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Swelling of pellets coated with a composite film containing ethyl cellulose and hydroxypropyl methylcellulose

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Abstract

The swelling behaviour of membrane-coated drug pellets has been investigated. A coating membrane containing ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC) in the range of 10–24% was used. By measuring the release rate of a drug during swelling experiments, it is possible to obtain an insight into the release mechanisms that are involved. The results revealed that the swelling of the membrane coat increased as the amount of HPMC increased. The expansion of the pellets continued until the release of the drug began. We have also evaluated the swelling of pure EC/HPMC, where no change in volume occurred. It is believed that the swelling of the pellet coat is a result of water imbibition due to osmotic pressure. © 1998 Elsevier Science B.V.

Keywords: Ethyl cellulose; Hydroxypropyl methylcellulose; Tensile stress; Swelling; Osmotic pumping

1. Introduction

One of the most widely used water-insoluble polymers in pharmaceutical film coating is ethyl cellulose (EC), due to its convenient film formability, good physiochemical properties, minimum toxicity and so on (Porter, 1989). Polymer mixtures of EC and water-soluble polymers, such as hydroxypropyl methylcellulose (HPMC), are used to control the release properties of a drug formulation (Lindholm and Juslin, 1982; Ritschel and Udeshi, 1987; Munday and Fassihi, 1989). Lindstedt et al. (1989) demonstrated that the rate of water across the coating layer into the pellet is the major release-regulating factor for EC films containing 24% HPMC or less. The imbibition of water induced by an osmotic pressure gradient creates hydrostatic pressure in the cores and thereby tensile stress on the membrane. The hydrostatic pressure is of great importance when it comes to making EC/HPMC (24% or less)-coated film permeable to drug (Hjärtstam et al., 1990).

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Table 1
Compositions of the polymer solutions

Coating	EC, 10 cP	HPMC, 6 cP	Dichloro-methane	2-propanol
EC 10	6.93	0.77	231	77
EC 18	6.31	1.39	231	77
EC 24	5.85	1.85	231	77

Values expressed in grams for each component.

Osmotic pumping is a consequence of water transport into the device and the inability of the device coat to expand. Formulations in which osmotic pumping is a major release mechanism have been presented, the most common of which is the elementary osmotic pump (Theeuwes, 1975). Examples of other research projects in which osmotic pumping has been proposed as the main mechanism have also been described by Zentner et al. (1985) and Thombre et al. (1989).

The aim of this study was to demonstrate the expansion of metoprolol succinate pellets coated with an EC/HPMC composite film and the release of metoprolol succinate to obtain a better understanding of the release mechanisms of EC/HPMC membrane-coated drug formulations.

2. Materials and methods

2.1. Materials

Ethyl cellulose N-10 (Ethocel Standard premium; ethoxy content, 46–48%; viscosity, 10 cP) was supplied by Dow Chemical Co., USA and hydroxypropyl methylcellulose (Pharmacoat 606, viscosity 6 cP) by Shin-Etsu, Japan. The solvents which were used, dichloromethane, (Merck, Germany) and 2-propanol (Prolabo, France), were of pharmacopeial grade (USP XXII, 1995) and the water was deionized and distilled (MAXIMA Ultra Pure Water, ELGA, UK). All materials were used as received.

2.2. Swelling of pure EC/HPMC membrane

The polymers were dissolved in the solvents and mixed overnight. Polymer solution, summarized in Table 1, was then cast on a glass plate at 22°C under controlled humidity. After casting, small circular film segments with a typical diameter of 4 mm and a thickness of 0.15 mm were cut from the free film. The swelling experiments were carried out on a ASKANIA, SMT 4 microscope (Germany) with an Dual-Screen HR 1024/DS (Optech Instrument, USA). Pure EC/HPMC membrane was immersed in distilled water at 37°C and the change in diameter was measured at specific time intervals.

2.3. Tensile testing

The mechanical characterization of the films was performed on a Hounsfield H2000 tensile apparatus using a 200 N load cell. Samples with a length of 50 mm and a width of 10 mm were cut from the free film. A sharp knife was used to avoid any jagged edges. The thickness of the film was measured with a micrometer. The initial gauge length was 20 mm and the measuring speed was 2 mm/min, i.e. 10% per minute. Five or more parallel measurements were made for each type of film both in the dry and in the hydrated state.

2.4. Preparation and characterization of pellets

Metoprolol succinate pellets (size fraction, 0.40–0.63 mm) were coated with the same polymer solutions as were used in all the other experiments. The solutions were sprayed on to the beads in a Wurster column. The thickness of the polymer coating layer was approx. 20 μm, measured by SEM (JSM-5400, Jeol Ltd, Japan).

