International Journal of Pharmaceutics, 56 (1989) 261–268
Elsevier

IJP 01917

Osmotic pumping as a release mechanism for membrane-coated drug formulations

Bengt Lindstedt, Gert Ragnarsson * and Johan Hjärtstam

Pharmaceutical R&D, AB Hässle, S-431 83 Mölndal (Sweden)

(Received 27 January 1989)
(Modified version received 2 June 1989)
(Accepted 6 June 1989)

Key words: Osmotic pumping; Drug release; Osmotic permeability; Reflectivity; Ethyl cellulose

Summary

By using osmotic pumping, it is possible to release a drug from a membrane-coated drug formulation although the drug diffusion through the membrane is very limited. Instead, the water permeability of the membrane is the primary release rate-regulating parameter. Free films made by spraying solutions of ethyl cellulose onto a rotating cylinder were shown to be semipermeable, i.e. the permeability includes water but to a large extent excludes the solute. The water permeability was estimated by diffusion experiments with tritiated water and a more conventional osmosis experiment. The permeability of ethyl cellulose was very low, only about one tenth of that of cellulose acetate, but was increased by incorporating hydroxypropyl methylcellulose (HPMC) in the film composition. Cores of potassium chloride (KCl) coated with mixtures of ethyl cellulose and up to 24% HPMC were shown to release their content mainly through osmotic pumping. When the HPMC content exceeded 24%, the permeability of KCl through the films also becomes substantial. Thus, for cores of KCl coated with such films, both drug diffusion and osmotic pumping mechanisms contribute to the drug release.

Introduction

Membrane coating is a very convenient way of regulating the release rate of oral formulations. The formulations may be large, single units (coated tablets), or small particle multiple units (coated pellets or crystals). To be able to develop pharmaceutical preparations that meet appropriate medical demands, based on drug substances with various intrinsic properties (e.g. solubility, diffusivity or lipophilicity), it is of importance to gain knowledge about the barrier properties of the membrane as well as the drug release mechanisms.

Membrane coatings are in general considered to release the drug by diffusion of the drug through the membrane material or through pores (Langer and Peppas, 1983). Formulations where osmotic pumping is a major release mechanism have been presented, the most common being the elementary osmotic pump (Theeuwes, 1975). In osmotic pumping formulations, the release-regulating process is the osmotic diffusion of water into the device, not the diffusion of the drug molecule itself.

The elementary osmotic pump is characterized by a core that dissolves in water giving a solution

* *Present address:* KABIPharma, Box 1828, S-171 26 Solna, Sweden.
Correspondence: B. Lindstedt, Pharmaceutical R&D, AB Hässle, S-431 83 Mölndal, Sweden.

of considerable osmotic pressure, a semipermeable membrane coat surrounding the core and a drilled exit port that permits the solution to flow out of the device. The term 'semipermeable' means in this case that the permeability of the solute is very much restricted compared to that of water. Ramadan and Tawashi (1987) made elementary osmotic pumps from potassium chloride cores, without giving any detailed information on the composition of the coat. Some experiments were made on tablets without drilled exit holes. The time lag, when practically no salt was delivered, increased from about 1 to 2 h but the release rate was not substantially decreased.

An interesting system, where potassium chloride tablets were coated with cellulose acetate, together with sorbitol, has been described (Zentner et al., 1985). The water-soluble sugar was leached out from the membrane coat, leaving a sponge-like structure. This acted as a semipermeable membrane, and an osmotic pumping mechanism was proposed by the authors. The proposal was confirmed by the fact that the release rate could be calculated from the osmotic permeability of the membrane and the diffusion rate of potassium through the membrane.

The aim of this report is to show the existence and importance of osmotic pumping in a membrane-coated drug formulation where no attempts have been made to create pores. We have chosen to use mixtures of ethyl cellulose and hydroxypropyl methyl cellulose (HPMC) as membrane coats. A simple technique to establish the osmotic permeability of free films of these materials will also be presented.

