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Osmotic pumping release from KCl tablets coated with porous and non-porous ethylcellulose

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Summary

A simple model is described for osmotic pumping drug release from membrane-coated formulations. The process requires at least two different areas in parallel in the membrane coat, which exhibit differing reflectivities to solute (drug and/or excipients). The model was used to calculate the reflectivities of membrane coats on potassium chloride tablets. Tablet coats of pure ethylcellulose (EC) had a low reflectivity of less than 0.005, and was not a major release rate regulating parameter. The higher reflectivity of the same membrane was 0.58, significantly lower than for a free relaxed film. The reduction in high reflectivity resulted in a corresponding lower drug release rate. Incorporation of hydroxypropyl methylcellulose (HPMC) in EC reduces the high reflectivity of the tablet coats even further. The reduction is accelerated when the HPMC content exceeds 24%. Since freezing water could be detected in free EC films with HPMC content of 24% and above, the formation of pores in these membrane coats is proposed. The pores are formed by the leaching of the water-soluble polymer HPMC, which is also found in the soaking liquid.

Introduction

Membrane coating of tablets and pellets to alter the dissolution rate of a pharmaceutically active substance has increased in popularity during the last two decades. To find the optimal film composition it is of great importance to know the mechanisms of drug release. Drug diffusion through the coat often offers the major release mechanism, but osmotic pumping, where convection is the release mechanism, may also contribute or even dominate.

Osmotic pumping release from tablets was described by Theeuwes in 1975. The formulation design, commonly known as OROS, consisted of a drug core coated with a semipermeable membrane coat including at least one drilled exit port. OROS is comparably easy to understand, as the osmotic inhibition of water through the semipermeable membrane is physically separated from the convective drug solution release through the drilled hole. The drawback of the OROS design lies in the complicated manufacturing process, where every membrane coat surrounding the drug particles has to be perforated.

A more simple manufacturing process was demonstrated by Zentner and co-workers in 1985. Here the membrane coat was made porous by incorporating leachable substances in the coating composition. Osmotic pumping was shown to be the major release mechanism, as the release rate was drastically reduced when the osmotic pressure in the dissolution medium was increased. The

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understanding of the osmotic pumping process was however lost, as no means of drug solution release was discussed. Therefore, the formulas derived by Theeuwes (1975) cannot be used to predict the drug release rate.

We have previously shown that osmotic pumping is the major release mechanism for potassium chloride (KCl) tablets coated with ethylcellulose (EC) alone or in combination with hydroxypropyl methylcellulose (HPMC) (Lindstedt et al., 1989). It has also been shown that the permeability of KCl through free EC films depends on tensile stress in the membrane, and that the salt is transported by convection (Hjärtstam et al., 1990).

The objective of this paper is to show a model for osmotic pumping that may be used in describing the release characteristics of membrane coated formulations, without preformed exit ports. Instead, all properties of the membrane necessary for osmotic pumping must be included in the model. An attempt is also made to explain the less effective osmotic pumping that is observed when the HPMC fraction of EC exceeds 24%.

Theoretical

To describe osmosis, the Kedem-Katchalsky equations are used (Friedman, 1986). The bulk volume flux, J_v, and the osmotic pressure difference, $\Delta\Pi$, are related by Eqn 1:

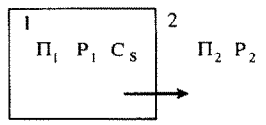
$$J_v = L_p(\Delta P - \sigma\Delta\Pi) \quad (1)$$

Here L_p and σ are the hydraulic permeability and the reflection coefficient of the membrane (for the solute giving $\Delta\Pi$). ΔP is the hydrostatic pressure difference.