The in vitro release of metoprolol was measured in a USP dissolution apparatus No. 2 (rotating paddle) at a speed of 100 rpm. The test

medium was 500 ml of distilled water at 37°C. Metoprolol was detected by UV spectrometry at 274 nm (Ultrospec II, LKB Biochrom, UK).

A representative fraction of the pellets was used to study the swelling of the pellets. The 'swelling apparatus', depicted schematically in Fig. 1, consists of two 10-cm test tubes fixed to a rotating arm with a speed of 30 rpm. The tubes were filled with 2.7-g pellets and distilled water at 37°C was then added. The length of the pellet column was noted, and the length of the pellet column and, thereby, the swelling was then measured at predetermined time intervals. Twice an hour, the water medium was replaced with new, fresh water. The total volume of water and pellets, was constant throughout the experiment.

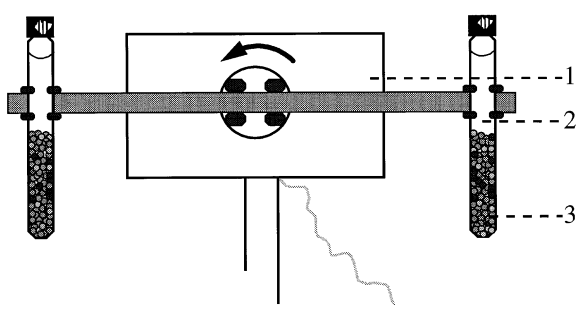

Fig. 1. Swelling apparatus. (1) Stirring equipment, (2) test tube with water, (3) pellets.

3. Results and discussion

3.1. Swelling of EC/HPMC-coated metoprolol succinate pellets

The results of the swelling experiments reveal that pellets in contact with water swell for a period of several hours, as presented in Fig. 2. The study of pure EC/HPMC membrane segments revealed no volume expansion at all in the same media. This indicates that the swelling of the particles is due to hydrostatic pressure created in the pellets as a result of water imbibition. Lindstedt et al. (1989) have determined the water permeability of EC/HPMC membrane, as shown in Table 2. The water permeability increases as HPMC increases in the free film, and the rate of

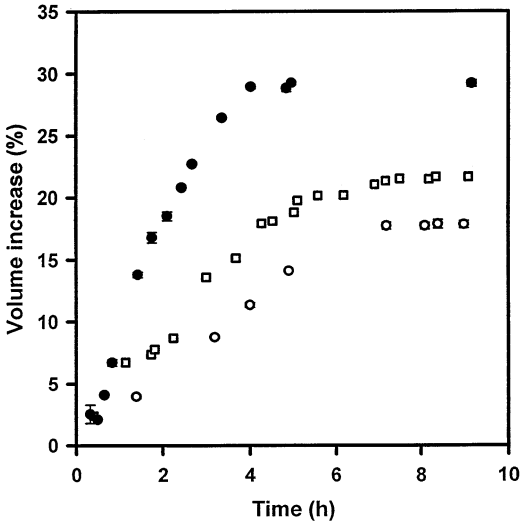

Fig. 2. Swelling of EC/HPMC-coated pellets at 37°C. (○) EC/10% HPMC, (□) EC/18% HPMC, (●) EC/24% HPMC.

swelling is therefore higher in EC 24 compared with EC 18 and EC 10.

As can be seen in Fig. 2, the maximum swelling is higher in a pellet coated with a polymer solution with an increasing amount of HMPC. An explanation of the observed behaviour is related to the mechanical properties of the films. Table 3 summarizes measurements made on dry EC/HPMC films. In these studies, we have used cast polymer films. According to Aulton (1982), a preferable method for determining the mechanical properties of a film coating material is to use a cast film. The results of tensile testing do not agree with the data obtained from the measurements of the swelling of the beads, where EC/24% HPMC appears to be more elastic. As shown in Table 3, a film with a higher amount of HPMC produces a membrane with a higher modulus of elasticity. The reason for increased modulus of

Table 2
Water permeability of free ethyl cellulose films

Film	P (m^2/s, $\times 10^{-12}$)
EC 10	2.38
EC 18	3.53
EC 24	7.38

All data from Lindstedt et al. (1989).