Materials and Methods

Materials

The film-forming polymers were mixtures of ethyl cellulose (Ethocel Std 10 premium, DOW Chemical, U.S.A.) and HPMC (Pharmacoat 606, Shin-Etsu, Japan), 0–30%. The solvents used, dichloromethane and 2-propanol, were of pharmacopeial grade (USP XXI). Potassium chloride for tablet preparation was according to EP (E. Merck, FRG) and contained 0.8% fumed silica. Sodium chloride was a dendritic form (AKZO Zout Chemie, The Netherlands), suitable for direct compression. Urea was of analytical grade (E. Merck, F.R.G.) and the deionized water was MilliQ (Millipore). Tritium labelled water (TRS 8B) was purchased from Amersham, U.K.

Free film preparation

Free films were prepared by spraying polymer solutions onto a rotating cylinder, according to a method described by Allen et al. (1972), at room temperature and 15 to 20% relative humidity. After drying for 30 min at 50 °C, the films were stripped off the perspex cylinder and allowed to dry for at least 24 h in the same conditions as used for spraying.

To show that the films obtained in this way do not differ significantly from films obtained in a conventional fluidized bed coating process, flat sodium chloride tablets ($\phi = 10$ mm, 530 mg) were coated in a laboratory Wurster column ($\phi = 10$ cm). Small circular film segments were removed from the tablets and used as reference samples.

Measurement of hydraulic permeability

An osmosis cell was designed to measure the hydraulic permeability of the free films prepared by spraying on a rotating cylinder (Fig. 1). A 1.5 molal solution of potassium chloride was used to give an osmotic pressure difference, $\Delta\Pi$, between the inside cell and the surrounding deionized water. The osmotic pressure of this solution is 7.0 MPa at 37 °C (Robinson and Stokes, 1964). The film in the osmosis cell is reasonably relaxed and the weight increase of the cell may thus be taken as the water osmosis through the film.

The total volume flux through the membrane is given in one of the Kedem-Katchalsky equations, which are described in a textbook by Friedman (1986):

$$J_v = \frac{A}{h} L_p(\sigma\Delta\Pi - \Delta P) \qquad (1)$$

where A is the membrane area, h its thickness, L_p the hydraulic permeability of the membrane and $\Delta\Pi$ is the osmotic pressure difference (the experiment is shown schematically in Fig. 2). σ is the

