and the mass transfer coefficient in the boundary layer in the release medium near the external coating surface, k_{ec}. It can be written as follows:

$$\frac{1}{k_T} = \frac{1}{k_{ic}(r_i^2/r_e^2)} + \frac{1}{k_c(r_i/r_e)} + \frac{1}{k_{ec}} \quad (5)$$

where r_i is the coating inner radius. The mass transport coefficient of the drug in the coating, k_c, is related to the effective diffusion coefficient of the drug in the coating, D_e, which can be written as:

$$D_e = k_c h \quad (6)$$

where h is the coating thickness.

The mass transport, k_{ic}, was estimated in a similar way as k_{diss}. The mass transfer coefficient k_{ec} was calculated using Eq. (2) and the Re number was calculated using a relative velocity between the pellet and the dissolution medium equal to 10^{-3} m/s (Borgquist et al., 2002).

2.3. Mass balance for the release medium

The mass balance in the release medium can be written as:

$$\frac{d(V_{rel}c_{rel})}{dt} = 4\pi r_e^2 k_T(c_s - c_{rel}) \quad (7)$$

where V_{rel} is the volume of the release medium.

3. Materials and methods

3.1. Materials

EC (EC N10CR) was supplied by The Dow Chemical Company, USA. HPC grade LF was supplied by Aqualon, USA. The uncoated pellets consisted of a SiO_2 particle surrounded by metoprolol succinate and were produced at AstraZeneca Södertälje, Sweden. The drug load of the uncoated pellets was 60%.

3.2. Preparation of the coated pellets

Metoprolol succinate pellets were sprayed with a mixture containing 8% (w/w) of the coating polymer and 92% (w/w) ethanol (95%) in a bottom spray fluidized bed (MiniGlatt 7070, Glatt GmbH). The EC/HPC polymer blend ratio used was 70:30. The process parameters used for coating were as follows: product temperature between 47 and 41 °C, spray rate between 2.2 and 3.6 g/min, atomization pressure 1.1 bar, nozzle diameter 0.5 mm and dew point 4 °C. Two batches of coated pellets were produced, one with a polymer coating of 33 g polymer/100 g coated pellets (pellets with a thin coating) and the other with 44 g polymer/100 g coated pellets (pellets with a thick coating).

3.3. Dimensions of the pellets used in the single-pellet release studies

Five pellets were randomly selected from each batch and their size determined with a light microscope (Zeiss Axioplan) equipped with a camera (Zeiss Axioplan HRc). Two images were acquired for each pellet, with different sides facing the light source. The images were analysed with the built-in software (Axiovision) and the projected area, A_p, was determined. The radius of the projected area was calculated as $r_e = \left(\sqrt{A_{p1}/\pi} + \sqrt{A_{p2}/\pi}\right)/2$, where A_{p1} and A_{p2} are the two projected areas determined for each pellet.

3.4. Film coating thickness determination for the pellets used in the single-pellet release studies

The pellet coating was imaged using a Nikon C1 laser scanning confocal unit (Nikon D-Eclipse C1) attached to an inverted fluorescence microscope (Nikon Eclipse TE 2000-e) equipped with a krypton/argon laser (wavelength 405 nm). The confocal fluorescence images were obtained using a 20× objective. EC fluoresces at the wavelength used, so no dye was added to the coating. Four *z*-scans were performed for each pellet. Images of the coating were obtained in the *x*–*z* and *y*–*z* planes from the series of *z*-images. The coating thickness was then determined from the images of the coating in the *x*–*z* and *y*–*z* planes. The coating thicknesses determined from the images were multiplied by the refractive index of EC to correct for the difference in the refractive index between air and the coating.

3.5. Pellet size distribution, average coating thickness and pellet density

The particle size distribution of the SiO_2 cores, the uncoated pellets (SiO_2 core plus drug) and the coated pellets was measured using a system for automatic analysis of dry particles (BeadCheck™ 830, PharmaVision Systems, Lund, Sweden). The average coating thickness was obtained by comparing the average size of the uncoated and the coated pellets. The average radius of the uncoated pellets and the thickness of the thin and thick coatings are reported in Table 1.

