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In situ gel based on gellan gum as new carrier for nasal administration of mometasone furoate

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ABSTRACT

The main purpose of this study was to prepare a novel in situ gel system for nasal delivery of MF and study its efficacy on allergic rhinitis model. An ion-activated in situ gel was developed and characterized with gellan gum as a carrier. The system was stable kept at 40 ± 2 °C for 6 months, and the micrographic results showed that in situ gel was safety without mucosa irritation when given at 20 μg once daily for 1 month to rats with allergic rhinitis. MF in gellan gum produced obviously effect on allergic rhinitis at the doses of 20 μg/body following intranasal administration, and the efficacy was significantly superior to that of the common suspension ($P < 0.01$). The in situ gel system is a promising approach for the intranasal delivery of MF for the therapeutic effects improvement.

1. Introduction

It is well known that allergic rhinitis is an inflammatory disease of the upper airway, which is accompanied by sneezing, itching, congestion, rhinorrhea and loss of the sense of smell. These symptoms are considered to be caused by antigen–antibody reaction on mast cells that are located on the epithelia of the nasal cavity (Kawabori et al., 1985). mometasone furoate (MF), a corticosteroids agent, has been used for relieving symptoms in patients with seasonal allergic rhinitis. When this drug is administered before allergen exposure, reduction of mast cell mediator release and retardation of inflammatory cell migration into the nasal tissue occur (Mygind, 1993; Meltzer, 1997).

At present MF nasal spray on the market is suspension since MF is a poorly water-soluble drug. As we know, suspension usually results in a delayed onset due to the slow dissolution of drug in suspension. This is not favorable for nasal application of MF because of the rapid elimination of the instilled drug from the nasal cavity by mucociliary beating (a clearance half-life of 15 min) (Illum et al., 1987; Gizurason, 1993). Therefore, viscosity enhancing (usually polymers) may be necessary in order to prevent drainage of the formulation and provide the prolonged contact between the drug and the absorptive sites in the nasal cavity.

In situ gel, or in vivo gel, environment sensitive gel, is a new dosage form which has been applied in nasal drug delivery recently. Compared with liquid nasal formulations, nasal in situ gels are instilled as low viscosity solutions into the nasal cavity, and upon contact with the nasal mucosa, the polymer changes conformation producing a gel, so it cannot only prolong the contact time between the drug and the absorptive sites in the nasal cavity, but also release drug slowly and continuously, hence, it is especially useful for those drugs used chronically. The phase transition can be induced by a shift in pH, as for cellulose acetate phthalate (Gurny et al., 1985), a shift in temperature as for the thermo gelling Poloxamer 407 (Miller and Donovan, 1982; Edsman et al., 1998) or by the presence of cations as for gellan gum (Rozier et al., 1997).

Gellan gum is an anionic deacetylated, exocellular polysaccharide secreted by *Pseudomonas elodea* with a tetrasaccharide repeating unit of 1β-L-rhamnose, 1β-D-glucuronic acid and 2β-D-glucose. The mechanism of gelation involves the formation of double-helical junction zones followed by aggregation of the double-helical segments to form a 3-D network by complexation with cations and hydrogen bonding with water (Grasdalen and

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Smidsroed, 1987; Chanrasekaran et al., 1988; Chanrasekaran and Thailambal, 1990). Since human nasal mucosa is covered with approximately 0.1 ml mucus, which consists of sodium, potassium, and calcium ions, a solution-gel phase transition can be expected.

In the present study, a nasal delivery system of ion-activated in situ gel for MF with gellan gum was developed, and its rheological characteristics, drug content, stability and hydrogel formation in vitro were investigated. The effects of MF in situ gel on nasal symptoms was compared to that of an intranasal solution in order to confirm whether the use of gellan gum would produce a prolonged therapeutic effect for MF.

2. Materials and methods

2.1. Materials

MF was gifted by the Department of Pharmaceutics, XianJu Pharmaceuticals Ltd. (Zhejiang, China). Nasonex (mometasone furoate suspension 0.05%) was purchased from Schering-Plough, USA. Gellan gum was obtained from ZhongWei Biochemical Ltd. (Shanghai, China). Xanthan gum was purchased from Saifu Ltd. (Shanghai, China). Egg albumin and aluminum hydroxide were purchased from Sinopharm Chemical Reagent Co., Ltd., China. Bordetella pertussis inactive microorganisms suspension were kindly provided from Wako Pure Chemical Industries, Ltd., Japan and all other reagents were of commercially analytical-grade.

The ion compositions of artificial nasal fluid included 150 ± 32 mM Na^+, 41 ± 18 mM K^+, 4 ± 2 mM Ca^{2+}, which was prepared according to the report (Lorin et al., 1972).

