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Drug release from pH-response polyvinylacetal diethylaminoacetate hydrogel, and application to nasal delivery

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Abstract

Nasal formulations of polyvinylacetal diethylaminoacetate (AEA) were prepared and the effect of AEA concentration on drug release was evaluated in in vitro and in vivo experiments. The profiles of release of drug from dialysis tubes had both a rapid and a slow phase, and had an inflection point, at which AEA hydrogel formation appeared to occur. The higher the AEA concentration, the lower the rate of drug release observed. The apparent disappearance rate constant (k_{app}) of drug was determined by the deposit method, which estimates changes in the amount of residual drug in the nasal cavity with the lavage technique following administration. Drug k_{app} values decreased with increase in AEA concentration. Hydrogel formation on mucous membranes was also visually confirmed in rat nasal cavity. AEA preparations which facilitate instillation into the nose but which form hydrogel on the mucous membrane are potentially useful for controlled-release nasal delivery systems.

Keywords: Polyvinylacetal diethylaminoacetate (AEA); pH-response polymer; Dialysis tube method; Rat nasal deposit method; Drug disappearance; Nasal formulation

1. Introduction

In recent years, an increasing number of individuals have been affected by nasal allergies such as pollenosis caused by cryptomerias and ragweeds with environmental changes, necessitating the development of prophylactic and therapeutic drug formulations (Secher et al., 1982; Perdona and Santoni, 1986; Benavides et al., 1995). Nasal spray dosage forms have been widely used for allergic rhinitis and sinusitis because of their easy handling and prompt relief of nasal symptoms. Several approaches have been used in designing nasal dosage forms with high absorption and

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lasting drug effects. Carbopol–PEG gel (Morimoto et al., 1985, 1987), methylcellulose (Harris et al., 1988), and hydroxypropyl methylcellulose (Pennington et al., 1988) have been tested for deposition of drug in the nasal cavity. However, in the development of lasting antiallergic nasal formulations, viscous polymers are not always useful since drug in formulations with such agents is rapidly absorbed and then rapidly disappears from the nasal cavity. Moreover, preparations with limited viscosity may be suitable for obtaining nasal spray pump devices optimal for treatment. In addition, viscous solutions have the disadvantage of being difficult to administer.

As a part of our research on controlled-release devices, polyvinylacetal diethylaminoacetate (AEA) has been studied as a pH-response polymer. AEA has been widely used in tablet form as a coating film and in microcapsule form as a gastric-soluble polymer (Kashihara et al., 1988; Shinkuma et al., 1989). AEA in solution forms a hydrogel with increase of temperature and finally forms a tight film (Shimano et al., 1994). We have recently studied hydrogel formation by AEA with pH change (Aikawa et al., 1998). AEA in acidic solution forms a hydrogel when pH is increased to around neutral in in vitro experiments. During this process, drug dissolved in water phase can be loaded into the hydrogel phase, and slow release kinetics can be obtained. In the present study, we prepared nasal formulations of AEA and evaluated the effect of AEA concentrations on hydrogel formation and the drug release from AEA hydrogel in in vitro. AEA hydrogel formation on the rat nasal mucous membrane and drug disappearance from the nasal cavity were also studied.

2. Materials and methods

2.1. Materials

Polyvinylacetal diethylaminoacetate (M_w 65000) was obtained from Sankyo (Osaka, Japan). Chlorpheniramine maleate (CM) was purchased from Sigma Chemical (St. Louis, MO). Tetrahydrozoline hydrochloride (TH) was purchased from Dolder (Basel, Switzerland). All other reagents were of analytical grade and used as received.

Dialysis tubes (Dialysis Membrene, Size 36, diameter 50 mm, M_w cutoff 10000–13000) were purchased from Wako Pure Chemical Industries (Tokyo, Japan), and appropriate closures were purchased from Spectrum (Los Angeles, CA).

2.2. Preparation of nasal formulations

Nasal formulations with various concentrations of AEA were prepared and are listed in Table 1. After dissolving 0.5% CM and 0.1% TH in distilled water, various concentrations of AEA were added and the pH of AEA solutions was adjusted to 4.0 with 1 N HCl. Nasal preparations were stored at 25°C until use.