Table 1
Parameters used in the calculations and average geometric values.

Metoprolol succinate solubility in water at 37 °C	276 kg/m^3
Average radius of an uncoated pellet	200 μm
Average thickness of the thin coating	34 μm
Average thickness of the thick coating	44 μm
Diffusion coefficient of the drug in a 5 g/l drug solution at 37 °C	7.6×10^{-10} m^2/s
Diffusion coefficient of the drug in a 155 g/l drug solution at 37 °C	4.9×10^{-10} m^2/s
Density of the solid phase of the drug	1200 kg/m^3

The density of the solid drug was calculated from the measured average weight of an uncoated pellet, the measured average radius of a SiO_2 core and that of an uncoated pellet, and the drug load of an uncoated pellet.

3.6. Diffusion coefficient of metoprolol succinate in water

The diffusion coefficient of metoprolol succinate in water at 37 °C at concentrations of 150 and 5 g/l, was measured using a holographic technique, electronic speckle pattern interferometry. The method has been described in detail elsewhere (Marucci et al., 2006). The measured diffusion coefficients were 4.9×10^{-10} m^2/s (150 g/l) and 7.6×10^{-10} m^2/s (5 g/l). The diffusion coefficient at 5 g/l was used to calculate k_{ec}, while the diffusion coefficient at 150 g/l was used to calculate k_{ic} and k_{diss}.

3.7. Coating film morphology

The morphology of the coating film was studied before and after the pellets had been immersed in the release medium for 50 min using scanning electron microscopy, SEM (SEM Quanta 200, FEI Company). The value of the voltage used was 10 kV. The pellets were coated with a thin layer of gold in an ion-sputtering device before observation (Cressington sputter coater 108 auto).

3.8. Single-pellet release

The single-pellet release was determined using an absorbance microplate reader (SpectraMax M2, Molecular Devices) set at an absorbance wavelength of 274 nm. The pellets were gently inserted with a spoon on the wells of the microplate. For each pellet a release medium consisting of 300 μl of a phosphate buffer solution, pH 6.8, was used. The system was continuously agitated and thermostatted to 37 °C. Measurements were made over time to characterize the release profile. As the absorbance of the release medium is proportional to the height of the release medium multiplied by the drug concentration and, as the absorbance was kept in the region where the dependency between the concentration and the absorbance is linear, the limited evaporation did not affect the measurements. Sink conditions were maintained.

3.9. Drug and HPC release from a whole dose

Pellets dose release experiments were performed at 37 °C using a Prolabo dissolution tester. The drug content of a dose of pellets with a thin coating was 200 mg. The drug content of a dose of pellets with a thick coating was 126 mg. The HPC content of a dose was 49.5 mg for both kinds of pellets. A dose of pellets with a thin coating consisted of about 8500 pellets, whereas a dose of pellets with a thick coating consisted of about 5350 pellets. A stirring rate of 75 rpm was used. The release medium was 500 ml phosphate buffer, pH 6.8. Samples of 1.5 ml were collected at predetermined times. Sink conditions were maintained. The drug concentration was determined with a spectrophotometer at an absorbance wave-

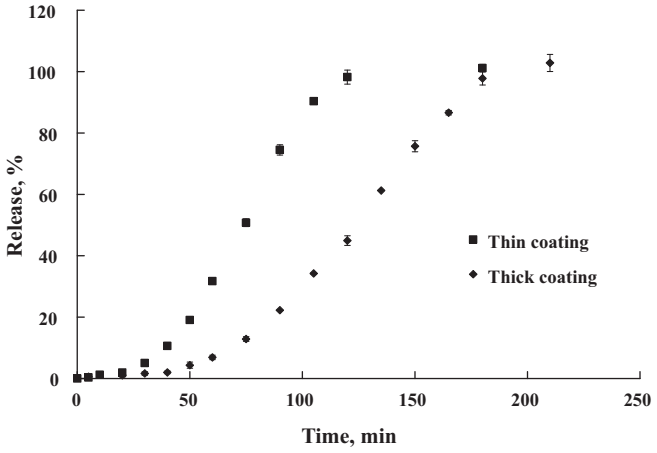

Fig. 1. Influence of film coating thickness on the drug release from a dose.

length of 274 nm, while the HPC concentration was determined with a size exclusion chromatography column equipped with a refractive index detector.