The solute flux, J_s, is related to J_v by Eqn 2:

$$J_s = CJ_v(1 - \sigma) + \omega\Delta\Pi \quad (2)$$

C is the solute concentration and ω is the permeability of the membrane for a solute with $\Delta\Pi$ as the concentration gradient. The direction of the fluxes is given in Fig. 1. Eqns 1 and 2 were derived for a single solute and conditions close to equilibrium, which the releasing tablet is far from. The



$$\Delta\Pi = \Pi_1 - \Pi_2$$

$$\Delta P = P_1 - P_2$$

Fig. 1. Direction of positive fluxes in Eqns 1 and 2.

equations have however been used to describe water flux in membrane-coated tablets with drilled exit ports (Theeuwes, 1975).

Since the formulator may alter the membrane thickness, h, and the area of the tablet, A, it is convenient to introduce these parameters into the equations. It is important to remember that by introducing the membrane thickness we assume that the water permeability is constant for the membrane material. This is correct for a spray-coated tablet, as the membrane consists of several layers of polymeric material of identical composition. The osmotic pressure is also not the most unambiguous driving force for solute diffusion. Therefore, P_s is used for solute permeability and ΔC as the concentration difference.

$$F_v = \frac{A}{h} L'_p(\Delta P - \sigma\Delta\Pi) \quad (3)$$

$$F_s = CF_v(1 - \sigma) + \frac{A}{h} P_s\Delta C \quad (4)$$

When F_v is directed out of the tablet, ($F_v > 0$, Fig. 1), C must be equal to the solubility of the drug, C_s. When it is directed into the tablet ($F_v < 0$), C is zero, since the releasing process is performed in 'sink condition' with very low drug concentrations in the intestinal lumen or in the dissolution medium in the in vitro experiment.

During zero-order release, a steady state is maintained, with no volume expansion of the tablets. Therefore, the net bulk volume flux through the membrane (Eqn 3) must be zero. It follows that this model can not describe osmotic pumping, as the release of solute is then exclusively diffusive and independent of osmotic pressure.

The simplest expansion of the former model is to incorporate two areas in the membrane, each with its own set of transport equations:

$$F_{v1} = \frac{A_1}{h_1} L'_{p1}(\Delta P - \sigma_1 \Delta \Pi) \quad (5)$$

$$F_{s1} = (1 - \sigma_1) F_{v1} C_1 + \frac{A_1}{h_1} P_{s1} \Delta C \quad (6)$$

$$F_{v2} = \frac{A_2}{h_2} L'_{p2}(\Delta P - \sigma_2 \Delta \Pi) \quad (7)$$

$$F_{s2} = (1 - \sigma_2) F_{v2} C_2 + \frac{A_2}{h_2} P_{s2} \Delta C \quad (8)$$

The two areas are in parallel, they separate the same two volumes, and thus the driving forces must be the same. The primary difference between them is that they react differently to the two driving forces, i.e. they possess different reflectivities. The essence in this model is that water is imbibed by osmosis through both areas into the tablet. The volume flux gives an increased hydrostatic pressure in the tablet core. The hydrostatic pressure reverses the volume flux through the area of lower reflectivity. During steady state the fluxes through areas 1 and 2 are of different direction but equal in size:

$$F_{v1} + F_{v2} = 0 \quad (9)$$

It is thus possible to calculate the flux through the area of low reflectivity, which is primarily a convective flux, from the osmotic flux through the reflective area.

We have thus assumed that the reflectivity in one area is very low, i.e. $\sigma_2 \ll 1$. In practice, this may be achieved by drilling a hole in the membrane (Theeuwes, 1975) or by incorporating leachable pore-formers in the coating (Zentner et al., 1985). It is also possible that tensile stress in the membrane gives an area with low reflectivity for solute (Hjärtstam et al., 1990).