2.3. Release experiment

Drug release from nasal preparations was examined using the dialysis tube method reported by Aoyagi et al. (1988). In brief, a dialysis tube (5×3 cm) containing 3 g preparation was immersed in 500 ml of 0.2 N phosphate buffer (pH 7.4) as receiver. A paddle was rotated at 100 rpm at 5 cm above the bottom of the vessel. The temperature of the receiver was maintained at 37 ± 0.5°C during the experiment. An aliquot of 1 ml was withdrawn at appropriate times and an equal volume of the phosphate buffer was added. Drug concentrations in the aliquot were determined by HPLC. A reverse-phase column (NUCLEOSIL 5SA; Chemco Scientific) was eluted at a rate of 1 ml/min with a mobile phase consisting

Table 1
Nasal formulations

Ingredient	Formulation			
	1	2	3	4
Chlorpheniramine maleate	0.5	0.5	0.5	0.5
Tetrahydrozoline hydrochloride	0.1	0.1	0.1	0.1
AEA	0	3	5	7
1 N HCl	Adjusted to pH 4.0			
Distilled water	Total 100 g			

AEA, polyvinylacetal diethylaminoacetate.

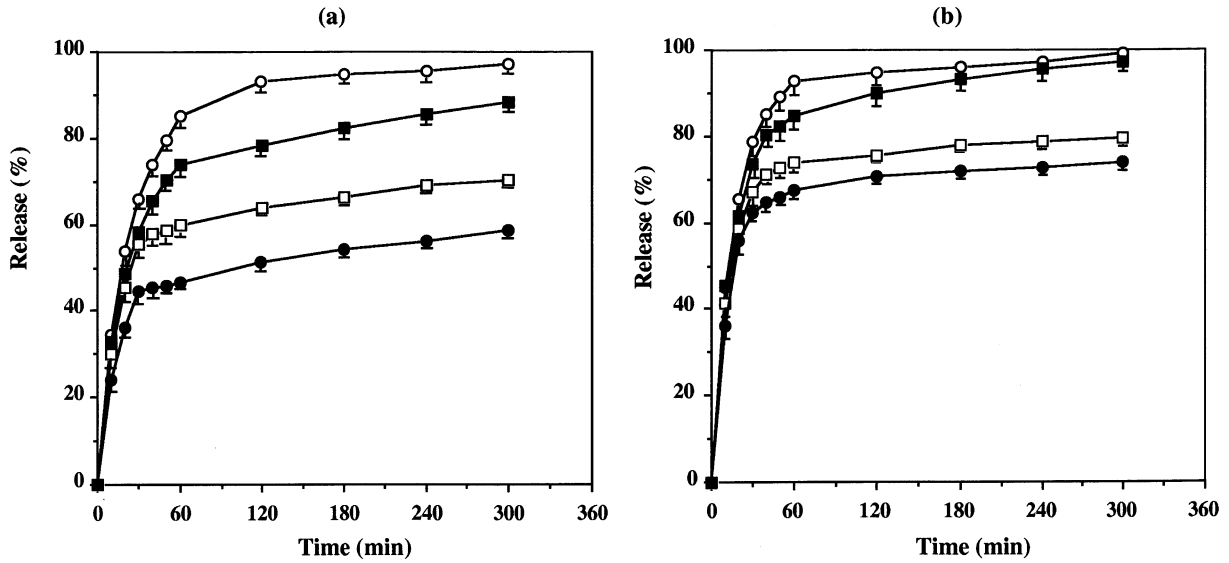

Fig. 1. Profiles of release of drug from nasal preparation. Drug release was determined in phosphate buffer, pH 7.4, at 37°C by the dialysis tube method. Each point shows the average of three determinations. (a) Chlorpheniramine maleate; (b) tetrahydrozoline hydrochloride. (○) Formulation 1; (■) formulation 2; (□) formulation 3; (●) formulation 4.

of acetonitrile and 0.2 N phosphate buffer (pH 4.0) (1:1, v/v). UV detection was performed at 210 nm. The retention times of CM and TH under these conditions were 10 and 8 min, respectively.

