DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(16), 2467-2477 (1994)

RESEARCH PAPERS

INVESTIGATING THE EFFECT OF WATER ON THE POROSITY OF POLYMER FILM FOR CONTROLLED DRUG DELIVERY

Jian-Hwa Guo
3M Pharmaceuticals, Pharmacy Research and Development
3M Center, 270-4S-02, St. Paul, MN 55144-1000, U.S.A.

ABSTRACT

This paper describes the effects of water on the properties of ethylcellulose films. The change of density, morphology, porosity, and drug transport properties of ethylcellulose films with the water contents in the polymer solutions were investigated. Due to the strong-hydrogen-bonding property of water, the process of dissolving and mixing of ethylcellulose in a solvent (ethanol) was dramatically changed when a nonsolvent (water) was added in this system. Since the solubility parameter difference between water and the rest of components, and the evaporating rate difference between ethanol and water could caused the phase separation of polymer solution during the film-forming process, the porosity of ethylcellulose films increased with water content in the polymer solutions. The film density and the drug permeability of ethylcellulose films were found to decrease and increase with water content in the polymer solutions, respectively; and these results are very consistent with the porosity increase of ethylcellulose films.

INTRODUCTION

The importance and pharmaceutical application of polymer films are established in providing controlling drug release from desired dosage form. These controlled release systems represent a relatively new development that evolves out of a continuing need to prolong and better control drug administration. For instance, polymers can be used to control the diffusion of drugs; by controlling how rapidly the drug molecules move through the polymer film (1-3). D'Emanuele and Staniforth (4) have studied the feedback controlled drug delivery using an electro-diffusion pump through the rate controlling polymer membrane. They concluded that feedback control of an electrophoretic device is potential method which drug release rates may be varied depending on actual therapeutic requirements. The effects of polyethylene glycol (PEG-600) on the properties of cellulose acetate films were investigated by Guo (5). He found that the formation of plasticizer channels on the polymer films at high plasticizer level could change the morphology and drug permeability of cellulose acetate films dramatically.

It has been noticed that the properties of polymer films are undoubtedly dependent on the solvents used to dissolve the polymer for preparing the films. Porosity of polymer films is one of the properties that can be greatly affected, and this means that each polymer or solvent can be characterized by its solubility parameter which should define its compatibility with every other solvent. The solubility studies on ethylcellulose used in film coating have been investigated by Kent and Rowe (6). They found that the solubility parameter alone is no more than a useful guide to predicting solubility, and their results illustrated that the potential of a combined approach of solubility parameter and a quantitative measure of the polymer solvent interaction by intrinsic viscosity measurements.

In this paper, the effect of water on the properties of ethylcellulose films was investigated, and the viscosity of polymer solution, and the density, porosity and drug permeability tests of ethylcellulose films were performed and discussed in this paper.

MATERIALS AND METHODS

Ethylcellulose (EC) and diethyl phthalate (DEP) (Sigma Chemical Company) were dissolved in H_2O/ethanol mixtures at a concentration of 2 or 4% (w/v). The H_2O/ethanol ratios were varied from 0/100 to 30/70 (v/v), and the DEP levels in the dry EC films were varied from 0 to 30% (w/w). The viscosities of those EC solutions were measured by viscometer (Brookfield, Stoughton, MA) at 100 rpm.

To form films, 2 mL of EC solutions was poured into aluminum evaporating pans and covered with an inverted funnel to prevent solvent removal by convection at room temperature. The morphology of EC free films was studied by using scanning electron microscopy. The densities of EC free films were calculated by measuring the weights and volumes of those films.