The release rate, Q, is the sum of the solute fluxes in areas 1 and 2:

$$Q = F_{s1} + F_{s2} = (1 - \sigma_1) F_{v1} C_1 + (1 - \sigma_2) F_{v2} C_2 + D_s \quad (10)$$

In this equation D_s is the diffusional release through areas 1 and 2:

$$D_s = \left(\frac{A_1}{h_1} P_{s1} + \frac{A_2}{h_2} P_{s2} \right) \Delta C \quad (11)$$

The bulk volume flux in area 1 is directed into the tablet and C_1 is zero. Then C_2 is equal to the concentration in the core, C_s. Eqn 10 can then be rewritten as:

$$Q = (1 - \sigma_2)(-F_{v1}) C_s + D_s = (1 - \sigma_2) \frac{A_1}{h_1} L'_{p1}(\sigma_1 \Delta \Pi - \Delta P) C_s + D_s \quad (12)$$

It is plausible that the low-reflective area is very small compared to the total area, because a membrane area with no reflectivity has a higher permeability, L'_p, than a more reflective area (the hole versus the highly reflective membrane). A_1 is then equal to the total area A, and the release rate can be calculated from Eqn 13:

$$Q = (1 - \sigma_2) \frac{A}{h} L'_{p1}(\sigma_1 \Delta \Pi - \Delta P) C_s + D_s \quad (13)$$

An estimate of σ_2 can be obtained from Eqn 7. The volume flux is directed out of the tablet and $F_{v2} > 0$. Thus:

$$\sigma_2 < \frac{\Delta P}{\Delta \Pi} \quad (14)$$

A maximum value of ΔP can be calculated from the maximum film stress and the geometry of the tablet (Hjärtstam et al., 1990). Often the hydrostatic pressure is negligible compared to the osmotic pressure, and the release rate can be calculated from Eqn 15:

$$Q = \frac{A}{h} L'_{p1} \sigma_1 \Delta \Pi + D_s \quad (15)$$

It is also very important to estimate the influence of unstirred layers in the tablet on the rate of water inhibition, since it is not agitated. This can be done with a model described by Pedley (1983). It is possible to use a model with a horizontal or vertical membrane. As the tablets are almost spherical and are tumbled during release (at least in vitro), the vertical model was chosen (Case VI

in Pedley's paper). Here agitation is caused by the differences in density of the solution when it is diluted during osmosis. The thickness of the unstirred layer, δ_0, is:

$$\delta_0 = 1.68\sqrt[4]{\frac{\nu D_l}{g' C_s}} \qquad (16)$$

where g' is $\frac{g}{\rho} \cdot \frac{\partial \rho}{\partial C}$

From Eqn 16 the effect of the presence of unstirred layers on the osmotic flux may be estimated using the osmotic permeability, the osmotic driving force and the diffusivity of the solute.

Experimental

Free films were prepared as described earlier (Lindstedt et al., 1989). Accurately weighed small film samples (film thickness about 70 μm) were soaked in deionized water at room temperature. After 0.25, 3 and 24 h soaking the samples were quickly blotted dry on a tissue paper and analyzed for total water content by Karl Fisher titration. The amount of leached HPMC in the soaking water was determined using a size exclusion chromatography method in water and RI detection. Freezing water was measured in a differential scanning calorimeter (Mettler DSC 30). Weighed film samples were soaked in water, blotted dry in a humid environment (> 90% relative humidity) and put in a standard DSC pan. The samples were quenched at $-30\,^{\circ}$C for 10 min, followed by a heating rate of 4 K/min to 25 °C. The measured melting endotherm was divided by the enthalpy of melting, 333.5 J/g (Loebel, 1975), and the amount of freezing water was calculated.

Results and Discussion

Reflectivities of tablet coats

Data for free film permeabilities from Lindstedt et al. (1989) are given in Table 1. Originally values for $\sigma L'_p$ were given, but since σ was shown to be 1 for films with not more than 24% HPMC, L'_p is given in Table 1. For 27 and 30% HPMC, estimates of the water permeabilities from tritiated water diffusion experiments are tabulated. For the free films with lower HPMC fraction, both methods (osmotic flux and tritium diffusion) yielded similar values for the water permeability.

