Permeation of Drugs in Chitosan Membranes

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ABSTRACT: The permeabilities of isoniazid and amitriptyline hydrochloride in chitosan membranes were investigated. Drug concentration was changed from 0.1 to 1.0% while membrane thickness was varied from 40 to 150 μm. The release rate was measured in water at 30 $\pm$ 0.1°C by spectrophotometric determination. The drugs presented quite different permeabilities, which were related to their molecular weights; the permeabilities did not change with thickness or drug concentration for the ranges investigated. © 2002 John Wiley & Sons, Inc. J Appl Polym Sci 84: 44–49, 2002; DOI 10.1002/app.10185

Key words: chitosan membranes; isoniazid; amitriptyline hydrochloride; permeability; membranes; drug delivery systems; UV–vis spectroscopy

INTRODUCTION

Polymer permeability is the basis for a number of important applications in various areas of pharmaceutical interest, such as tablet coatings,[1] haemodialysis, and wound dressing.[2] In addition to these applications, a considerable amount of research is concerned with the use of polymers as agents for the controlled release of drugs from various types of formulated products, for example, tablets, implants, and adhesives strips. Evidence of the high degree of interest in the design of such dosage forms is provided by the number of reviews[3–5] and books[6–9] that have been concerned with these subjects.

A controlled-release dosage form consists essentially of a drug-containing device that permits the release of the drug at a predetermined rate when the dosage form is placed in the body. The usefulness of polymeric materials arises from the tremendously wide variations that can be obtained in their properties through the variation of the nature and/or concentration of comonomers, crosslinkers, and plasticizers.

Various types of polymeric membranes may be used in this field. In general, they can be classified according to the release mechanism as (1) hydrophobic, nonporous membranes, (2) microporous membranes, and (3) water-swollen, hydrophilic membranes (hydrogels). For the first type, the release process involves the consecutive process of drug partition between the core formulation and the membrane, diffusion of the drug in solution across the latter, and subsequent partition of the drug into an aqueous environment. For the second, it involves transfer of the dissolved drug through discrete, liquid-filled pores. Partition of the drug between the core formulation and the liquid in the pores of the membrane must occur before membrane transport can proceed. Finally, for the third type, permeability is strongly affected by the solubility of the diffusant in the aqueous continuous phase of these systems.

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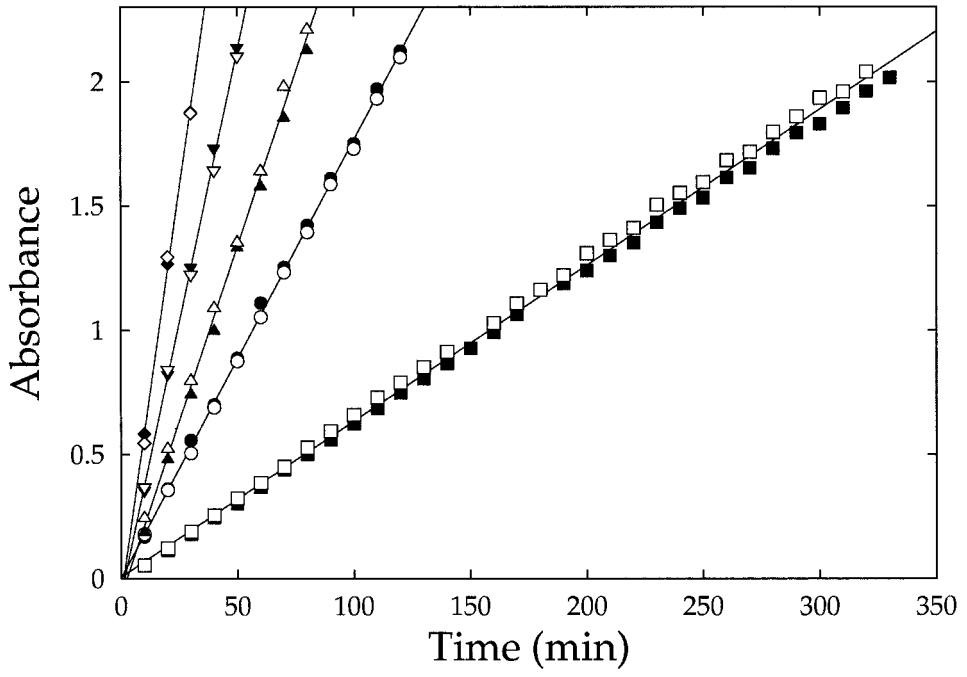

Figure 1 Absorbance as a function of time for permeation experiments with isoniazide solutions at different concentrations: 0.1% (squares), 0.3% (circles), 0.5% (up triangles), 0.7% (down triangles), and 1.0% (diamonds). $L = 35 \pm 3$ μm.

