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ScienceDirect
International Journal of Pharmaceutics 336 (2007) 67–74
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Evaluation of osmotic effects on coated pellets using a mechanistic model

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Received 19 July 2006; received in revised form 8 November 2006; accepted 11 November 2006
Available online 17 November 2006

Abstract

The aim of this study was to develop a simple experimental methodology and to develop a mechanistic model to characterize the release mechanism from pellets developing cracks during the release process with special focus on osmotic effects. The release of remoxipride from pellets coated with an ethyl cellulose film was chosen as a case study. Dose release experiments at different bulk osmotic pressures revealed that the release process was mainly osmotically driven. The model was used to calculate the solvent permeability of the coating, 1.1×10^{-10} m^2 h^{-1} MPa^{-1}. The model was validated by release experiments using similar pellets having different coating thicknesses. The effective diffusion coefficient of remoxipride in the coating was also calculated and found to be 1.7×10^{-10} m^2 h^{-1}. A series of experiments was performed in which the osmotic pressure of the receiving solution was changed during the experiment. From the results of these experiments, the area of the cracks in the film, formed by the hydrostatic pressure built up inside the pellets, was estimated to be 3.5×10^{-5} m^2/m^2 coating. It could also be deduced that the solvent permeability of the coating film was affected by swelling in the same way at different osmotic pressures.

Keywords: Release mechanism; Modelling; Osmotic pumping; Diffusion; Pellets; Ethyl cellulose

1. Introduction

Among novel drug delivery technologies, oral systems hold the major market share because of their ease of administration and better patient compliance (Verma and Garg, 2001). Osmotic systems play an important role in controlled release and a large number of design options are available (Santus and Baker, 1995). In osmotic systems, the coating is a semi-permeable film, and the release rate is primarily controlled by solvent diffusion through the coating (Cussler, 1997). Solvent transport through the coating induces a hydrostatic pressure in the drug delivery system. Drug transport occurs mainly by convection with a small contribution from pure diffusion. The convective out-flux of the drug through the coating can occur via drilled holes (Theeuwes, 1975), via pores produced by leachable substances (Zentner et al., 1985), or via cracks (Schultz and Kleinebudde, 1997; Schultz et al., 1997). Cracks are formed when the hydrostatic pressure inside the pellet is higher than that tolerated from the coating. They are formed if there is no drilled hole in the coating, or if the coating does not contain an adequate amount of pore-forming agent. The lag time before crack formation depends on: the fluid permeability of the coating, the difference in osmotic pressure across the coating, the geometry of the pellet/tablet, the coating thickness and the mechanical properties of the coating. SEM is often used to observe crack or pore formation and to compare the film structure before and after the release (Nevsten et al., 2005; Ozturk et al., 1990; Schultz and Kleinebudde, 1997; Verma and Garg, 2004).

In the development of new pharmaceutical formulations for oral delivery it is essential to study the properties of the film, in order to elucidate the release mechanism (pure diffusion and/or convection) and to optimize the coating design. Knowledge concerning fluid permeability and solute effective diffusion coefficient is required to fully describe the film used. Experimental methodologies have been developed to characterize transport through free, semi-permeable film (Hjärtstam et al., 1990; Lindstedt et al., 1989; Marucci et al., 2006). Some data concerning the measured fluid permeability of a free film can be found in the literature (Lindstedt et al., 1989; Theeuwes, 1975; Zentner et al., 1986). The properties of a free film, however, may differ from those of a coating film. The influence of hydrostatic

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doi:10.1016/j.ijpharm.2006.11.032

Nomenclature

A	area (m^2)
A'	area of the intact coating film (m^2)
A''	area of the cracks (m^2)
c	drug concentration (kg/m^3)
c_s	drug concentration at saturation (kg/m^3)
D	effective diffusion coefficient of the drug in the coating (m^2/h)
$D_{coat.}$	diffusion coefficient of the drug in the intact coating (m^2/h)
D_0	diffusion coefficient of the drug in the cracks (m^2/h)
h	coating thickness (m)
J'	volume flow through the intact coating (m^3/h)
J''	volume flow through the cracks (m^3/h)
J_s	drug flow (kg/h)
L'_p	solvent permeability coefficient of the intact film (m/h MPa)
L''_p	solvent permeability coefficient of the cracks, (m/h MPa)
$L'_p h$	solvent permeability of the intact film (m^2/h MPa)
$L''_p h$	solvent permeability of the cracks (m^2/h MPa)
P	pressure (MPa)
Greek symbols	
π, π'	osmotic pressure (MPa)
σ'	reflection coefficient of the intact coating film
σ''	reflection coefficient of the cracks

pressure, that is actually affecting coated pellets, is in general not considered in studies of free films. Thus, it is important to measure or calculate the permeability of the final coating film formulation. However, data concerning the calculated fluid permeability of the coating film are seldom provided (Lindstedt et al., 1991).