2.4. Rat nasal cavity experiment

The rat nasal cavity experiment was performed using the procedure we previously described (Nasal deposit method) (Aikawa et al., 1991). In brief, Wistar rats weighing 200–230 g were anesthetized by intraperitoneal injection of 0.6 ml of 40% polyurethane (1.3 mg/kg). An incision was made in the cervical region, and the trachea was cannulated with a polyethylene tube (SP116) to maintain respiration. Another SP116 tube was inserted from the esophagus toward the posterior portion of the nasal cavity (nasal cannula). The nasopalatine fossa was closed with an adhesive bond (Alone Alpha) to prevent drainage of the drug from the nasal cavity to the mouth. Drug preparation (25 μl) was deposited in one of the nostrils with a micropipette. After specified times of deposition (3, 5, 10, 20, 40 or 60 min), the residual drug in the nasal cavity was recovered by washing thoroughly with 4 ml of physiological saline at a rate of flow of 2 ml/min from the nasal cannula. The profiles of drug disappearance were determined from the amounts of drug in the lavage fluid. Drug concentrations in the lavage fluid were determined by HPLC as described above.

2.5. Study of hydrogel formation in rat nasal cavity

Rats were anesthetized by intraperitoneal injection of 0.6 ml of 40% polyurethane (1.3 mg/kg). The nasal preparation (100 μl) was administered in one of the nostrils with a micropipette. Thirty minutes after administration, the nasal cavity was incised and hydrogel formation on the mucous membrane was visually observed.

3. Results and discussion

3.1. Drug release from nasal preparation

Drug release from nasal preparations was determined in in vitro using the dialysis tube method in phosphate buffer, pH 7.4, at 37°C. The profiles of

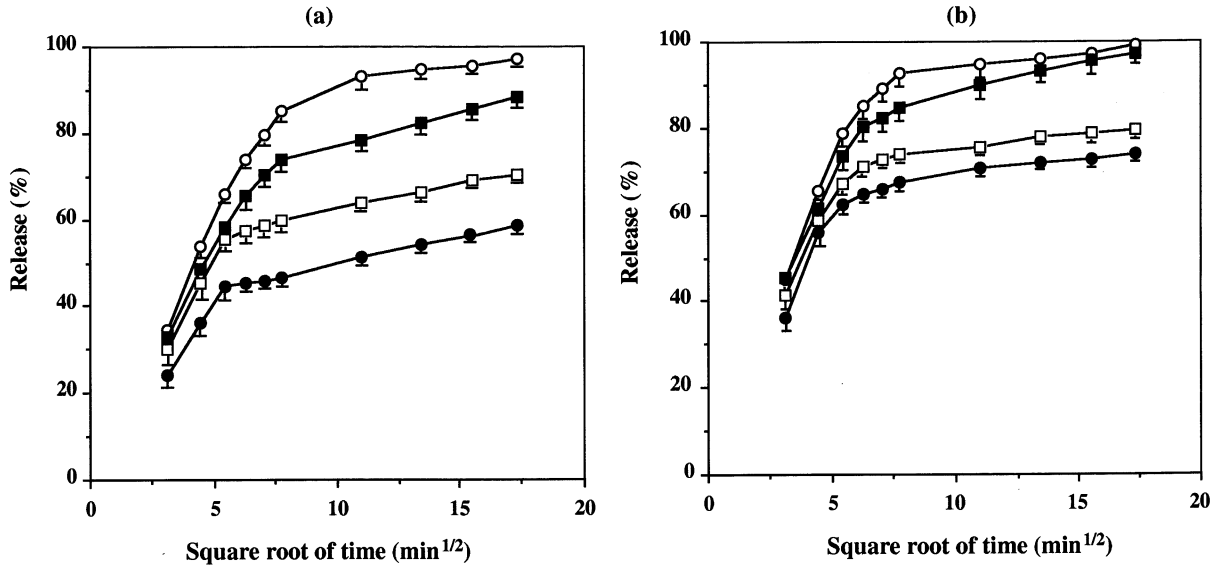

Fig. 2. Higuchi plots of release of drug from nasal preparation. (a) Chlorpheniramine maleate; (b) tetrahydrozoline hydrochloride. (○) Formulation 1; (■) formulation 2; (□) formulation 3; (●) formulation 4.

