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The effect of tensile stress on permeability of free films of ethyl cellulose containing hydroxypropyl methylcellulose

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Summary

The effect of tensile stress on potassium chloride permeability in composite films containing ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC) has been measured in a novel pressurized cell. Such a tensile stress is expected to develop in a film-coated drug formulation as a result of osmotic water imbibition. Free composite films of EC with HPMC contents ranging from 0 to 30 wt% were prepared by spraying a polymer solution on a rotating cylinder. It was found that films with 24% HPMC or less became permeable to potassium chloride only under the influence of an applied tensile stress. Increasing the film HPMC content lowered the magnitude of the applied tensile stress required to induce permeability. This tensile stress correlated with the breaking stress of the film. Additionally, provided that the tensile stress remained below the breaking stress of the film, the permeability properties were found to be reversible with respect to changes in the applied tensile stress. It is believed that the application of a tensile stress causes small alterations in film structure which affect transport and mechanical properties of the films.

Introduction

Membrane coating of pharmaceutical formulations (tablets, pellets or crystals) is a convenient way of regulating drug release rates. Mixtures of ethyl cellulose and water-soluble polymers are often used as coatings for pellets and tablets and generally have release properties that are pH-independent (Donbrow and Friedman, 1975; Donbrow and Samuelov, 1980; Rowe, 1986). Lindstedt et al. (1989) recently showed that the rate of water ingress into the coating is the major release-regulating factor for potassium chloride tablets coated with ethyl cellulose (EC)/hydroxypropyl methylcellulose (HPMC) mixed films containing 24% HPMC or less. Water imbibition leads to an internal hydrostatic pressure across the film which creates a tensile stress on the membrane.

A common technique to measure membrane semipermeability is that used, for example, by Reid and Breton (1959). The salt solution of interest is forced through the supported membrane with an applied pressure and the salt content of the resulting filtrate is determined. The salt rejected by the membrane is taken as a measure of semipermeability. Because this method involves the application of an applied pressure, the membrane is exposed to a tensile stress. However, the

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method of Reid and Breton was not designed to quantify or control the magnitude of the resulting tensile stress of the membrane nor to evaluate the effect of tensile stress on the membrane permeability.

The aim of this study was to investigate the effect of an applied tensile stress on the transport properties of mixed films of EC and HPMC. A new measurement technique was developed which permitted the application of a constant and adjustable tensile stress on the film during a transport experiment. The advantage of this new technique is that the effect of an externally applied tensile stress on membrane permeability can be readily studied.

Materials and Methods

Materials

The filmformers studied were ethyl cellulose (Hercules, EC N10NF), hydroxypropyl methylcellulose (Shin-Etsu, Pharmacoat-606) and cellulose acetate (FMC, CA grade 398-10). All materials were used as received.

Preparation of free films

Table 1 summarizes the compositions of the films used in this work. The polymers were dissolved in the solvents and mixed overnight. The polymer solutions were then sprayed on a rotating cylinder, as described earlier (Allen et al., 1972; Lindstedt et al., 1989). After drying for 30 min at 50 ° C, the films were peeled off the cylinder. The thicknesses of the films were 20 ± 1 μm as measured with a micrometer.

TABLE 1

Compositions of the film-spraying solutions

Film	EC 10 cps	HPMC 6 cps	Dichloromethane	2-Propanol
EC 0	7.70	–	231	77
EC 18	6.31	1.39	231	77
EC 24	5.85	1.85	231	77
EC 30	5.39	2.31	231	77
Film	CA 398-10	Ethyl acetate	Acetone	
CA 0	10.00	50	200	

Values expressed in g for each component.

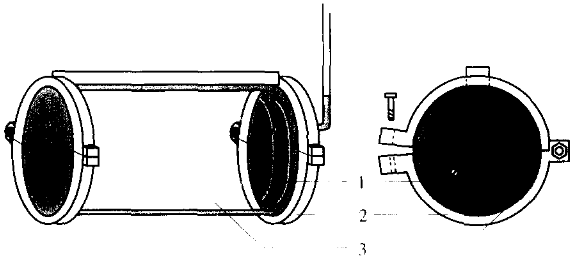

Fig. 1. The cylinder-shaped pressurized cell. (1) Inner compartment, (2) locking device, (3) free film.