2.2. Preparation of nasal formulations

A certain amount of gellan gum (0.2%, 0.5%, 1.0% w/v) was added to deionized water and dissolved by heating to 100 °C with moderate stirring. Thereafter, the solution was cooled to below 40 °C, MF (0.05%, w/v), xanthan gum (0.15%, w/v), chlorhexidine acetate (0.01%, w/v) and glycerol (2%, w/v) were added and mixed well. The pH of formulation was between 4.0 and 5.0. In this formulation, gellan gum was a gel base, xanthan gum as a suspending agent, chlorhexidine acetate as a preservative.

2.3. In vitro gelation study and viscosity measurement of in situ gels

MF in situ gel (100 μl/spray) and artificial nasal fluid (100 μl) described above were mixed (1:1, v/v) and gelation was observed by visual examination. The viscosity of the gellan gum formulation, either in solution or in gel made with artificial nasal fluid were determined with a rotational viscometer (NDJ-5S, Shanghai, China) using a 20 ml aliquot of the sample. Measurements were performed using suitable spindle number at 6, 12, 30, 60 rpm, and the temperature was maintained at 33 °C. The viscosity was read directly from the viscometer display. All measurements were made in triplicate.

2.4. Re-dispersion for MF in situ gel

The model formulations of MF in situ gel was poured into a 5 ml colorless polypropylene container, and centrifuged at 12,000 rpm for 10 min to sediment the suspended particles. After the precipitation process, the bottles were rotated by a Variable mix rotor VMR-5 at 60 rpm to observe the re-dispersion effect.

2.5. Determination of drug content

The amount of MF in each sample was determined by HPLC (LC-10A, Shimadzu Co Ltd., Kyoto, Japan). Chromatographic separation was achieved using a Dikma DiamonsilTM C18 column (5 μm, 200 mm × 4.6 mm) at 40 °C. The mobile phase was a mixture of methol and water (75:25, v/v) at a flow rate of 1.2 ml/min. The UV absorbance of the effluent was monitored (SPD-10A, Shimadzu) at a wavelength of 254 nm.

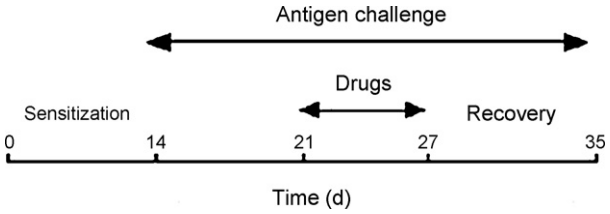

Fig. 1. Protocol for antigen sensitization and challenge.

2.6. Stability studies

Stability studies were carried out on gel formulation according to ICH (International Conference on Harmonization) guidelines (Cui (2003)). A sufficient quantity of in situ gel in nasal spray bottles was stored in desiccator containing saturated solution of sodium chloride, which gave a relative humidity of 75 ± 5%. The desiccator was placed in a hot air oven maintained at 40 ± 2 °C, and samples were withdrawn at 0, 30, 60, 90, and 180 days. The physical stability of gel was observed periodically the occurrence of turbidity or gelation. The drug content remaining and the viscosity of formulation were measured at predetermined time interval.

Fig. 2. Photography showing the appearance of in situ gel formed in simulated artificial nasal fluid. In situ gel (0.5% gellan gum, w/v) and artificial nasal fluid (1:1, v/v). The formed hydrogel equality and clarify.

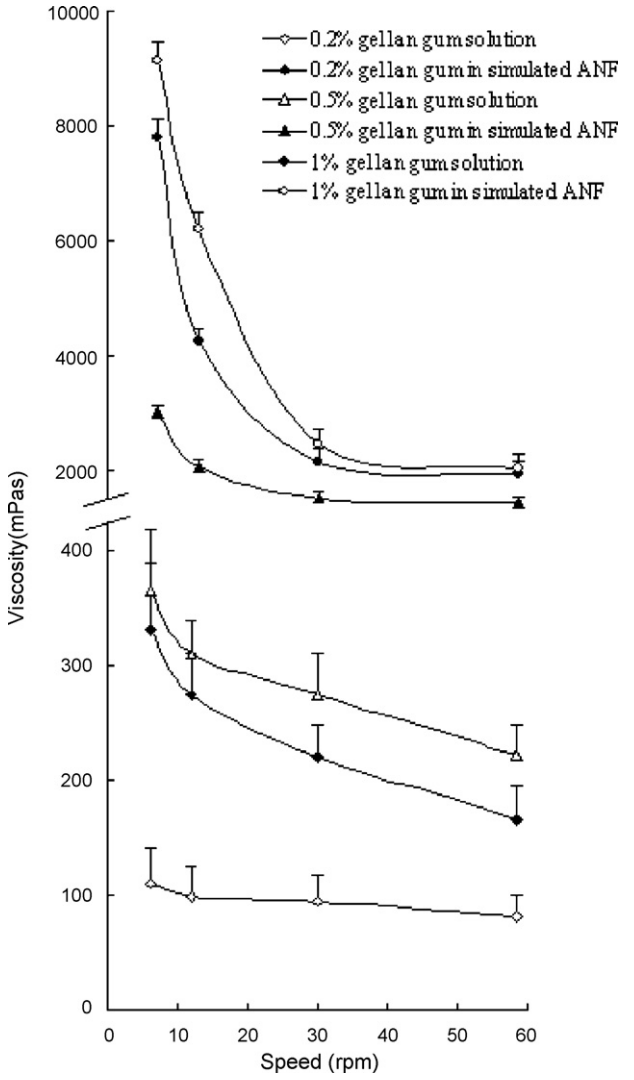

Fig. 3. Viscosity for the various gellan gum solution (open symbols) and for the gellan gum preparation with artificial nasal fluid (filled symbols), simulating the in vivo gelation.

