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Novel chronotherapeutic rectal aminophylline delivery system for therapy of asthma

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ABSTRACT

The aim of this study was to develop a new chronotherapeutic pharmaceutical preparation as a sustained-release suppository for prevention and therapeutic use against bronchial asthma in the early morning. Sustained-release hollow-type (SR-HT) suppositories using sodium alginate (Alg-Na), sodium polyacrylate (PANa) or polyacrylate-PANa co-polymer (PA-PANa) as gelling polymers (gel agent) were prepared and pharmaceutical characteristics of these suppositories were investigated. Type A SR-HT suppositories comprised a suppository shell prepared with oleaginous base and containing aminophylline only or aminophylline with Alg-Na or PANa in the cavity (hollow space). Type B SR-HT suppositories comprised a suppository shell prepared with oleaginous base and gel agent (30%), with aminophylline in the hollow space. In drug-release studies, the acrylate polymer-containing suppositories showed linearity of delayed release rate, providing significantly decreased the highest concentration of theophylline in plasma (C_{max}) and delayed the time required to reach C_{max} (t_{max}) and the mean residence time (*MRT*) after rectal administrated in rabbits. In particular, suppositories containing PA-PANa maintained significantly higher theophylline concentrations than control suppositories at 12 h after rectal administration. Furthermore, histopathological examination indicated that these suppositories using acrylate polymers did not result in rectal lesions. The SR-HT suppository, particularly using PA-PANa as a gel agent, may thus be useful against nocturnal symptoms of asthma. In this study, we confirmed new formulation of sustained-release suppository for chronotherapy of theophylline using oily base material in combination with polymer such as PA-PANa. The hollow-type suppository containing oleaginous base and hydrophilic polymer in the shell could be useful device for rectal administration of various drugs with prolongation of plasma concentration.

1. Introduction

Theophylline has been widely used as an effective therapeutic agent in the treatment of bronchial asthma for over 70 years. Increasing evidence shows that theophylline has anti-inflammatory effects in asthma (Sullivan et al., 1994; Reed et al., 1998; Ito et al., 2002) and improves pulmonary function during the late asthmatic response (LAR) (Kraft et al., 1996). An oral route has generally been recommended for administration of theophylline and the effectiveness of sustained-release products has been reported (Minotti et al., 1992). However, drugs are difficult to administer to patients with symptoms of dysphagia such as vomiting or nausea, or unconscious condition. In such cases, rectal administration by suppository instead of oral administration would be very advantageous for drug delivery (De Boer et al., 1984). We have previously reported several basic (Watanabe et al., 1998; Kowari et al., 2002) and clinical (Matsumoto et al., 1990; Watanabe et al., 1999) studies concerning a unique rectal drug delivery system, the hollow-type (HT) suppository developed by Watanabe et al. (1986), containing various drugs. The aim of this study was to develop a new chronotherapeutic rectal delivery system, sustained-release preparation in a modified HT suppository, for therapeutic use against bronchial asthma in the early morning.

Mucoadhesive polymer is widely used to add sustained-release functions to pharmacotherapies (Ryu et al., 1999). Alginate has a backbone of (1 → 4) linked β-D-mannuronic acid and α-L-guluronic acid residues and displays sustained-release properties (Tønnesen and Karlsen, 2002). Acrylate polymer is also mucoadhesive and shows sustained-release properties (Ryu et al., 1999). These substances are generally used in drug delivery systems for drug-release control as polymer coatings, hydrogels, and emulsions (Tønnesen and Karlsen, 2002). Numerous reports have described various formulation strategies such as using hydrogel or xerogel suppositories (Umejima et al., 1993, 1995), rectal gels (Watanabe