Breaking stress measurement

Rectangular strips from the free films of length 120 mm and width 10 mm were hydrated in distilled water for about 18 h. The breaking stress was then measured in a Hounsfield H2000 tensile apparatus using a 200 N load cell and an extension speed of 10%/min.

Design of the pressurized cell

The pressurized cell consisted of a hinged cylindrical metal clamp into which rectangular strips (5 × 9.5 cm) of the free films were mounted. The clamp made contact with the film via rubber gaskets and the cell was secured with locking screws at either end. The cell is depicted schematically in Fig. 1. The film thus arranged formed the jacket of the cylinder and separated the inner compartment from the exterior of the cell. Areas of the original sprayed film containing surface imperfections or other flaws were carefully avoided in cutting out the film for the pressurized cell. The inner compartment was filled with an aqueous solution of choice and was connected to a vertical column containing the same solution which allowed for the application of a hydrostatic pressure across the film. This resulted in a uniformly distributed tensile stress (s) on the film which could be computed as (Bodelind and Persson, 1968):

$$s = \frac{\Delta p \cdot d}{2 \cdot h} \quad (1)$$

A relatively large cell length (5 cm) was used to minimize edge effects resulting from the presence of the clamps.

Experimental protocol

Using the pressurized cell as described, two types of experiments were performed. In the first experiment, shown schematically in Fig. 2, the cell interior was filled with 1.5 M KCl solution and was placed in 1000 ml thermostatted vessel (37 ° C) containing 0.1 M NaCl solution (exterior solution). In the second experiment, the cell interior was filled with deionized water and placed in a 1.5 M KCl solution. In each case, a magnetic stirring bar was placed in the bottom of the vessel and the static pressure ($\Delta p = \rho g l$) was applied by a column of inner-cell liquid. With these simple experimental arrangements, it was easy to alter the tensile stress on the film by adjusting the height of liquid in the vertical column. During the course of any experiment the column height remained constant. The permeation of K^+ was determined in each experiment with a K^+-selective electrode (K-Selektrod, Radiometer) placed directly in the external solution (first experiment) or placed in samples removed from the inner-cell compartment (second experiment).

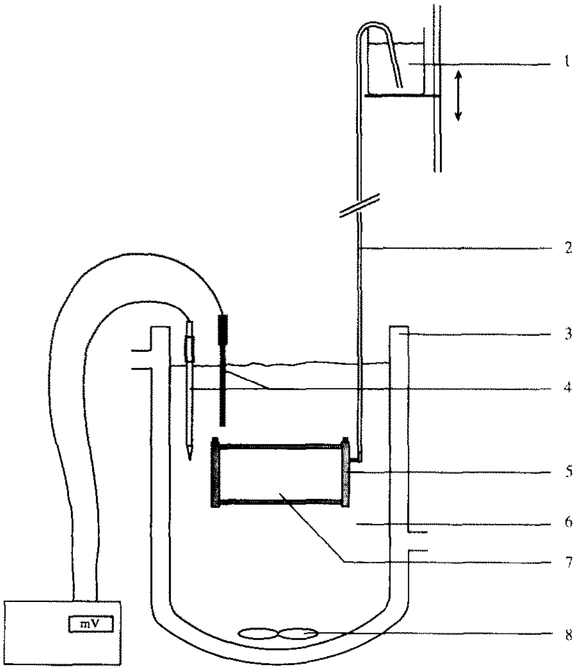

Fig. 2. Apparatus for the pressurized cell. (1) Beaker with 1.5 M KCl, (2) silicon tube, (3) water-jacketed vessel, (4) electrode, (5) cylinder cell, (6) 0.1 M NaCl, (7) free film, (8) magnetic bar.

As an operational check of the cell, cellulose acetate membranes, which are known to be impermeable to K^+ (Reid and Breton, 1959), were mounted in the cell. The inner compartment was filled with 1.5 M KCl and the cell was immersed in 0.1 M NaCl solution. The appearance of K^+ was monitored in the external solution. It was found that no K^+ was detected in the external solution even with applied tensile stresses up to 20 MPa. This indicates that no edge-leakage occurred from the internal compartment of the pressurized cell.