Table 2
Effect of AEA concentration on apparent time to hydrogel formation and release rate of drug from nasal preparation

Formulation	AEA concentration (%)	Apparent time to hydrogel formation[a] (min)		Release rate[b] (mg/min)	
		CM	TH	CM	TH
1	0	—	—	—	—
2	3	60	60	$7.5\times10^{-3}\pm2.0\times10^{-3}$	$1.6\times10^{-3}\pm0.6\times10^{-3}$
3	5	60	60	$9.0\times10^{-3}\pm3.8\times10^{-3}$	$1.3\times10^{-3}\pm1.0\times10^{-3}$
4	7	30	40	$7.9\times10^{-3}\pm1.7\times10^{-3}$	$1.6\times10^{-3}\pm1.2\times10^{-3}$

[a] Apparent time to hydrogel formation was obtained from the inflection point of cumulative release against the square root of time (Fig. 2).
[b] Release rate of drug was calculated as the average of each plot of rate of release from nasal preparation after apparent time to hydrogel formation.

release of CM and TH are shown in Fig. 1a and Fig. 1b, respectively. For both drugs, the initial rate of release from AEA preparation was very rapid, but the release became very slow after about 30 min and remained so. The release profiles exhibited an inflection point, which indicated AEA hydrogel formation, since at that point the transparent AEA solution in the dialysis tube became cloudy. During hydrogel formation, a portion of the drug may be loaded into the hydrogel phase, and thus drug release becomes slow. The amount of drug loaded into the hydrogel phase depended on lipophilicity, because the percentages of release of CM were lower than those of TH in the initial release process (Fig. 1). Moreover, it resulted that when the AEA hydrogel was left at 25°C for 2 days, shrinkage of the hydrogel occurred, and the water phase gradually separated from the hydrogel, the amount of CM in the hydrogel phase increased with a lapse of time, while those of TH were independent of time (data not shown). The profile of drug release from AEA preparations depended on AEA concentration: the higher the AEA concentration, the lower the rate of drug release.

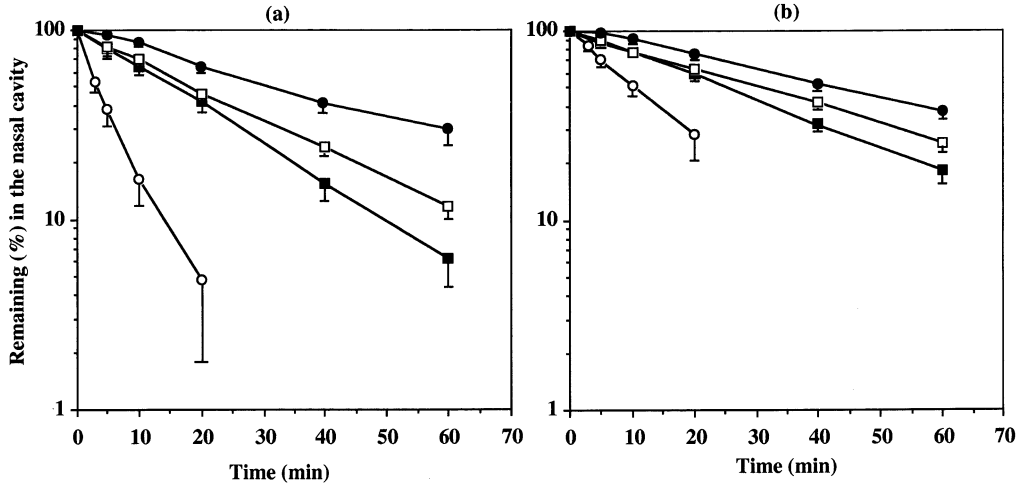

Fig. 3. Effect of AEA concentration on remaining percent of drug in the nasal cavity measured by the deposit method in rat. Each point shows the average of three determinations. (a) Chlorpheniramine maleate; (b) tetrahydrozoline hydrochloride. (○) Formulation 1; (■) formulation 2; (□) formulation 3; (●) formulation 4.