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et al., 1996), double-phased mucoadhesive suppositories (Yahagi et al., 1999) and poloxamer-based solid suppositories (Yong et al., 2005) to achieve sustained release in a suppository form. However, these conventional suppositories include unresolved problems such as difficulties achieving easy and exact dose-volume control, interaction of the drug with base materials and degeneration by heating during preparation. The HT suppository addresses these issues and offers a highly convenient preparation. The HT suppository contains a hollow space for filling with the main drug. One of the characteristics of highly convenient preparations is freely changeable filling with the main drug in each suppository. In addition, HT suppositories can contain drugs in various forms, eliminate interactions between the drug and base materials and allow control of the drug dose. We developed a novel SR-HT suppository to sustain plasma theophylline concentrations and prevent nocturnal symptoms of asthma, using natural and synthetic polymers as gel agents. Alginic acid (Alg) is a natural polysaccharide polymer isolated from brown seaweed, and is a useful material for mucoadhesive polymer. We selected sodium alginate (Alg-Na) as a natural polysaccharide, and sodium polyacrylate (PANa) and polyacrylate-PANa co-polymer (PA-PANa) as acrylate polymers that can be applied to pharmaceutical preparations, then evaluated the *in vitro* and *in vivo* release of theophylline from SR-HT suppositories using these polymers to achieve long-term plasma levels of theophylline.

2. Materials and methods

2.1. Materials

Aminophylline and Vosco® H-15, an oleaginous suppository base material (hard fat) of mixture of triglycerides (mp 33.5–35.5 °C), were purchased from Eisai (Tokyo, Japan) and Maruishi Pharmaceutical (Osaka, Japan), respectively. Alg-Na (Keltone HVCR) was kindly supplied by ISP Japan (Tokyo, Japan). PANa (F-480SS) and PA-PANa (NP-700) were obtained from Showa Denko (Tokyo, Japan). All other reagents were analytical-grade commercial products.

2.2. Preparation of suppository

A schematic illustration of the HT suppository is shown in Fig. 1. SR-HT suppositories weighing approximately 2.5 g were prepared in the same manner as described previously (Watanabe et al., 1986, 1998). Suppositories used in this study were 37 mm long with a diameter of 7 mm. The volume of the hollow-space is approximately 0.5–0.6 mm^3. HT suppositories were prepared using Vosco® H-15 with Alg-Na or PANa. Control suppositories (Type A-I) were prepared without polymers. An aliquot of Alg-Na or PANa was mixed in melted suppository base at 40 °C, then well dispersed by sonication using a US-4 ultrasonic cleaner (Iuchiseieido, Osaka, Japan) for 10 min at 40 °C. The mixture was quickly poured into a metallic mold equipped with an adapter for the preparation of HT suppositories, then allowed to solidify at room temperature. After construction of the shell, gel agent was either mixed with aminophylline and filled into the hollow space (Type A-II and Type A-III) or mixed into the HT suppository shell (Type B-I, Type B-II, Type B-III). Compositions of the different suppository types are shown in Table 1. The amount of contained gel agent was set at 30% (w/w) based on preliminary tests and represents the maximum dose of formulation able to be used in a HT suppository constructed. With the use of aminophylline powder only, the drug was accurately measured and added to the cavity. For mixtures of aminophylline and polymer, the components were mixed in a mortar and then added to the cavity. All suppositories were stored in a refrigerator prior to use.

Table 1
Composition of suppositories.

Type	Shell	Materials filled into hollow space
A-I	H-15	Aminophylline (50 mg)
A-II	H-15	Alg-Na (100 mg), aminophylline (50 mg)
A-III	H-15	PANa (50 mg), aminophylline (50 mg)
B-I	H-15, Alg-Na (30%)	Aminophylline (50 mg)
B-II	H-15, PANa (30%)	Aminophylline (50 mg)
B-III	H-15, PA-PANa (30%)	Aminophylline (50 mg)

2.3. Drug release

The release study was performed with a slight modification using an instrument (model TMS-103; Toyama Sangyo, Osaka, Japan) reported by Muranishi et al. (1979). The dissolution medium was 500 ml of phosphate buffer solution (PBS, pH 7.4). To observe differences in percentage of theophylline released between conventional and HT suppositories *in vitro*, each suppository was placed directly on a metallic net of plastic cylindrical cells without a mem-

