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In vitro and in vivo nasal mucoadhesion of some water-soluble polymers

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Abstract

In this study the adhesion of water-soluble neutral polymers, i.e. hydroxypropylcellulose (HPC), xanthan gum (XG), tamarind gum (TG) and polyvinyl alcohol (PVA), to nasal mucosa was evaluated in vivo and in vitro. The polymers mixed with a dye were applied to the nasal cavity of rabbits in powder form, and residue of the dye was observed through a thin fiberscope. XG showed the longest residence of the dye in the cavity, followed by TG, HPC and PVA in this order. These polymers should thus prove useful as bases for mucoadhesive powder formulations. At a ratio of 2:8, a mixture of PVA and XG showed nearly the same residence time as those of HPC and TG, suggesting that it is feasible to control the residence time by mixing two or more polymers differing in adhesiveness. The order of adhesion of these polymers to agar plates in two in vitro methods agreed with that of their mucoadhesion in vivo. These in vitro methods may thus be of use for predicting the nasal mucoadhesion of powder formulations of neutral polymers.

Keywords: Nasal mucoadhesion; Water-soluble polymers; Xanthan gum; Tamarind gum

1. Introduction

The nasal cavity is an attractive alternative to the oral route for macromolecules, such as peptides and proteins, with less gastrointestinal absorption, or for drugs that are subject to an extensive first-pass effect. However, a drug in the nasal cavity generally shows limited efficacy due to its rapid disappearance from the cavity by ciliary movement and secretion of fluids. Thus, to improve localization of the drug and heighten its systemic or local effects, polymer-based formulations have been studied in solution (Pennington et al., 1988; Harris et al., 1989), gel (Morimoto et al., 1984, 1987), and powder (Nagai et al., 1983, 1984; Yamamoto et al., 1984; Kuroishi et al., 1984; Suzuki et al., 1985).

Liquid preparations are applied to the nasal cavity by spraying, because a definite amount of

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drug must spread on the mucosa for prompt absorption and efficacy and to remove discomfort due to its presence. Spray formulations are limited to those with viscosity of ca. 500 mPa·s in general, and thus long lasting mucoadhesion is hardly expected. A preparation as a solution or gel with viscosity higher than that level allows prolonged mucoadhesion, but its application to the nasal cavity is difficult.

Powder preparations, especially polymer-based ones, show no adhesion until their absorption of mucus occurs on the nasal mucosa. This allows easy application to the nasal cavity even if they are highly mucoadhesive, and makes it feasible to control the time of mucoadhesion. Although dosage forms containing water like solutions and gels are unsuitable for unstable drugs in aqueous solution, the powder form is also considered applicable.

Some reports are available on mucoadhesion powders in the nasal cavity and these powder formulations use cellulose derivatives and acryl copolymers as the base (Nagai et al., 1983, 1984; Yamamoto et al., 1984; Kuroishi et al., 1984; Suzuki et al., 1985). To develop powders retained by adhesion on the nasal mucosa, mucoadhesion of water-soluble neutral polymers was evaluated in vitro and in vivo. Synthetic polymers, hydroxypropylcellulose (HPC) and polyvinyl alcohol (PVA), and natural polymers, xanthan gum (XG) and tamarind gum (TG), were used as water-soluble polymers. XG is a polysaccharide produced by microorganisms by the fermentation of glucose and used as a viscous agent in salad dressings, etc. TG is a polysaccharide obtained from the seeds of tamarind and used as a viscous agent in sauces, etc.

As methods to evaluate mucoadhesion of polymers in vitro, those to determine adhesion of homogeneous mucus to polymer coated on the glass plate (Smart et al., 1984), and measure mucociliary transport on the flog palate (King, 1980; Lin et al., 1993), have been reported. There is an in vivo method by which the residue of sample labelled with dye or tritium in the nasal cavity is evaluated after a definite time following autopsy or autoradiography (Yamamoto et al., 1984). In this study, in vitro adhesion of polymers was evaluated by two simple methods using agar plates. In an in vivo study, a polymer sample mixed with dye was applied to the nasal cavity of a rabbit and the dye was observed using a thin fiberscope. This method is considered suitable for determination of many samples or cross-examinations, as the animals can be used repeatedly.