The primary objectives of this study were: (1) to develop an easy experimental method of determining the release mechanism for a coated formulation; (2) to further develop a theoretical model presented in the literature (Lindstedt et al., 1991) to describe the release process by osmotic pumping from pellets coated with a semi-permeable film; (3) to use the experimental data and the model to quantify the transport properties of the film by calculating its solvent permeability and the effective diffusion coefficient of the drug; (4) to study the change in film properties during the initial lag time in the release process by varying the osmotic pressure of the receiving bulk solution during release experiments; (5) to gain a fundamental understanding of the complete release process.

In this study, the release of remoxipride from pellets coated with a film containing ethyl cellulose with 10% (w/w) triethyl citrate has been studied on a dose level. The pellets used were from the same batch as that used in previous studies (Borgquist et al., 2002, 2004; Nevsten et al., 2005; Ringqvist et al., 2003).

2. Theory

For pellets coated with a semi-permeable film, there are two parallel transport processes through the coating: transport through the intact coating and transport through pores, cracks or a drilled hole (Lindstedt et al., 1991). The volume flows through the intact coating and through pores, cracks or a drilled hole, J' and J'', respectively, can be derived from irreversible thermodynamics theory (Mulder, 1991) and written as (Lindstedt et al., 1991):

$$J' = A' L'_p(\sigma' \Delta\pi - \Delta P) \quad (1)$$

$$J'' = A'' L''_p(\sigma'' \Delta\pi - \Delta P) \quad (2)$$

In Eqs. (1) and (2), A' is the area of the intact coating, A'' the area of the cracks, L'_p the solvent permeability coefficient of the intact part of the coating and L''_p is the solvent permeability coefficient of the cracks. The reflectivity of the coating film, σ', and that of the crack area, σ'', are expected to be different. The flows J' and J'' are different in sign, J' is an in-flow while J'' is an out-flow. At steady state, the sum of the flows J' and J'' is equal to zero (Lindstedt et al., 1991) and the drug flow can be written as Eq. (3) if ΔP is small compared to $\Delta\pi$ (Lindstedt et al., 1991):

$$J_s = c_s(1 - \sigma'')A' L'_p \sigma' \Delta\pi + \frac{D}{h}\Delta c(A' + A'') \quad (3)$$

Eqs. (1)–(3) are valid for pellets which contain only one drug substance and which are immersed in a receiving solution where the drug is the only solute. In Eq. (3), D is the effective diffusion coefficient of the drug in the cracked coating, and J_s is related to the main parameters that characterize drug release by osmotic pumping. However, the calculation of the solvent permeability of the coating by Eq. (3) is complicated by the fact that many parameters are unknown at the same time in the equation.

To facilitate and enable an evaluation of the release mechanism, we are introducing Eqs. (4) and (5). Eq. (3) changes to Eq. (4) when a solute that does not penetrate the membrane and that is different from the drug is present in the receiving solution:

$$J_s = c_s(1 - \sigma'')A' L'_p(\sigma' \Delta\pi - \pi') + \frac{D}{h}\Delta c(A' + A'') \quad (4)$$

In Eq. (4), π' is the osmotic pressure caused by the presence of a solute different from the drug in the receiving solution. The drug reflectivity of the crack area is very small, $\sigma'' \ll 1$. Differentiating Eq. (4) with respect to π', and subsequent rearrangement, gives the following relationship for L'_p:

$$\frac{dJ_s}{d\pi'} = -L'_p c_s A' \quad (5)$$

The derivative of J_s with respect to π' can be calculated by performing release experiments at various osmotic pressures of the receiving solution and calculating the drug release rate when the drug is being released under steady state conditions. From the derivative of J_s it is possible to calculate the solvent permeability of the coating. The main advantages of using Eq. (5) in the calculation of the solvent permeability instead of Eq. (3) are

that in Eq. (5) the solvent permeability is the only unknown parameter, and the calculation does not require exact knowledge of the osmotic pressure at saturation for the specific drug of interest. This method may, if shown valid, be of large general interest as the osmotic pressure across the film of coated pellets may be difficult to be measured and may depend not only on the drug but also on any soluble excipient.

3. Materials and methods

3.1. Materials

Film-coated remoxipride ($BrH_{23}N_2C_{16}O_3{\cdot}HCl{\cdot}H_2O$) pellets were obtained from AstraZeneca Tablet Production, Södertälje, Sweden. The pellet core consists of remoxipride (∼80%) and microcrystalline cellulose. Ethyl cellulose and the plasticizer triethyl citrate (10%, w/w) were dissolved in ethanol and sprayed onto the primary pellets (Borgquist et al., 2002, 2004).

3.2. Measurement of remoxipride and glucose osmolality in water and calculation of the corresponding osmotic pressure

The measurement of the osmolality of remoxipride and glucose solutions at different concentrations was performed with an Advanced Micro-Osmometer®, model 3300 (Norwood, MA, USA), which uses the freezing point depression method. From the measured osmolality, it was then possible to calculate the temperature of freezing point, the water activity and the osmotic pressure of the aqueous solutions, according to a procedure described in the literature (Kiyosawa, 2003).