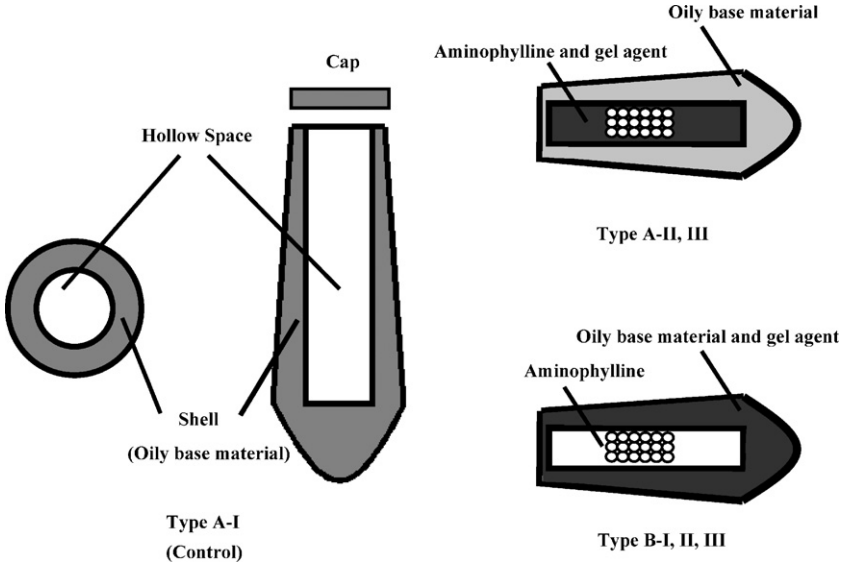

Fig. 1. Schematic of hollow-type (HT) suppositories used in this study.

brane. The dissolution medium was kept at 37 °C. The inner cell solution was stirred at 10 rpm and the dissolution medium was stirred at 100 rpm. An aliquot of 1 ml of dissolution medium was collected and the same volume of PBS was added to maintain a constant volume. The concentration of theophylline was determined by spectrophotometry at 273 nm (U-best 30; JASCO, Tokyo, Japan).

2.4. Rectal administration

Male albino rabbits weighing 2.0–3.95 kg (Sankyo Labo Service, Tokyo, Japan) were used. Animals were provided with *ad labitum* access to food and water and housed individually in cages in a forced-air facility maintained at 23 ± 1 °C and 55% relative humidity, under a 12-h light/dark cycle. All experiments were approved by the Institutional Animal Ethics Committee of Showa Pharmaceutical University (Tokyo, Japan). Animals with *ad libitum* access to water were fasted for 1 night prior to each experiment. The rabbits were restrained with light-fitting neck stocks that allow them to assume a natural resting (crouching) posture, and a suppository was inserted into the rectum (Watanabe et al., 1986). After rectal administration of each suppository, surgical adhesives were applied to prevent leakage. A 1-ml blood sample was collected from the auricular vein in a syringe containing ethylenediamine-tetraacetic acid disodium salt (EDTA-2Na) at predetermined time intervals. After 6 h for blood sample collection, the rabbits were secured in the cage except for the time of blood collecting. These samples were centrifuged at 3000 rpm for 10 min to separate the plasma. Each plasma sample was stored at −30 °C until assays for theophylline were performed.

2.5. Determination of theophylline in plasma

Plasma (0.1 ml) was added to 0.5 ml of methanol containing internal standard solution (4 μl/ml) and centrifuged at 12,000 rpm for 1 min, then 200-μl aliquots of this solution were injected onto the high performance liquid chromatography (HPLC) system.

HPLC consisted of a 600 system controller, CHM-D column oven, 600E pump, 486 UV detector and 717 Plus autosampler (Waters, MA, USA). Separation was performed on a 4.6 mm × 150 mm Wakosil-II 5C18 column (Wako Pure Chemical Industries, Osaka, Japan). The mobile phase was 0.1% phosphate buffer-methanol (85:15). Flow rate was 1.0 ml/min. Column temperature was maintained at 30 °C. The UV detector was set at 273 nm. The concentration of theophylline was calculated from peak height to internal standard ratio. The internal standard used was 7-(2-hydroxyethyl) theophylline (Sigma, MO, USA).