The theophylline (Boehringer Ingelheim) permeability tests of EC free films were performed in a standard diffusion cell system at 25°C. The system included a MGW Lauda M3 water circulator (Messgerate-Werk Lauda, Lauda-Konigsofen, West Germany) and 3 mL Side-by-Side diffusion cells (Crown Glass Co., Vineland, NJ). Before each permeability experiment was performed, the thickness of the film was measured. Two 3 mm silastic gaskets were placed on each side of the circular film and placed between each half of diffusion cell. The cells were then clamped to prevent leakage. In the donor side of the system, a saturated theophylline solution in the presence of excess theophylline was placed, while distilled water was added to the receiver side. In order to reduce boundary layer effects, stirring bars were added into both cells. Periodically, the water solution in the receiver side was sucked out and replaced by the new distilled water. The theophylline permeability of ethylcellulose films can be calculated from

$$P \times S \times \nabla C = \frac{dM}{dt}$$

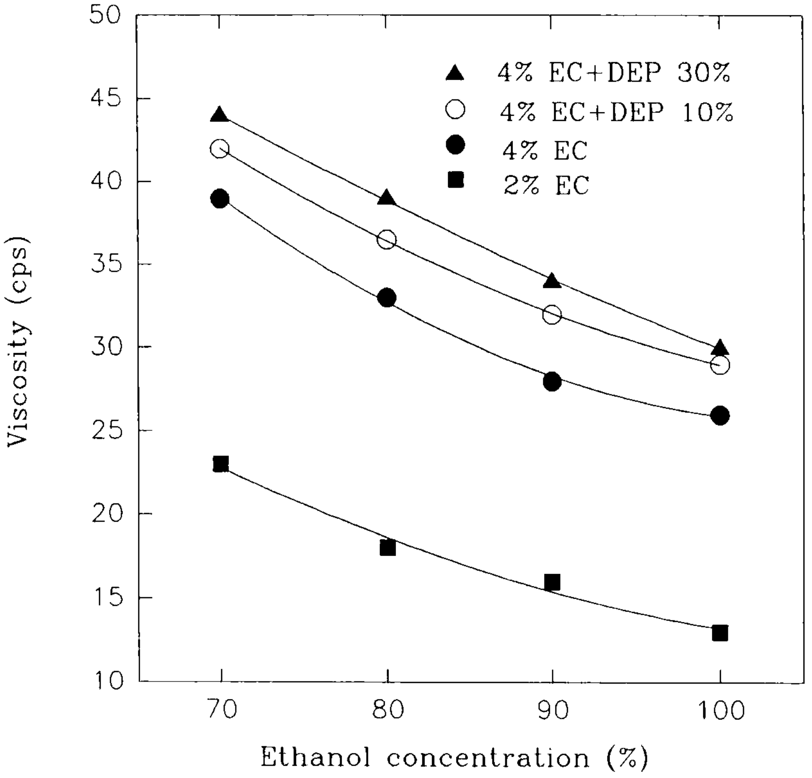


FIGURE 1

The viscosities of ethylcellulose solutions which were prepared at different ethylcellulose (EC), water, and diethyl phthalate (DEP) concentrations.

where P is the theophylline permeability coefficient of EC film, S is the surface area of the film that contacts with solution, ∇C is the concentration difference of theophylline between the two diffusion cells, and dM/dt is the weight change of theophylline with respect to the time in the receiver cell.

RESULTS AND DISCUSSION

The viscosities of various EC solutions were presented in Figure 1, and it was found that the viscosity of EC solution increased with EC, water and DEP concentrations in the polymer solutions. It has been recognized that the solubility