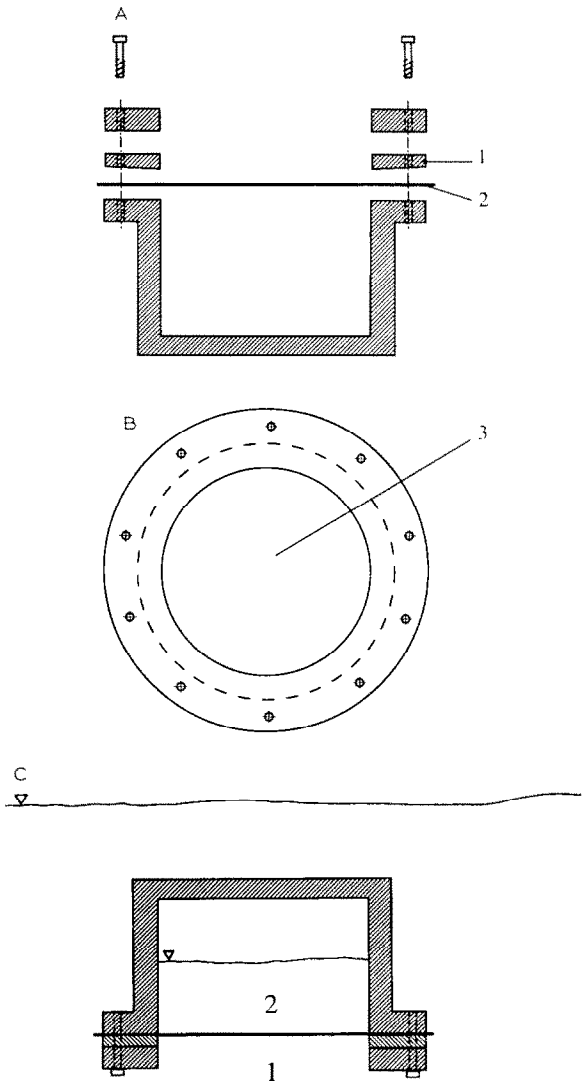

Fig. 1. A: osmotic diffusion cell. Top view (A) and cross section (B). 1, PTFE gasket; 2, polymer film; 3, exposed area 24.3 cm^2. C: osmotic diffusion cell in thermostated water. 1, deionized water at 37 °C; 2, osmotic solution.

reflectivity of the membrane for the solute and cannot be evaluated separately in this experiment. ΔP, the hydrostatic pressure difference between the cell halves, is very small compared to $\Delta \Pi$ (7 MPa) and can be neglected in the calculation of σL_p:

$$\sigma L_p = \frac{J_v h}{A \Delta \Pi} \qquad (2)$$

Tracer diffusion experiments

Diffusion experiments with tritiated water on the free films were performed in a cell originally designed by Ussing and Zerahn (Fig. 3, 1951). For the films prepared by spraying on a rotating cylinder, a cell with a diameter of 10 mm was used. The free films from the flat NaCl tablets were mounted in a smaller cell with a diameter of 8 mm.

At the beginning of each experiment, 15 ml of deionized water was added to both cell compartments and the circulation by air-bubbling was started. A small amount (10 μl, containing about 400 kBq) of tritiated water was then added to the donor compartment. Sample volumes of 500 μl were withdrawn at specified time intervals from the receiver compartment, weighed, and analyzed in a γ-scintillator.

The increase in tritium activity in the receiver compartment was divided by the tritium activity per unit volume in the donor cell. In this way, the total exchange flux, F, is evaluated, not the true osmotic flux, J_v. As the tritium activity in the donor compartment is much higher than in the receiver, the counter-diffusion of tritium was neglected.

Osmotic pressure is a way to describe an activity difference between a solution and the pure solvent, water, Eqn. 3:

$$\Pi = -\frac{RT}{v} \ln a \qquad (3)$$

where v is the molar volume and a is the chemical

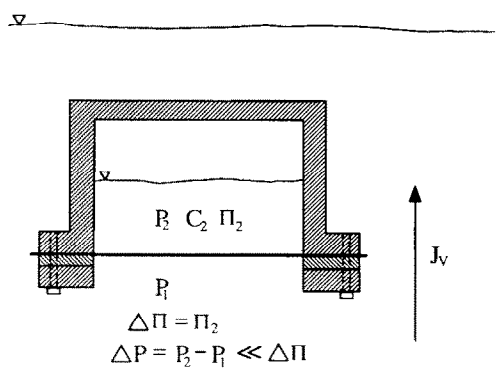

Fig. 2. Schematic presentation of the osmotic experiment.

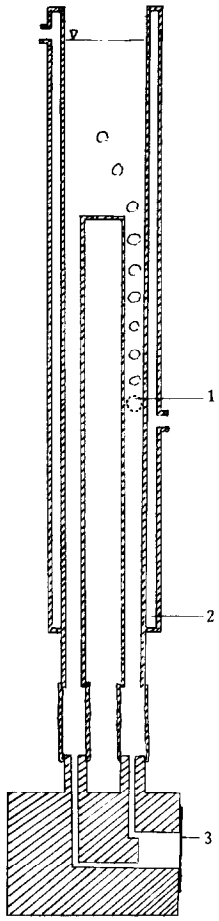

Fig. 3. Ussing diffusion cell. Left cell half. 1, Air bubbling inlet; 2, water jacket (37 °C); 3, polymeric membrane.

activity of water. The tracer diffusion experiment is better described through an activity difference, rather than an osmotic pressure.

