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COMMUNICATIONS

IN VITRO CHARACTERIZATION OF POLYMERIC MEMBRANE USED FOR CONTROLLED RELEASE APPLICATION

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ABSTRACT

The application of a polymer film coat is a common practice in the preparation of controlled release dosage forms. In vitro characterization of the polymeric membrane is essential for optimization of the membrane formulation. Polymers selected in this study were cellulose acetate (CA), ethylcellulose (EC) and copolymers of acrylic and methacrylic esters (Eudragit RL100). Plasticizers used in this study were dibutyl sebacate (DBS), triethyl citrate (TEC) and triacetin. Polymer dispersions containing different plasticizers were cast into membranes on a teflon-coated plate. The resulting membranes were evaluated for permeability and mechanical properties. Membrane permeability was determined by quantifying the transport of a model drug, theophylline, across a circular polymeric membrane mounted in a thermostatted, two-compartment horizontal diffusion cell. Mechanical properties of the membranes, such as tensile strength, percent elongation and modulus of elasticity, were determined using an Instron 4301. The results of this study indicate that the CA and EC membranes were found to be effective in preventing the diffusion of theophylline. The addition of Eudragit RL100 to the CA or EC membranes increased the permeability but decreased the mechanical strength of the resulting membrane(s). A significant increase in permeability was observed at a CA:Eudragit RL100 ratio of 60:40. This could be explained by a change in the mechanism of drug transport, principally from partitioning into the membrane to diffusing through the liquid-filled pores of the resulting membrane(s). The results of the mechanical deformation studies indicate that triacetin has a greater potential for partitioning into the CA polymer than does TEC or DBS. DBS has a greater potential for partitioning into the EC polymer than does TEC or triacetin. The addition of Eudragit RL100 to the CA membrane(s) caused a significant decrease in the tensile strength, percent elongation and modulus of elasticity, thus resulting in weaker and softer membranes. The results indicate that the test methods employed were sufficiently sensitive to quantify the test parameters for the changes in

membrane compositions which could provide valuable information for optimization of the membrane formulation.

INTRODUCTION

The application of a polymer film coat is a common practice in the preparation of controlled release dosage forms. Since diffusion through a membrane is a simple approach to obtain a predictable release rate, membrane-controlled devices have been widely used. A device for constant release consists of a central reservoir of a drug enclosed by a polymeric membrane that allows the drug to diffuse from the reservoir at a predetermined rate. In vitro characterization of the polymeric membrane is essential for optimization of the membrane formulation. In this study, the effects of types of polymers and plasticizers on permeability and mechanical properties of the membranes were evaluated. Cellulosic polymers and copolymers of acrylic and methacrylic esters (Eudragit RL100), which have been widely used as controlled release coating polymers (1-3), were selected for evaluation. Dibutyl sebacate, triethyl citrate and triacetin were used as plasticizers in this study.

MATERIALS AND METHODS

Materials: Cellulose acetate (CA; CA-398-10 grade) and ethylcellulose (EC) were received from FMC Corporation, Delaware, New Jersey and Dow Chemical Company, Midland, Michigan, respectively. Eudragit RL100 was received from Rohm Tech, Inc., Malden, Massachusetts. Dibutyl sebacate (DBS), triethyl citrate (TEC) and triacetin were received from Morflex Inc., Greensboro, North Carolina.

Free Film Preparation: The film was formed by casting a dispersion of 10% w/w polymer in the mixed solvent acetone:absolute alcohol (9:1) with a Gardner Knife (Gardner Laboratory, Silver Spring, Maryland) onto a teflon-coated glass plate. The plasticizer was used at a level of 30% of the polymer weight. The free film was cured overnight at 40°C and kept in a tight container.

