Arch. Pharm. Res. 10(2), 88-93 (1987)

Pharmaceutical Studies on Chitosan Matrix: Controlled release of aspirin from chitosan device

Chí Young Lee and Sung Ho Kim
College of Pharmacy, Chosun University, Kwang Ju 500, Korea
(Received February 25, 1987)

Abstract □ Chitosan (β-D-glucosaminan) is chemically prepared from chitin (N-acetyl-β-D-glucosaminan) which is an unutilized natural resource. We now report on the suitability of the chitosan matrix for use as vehicles for the controlled release of drugs. Salicylic acid and aspirin were used as model drugs in this study. The permeation of salicylic acid in the chitosan membranes was determined in a glass diffusion cell with two compartments of equal volume. Drug release studies on the devices were conducted in a beaker containing 5% sodium hydroxide solution. Partition coefficient (Kd) value for acetate membrane (472) is much greater than that for fluoro-perchlorate chitosan membrane (282). Higher Kd value for acetate chitosan membrane appears to be inconsistent with the bulk salicylic acid concentration. The permeability constants of fluoro-perchlorate and acetate chitosan membranes for salicylic acid were 3.139×10^{-7} cm²/sec. and 4.255×10^{-7} cm²/sec, respectively. It was also found that release rate of 30% salicylic acid in devices was 3.792×10^{-2} mg/cm²/min up to 60 min and that of 30% aspirin in the devices was 4.739×10^{-2} mg/cm²/sec up to 60 min. As the loading dose of aspirin in a chitosan device increased, water up-take of chitosan device increased, but in case of salicylic acid it decreased. The release rate increased with increase in the molecular volume of the drugs. These results suggest that the release mechanism may be controlled mainly by diffusion through pores.

Keywords □ Device, Matrix, Chitosan Membrane, Permeability Constant, Diffusion Coefficient, Partition Coefficient, Release Rate, Water Fraction.

A widely occuring natural glucosamin, chitin, [(1-4)-2-acetamide-2-deoxy-β-D-glucan] and its alkaline deacetylation product, chitosan are biodegradable by lysozyme[1] and do not present any biological hazard[2]. Chitin and chitosan are structurally analogous to cellulose and have been reported to be useful for pharmaceutical preparations[3-7]. Recently, the film-forming ability of chitosan is well documented. Many articles have dealt with the use of chitosan membranes for the removal of toxic metal ions[8], hemodialysis[9], treatment of brine[10], and immobilization of enzymes[11,12]. However, few studies have been reported on the permeation of drugs through chitosan membrane except for some work with urea, uric acid[13], and vitamin B_{12}[14] to evaluate chitosan for use as a dialysis membrane. Therefore, it could be worthwhile to evaluate chitosan membrane as a possible carrier for the control of drug release.

The purposes of this article are to report the mechanism of permeation of salicylic acid through chitosan membrane, and the release of aspirin and salicylic acid from chitosan devices. The presen contribution is restricted to possible application o chitosan in medicine, as a carrier such as heparii complex[15] or sulfonate chitosan[16].

EXPERIMENTAL METHODS

Materials

Salicylic acid (S.A.), aspirin (A.S.A.), an chitosan were purchased from Sigma Co. (Sain Louis, Mo, U.S.A.). The other reagents were ob tained from various commercial sources and th highest grade available.

Preparation of perchloro-fluorate chitosan men brane (membrane I) and chitosan acetate men brane (membrane II)

Perchloro-fluorate chitosan membrane w prepared according to the method reported b Yaku and Yamashita[17]. Chitosan (300 mg) w dissolved in 3% $HClO_4$ (10 m*l*) and 2% HF (10 m solution at room temperature to give a viscous sol

tion. The solution was centrifuged at 3500 rpm for 5 min, diluted with 95% methanol, and then poured into a glass Petri dish to give a thin liquid layer. This liquid layer was washed with ether and air-dried to give the corresponding membrane. Finally, the membrane was removed from the glass Petri dish, soaked in 10% NaOH solution for 24 hours and washed with water.