2.6. Pharmacokinetic analysis

The highest concentration of theophylline observed in plasma (C_{max}) was employed, and the time required to reach C_{max} was defined as t_{max}. The area under the plasma concentration–time curve (AUC_{0-24}) was calculated using the trapezoidal rule. Mean residence time (*MRT*) was obtained using the area under the moment–time curve (*AUMC*) as calculated by the trapezoidal rule/AUC_{0-24}.

2.7. Statistical analysis

Data were analyzed for statistically significant differences by one-way analysis of variance (ANOVA), followed by Dunnett's test. The level of significance was taken as $p < 0.05$.

2.8. Histopathological evaluation

Male albino rabbits weighing 1.4–2.1 kg were purchased from Sankyo Labo Service and Japan Laboratory Animals (Tokyo, Japan). Animals with *ad libitum* access to water were fasted for 36 h prior to each experiment. At 6 h after rectal administration of the suppository, the rectum was resected. The segment was then removed and immersed in 10% neutral formalin buffer. Segments were prepared and stained with hematoxylin–eosine and examined by light microscopy for the following measures of histopathological abnormality: flattening and shrinkage of epithelial cells; erosion; inflammatory cell infiltration; and crypt atrophy. These abnormalities were quantified on an arbitrary scale of from 0 (no effect) to 4 (severe effect) (van Hoogdalem et al., 1990).

3. Results and discussion

3.1. Drug release from suppositories

Release profiles of theophylline from prepared suppositories are shown in Fig. 2. Release of theophylline from the control suppository (Type A-I) was very rapid and was completed within 30 min (Fig. 2a). Release of theophylline from Type A-II and A-III suppositories was decreased compared to Type A-I. Theophylline release from Type A-III suppositories was more sustained than that from Type A-II. However, percentage of drug release reached 80% at 2 h and plateaued level. A previous study reported that sufficient sustained-release function *in vivo* requires a more linear and sustained-release capacity over at least 6 h in an *in vitro* study (Hayashi et al., 2007).

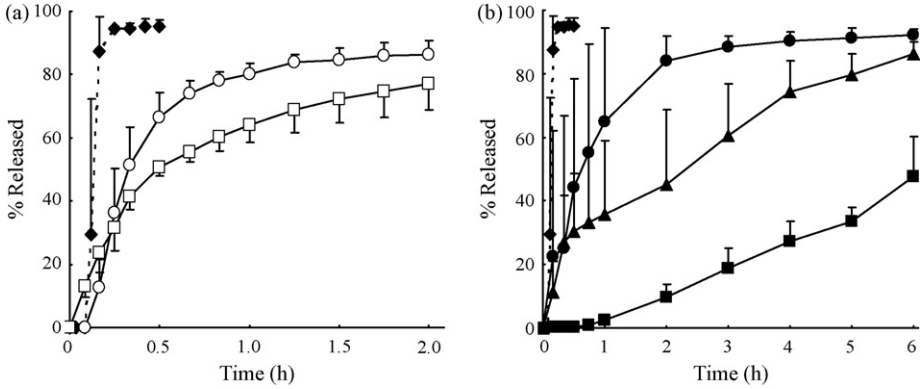

Fig. 2. *In vitro* release profiles of theophylline from suppositories containing gel agent in hollow space or in shell. (♦) TypeA-I (aminophylline powder in hollow-space). (○) Type A-II (aminophylline 50 mg with Alg-Na 100 mg in hollow space). (□) Type A-III (aminophylline 50 mg with PANa 50 mg in hollow space). (●) Type B-I (aminophylline 50 mg in hollow space and 30% Alg-Na in shell). (■) Type B-II (aminophylline 50 mg in hollow space and 30% PANa in shell). (▲) Type B-III (aminophylline 50 mg in hollow space and 30% PA-PANa in shell). Each point represents the mean ± SD of three experiments.

