Drug Development and Industrial Pharmacy, 2010; 36(12): 1436–1443

informa
healthcare

ORIGINAL ARTICLE

Effect of zinc oxide on the rheological and mucoadhesive properties of poloxamer 407-based mucoadhesive thermosensitive gel

Tae-Hwan Park[1], Sung Tae Kim[1,2], Jeong-Sook Park[3], Han-Gon Choi[4], Hyung Tae Kim[5] and Chong-Kook Kim[1,6]

[1]Laboratory of Excellency for Drug and Gene Delivery, College of Pharmacy, Seoul National University, Seoul, Republic of Korea, [2]Department of Biochemistry and Division of Brain Korea 21 Program for Biomedical Science, College of Medicine, Korea University, Seoul, Republic of Korea, [3]College of Pharmacy and Institute of Drug Research and Development, Chungnam National University, Daejeon, Republic of Korea, [4]College of Pharmacy, Hanyang University, Republic of Korea, [5]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Republic of Korea and [6]Department of Pharmaceutical Engineering, Inje University, Gimhae Gyungnam, Republic of Korea

Abstract

Background: To improve the therapeutic efficacy of drugs for hemorrhoid, mucoadhesive thermosensitive gel (MTG) system was developed. *Methods*: The MTG was prepared using poloxamer 407 (P407, 13% and 14%), polycarbophil (PC, 0.2% w/v), phenylephrine hydrochloride (0.25% w/v), lidocaine hydrochloride (1.88% w/v), and prednisolone acetate (0.05% w/v). Then, zinc oxide (ZnO) was added as an astringent as well as mucoadhesiveness-enhancing agent. Two kinds of poloxamer-based MTGs were compared in aspects of rheology, mucoadhesiveness, syringeability, and in vitro release study. *Results*: Both the two MTGs (13% and 14% P407) showed Newtonian behavior at 20°C whereas pseudoplastic flow at 37°C. The addition of ZnO into MTGs enhanced the mucoadhesiveness and syringeability and led the drug components to be released in accordance with Fickian mechanism. *Conclusions*: Taken together, the MTG-containing ZnO can be a more effective and convenient delivery system for the treatment of hemorrhoid with a reduced dosage interval.

Key words: *Hemorrhoid; mucoadhesive; poloxamer 407; thermosensitive gel; zinc oxide*

Introduction

Hemorrhoid is one of the most common gastrointestinal diseases and affects between 4.4% and 36.4% of general population[1]. Hemorrhoid is pathologically characterized by prolapse and bleeding of hemorrhoid cushion composed of vascular and connective tissue and is classified by the degree of symptom (Grades I–IV)[2]. To alleviate and cure the symptoms, either surgical or nonsurgical treatment has been currently used. Of many approaches for the treatment of hemorrhoid, cream, ointment, and pastes were topically applied to relieve pain and pruritus before the outpatient treatment[1,3].

Treatments with conventional solid suppository, which melts in the rectal site, could be discomfort and thus refused by the patient with hemorrhoid. The conventional solid suppository without mucoadhesiveness can only be reached at the end of colon and, furthermore, can cause the inconvenience to manufacture and to handle the commercial product under the industrial process such as a packaging[4,5]. To overcome the disadvantages of solid suppository, developing the liquid suppository, which is easy to administer to patient with good compliance and remains at the target location without first-pass effect, would be attempted. In the previous reports, there have been several attempts of

Address for correspondence: Prof. Chong-Kook Kim, College of Pharmacy, Seoul National University, 599 Gwanak-ro, Gwanak-gu, Seoul 151-015, Republic of Korea. Tel: +82 31 712 2134, Fax: +82 31 712 7610. E-mail: ckkim@plaza.snu.ac.kr

(Received 29 Dec 2009; accepted 10 Apr 2010)

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI: 10.3109/03639045.2010.487266

the gel-based liquid suppository for the mucosal administration[4–10]. In particular, the mucoadhesive thermosensitive gel (MTG) system is desired to be an ideal suppository because it has a good patient compliance, thermosensitive gel formation in the body temperature, and mucoadhesiveness. The MTG system can remain at the anus with less leakage due to gelation and mucoadhesiveness after the rectal administration.

Up to date, many kinds of polymers having the property of heat-induced gelation have been developed. Of polymers, triblock poly(ethylene oxide)-*co*-poly(propylene oxide)-*co*-poly(ethylene oxide) (PEO-PPO-PEO) copolymer, also called 'Pluronics®' or 'Poloxamer', was the first thermosensitive polymer approved by the FDA[11,12]. Poloxamer 407 (P407) has low toxicity as well as excellent compatibility with other chemicals and can be transformed from low viscous liquid to semisolid gel upon heating until physiological temperature, although poloxamer-based system depends on the concentration of polymer and additives[4,13]. Moreover, polycarbophil (PC), a polyacrylate polymer, is known to bind the mucosal surfaces through hydrogen-bonding interactions[14]. It may enhance the drug absorption due to increasing the mucoadhesiveness at anus and contact time with mucus. Generally, zinc oxide (ZnO) has been widely used as astringents, which present protective and antiseptic action[15–18], and antiulcer effect[19]. However, it had been recently reported that the metal ions such as divalent or trivalent cations including ZnO enhance the adhesive property with gastrointestinal mucosa[20].