2.7. Nasal ciliotoxicity

Nasal ciliotoxicity studies were carried out using an in situ toad palate model (Jiang et al., 1995). In brief, the upper palate of the toads (30–40 g, male and female, Experimental Animal Center of Fudan University, China, $n = 6$) was exposed and treated with about 0.5 ml in situ gel (0.5% gellan gum) for 4 h. Then the test formulation was removed by washing the palate with saline, about 5 mm × 3 mm of the palate was dissected and the mucocilia was examined with a electron microscope (Nikon Fx-35A, Tokyo, Japan) at enlargements of 400×, the lasting time of cilia movement was recorded. Saline and sodium deoxycholate (one of the agents with serious nasal ciliotoxicity, 1% (w/v) solution) were used as the negative and positive controls, respectively.

2.8. Effect on allergic rhinitis model

2.8.1. Animals

Six-week-old male Wistar strain rats were used for this study. The animals were housed in an air-conditioned room, maintained at 25 °C. The animal experiment was carried out in compliance with the protocol of Animal Use and Care by Medical Center of Fudan University.

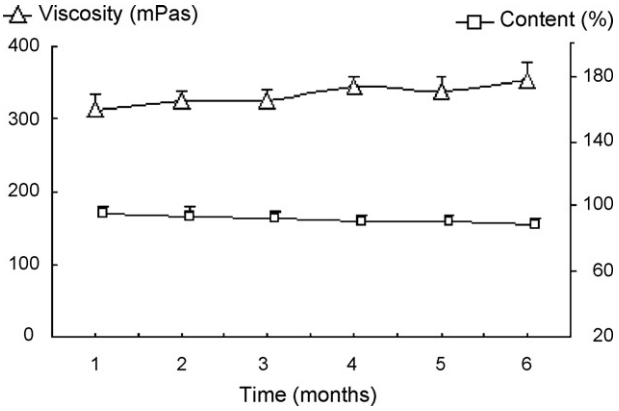

Fig. 4. Stability studies of MF in situ gel.

2.8.2. Sensitization

Studies were carried out using a redesigned allergic rhinitis model (Yukio et al., 2000a,b; Tae et al., 2005). In brief, rats were systemically sensitized by injection of 0.6 ml of physiological saline containing egg albumin (1 mg), aluminum hydroxide gel (2 mg) and 1×10^{10} B. pertussis into the four foot pads on the first day. Five days later, a booster was administered by the subcutaneous injection of 1 ml of physiological saline containing egg albumin (0.5 mg) on the back randomly. Then, local sensitization was performed every day from day 14 to day 35 by dripping the egg albumin dissolved in physiological saline (1 mg/ml, 10 μl per each nostril) into the bilateral nasal cavities using a micropipette (Fig. 1). After each administration, the number of sneezing and nasal rubbing were counted for 30 min.

2.8.3. Effects of in situ gel on antigen-induced nasal symptoms in sensitized rats

In this study, the rats received the test drugs from day 21 to day 27 after the sensitization. MF suspension and in situ gels were administered topically at a volume of 10 μl into the bilateral nasal cavities by a micropipette 1 h before the nasal antigen challenge and then the numbers of sneezes and nasal rubbing movements induced by the antigen were counted for 30 min.

2.8.4. Mucosa histopathology

After the treatment, the rats were sacrificed and the nasal septum with the epithelial cell membrane on each side was carefully separated from the bone. The septum was fixed with 10% formalin, sliced on a microtome, stained with haematoxylin–eosin and observed using a light microscope (Axiovert 200MAT, Carl Zeiss, Germany). The nostril given saline was used as a control.

Table 1
Influence of in situ gel on the duration of ciliary movement on palate mucosa.

	Saline	Sodium deoxycholate	Blank gel base	In situ gel (0.05% drug)
Lasting time	687.6 ± 23.1	27.7 ± 8.6	554.4 ± 15.1	516.0 ± 75.0[#]
F%		4.0%	80.6%	75.0%

Note: *F*% = test group (time)/negative controls (time) × 100%.
[#] Significantly different from positive controls ($P < 0.05$).

2.8.5. Statistical analysis

The results were expressed as mean ± S.E.M. ANOVA was used to test the differences between the calculated parameters using the SPSS Statistical Package (Version 10, SPSS Inc., Chicago, IL, USA). Differences were considered statistically significant when $P < 0.05$ or 0.01.

