Release of Diclofenac Through Gluteraldehyde Crosslinked Poly(vinyl alcohol)/Poly(acrylic acid) Alloy Membranes

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ABSTRACT: A controlled-release preparation of diclofenac sodium for transdermal administration has been developed. Poly(vinyl alcohol) (PVA) and PVA/poly(acrylic acid) (PAA) alloy membranes were prepared from a solvent-casting technique using different PVA/PAA (v/v) ratios. The release of the drug from the membrane was evaluated under *in vitro* conditions at pH 7.4. The delivery system provided linear release without time lag, burst effect, and boundary layer resistance. Effects of variables such as film thickness and PVA/PAA ratio on the permeation behavior of the polymeric membranes were discussed. The optimal PVA/PAA was determined as 50/50. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 91: 72–77, 2004

Key words: diclofenac; membranes; drug delivery systems; hydrophilic polymers; water-soluble polymers

INTRODUCTION

In recent years there has been an increased interest in controlled delivery of drugs, which is an efficient technique for the use of medicines. Controlled drug delivery occurs when a polymer, whether natural or synthetic, is combined with a drug in such a way that the agent is released from the material in a predesigned manner. The release of drug may be constant over a long period of time or it may depend on several environmental events (such as temperature, pH, concentration, pressure).[1,2] In any case the purpose of drug delivery is to reach effective therapies while eliminating the side effects or overdosing. Controlled delivery provides two important uses: effective management of a medical drug by the maintenance of the drug level and directed drug delivery whereby a polymer serves as a carrier to bring a drug to a specific site in the body.

There are several potential disadvantages for controlled-release systems: toxicity or nonbiocompatibility of materials used, degradation, required surgery in the case of implants, for example; therefore, the ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple for application removal, and easy to fabricate and sterilize.[3]

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Various types of polymeric membranes may be used in the field of drug release and in general they can be classified according to release mechanism as hydrophobic-nonporous, microporous, and water-swollen hydrophilic membranes.[4] The transfer of drugs through the membranes occurs in general by molecular diffusion. The molecular diffusion of drug is nearly related with the molecular size of the drug and the properties of the polymer.

Poly(vinyl alcohol) (PVA) has been used in a wide variety of fields since its discovery in 1924[5] because of desirable properties such as nontoxicity and noncarcinogenicity.[6] It finds extensive applications as biomaterials[2,6–10] such as contact lenses, artificial blood vessels, artificial intestines,[5] and artificial kidneys.[9] Studies have been carried out for the drug release with PVA hydrogels; which are biocompatible, chemically stable, and desirable for both bioseparations and cell encapsulation.[6,10–12]

However, PVA is a highly hydrophilic polymer and has poor stability in water; thus its solubility must be prevented for use in aqueous systems. To overcome this problem, PVA should be insolubilized by blending,[13] copolymerization,[14] grafting,[15,16] and crosslinking.[17–21]

Gluteraldehyde is the most common reagent used in the crosslinking processes.[14,16,17,19,22] The reaction between PVA and gluteraldehyde occurs between the hydroxyl groups of PVA and the aldehyde groups of gluteraldehyde to form an acetal bridge. The reaction produces water and thus no toxic products form from the reaction, although the crosslinking process decreases the hydrophilic character of PVA. One way to increase the hydrophilicity is crosslinking in the pres-

ence of a hydrophilic polymer. Poly(acrylic acid) (PAA) is a hydrophilic polymer because of its characteristic carboxyl groups.

In the present study PVA membranes were crosslinked with gluteraldehyde in the presence of a hydrophilic polymer, PAA. The release behavior of diclofenac, a nonsteroidal anti-inflammatory agent[23,24] used in the treatment of rheumatoid arthritis and other rheumatoid disorders,[25] was investigated. Because of its low solubility diclofenac, commercially available as diclofenac sodium and sodium[2-(2,6-dichloroanilino) phenyl acetic acid], is a weak acid with pK_a of 4.[23–26] It has low solubility in acidic solution and intramolecular cyclization occurs under acidic conditions, which leads to its inactivation,[23] and because of its short biological half-life the drug has to be administered quite frequently.[27] Moreover, it undergoes substantial hepatic first-pass metabolism, and thus only about 50% of the administered drug reaches the circulation. Therefore, there is a need to search for an alternative route of administration, which may bypass the hepatic first-pass metabolism. The transdermal patch delivery system may be an attractive choice of an alternative route of administration of this drug. There are many controlled delivery studies for diclofenac.[28–38] Rodriguez et al.[38] studied the release of sodium diclofenac by using an alginate/chitosan system at different pH values. Vyas et al.[24] reported the release behavior of diclofenac by using cadaver skin and polymeric membrane (polyvinyl pyrrolidone at different combinations with Eudragid RL-100).