Results and Discussion

The effect of an externally applied tensile stress on the permeation rate of K^+ through pure EC films is shown in Fig. 3. Transport of K^+ through the film is virtually zero when the tensile stress is low (up to 4 MPa) but increases somewhat as tensile stress is further increased. This indicates that a relaxed film has a very low permeability to KCl but the application of a tensile stress influences the transport properties of the film. Penetration commences when the tensile stress is increased above a threshold value, although this value is difficult to determine due to the scatter in the data. The most likely cause of variability in these experiments is the difficulty in obtaining films of uniform thickness.

The effect of tensile stress on the permeation rate of EC/HPMC composite films containing 18, 24 and 30% HPMC is represented in Figs. 4–6, respectively. The permeation of K^+ is very low through these films when the applied tensile stress is low but increases as the tensile stress increases past a threshold value. However, the threshold value is significantly lowered by increasing film HPMC content.

The influence of HPMC content on the breaking stress of free films hydrated for 18 h in deionized water is shown in Fig. 7. The breaking stress appears to decrease linearly with increasing

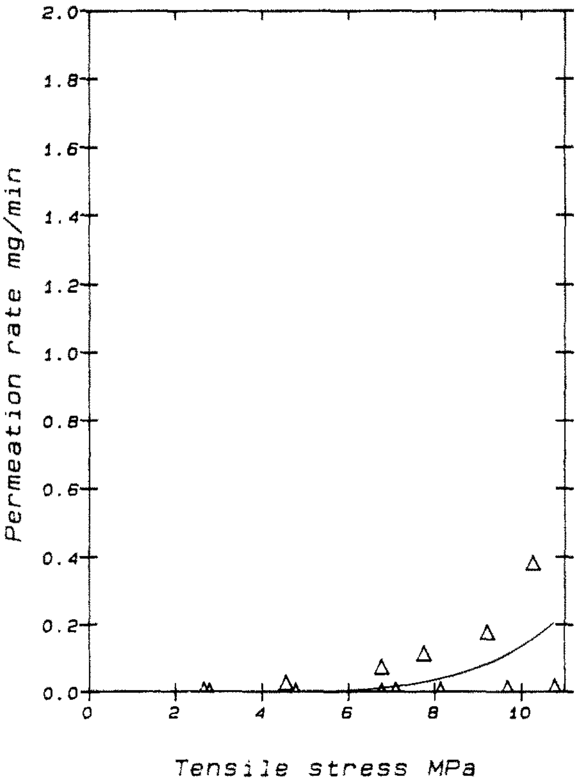

Fig. 3. Effect of tensile stress on the release of K^+ through EC-film without HPMC.

HPMC content from a value of 28 MPa for the pure hydrated EC film to approx. 15 MPa for the film containing 24% HPMC. In all cases, the breaking stresses were well above the maximum applied tensile stresses for all permeation experiments. These results clearly indicate that the increase in K^+ permeation observed above the threshold tensile stress of each film (Figs 3–6) is not caused by mechanical failure of the film.

It is important to note that the breaking strain for the hydrated films was lower than the yield strain, and thus the films can be characterized as brittle. For such EC films, we propose that a change in mechanical properties is involved in the increased permeability of the free films, but that the magnitude of these changes is well below that for film failure.

To gain more insight into the transport processes involved, experiments were performed in which the applied tensile stress was alternated four times between a low value (2 MPa) and a higher value (5.5 MPa) for a single pure EC film-strip, with the K^+ permeability being measured at each constant value of tensile stress. As shown in Fig. 8, the permeation rate at 2 MPa increased from 0.02 to 0.08 mg/min after the first exposure to the higher tensile stress. Such an increase in permeation rate, however, was not observed when the film was exposed to a constant tensile stress of 2 MPa for more than 12 h. Subsequent cycles produced no significant change in the permeation rate at the low tensile stress, but did give rise to successively increasing permeation rates at the high tensile stress.