In this study, we developed the MTG-containing poloxamer and PC, and then characterized the rheological properties of the MTG containing the multidrug (phenylephrine hydrochloride, lidocaine hydrochloride, prednisolone acetate, and ZnO). Furthermore, we characterized the effect of ZnO on MTG in aspect of rheological as well as mucoadhesive properties.

Materials and methods

Materials

P407 (Pluronic F-127®) was obtained from BASF (Ludwigshafen, Germany). PC was supplied from BF Goodrich (Brecksville, OH, USA). ZnO, phenylephrine hydrochloride, prednisolone acetate, and lidocaine hydrochloride were purchased from Sigma (St. Louis, MO, USA). All other chemicals were of reagent grade and were used without further purification.

Preparation of formulations

MTGs were prepared according to the general cold method described by Choi et al.[4] and Miyazaki et al.[21] Briefly, various components such as phenylephrine hydrochloride (0.25% w/v), lidocaine hydrochloride (1.875% w/v), and PC (0.2% w/v) were solubilized in distilled deionized water and then allowed to dissolve overnight at 4°C. Then, to give gelation property depending on temperature, 13% or 14% (w/v) of P407 was slowly added to each solution with continuous agitation until a clear solution was obtained at 4°C. To provide the mucoadhesiveness, PC was also added into P407-based gel. PC content was fixed as 0.2% because of high viscosity and difficulty in administration of the MTG containing PC higher than 0.2%. Then, prednisolone acetate (0.05% w/v) and ZnO (7.5% w/v), a grain form with a diameter of 30–50 nm, were added into the MTGs after screening with a sieve (pore size, 75 μm).

Rheological measurements

Rheological measurements were performed using a Bohlin rheometer CVO (Bohlin Instruments, Mühlacker, Germany) with a cone and plate. The cone had a 40 mm diameter and a 4° angle. The sol–gel transition temperature was determined at 1 Hz of the oscillation mode and the temperature was increased in steps of 1°C/min from 15°C to 50°C[22]. The sol–gel transition (gelation) temperature was defined as the point where the elastic modulus (G') was half way between G' for the solution and G' for the gel[13]. The transition temperature graph was determined by sweeping temperature as a function of the elastic modulus.

The flow curves of MTGs were determined in the viscometry mode. For each sample, continuous variation of the shear rate (0.5–1000 s^{-1}) was applied and the resulting shear stress and viscosity were measured. To test the effect of temperatures, the measurements were made at 20°C and 37°C[9]. Each data point was the mean of at least three analyses. Error bars have been omitted to retain clarity; however, in all cases the coefficient of variation of replicate analyses was less than 5%.

Evaluation of mucoadhesive force

The mucoadhesive strength was determined using a TA-XT Plus Texture Analyzer (Stable Micro Systems, surrey, UK) in adhesion mode, as previously described[23]. Briefly, rectal mucosal tissues were removed from Sprague–Dawley rats and horizontally attached to the lower end of an analytical probe using a rubber band. Samples of each formulation were placed under the probe and the probe was lowered until the rectal tissues contacted the surface of the sample. Upon making contact between the tissues and the sample, a constant force of 0.1 N was imposed for 1 min to ensure intimate contact. The mucoadhesive strength of the samples was determined by measuring the resistance to the withdrawal of

the probe (maximum detachment force in Newton 'N') reflecting the mucoadhesion of the gel with the mucus. The study was performed in triplicate at room temperature.

Measurement of the work required to expel each formulation from a syringe

The work required to expel each formulation from a syringe was measured at room temperature using a Stable Micro Systems texture analyzer in compression mode, as previously described[8]. Briefly, liquid forms of MTGs were carefully packed into identical 1-mL plastic syringes to a height of 30 mm, avoiding the introduction of air bubbles. Then, the syringe was vertically clamped with the opening part downward. Although the opening of the syringe was not closed, MTG solution in the viscous sol state did not leak out from the syringe before starting the measurement. The analytical probe was then lowered until initial contact with the plunger of the syringe was observed. The probe was lowered at a constant speed (2.0 mm/s) through a distance of 30 mm until all the contents were forced out from the syringe. The work required to expel all the contents from the syringe was determined from the area under the force–time curve recorded during the compression of the plunger.

In vitro drug release study

In vitro release experiments were carried out according to the method in a previous work[24]. MTGs were packed into a semipermeable membrane tube where both sides of the tube were tied up with a thread to prevent leakage. The semipermeable membrane tube was then placed into the dissolution medium, phosphate buffer (pH 6.8). The medium was maintained at 37 ± 1°C and stirred at 100 rpm. At various time intervals, 10 mL of the dissolution medium was collected and the same volume of buffer was added. This experiment was carried out in triplicate.

The filtrate was analyzed by atomic absorption spectrophotometer (Shimadzu, Tokyo, Japan) to determine the amounts of ZnO released at each time interval. The levels of other drugs such as phenylephrine hydrochloride, lidocaine hydrochloride, and prednisolone acetate were analyzed using an HPLC with UV detector (Shimadzu). Both atomic absorption spectrophotometry and HPLC method were validated before analysis. The amounts of lidocaine hydrochloride, phenylephrine, and prednisolone acetate dissolved were monitored at a wavelength of 269 nm as a previous report[25]. Each 50 μL of sample was injected onto a C_{18} Luna column (150 × 4.6 mm, Phenomenex, Torrance, CA, USA). The mobile phase consisted of methanol and phosphate buffer (3 : 7, v/v) with a flow rate of 0.3 mL/min. The UV detector was set at 269 nm.