Diffusion Studies: Membrane permeability was determined by quantifying the transport of theophylline across a circular polymeric membrane mounted in a thermostatted, two-compartment horizontal diffusion cell (Crown Glass Inc., Somerville, NJ). Surface area and thickness of the test membrane were 7.55 cm^2 and 55 ± 5 μm, respectively. The receptor cell contained 100 mL of purified water and the donor cell contained a saturated solution of theophylline (1.5 g theophylline in 100 mL of purified water). The media in both cells were equilibrated at 37°C and stirred with magnetic bars in order to reduce boundary layer effects. The analysis was performed using a UV-spectrophotometric method.

Mechanical Deformation Studies: Mechanical properties of the membranes were determined by the ASTM method, D-882, Method A (4) using an Instron 4301 with Automated Materials Testing System (Instron Corporation, Braintree, Massachusetts).

Specimen size was 1 inch in width and 0.002 inches in thickness. Grip length was 2 inches and the test speed of the machine was 0.2 inches per minute. Experiments were performed at 23°C and 50% RH. Load and displacement relationships of the membrane were recorded. Typical test parameters, such as tensile strength, percent elongation and modulus of elasticity, were automatically computed by the Instron Series IX material testing software.

RESULTS AND DISCUSSION

Diffusion Studies: Diffusion is defined as a process of mass transfer of individual molecules of a substance, brought about by random molecular motion and associated with a concentration gradient (5). Diffusion through a nonporous membrane is described by the following equation (6):

$$\frac{dM}{dt} = P.S.\Delta C \qquad (1)$$

where P is the permeability coefficient, S is the surface area of the membrane, Δ C is the concentration difference of a drug between the donor cell and the receptor cell, and dM/dt is the amount of drug diffused through the membrane with respect to time. The permeability coefficient can be described by the following equation:

$$P = \frac{K.D_{iw}}{h} \qquad (2)$$

where K is the partition coefficient which is related to the solubility of the drug in the membrane, D_{iw} is the diffusion coefficient of the drug, and h is the thickness of the membrane. This type of diffusion is referred to as a simple molecular diffusion through a nonporous membrane, whereas a second process may involve passage of a substance through liquid-filled pores of a membrane where the pore sizes are usually in the range of 0.1-1.0μm (7-8). Diffusion through this type of membrane is described by the following equation:

$$\frac{dM}{dt} = \frac{D_{eff}.S.\Delta C}{h} \qquad (3)$$

The effective diffusion coefficient (D_{eff}) is defined by:

$$D_{eff} = \frac{D_{iw} \cdot \epsilon}{\tau} \quad (4)$$

where ϵ and τ are void fraction (porosity) and tortuosity of the membrane, respectively.

Both CA and EC membranes were found to be effective in preventing theophylline diffusion, as shown in Figure 1. The amount of theophylline diffusing across these membranes was negligible compared to the amount of drug present in the donor cell. The results indicate that drug transport through these dense membranes occurs principally by simple molecular diffusion. The diffusion profiles of theophylline through CA membranes were comparable, irrespective of the plasticizer used. The permeability of EC membranes was significantly increased when DBS was used as a plasticizer, compared to TEC or triacetin. This could be explained by the increase in the values of the partition coefficient (K) or diffusion coefficient (D_{iw}) of theophylline in the resulting EC membrane. DBS is more hydrophobic than triacetin or TEC, as indicated by their solubility in water as shown in Table I. The EC membrane containing DBS was more hydrophobic than the one containing TEC or triacetin. A hydrophobic drug, like theophylline, would have a greater partitioning into the EC membrane containing DBS than one containing either triacetin or TEC. Also, the greater solvating power of DBS for the EC over either triacetin or TEC could interfere with the polymer-polymer attachments (9), thus increasing the D_{iw} value of theophylline in the EC membrane.

The addition of Eudragit RL100 to CA or EC membranes containing DBS increased the permeability of the resulting membrane(s), as shown in Figure 2. The effect was more pronounced in the case of the EC membranes. A significant increase in membrane permeability was observed when greater than 40% of Eudragit RL100 was added to the CA membrane, as shown in Figure 3. This could be explained by the change in the mechanism of transport. The addition of Eudragit RL100 to the CA polymer at levels greater than 40% may contribute to a substantial increase in the microporosity of the resulting membrane(s). Therefore, drug transport occurs principally by diffusion through the liquid-filled pores of the membranes rather than by partitioning into the membranes. The addition of Eudragit RL100 to the EC polymer at levels greater than 20% resulted in membranes which were too soft to perform diffusion studies.