Fig. 2 shows Higuchi plots of the data given in Fig. 1 (Higuchi, 1961, 1963). In general, drug release from tablets or ointments follows the Higuchi equation (Eq. (1)):

$$M_t = AM_0[C_s(D\epsilon/\tau)(2C_d - C_s)t]^{1/2} \quad (1)$$

where M_t is the amount of drug released from the AEA hydrogel at time t, M_0 is the total amount of drug, A is the surface area of the hydrogel, D is the diffusivity of the drug, C_s the solubility, C_d the concentration of drug, ϵ the tortuosity and τ the porosity. In the early stage, drug release profiles did not follow the Higuchi equation, indicating that the structure of the micropores in the hydrogel phase and the amount of drug loading changed during the process of hydrogel formation. On the other hand, after hydrogel formation, the drug release profiles of each AEA preparation were linear and followed the Higuchi equation.

Table 3
Effect of AEA concentration on apparent disappearance rate constant for the nasal cavity determined by the deposit method in rat

AEA (%)	k_{app} (per min)	
	Chlorpheniramine maleate	Tetrahydrozoline hydrochloride
0	0.149	0.063
3	0.047	0.029
5	0.036	0.022
7	0.021	0.017

The parameters for apparent time to hydrogel formation and release rates of drug from nasal preparation are summarized in Table 2. The apparent time to hydrogel formation, which was obtained from the inflection point of cumulative release against the square root of time (Fig. 2), decreased with increase in AEA concentration. During the process of hydrogel formation, drug release rates gradually decreased with increase in AEA concentration. It was suggested that the AEA concentration affected both the rate of hydrogel formation and the amount of drug loaded into the hydrogel phase. After hydrogel formation the release rates were independent of AEA concentration. Markedly effective controlled release of drug was obtained at 7% AEA concentration, compared with the AEA-free preparation.

3.2. Drug disappearance from rat nasal cavity

In order to evaluate disappearance of drug from nasal preparations following nasal administration, the concentrations of remaining drug in AEA hydrogel in the nasal cavity were deter-

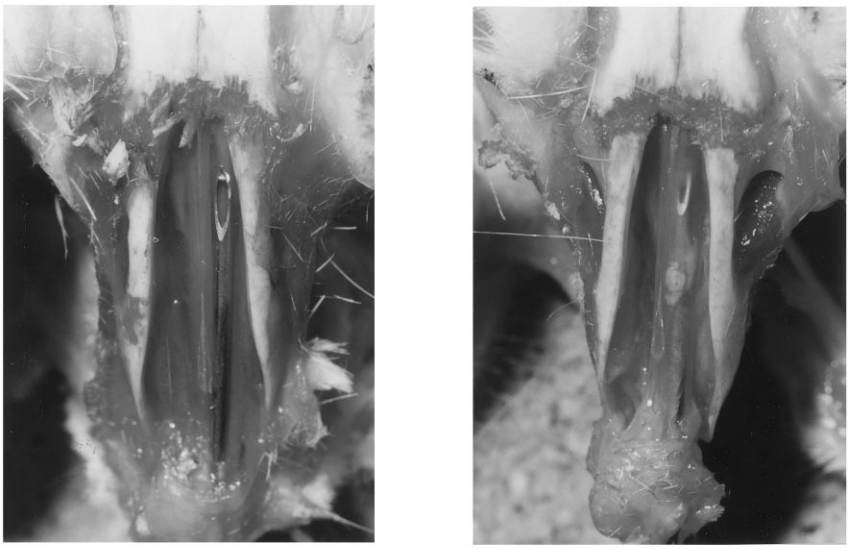

Fig. 4. Photographs of nasal preparation in rat nasal cavity AEA. (7%) solution formed hydrogel on the mucous membranes in rat nasal cavity at 30 min after administration.