3. Results and discussion

3.1. In vitro gelation study and viscosity measurement of in situ gels

To gain a better understanding of the existence of gel, hydrogel formation in vitro was observed. The two main prerequisites of in situ gelling systems are optimum viscosity and gelling capacity (speed and extent of gelation). The formulation should have an optimum viscosity that will allow easy spray as a liquid, which then undergoes a rapid sol–gel transition due to ionic interaction. In addition, the formed gel should preserve its integrity to facilitate sustained release of drugs locally for prolonged period without dissolving or eroding quickly. Fig. 2 showed that the developed formulation, gelled under the conditions of artificial nasal fluid. Because of the small quantities of ions that are required for gel formation, rapid gelation in vivo can be expected.

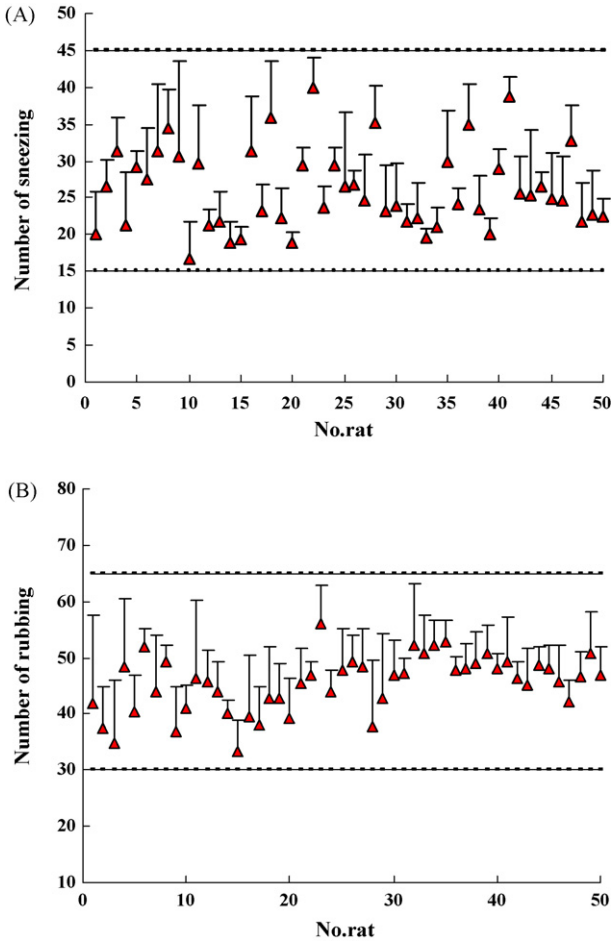

Fig. 5. Fundamental data of sneezing and rubbing in sensitized rats after antigen challenge from day 14 to day 21. Nasal sneezing and rubbing were both observed for 30 min. (A) Mean background count of nasal sneezing; (B) mean background count of nasal rubbing.

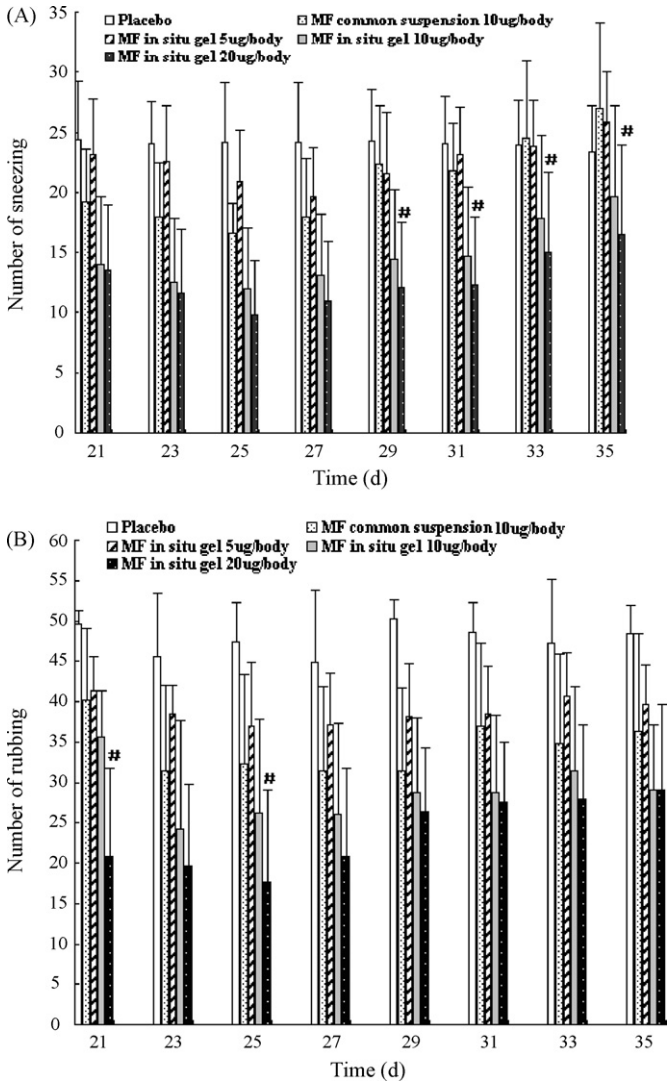

Fig. 6. Effects of MF in situ gel and common suspension (0.05% MF 10 μg/body) on nasal sneezing and rubbing after antigen challenge in sensitized rats. (A) The count of nasal sneezing of all groups; (B) The count of nasal rubbing of all groups. Nasal sneezing and rubbing were both observed for 30 min. Each column and vertical bar represents means ± S.E.M. (#) Significantly different from the placebo group ($P < 0.01$).