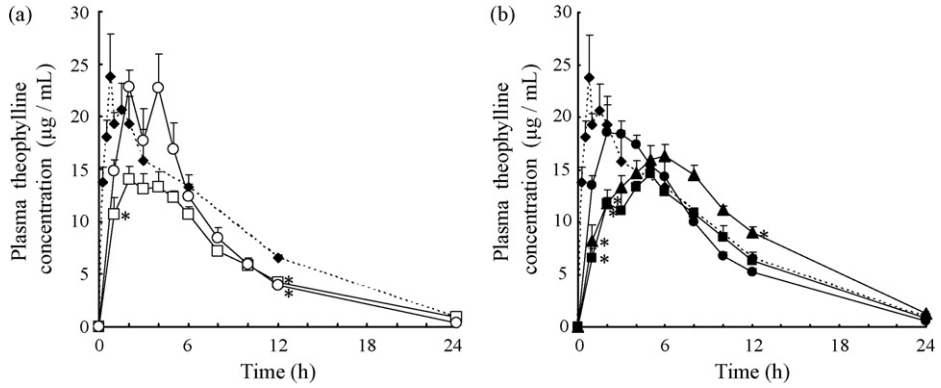

Fig. 3. Plasma theophylline concentration after rectal administration of various suppositories prepared. (♦) Type A-I (aminophylline powder in hollow space). (○) Type A-II (aminophylline 50 mg with Alg-Na 100 mg in hollow space). (□) Type A-III (aminophylline 50 mg with PANa 50 mg in hollow space). (●) Type B-I (aminophylline 50 mg in hollow space and 30% Alg-Na in shell). (■) Type B-II (aminophylline 50 mg in hollow space and 30% PANa in shell). (▲) Type B-III (aminophylline 50 mg in hollow space and 30% PA-PANa in shell). Each point represents mean ± SE of 3–4 experiments. $^{*}p < 0.05$ compared to Type A-I (control).

To increase sustained-release function, we investigated Type B suppositories. Release of theophylline from Type B-I suppository was also decreased compared to Type A-I (Fig. 2b). Unfortunately, about 80% of theophylline was released at 2 h. Therefore, sustained-release function of Type B-I suppository was insufficient. Conversely, theophylline release from Type B-II suppository was markedly delayed, with about 40% released after 2 h. Type B-II suppository release was more delayed compared to Type B-I, suggesting linear release after about 80% of theophylline had been released at 6 h. In particular, Type B-III suppository showed higher sustained-release function than Type B-II suppository, although both types displayed sufficient sustained-release function. Release of theophylline from Type B-II or Type B-III gel agent-containing suppository shells apparently followed zero-order kinetics. Furthermore, TypeB-II and Type B-III suppositories showed marked sustained-release function compared with Type A-I. Whereas Type A-II and Type A-III contained 100 mg Alg-Na or 50 mg PANa in the hollow space, Type B suppositories contained about 750 mg of gel agent in the shell. This difference appears responsible for the markedly delayed release provided by Type B suppositories using PANa or PA-PANa. The difference of sustained-release function between Type B-II and Type B-III may be related to natures of PANa and PA-PANa. PANa forms more sticky gel after melting of the shell consist of oleaginous base material, consequently, theophylline was included in the gel matrix for long period. On the other hand, in Type A, theophylline tended to dissolve more quickly by contact with water prior to formation of the gel matrix after melting of the shell. The difference of release retardation between Type A-II and Type A-III is less than that of release retardation by Type B suppositories. It seems that natures of polymers are less effective when Type A suppositories are used. The effects of polymer concentration on drug release have been reported for 17 grades of various alginates (Liew et al., 2006). The most common explanation for the effect of polymer on drug release was that increased polymer content increases viscosity of the gel matrix, causing a reduction in the effective diffusion coefficient of the drug (Liew et al., 2006). Further reductions in drug release may be expected using different grades of Alg.