3.3. Drug release measurements

The release experiments were performed in an automatic USP XXIII dissolution apparatus type 2 (Vankel VK 7010, Cary, NC, USA), in line with a UV–visible spectrophotometer (Varian Cary 50 Bio, Cary, NC, USA), set at the wavelength of maximum absorbance of the active compound, 286 nm. The release rate was studied at a stirring rate of 100 rpm. Previous work (Borgquist et al., 2004) has shown that the release profile is independent of the stirring rate within the range of 50–150 rpm. Measurements were performed on pellets with a coating layer of 40 and 70 mg polymer/g pellet. In both cases the drug release from 200 mg of pellets (about 220 pellets) was measured. The receiving solution had a volume of 900 ml. Experiments were run at various osmotic pressures of the receiving bulk solution to study the effect of the osmotic pressure difference across the coating on the release kinetics. This was done in order to understand the release mechanism, to calculate the solvent permeability of the coating and to calculate the effective diffusion coefficient of remoxipride in the coating. The effect of bulk osmotic pressure in the release was studied for the case when the bulk osmotic pressure was lower than that inside the pellet (2.6 MPa for a saturated solution of remoxipride at 37 °C) as well as the case when it was higher. The osmotic pressures investigated were: 0, 0.83, 1.77, 3.98, 5.42 and 10.47 MPa. It should be noted that the osmotic pressures were only selected to study the influence on drug release, and thus to investigate the release mechanism. The aim was consequently not to mimic any in vivo situation, although the osmotic pressures characteristic of gastric and jejunal fluid in the fasted state, 0.49 ± 0.09 and 0.7 ± 0.04 MPa, respectively (Lindahl et al., 1997), were in the range of osmotic pressures studied. The receiving solutions used were distilled water and solutions of glucose in distilled water. As the diffusion coefficient of glucose in water is three orders of magnitude higher than in ethyl cellulose film, the rate-determining step for glucose diffusion from the bulk solution into the pellet is diffusion in the coating. Thus, the glucose resistance in the boundary layer could be neglected, and, at stirring rates between 50 and 150 rpm, glucose diffusion is not influenced by stirring rate. Samples of the receiving solutions were collected continuously and the release experiments were monitored for at least 23 h and at most 66 h to collect sufficient data for the evaluation. Four or six replicates of each experiment were performed. Because of the very low coefficient of variation (∼2–3%), the number of experiments and the dose used were considered sufficient to obtain a representative description of the dose release. This variation is in accordance with a previous study on pellets from the same batch (Borgquist et al., 2004). The pellets have been characterized in terms of pellet diameter and film coating thickness in an earlier study (Borgquist et al., 2002). Physical and geometric data used for the calculation of solvent permeability and drug diffusion coefficient are given in Table 1.

Table 1
Physical and geometric data

Remoxipride solubility at 37 °C	540 kg/m^3
Diameter of pellets with a coating of 40 mg polymer/g pellet	1.0 mm
Film thickness of the coating at 40 mg polymer/g pellet	7.9 μm
Diameter of pellets with a coating of 70 mg polymer/g pellet	1.0 mm
Film thickness of the coating at 70 mg polymer/g pellet	12.7 μm

4. Results and discussion

4.1. Osmotic pressure of remoxipride and glucose solutions

The osmotic pressure of remoxipride and glucose solutions at different concentrations is shown in Fig. 1. At low concentrations, for both the solutes, the osmotic pressure and the solute concentration were well correlated according to van't Hoff's law (remoxipride dissociates into two subunits) (Atkins, 1994). However, at higher concentrations, the systems deviate from the ideal behaviour. For glucose solutions, the measured osmotic pressure at higher concentrations was higher than expected from van't Hoff's law, while the opposite was observed for remoxipride solutions. When measuring the osmolality of a solution with the freezing point depression method, it is necessary that the saturated concentration of the solute at the temperature of freezing point is higher than the concentration of the solute in the solution investigated. Thus, it was not possible to measure the osmotic pressure of a saturated solution of remoxipride at 37 °C. The osmotic pressure expected for a saturated solution

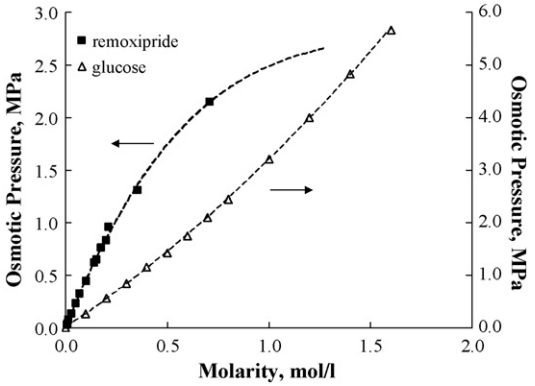

Fig. 1. Osmotic pressure for remoxipride and glucose solutions obtained with the freezing point depression method.

at 37 °C was instead extrapolated from the experimental data (2.6 MPa). The range of measurement of the osmometer used in this study was 0–2000 milliosmolal. Therefore, the osmotic pressure corresponding to a 2.54 M solution of glucose was obtained by extrapolating the experimental data, and was found to be 10.5 MPa.