2. Materials and methods

2.1. Materials

XG (Echogum T®) and TG (Glyloid 3S®) were supplied by Dainippon Pharmaceutical Co. Ltd. (Osaka, Japan). PVA (PVA-224S®; 44.0 mPa·s in 4% w/v aqueous solution at 20°C; 88 mol% in saponification value) was supplied from Kuraray Co. Ltd. (Osaka, Japan). HPC (HPC-H®, 1500 mPa·s in 2% w/v aqueous solution at 20°C) was supplied by Nippon Soda Co. Ltd. (Tokyo, Japan). All other reagents used were of special grade.

2.2. Preparation of samples from bulk powder

Samples other than mixtures of XG and PVA were prepared from the bulk powder by passing through stainless steel sieves to obtain particle size of 22–150 μm. XG and PVA atomized with a jet-mill (Turbo-counter Jet-mill T120, Turbo Kogyo Co. Ltd., Kanagawa, Japan) to 15 μm or less in particle size, were mixed in a tablet mill (KC-HUK, Konishi Seisakusho Co. Ltd., Osaka, Japan) for 3 min, and pressed with the tableting machine (RIKEN POWER P-168, Riken Seiki Co. Ltd., Tokyo, Japan) at 400 kg/cm^2. After atomizing the tablets, they were passed through stainless steel sieves to 22–150 μm in particle size, and used as a mixture of XG and PVA.

2.3. Measurement of physico-chemical properties

XG, TG, HPC and PVA or mixtures of XG and PVA, were prepared as aqueous solutions at 0.1, 0.25, 0.5, 1 and 2% w/v. The viscosity of these solutions at 37°C was measured using an E-type viscometer (VISCONIC ED, Tokyo Keiki Co.

Ltd., Tokyo, Japan) at share rate of 76.8 s^{-1} and a cone of 1°34′.

One hundred mg of each sample was placed in the apparatus shown in Fig. 1, and water absorption was determined with time.

Solutions of each sample at 3, 6, 9 and 12% w/v were prepared, and a disk attachment 20 mm in diameter was connected to the Rheometer (PT-2002 D.D., Fudou Kogyo Co. Ltd., Tokyo, Japan). Stress of the gel under compression of 10 mm at a rate of 5 mm/min was determined at 20°C.

2.4. Measurement of mucoadhesiveness in vitro

In vitro adhesion of sample was examined by two methods using agar plates.

2.4.1. Method 1

This parameter was determined by a method modified from that of Suzuki et al. (1985). An agar plate (containing agar at 1.5% w/v) of 7 cm in diameter was prepared with pH 7.2 phosphate buffer (JP XII). Five mg of the sample was placed on the center of the agar plate and made a circle 5 mm in diameter. The plate was slanted at 30°, and the longest movement distance of the sample at 23°C was measured.

2.4.2. Method 2

A new method was developed for this study. On an agar plate of 7 cm in diameter prepared with pH 7.2 phosphate buffer (JP XII), 5 mg of the sample in Finntip® was sprayed from a point 5 cm above using a rubber spoid (Publizer®, Teijin Co. Ltd., Osaka, Japan). Five min later, as shown in Fig. 2, the plate was attached to the disintegration test apparatus (JP XII), and moved up and down in pH 7.2 phosphate buffer at 37 ± 1°C. The sample on the plate immersed into the solution at the lowest point, and was out of the solution at the highest point. The residence time of the samples on the plate was observed with the naked eye.

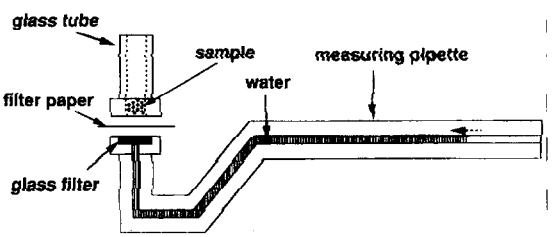

Fig. 1. Apparatus used for measurement of water absorption property of polymers.

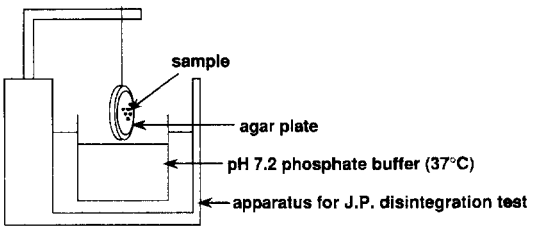

Fig. 2. Apparatus used for measurement of residence times of polymers.