These membranes can be considered intermediate between porous and nonporous ones.

Much of the previous work on controlled-release drug-delivery systems has used polydimethylsiloxane[10] because of its biocompatibility and high permeability to hydrophobic drugs or polyurethanes[10] due to the possibility of different copolyether–urethane combinations.

In this study, the potential use of chitosan in controlled-release drug-delivery devices was investigated. Chitosan [β-(1–4)-2-amino-2-deoxy-D-glucose], derived from chitin by deacetylation, is a natural polycationic polymer that possesses valuable properties as a biomaterial for biomedical applications.[11] The film-forming property of chitosan offers many applications for various membrane separations fields. The selectivity of the membrane is a critical parameter in membrane separation, being affected by factors such as membrane molecular weight,[12] chain flexibility,[13] thickness,[14] and preparation conditions,[15] which have been investigated. To obtain insight into the process of molecular separation, we prepared chitosan membranes of different thicknesses and used two drugs of different molecular weights.

EXPERIMENTAL

Materials

Chitosan was supplied by Polymer Ltd. (Fortaleza, Brazil). Its deacetytilation degree was about 80 mol %. The solutes used for the transport experiment were amitriptyline hydrochloride [weight-average molecular weight (M_w = 313.57, pH = 5.5–6.5 in aqueous solution, λ = 263 nm] and isoniazid (M_w = 137, pH = 5.0–6.0 in aqueous solution, λ = 239 nm). These were purchased from Sigma (St. Louis, MO). We chose these drugs, taking into account their molecular weights, water solubility, pH, and suitability in ultraviolet (UV) absorption.

Membrane Preparation

We prepared the chitosan solution by dissolving chitosan in an aqueous 2% acetic acid solution at ambient temperature with stirring overnight. The concentration of chitosan in the acid solution was changed according to the desired membrane thickness. The solution was filtered with a G4 glass filter and allowed to stand for about half a

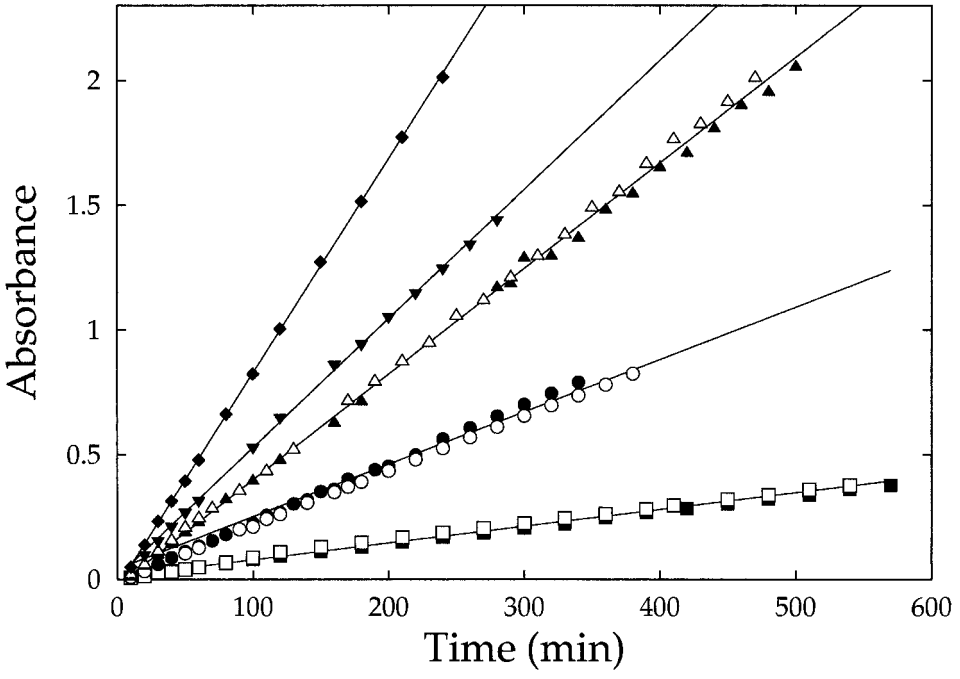

Figure 2 Absorbance as a function of time for the permeation of amitriptyline at different solution concentrations: 0.1% (squares), 0.3% (circles), 0.5% (up triangles), 0.7% (down triangles), and 1.0% (diamonds). $L = 35 \pm 3$ μm.