4.2. Characterization of the release mechanism and calculation of the transport parameters

The effect of the osmotic pressure of the bulk solution on remoxipride release rate was studied. The results of the release experiments using pellets with a coating thickness of 70 mg/g are shown in Fig. 2. It can be observed that the drug delivery rate decreased considerably when the bulk osmotic pressure was increased. This means that the main release mechanism of remoxipride through the ethyl cellulose coating is by osmotic pumping for pellets immersed in a receiving solution with an osmotic pressure less than that inside the pellet. As the osmotic pressure inside the pellet is 2.6 MPa when the solution is saturated with remoxipride, it can be stated that, at receiving solution osmotic pressures of 0, 0.83 and 1.77 MPa, drug release occurred mainly by convection with a small contribution from diffusion. As cracks were observed on the coating at the end of the release experiments (Nevsten et al., 2005), it can be deduced that the convective flow occurred through these cracks. At the other osmotic pressures, there was not sufficient driving force to accumulate water and to build-up a hydrostatic pressure inside the pellet to an extent that would give rise to cracks. Thus, drug release occurred by diffusion. Drug release also occurred at a negative difference in osmotic pressure between the pellet and the receiving solution. This has been observed in another study on pellets coated with a semi-permeable membrane (Herbig et al., 1995). In all the present release experiments, the release rate increased during an initial lag-time until a constant value was reached ("zero order release"), and at the end decreased to a rate close to zero. Interestingly, the fraction of remoxipride released during the zero order release phase decreased at higher osmotic pressure of the receiving solution, as can be observed in Fig. 2. It can also be concluded from Fig. 2 that the concentration of glucose inside the pellets never reached the concentration in the bulk. In fact, if at the bulk osmotic pressures of 3.48, 5.42 and 10.43 MPa the glucose concentration inside the pellet had approached the same value as in the receiving bulk solution, a higher osmotic pressure would have been created inside the pellet, leading to increased osmotic transport of solvent, increasing the release rate of remoxipride. But this was not observed.

The slopes of the release curves in the zero order release region, i.e. J_s at steady state, were estimated by a linear interpolation of the release data. Typically, data collected between 50 and 200 min of the dissolution experiments were used for linear interpolation. The regression coefficient was greater than 0.997 for all the experiments. The values of J_s at steady state are shown in Fig. 3 as a function of the bulk osmotic pressure. The data fit a straight line very well ($R = 0.995$) up to 1.77 MPa, i.e. the highest tested osmotic pressure of the receiving solution that did not exceed the osmotic pressure inside the pellet. The derivative of J_s with respect to the osmotic pressure of the receiving bulk solution was calculated. The solvent permeability was then calculated according to Eq. (5) and found to be 1.1×10^{-10} m^2 h^{-1} MPa^{-1}. The error in the calculation of the solvent permeability introduced by using the initial pellet size is negligible as the swelling of the pellet is only 2–3% (Ringqvist et al., 2003). At sufficient osmotic pressure of the receiving solution, the convective transport will be negligible compared to the diffusive transport (in the right-hand side of Eq. (4), the first term

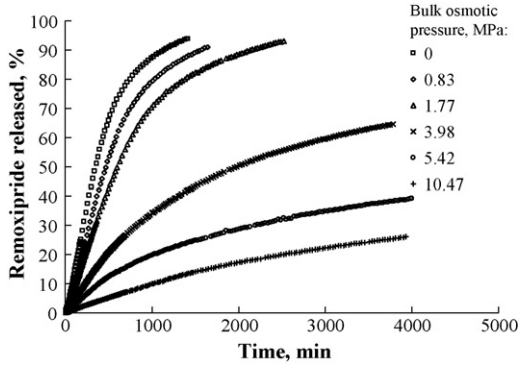

Fig. 2. Release profiles of remoxipride (coating layer: 70 mg polymer/g pellet) for different bulk solution osmotic pressures. Glucose was used to increase the osmotic pressure of the bulk solution.

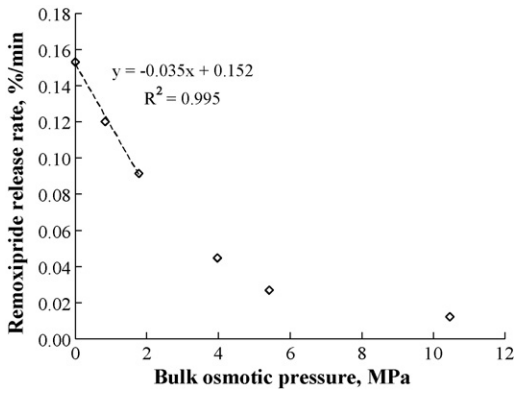

Fig. 3. Remoxipride release rate in the zero order release phase (coating layer: 70 mg polymer/g pellet). Data obtained from Fig. 2.