3.2. Rectal administration

To investigate the effect of polymers on rectal absorption of theophylline from SR-HT, suppositories using shells containing Alg-Na, PANa or PA-PANa were administered. Fig. 3 shows plasma concentration-time profiles of theophylline after rectal administration of prepared suppositories. The pharmacokinetic parameters obtained are summarized in Table 2. All suppositories contained the same dose (50 mg) of aminophylline. After administration, Type A-II suppository showed rapidly increased plasma theophylline concentration in the early phase, but no significant differences in pharmacokinetic parameters. When Type A-III suppository was administered, rapid increases in plasma theophylline concentration in the early phase after administration and C_{max} were significantly decreased compared to that observed after administration of Type A-I (Fig. 3a). Unfortunately, AUC_{0-24} was also significantly decreased compared to those for Type A-I (Table 2). The decrease in AUC_{0-24} indicated by sustained-release function is similar to previous data reported by Kawashima et al. (1989, 1990). This finding may be due to decreased release of theophylline caused by increased viscosity of the rectal fluid interfering with complete theophylline release, as shown in an *in vitro* release study (Fig. 2). Conversely, Type B-I suppository displayed significantly decreased plasma theophylline concentration after 1 h compared to Type A-I (Fig. 3b). However, C_{max}, t_{max}, AUC_{0-24} and *MRT* were not significantly different. Type B-II and Type B-III suppositories also showed significantly decreased plasma theophylline concentrations at 1 h after administration, with decreased plasma levels continuing 4 h after administration of Type B-III suppository. Not only were significant decreases seen in rapidly increased plasma theophylline concentration in the early phase after 2 h as compared to Type A-I suppository, but higher plasma concentrations were observed at 5–12 h compared to Type A-I. Significant delays in t_{max} and *MRT*, along with decreased C_{max}, were seen after administration of Type B-II suppository. This result might be due to the sustained-release properties of PANa, with the linear release profile contributing to sustained-release properties (Fig. 2b). These results suggest that Type B-III suppositories using PA-PANa have higher sustained-release function than Type B-II suppository using PANa. In pharmacokinetic parameters, significant delays in t_{max} and decreases in C_{max} were observed after adminis-

Table 2
Pharmacokinetic parameters of theophylline following rectal administration of suppositories containing gel agent.

Type	t_{max} (h)	C_{max} (μg/mL)	AUC_{0-24} (h μg/mL)	*MRT* (h)
A-I	1.4 ± 0.4	25.1 ± 3.4	202.2 ± 8.2	6.7 ± 0.2
A-II	2.7 ± 0.7	23.9 ± 2.5	172.3 ± 18.3	6.0 ± 0.2
A-III	2.0 ± 0.0	14.0 ± 1.2*	140.7 ± 11.5*	7.2 ± 0.5
B-I	3.0 ± 0.6	19.8 ± 1.5	177.9 ± 5.6	6.7 ± 0.2
B-II	5.0 ± 0.0*	13.9 ± 0.9*	164.0 ± 7.1	7.8 ± 0.3
B-III	5.3 ± 0.5*	16.6 ± 3.2*	210.2 ± 6.1	8.3 ± 0.3*

Each value represents the mean ± SEM of 3–4 experiments.
* $p < 0.05$ compared to Type A-I.

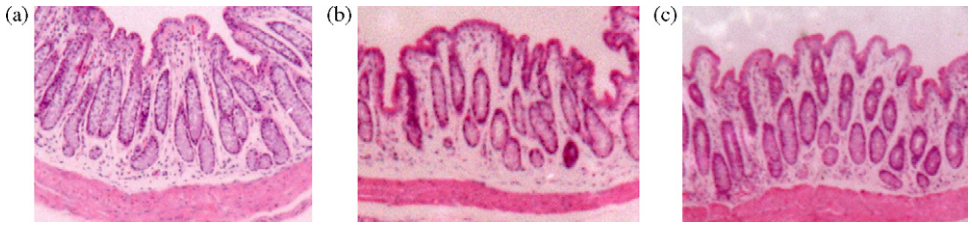

Fig. 4. Histological observation of rectal mucosa at 6 h after rectal administration of suppositories. Untreated (a) or treated using SR-HT suppositories with 30% PANa in shell (b) and 30% PA-PANa in shell (c). Each suppository contained 50 mg of aminophylline. Magnification, ×120.