day to remove air bubbles. The solution was then cast onto a glass plate and placed in a drying air oven at 50°C for 24 h. The dry film was immersed in a 5% aqueous solution of NaOH for 2 h. The chitosan membrane was repeatedly washed with water and placed on a extensor for drying. The dry membrane thickness was measured with a digital micrometer Check-line (model DCF-900).

Permeation Experiments

The diffusion cell consisted of two cylindrical half-cells 230 cm^3 in volume. The chitosan membrane was placed between the compartments and was not supported. The membrane area was 8.55 cm^2. Each compartment was stirred continuously by externally mounted constant-speed synchronous motors. The diffusion cell was placed in a water bath maintained at 30 ± 0.1°C. The chitosan membranes were initially immersed in water for 12 h before the experiment.

The feed solution was prepared by dissolution of the solute in water at different concentrations. The receiving solution was distilled water. Samples of 2.5 cm^3 of the receiving solution were taken at various time intervals, and the solute concentration was analyzed by a Varian UV spectrophotometer model, and then it was returned to the receiving solution. All the experiments were done in duplicate.

Permeability (P) values were determined with the model proposed by Crank[16] for flow through a membrane described as following: one face of the membrane ($x = 0$) was kept at constant concentration c_1, the other ($x = L$) was kept at concentration c_2, and the membrane was initially at a uniform concentration c_0.

According to our experimental arrangement, we could assume that the membrane was initially at zero concentration ($c_0 = 0$) and that the concentration at one face was much higher than the concentration on the emerging face (i.e., $c_1 \gg c_2$) and, therefore, $c_1 - c_2 \cong c_1$. In this case, the total amount of diffusing substance (Q_t), which has passed through the membrane in time t is given by

$$Q_t = \frac{Dc_1}{L}\left(t - \frac{L^2}{6D}\right) \quad (1)$$

where D is the diffusion coefficient and L is the membrane thickness.

Because the amount of drug released was measured spectroscopically, Q_t is given by:

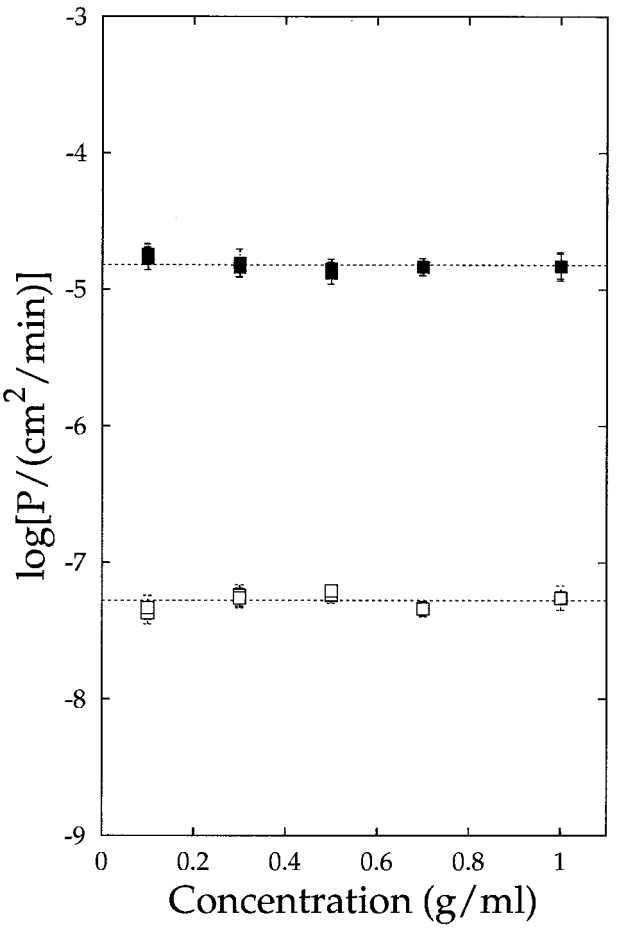

Figure 3 Permeability as a function of concentration for (■) isoniazide and (□) amitriptyline.