In our work PVA and PVA/PAA membranes at different combinations were prepared for the release of diclofenac under *in vitro* conditions. Effects of membrane thickness and PAA content of the membrane on the permeation characteristics were the focus of our investigation.

EXPERIMENTAL

Materials

PVA (M_w = 72,000) was supplied by Merck (Darmstadt, Germany) and PAA (M_w = 2000) was purchased from Aldrich (Milwaukee, WI) and were used as received. Diclofenac was kindly provided by Novartis (Summit, NJ). Na_2HPO_4, NaH_2PO_4, and gluteraldehyde were all Merck products. Bz_2O_2 (Merck) was purified by solving in chloroform and recrystallizing in a 2× volume of ice-cold ethanol.

TABLE I
Preparing Conditions of Membranes

Membrane	PVA/PAA (v/v)
PVA–M	100/0
PVA/PAA–M_1	75/25
PVA/PAA–M_2	50/50
PVA/PAA–M_3	25/75

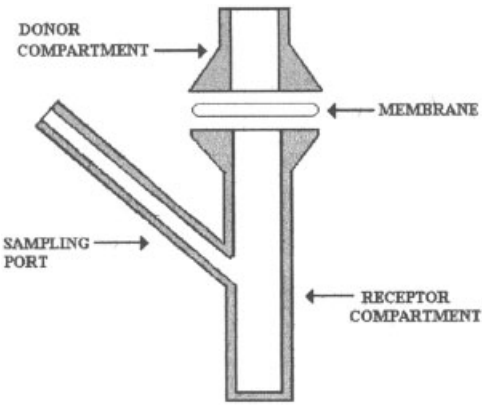


Figure 1 Permeation cell.

Preparation of PVA membranes

PVA membranes were prepared by using an aqueous solution of PVA at a concentration of 5% (m/v). A predetermined amount of polymer solution was cast onto petri dishes (9 cm in diameter). They were dried at 35°C and crosslinked with gluteraldehyde solution (10% gluteraldehyde in acetone containing 0.05% HCl) at 40°C. The excess gluteraldehyde on the membranes were removed by soaking in methanol at 40°C for 1 day and then the membranes obtained at different thicknesses (10–60 μm) were preserved in distilled water until use.

Preparation of PVA/PAA membranes

Membranes were prepared by using homogeneous mixtures of PVA and PAA aqueous solutions at a concentration of 5.0% (m/v). Different amounts of PVA and PAA solutions were mixed at room temperature and stirred for 1 day to obtain a homogeneous polymer solution. The prepared solution was cast onto petri dishes and then crosslinked as in PVA membranes (Table I).

Scanning electron microscope (SEM) studies

For SEM analysis the free-dried membranes were sputtered with gold in vacuum before viewing under the microscope (Model JEM-100CXII; JEOL, Peabody, MA).

Permeation experiments

Permeation experiments were carried out at 37 ± 1°C[36,37,39–45] by using a Franz diffusion cell (Fig. 1). Diclofenac (as sodium salt; 3 mL of 25 mg/mL) was