Exposure to higher tensile stresses (5 MPa) apparently creates changes in film structure, such as the formation of microvoids, which remain after the tensile stress has been lowered. These alterations, however, did not produce macroscopic cracks or flaws in the films as determined by

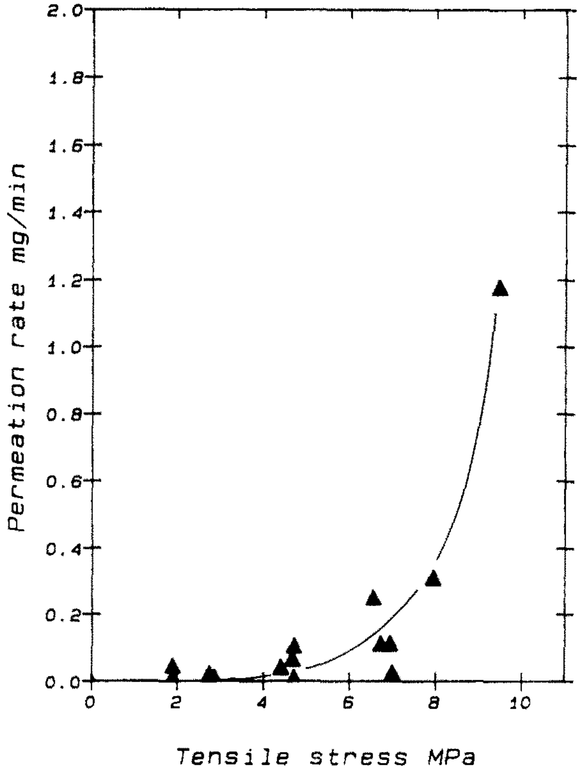

Fig. 4. Effect of tensile stress on the release of K^+ through EC-film with 18% HPMC.

visual inspection. When the pure EC films without HPMC were exposed to even higher tensile stresses (15–20 MPa and above), macroscopic cracks were formed, which were visually observed in the outstreaming salt solution and a concomitant rapid increase in K^+ concentration in the external solution.

The flux of water and solute through semipermeable membranes is described by the Kedem-Katchalsky equations (Friedman, 1986). A full list of definitions of symbols is given in the glossary (p. 107).

$$J_v = L_p(\Delta p - \sigma \Delta \Pi) \quad (2)$$

$$J_s = C(1 - \sigma) J_v + \omega \Delta \Pi \quad (3)$$

The total volume flux (J_v) is given in Eqn 2, and cannot be measured in the pressurized cell. The permeation of KCl through the film is described by Eqn 3. The flow of K^+ (J_s) can be caused either by convection (first term) and/or diffusion through the membrane (second term). In order to clarify the transport mechanism, experiments of the second type were performed, where an 18% HPMC film was exposed to a constant tensile stress of up to 12 MPa and the resulting K^+ permeation, was measured in the usual way. In these experiments, the external solution of the cell initially contained KCl solution while the interior solution contained deionized water. It was found that no increase in K^+ concentration was detectable in the internal solution of the cell for up to 6 h. As the K^+ concentration gradient across the film was substantial, transport involving a diffusion mechanism cannot explain the increased release from the pressurized cell above the threshold values of tensile stress. Therefore, K^+ is transported by convection as driven by the hydrostatic pressure difference across the films that generates the tensile stress in the free films.

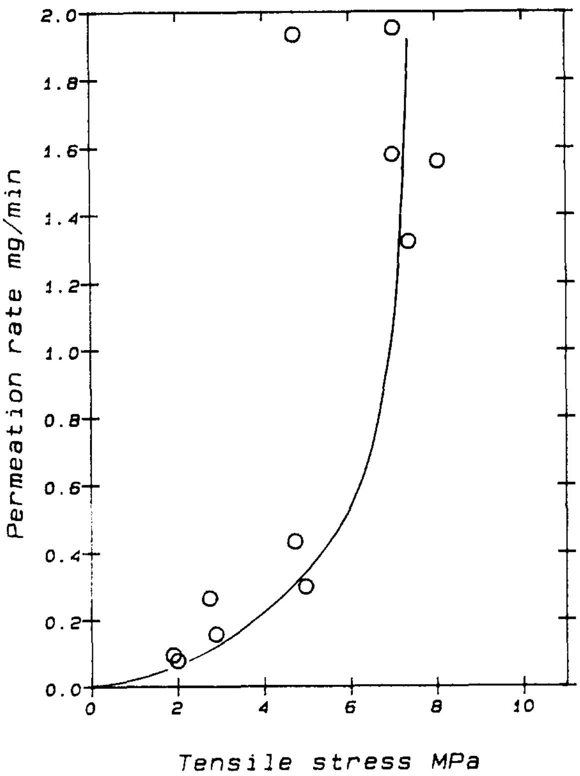

Fig. 5. Effect of tensile stress on the release of K^+ through EC-film with 24% HPMC.