2.5. Measurement of mucoadhesiveness in vivo

As shown in Fig. 3, the top of Finntip® was filled with 3 or 5 mg of sample containing 5% w/v Brilliant Blue (200 mesh pass), and applied to the nasal cavity 3 cm deep from the nostril of a rabbit (NZW, male, body weight 3.5–4.5 kg) using the silicone tube and the rubber spoid. The dye was observed 2, 4 and 6 h later using a fiberscope (PF-22, Olympus Co. Ltd., Tokyo, Japan; 1.8 mm in diameter; field of 75°; the tip of scope can bend upward or downward till 120°). As the control, 10 μl of 0.25% w/v aqueous solution of the dye was introduced by microsyringe to the same site and observed similarly.

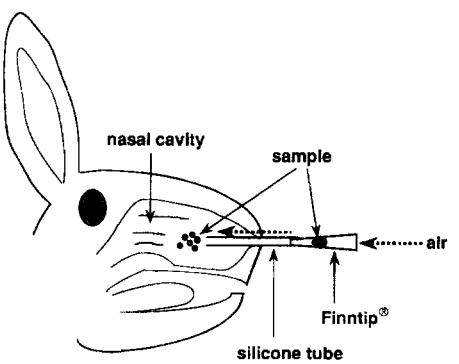

Fig. 3. Administration of polymers in nasal cavity of rabbit.

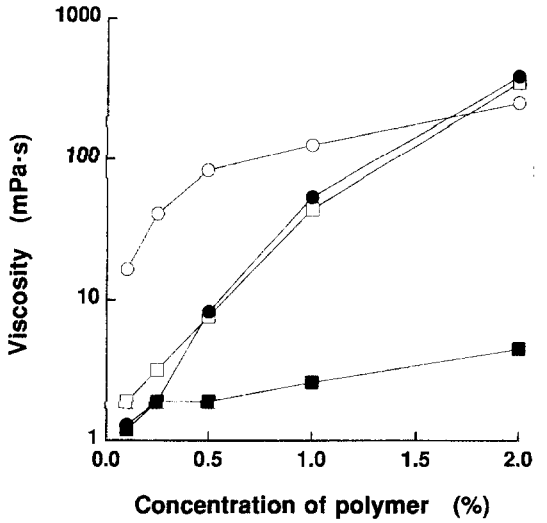

Fig. 4. Viscosity of aqueous solutions of XG(○), TG(□), HPC(●), and PVA(■).

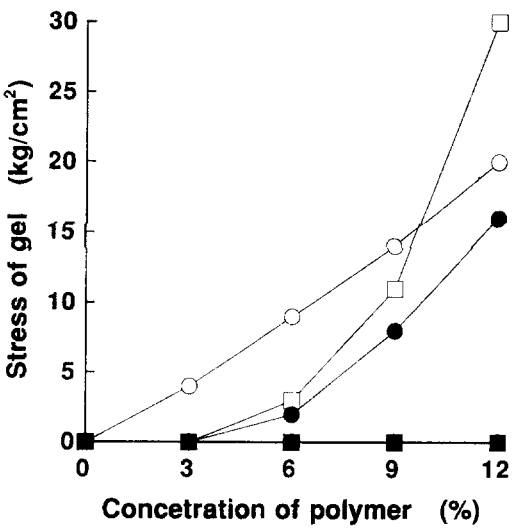

Fig. 5. Compression stress of aqueous gels of XG(○), TG(□), HPC(●), and PVA(■).

3. Results

3.1. Physico-chemical properties

Fig. 4 shows the viscosity-concentration curve of each sample solution. The viscosity of TG and HPC was 8 mPa·s each at 0.5% w/v, and 351 mPa·s and 387 mPa·s respectively at 2% w/v, and thus nearly the same curves were obtained. XG showed higher viscosity of 83 mPa·s at 0.5% w/v compared with other samples, and even at lower concentrations, relatively high viscosity was maintained. PVA showed 5 mPa·s at 2% w/v and the viscosity was low even at high concentrations.