tration of Type B-II and Type B-III suppositories. However, AUC_{0-24} was not significantly different between these two types and Type A-I. Use of acrylate polymers in suppositories might have contributed to prolonged theophylline concentrations. The quantity of gel agent contained in each shell was 7.5- to 15-fold compared to filling gel agent, accentuating these results. Sustained-release function can this be added without decreasing the hollow space used for the pharmacotherapeutic agent. Clinical use requires convenience with less frequent daily dosing. Many tablet forms of sustained-release theophylline preparation are given as once-a-day dosing to asthmatic patients (Minotti et al., 1992). Our results indicate that shells containing 30% gel agent as SR-HT suppositories showed higher controlled release function compared to gel agent used as filling with aminophylline in normal HT suppository shells. SR-HT suppositories using PANa or PA-PANa at concentrations of 30% in the shell showed significantly delayed t_{max} and decreased C_{max}. When the concentration of acrylate polymers was decreased, t_{max} tended to be shortened and sustained-release function was thus insufficient. Theophylline has dose-related effects that limit use (Sullivan et al., 1994), so Type B-II and Type B-III suppositories may be effective in preventing such side effects. In particular, Type B-III suppository using PA-PANa is expected to prolong plasma theophylline concentration in the therapeutic range, with no significant decrease in AUC_{0-24}, but significant prolongation of *MRT*. These results suggest that Type B-III suppository may allow less frequent dosing and should be applicable to nocturnal symptoms of asthma as a highly versatile formulation.

Following rectal administration of prepared suppository consisted of oily base material in combination with PA-PANa, hydrogel is formed when polymer is dissolved in the rectal fluid after melting of oily base in the shell. This function is useful for sustained-release and prolongation of plasma concentration of drug.

3.3. Histopathological evaluation

Alg and its sodium and calcium salts are generally regarded as non-toxic (Umejima et al., 1993). In a previous report, Alg-Na did not induce morphological changes in rectal mucosal membranes (Ryu et al., 1999). Histopathological evaluations have not previously been reported for rectal effects of PANa and PA-PANa. The present study therefore included histopathological evaluation. Histopathological images of rabbit rectal mucosa at 6 h after administration of Type B-II suppositories using PANa or Type B-III suppositories using PA-PANa are shown in Fig. 4. In all rabbits tested, histopathological findings showed no change or only very slight damage, with the exception of crypt atrophy. For crypt atrophy, rabbits showed no change to slight damage for untreated rabbits and Type B-II suppositories. These results are similar to previous reports (Miyazaki et al., 1998) of rabbit rectum without treatment. These previous results indicate no apparent histological damage from PANa and PA-PANa in suppositories with the use of a single dose, similar to untreated cases. The rectal mucous membranes with anionic charges have oligosaccharides composed sialic acid. PANa and PA-PANa might less interact with the rectal mucous membranes because of sodium salts. Probably, this is a reason why no damage in the rectal tissue is observed using our suppositories.

4. Conclusions

The present study investigated novel SR-HT suppositories using Alg-Na, PANa and PA-PANa, which may be aimed for bronchial asthma occurring in the early morning. Type B suppositories using PANa and PA-PANa in the shells showed significantly delayed t_{max} and *MRT* and decreased C_{max}, without significant decreases in AUC_{0-24}. Type B-III suppository using PA-PANa prolonged plasma theophylline concentration the most. Unfortunately, Alg does not have affective property of sustained-release of theophylline from suppository. SR-HT suppositories prepared using PANa and PA-PANa contained in the shell may thus be effective and convenient preparation for bronchial asthma in the early morning.

In this study, we confirmed new formulation of sustained-release suppository for chronotherapy of theophylline using oily base material in combination with polymer such as PA-PANa. The developed hollow-type suppository containing oleaginous base and hydrophilic polymer in the shell could be useful device for rectal administration of various drugs with prolongation of plasma concentration.

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