Table 3
Results of tensile testing on dry films and free films immersed in water at 37°C for 2 h

Film	Stress at break ± S.D. (N/mm^2)	Elongation at break ± S.D. (%)	Elastic modulus ± S.D. (N/mm^2)
Dry films			
EC 10	26.9 ± 2.9	11.6 ± 4.7	654.7 ± 39.9
EC 18	34.2 ± 6.6	8.6 ± 3.3	851.1 ± 72.3
EC 24	29.9 ± 4.8	6.7 ± 2.2	938.3 ± 86.7
Immersed films			
EC 10	20.6 ± 4.8	5.9 ± 0.9	471.7 ± 35.5
EC 18	16.1 ± 1.8	5.3 ± 0.8	426.9 ± 38.3
EC 24	11.9 ± 1.6	4.9 ± 0.7	308.4 ± 4.4

elasticity as a result of increasing level of HPMC, can be either an incompatibility between the two polymers or a comparatively higher *E* modulus of the added polymer giving the admixture a higher modulus. Fig. 3 presents SEM images of the membrane with and without 24% HPMC, and it is obvious and has also been reported by others (Sakellariou et al., 1988) that HPMC appears as isolated domains in the EC film and thus makes the film more brittle and increases the modulus of elasticity.

However, after hydrating the free films in distilled water for 2 h, the tensile test produced another interesting result. The results, shown in Table 3, indicate that the modulus of elasticity, and thereby the mechanical properties, have been changed. The EC/24% HPMC film has become more soft. Water acts as a softening agent and this is more pronounced in the EC film containing more HPMC. The swelling thus increases as the amount of HPMC in the EC film increases.

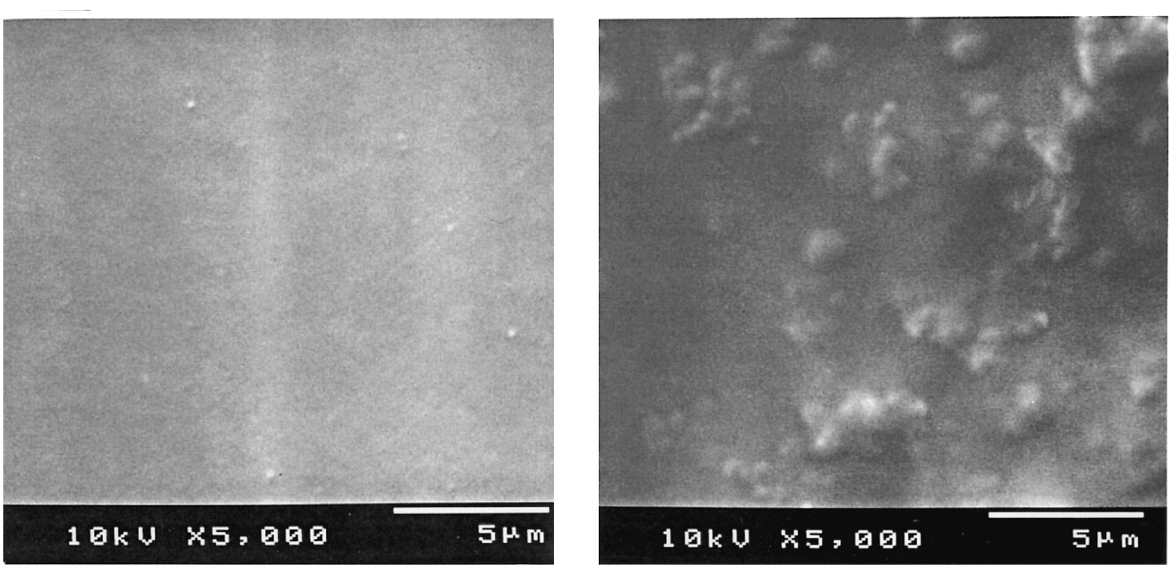

Fig. 3. SEM photomicrographs of: (A) ethyl cellulose film and (B) ethyl cellulose film containing 24% hydroxypropyl methylcellulose.

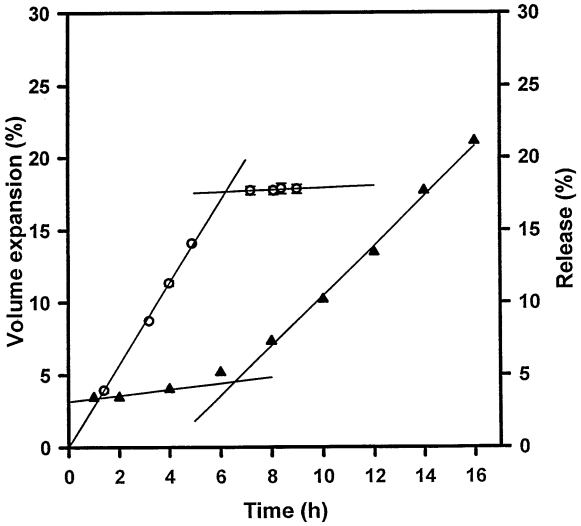

Fig. 4. Release of metoprolol succinate (▲) from EC/10% HPMC-coated pellets and volume increase in the pellets (○).