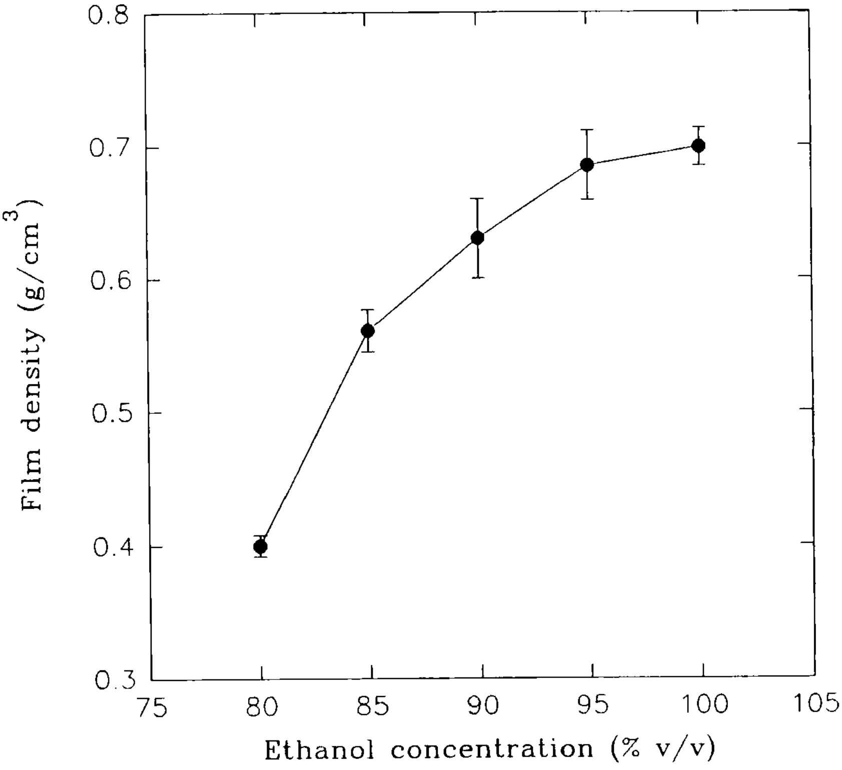


FIGURE 2

The effect of water on the film density of ethylcellulose films (30% w/w DEP).

of polymer decreases when strong intermolecular forces are present in the polymer solution. The process of dissolving an polymer in a solvent is reigned by the free energy of mixing, and it has been studied by Hildebrand and Scott (7) and can be simply expressed by

$$\frac{\nabla H_m}{V} = \phi_1 \phi_2 (\delta_1 - \delta_2)^2$$

where the ∇H_m is the enthalpy change on mixing, V is the molar volume of the polymer solution, ϕ_1, ϕ_2 are the volume fractions of the components, and δ_1, δ_2