Chitosan acetate membrane was prepared according to the method reported by Hirano[18]. Chitosan (250 mg) was dissolved in 2% acetic acid at room temperature to give a viscous solution. The solution was diluted with 95% methanol and poured into a glass Petri dish to give a thin liquid layer. To the liquid layer was added two mol equivalent of a carboxylic anhydride, which had been dissolved in 95% methanol. The solution was mixed to give a gelled layer, and the solution was decanted. The treatment was repeated several times. The membrane was washed with ether and air-dried to give the corresponding membrane. Finally, this membrane was soaked in 10% NaOH solution for 24 hours and washed with water.

Preparation of chitosan devices

Devices of chitosan and A.S.A. or S.A. were prepared on glass Petridish by casting process. Chitosan was dissolved in 3% acetic acid. This solution was added to the S.A. or A.S.A., and stirred to obtain a homogenous mixture. This mixture was applied to Petri dish and then solvent was removed under high vacuum. After casting at room temperature for 24 hours, the devices were removed from Petri dish and vacuum dried at room temperature for 24 hours. All divices were washed with deionized water to remove surface contaminants. The composition of devices were shown in Tables I and II.

Table I. Preparation and composition of A.S.A. chitosan devices

Composition of film-forming solution		Drug concentration in film, w/w%	Preparation of film*
Chitosan w/v%	A.S.A. w/v%		
2.85	0.15	5	Glass substrate
2.70	0.30	10	"
2.40	0.60	20	"
2.10	0.90	30	"

*All devices were made on the glass Petri dish.

Table II. Preparation and composition of S.A. chitosan devices

Composition of film-forming solution		S.A. concentration in films, W/W%	Preparation of film*
Chitosan w/v%	S.A. w/v%		
2.85	0.15	5	Glass substrate
2.70	0.30	10	"
2.55	0.45	15	"
2.40	0.60	20	"
2.10	0.90	30	"

*All devices were made on the glass petri dish.

Measurement

The diffusion coefficients of S.A. in the chitosan membranes were determined in a glass diffusion cell (Fig. 1) with two compartments of equal volume (176 m*l*). The membrane I (14.2 cm^2) or II (15.3 cm^2) was clamped between the compartments. Each compartment was stirred continuously at 1600 rpm by externally mounted constant-speed synchronous motors. Initially, one chamber was filled with 5% NaOH solution. The second chamber was filled with 5% NaOH solution containing 60 $\mu g/ml$ (membrane I) and 50 $\mu g/ml$ of S.A. (membrane II), respectively. The thickness of the membranes were measured at several points by micrometer, and the mean values were obtained as 0.05 cm and 0.03 cm for the perchloro-fluorate chitosan membrane (membrane I) and chitosan acetate membrane (membrane II), respectively.

The chitosan membrane containing S.A. or A.S.A. were immersed in 500 m*l* beaker containing 200 m*l* of 5% NaOH solution at room temperature (24 ± 1 °C) to study drug release on the film devices. To minimize the boundary layer effect, the releasing media were stirred continuously by constant

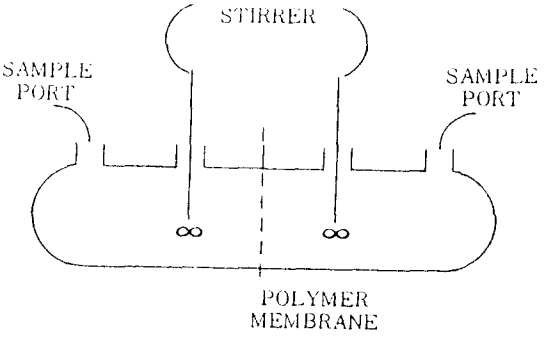

Fig. 1. Schematic diagram of the diffusion cell.

Table III. Diffusion coefficient (D), partion coefficient (Kd), and permeability (P) for S.A. in chitosan membrane at room temperature

	$D \times 10^6$ (cm^2/sec)	Kd	$P \times 10^7$ (cm^2/sec)
membrane I*	1.113	282	3.139
membrane II**	0.902	472	4.255

*Membrane I : Perchloro-fluorate chitosan membrane, thickness 0.05 cm, surface area 14.2 cm^2.

**Membrane II : chitosan acetate membrane, thickness 0.03 cm, surface area 15.3 cm^2.

speed synchronous motors. The releasing media were withdrawn at timed intervals and replaced with fresh solvent.