TABLE 1

Water permeability of free films and tablet coats and the corresponding reflectivity σ_l

% HPMC	Free films L'_p ($\times 10^{10}$) (m^2/h per MPa)	Table coats $\sigma_l L'_p$ ($\times 10^{10}$) (m^2/h per MPa)	σ_l
0	0.36	0.21	0.58
18	0.92	0.41	0.45
20	1.10	0.46	0.42
24	1.68	0.52	0.31
27	2.34 [a]	0.53	0.23
30	5.58 [a]	0.38	0.07

[a] The permeabilities of the free films with 27 and 30% HPMC were only measured with tritiated water diffusion.

First it is important to estimate the possible influence of unstirred layers within the tablets with Eqn 16. The analysis shows that although the thickness of the unstirred layer is about 60 μm, the effect on the water permeation rate is 1.5% (24% HPMC) or less, due to the low water permeabilities of the membranes and the relatively high diffusivity of potassium chloride.

To calculate the high reflectivities of the tablet coats from Eqn 15, D_s was estimated by extrapolating the release rates to $\Delta\Pi = 0$. For the tablet coats with not more than 24% HPMC, D_s was zero. For 27 and 30% HPMC, D_s was 17 and 64% of the release rate in pure water.

TABLE 2

Maximum tensile stress for free films and the following approximations in Eqn 13

% HPMC	Tensile stress (MPa)	σ_2 (max)	$\Delta P/\sigma_1\Delta\Pi$ (max)
0	15	0.005	0.008
18	10	0.003	0.007
24	8	0.003	0.008
30	5	0.002	0.02

The approximations made in Eqn 15 should also be checked. Permeation rate versus tensile stress has been previously measured (Hjärtstam et al., 1990). From those results it is possible to extract the maximum tensile stress in the tablet coats during release. Knowing the diameter of the tablet (3 mm) and the film thickness (13 μm) it is possible to estimate the maximum hydrostatic pressure in the tablet. From Eqn 14 it is easy to compute the maximum reflectivity of the nonreflective area, σ_2. In Table 2 it is shown that σ_2 is negligible compared to 1 for all HPMC fractions and does not influence the release rate.

The influence of hydrostatic pressure on the release rate is also very small (fourth column in Table 2). Due to the very low reflectivity in 30%