Mechanical Deformation Studies: The stress-strain relationship of a thermoplastic material is a measure of resistance of a solid to dimensional change and serves to characterize polymer properties (10).

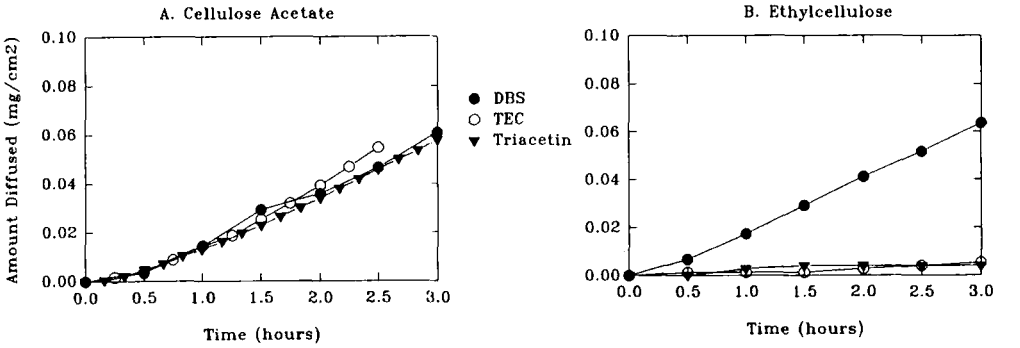

Figure 1: Effect of plasticizers on the diffusion profiles of theophylline through cellulose acetate and ethylcellulose membranes

TABLE I

Solubility of Plasticizers in Water at 25 °C

Plasticizers	Solubility (g/100 mL)
DBS	<0.1
TEC	6.5
Triacetin	7.1

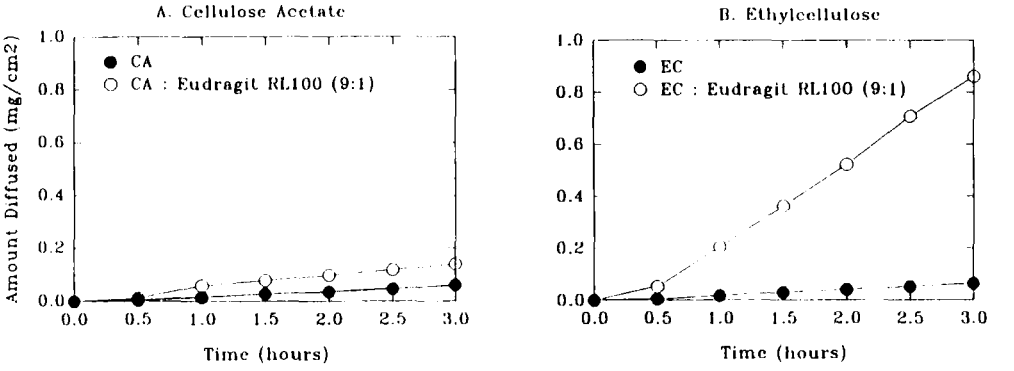

Figure 2: Effect of Eudragit RL100 on the diffusion profiles of theophylline through cellulose acetate and ethylcellulose membranes containing 30% DBS