4. Results

4.1. Drug and HPC release from a dose

The drug dose release profiles from pellets with a thin and a thick EC/HPC coating are shown in Fig. 1. A sigmoid release profile was obtained in both cases. The lag times were 20 and 40 min for the thin and thick coatings, respectively, during which no drug was released. This was followed by a phase during which rapid drug release occurred. In a previous study on free films of EC/HPC, we showed that the films were initially not permeable to the drug investigated, that the lag time was determined by the time required for pores to be created in the film due to HPC leaching and that the release occurs mainly through the water-filled pores (Marucci et al., 2009).

In order to understand how HPC leaching affects the structure of the coating film, SEM images of the coating were obtained before and after wetting. No pores were observable in the coating of pellets that had not been exposed to the release medium, as can be seen in Fig. 2A. HPC leaching produced small pores in the coating of pellets that had been exposed to the release medium, as can be seen in Fig. 2B.

HPC leaching from the film coating of the pellets was studied quantitatively in order to gain an understanding of how the composition and transport properties of the coating changed with time. HPC leaching starts immediately, as can be seen in Fig. 3. The HPC leaching profile depends on the film thickness, and a slower release rate was observed for the thicker coating. When all the drug had been released, 33% and 28% of the HPC present in the coating had been leached out from the pellets coated with the thin and thick films, respectively. Forty percent of the HPC initially present in the coating was leached out after 12 h for the pellets with a thin coating, and after 24 h for the pellets with a thick coating.

Upon comparing the drug release profile with the HPC release profile, it was found that drug release started when the amount of HPC leached was about 8%, for both the thin and thick film coating. It seems that a critical amount of HPC has to be leached out for the coating to become porous, allowing drug release. As HPC is released, the coating will become increasingly more porous and the effective diffusion coefficient of the drug in the coating will increase. This can be partially confirmed by comparing the amount of drug released in the decaying phase with that theoretically expected for a pellet coated with a film for which the effective diffusion coefficient of the drug is constant. This theoretical fraction, F, can be calculated from Eq. (8).

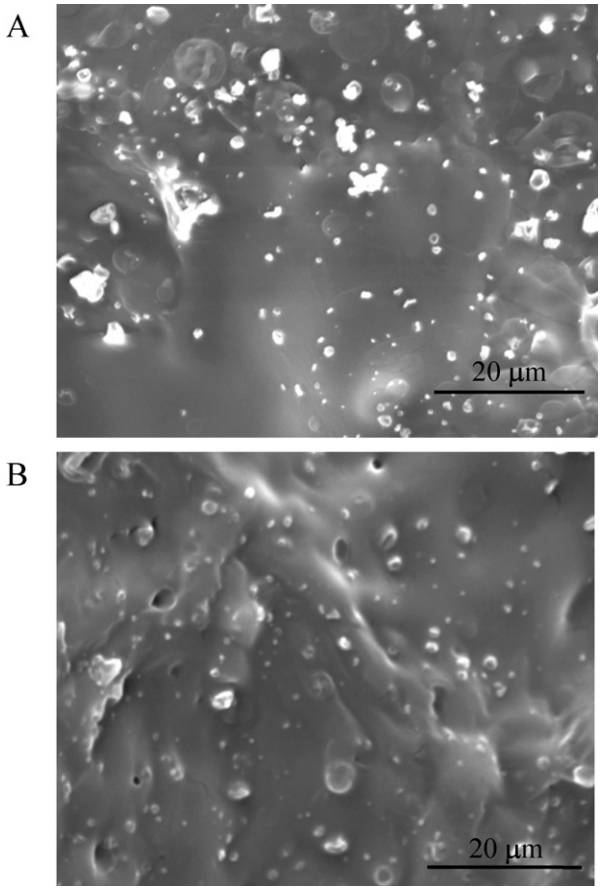

Fig. 2. SEM images of the pellet coating before (A) and after (B) the pellets were in contact with the release medium for 50 min for pellets belonging to the batch with a thick coating. Pores can be seen on the surface of the pellets that had been in contact with the release medium due to HPC dissolution and leaching in the release medium.

