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International Journal of Pharmaceutics 120 (1995) 115–118

international journal of pharmaceutics

Collagen-chitosan composite membranes for controlled release of propranolol hydrochloride

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Received 18 August 1994; revised 29 November 1994; accepted 12 December 1994

Abstract

Composite membranes consisting of collagen and chitosan in various proportions were prepared and characterized by Fourier transform infrared spectroscopy and equilibrium swelling studies. The permeability properties of these membranes for propranolol hydrochloride were studied and compared with those of collagen and chitosan membranes. The permeability properties of the composite membranes were found to depend on the concentration of collagen and chitosan in the membranes.

Keywords: Composite membrane; Collagen; Chitosan; Propranolol hydrochloride

Many composites consisting of a combination of biopolymer, collagen or chitosan and a synthetic polymer have become available for various biomedical applications (Panduranga Rao and Joseph, 1988; Stol, 1991; Nakatsuka and Andrady, 1992). Collagen and chitosan are highly biocompatible and possess favorable physicochemical properties for this purpose. Recently, collagen-chitosan composite membranes and hydrogels have been investigated for their potential applications in biomedical and pharmaceutical fields (Shahabeddin et al., 1991; Taravel and Domard, 1993). In the present investigation, composite membranes consisting of collagen and chitosan in various proportions were prepared by the solvent evaporation technique. These membranes were characterized by Fourier transform infrared (FT-IR) spectroscopic, and equilibrium swelling studies. The permeability properties of these membranes for Propranolol hydrochloride (prop-HCl) were studied and the results were compared with those of collagen and chitosan membranes.

Soluble collagen was extracted from fetal calf skin by a procedure standardized in our laboratory which is a slight modification of the method reported by Weiss and Elstow (1983). After extraction, collagen was made telopeptide-poor by pepsin treatment. Collagen-chitosan composite membranes were prepared as follows: 0.5% (w/v) solutions of chitosan (a gift from Central Institute for Fisheries Technology (CIFT), India) and collagen were prepared in 0.5 M acetic acid. These two solutions were thoroughly mixed in various

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SSDI 0378-5173(94)00423-4

proportions using a vortex mixer. The resulting solution was allowed to stand at 4°C until all air bubbles had disappeared. The bubble-free solution was then poured on a rimmed perspex plate and allowed to dry at 4°C. The membranes thus obtained were neutralized by immersion in 1% aqueous NaOH for 30 min, washed thoroughly with distilled water and dried at 4°C. The membranes were stored in the refrigerator for further studies. Composite membranes consisting of collagen and chitosan in 1:3 (Co_1Ch_3), 1:1 (Co_1Ch_1) and 3:1 (Co_3Ch_1) ratios by weight were prepared in this manner.

The water sorption capacity of membranes was determined by swelling the membranes in distilled water at room temperature (27°C). For this, a known weight of the membrane was placed in water for the required period of time. The swollen membrane was weighed immediately on an electronic balance after removing the adsorbed water with filter paper. The percent swelling of the membranes at various time periods was then calculated. Fig. 1 compares the swelling behavior of collagen-chitosan composite membranes with that of collagen and chitosan membranes. The equilibrium swelling (E_{sw}) of the composite membrane (Co_3Ch_1) was found to be closer to that of the collagen membrane, whereas E_{sw} of the composite membrane (Co_1Ch_3) was found to be nearer to that of the chitosan membrane. The E_{sw} of the composite membrane (Co_1Ch_1) was found to be intermediate between those of collagen and chitosan membranes. These results clearly indicated that by varying the collagen-chitosan ratio in the composite, it is possible to regulate its swelling property which in turn significantly influences the permeability properties of the membranes.