In the selection of the concentration of the gelling polymer, a compromise is sought between a satisfactory gel strength for use as a delivery vehicle and an acceptable viscosity for ease of spraying. All gellan gum formulations, either in solution or in gel, showed pseudo plastic behavior (Fig. 3). The viscosity of the test gels increased with increasing concentrations of gellan gum, and a large viscosity change was found when gellan gum underwent sol–gel transition at lower concentrations (0.2% and 0.5%). Due to a very viscous solution obtained with 1% gellan gum, a slight viscosity increase was observed after gel formation. The observed increase in viscosity with increase in concentration has been noted previously for gellan gum and is attributed to a consequence of increasing chain interaction with polymer concentration rising.

3.2. Re-dispersion for the model formulations of MF in situ gel

The re-dispersion times of the test gels increased with increasing concentrations of gellan gum, and a corresponding times were

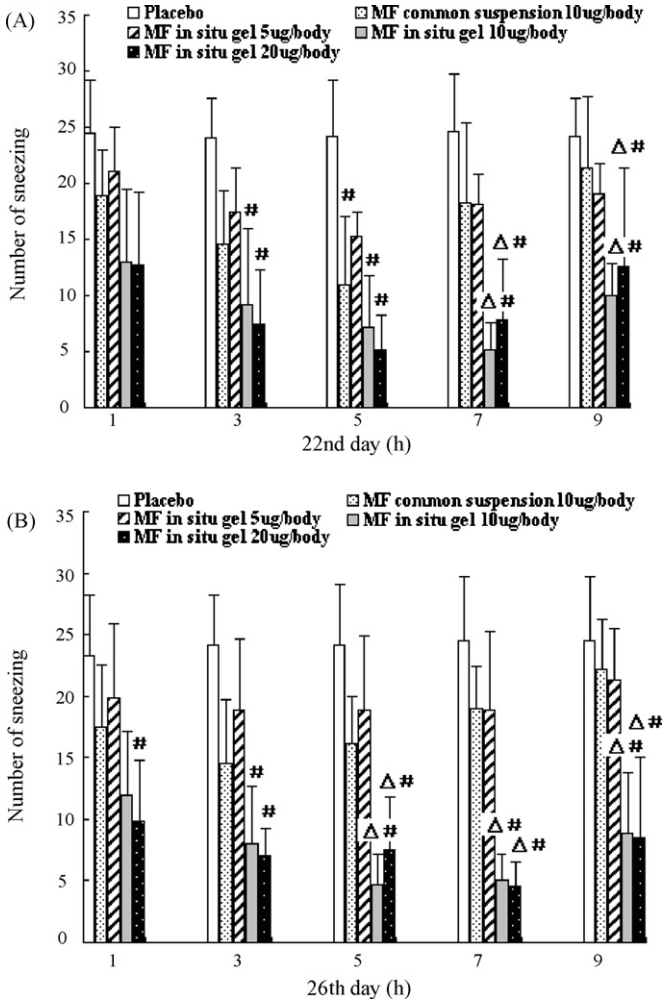

Fig. 7. Effects of MF in situ gel and common suspension (0.05% MF 10 μg/body) on nasal sneezing after antigen challenge in sensitized rats on the 22nd and 26th day. Nasal sneezing were both observed for 30 min. Each column and vertical bar represents means ± S.E.M. (#) Significantly different from the placebo group ($P < 0.01$). (Δ)significantly different from common suspension ($P < 0.05$).

15 ± 3.5, 33 ± 5.6 and 152 ± 13.5 s for formulations #1, #2 and #3 (0.2%, 0.5%, 1.0% gellan gum), respectively. An obviously longer time needed for formulation #3 to redisperse was found when gellan gum at concentrations of 1.0%. So the proper concentration of gellan gum was 0.5%.

3.3. Stability

Based on visual identification, the in situ gel has remained as liquid for a period of 6 months without the occurrence of turbidity or gelation at 40 ± 2 °C. As illustrated in Fig. 4, the viscosity of the gel slightly changed from 313 mPa s at 0 month to 354 mPa s at the 6th month. The samples also were analyzed for MF content by HPLC analysis. The results showed that about 4.12% content decrease was found when the in situ gel was kept at 40 ± 2 °C for 6 months. Since the overall degradation is <5%, a tentative shelf life of 2 years may be assigned to the formulation.