$$F = \frac{c_{sat}}{\rho_c} \tag{8}$$

The amount of drug released in the decaying phase, about 10% for both batches, was much lower than that theoretically predicted, 23%. This indicates that the effective diffusion coefficient of the drug in the coating at dose level increases with time, i.e. increases with

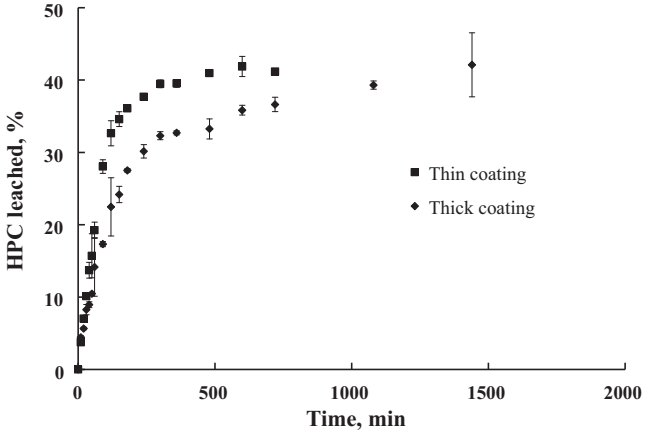

Fig. 3. Influence of film coating thickness on the HPC release from a whole dose. The HPC leaching calculation is based on the amount originally present in the coating.

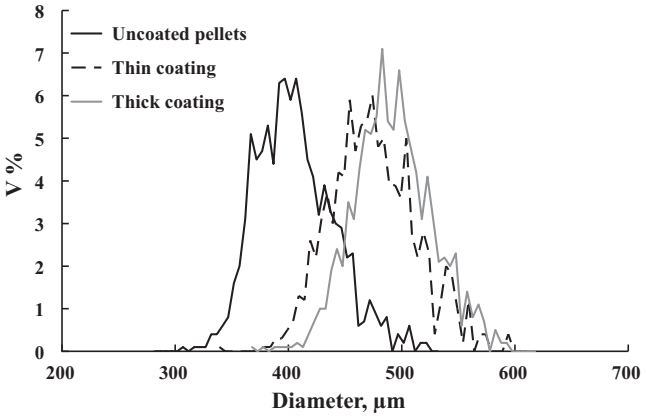

Fig. 4. Particle size distributions of uncoated and coated pellets.

HPC leaching. The effective diffusion coefficient of the drug in the coating, calculated for the entire dose, may be different from that calculated for a single pellet. It has also been shown than that dose release profiles can be misleading in some cases when the release process is mechanistically studied, when there are large differences between the release profiles of the single pellets (Hoffman et al., 1986). Studies of the characteristics of individual pellets revealed differences in the pellet size and coating film thickness, as can be seen in Fig. 4, which will affect the individual release profile. Moreover, there may be differences between the structures of the coating on different pellets. Single-pellet release experiments are therefore necessary to properly study how the leaching of the water-soluble polymer influences the most important parameter of drug release, i.e. the effective diffusion coefficient of the drug in the coating.