The chemical activity difference between the compartments for the tritiated water is unity, as no labelled water exists in the receiving compartment at the beginning of the experiment. For the protium water, however, the activity difference is close to zero. We can thereby calculate the permeability, P_t, for the membrane material from these experiments, using Eqn. 4:

$$P_t = \frac{Fh}{A} \tag{4}$$

The permeability has the form of a diffusion coefficient. Our measurements are made in water, not in the polymer phase, and the true diffusion coefficient is not measured. The calculated permeability is strictly valid for tritiated water. We can assume, however, that protium water has a permeability not differing from this more than the experimental errors.

Tablets

Small tablets weighing about 25 mg were manufactured by mixing potassium chloride with 0.5% magnesium stearate and compressing with 3 mm punches. The tablets were coated in a Wurster column with the same polymer compositions as for the free films. The release rates of the tablets were determined in a USP no 2 apparatus (paddle, 100 rpm), using 500 ml of deionized water or 500 ml of urea solutions, and 5 tablets in each run. The amount of KCl released was measured with a calibrated potassium-selective electrode (K-Selektrod, Radiometer).

The osmotic pressure for a saturated KCl solution at 37 °C was calculated to be 27.0 MPa using values given by Robinson and Stokes (1964). The osmotic pressures of the urea solutions were calculated from tabulated freezing points (Wolf et al., 1975).

The coated tablets were also observed in a scanning electron microscope (JEOL JSM 20T). The film coat thickness was measured from photomicrographs.

Results and Discussion

Permeability from osmosis

The permeability values from the osmosis experiments on free films are given in the left column of Table 1. We performed measurements on films with not more than 24% HPMC, as the films with higher HPMC content had very low tear strength. The permeability increases with an increase in HPMC content. From 18% HPMC, a minor increase in HPMC content results in a drastic increase in permeability.

Tracer diffusion experiments

A typical result from a tracer diffusion experiment is shown in Fig. 4. From the least square fit,

TABLE 1

Hydraulic permeability of ethyl cellulose films, free films or KCl tablet coats

% HPMC	Free films, σL_p ($m^2 h^{-1} MPa^{-1} \times 10^{10}$)	Tablet coats, σL_p ($m^2 h^{-1} MPa^{-1} \times 10^{10}$)
0	0.36	0.21
10	0.55	
18	0.92	0.41
20	1.10	0.46
22	1.16	
24	1.68	0.52
27		0.80
30		1.04

the permeability, P_t, of the film was calculated, using Eqn. 4. The results from the different film compositions are given in Table 2, together with the values from the osmosis experiment, recalculated using Eqns. 3 and 5:

$$P_{osm} = \frac{J_v h}{A(a_1 - a_2)} \quad (5)$$

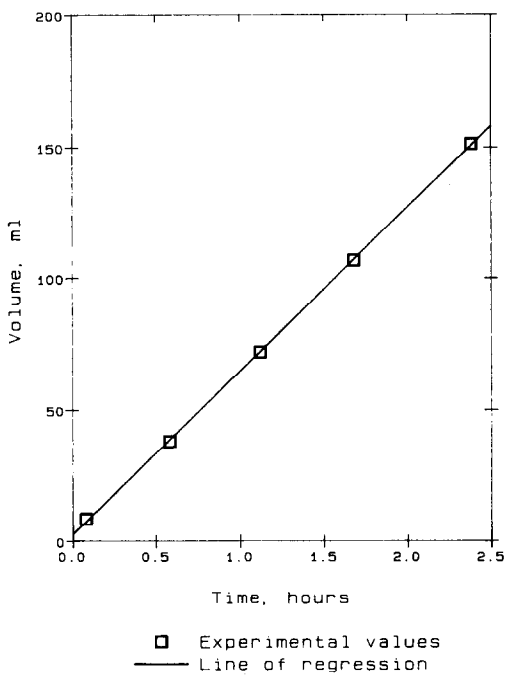

Fig. 4. Result from tritium diffusion through a free film of ethyl cellulose/HPMC 4/1. Experimental data and linear regression.