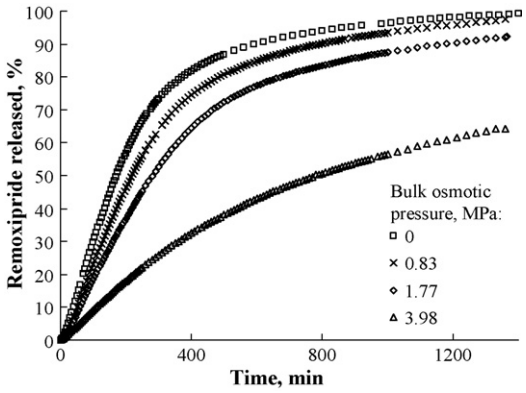

Fig. 4. Release profiles of remoxipride (coating layer: 40 mg polymer/g pellet) for different bulk solution osmotic pressures. Glucose was used to increase the osmotic pressure of the bulk solution.

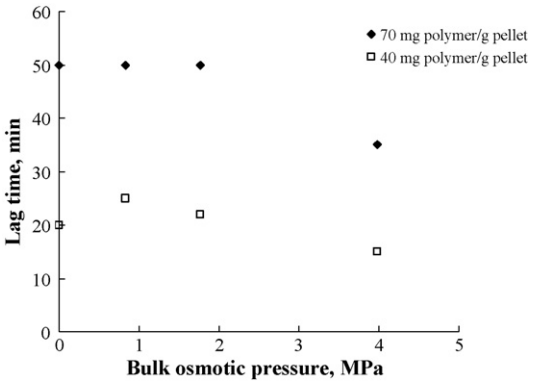

Fig. 6. Lag time derived from the release experiments on pellets with a coating of 70 and 40 mg polymer/g pellet. Glucose was used to increase the bulk osmotic pressure of the receiving bulk solution. The lag time was calculated from the intercept of the line fitting the zero order release phase.

becomes much smaller compared to the second one). Thus, the effective diffusion coefficient can be estimated by Eq. (4). In this study, the effective diffusion coefficient of remoxipride in the coating was estimated by extrapolating the fit of the release rate data to the osmotic pressure of 2.6 MPa, and was calculated to be 1.7×10^{-10} m^2 h^{-1}. Therefore, the pellet coating was fully characterized in terms of transport properties.

Release experiments were performed at different bulk osmotic pressures also with pellets with a smaller amount of coating, 40 mg/g, and the results are shown in Fig. 4. The release process was still osmotically driven. The slope of the linear region, i.e. J_s at steady state, was calculated for the different curves and is plotted in Fig. 5 as a function of the bulk osmotic pressure, in the same way as for the previous pellet system. The solvent permeability of the coating was found to be 1.5×10^{-10} m^2 h^{-1} MPa^{-1}. The effective diffusion coefficient of remoxipride in the coating was calculated and found to be 2.8×10^{-10} m^2 h^{-1}. The calculated solvent permeability and effective diffusion coefficient are in good agreement with those calculated for a coating thickness of 70 mg/g. This confirms the validity of using Eq. (5) and the methodology proposed to calculate the solvent permeability and the drug effective diffusion coefficient. The small difference in the results between the 70 and 40 mg/g compositions may be due to the fact that the two coating films were slightly different, as crystals of remoxipride were found on the surface of the pellets, and the amount of crystals was higher in the pellets with the thinner coating (Ringqvist et al., 2003).

Fig. 6 shows the lag time in the release experiments for the two coating thicknesses investigated at different bulk osmotic pressures. As expected, the thicker the film the longer the lag time. For the pellets with the thicker coating, the water influx is lower, and, moreover, a higher pressure can be withstood before the coating rupture. The lag time data show the same trend for both film thicknesses, i.e. it is almost constant at bulk osmotic pressures that are lower than the calculated osmotic pressure inside the pellets, and then decreases to some extent at higher pressures. For a cracking coating system, it is reasonable to assume that the lag time is composed of two periods: the time required for the cracks to occur in the coating, and the time required for the pellets to reach the internal pressure sufficient for steady-state flow once the film has ruptured. It can be seen from Fig. 6 that the lag time was not significantly affected by the bulk osmotic pressure. The shorter lag time at an osmotic pressure of 3.98 MPa can be explained as the consequence of the significant contribution of pure diffusion in the release process. Thus, the lag time was mainly affected by the time required to establish steady-state drug diffusion conditions.

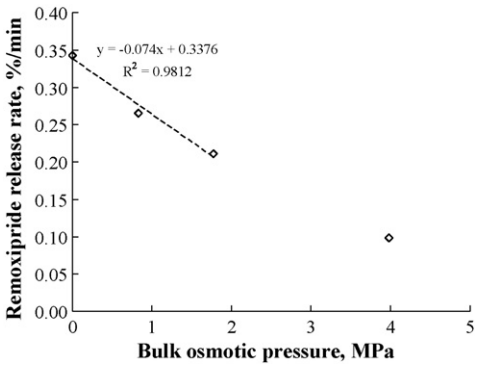

Fig. 5. Remoxipride release rate in the zero order release phase (coating layer: 40 mg polymer/g pellet). Data obtained from Fig. 4.