The concentrations of released drugs were assayed by spectrophotometry at 295 nm (Shimazu 210 A set). The experiments were performed in triplicate and the mean values were reported. The water content of these devices was determined by measuring the weight of wet and dry devices.

RESULTS AND DISCUSSION

Permeation of S.A. through membranes I and II

1) Partition coefficients (Kd)

Kd was determined by a solution depletion technique[19] in which S.A. solutions were equilibrated with known volumes of membranes. The parameter is estimated by following equation:

$$Kd = \frac{Vs(Co - Cs)}{Vm \cdot Cs}$$

where Vs, Vm, Co, and Cs are the volume of solution, volume of polymer membrane, initial S.A. concentration, and S.A. concentration in solution at equilibrium, respectively. Partition coefficients of chitosan membranes were found to be 282 and 472 for membranes I and II, respectively (Table III). The values were dependent on the concentration of S.A. in the bulk solution; Kd tended to be increased as the bulk concentration decreased. For chitosan membranes the partition coefficients were dependent on the S.A. concentration in the 5% NaOH phase. Fig. 2 illustrated the observed behavior of membranes I and II. This result may be due to adsorption of the solute at the membrane surface.

2) Diffusion coefficients (D)

Solute transport through membrane is generally described in terms of either a pore flow or solution-diffusion mechanism[19]. In a pore flow mechanism the solute diffuses through solvent filled microchannels (pore) within the polymer network. The solution – diffusion mechanism involves solute dissolution within the polymer network with ensuring diffusion along and between the polymer chains. The permeation of solute through porous polymer membranes follows Fick's first law of diffusion. Craig and King[20] have shown that permeation rates of various solutes in porous polymer membranes were linearly propotional to the inverse molecular volume of the solutes. Equation (I) was developed from Fick's first law of diffusion for the case of quasi-steady state diffusion in a membrane assuming that the amount of solute within the membrane was negligible. The permeation coefficient for S.A. in the two membranes were calculated from the following equation:

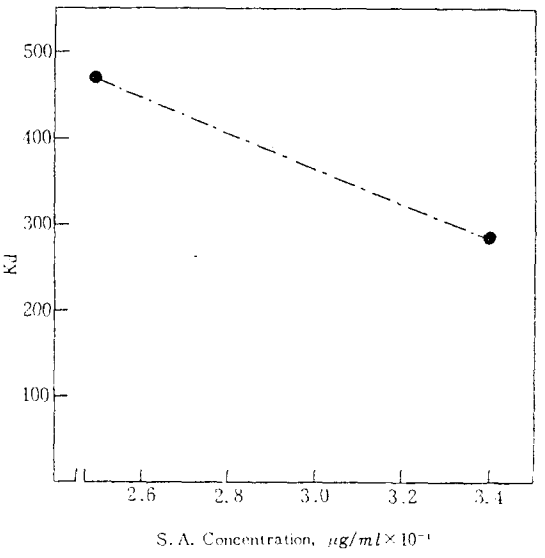

Fig. 2. Partition coefficient dependence of chitosan membrane on the bulk S.A. concentration.

$$\ln\left(1 - \frac{2C}{Co}\right) = \frac{2P \cdot S}{V \cdot L} \times t \qquad (I)$$

where C is the concentration in compartment B at time t, Co is the initial concentration in compartment A, P is the permeability constant, L is the thickness of the membrane, V is the volume of solution in the compartments, and S is the effective surface area of the membrane. The diffusion coefficient is obtained from equation $P = D \cdot Kd$.