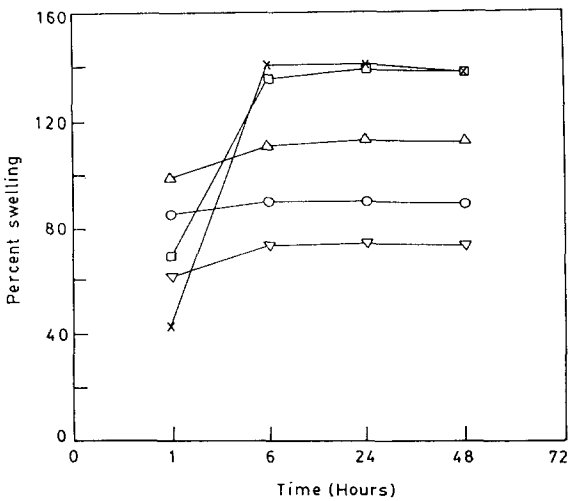

Fig. 1. Percent swelling of collagen, chitosan and various collagen-chitosan composite membranes in distilled water. Collagen (×), chitosan (▽), Co_1Ch_1 (△) Co_1Ch_3 (○), Co_3Ch_1 (□). Values are average of six determinations.

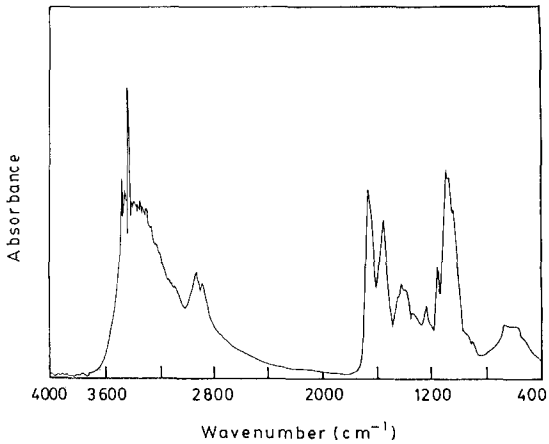

Fig. 2. FT-IR spectrum of collagen-chitosan composite membrane.

The FT-IR spectrum of collagen-chitosan composite membrane consisting of collagen and chitosan in 1:1 ratio by weight recorded with a Nicolet DX-20 FT-IR spectrometer is shown in Fig. 2. The characteristic bands in the spectrum included a peak at 3330 cm^{-1} which corresponds to N-H stretching, a peak at 1650 cm^{-1} which corresponds to amide I C = O stretching, a peak at 1550 cm^{-1} which corresponds to amide II N-H bending and C-N stretching, and a peak between 1150 and 1250 cm^{-1} which corresponds to amide III C-N stretching and N-H bending vibrations. These absorption bands that are characteristics of native collagen revealed that the structure of collagen is intact in the composite membranes. The presence of chitosan in the composite is revealed by a strong absorption band between 800 and 1200 cm^{-1}, which is characteristic of the presence of pyranose rings, and a large OH absorption band near 3450 cm^{-1}.

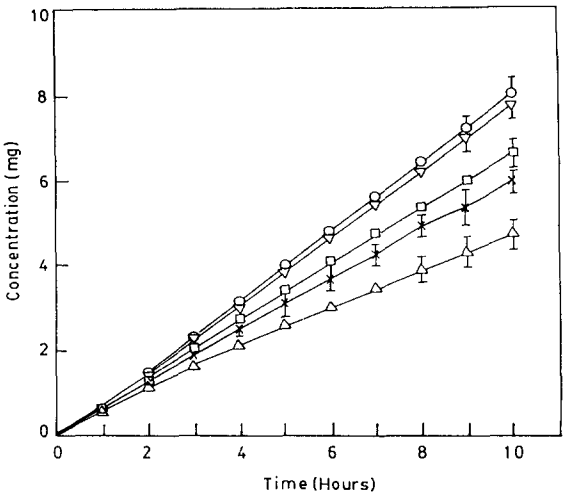

Fig. 3. Cumulative amount of prop-HCl permeated through unit area of collagen, chitosan and various collagen-chitosan composite membranes. Collagen (○), chitosan (△), Co_1Ch_1 (□) Co_1Ch_3 (×), Co_3Ch_1 (▽). Values are mean ± SD ($n = 6$).