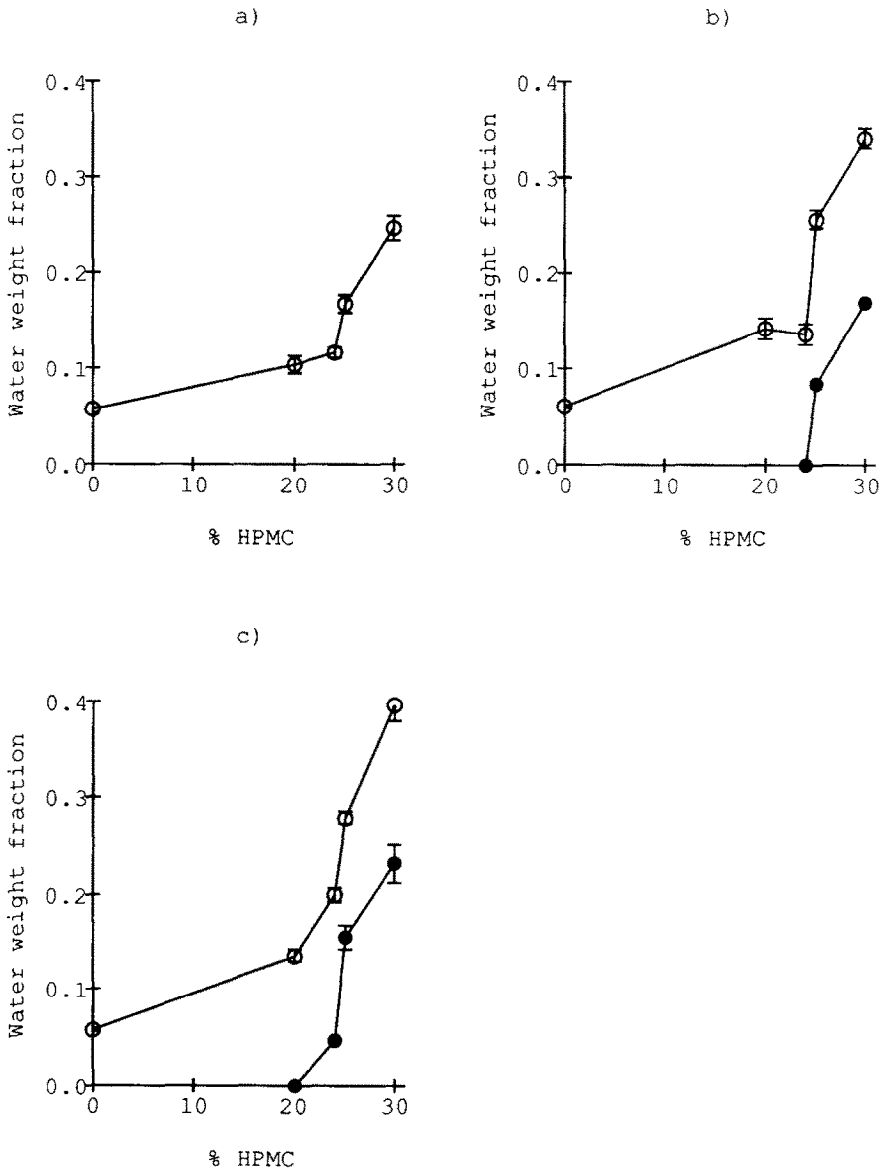


Fig. 2. Water content as weight fraction of dry film versus HPMC fraction. Error bars indicate standard deviation. ○ total water, ● freezing water at (a) 15 min, (b) 3 h and (c) 24 h soaking.

HPMC, ΔP may reduce the osmotic pumping, but still only insignificantly compared to the experimental errors.

The reflectivity (σ_1) of pure ethylcellulose is 0.58 using the model with two different reflectivities. This is significantly lower than for the relaxed free film. We suggest that this discrepancy originates from the oversimplified model. We have previously shown that tensile stress in EC membranes results in loss of reflectivity for KCl (Hjärtstam et al., 1990). It was also suggested that the major part of the membrane still maintains its reflectivity. This study, however, shows that the membrane coat suffers a reduction in reflectivity, calculated on the whole surface area. From data presently available it is not possible to establish how this loss is distributed in the tablet coats.

Incorporation of HPMC reduces the reflectivities of the membranes even further, although the release rates increase. For 27% HPMC drug diffusion contributes to release, and for 30% this is the dominant release mechanism. The reflectivities of these membranes are 0.23 and 0.07, respectively. Osmotic pumping is thus very much reduced for these compositions.

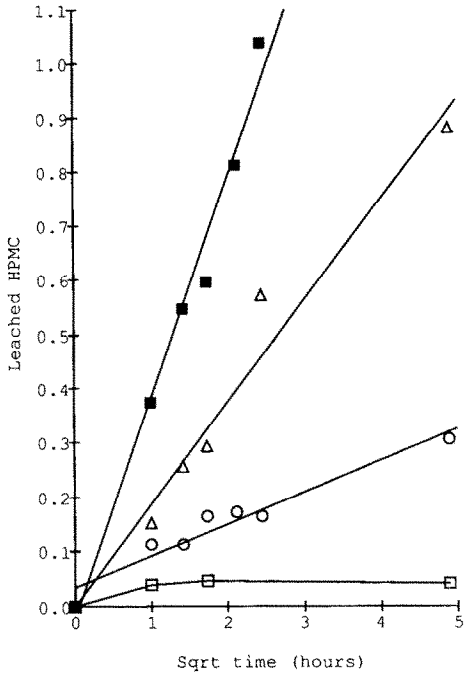


Fig. 3. Fraction HPMC leached from free films versus square root of time. □ 20% HPMC ○ 24% HPMC △ 25% HPMC ■ 30% HPMC.