4.3. Crack characterization

In an osmotic pumping delivering system with a drilled hole, the area of the hole should be large enough to avoid a build-up of pressure greater than that tolerated by the coating and small enough to minimize the contribution to the delivery rate of solute diffusion through the hole (Theeuwes, 1975). For coating films subject to cracking, performing experiments at different bulk osmotic pressures allows the main delivery mechanism to be identified, providing information on whether the crack area is small enough to result in predominantly osmotic delivery. In the present study, the remoxipride release rate was 3.5 times higher in distilled water than in a glucose solution with an osmotic pressure of 3.98 MPa (Figs. 3 and 5). This proves that the area of the cracks formed during the lag phase of the release was sufficient to result in osmotically driven release.

To study the area of the cracks, experiments were performed in which the bulk osmotic pressure was changed from 0 to 10.47 MPa 50 min after the experiment had been started. (A time of 50 min was sufficient to attain zero order release and, therefore, to cause crack formation in the coating while ensuring that the concentration inside the pellets was still at saturation.) When the bulk osmotic pressure is increased to such a high value, release no longer occurs by convection and diffusion, but only by diffusion. The release through the cracked coating is the result of two parallel contributions: diffusion in the intact part of the coating and diffusion in the cracks. When the bulk osmotic pressure is 10.47 MPa for the whole experiment, the release occurs only by diffusion through the coating as no hydrostatic pressure is built up in the pellet and no cracks are formed on the coating. A comparison between the release obtained when the bulk osmotic pressure is changed from 0 to 10.47 MPa and the release obtained when the bulk osmotic pressure was 10.47 MPa for the whole experiment is shown in Fig. 7. In Fig. 7, the amount of remoxipride released that is present in the receiving vessel is plotted. This represents the entire amount of remoxipride released when the receiving solution is not replaced, i.e. when the osmotic pressure is kept constant. When the bulk osmotic pressure is changed, by replacing the whole receiving solution after 50 min by a fresh solution of glucose, the remoxipride released during the first 50 min is completely removed from the receiving vessel. Thus, in this case, the amount of remoxipride released that is present in the receiving solution is 0 after 50 min. The release rate at steady state was calculated for both the release profiles shown in Fig. 7. In the experiments in which the bulk osmotic pressure was varied from 0 to 10.47 MPa, remoxipride release rate at steady state was 30% greater than when the bulk osmotic pressure was 10.47 MPa for the whole experiment. Assuming that the difference between the release rates is due only to diffusion in the cracks, the area of the cracks A'' can be estimated from Eq. (6):

$$A'' = \frac{(J_a - J_b)h}{D_0 c_s} \tag{6}$$

In Eq. (6), J_a is the steady-state release rate through the cracked coating, when the bulk osmotic pressure is changed from zero to a value equal to the osmotic pressure inside the pellet after crack formation. J_b is the steady-state release rate that is attained when the difference in osmotic pressure across the film is zero for the whole experiment. D_0 is the drug diffusion coefficient in the cracks and can be approximated by the diffusion coefficient in solution for small drugs in thin membranes with negligible tortuosity. D_0 is related to the effective diffusion coefficient in the cracked coating, D, and to the diffusion coefficient in the intact part of the coating, $D_{coat.}$, by Eq. (7):

$$\frac{D}{h}\ \Delta c(A' + A'') = \frac{D_0}{h}\ \Delta c A'' + \frac{D_{coat.}}{h}\ \Delta c A' \tag{7}$$

The diffusion coefficient of remoxipride in the glucose solution has been calculated at 37 °C with the Wilke–Chang equation (Cussler, 1997) and found to be 1.0×10^{-10} m^2/s. The ratio of the crack area to the coating area was then estimated to be 3.5×10^{-5} m^2/m^2. In the osmotic pumping system developed by Theeuwes (1975) zero order release was achieved when the ratio of hole to coating area was between 1.7×10^{-5} and 2.7×10^{-4} m^2/m^2, which is in the same range as the crack area calculated in the present study.

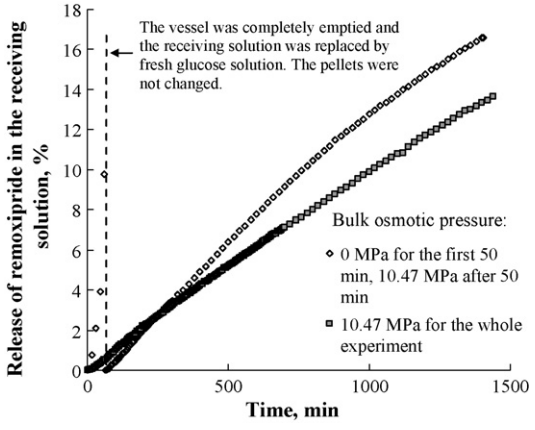

Fig. 7. Comparison of remoxipride release (coating layer: 70 mg polymer/g pellet) between the case when the osmotic pressure of the receiving solution was 10.47 MPa for the whole experiment (■) and the case when the osmotic pressure was changed from 0 to 10.47 MPa 50 min after the experiment had started (◇). The receiving solution was not replaced in the experiments performed at a constant bulk osmotic pressure. In the experiments in which the osmotic pressure was changed, the whole receiving solution was replaced by another solution and the remoxipride released during the first 50 min was completely removed from the receiving vessel. The *y*-axis thus shows the release of remoxipride in the receiving solution. This coincides with the entire remoxipride released when the receiving solution is not replaced.