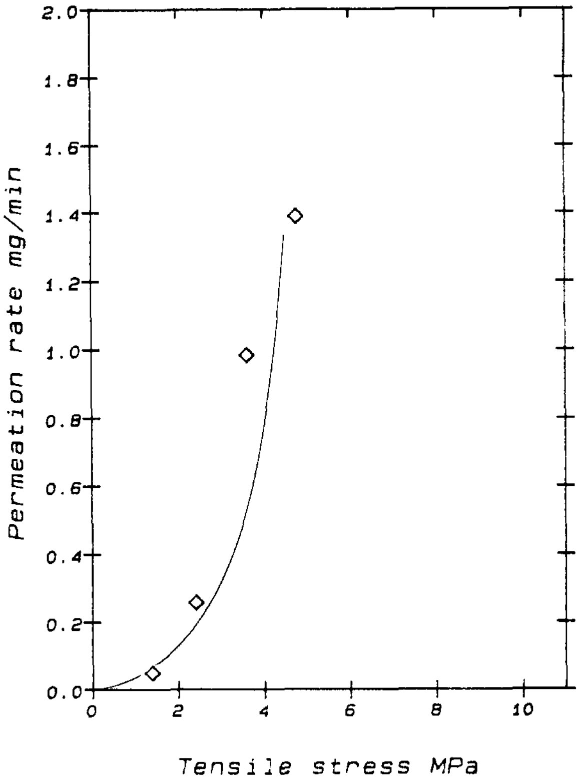

Fig. 6. Effect of tensile stress on the release of K^+ through EC-film with 30% HPMC.

The experiments with the free film in the pressurized cell were performed in order to gain a better understanding of the osmotic pumping release mechanisms of membrane coated drug formulations. We have shown that when a free film of EC is exposed to tensile stress, solution may be transported through the film as driven by hydrostatic pressure. When a membrane coated drug formulation is placed in a water solution, water may be imbibed by osmosis (Eqn 2). This results in a build up of pressure (Δp in Eqn 2) in the formulation. The pressure in the formulation creates a tensile stress in the spherical membrane coat:

$$s = \frac{\Delta p \cdot d}{4 \cdot h} \tag{4}$$

This pressure will depend on the fraction of HPMC in the membranes, as discussed above. A smaller diameter will also give a higher pressure in the formulation core, which will result in a decreased transport of solvent (Eqn 2). In the extreme case, water transport will be halted completely and no drug will be delivered by osmotic pumping. For ethyl cellulose without HPMC, to become permeable, rather large particle diameters may be required to generate sufficient tensile stress.

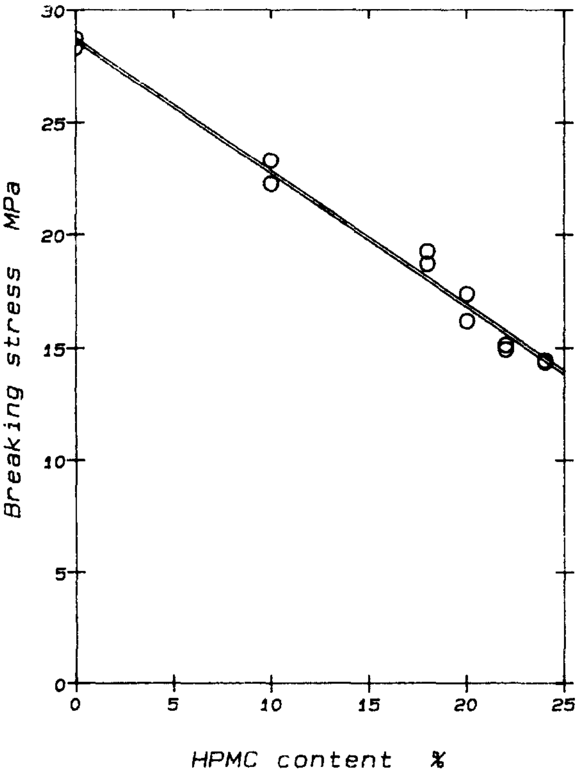

Fig. 7. Breaking stress in EC-films with different amounts of HPMC.