The values of D for the two chitosan membranes are also shown in Table III. Fig. 3 is plots of the fraction of S.A. diffused versus time for membranes I and II. The diffusion coefficients of mem

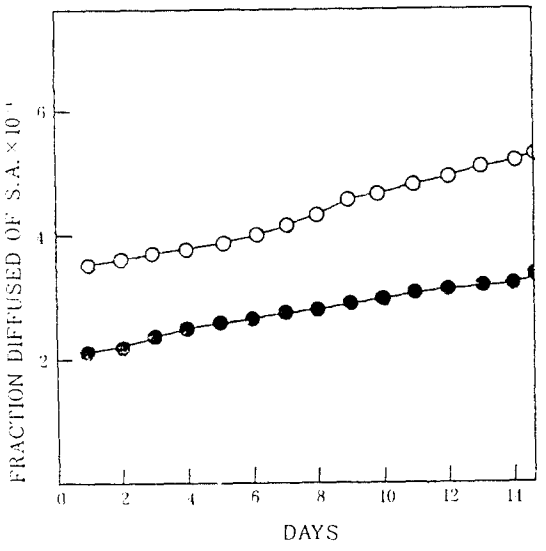

Fig. 3 Fraction diffused versus time for S.A. permeation through chitosan membrane.

○ = perchlorate-fluorate chitosan membrane
● = chitosan acetate membrane

branes I and II were 1.113×10^{-9} cm²/sec and 0.902×10^{-9} cm²/sec, respectively.

3) Permeability (P)

The permeabilities of the membranes I and II

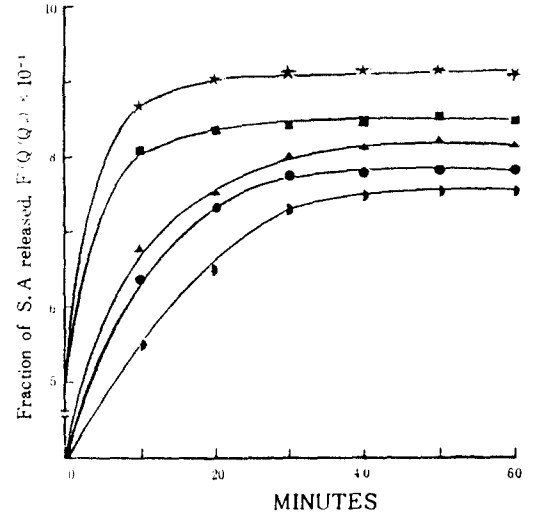

Fig. 4. Fractional release of S.A. from chitosan matrices with different S.A. loading.

★ = 30 w/w % S.A.
◆ = 20 "
▲ = 15 "
● = 10 "
◗ = 5 "

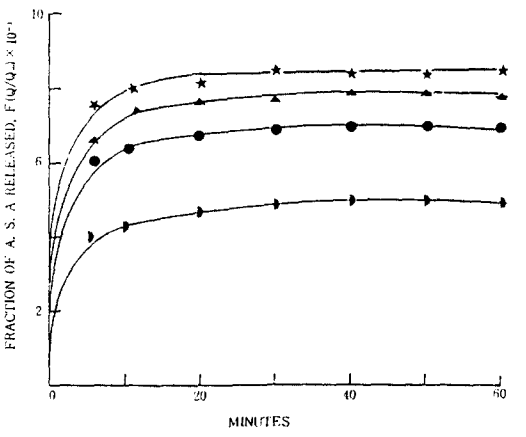

Fig. 5. Fractional release of A.S.A. from chitosan matrices with different A.S.A. loading.

★ = 30 w/w % A.S.A.
▲ = 20 "
● = 10 "
◗ = 5 "

were 3.139×10^{-7} cm²/sec. and 4.255×10^{-7} cm²/sec, respectively. (Table III). These results suggested that the permeation of S.A. through a chitosan membrane may be proceed on the base of diffusion pores.

Release of S.A. and A.S.A. from chitosan devices

1) Effect of loading dose of S.A. and A.S.A. in chitosan devices

The effects of S.A. and A.S.A. concentration on the release rate constant were tested using five and four different S.A. and A.S.A. concentrations, respectively, from 5 to 30%, in chitosan devices.

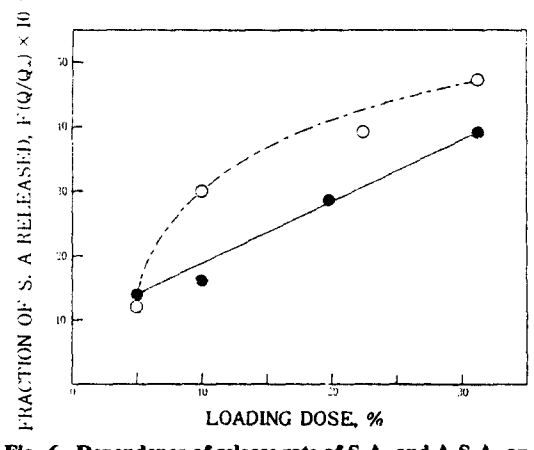

Fig. 6. Dependence of release rate of S.A. and A.S.A. on loading dose in chitosan matrices.