$$Q_t = \frac{VA}{\varepsilon bS} \tag{2}$$

where V is the half cell volume, A is the absorbance, S is the membrane area, b is the cell path length, and ε is the extinction coefficient. Substituting eq. (2) in eq. (1), we get

$$A(t) = \frac{Dc_1\varepsilon bS}{VL}\,t - \frac{c_1L\varepsilon bS}{6V} \tag{3}$$

Because we do not have the c_1 value, the diffusion coefficient cannot be calculated. Instead, we can determine the permeability coefficient, which can be related to the diffusion coefficient by

$$P = KD \tag{4}$$

where K is the partition coefficient given by

$$K = \frac{c_1}{C_1} = \frac{c_2}{C_2} \tag{5}$$

where C_1 and C_2 are the concentrations on each side of the cell. When eq. (5) is substituted in eq. (4) and then in eq. (3) it follows that

$$A(t) = \frac{PC_1\varepsilon bS}{VL}\,t - \frac{c_1L\varepsilon bS}{6V} \tag{6}$$

from which P can be calculated with the slope of the curve of $A(t)$ against t in the steady state.

RESULTS AND DISCUSSION

The results from the permeation experiments with isoniazide and amitriptyline, $L = 35 \pm 3$ μm, are plotted in Figures 1 and 2, respectively. Apparently, there was no occurrence of time lag. The time lag is usually related to a build-up period necessary to establish an equilibrium at the interface between the more concentrated side (C_1) and the membrane. The absence of a time lag indicates, therefore, that for these experiments, the equilibrium seemed to be instantaneously established. This behavior can be understood if we remember that the membranes used were already swollen with water because they were immersed in it for 12 h before the experiments. The swollen membrane had a high water content, which facilitated the permeation of water-soluble solutes like isoniazide and amitriptyline. The absence of a time lag indicates, as a consequence, that either the mechanism involved in the permeability was related to a microporous membrane or the combination of thickness (L) and diffusion coefficient (D) led to values of $L^2/6D$ that were negligible relative to the time scale of the experiment.

Although drug flux increased with solution concentration in both cases, as indicated by the increasing slopes of the resultant curves, permeability did not change as the concentration increased, as shown in Figure 3. From this, one can confirm that the drugs were liberated at a constant rate for periods of time up to 6 h. This also gives us two indications: (1) the diffusion process can be said to be Fickian, and (2) the partition coefficient between water and chitosan was independent of concentration for this range of concen-

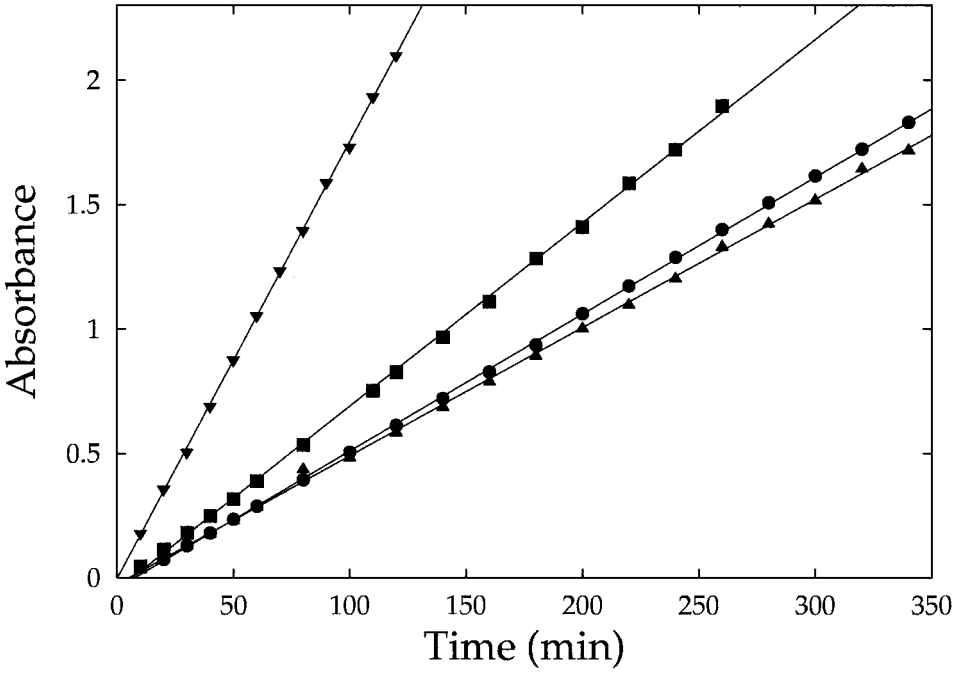

Figure 4 Absorbance as a function of time for isoniazide, with different chitosan film thicknesses: (▲) 149 μm, (●) 129 μm, (■) 94 μm, and (▼) 34 μm.