mined. Fig. 3 shows the effect of AEA concentration on percent of drug remaining in the nasal cavity. When the test solution was administered to the nasal cavity in the deposit method, the pH of the test solution was immediately changed to around neutral by the buffering capacity of the microclimatic pH of mucous membrane (Aikawa et al., 1991). This suggests that the ratio of the undissociated form of drug in the nasal cavity is the same irrespective of AEA hydrogel formation or AEA-free preparation. The percent of CM and TH remaining depended on AEA concentration, while the rate of disappearance of drug from the nasal cavity depended on lipophilicity. For CM, these values at 20 min after administration were 4.8, 42.3, 46.4 and 55.4% for the AEA-free preparation and 3, 5, and 7% for AEA preparations, respectively, while for TH they were 28.5, 59.8, 62.5, and 75.5%, for the AEA-free preparation and 3, 5, and 7% AEA preparations, respectively. In particular, the percentages of drug remaining at 60 min for the 7% AEA preparation were much higher than those for the AEA-free preparation: 32.2% for CM and 43.2% for TH. Thus, longer nasal deposition of drug was achieved with the use of AEA preparation.

The apparent disappearance rate constant (k_{app}) was calculated for each drug from regression lines for AEA preparations (Fig. 3). As shown in Table 3, k_{app} decreased with increasing AEA concentration. The k_{app} of CM for 7% AEA preparation was 1/7.1 that for the AEA-free preparation, while that of TH was 1/3.7 that of the AEA-free preparation.

Drug disappearance from the nasal cavity occurs as follows: first, AEA in solution (pH 4) forms hydrogel with change in environmental pH following nasal administration. The rate of hydrogel formation depends on concentration of AEA. Second, during hydrogel formation a portion of drug is loaded into the hydrogel phase, while the remainder is in the water phase. Third, after gel formation the drug is slowly released from hydrogel over time and disappears from the nasal cavity. AEA concentration affected the tortuosity and porosity in the hydrogel phase. The extent of drug disappearance from the nasal cavity was inversely proportional to AEA concentra-

tion. Geometric structure may thus affect the rate of drug release from hydrogel following nasal administration of AEA solution.

3.3. Observation of gel formation in rat nasal cavity

Thirty minutes after intranasal administration of 7% AEA preparation, hydrogel formation was observed in the rat nasal cavity, as shown in Fig. 4. However, at 3 and 10 min after administration, clear hydrogel formation was not observed, as shown in Fig. 4, possibly because hydrogel formation from solution was still occurring. If the deposition time of the drug in the nasal cavity could be estimated from the release profiles in Fig. 1, drastically prolonged retention of drug would be expected with the deposit method. However, moderate rather than pronounced controlled release of drug was observed in the rat nasal experiment (Fig. 3). This probably occurred because the rate of hydrogel formation was slow on mucous membranes in the rat nasal cavity, permitting the drug in water phase to reach the mucous membrane during the process of hydrogel formation.

AEA has been considered to be less irritative against the gastrointestinal mucous membrane, and excreted without digestion or degradation. AEA hydrogel formed in the nasal cavity thus may be less irritative. AEA hydrogel may be excreted by nasal secretion and/or mucociliary clearance without degradation, and lead to the prolongation of the residence of formulations at the nasal cavity.

4. Conclusion

The effects of concentration of pH-response polymer AEA, which undergoes hydrogel formation from aqueous solution with pH change, on drug release were evaluated by the dialysis tube method. The higher the AEA concentration, the lower the rate of drug release observed. Rat nasal cavity experiments with AEA preparations were also performed to determine whether this pH-response behavior occurred in physiological pH conditions, such as those in the nasal mucous membranes. Hydrogel formation of AEA preparation was observed on the mucous membrane following nasal administration, and the apparent disappearance rate constant of drug decreased with increase in AEA concentration. Assuming that the spray droplets of AEA preparation become spheres with a gel wall as a result of nasal mucous buffering capacity when AEA solution is administered to the nose by spray pump, the hydrogel formation may lead to a controlled release of drug. These findings suggest that AEA formulation is potentially useful for controlled release of drug in nasal delivery. Further study will focus on the mucoadhesive properties of hydrogel in neutral or slightly alkaline environments, and shortening the time required for hydrogel formation with pH response.

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