Statistical analysis

Statistical analysis of data was performed to compare the differences among each group using Student *t*-test and ANOVA ($P < 0.05$).

Results and discussion

Thermosensitive rheological properties

To determine the sol–gel transition temperature of MTGs, the elastic modulus (G') of the MTGs was measured at different temperatures. The elastic modulus and transition temperatures of the MTGs were analyzed by altering the addition of ZnO. The sol–gel transition temperatures of both MTGs (13% and 14%, w/v) were lowered by addition of ZnO (Figure 1). The transition temperatures for 13% and 14% MTGs containing ZnO were 32.21°C (Figure 1a) and 29.01°C (Figure 1b), respectively, as based on the definition[6]. Generally, if the sol–gel transition temperature is lower than 25°C, the formation of gel might occur at room temperature (20°C) leading to difficulties in manufacturing, handling, and administering it, whereas a liquid dosage form still remains at the physiological temperature if the sol–gel transition temperature is higher than the physiological temperature (37°C)[4,9,26]. As the temperature increased, the elastic modulus and rheological behaviors were changed into the gel-likeflow (non-Newtonian flow). The increase in elastic modulus (G') according to the temperature means the gel formation because the increase of this value, related to the storage of energy, means the solid-like behavior of the system[6,24]. Given the positive relationship between the viscosity and elasticity modulus, distinct change of elasticity modulus values of MTG was expected upon temperature change from 20°C to 37°C. However, the 13% MTG without ZnO showed no change of elasticity modulus depending on temperature (Figure 1a). Moreover, it was reported that the elastic modulus values of 16% or 17% of P407 increased under 40°C in the presence of propanediol-1,2[27]. In the presence of ZnO, the elastic modulus of 13% MTG was 3281.7 Pa (Figure 1a), which was about one-third of that of 14% MTG modulus, 9582.7 Pa (Figure 1b). Because monopolymeric formulation composed of 15% P407 exhibited shear-thinning behavior[28], the MTGs composed of P407 less than 15% were prepared to investigate the effect of ZnO on the rheological behavior of the MTG.

The thermosensitive rheological property of the two MTGs (13 and 14 w/v%) was also evaluated by rheological parameters, such as shear stress and shear rate, and by rheological behavior with temperature (Figure 2 and Table 1). From a different aspect, the transition of sol–gel

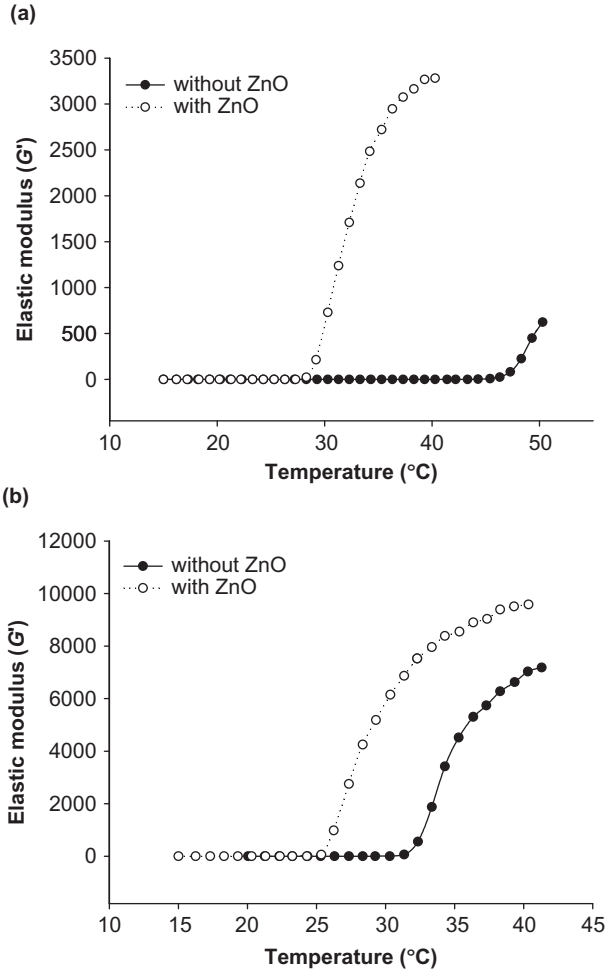

Figure 1. Temperature-dependent changes of the elastic modulus. The sol–gel transition temperature was determined in the oscillation mode. As the temperature was increased by 1°C/min, each elastic modulus (G') of both (a) 13% MTG and (b) 14% MTG was analyzed according to either with ZnO or without ZnO. The transition temperature curve was analyzed by sweeping temperature as a function of the elastic modulus.