trations. Seo et al.[17] reported the dependence of permeant concentration and permeability for chitosan membranes. According to the authors, the permeation should increase with increases in C_1 until membrane saturation is reached (c_1). In our experiment, this increase in permeability was not observed. Therefore, we can conclude that the initial concentration used (0.1%) was already above the saturation concentration of our membranes.

The Fickian character of the diffusion is also depicted by Figure 4, which shows the absorbance in the less concentrated compartment as a function of time for membranes with different thicknesses, as well as Figure 5, which shows the calculated values of permeability for the same membranes. Permeability was not a function of membrane thickness, as expected for the case of Fickian diffusion. The permeability of isoniazide was also much higher than that of amitriptyline, which could be explained through the analysis of their molecular dimensions, which are directly related to their molecular weights. It is clear that the permeation of amitripytiline did not occur in the same extent as in the case of isoniazide, which is hydrodynamically explained by larger Stokes's radius in the case of amitriptyline, the compound with highest molecular weight.[17] This difference in permeability shows that chitosan membranes could be quite specific in terms of these two drugs. If this selectivity is defined as the ratio between the permeability to isoniazide and the permeability to amitriptyline, the specificity is around 3 $\times$ 10^2, which indicates that the membrane was very selective in relation to amitriptyline.[15]

CONCLUSIONS

The diffusion of isoniazide and amitriptyline in chitosan membranes obeyed all the ideal equations for permeation used in the modeling, which were based on a solution-diffusion mechanism. The absence of a time lag for swollen membranes was probably due to the small membrane thickness (L) used that led to values of $L^2/6D$ that were negligible relative to the time scale of the experiment (t). Both drugs were liberated at a constant ratio. Their permeabilities were strongly dependent on their molecular dimensions: isoniazide (the compound with the lower molecular weight) had a much higher value of permeability. The membranes, therefore, were highly selective in relation to these two drugs. From these two properties, a constant ratio and a high selectivity,

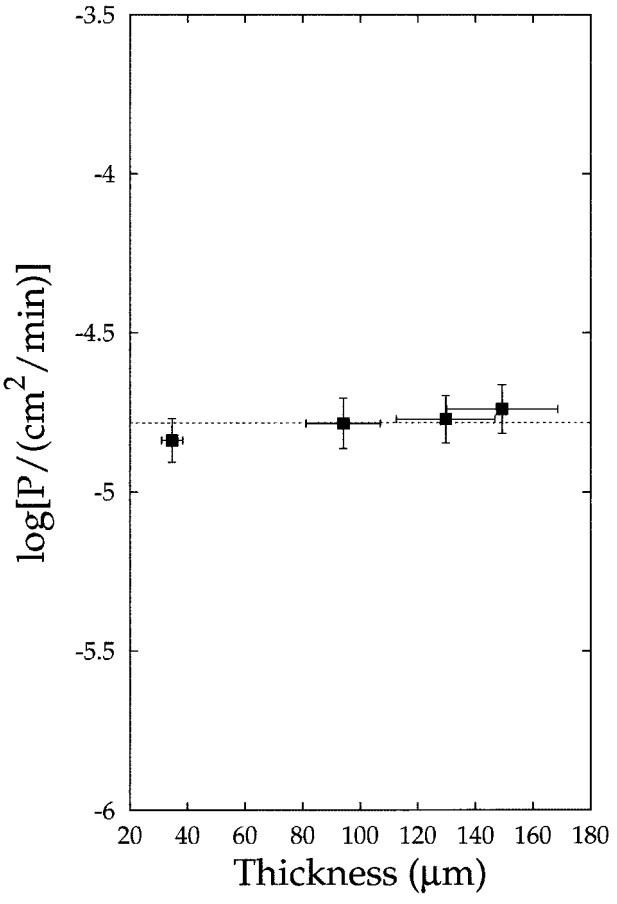

Figure 5 Permeability as a function of film thickness for isoniazide.

we conclude that chitosan membranes can potentially be used in a controlled-release system.

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