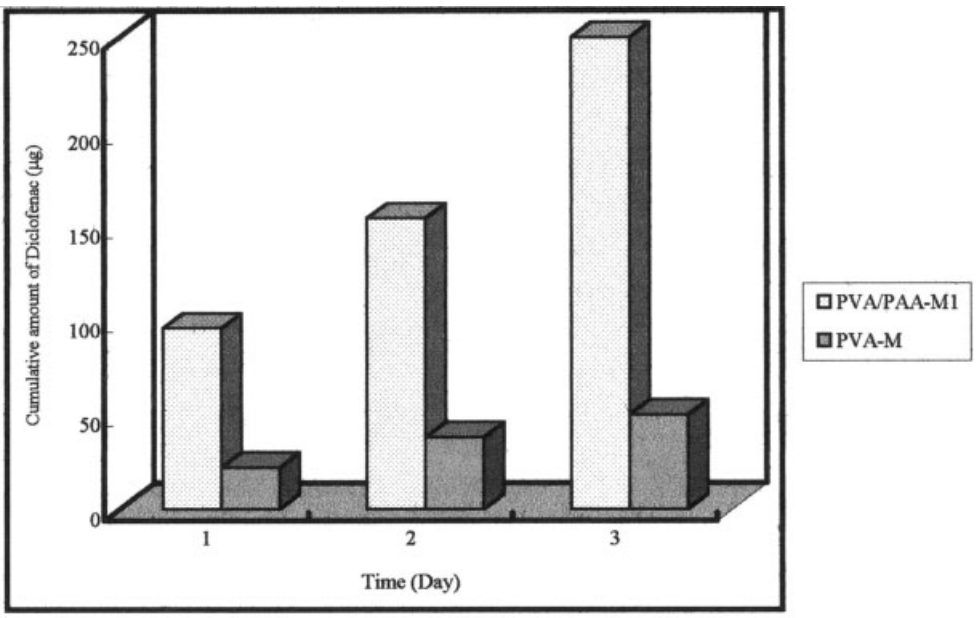


Figure 2 Cumulative amount of diclofenac (μg) from PVA–M and PVA/PAA–M_1 membranes (membrane area: 2.27 cm^2).

placed into the upper compartment of the cell and a phosphate buffer solution of pH 7.4 was placed in the lower part. The lower compartment of the cell was stirred magnetically for uniform composition during the permeation. The analysis of the samples was carried out spectrophotometrically at 275 nm by using a Unicam UV2–100 UV–vis spectrophotometer (UK). All of the data points are the average of at least three experimental results. The experiments are fairly reproducible.

RESULTS AND DISCUSSION

Figure 2 shows the release of diclofenac from PVA–M and PVA/PAA–M_1 membrane. As reflected from the figure the drug release from the PVA/PAA–M_1 membrane is higher than that from PVA–M, indicating the considerable influence of the PAA incorporated into the membrane because of the hydrophilic side groups (–COOH) of PAA. If a hydrogel consists of macromolecular chains that includes carboxylic groups inside the network, then the possible dissociation of these acidic groups in a neutral or slightly alkaline pH will result in extensive swelling and subsequent release of the drugs.

The rate of release of an active material from a reservoir device will be controlled by the permeability of the membrane and by the configuration of the device. For a device containing drug of the appropriate form, permeability was determined using the time-lag equation proposed by Crank.[46] Because of the steady-state condition in the receiver cell the equation reduces to

$$M_t = \frac{ADC_0}{L}\left(t - \frac{L^2}{6D}\right) \tag{1}$$

where M_t is the total amount of the solute that has diffused across the membrane at time t; C_0 is the concentration within the membrane at the donor face ($x = 0$), and D is the diffusion coefficient. Taking $Q_t = M_t/A$ eq. (1) reduces to

$$Q_t = \frac{DC_0}{L}\left(t - \frac{L^2}{6D}\right) \tag{2}$$

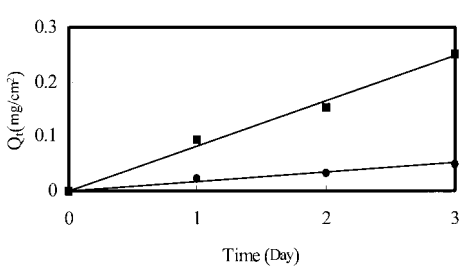


Figure 3 Permeation of diclofenac for PVA–M and PVA/PAA–M_1 membranes: ●, PVA–M; ■, PVA/PAA–M_1.

TABLE II
Change of Permeability Constant with the Thickness of the Membrane

Thickness, L (μm)	$P \times 10^5$ (cm^2/h) (PVA/PAA–M_1)
10	4.5
20	3.1
40	1.2
60	1.0

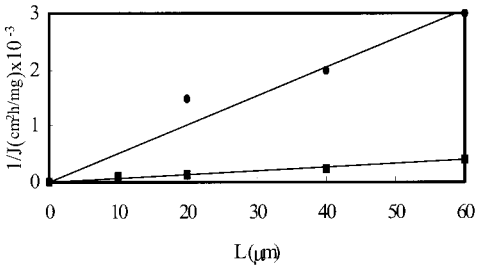


Figure 4 Variation of $1/J$ with thickness (L) of the membranes: ●, PVA–M; ■, PVA/PAA–M_1.