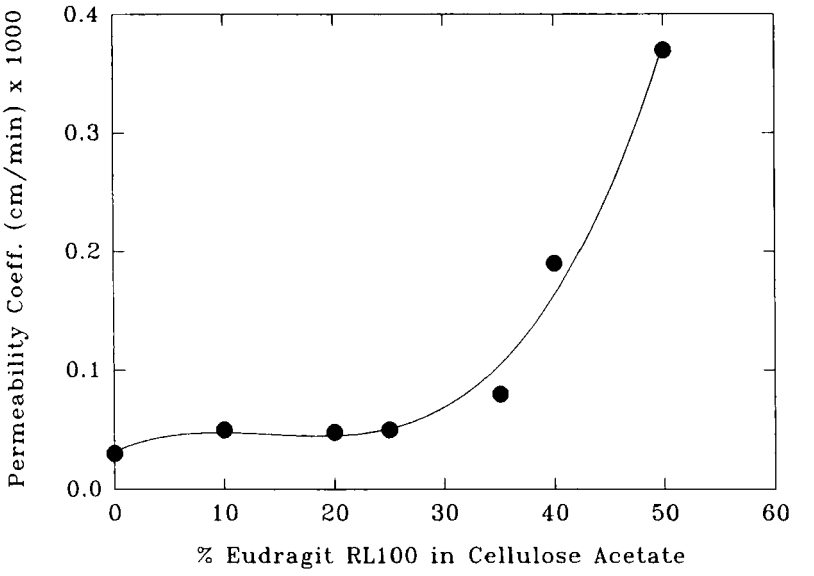

Figure 3: Effect of Eudragit RL100 and cellulose acetate ratio with 30% DBS on the permeability of theophylline

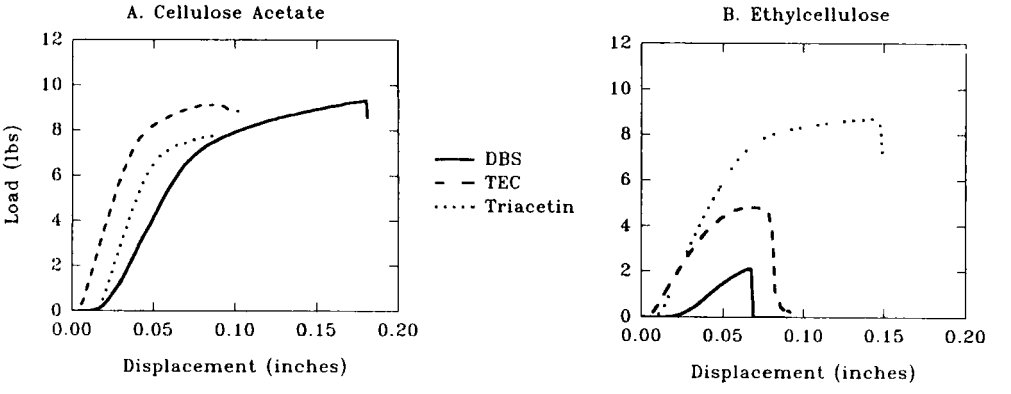

Figure 4: Effect of plasticizers on load-displacement curves of cellulose acetate and ethylcellulose membranes

TABLE II

Mechanical Properties of the CA and EC Membranes

Polymer	Plasticizer[1]	Tensile Strength[2] ± SD (psi)	Elongation[2] ± SD (%)	Modulus of Elasticity ± SD (ksi)
CA	DBS	4845 ± 175	7.8 ± 1.0	176.7 ± 1.3
	TEC	4387 ± 116	4.9 ± 0.3	224.4 ± 4.8
	Triacetin	3418 ± 110	3.5 ± 0.3	217.2 ± 2.8
EC	DBS	1076 ± 115	1.9 ± 0.3	67.3 ± 5.4
	TEC	2189 ± 110	3.0 ± 0.1	111.0 ± 3.8
	Triacetin	4201 ± 135	6.3 ± 0.4	180.4 ± 3.4

[1] 30% of the polymer weight.
[2] at peak of three replicate samples.