Structure of the tablet coats

To understand better the drastic loss of reflectivity when the HPMC fraction exceeded 24%, we measured the water content in free hydrated films. Water was detected as either total water or freezing water. The results from different soaking times are shown in Fig. 2. For the films of low HPMC content, up to 20%, no freezing water could be detected. The total water content increases only slowly by increasing HPMC fraction, and furthermore an equilibrium water content was reached after a very short soaking time (only a minor increase from 15 minutes to 3 hours soaking for 20% HPMC was detected).

For the films with much HPMC (30%), total water increases with time and reaches 40% of the dry film at 24 h. A large fraction is freezing water: 59% after 24 h soaking. However, after only 15 min soaking, no freezing water was detected. It is then evident that a slow process is involved in the formation of freezing water. This is probably the leaching of HPMC, which is shown in Figure 3. The leaching of HPMC seems to be linear with the square root of the time. We propose that HPMC is leached from the membrane, leaving pores that contain the freezing water. The leaching of the large molecule HPMC implies that the pores are interconnecting. These water-filled pores may thus offer opportunities for solute transport by diffusion through the membrane coats of the tablets.

There is an important difference between the films with 25 and 24% HPMC. With 24% HPMC content freezing water is present after 24 hours, but is present in the films with 25% HPMC after only 3 hours. It is shown in Fig. 3 that leaching of HPMC is much slower in the films with 24% HPMC, and reaches only 30% after one day of soaking. Freezing water is also formed in the film with 24% HPMC, after several hours of leaching. It is therefore possible that this film changes its transport properties with time, and the process occurs in a time-frame of hours. In the film with 20% HPMC, some water-soluble polymer is also leached, but the extent levels off at only about 5%.

This polymer probably originates from the surface of the film, since no freezing water could be detected in that film.

Conclusions

It is not possible to describe osmotic pumping release from a membrane-coated formulation with only one single reflectivity parameter for the membrane. So far an area with no reflectivity has been anticipated, as for the OROS (Theeuwes, 1975). If, however, two different areas possessing different reflectivities are included, a useful model can be derived. This model may be used to calculate the osmotic pumping release rate from membrane-coated tablets without a preformed means for drug solution transport.

We have shown a significant difference between EC/HPMC films of low and high HPMC fraction. At low HPMC content very little polymer is leached and no pores are formed. When the HPMC content is increased to 24%, the water-soluble polymer can be leached from the polymer film. This results in pore formation, which increases the diffusive release of the drug. At 24% HPMC the leaching of HPMC takes several hours, during which the barrier properties of the film may change. If the HPMC content is increased to 30%, the leaching is faster, and thereby the time for pore formation is decreased.

The formation of pores by leaching of HPMC from EC does not promote osmotic pumping, since the reflectivity of the membrane is reduced. An increased osmotic pumping rate is achieved by increasing the water permeability of the membrane without decreasing the reflectivity.

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Glossary

Symbol	Meaning
A	Area of membrane
C	Concentration of solute
C_s	Solubility of solute (the drug)
D	Solute diffusivity in solution
D_s	Release rate of solute by diffusion
F_v	Volume flow through a membrane
F_s	Flow of solute through a membrane
g	Gravity
g'	Reduced gravity
h	Membrane thickness
J_v	Bulk volume flux
J_s	Flux of solute
l	Membrane height
L_p	Hydraulic permeability of membrane
L'_p	Hydraulic permeability of membrane material
P	Hydrostatic pressure
P_s	Permeability of membrane for solute (concentration difference as driving force)
Q	Release rate of solute
δ_0	Thickness of unstirred layer
ω	Permeability of membrane for a solute (osmotic pressure as driving force)
Π	Osmotic pressure
ρ	Density of solution
σ	Reflectivity of membrane for a solute

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