● = S.A.
○ = A.S.A

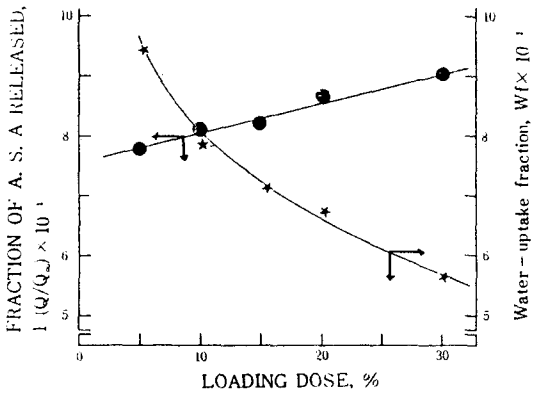

Fig. 7. Effect of loading dose of S.A. in chitosan matrices on fractional release of S.A. and fractional water up-take.

● = fractional release of S.A.
★= fractional water up-take

The results were shown in Fig. 4 and 5. The fraction of S.A. released in 95% chitosan devices deposition system was shown 0.745 at 60 min and the corresponding value of 70% chitosan devices deposition system was 0.909. In Fig. 5, the fraction of A.S.A. released in 95 and 70% chitosan devices deposition system was shown 0.481 and 0.830 at 60 min, respectively. It was also found that release rate of 5% S.A. devices was 1.037×10^{-2} mg/cm^2/min up to 60 min and that of 30% S.A. device was 3.792×10^{-2} mg/cm^2/min. On the other hand, the A.S.A. release rate of 5% A.S.A. was 1.339×10^{-2} mg/cm^2/min up to 60 min and that of 30% A.S.A. was 4.739×10^{-2} mg/cm^2/min. The results were shown in Fig. 6. The S.A. and A.S.A. release rate

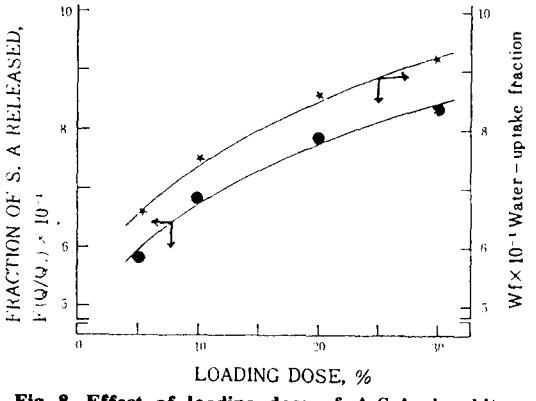

Fig. 8. Effect of loading dose of A.S.A. in chitosan matrices on fractional release of A.S.A. and fractional water up-take.

● = fractional release of A.S.A.
★= fractional water up-take

of chitosan segment deposition system is increased with increasing loading dose of S.A. and A.S.A.

2) Effect of loading dose on water up-take in chitosan segment devices

As seen in Fig. 7, the fractions of water in 5 and 30% of S.A. in chitosan segment devices were 0.950 and 0.551, respectively. The fraction of water decreases as the loading dose of S.A. increased. On the other hand, as shown in Fig. 8, the fractions of water in 5 and 30% of A.S.A. in chitosan segment devices were 0.656 and 0.909, respectively and the fraction was increased with increasing loading dose of A.S.A..

The different phenomena may be due to relationship between concentration of S.A. and A.S.A., and stress-strain on chitosan polymer. The swelling behavior of this polymer in water has been shown to be a complex function of temperature, stress-strain, solvent type, and solvent concentration[21].