3.4. Nasal ciliotoxicity

The knowledge of effects of drugs and excipients on ciliary beating is very important in the development of an intranasal drug delivery system, especially for drugs to be used in chronic illnesses. In the present study, we chose the toad palate model for the study of ciliotoxicity because the toad palate is robust tissue giving reproducible results and the experimental technique is easy.

The investigations showed that normal saline did not significantly affect ciliary beating, the lasting time was 687.6 min. On the other hand, the sodium deoxycholate cause serious nasal ciliotoxicity and cilia treated with sodium deoxycholate could only beat 27.7 min. It was found that animals treated with the in situ gel showed a mild effect on ciliary beating. The cilia density was judged normal compared with the saline. Overall, the effects of the in situ gels and blank gel base on the cilia safety. No severe damage was observed in all test gels (see Table 1).

3.5. Effects of mometasone furoate on nasal symptoms

3.5.1. Changes in nasal symptoms after antigen challenge

The main symptoms of allergic rhinitis in humans are sneezing, pruritus, mucus secretion, mucosal edema and nasal congestion.

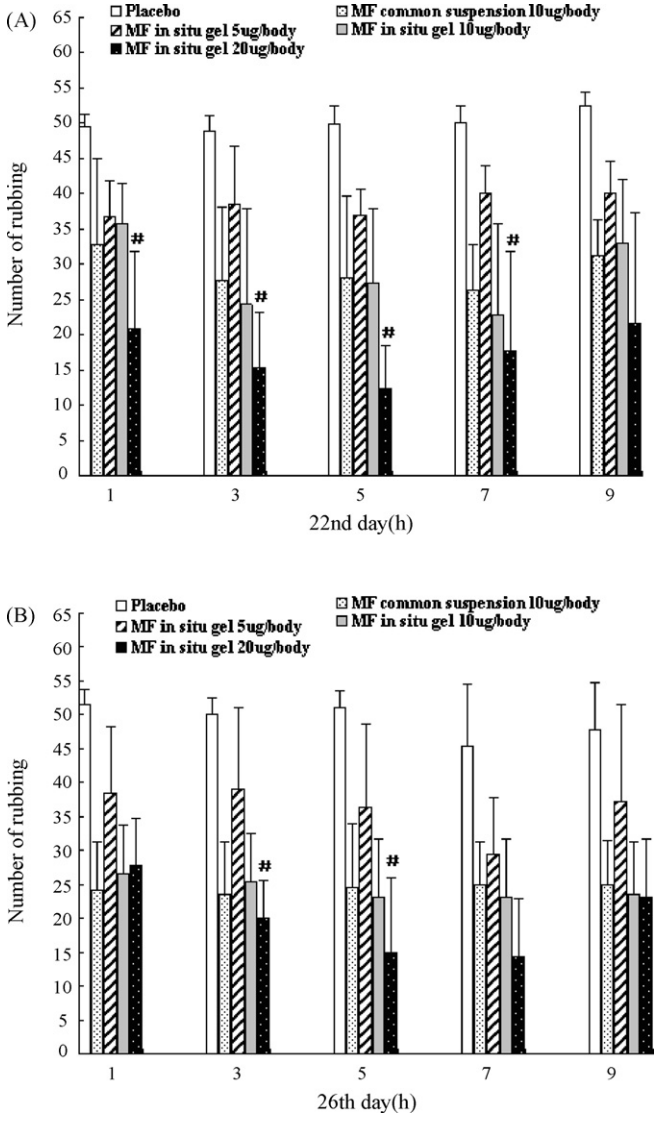

Fig. 8. Effects of MF in situ gel and common suspension (0.05% MF 10 μg/body) on nasal rubbing after antigen challenge in sensitized rats on the 22nd and 26th day. Nasal rubbing were both observed for 30 min. Each column and vertical bar represents means ± S.E.M. (#) Significantly different from the placebo group ($P < 0.01$). (Δ) Significantly different from common suspension ($P < 0.05$).

Therefore, an animal model showing similar nasal allergic symptoms for evaluation of the effectiveness of anti allergic drugs was developed in this study according to the report (Yukio et al., 2000a,b; Tae et al., 2005). Before the study, a group of unsensitized rats ($n = 10$) were observed for the number of sneezing (3 ± 1.2) and rubbing (10 ± 3.5) for 30 min. During the study, both sneezing and nasal rubbing movements were observed immediately after topical antigen challenge and each observation lasted for 30 min from day 14 to day 21. Fig. 5 showed the basal data of sneezing and rubbing in sensitized rats after antigen challenge from day 14 to day 21. The numbers of sneezes and nasal rubbing movements were observed after general sensitization. Antigen-induced nasal symptoms were markedly increased by intranasal sensitization, and these symptoms were maintained during local sensitization (Fig. 5).