Fig. 5 shows the relation between concentration and stress of the gel for each sample solution. The gel stress of TG and HPC was 0 kg/cm^2 each at 3% w/v, 3 and 2 kg/cm^2 at 6% w/v, and 30 and 16 kg/cm^2 at 12% w/v, respectively, suggesting that the higher the concentration of the sample, the stronger the stress of the gel in TG, compared with that of HPC. XG showed stronger gel stress of 4 kg/cm^2 at 3% w/v compared with other samples, and relatively high gel stress was maintained even at lower concentrations. Stress of the gel with PVA remained at 0 kg/cm^2 even at 12% w/v.

Fig. 6 shows the water absorption profile of each sample. The volume of water absorbed by TG and HPC was 26 and 23 μl at 5 min, and 46 and 50 μl at 20 min, respectively, thus demonstrating essentially the same water absorption property. XG showed 62 μl at 5 min and 134 μl at 20 min, showing ca. 2.5 times the water absorption of TG or HPC. PVA showed the lowest water absorption and it was 24 μl at 20 min.

In brief, XG showed the highest water absorption and less reduction in stress of the gel and

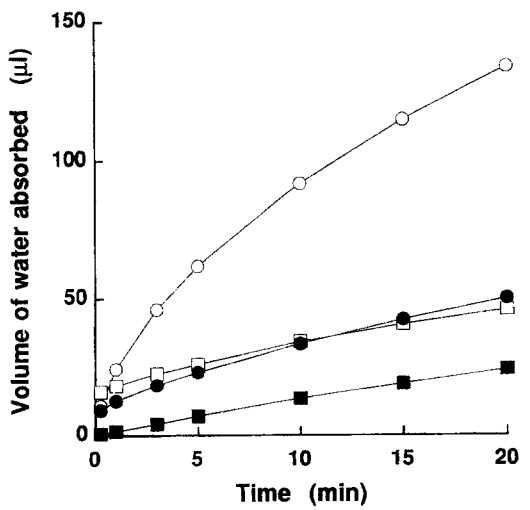

Fig. 6. Water absorption profiles of XG(○), TG(□), HPC(●), and PVA(■).

Table 1
Movement of polymers on the agar plate (cm)

Sample	Time (h)			
	1	2	3	4
XG	0	0	0	0.1
TG	0.3	0.8	1.9	>3
HPC	0.4	2.5	>3	n.d.
PVA	>3	n.d.	n.d.	n.d.

n.d., not determined. $n = 3$.

viscosity due to decrease in concentration than TG or HPC, while TG and HPC showed nearly the same viscosity, gel stress, and water absorption. PVA showed the lowest viscosity, gel stress, and water absorption compared with the others.

3.2. Mucoadhesiveness in vitro

Table 1 shows the results of movement of bases on the agar plate obtained according to Method 1. Hardly any shift was noted with XG even after 4 h. On the other hand, more than 3 cm of movement was noted at 4 h with TG, at 3 h with HPC, and at 1 h with PVA.

Table 2 shows the residence time of each sample on the agar plate obtained according to Method 2. The residence time of XG, TG, HPC and PVA was 41, 14, 13 and 4 min, respectively.

In both of the two different in vitro test methods, TG showed slightly higher residence than HPC, while XG showed very high residence compared with TG and HPC. PVA showed very low residence compared with other polymer bases.

3.3. Mucoadhesiveness in vivo

Fig. 7 shows the results of in vivo adhesiveness, as the ratio of the number of rabbits in which the remains of dye was observed to the total number of rabbits tested. In the case of solution, the dye was lost completely within 2 h. In the groups of TG 3 mg and HPC 5 mg, the remaining dye was 100% and 80%, respectively, at 2 h after administration. They showed nearly the same behavior and remaining rates at 4 h and 6 h after administration was 60% and 20%, respectively. In the group of XG 3 mg, even 6 h later the dye could be seen in all animals, showing fairly high residence, while PVA had the lowest residence property.