The permeability properties of the membranes were investigated by permeation studies conducted in side-to-side static glass diffusion cells according to a procedure similar to that reported elsewhere (Thacharodi and Panduranga Rao, 1993). Fig. 3 shows the cumulative amount of prop-HCl permeated through unit area of collagen-chitosan composite, collagen and chitosan membranes. All the membranes were found to release the drug with zero-order kinetics. The fluxes of prop-HCl at steady state of diffusion through different composite membranes are compared with that of collagen and chitosan membranes in Table 1. The flux for the composite membrane Co_3Ch_1 (where collagen content is high) was found to be closer to that of the collagen membrane, whereas that for the composite membrane Co_1Ch_3 (where the chitosan content is high) was found to be near to that of the chitosan membrane. The flux for the composite membrane Co_1Ch_1 was found to be intermediate between that of collagen and chitosan membranes. This difference in drug flux between the membranes is due to a difference in the permeability coefficient of the membranes which is a function of the drug diffusion coefficient within the membranes and the drug/membrane partition coefficient.

The diffusion coefficients of prop-HCl (D) within the composite membranes were calculated from the Daynes and Barrer lag time equation. The values are compared with that of collagen and chitosan membranes in Table 1. The data show that D is very high in collagen membranes when compared with that of chitosan and collagen-chitosan composite membranes. This may be due to the greater porosity of collagen membranes associated with considerable free interfibrillar spaces for passive drug diffusion. D values in all the composite membranes were found to be significantly lower than that found in collagen but nearer to and less than that of the chitosan membrane. Moreover, among the three composite membranes studied, the one with higher chitosan content (composite membrane-Co_1Ch_3) showed maximum D, which is close to that of the chitosan membrane. In this membrane, chitosan occupies the major portion and there are few collagen fibrils. The diffusion coefficient would then be almost equal to that of the chitosan membrane. On the other hand, the composite membrane Co_3Ch_1 (composite membrane with less chitosan content) showed minimum D. In this membrane the collagen concentration is high and chitosan occupies only a limited space in

Table 1
Permeability properties of collagen, chitosan and various collagen-chitosan composite membranes (drug flux (J), diffusion coefficient (D), partition coefficient (K) and permeability coefficient (P); values are mean ± SD ($n = 6$))

Nature of membrane	J (mg cm^{-2} h^{-1})	D ($\times 10^{-7}$) (cm^2 h^{-1})	K ($\times 10^3$)	P ($\times 10^{-3}$) (cm^2 h^{-1})
Co_3Ch_1	0.78 ± 0.001	26.33 ± 3.4	29.98 ± 0.05	78.95 ± 2.8
Co_1Ch_3	0.60 ± 00	37.00 ± 5	15.05 ± 0.07	55.68 ± 3.3
Co_1Ch_1	0.67 ± 005	31.83 ± 6.87	20.96 ± 1	66.73 ± 3.3
Collagen	0.83 ± 00	267.00 ± 00	3.05 ± 0.05	81.30 ± 3.5
Chitosan	0.48 ± 03	40.00 ± 00	11.53 ± 2	46.13 ± 2.0

between the collagen fibrils. The diffusion of prop-HCl in such composite membranes takes place mainly through the interfibrillar space which is occupied by chitosan. A low D value in the membrane may be due to a smaller area for passive drug diffusion.

Prop-HCl/membrane partition coefficients (K) values are listed in Table 1. The data clearly indicate that the partitioning of prop-HCl into the composite membranes is much greater as compared to that of the drug into either collagen or chitosan membranes. Chitosan is a polycationic biopolymer and collagen contains both positive and negative charges, hence the higher partition coefficients exhibited by collagen-chitosan composite membranes could be attributed to the lower polarity of composite membranes due to charge neutralization and thereby better interaction with the drug molecules.

The permeability coefficients (P) of the membranes for prop-HCl were calculated from Fick's first law of diffusion. Table 1 compares the P values of collagen-chitosan composite membranes for prop-HCl with those of collagen and chitosan membranes. P values for the composite membranes were found to be lower than that of the collagen membrane but higher than that of chitosan membrane. The permeability data show that propranolol hydrochloride is transported through the composite membranes by partitioning into the membrane and diffusing through the polymer itself (partition mechanism) rather than via passive diffusion through microchannels. This study concludes that the collagen-chitosan composite membrane's permeability to drugs could be tailored according to need by varying the concentration of any one of the components in the composite and thereby these membranes represent promising candidates for controlled drug delivery applications.

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