Pauwels (1986) reported that serum antigen-specific IgE antibody level of Wistar rats was elevated until day 14 after sensitization and was decreased thereafter. However, in this study we think high IgE antibody levels may be maintained for a long time by repeated local booster sensitization (Yukio et al., 2000a,b). Thus, we have established a chronic allergic rhinitis model by repeated topical application of antigen into the nasal cavity in sensitized rats.

3.5.2. Effects of mometasone furoate on nasal symptoms

Corticosteroids are the only drugs which are effective in all the symptoms of rhinitis. Many papers have reported that MF inhibited dye leakage into the nasal cavity induced by antigen in actively sensitized rats when applied topically (Tae et al., 2005; Parameswaran et al., 2006).

Fig. 6A shows the effects of MF in situ gel on antigen-induced sneezing in actively sensitized rats. MF caused a concentration-dependent inhibition in this response, and at concentrations of 20 μg/body it significantly decreased the number of nasal sneezing. Fig. 6B shows the effects of MF on antigen-induced nasal rubbing. Similar to nasal sneezing, MF significantly decreased the number of sneezes at concentrations of 20 μg/body during the process of study. The number of sneezing and rubbing of the control group had no obvious decline in 21–35 days, which still be maintained on the original level helped to observe the effect of treatment group.

3.5.3. Long-lasting effects of mometasone furoate on nasal symptoms

In the present study, In situ gel inhibited the increase in nasal symptoms with a dose-dependent manner. Long-lasting effects of MF on antigen-induced nasal sneezing in actively sensitized rats are shown in Fig. 7. Intranasal MF in situ gel at a dose of 10 and 20 μg/body decreased the degree of nasal sneezing significantly in the rats compared with the suspension group (10 μg/body) ($P < 0.01$). In addition, although the dose of MF suspension and in situ gel was the same, the count of nasal sneezing decreased obviously differently on one day (especially on 26th day), suggesting that a better effect might be expected. These results were supported by the previous findings that because of the mucociliary clearance mechanism, suspension formulations, that are not mucoadhesive, are generally rapidly cleared from the nasal cavity and result in a short duration (Cao et al., 2007). However, this phenomenon was not appear in the study of nasal rubbing because of some physiological responses of rats such as sleepiness and fatigue (Fig. 8).

3.5.4. Assessment of nasal mucosal integrity

The successful use of mucoadhesive nasal delivery systems is not only limited to their bioadhesive efficacy, but equally important, is their safety. Hence, it was important to investigate the safety of the optimized in situ gel formulation. Fig. 9 shows light photomicrograph taken from anterior cross section of rat nasal cavity following 35-day exposure to the mucoadhesive in situ gel (0.5% gellan gum and 0.05% MF). Examination the nasal cavity of in situ gel showed intact ciliated respiratory epithelium and normal goblet cell appearance. Signs of irritation such as vascular congestion

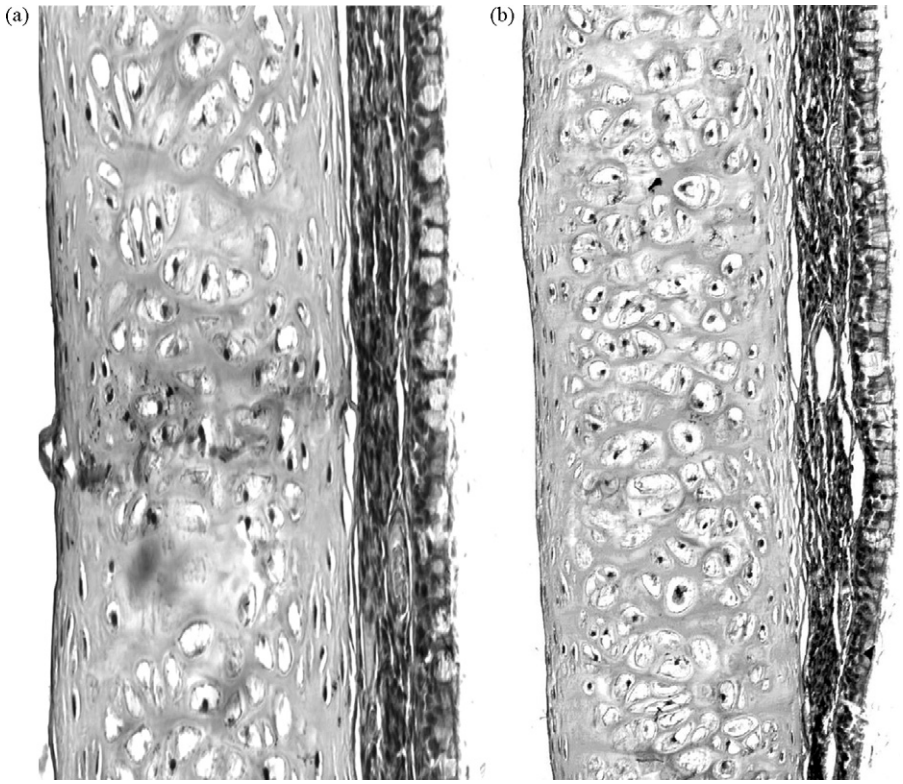

Fig. 9. Light photomicrograph of the anterior cross-section of the rat nasal cavity following 35-day exposure to nasal (a) in situ gel; (b) negative control-saline.

and subepithelial edema were not observed. Moreover, none of severe signs such as appearance of epithelial necrosis, sloughing of epithelial cells and hemorrhage was detected in any of the rats.