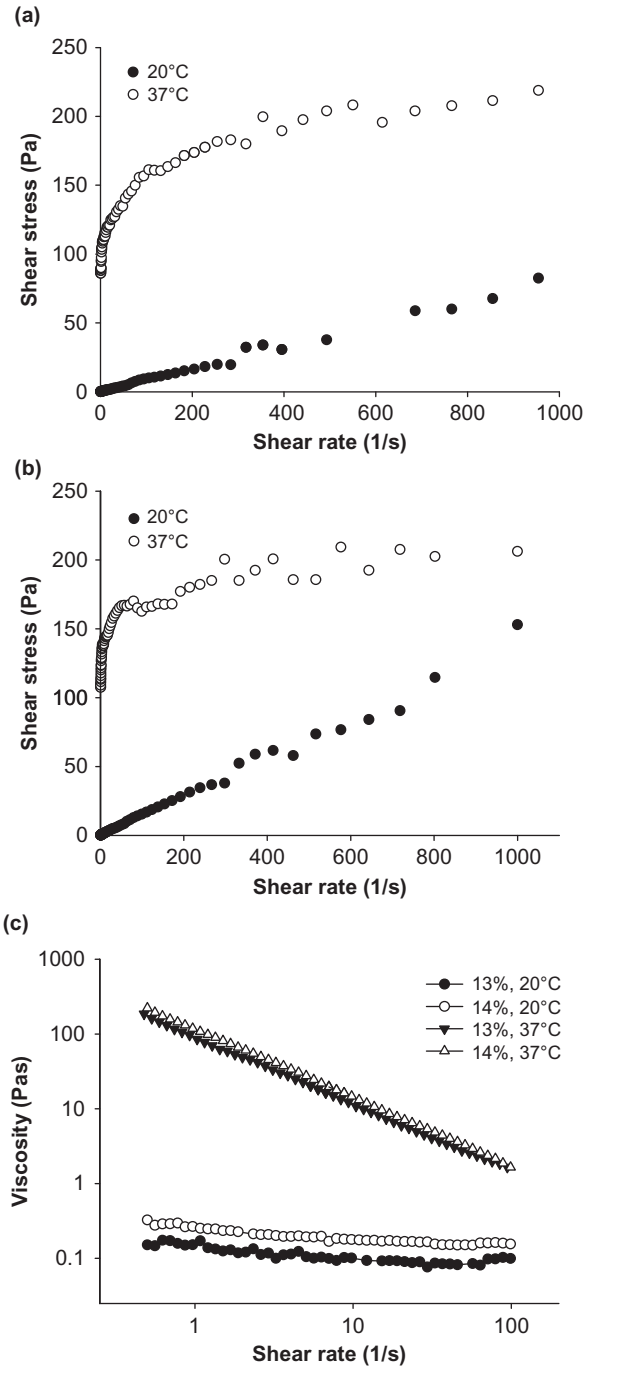

Figure 2. Flow curves and shear viscosity of MTGs with ZnO at different temperatures of 20°C and 37°C. Each 1 ml of two formulations was inserted into the rheometer and then was determined in the viscometry mode. For each sample, continuous variation of the shear rate was applied from 0.5 to 1000 s^{-1} and the shear stress was determined. The flow curves of (a) 13% MTG with ZnO and (b) 14% MTG with ZnO were measured and each shear viscosity of MTGs as a function of shear rate (c) was also determined.

could be explained by the rheological parameters[29–32]. The shear stress (τ) depended on the shear rate ($\dot{\gamma}$) as shown in Figure 2a and b, and it was found that the curves of rheogram fit to the Herschel–Bulkley model adequately (Table 1). Briefly, the Herschel–Bulkley model is represented as $\tau = \tau_0 + K(\dot{\gamma})^n$, where τ is the shear stress, τ_0 the yield stress, $\dot{\gamma}$ the shear rate, K the consistency coefficient, and n the flow behavior index[33]. The flow behavior index n value of two formulations were nearly equal to 1 at 20°C, indicating both 13% and 14% formulations behaved in a Newtonian pattern, whereas both rheograms of two formulations showed a non-Newtonian behavior of the pseudoplastic flow with yield values. Based on the Herschel–Bulkley model, although the yield value (τ_0) was considered as negligible at 20°C, it increased considerably at 37°C. The increase in the yield value indicates a gradual strengthening of the three-dimensional network structure of the gels. In addition, the shear viscosity of both 13% and 14% MTGs at different temperatures as a function of the

Table 1. Herschel–Bulkley parameters resulting from the MTGs at various temperatures.

Contents of P407 (%)	Temperature (°C)	Yield value, τ_0 (Pa)	Viscosity, K (Pa·S)	Rate constant, n
13	20	0.05	0.10	0.97
	37	54.06	36.69	0.22
14	20	0.66	0.12	1.02
	37	62.79	179.70	0.06

shear rate was also measured (Figure 2c). As the shear rates increased from 0.5 to 100, the viscosity dropped 111.5- and 134.2-fold for the formulation with 13% and 14% P407, respectively, because of the formation of gel structure induced by temperature.

Rheological behaviors can be explained by the power law constitutive equation written as follows: $\eta = m.\bar{y}^{n-1}$, where η is the viscosity, $\bar{y}$ the shear rate, m the consistency index, and n the flow index[9,26]. Based on the power law model, both consistency index (m) and flow index (n) of the two MTGs were calculated (Table 2). Flow index of two MTGs closely approached 1 at room temperature (20°C) which means the Newtonian behavior. However, the flow index was decreased dramatically at physiological temperature (37°C). Moreover, the percentage of P407 may affect the extent of shear-thinning comparing 13% and 14% MTGs. When comparing consistency index (m), the m value of 14% MTG is slightly higher than 13% MTG.

Based on these parameters such as yield value, viscosity, and rate constant, it can be explained that the increase in temperature to physiological temperature affects the sol–gel transition[26,34]. For the topical formulations through rectal route, the yield value must be sufficiently low to permit the removal from the syringe at room temperature and to facilitate spreading on the administered sites and yet sufficiently high to prevent the preparation leaking out from the administered sites. In addition, the similar results were achieved in aspect of shear viscosity in Figures 2c and 4b.