TABLE 2

Permeability of free ethyl cellulose films from osmosis (recalculated from Table 1), P_{osm}, and with tracer diffusion on cylinder-sprayed films, P_t, or free films from NaCl tablets, P_t(tabs)

% HPMC	Osmosis P_{osm} ($m^2 s^{-1} \times 10^{12}$)	Tracer P_t ($m^2 s^{-1} \times 10^{12}$)	Tracer P_t(tabs) ($m^2 s^{-1} \times 10^{12}$)
0	1.44	1.85	1.62
10	2.21	2.38	
18	3.70	3.53	3.49
20	4.42	4.46	
22	4.68	5.54	
24	6.86	7.38	6.44
27		9.57	
30		22.8	

The agreement between the methods is very good, indicating that the osmotic permeability can be estimated in the tracer diffusion experiment. We also conclude that the reflectivity of the films with not more than 24% HPMC for KCl is very high, and σ is close to unity.

The films from the sodium chloride tablets had permeabilities very close to those sprayed on the rotating cylinder (Table 2). It is thus plausible that the method of free film preparation gives films that correspond well to those on tablets or granules coated using an air suspension technique. This may, however, not be the case for cast films based on ethyl cellulose and HPMC, as the polymers show a limited phase mixing (Sakellariou et al., 1988). The slow evaporation in casting can give a different morphology than the much faster spraying technique.

The water permeability of pure ethyl cellulose is very low, only about one tenth of the values obtained from cellulose acetate in a diffusion cell, $16.9 \cdot 10^{-12}$ $m^2 s^{-1}$ (Bindshaedler et al., 1986). This may explain the limited use of ethyl cellulose for coating osmotic formulations. The permeability is, however, high enough to influence the release characteristics of coated formulations, as is shown below.

Release characteristics of coated tablets

To analyze the release mechanisms of the coated tablets, we decided to measure the release rate in solutions with varied osmotic pressure. In this

way, the osmotic pressure difference, or the difference in water activity, is changed. A lower $\Delta\Pi$ will give a lower osmotic flux (Eqn. 1). It is not possible to use KCl to reduce the osmotic pressure difference, however, as this would reduce the release rate by diffusion through the membrane. In the derivation of Eqn. 1, only a single solute was considered. The following approximation may, however, be used (Friedman, 1986):

$$J_v = \frac{A}{h} L_p(\sigma_1 \Delta\Pi_1 + \sigma_2 \Delta\Pi_2 - \Delta P) \qquad (6)$$

Index 1 refers to potassium chloride and 2 to urea, which is used to increase the osmotic pressure in the receiving compartment. We have shown that σ_1 is close to unity, at least for the films with up to 24% HPMC. A reasonable assumption is that σ_2 is also close to unity, or the deviation from that value is of the same order as for KCl. Assuming that ΔP is much smaller than $\Delta\Pi$, Eqn. 6 can be rewritten as:

$$J_v = \frac{A}{h} L_p \Delta\Pi \qquad (7)$$

The resulting release rates are given in Fig. 5. Tablets coated with 0 to 24% HPMC show a very low release at zero $\Delta\Pi$. For 27 and 30% HPMC, the release is substantial although J_v should be very low. The release rate is higher in low urea concentrations than in pure water. It is plausible that urea affects the permeability of the membrane, possibly by dehydrating the HPMC in the film coat. The film with 24% HPMC also to some extent shows an increased permeability in urea solutions. The release rate at lower $\Delta\Pi$ decreases towards zero, however.

As the release rate is affected by the osmotic flux, osmotic pumping is important for the release of potassium chloride in these formulations. For up to 24% HPMC, the release rate is halted when $\Delta\Pi$ is zero, indicating that osmotic pumping is the only important delivery mechanism. The release of potassium in the same medium for the tablets coated with 27 and 30% HPMC proves that diffusion of KCl is also an important delivery mechanism.