If the linear plot of Q_t versus t is extrapolated to the Q_t axis, the resulting intercept includes the $(L^2/6D)$ term, which is called the time lag.

Figure 3 depicts the dependency of Q_t versus t; apparently there was no occurrence of time lag and burst effect. The absence of a time lag thus indicates that for these experiments, the equilibrium seemed to be instantaneously established. This may be attributed to the use of swollen membranes because they were preserved in distilled water until use. The swollen membrane has a high water content, which facilitated the permeation of a water-soluble solute like sodium diclofenac. Lack of a time lag also shows that the $(L^2/6D)$ term in eq. (2) is negligible relative to the time scale of the experiment.

Permeability coefficients,[4] related to the diffusion coefficients by eq. (3), can be calculated as follows:

$$P = KD \tag{3}$$

where K is the partition coefficient given by

$$K = \frac{C_0}{C_0^D} = \frac{C_1}{C_1^R} \tag{4}$$

in which C_0^D and C_1^R are the concentrations on the donor and receptor sides of the cell, respectively. When eqs. (3) and (4) are substituted in eq. (2), Q_t depends on t as

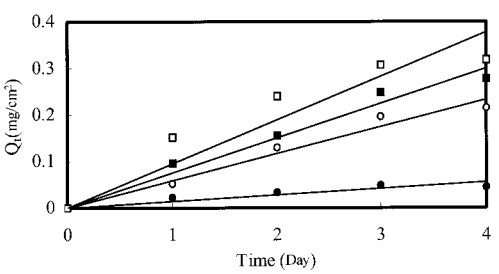


Figure 5 Effect of PAA content of membranes on permeability: ●, PVA–M; ■, PVA/PAA–M_1; □, PVA/PAA–M_2; ○, PVA/PAA–M_3.

TABLE III
Permeability Constants for Different Membranes

Membrane	$P \times 10^5$ (cm^2/h)
PVA–M	0.2
PVA/PAA–M_1	1.2
PVA/PAA–M_2	1.3
PVA/PAA–M_3	1.0

$$Q_t = \frac{PC_0^D}{L}\left(t - \frac{L^2}{6D}\right) \tag{5}$$

from which P can be calculated from the slope of the curve Q_t versus t in steady state. In this study the slopes were estimated at a confidence limit of 96–99%.

Effect of membrane thickness and the boundary layer

Membranes of different thicknesses ranging from 10 to 60 μm were placed into the Franz diffusion cell and the results are presented in Table II. It is clear that as the thickness of the membranes increases the permeability of the membranes decreases, as expected from Fick's law.

To study the boundary layer effects in permeability measurements, flux (J) (kg/cm^{2}h) of the PVA–M and