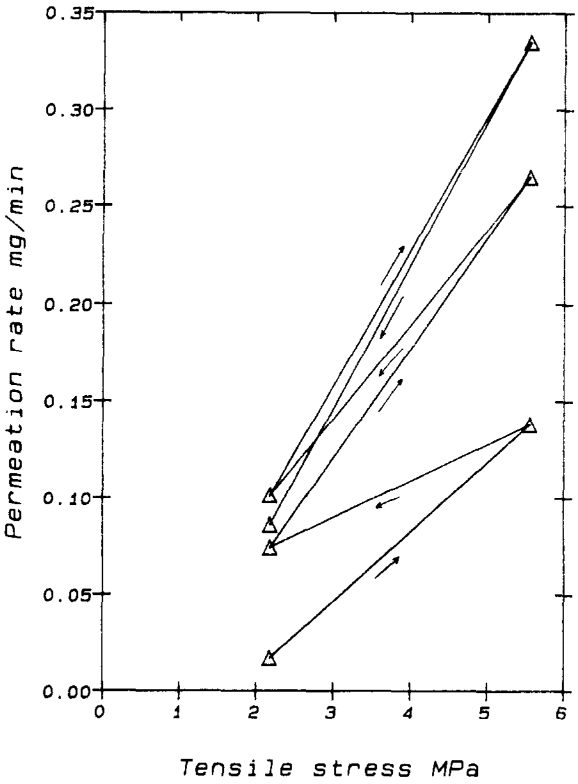

Fig. 8. Effect on release through EC-film without HPMC of changing the tensile stress from a low value to a higher and back.

At this stage we refer to a study by Rowe (1986), who investigated small beads coated with various viscosity grades (average molecular weight) of EC and 10% HPMC. Although no physiochemical data on the drug were given, it is plausible that osmotic pumping was of great importance for the release. Rowe found that the pellets coated with the lower viscosity grades released drug with a faster rate than the higher viscosity grades, and that the release rate was affected by incorporation of plasticizer in the low molecular weight grades. We suggest that different viscosity grades will have different threshold tensile stresses, especially the more brittle lower molecular weight grades. This will result in different hydrostatic pressure in the cores and thus different tensile stresses on the membrane, which gives different water fluxes into the pellets (Eqn 2). The lowest molecular weight grades result in the lowest hydrostatic pressure, and thereby the highest release rate. To avoid this, larger pellets or small tablets could be made as described earlier by Lindstedt et al. (1989). They showed that for the small tablets with a diameter of 3 mm the hydrostatic pressure was negligible compared to the osmotic pressure of a saturated KCl solution, 27 MPa.

Conclusions

With the 'pressurized cell' method, we have employed EC films containing from 0 to 30% HPMC for investigation of the influence of tensile stress on the K^+ permeability of membranes. It was found that K^+ ion was transported through these films by convection only under an applied tensile stress. The threshold value of tensile stress needed for films to become permeable was decreased by increasing of HPMC content in the films. It was also shown that changes in transport properties of the film were caused by cycling of the tensile stress.

The release rate from formulations coated with EC films is determined by the rate of water ingress. Water is imbibed by osmosis and produces a tensile stress in the film coat. If drug solution is to pass the membrane without reflection, the membrane will have to be submitted to stress, provided by a hydrostatic pressure in the core. The diameter of the formulation therefore has to be considered, as well as the resistance of the membrane material to stress.

Glossary

Symbol	Meaning
s	tensile stress
Δp	hydrostatic pressure
d	diameter of cell
h	thickness of film
ρ	density
g	acceleration due to gravity
l	column height
J_v	total volume flux
L_p	hydraulic permeability
σ	reflectivity of the membrane for the solute used
$\Delta \Pi$	osmotic pressure difference
J_s	molar flux of solute
C	concentration of solute
ω	permeability of the membrane for solute

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