LITERATURE CITED

1. Harald, B., and Jensen, K.K.: Studies on T_4. lysozyme. *Eur. J. Biochem.* **26,** 305 (1972).
2. Sugano, M., Fujikawa, T., Hiratshuhe, and Hasegawa, Y.: A novel use of chitosan as a hypocholesterolemic agent in rats. *Am. J. Clin. Nutr.* **33,** 788 (1980).
3. Miyazaki, S., Ishii, K., and Nakai, T.: The use of chitin and chitosan as drug carriers. *Chem. Pharm. Bull.* **29,** 3067 (1981).
4. Sawayanagi, Y., Nambu, N., and Nagai, T.: Directly compressed tablets containing chitin or chitosan in additon to lactose or potato starch. *Chem. Pharm. Bull.* **30,** 2935 (1982).
5. Sawayanagi, Y., Nambu, N., and Nagai, T.: Directly compressed tablets containing chitin or chitosan in additon to mannitol. *Chem. Pharm. Bull.* **30,** 4216 (1982).
6. Sawayanagi, Y., Nambu, N., and Nagi, T.: Enhancement of dissolution properties of griseofulvin from ground mixtures with chitin or chitosan. *Chem. Pharm. Bull.* **30,** 4464 (1982).
7. Sawayanagi, Y., Nambu, N., and Nagi, T.: Enhancement of dissolution properties of prednisolone from ground mixtures with chitin and chitosan. *Chem. Pharm. Bull.* **31,** 2507 (1983).
8. Muzzarelli, R.A.A., Tanfani, R., and Emanuelli, M.: The Chelation of cupric ion by chitosan membranes. *J. Appl. Biochem.* **2,** 380 (1980).
9. Hirano, S., tobetto, K., Hasegawa, M., and

Matsuda, N.: Permeability properties of gels and membranes derived from chitosan. *J. Biomed. Mat. Res.* **14,** 477 (1980).
10. Hirano, S., Tobetto, K., and Noishiki, Y.: SEM ultrastructure studies of N-acyl and N-benzylidine chitosan and chitosan membranes. *J. Biomed. Mat. Res.* **15,** 903 (1981).
11. Muzzarelli, R.A.A.: Immobilization of enzymes on chitin and chitosan. *Enz. Microb. Technol.* **2,** 177 (1980).
12. Nozawa, Y. and Matsuchita, T.: Immobilization of trypsin on chitin and chitosan by solid-state mix grinding. *Brotech. and Bioenz.* **26,** 753 (1982).
13. Mima, S., Yoshikawa, S., and Miya, M.: Japanese patent 130870 (1975); *Chem. Abstr.* **84,** 75239 (1975).
14. Mima, S., Miya, M., Yoshikawa, S., and Iwamoto, R.: Japanese patent 81705 (1980) *(Chem. Abstr.* **93,** 222510 (1980)).
15. Kikuch, Y., and Noda, A.: Polyelectrolyte complexes of heparin with chitosan. *J. Appl. Polym. Sci.* **20,** 2561 (1976).
16. Muzzarelli, R.A.A.: Heparin-like substances and blood-compatible polymers obtained from chitin and chitosan. *Polymer science,* ed. by Chiellini, E. and Gusti, P. Pleum Press, New York (1983).
17. Yaku, T., and Yamashita, I.: Japanese patent 19, 213 (1973) quoted in Hirano, S.: A facile method for the preparation of novel membrane from N-acyl and N-arylidine-chitosan gels. *Agric. Biol. Chem.* **42,** 1939 (1978).
18. Hirano, S.: A facile method for the preparation of novel membrane from N-acyl and N-arylidine-chitosan gels. *Agric. Biol. Chem.* **42,** 1939 (1978).
19. Claig, L.C. and Kinogesberg, W.J.: *J. Phys. Chem.* **65,** 116 (1961), quoted in Zentner, G.M.: Membrane of Hydrogel (Ph.D. thesis, The Univ. of Utah 1981).
20. Claig. L.C. and King, T.P.: *J. Amer. Chem. Soc.* **77,** 6620 (1955), quoted in Zentner, G.H.: Membrane of Hydrogel (Ph.D. thesis, The Univ. of Utah 1981).
21. Warren, T.C. and Prins, W.: *Macromolecules* **5,** 506 (1972), Quoted in Zentner, G.H.: Membrane of Hydrogel (Ph.D. thesis, The Univ. of Utah 1981).