The morphological study revealed the safety of the tested formula which was deposited for 35 days to the nostril of rats.

4. Conclusion

In amount, MF nasal in situ gel can be prepared by mixing the MF, xanthan gum and gellan gum 0.5% (m/v). MF in situ gel was typically of pseudo plastic systems and presented safety during study. The animal experiment suggested that MF in situ gel could be more effective than the nasal suspension in the treatment of allergic rhinitis. In conclusion, the in situ gel system is a promising approach for the intranasal delivery of MF for the therapeutic effects improvement.

Acknowledgments

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References

Cao, S.L., Zhang, Q.Z., Jiang, X.G., 2007. Preparation of ion-activated in situ gel systems of scopolamine hydrobromide and evaluation of its antimotion sickness efficacy. Acta. Pharmacol. Sin. 28, 584–590.
Chanrasekaran, R., Puigjaner, L.C., Joyce, K.L., Arnott, S., 1988. Cation interaction in gellan: an X-ray study of the potassium salt. Carbohydr. Res. 181, 23–40.
Chanrasekaran, R., Thailambal, V.G., 1990. The influence of calcium ions, acetate and l-glycerate groups on the gellan double helix. Carbohydr. Polym. 12, 431–432.
Cui, F.D., 2003. Pharmaceutical. People's Medical Publishing House, pp. 277–279.
Edsman, K., Carlfors, J., Petersson, R., 1998. Rheological evaluation of poloxamer as an in situ gel for ophthalmic use. Eur. J. Pharm. Sci. 6, 105–112.
Gizurason, S., 1993. The relevance of nasal physiology to the design of drug absorption studies. Adv. Drug. Del. Rev. 11, 329–347.
Grasdalen, H., Smidsroed, O., 1987. Gelation of gellan gum. Carbohydr. Polym. 7, 371–393.
Gurny, R., Boye, T., Ibrahim, H., 1985. Ocular therapy with nanoparticulate systems for controlled drug delivery. J. Control. Release 2, 353–261.
Illum, L., Jorgensen, H., Bisgaard, H., Krogsgaard, O., Rossing, N., 1987. Bioadhesive microspheres as a potential nasal drug delivery system. Int. J. Pharm. 39, 189–199.
Jiang, X.G., Cui, J.B., Fang, X.L., Wei, Y., Xi, N.Z., 1995. Toxicity of drugs on nasal mucocilia and the method of its evaluation. Acta. Pharm. Sin. 30, 848–853.
Kawabori, S., Okuda, M., Unno, T., Nakamura, A., 1985. Dynamics of mast cell degranulation in human allergic nasal epithelium after provocation with allergen. Clin. Allergy 15, 509–515.
Lorin, M.I., Gaerlan, P.F., Mandel, I.D., 1972. Quantitative composition of nasal secretions in normal subjects. J. Lab. Clin. Med. 2, 275–281.
Meltzer, E.O., 1997. The pharmacological basis for the treatment of perennial allergic rhinitis and non-allergic rhinitis with topical corticosteroids. Allergy 52 (Suppl. 36), 33–40.
Miller, S.C., Donovan, M.D., 1982. Effect of Poloxamer 407 gel on the miotic activity of pilocarpine nitrate in rabbits. Int. J. Pharm. 12, 147–152.
Mygind, N., 1993. Glucocorticosteroids and rhinitis. Allergy 48, 476–490.
Parameswaran, K., Fanat, A., O'Byrne, P.M., 2006. Effects of intranasal fluticasone and salmeterol on allergen-induced nasal responses. Allergy 61, 731–736.
Pauwels, R., 1986. Mode of action of corticosteroids in asthma and rhinitis. Clin. Allergy 16, 281–218.
Rozier, A., Mazuel, C., Grove, J., Plazonnet, B., 1997. Functionality testing of gellan gum, a polymeric excipient material for ophthalmic dosage forms. Int. J. Pharm. 153, 191–198.
Tae, T., Masami, O., Kazuhisa, M., 2005. Effects of mometasone furoate on a rat allergic rhinitis model. Eur. J. Pharmacol. 524, 155–158.
Yukio, S., Keisuke, I., Kouichi, S., 2000a. Effect of mometasone furoate by Topical Application on Allergic Rhinitis Model in rats. Pharmacology 61, 91–95.
Yukio, S., Etsuko, K., Zhong, C., Chiaki, K., 2000b. A new model of allergic rhinitis in rats by topical sensitization and evaluation of H-receptor antagonists. Immunopharmacology 48, 1–7.