Mucoadhesive force and syringeability

To evaluate indirectly the retention of MTG in rectal site, the mucoadhesive force and syringeability of two MTGs were measured. When comparing 13% and 14% MTGs without ZnO, the mucoadhesive force of 14% MTG dramatically improved about 80% higher than that of 13% MTG as shown in Figure 3a. In detail, the mucoadhesive force of MTGs with ZnO improved about 89% as the content of P407 increased from 13% to 14%. Considering the influence of ZnO on the mucoadhesiveness of MTG, the 13% MTG with ZnO was about 26% higher than that of without ZnO ($P < 0.001$). The mucoadhesive force of 14% MTGs with ZnO increased about 33% higher than that of without ZnO ($P < 0.01$). As a result, the syringeability depended on the content of P407 and this value was slightly increased whether ZnO exists or not (Figure 3b). However, the effect of ZnO on the syringeability was not statistically different.

The mucoadhesiveness of MTGs was increased by the addition of ZnO. In general, as the rectal mucosal

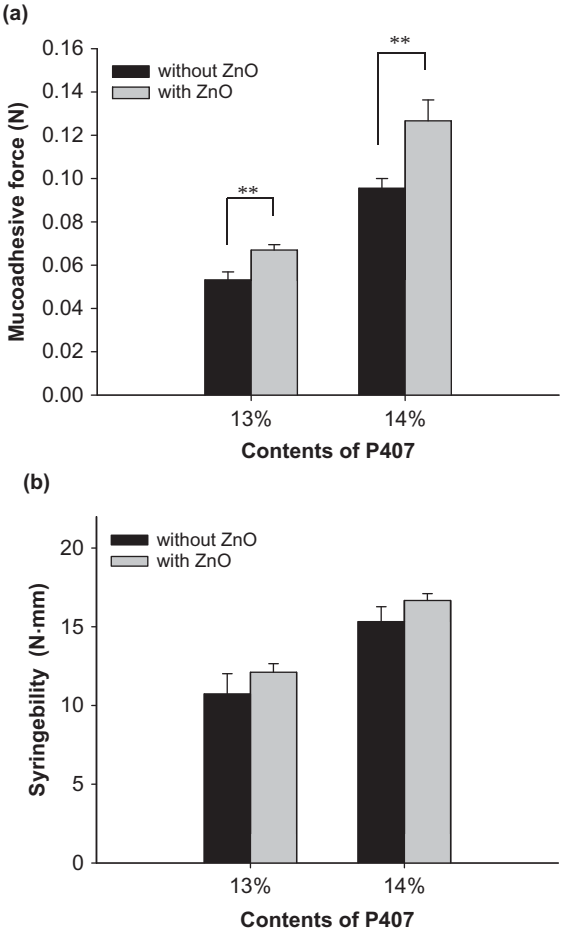

Figure 3. (a) Mucoadhesive force and (b) syringeability of MTGs. The mucoadhesive force of 13% and 14% MTGs either with ZnO or without ZnO was measured using a texture analyzer in adhesion mode. The mucoadhesive force was determined by the resistance to the withdrawal of the probe reflecting the mucoadhesion of the MTG with mucus. The syringeability was determined using a texture analyzer in compression mode. The work required to expel all the contents from the syringe was determined from the area under the force–time curve recorded during the compression of the plunger. Results of mucoadhesiveness ($n = 5$) and syringeability ($n = 3$) represent mean ± standard deviation (*$P < 0.01$, **$P < 0.001$).

Table 2. Power law parameters of the MTGs at various temperatures.

Contents of P407 (%)	Temperature (°C)	Consistency index, m	Flow index, n
13	20	0.14	0.86
	37	90.81	0.08
14	20	0.26	0.86
	37	115.40	0.10

membranes consist of oligosaccharide chains with L-fucose and sialic acid, the carboxyl group in PC can strongly bind to oligosaccharide chains, resulting in strong mucoadhesiveness[35]. Moreover, it has been proposed that the interactions between the mucus and the mucoadhesive polymer are the results of secondary binding, mainly hydrogen bond, and physical entanglement[36]. In addition, ZnO affected the mucoadhesive property of MTGs[21]. ZnO, as an astringent, improved the mucoadhesiveness of 13% and 14% MTGs, which is due to the presence of partially ionized metal compounds on the surface of the polymer. Cationic metal compounds such as ZnO can interact with negatively charged glycosubstances such as sialic acid and L-fucose group on the mucosal membrane surface because of the affinity with mucin chains[20]. As shown in Figure 3a, the mucoadhesive force statistically increased in both formulations, but with little effects on the syringeability because the slight increase is not significantly statistical. With respect to the simultaneous function, ZnO could be an effective agent of MTGs because it could be considered that the ZnO slightly increased the mucoadhesiveness but not syringeability. The water-insoluble metal compounds can be incorporated into the polymer by one of the following mechanisms: (a) physical mixtures which result in entrapment of the metal compound; (b) ionic interaction between metal compound and polymer; (c) surface modification of the polymers which would result in exposed metal compound on the surface; (d) coating techniques such as fluidized bed, pan coating, or any similar methods known to those skilled in the art, which produce a metal compound enriched layer on the surface of the device[20].