4.4. Effect of crack-promoting osmotic pressure on the solvent permeability of the coating

As discussed above (Section 4.2), it is possible to calculate the solvent permeability from the derivative of J_s with respect to the osmotic pressure using Eq. (5). As shown experimentally, pellets coated with a semi-permeable film swell however before crack formation (Schultz and Kleinebudde, 1997). Interestingly, the swelling of the pellet may depend on the bulk osmotic pressure at which cracks occur (Schultz and Kleinebudde, 1997). It has been shown that osmotic pressure may cause swelling and influence the drug release rate also in systems where no apparent cracks are formed (Hjärtstam, 1998). The effect on the drug permeability and on the solvent permeability may be due to factors such as decreased film thickness due to swelling, widening of inherent pores in the coating. To verify that the release rate at different bulk osmotic pressures is a useful tool to calculate the solvent permeability of the coating, it is necessary to study the potential effect of osmotic pressure per se on solvent permeability. Thus, experiments were performed in which the receiving solution was changed after two hours from pure water to a glucose solution with an osmotic pressure of 1.77 MPa. (Two hours was sufficient to establish steady-state delivery, thus for cracks to occur, while ensuring that the concentration inside the pellets was still at saturation.) A

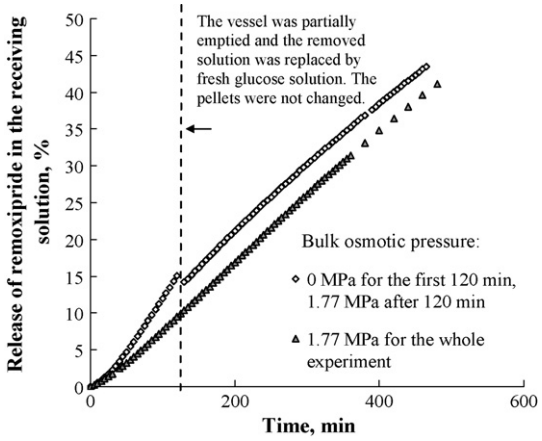

Fig. 8. Comparison of remoxipride release (coating layer: 70 mg polymer/g pellet) between the case when the osmotic pressure of the receiving solution was 1.77 MPa for the whole experiment (▲) and the case when the osmotic pressure was changed from 0 to 1.77 MPa 120 min after the experiment had started (◊). The receiving solution was not replaced in the experiment performed at a constant bulk osmotic pressure. In the experiments in which the osmotic pressure was changed, the receiving solution was partially replaced by another solution and a part of the remoxipride released during the first 120 min was removed from the receiving vessel. The *y*-axis thus shows the release of remoxipride in the receiving solution. This coincides with the entire remoxipride released when the receiving solution is not replaced.

comparison with the release experiments performed directly at the receiving bulk osmotic pressure of 1.77 MPa is shown in Fig. 8. The swelling of the pellets before crack formation is supposed to be different in the two series of experiments, as the osmotic pressure at which cracks occurred was different. In Fig. 8, the amount of remoxipride released that is present in the receiving solution is plotted. This coincides with the entire remoxipride released when the receiving solution is not replaced. For the case in which the bulk osmotic pressure is varied, the receiving solution is partially replaced after 120 min by another solution, and part of the remoxipride released during the first 120 min is removed from the receiving vessel. The remoxipride release rate was calculated at steady state for both release curves, and no significant difference was obtained. Since the release at these bulk osmotic pressures (0–1.77 MPa) is mainly due to osmotic pumping, the release rate is determined essentially by the solvent permeability of the coating. As no difference in the release rate was observed between the two curves, it can be deduced that in both cases the coating had the same solvent permeability. This means that, at the bulk osmotic pressures investigated (0 and 1.77 MPa), the osmotic pressure of the receiving solutions at which cracks occurred and the corresponding swelling had the same effect on the solvent permeability of the coating. This also supports the suggestion that release rate data at different bulk osmotic pressures can be used to calculate the solvent permeability of the coating.

5. Conclusions

In this study, the release mechanism of remoxipride from pellets coated with a film containing ethyl cellulose with 10% (w/w) triethyl citrate has been elucidated via release experiments performed in receiving solutions with different osmotic pressures. Remoxipride release was found to be mainly osmotically driven. This means that the area of the cracks formed in the coating during the lag time was small enough to ensure the build-up of the hydrostatic pressure necessary for the convective transport of the drug.

A model derived from irreversible thermodynamics theory has also been further developed in order to easily calculate the solvent permeability of the coating. For the calculation, the model requires data concerning release rate at steady state, from release experiments performed in receiving solutions at different osmotic pressures. For the ethyl cellulose coating, the solvent permeability was calculated and found to be $1.1 \times 10^{-10}\ m^2\ h^{-1}\ MPa^{-1}$. The effective diffusion coefficient of remoxipride in the coating was found to be $1.7 \times 10^{-10}\ m^2\ h^{-1}$. Thus, the osmotic pumping release of remoxipride through the coating was fully characterized.