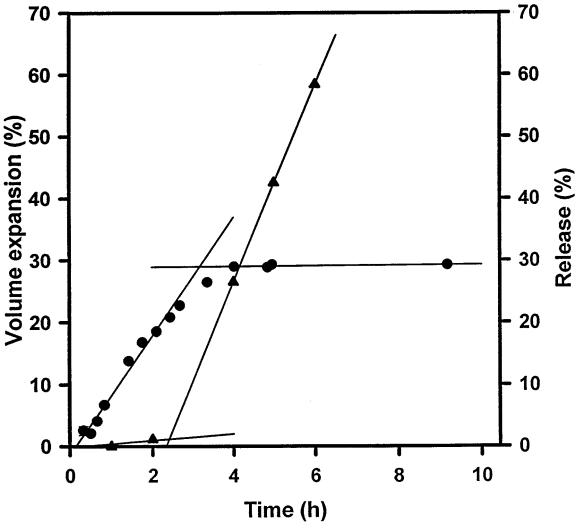

Fig. 6. Release of metoprolol succinate (▲) from EC/24% HPMC-coated pellets and volume increase in the pellets (●).

3.2. Release of metoprolol succinate

The release of metoprolol succinate from pellets coated with EC/HPMC composite films containing 10, 18 and 24% HPMC is shown in Figs. 4–6, respectively. The rate of drug release increases when the amount of HPMC increases. These figures also present the volume expansion. The release of metoprolol is low and constant until the point of maximum swelling for the pellets is reached or, in fact, until the release of metoprolol starts. As seen in the figures, the amount of metoprolol at time zero is not zero. The cause for this is that some pellets have a defective coating layer, resulting in an immediate release of the drug. However, in order to make the coating layer permeable to metoprolol, tensile stress affecting the membrane, which generates an expansion of micropores, is necessary. These results correspond with the study by Hjärtstam et al. (1990). They noticed that a tensile stress was needed to make EC films containing up to 20% HPMC permeable to potassium chloride. It is also important to note that, during the release phase, no expansion of the coat occurs. This is in agreement with the osmotic pump mechanism theory.

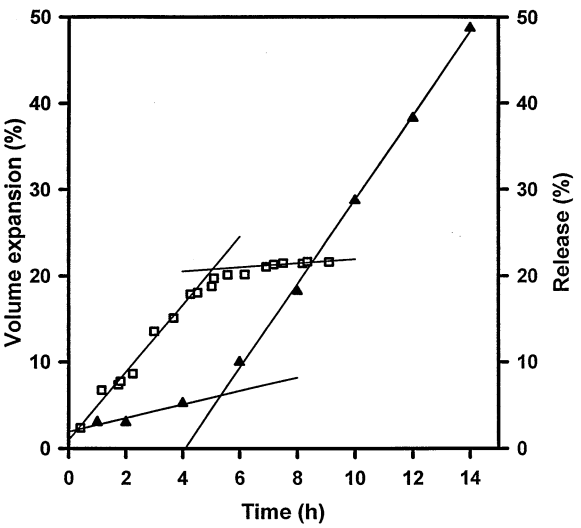

Fig. 5. Release of metoprolol succinate (▲) from EC/18% HPMC-coated pellets and volume increase in the pellets (□).

An other interesting reflection is that the surface area of the composite increases, because of the expansion of the pellets during the time lag. As can be seen from Figs. 4–6, the highest rate of drug release is obtained from pellets with highest volume expansion. The increase of the surface and its effect on drug release will not be discussed further in this paper. However, the release rate cannot only be explained by convection. Lindstedt et al. (1991) have shown that, when the HPMC

content is increased to 24%, some water-soluble polymers are leached from the film coat after 2–3 h and thus produce pores, which increase the diffusive release. Another reason for this assumption is the fact that the delivery rate of metoprolol increases to a greater degree with a higher amount of HPMC than the water permeability increases in the range of 10–24%.

4. Conclusions

The most likely cause of the volume increase is the imbibition of water, the development of hydrostatic pressure and the effect on the membrane coat. An osmotically driven release is involved and produces a pellet in which the change in volume occurs during a time lag, a period in which water is absorbed, the drug solubilizes and no active substance leaves the formulation.

As soon as the maximum swelling has occurred and the release begins, the volume expansion ends. The rate of delivery is then controlled by the water permeability of the membrane, which increases as the amount of HPMC and the osmotic pressure increase.

Furthermore, the release rate cannot only be explained by convection. Some diffusion is probably also involved in the film containing 24% HPMC. The reason is that the percentage increase in the drug delivery rate is greater than the increase in water permeability, when the amount of HPMC increases in the membrane. However, the main mechanisms are caused by osmotic pumping.

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