In vitro drug release from MTG

The release studies of various components such as phenylephrine hydrochloride, lidocaine hydrochloride, prednisolone acetate, and ZnO in the MTGs were performed in each formulation of MTGs as shown in Figure 4a and b. Although the viscosity of two MTGs was 36.69 Pa·S in

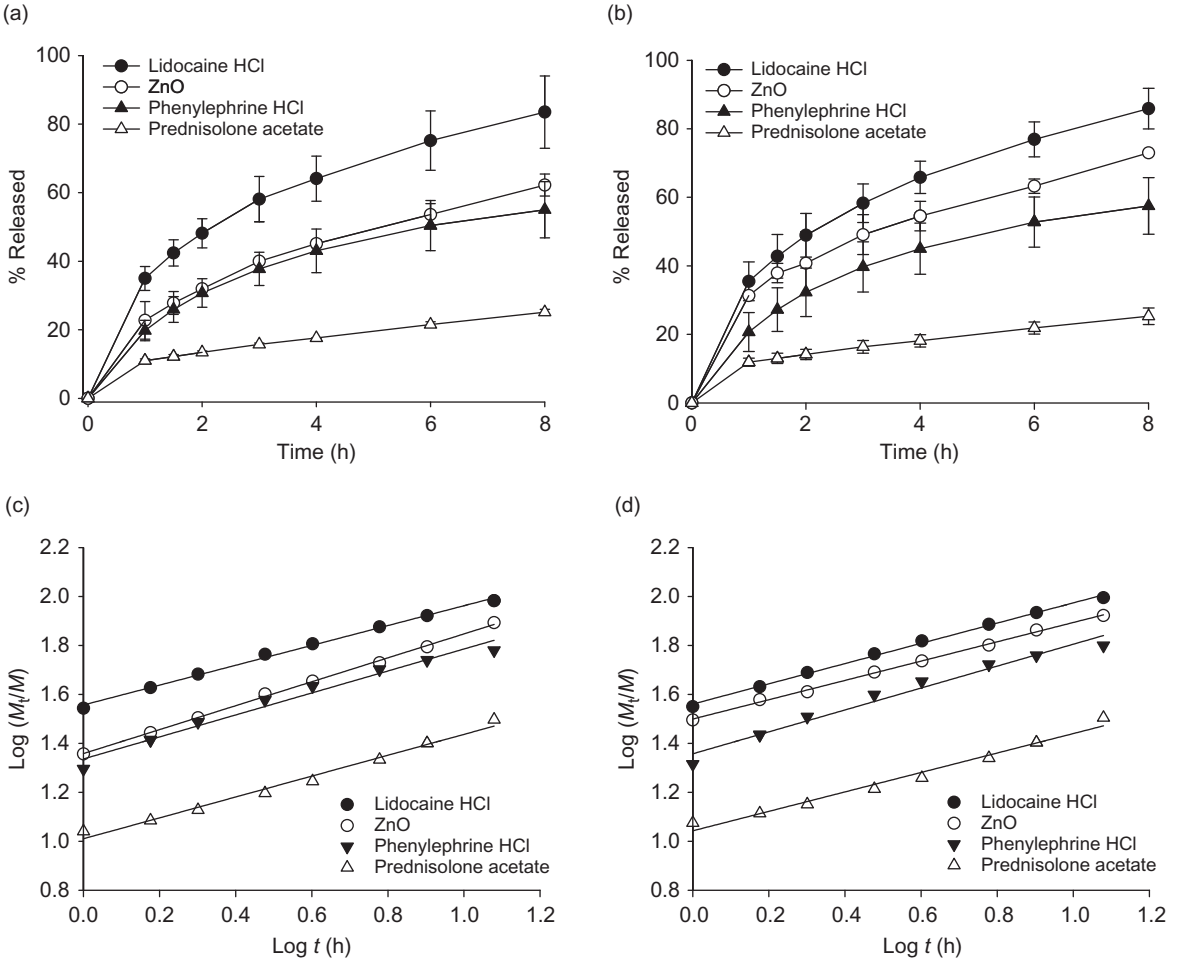

Figure 4. In vitro release of various drugs from the MTGs containing (a) 13% MTG and (b) 14% MTG and the log value of released fraction from (c) 13% MTG and (d) 14% MTG. Phenylephrine hydrochloride, lidocaine hydrochloride, prednisolone acetate, and ZnO were released at phosphate buffer (pH 6.8) and then quantitatively analyzed by HPLC and atomic absorption spectrophotometer. Results represent mean ± standard deviation ($n = 3$).

13% P407 and 179.70 Pa·S in 14% P407 at 37°C (Table 1) and the mucoadhesive forces of 14% MTG dramatically improved about 80% higher than that of 13% MTG, three components of drugs (phenylephrine hydrochloride, lidocaine hydrochloride, and prednisolone acetate) showed similar release profiles when comparing the release profiles of 13% and 14% MTGs. Briefly, in the phenylephrine hydrochloride, the percentages of release from 13% and 14% MTGs were 55.02 ± 8.20 and 57.46 ± 8.26, respectively. In the release of lidocaine hydrochloride, the percentage of release from 13% and 14% MTGs were 83.50 ± 10.55 and 85.88 ± 5.92 and the percentage of prednisolone acetate of 13% and 14% MTGs were 25.12 ± 0.88 and 25.30 ± 2.43 due to the hydrophobic characteristics. In comparison of ZnO release profiles of two MTGs, the level of 14% MTG (72.96 ± 0.36%) was slightly higher than that of 13% MTG (62.23 ± 3.21%). Interestingly, the release percentages of each component were not significantly different between 13% and 14% MTG. Although higher polymer content could be expected to present slower release of component loaded in polymer gel, our results disagree with general release pattern by polymer. It might be due to one of the following reasons: (a) here we did not alter the mucoadhesive polymer content in MTG, which could alter the release patterns of components from polymeric gel; (b) the MTGs do not encounter water when we measure the viscosity and mucoadhesive force, but the MTGs upon in vitro release were exposed to the aqueous medium, in which some MTGs could exist as micelles to solubilize and promote release of drugs[7].