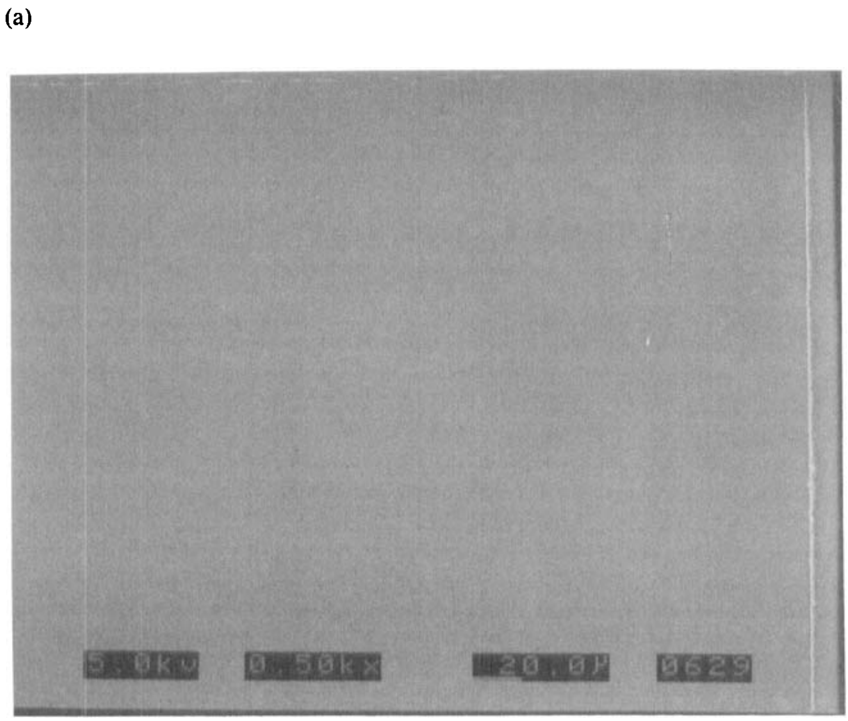


FIGURE 3

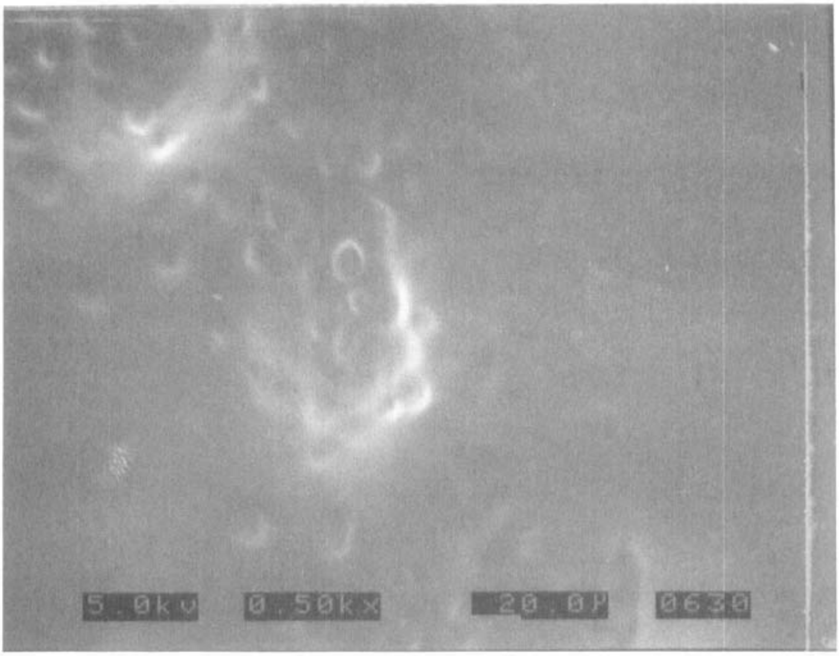
The scanning electron micrographs of ethylcellulose films (30% w/w DEP). (a) film prepared from the polymer solution without water, (b) film prepared from the polymer solution with 10% v/v water, (c) film prepared from the polymer solution with 20% v/v water.

are the solubility parameters of the components. Einstein (8) has postulated the relation between the specific viscosity (η_{sp}) and the volume fraction (ϕ_2) of polymer, and it is given by

$$\eta_{sp} = b_1\phi_2 + b_2\phi_2^2 + b_3\phi_2^3 + \cdots\cdots$$

where b_1, b_2, $b_3 \cdots\cdots$ are constant. Since the volume fraction of EC, ϕ_2, is equal

(b)



(c)

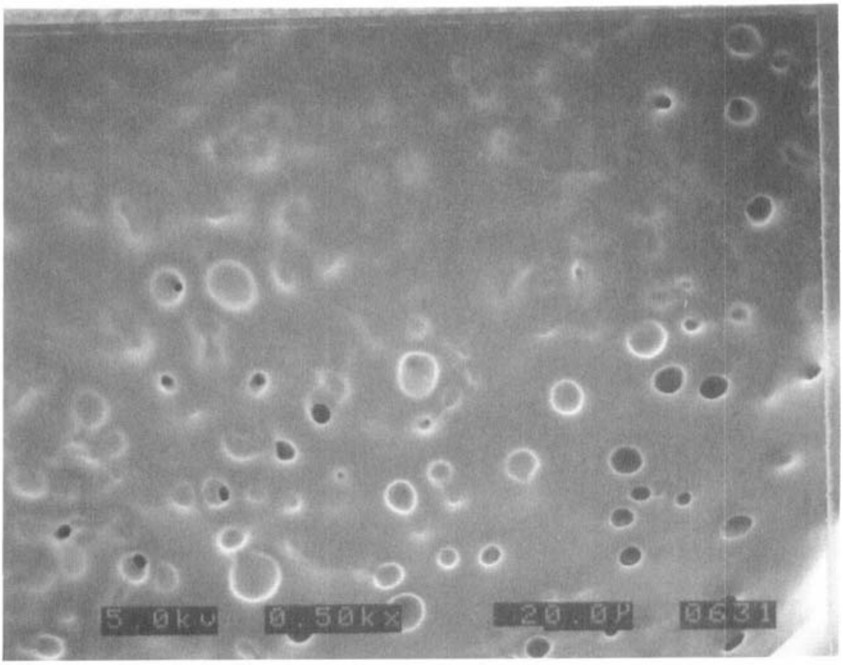


FIGURE 3 Continued.

to $(V_d/M_2)C_2$, where V_d is the effective hydrodynamic volume of polymer particle, M_2 is the molecular weight of polymer, and C_2 is the concentration of polymer solution, the η_{sp} can be expressed by

$$\eta_{sp} = b_1 (V_d/M_2)C_2 + b_2(V_d/M_2)^2C_2^2 + \cdots\cdots$$

therefore, when the concentration of EC increased, the viscosity of polymer solution increased as well.