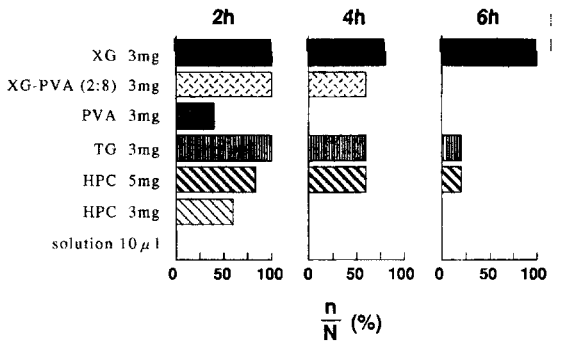

Fig. 7. Musocal adhesion of polymers in nasal cavity of rabbit. n, number of rabbits in which remaining dye was observed. N, total number of rabbits tested ($N = 5–6$).

Table 2
Residence time of polymers on the agar plate

Sample	Residence time (min)
XG	41
TG	14
HPC	13
PVA	4

$n = 3$.

3.4. Control of mucoadhesion by mixing two polymers differing in viscosity

Accumulation of the drug should be feared, if the residence following administration is too long. Thus, PVA with the lowest residence was mixed with XG with the highest residence property in vivo to adjust the residence time to those of HPC and TG. Table 3 shows the distance moved by each

Table 3
Movement of mixtures of XG and PVA on the agar plate (cm)

Sample	Time (h)			
	1	2	3	4
XG	0.1	0.1	0.1	0.1
XG-PVA(3:7)	0.2	0.5	0.8	0.8
XG-PVA(2:8)	0.5	1.5	2.1	>3
XG-PVA(1:9)	>3	n.d.	n.d.	n.d.
PVA	>3	n.d.	n.d.	n.d.

n.d., not determined. $n = 3$.

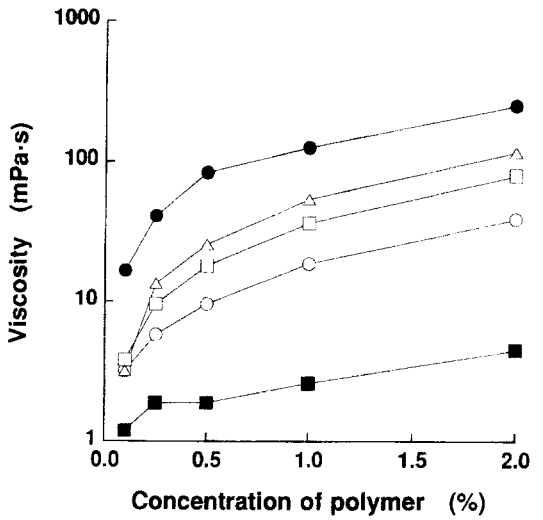

Fig. 8. Viscosity of aqueous solutions of XG(●), PVA(■) and mixtures. Weight ratio in mixtures of XG and PVA, 3:7(△), 2:8(□) and 1:9(○).

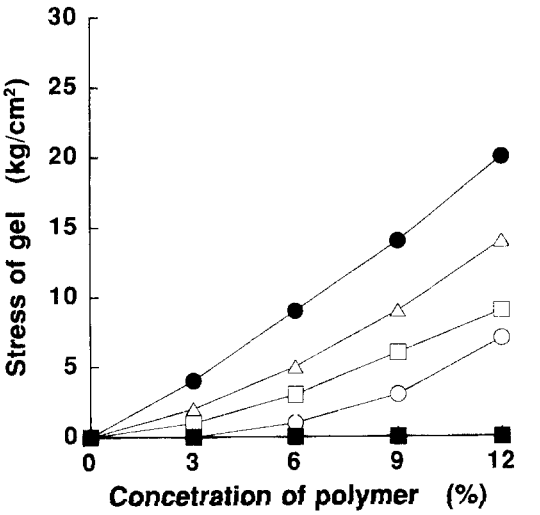

Fig. 9. Compression stress of aqueous solutions of XG(●), PVA(■) and mixtures. Weight ratio in mixtures of XG and PVA, 3:7(△), 2:8(□) and 1:9(○).

mixture at various mixing ratios of XG and PVA on the agar plate obtained according to Method 1. When XG was mixed with PVA at a ratio of 2:8, the distance was over 3 cm in 4 h, being closest to the behavior of TG and HPC (Table 1). Thus, the residence of the mixture in vivo should be nearly the same as those of TG and HPC at this mixing ratio.

As shown in Fig. 7, XG-PVA mixture at the ratio of 2:8 showed similar residence property in vivo as TG and HPC except for the result at 6 h after administration. As a result, it was confirmed that the residence of XG in vivo could be controlled by mixing with PVA as in vitro.