To investigate the mechanism of drug release, the release data of drugs were transformed to the general release equation using logarithmic transformations and least-squares regression analysis as follows (Figure 4c and d): $\log(M_t/M) = \log k + n \cdot \log t$, where M_t/M is the fraction of the released drug at time t; k is a constant incorporating structural and geometrical characteristics of the device; and n is the release exponent which may indicate the drug release mechanism. In Table 3 and Figure 4c–d, release kinetic parameters of four components of drugs were calculated and release component (n) was approximately 0.5, indicating Fickian diffusion patterns although the n values were slightly different[9,29]. Comparing to the kinetic constant (k), the k value could be ordered as follows; lidocaine hydrochloride > ZnO > phenylephrine hydrochloride > prednisolone acetate. Taken together, four components of drugs in MTG were slowly released although the lidocaine hydrochloride had relatively higher release profiles. The poloxamer system is one of the swelling-controlled systems that function by a process of continuous swelling of the polymer carrier that is associated with simultaneous or subsequent dissolution of the polymer carrier. In our results, the zero-order drug release from P407 gel formulations can be explained by the mechanism of dissolution-controlled release[37]. Poloxamer degradation involves the hydration of water-insoluble side groups that are converted to water-soluble polymers as a result of ionization, protonation, or hydrolysis of the groups.

Table 3. Release kinetic parameters of various drugs in the MTGs using logarithmic transformations and least-squares regression analysis.

P 407 (%)	Drugs	Release exponent, n	Kinetic constant, k	Correlation coefficient, r
13	Lidocaine HCl	0.4056	36.05	0.9982
	ZnO	0.4889	22.82	0.9994
	Phenylephrine HCl	0.4492	21.70	0.9868
	Prednisolone acetate	0.4265	10.24	0.9926
14	Lidocaine HCl	0.4136	36.36	0.9987
	ZnO	0.3945	31.58	0.9991
	Phenylephrine HCl	0.4478	22.77	0.9863
	Prednisolone acetate	0.3974	11.04	0.9894

Conclusions

The MTGs with ZnO, as an astringent as well as an enhancing agent of mucoadhesive property, were effective rectal formulation for the treatment of hemorrhoid in aspect of rheological properties and mucoadhesiveness. Furthermore, it was considered that the MTGs with ZnO could have a potential to be developed as a more convenient and effective rectal delivery system.

Declaration of interest

This research was supported by a grant from the Ministry of Education and Human Resources Development (MOE), the Ministry of Commerce, Industry and Energy (MOCIE), and the Ministry of Labor (MOLAB) through the fostering project of the Laboratory of Excellency, Republic of Korea. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1. Hardy A, Chan CLH, Cohen CRG. (2005). The surgical management of hemorrhoids–a review. Dig Surg, 22:26–33.
2. Altomare DF, Roveran A, Pecorella G, Gaj F, Stortini E. (2006). The treatment of hemorrhoids: Guidelines of the Italian Society of Colo-Rectal Surgery. Tech Coloproctol, 10:181–6.
3. Briel JW, Zimmerman DDE, Schouten WR. (2000). Treatment of acute strangulated internal hemorrhoids by topical