The mechanism of the mutual solubility and mixing for a binary mixture can be easily understood and followed. However, the polymer system which we prepared was ternary (without plasticizer) or quaternary (with plasticizer), and in this ternary or quaternary systems, the chemical potential of each component is characterized by three or more pair interaction parameters. Especially, the ternary and quaternary systems which we prepared both contained the strong-hydrogen-bonding nonsolvent, water. The solubility parameter of water is 47.9 $MPa^{1/2}$, and it is much higher than that of EC (~17 $MPa^{1/2}$) or ethanol (26 $MPa^{1/2}$) (9). Therefore, a dramatical change of the mixing result, the viscosity of polymer solution, and the properties of EC films were caused by the huge solubility parameter difference between water and the rest of components.

Kent and Rowe (6) have suggested that the optimum plasticizer for a polymer will be one that has a solubility parameter close to that of the polymer. The effects of DEP on the mechanical and transport properties of EC solvent and aqueous latex films have been studied by Guo,et al (10), and shown that DEP (ω = 20.5 $MPa^{1/2}$) is a good plasticizer for EC system. The increase of viscosity of EC solution with DEP levels in this solution could be due to the higher viscosity of DEP than the polymer solution itself.

The densities of EC films (4% EC, 30% DEP) prepared at different ethanol concentrations are shown in Figure 2. The film density was found to decrease with the water content in the polymer solution. It was found that a homogeneous free film only can be obtained from the polymer solution which contained high DEP level when it contained high water ratio. For instance, the polymer solution which contained 0% or 10% (w/w) DEP would not form a homogeneous film when it contained above 10% (v/v) water.

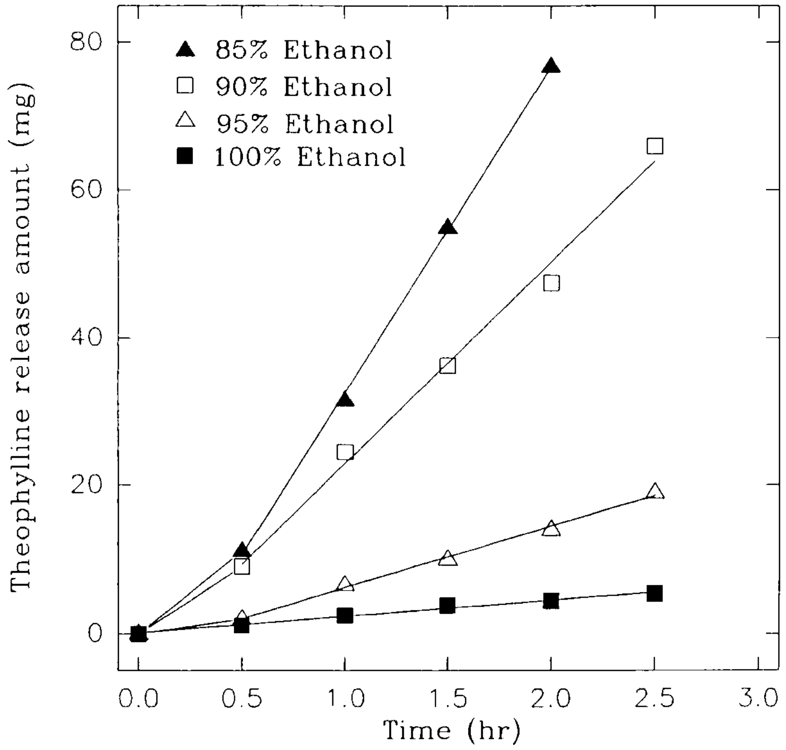


FIGURE 4

The effect of ethanol concentration on the theophylline permeability of ethylcellulose films (30% w/w DEP).