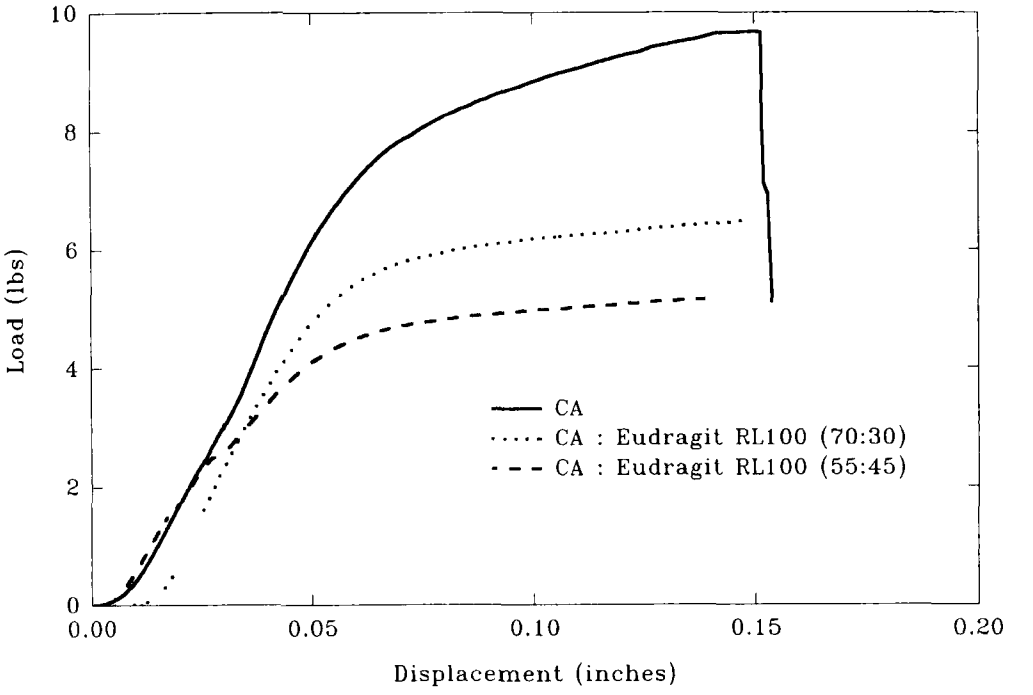

Figure 5: Effect of Eudragit RL100 on load-displacement curves of cellulose acetate membranes containing 30% DBS

TABLE III

Effect of CA : Eudragit RL100 Ratios on Mechanical Properties of the Resulting Membranes[1]

CA : Eudragit RL100	Tensile Strength[2] ± SD (psi)	Elongation[2] ± SD (%)	Modulus of Elasticity ± SD (ksi)
100:0	4845 ± 175	7.8 ± 1.0	176.7 ± 1.3
70:30	3060 ± 195	6.7 ± 0.8	151.4 ± 7.2
55:45	2503 ± 62	6.0 ± 0.5	115.8 ± 1.2

[1] DBS used as a plasticizer at 30% of the polymer weight.
[2] at peak of three replicate samples.

Load-displacement curves of the CA and EC membranes containing different plasticizers are shown in Figure 4. The results of tensile strength, percent elongation and modulus of elasticity of the membranes are summarized in Table II. Tensile strength, which is defined as the applied load per unit cross-sectional area, indicates the strength of the membrane. Elongation, which is a strain or the increase in length upon the stress, represents the ductility of the membrane. Modulus of elasticity, which is measured by the slope of the curves, indicates the hardness of the membrane. Toughness of the membrane is characterized by the area under the curve.

The results of this study indicate that a lower tensile strength of the CA membrane was obtained when triacetin was incorporated into the membrane than when either TEC or DBS was incorporated. This is most likely due to the greater partitioning of triacetin into the CA membrane. DBS has a greater potential for partitioning into the EC polymer than does TEC or triacetin. The EC membrane containing DBS therefore formed a weaker and softer membrane than one containing either TEC or triacetin. These results confirmed the earlier findings that DBS increased the permeability of the EC membrane by decreasing the rigidity of the polymer structure.

The addition of Eudragit RL100 to the CA membrane(s) containing DBS caused a significant decrease in the tensile strength, percent elongation and modulus of elasticity, thus providing weaker and softer membranes (Figure 5 and Table III).

CONCLUSIONS

The results indicate that the test methods employed were sufficiently sensitive to quantify the test parameters for the changes in membrane compositions which could provide valuable information for optimization of the membrane formulation for controlled release application.

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