application of isosorbide dinitrate ointment. Int J Colorectal Dis, 15:253–4.
4. Choi HG, Jung JH, Ryu JM, Yoon SJ, Oh YK, Kim CK. (1998). Development of in-situ gelling and mucoadhesive acetaminophen liquid suppository. Int J Pharm, 165:33–44.
5. Yun MO, Choi HG, Jung JH, Kim CK. (1999). Development of a thermo-reversible insulin liquid suppository with bioavailable enhancement. Int J Pharm, 189:137–45.
6. Choi HG, Lee MK, Kim MH, Kim CK. (1999). Effect of additives on the physicochemical properties of liquid suppository bases. Int J Pharm, 190:13–9.
7. Park JS, Oh YK, Yoon H, Kim JM, Kim CK. (2002). In situ gelling and mucoadhesive polymer vehicles for controlled intranasal delivery of plasmid DNA. J Biomed Mat Res Part A, 59:144–51.
8. Park JS, Oh YK, Kang MJ, Kim CK. (2003). Enhanced mucosal and systemic immune responses following intravaginal immunization with human papillomavirus 16L1 virus-like particle vaccine in thermosensitive mucoadhesive delivery systems. J Med Virol, 70:633–41.
9. Chang JY, Oh YK, Kong HS, Kim EJ, Jang DD, Nam KT, et al. (2002). Prolonged antifungual effects of clotrimazole-containing mucoadhesive thermosensitive gels on vaginitis. J Control Release, 82:39–50.
10. Kim JK, Kim MS, Park JS, Kim CK. (2009). Thermo-reversible flurbiprofen liquid suppository with HP-β-CD as a solubility enhancer: Improvement of rectal bioavailability. J Inclusion Phenom Macrocyclic Chem, 64:265–72.
11. Merril EW, Pekala RW. (1987). Hydrogel for blood contact. In: Peppas NA, ed. Hydrogels in medicine and pharmacy, vol. III. Bocoraton, FL: CRC Press.
12. BASF Performance Chemicals. (1993). FDA and EPA status. North Mount Olive, NJ: BASF.
13. Edsman K, Carlfors J, Petersson R. (1998). Rheological evaluation of poloxamer as an in situ gel for ophthalmic use. Eur J Pharm Sci, 6:105–12.
14. Ludwig A. (2005). The use of mucoadhesive polymers in ocular drug delivery. Adv Drug Deliv Rev, 57:1595–639.
15. Papageorgiou PP, Chu AC. (2000). Chloroxylenol and zinc oxide containing cream (Nels cream) vs. 5% benzoyl peroxide cream in the treatment of acne vulgaris. A double-blind, randomized, controlled trial. Clin Dermatol, 25:16–20.
16. Sawai J. (2003). Quantitative evaluation of antibacterial activities of metallic oxide powders (ZnO, MgO and CaO) by conductimetric assay. J Microbiol Method, 54:177–82.
17. Adams KL, Lyon DY, Alvarez PJJ. (2006). Comparative eco-toxicity of nanoscale TiO_2, SiO_2, and ZnO water suspensions. Water Res, 40:3527–32.
18. Colon G, Ward BC, Webster TJ. (2006). Increased osteoblast and decreased Staphylococcus epidermidis functions on nanophase ZnO and TiO_2. J Biomed Mater Res A, 78:595–604.
19. Sharma J, Singla AK, Dhawan S. (2003). Zinc-naproxen complex: Synthesis, physicochemical and biological evaluation. Int J Pharm, 260:217–27.
20. Jacob JS, Mathiowitz E. (2002). Method and compositions for enhancing the bioadhesive properties of polymers. US patent no. 6368586.
21. Miyazaki S, Ohkawa Y, Takada M, Attwood D. (1992). Antitumor effect of pluronic F-127 gel containing mitomycin C on sarcoma-180 ascites tumor in mice. Chem Pharm Bull, 40:2224–6.
22. Mulik R, Kulkarni V, Murthy RSR. (2009). Chitosan-based thermosensitive hydrogel containing liposomes for sustained delivery of cytarabine. Drug Dev Ind Pharm, 35:49–56.
23. Jones DS, Woolfson AD, Brown AF, Coulter WA, McClelland C, Irwin CR. (2000). Design, characterization and preliminary clinical evaluation of a novel mucoadhesive topical formulation containing tetracycline for the treatment of periodontal disease. J Control Release, 67:357–68.
24. Yong CS, Yang CH, Rhee JD, Lee BJ, Kim DC, Kim DD, et al. (2004). Enhanced rectal bioavailability of ibuprofen in rats by poloxamer 188 and menthol. Int J Pharm, 269:169–76.
25. Erk N, Kartal M. (1998). Simultaneous high performance liquid chromatographic and derivative ratio spectra spectrophotometry determination of chlorpheniramine maleate and phenylephrine hydrochloride. Il Farmaco, 53:617–22.
26. Owen DH, Peters JJ, Katz DF. (2000). Rheological properties of contraceptive gels. Contraception, 62:321–26.
27. Koffi AA, Agnely F, Ponchel G, Grossiord JL. (2006). Modulation of the rheological and mucoadhesive properties of thermosensitive poloxamer-based hydrogels intended for the rectal administration of quinine. Eur J Pharm Sci, 27:328–35.
28. Jones DS, Bruschi ML, de Freitas O, Gremião MPD, Lara EHG, Andrews GP. (2009). Rheological, mechanical and mucoadhesive properties of thermoresponsive, bioadhesive binary mixtures composed of poloxamer 407 and carbopol 974P designed as platforms for implantable drug delivery systems for use in the oral cavity. Int J Pharm, 372:49–58.
29. Peppas NA. (1985). Analysis of Fickian and non-Fickian drug release polymers. Pharm Acta Helv, 60:110–1.
30. Fawaz F, Koffi A, Guyot M, Millet P. (2004). Comparative in vitro-in vivo study of quinine rectal gel formulations. Int J Pharm, 280:151–62.
31. Shaheen SM, Takezoe K, Yamaura K. (2004). Effect of binder additives on terbutaline hydrogels of a-PVA/NaCl/H_2O system in drug delivery: I. Effect of gelatin and solution starch. Biomed Mater Eng, 14:371–82.
32. El-Kamel A, El-Khatib M. (2006). Thermally reversible in situ gelling carbamazepine liquid suppository. Drug Deliv, 13:143–8.
33. Herschel WH, Bulkley R. (1926). Konsistenzmessungen von Gummi-Benzollosungen. Kolloid Z, 39:291–300.
34. Grattoni AC, Al-Sharji HH, Yang C, Muggeridge AH, Zimmerman RW. (2001). Rheology and permeability of crosslinked polyacrylamide gel. J Colloid Interface Sci, 240:601–07.
35. Choi HG, Kim CK. (2000). Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva. J Control Release, 68:397–404.
36. Mortazavi SA, Carpenter BG, Smart JD. (1993). A comparative study on the role played by mucus glycoproteins in the rheological behavior of the mucoadhesive/mucosal interface. Int J Pharm, 94:195–201.
37. Zhang L, Parsons DL, Navarre C, Kompella UB. (2002). Development and in-vitro evaluation of sustained release poloxamer 407 (P407) gel formulations of ceftiofur. J Control Release, 85:73–81.