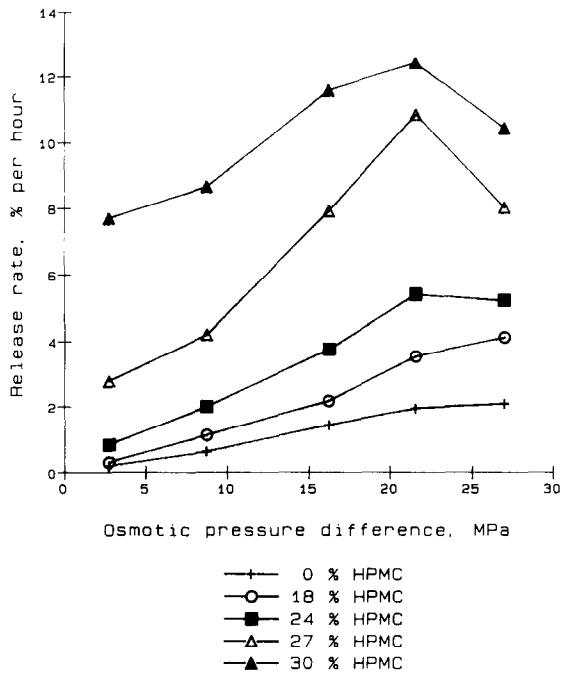

Fig. 5. Release rates vs osmotic pressure differences for potassium chloride tablets coated with ethyl cellulose and HPMC.

The fraction of released potassium chloride versus time in deionized water is shown in Fig. 6. There is no 'time lag effect' as was found by Ramadan and Tawashi (1987). The release rates fit a zero order release, as indicated by theoretical considerations (Theeuwes, 1975). The release rate is much higher for the more permeable film coating compositions.

The permeabilities of the membrane coats were calculated for each polymer composition. Each tablet contained 25.8 mg KCl, had a surface area of $37 \cdot 10^{-6}$ m^2 and an average membrane thickness of $13 \cdot 10^{-6}$ m. From the release rate in deionized water, we calculated the permeability of the membrane coat of the tablets. The release rate is divided by the solubility of KCl, 335 g/l solution (Bindshaedler et al., 1986), giving J_v. The values are given in the right column of Table 1.

The values are significantly lower than those obtained for the free films. This is equal to a lower release rate than predicted. We have seen, however, that the free films removed from coated NaCl tablets showed the same permeability as the

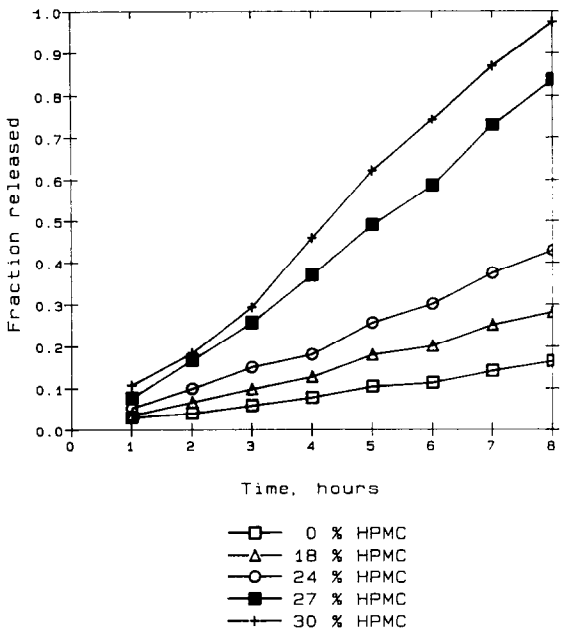

Fig. 6. Release profiles for the potassium chloride tablets of Fig. 5, in deionized water.

free films from spraying on a rotating cylinder, as discussed above. The smaller tablets thus appear to have a denser film coat, with a markedly lower permeability, or the effect of unstirred layers in the tablets gives a lower effective driving force and possibly also a lower concentration in the outflowing drug solution.