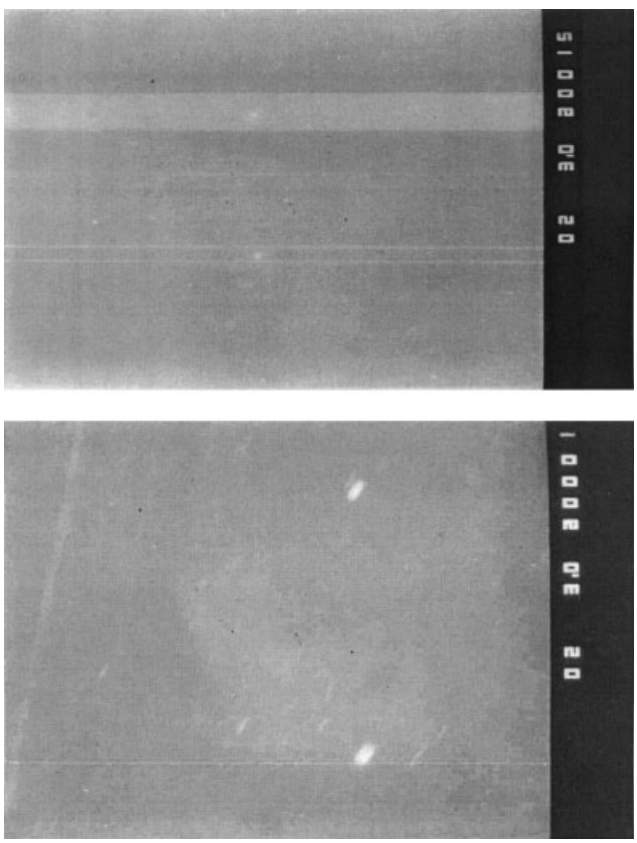


Figure 6 SEM micrographs of the membranes: (a) PVA (×3000); (b) PVA/PAA–M_1 (×3000).

PVA/PAA–M_1 membranes at different thicknesses was determined according to the equation derived from Fick's law of diffusion, which can be expressed as

$$J = \frac{1}{A}\frac{dM_t}{dt} = P\frac{\Delta C}{L} \quad (6)$$

where dM_t/dt is the amount of solute that permeates through the membrane in unit time and ΔC is the concentration difference between the donor and receptor side. In systems where a boundary layer develops on either side of the membrane, effective thickness of the membrane increases and the flux will be decreased. Equation (6) can be modified as follows[40]:

$$\frac{1}{J} = \frac{1}{P\Delta C}(L + PR_b) \quad (7)$$

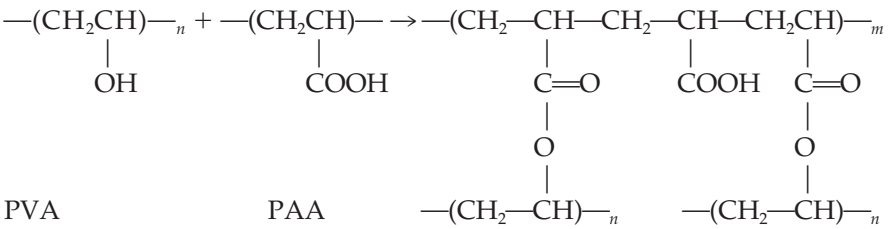
where R_b is the boundary layer resistance. In the case where a boundary layer is present the plot of $1/J$ versus L will yield a positive intercept. As reflected from Figure 4 $1/J$ is linearly dependent on L, with the line passing through the point of origin. This indicates the absence or nonmeasurable effect of a boundary layer.

Effect of PVA/PAA ratio on permeability

Membranes with PVA/PAA ratios ranging from 25/75 to 75/25 were prepared and the permeation of diclofenac through these membranes was conducted. As reflected from Figure 5 and Table III, the permeability of modified PVA membranes improved upon the incorporation of PAA polymer up to PVA/PAA 50/50. On the other hand increases of PAA content higher than this caused a decrease in permeability.

The increase in permeability can be attributed to the introduction of the carboxyl groups. However, the decrease in permeability at high PAA contents was probably attributable to the additional crosslinks produced between PVA chains and PAA, which led to the more dense structure of the membrane. An increase in the number of generated crosslinks will decrease the mesh size, thus leading to decreases in the water content and the swelling.[15,19,47]

The reaction between PVA and low molecular weight PAA was studied by Rhim et al.[48] They proposed a reaction mechanism as given in the following equation:



PVA PAA (8)

PVA was crosslinked through the reaction between the hydroxyl group in PVA and the carboxyl group in PAA.

Microstructure of membranes

Measurable pores were not observed on the film surfaces even at a magnification of ×3000 (Fig. 6). SEM microfilms revealed that the wholly dense structure and smooth surfaces were independent of the presence of PAA.

CONCLUSIONS

Based on the preceding study the following conclusions may be drawn:

1. The release profile of diclofenac from PVA and PVA/PAA membranes showed linear dependency on time with the lack of burst effect, lag time, and boundary layer resistance.
2. The presence of PVA in the membranes greatly influenced the resultant membrane performance. As the PAA content of the membranes increased, first a significant improvement in the permeability properties was observed. However, at high PAA contents permeabilities decreased. The optimum PVA/PAA ratio was found as 1 : 1.
3. High release rates were obtained for thin membranes (10 μm), whereas low release rates were observed with thick membranes.
4. The prepared transdermal delivery system of diclofenac could be used with improved performance and it holds promise for further studies.

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