4.2. Single-pellet release and calculation of the effective diffusion coefficient for thin- and thick-coated pellets

The results of the single-pellet release experiments are shown in Fig. 5. Five pellets, randomly chosen from each batch, were studied. The release is reported in mg to enable a comparison between the drug content of different pellets. As was seen in whole dose release, the release profiles had a sigmoidal shape, i.e. were characterized by an initial lag phase with no or marginal drug release, followed by rapid release. The release profiles were rather homogeneous in terms of the final amount of drug released, which means that the pellets had a similar drug load. The release profiles also had a similar shape, and only one of the five pellets investigated in each batch showed a slightly higher release rate. The amount of drug released in the decaying phase was lower than that predicted theoretically,

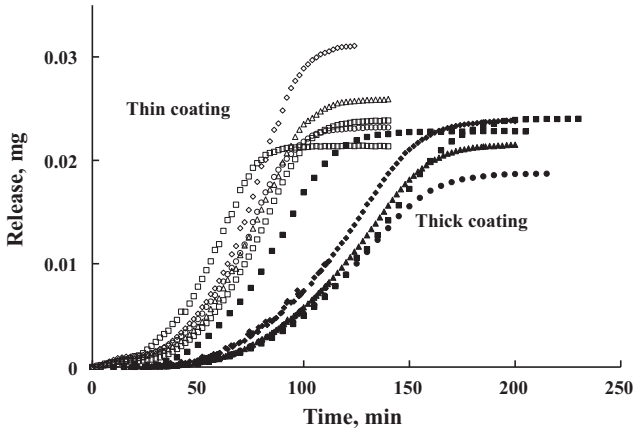

Fig. 5. Single-pellet release profiles for pellets from the batch with a thin coating (empty symbols) and pellets from the batch with a thick coating (full symbols).

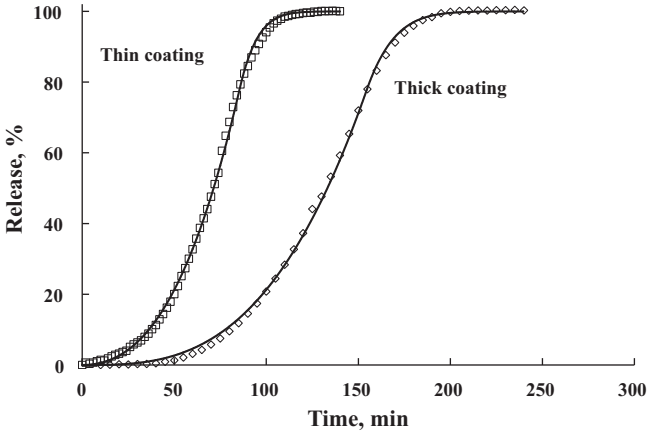

Fig. 6. Typical single-pellet release data (symbols) and simulations provided by the mathematical model (curves) for pellets belonging to the batch with a thin coating and pellets belonging to the batch with a thick coating.

which means that the initial assumption of increasing effective diffusion coefficient with time is valid not only at the total dose level, but also at the single-pellet level.

The effect of HPC leaching on the effective diffusion coefficient of the drug in the coating of individual pellets was studied. The model described above was used to fit the experimental data and to calculate the D_e of the drug in the coating. D_e was the only parameter tuned in the model as each pellet had been characterized in terms of size and film coating thickness before the release experiments. The coating thickness on each pellet was rather homogeneous. For the thin-coating batch, the thickness of the coating varied between 30 and 36 μm, and the standard variation for each pellet varied between 2 and 4 μm. For the thick-coating batch the thickness of the coating varied between 39 and 45 μm, and the standard variation for a single pellet also varied between 2 and 4 μm. For the thin-coated batch, the radius of the coated pellets varied between 230 and 267 μm. For the thick-coated batch, the radius of the coated pellets varied between 230 and 261 μm. The drug load was calculated from the final amount of drug released. The radius of the internal SiO_2 core was calculated from the drug load and the density of the solid phase of the drug.