The release mechanism for osmotic pumping preparations can be separated into two different phenomena: water osmosis and drug solution release. It is thus necessary that the saturated solution can permeate the membrane for osmotic pumping to take place. The route is self-evident for the elementary osmotic pump as the membrane coat has been perforated. The tablets described by Zentner et al. (1985) are coated with very porous film coats, which provide a means for the permeation of the drug solution. It is possible that the film coats with 27 and 30% HPMC also contain pores through which the solution can permeate but the films with a lower content of water-soluble polymer appear to be highly impermeable to KCl. We have performed further work to be able to explain this, which will be described in a later publication.

Conclusions

It is important to include osmotic pumping mechanisms when analyzing release characteristics of membrane coated drug formulations. Even a very low osmotic permeability, as for pure ethyl cellulose, may be sufficient to induce osmotic pumping. When the membrane coat is made more permeable to the drug, drug diffusion and osmotic pumping may both contribute to drug release.

Changing the osmotic pressure in the release medium is a convenient way to evaluate the release mechanisms of the drug preparation. It is important to consider the theoretical limitations, however, and to choose proper osmotic species.

The osmotic pressure of the core, from both the drug itself and excipients, is an important drug release rate-regulating factor, as well as the solubility of the drug. Drug diffusion data based on experiments with free films cannot alone be used to predict the release rate from coated drug particles. Further, it is possible with osmotic pumping to deliver drugs of high molecular weight or unfavourable membrane solubility, in spite of a very low permeability through the membrane coat.

Acknowledgements

Experimental assistance from and valuable discussions with our colleagues at Hässle is gratefully acknowledged, especially from Ms Karin Borg, during her work for the MSc thesis, and Ms Marie Sjöberg.

List of symbols

A = exposed area
a = chemical activity
F = total exchange flux
h = thickness of a membrane
J_v = total volume flux
L_p = hydraulic permeability
P = hydrostatic pressure
P_{osm} = permeability measured with osmosis
P_t = permeability measured with tracer diffusion

Π = osmotic pressure
v = molar volume
σ = reflectivity of a membrane for the solute.

References

Allen, D.J., DeMarco, J.C. and Kwan, K.C., Free films 1: apparatus and preliminary evaluation. *J. Pharm. Sci.*, 61 (1972) 106–109.

Bindschaedler, C., Gurny, R. and Doelker, E., Osmotically controlled drug delivery systems produced from organic solutions and aqueous dispersions of cellulose acetate. *J. Contr. Rel.*, 4 (1986) 203–212.

Friedman, M.H., *Principles and Models of Biological Transport*, Springer, Berlin, 1986, pp. 105–133.

Langer, R. and Peppas, N., Chemical and physical structure of polymers as carriers for controlled release of bioactive agents: a review. *Rev. Macromol. Chem. Phys.*, C23 (1983) 61–126.

Ramadan, M.A. and Tawashi, R., The effect of hydrodynamic conditions and delivery orifice size on the rate of drug release from the elementary osmotic pump system (EOP). *Drug Dev. Ind. Pharm.*, 13 (1987) 235–248.

Robinson, R.A. and Stokes, R.H., *Electrolyte Solutions*, Butterworths, London, 2nd edn, 1964, 476 pp.

Sakellariou, P., Rowe, R.C. and White, E.F.T., A study of the leaching/retention of water-soluble polymers in blends with ethylcellulose using torsional braid analysis. *J. Contr. Rel.*, 7 (1988) 147–157.

Theeuwes, F., Elementary osmotic pump. *J. Pharm. Sci.*, 64 (1975) 1987–1991.

Ussing, H.H. and Zerahn, K., Active transport of sodium as the source of electric current in the short circuited isolated frog skin. *Acta Physiol. Scand.*, 23 (1951) 110–127.

Wolf, A.V., Brown, M.G. and Prentiss, P.G., Concentrative properties of aqueous solutions: conversion tables. In Weast, R.C. (Ed.), *Handbook of Chemistry and Physics*, 56th edn., CRC Press, Cleveland, 1975, D264–D265.

Zentner, G.M., Rork, G.S. and Himmelstein, K.J., Osmotic flow through controlled porosity films: an approach to delivery of water soluble compounds. *J. Contr. Rel.*, 2 (1985) 217–229.