Physico-chemical properties of XG-PVA mixtures were evaluated. Fig. 8 shows the viscosity of XG solution mixed with PVA. At mixing ratios of XG with PVA at 1:9, 2:8 and 3:7, the viscosity was 10, 18 and 26 mPa·s at 0.5% w/v, while 39, 79 and 117 mPa·s at 2% w/v, respectively. Fig. 9 shows gel stress of each mixture of XG and PVA. At ratios of 1:9, 2:8 and 3:7, the gel stress was 10, 17 and 25 kg/cm^2 at 12% w/v, respectively. Fig. 10 shows the time course of water absorption for each mixture of XG and PVA. At ratios of 1:9, 2:8 and 3:7, the water absorption was 43, 60 and 70 μl in 20 min, respectively. A mixture at 2:8 showed water absorption nearly the same as those of TG and HPC (Fig. 6). Viscosity of the mixture was lower than those of TG and HPC at such high concentration as 2% w/v, but higher at such low concentration as 0.5% w/v (Fig. 4). This is considered as a rheological property of XG.

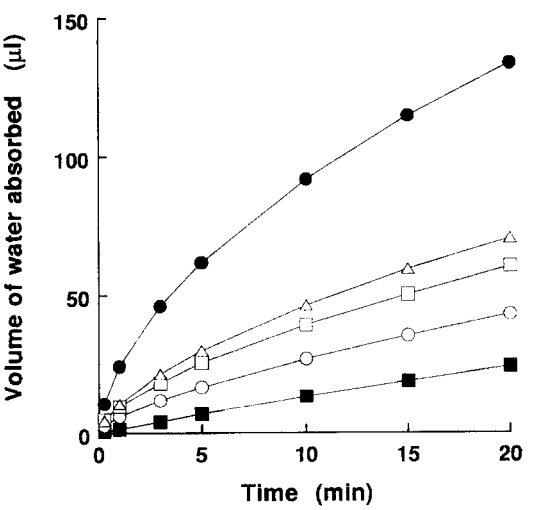

Fig. 10. Water absorption profiles of XG(●), PVA(■) and mixtures. Weight ratio in mixtures of XG and PVA, 3:7(△), 2:8(□) and 1:9(○).

4. Discussion

The nose is an olfactory organ, and also prevents intrusion of foreign matter into the respiratory system. In general, foreign matter trapped is gradually excreted into the throat by ciliary movement of the nasal mucosa in 5–6 min (Proctor et al., 1973; Sakakura et al., 1983). When an aqueous solution of polymer is applied to the nasal cavity, the residence time will further be influenced by various factors other than ciliary movement.

A ciliary beat frequency on the flog palate is reduced by increase in the viscosity of a polyvinylpyrollidone solution (Chen and Dulfano, 1978). Thus, the residence time in nasal cavity should be extended by increased viscosity of aqueous solution. A cationic polymer with higher charge density causes stronger adhesion of aqueous solution on the mucosa (Park and Robinson, 1987). This fact suggests that electrostatic interaction between the polymer base and mucosa may be a factor for adhesion. The clearance from the nasal cavity is influenced by diseases with symptoms such as change in mucus volume like rhinostenosis (Sakakura et al., 1983). Stimulation of the mucosa by a base might cause such symptoms, thereby changing the residence time of the base in the nasal cavity. When aqueous solution is applied to the anterior part of the nasal cavity (non-ciliary), the solution moves slowly to the throat, but when it is done to the posterior part (ciliary), it moves rapidly (Hardy et al., 1985). This suggests that residence time may differ much according to administration sites in the nasal cavity. In other words, the residence time may differ by the factors affecting the site of administration, such as administration method and particle size.

Peppas and Buri (1985) showed the structure of mucosal surface with a simple model to be a network of glycoproteins. Substances adhering to the mucosa diffuse in such a network and then disappear from it. The fate of water-soluble polymers in powder form following adherence to the mucosal surface is considered to be as follows; at the initial stage, particles of polymers absorb water from mucus in the nasal mucosa and gradually become gel that continues to adhere to the site. When water absorption advances further, outside of the gel starts to dissolve, gradually spreading out on the mucosal surface. Since such a solution shows high viscosity at this stage, it is strong in adhesion, hardly affected by ciliary movement, and moves on the mucosa slowly. However, adhesion to the mucosa is reduced due to decreased viscosity caused by further water absorption with time passage. In this stage, aqueous solution of polymer is strongly affected by ciliary movement and the polymer is quickly excreted into the throat.