A method of estimating the crack area was also developed. The crack area was estimated to be $3.5 \times 10^{-5}\ m^2/m^2$ coating, which is in the range proposed by Theeuwes (1975) for his system. From experiments involving changing the osmotic pressure during the release process, it could be deduced that the solvent permeability of the coating was affected in the same way at different osmotic pressures in the receiving bulk solution by the swelling before crack formation.

Acknowledgments

The Swedish Research Council and AstraZeneca are gratefully acknowledged for their financial support.

References

Atkins, P.W., 1994. Physical Chemistry, 5th ed. Oxford University Press, Oxford.
Borgquist, P., Nevsten, P., Nilsson, B., Wallenberg, L.R., Axelsson, A., 2004. Simulation of the release from a multiparticulate system validated by single pellet and dose release experiments. J. Control. Release 97, 453–465.
Borgquist, P., Zackrisson, G., Nilsson, B., Axelsson, A., 2002. Simulation and parametric study of a film-coated controlled-release pharmaceutical. J. Control. Release 80, 229–245.
Cussler, E.L., 1997. Diffusion. In: Mass Transfer in Fluid Systems, 2nd ed. Cambridge University Press, Cambridge.
Herbig, S.M., Cardinal, J.R., Korsmeyer, R.W., Smith, K.L., 1995. Asymmetric-membrane tablet coatings for osmotic drug delivery. J. Control. Release 35, 127–136.
Hjärtstam, J., 1998. Ethyl cellulose membranes used in modified release formulations. PhD Thesis. Chalmers University of Technology, Göteborg, Sweden.
Hjärtstam, J., Borg, K., Lindstedt, B., 1990. The effect of tensile-stress on permeability of free films of ethyl cellulose containing hydroxypropyl methylcellulose. Int. J. Pharmceut. 61, 101–107.
Kiyosawa, K., 2003. Theoretical and experimental studies on freezing point depression and vapor pressure deficit as methods to measure osmotic pressure of aqueous polyethylene glycol and bovine serum albumin solutions. Biophys. Chem. 104, 171–188.
Lindahl, A., Ungell, A., Knutson, L., Lennernäs, H., 1997. Characterization of fluid from the stomach and proximal jejunum in men and women. Pharmaceut. Res. 14, 497–502.
Lindstedt, B., Ragnarsson, G., Hjärtstam, J., 1989. Osmotic pumping as a release mechanism for membrane-coated drug formulations. Int. J. Pharmceut. 56, 261–268.

Lindstedt, B., Sjöberg, M., Hjärtstam, J., 1991. Osmotic pumping release from KCl tablets coated with porous and nonporous ethylcellulose. Int. J. Pharmceut. 67, 21–27.

Marucci, M., Ragnarsson, G., Axelsson, A., 2006. ESPI: a novel non-invasive tool for studying drug transport rate and drug permeability through free films. J. Control. Release 114, 369–380.

Mulder, M., 1991. Basic Principle of Membrane Technology. Kluwer Academic Publishers, Netherlands.

Nevsten, P., Borgquist, P., Axelsson, A., Wallenberg, L.R., 2005. XEDS-mapping for explaining release patterns from single-pellets. Int. J. Pharmceut. 290, 109–120.

Ozturk, A.G., Ozturk, S.S., Palsson, B.O., Wheatley, T.A., Dressman, J.B., 1990. Mechanism of release from pellets coated with an ethylcellulose-based film. J. Control. Release 14, 203–213.

Ringqvist, A., Taylor, L.S., Ekelund, K., Ragnarsson, G., Engstrom, S., Axelsson, A., 2003. Atomic force microscopy analysis and confocal Raman microimaging of coated pellets. Int. J. Pharmceut. 267, 35–47.

Santus, G., Baker, R.W., 1995. Osmotic drug delivery: a review of patent literature. J. Control. Release 35, 1–21.

Schultz, P., Kleinebudde, P., 1997. A new multiparticulate delayed release system. Part I. Dissolution properties and release mechanism. J. Control. Release 47, 181–189.

Schultz, P., Tho, I., Kleinebudde, P., 1997. A new multiparticulate delayed release system. Part II. Coating formulation and properties of free films. J. Control. Release 47, 191–199.

Theeuwes, F., 1975. Elementary osmotic pump. J. Pharmceut. Sci. 64, 1987–1991.

Verma, R.K., Garg, S., 2001. Current status of drug delivery technologies and future directions. Pharm. Technol. On Line 25, 1–14.

Verma, R.K., Garg, S., 2004. Development and evaluation of osmotically controlled drug delivery system of glipizide. Eur. J. Pharmaceut. Sci. 57, 513–525.

Zentner, G.M., Rork, G.S., Himmelstein, K.J., 1985. The controlled porosity osmotic pump. J. Control. Release 1, 217–229.

Zentner, G.M., Rork, G.S., Himmelstein, K.J., 1986. Osmotic flow through controlled porosity film: an approach to the delivery of water soluble compounds. In: Anderson, J.M., Kim, S.W. (Eds.), Advances in Drug Delivery System. Elsevier, New York, pp. 217–230.