As the properties of the coating change with time, due to HPC leaching, D_e was not assumed to be constant in the mathematical model. Different mathematical expressions can be chosen to describe D_e If the pellet core contains drug even when all the leachable water-soluble-polymer has been leached out, D_e increases during the release process until it approaches a constant value if the diffusion coefficient of the drug in the drug solution does not vary with the drug concentration. In this case, a function that increases and finally reaches a plateau is suitable. In this study, the HPC leaching process is longer than the drug release process, and thus D_e does not reach a constant value. A third-order polynomial function was found to be suitable to describe D_e. In this function the independent variable was the time. Fig. 6 shows typical experimental release data and simulated release profiles. The agreement between experimental and simulated curves is very good. However, it should be borne in mind that when the drug concentration inside the pellet approaches the drug concentration in the dissolution medium, the driving force for drug release becomes zero. This means that possible errors in the calculation of D_e in the late release phase will not be evident when comparing the experimental and the simulated release curves. The value of D_e reported in Fig. 7 was calculated from the time at which release starts until 80% of the drug had been released. As the driving force for drug release is still high when 80% of the drug has been released, the value of D_e is accurate.

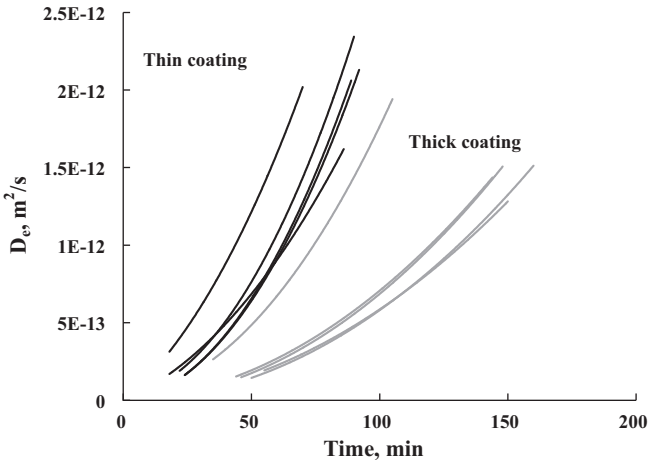

Fig. 7. Calculated effective diffusion coefficient, D_e, of metoprolol succinate in the coating of individual pellets.

D_e increased by almost an order of magnitude in the release range investigated, and is rather homogeneous for the pellets investigated. This similarity reflects the similarity in the film structure and the pore formation process when the pellets are immersed in the release medium. Only one of the 5 pellets investigated in each batch showed a higher release rate. These both had a thinner coating layer than the others in the same batch, and we have shown that D_e increases more rapidly for pellets coated with a thinner film. This can be explained by the decrease in HPC leaching rate with greater coating film thickness. As HPC leaching influences pore formation, pores are created at a slower rate in a thicker film. This finding is quite important, since it implies that the release rate from pellets coated with a blend of polymers, one of which is water-soluble and leaches out, is not necessarily linearly dependent on the inverse of the coating thickness during the whole release period.

5. Conclusions

Metoprolol succinate release from pellets coated with an EC/HPC film containing 30% HPC was related to changes in the coating structure due to HPC leaching. The film coating was initially not permeable to metoprolol succinate and the lag time was found to be dependent on the film coating thickness. The film coating become permeable to metoprolol succinate and release started when about 8% of the HPC had been leached out of the coating. SEM images revealed that pores caused by HPC leaching were observable in the coating after the pellets had been exposed to the release medium. The HPC leaching process was slower than the drug release for the drug load investigated. Thus, pores were still being formed in the coating during the whole release process.

The effect of HPC leaching on the coating structure was quantitatively characterized by calculating the effective diffusion coefficient of metoprolol succinate in the coating of some randomly chosen pellets. Each of these pellets was analysed in term of size and film coating thickness before the release experiments. Thus, when a mechanistic model was used to fit the release data, D_e was the only parameter optimized. D_e was not an average parameter but was the one truly characteristic of each coating as no average parameters were used in the calculations. D_e was not constant but increased during the release process. Importantly, it was shown that D_e depended on the film thickness and increased significantly more rapidly for pellets with a thinner coating.

The accurate calculation of D_e requires the combination of a modelling technique with many advanced experiments. However, it is essential to quantitatively characterize the transport properties of the coating and, for coatings containing a leachable polymer, to understand how D_e depends on the coating thickness. This understanding can be a strong support to optimize the coating thickness of new coated pellets.

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