Therefore, the rate of water absorption, stress of the gel and viscosity when the powdery polymer turns to a gel and then to a liquid, are considered to greatly relate to residence of the polymer on the nasal mucosa. However, the volume of water supplied from the nasal mucosa is less than that in the water absorption experiment of this study, and thus the water absorption may be a rate-limiting process of nasal residence of highly water-absorbing bases, such as XG, TG and HPC (Fig. 6). This result suggests that stress of the gel and viscosity may greatly affect the residence of polymer by adhesion in this study. The differences in residence in the nasal cavity for XG, TG, HPC and PVA (Fig. 7) can be explained by these factors. After all, a base with strong gel stress and/or high viscosity at low concentration may show high nasal mucoadhesion due to slow movement on the mucosa and prevention of the ciliary movement.

Adhesion of neutral polymers to nasal mucosa is influenced by interaction between polymer molecules and mucosa, and exclusion of the polymers by the ciliary movement. It is considered that adhesion of polymers as powder or gel is mainly due to the physical interaction such as water absorption of the polymers, and that as solution is mainly due to the physical one such as viscosity of the solution and the chemical one such as hydrogen bond.

Among the polymer bases examined in this study, polymers with higher water absorption showed stronger gel stress at lower concentrations (Figs. 5 and 6). This result indicates that polymer with higher water absorption may show higher

moisture retention, and maintain the gel state even at lower concentrations.

The supply of water from agar to polymers in Method 1 is a little compared with that from the buffer solution in Method 2. Further, a larger stress is given by up and down movement in Method 2 than by the slant in Method 1. Therefore, it is considered that the scale of adhesion in Method 1 would be larger than that in Method 2 and a difference in adhesion between HPC and TG would be great in Method 1 and a little in Method 2 (Tables 1 and 2).

In a previous study, HPC resided in the nasal cavity of rabbits for 2–4 h after nasal application at 5 mg (Yamamoto et al., 1984). The in vivo results of the present study (Fig. 7) indicate a slightly longer residence time of HPC. In the study by Yamamoto et al. HPC was applied to the nasal cavity just from the nostril but it was applied from the point of 3 cm deep from the edge of the nostril in the present study. The slightly longer residence of HPC in the present study may be due to differences in distribution of HPC in the nasal cavity owing to the differences in the administration method of HPC and in the physicochemical properties such as particle size distribution and viscosity.

The time required for change of a polymer from powder to solution and viscosity of the polymer solution depend on the amount of polymer administered because the amount of water supplied to the polymer in the nasal cavity is limited. So, it is considered that adhesion time of HPC in vivo at 5 mg dose would be longer than that in 3 mg dose (Fig. 7).

As shown in Table 1, movement of HPC on the agar plate was larger than TG. However, it seemed that HPC should show similar movement to TG when more HPC is placed, owing to the similar viscosity to TG. As shown in Table 3, the mixture of XG and PVA at 2:8 showed a moving distance of 1.5 cm in 2 h and 2.1 cm in 3 h. The fast movement of the mixture at the initial stage may depend on the lower viscosity of PVA than the other polymers, and slow movement at the next stage may depend on the gradual reduction of viscosity of XG caused by decreased concentration. In the case of a preparation that required prompt efficacy, it is considered more appropriate to use a mixture of XG and PVA with a greater rate of diffusion at the initial stage.

The results of this study suggest that the residence time of a drug in the nasal cavity may be prolonged by using water-soluble polymers, HPC, XG and TG, as bases for powder preparations of intranasal administration, and residence time may be controlled by mixing two or more polymers differing in mucoadhesion. Mucoadhesion in vitro and in vivo follows the order, XG $\gg$ TG $>$ HPC $\gg$ PVA, and the results of the in vivo study reflect in vitro. Accordingly, the in vitro test methods used in this study should prove useful for estimation of the residence property of powder formulations made of neutral polymers by adhesion in the nasal cavity in vivo.

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