The scanning electron micrographs of EC films prepared at different ethanol concentrations, are illustrated in Figure 3(a)-3(c). The porosity of EC films was found to increase with the water content in the polymer solution. Apparently, the film density decrease is due to the porosity increase of the polymer films. The effects of water on the morphology and porosity of EC films could be due to the phase separation of the EC solution during the film-forming process. Both the solubility parameter difference between water and the rest of components, and the evaporating rate difference between ethanol and water could be the reasons that caused the phase separation of the EC solution and increased the porosity of EC films.

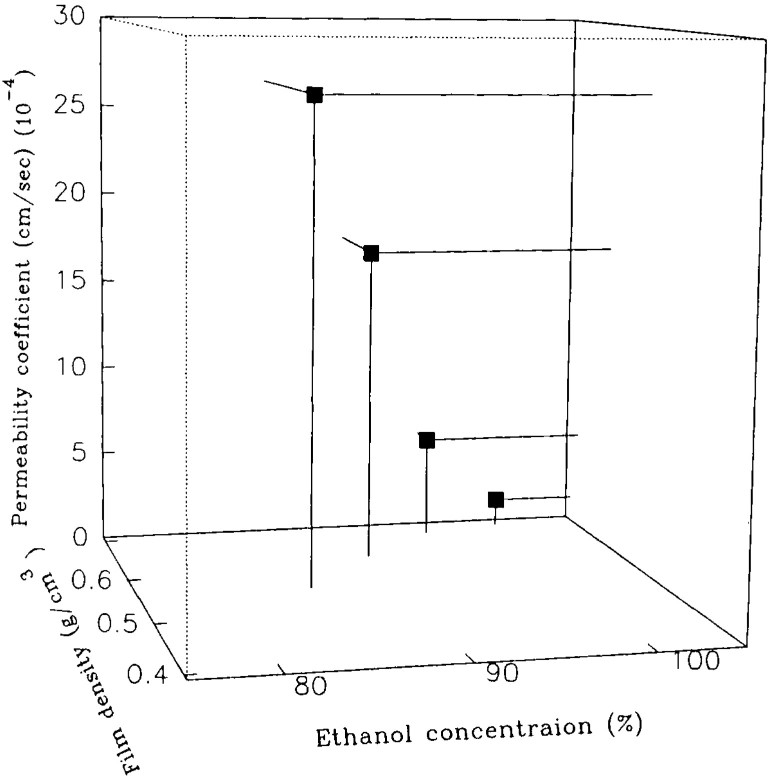


FIGURE 5

The three-dimensional diagram of the theophylline permeability and film density of ethylcellulose films, and the ethanol concentration of polymer solutions.

The theophylline release profiles through the EC films are presented in Figure 4, and it was found that the theophylline release rate increased with water content in the polymer solution as well. This result is very consistent with the decrease of film density and the increase of film porosity of EC films. The three-dimensional diagram of permeability coefficient of theophylline, film density of EC free films and ethanol concentration of polymer solutions is demonstrated in Figure 5. A clear relation between those three parameters is presented in Figure 5 and a desired permeability of drug could be obtained by changing another two parameters.

REFERENCES

1. R.S. Langer and N.A. Peppas Biomaterials 2, 201-214 (1981).
2. R.W. Korsmeyer and N.A. Peppas J. Membr. Sci. 9, 211-227 (1981).
3. I. Ghebre-Sellassie, R.H. Gordon, R.U. Nesbitt and M.B. Fawzi Int. J. Pharm. 37, 211-218 (1987).
4. A. D'Emanuele and J.N. Staniforth J. Control. Rel. 23, 97-104 (1993).
5. J-H. Guo Drug Devel. Indus. Pharm. (1993) (accepted).
6. D.J. Kent and R.C. Rowe J. Pharm. Pharmac. 30, 808-810 (1978).
7. J.H. Hildebrand and R.L. Scott The solubility of nonelectrolytes, Reinhold, NY 1959 (3rd Ed.).
8. Einstein, A. Ann. Phys. 19, 289-306 (1906).
9. J. Brandrup, and E.H. Immergut Poymer Handbook (3rd Ed.), Wiley-Interscience, NY 1989, pp. VII 529-546.
10. J-H. Guo, R.E. Robertson and G.L. Amidon Pharm. Res. 10, 405-410 (1993).