Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 356 (2008) 88–94
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Gastroretentive drug delivery system of DA-6034, a new flavonoid derivative, for the treatment of gastritis

Sun Woo Jang [a], Jung Woo Lee [a], Sung Hyun Park [a], Jeong Hoon Kim [a], Moohi Yoo [a], Dong Hee Na [b], Kang Choon Lee [c,*]

[a] *Research Laboratory, Dong-A Pharmaceutical Company, 47-5 Sanggal-dong, Kiheung-ku, Yongin 446-905, South Korea*
[b] *College of Pharmacy, Kyungsung University, 110-1 Daeyeon-dong, Nam-ku, Busan 608-736, South Korea*
[c] *Drug Targeting Laboratory, College of Pharmacy, SungKyunKwan University, 300 Chonchon-dong, Jangan-ku, Suwon 440-746, South Korea*

Received 20 August 2007; received in revised form 30 November 2007; accepted 27 December 2007
Available online 9 January 2008

Abstract

A gastroretentive drug delivery system of DA-6034, a new synthetic flavonoid derivative, for the treatment of gastritis was developed by using effervescent floating matrix system (EFMS). The therapeutic limitations of DA-6034 caused by its low solubility in acidic conditions were overcome by using the EFMS, which was designed to cause tablets to float in gastric fluid and release the drug continuously. The release of DA-6034 from tablets in acidic media was significantly improved by using EFMS, which is attributed to the effect of the solubilizers and the alkalizing agent such as sodium bicarbonate used as gas generating agent. DA-6034 EFMS tablets showed enhanced gastroprotective effects in gastric ulcer-induced beagle dogs, indicating the therapeutic potential of EFMS tablets for the treatment of gastritis.

Keywords: DA-6034; Flavonoid derivative; Gastroretentive drug delivery; Effervescent floating matrix system; Gastroprotective effect

1. Introduction

Eupatilin (5,7-dihydroxy-3′,4′,6-trimethoxy flavone), the main component of extracts from Artemisiae plants, has been shown to possess anti-inflammatory and antioxidative activities (Seo and Surh, 2001). DA-6034 (7-carboxymethyloxy, 3′,4′,5-trimethoxy flavone; Fig. 1) is a new synthetic derivative of eupatilin, which has a local anti-inflammatory effect on intestinal mucosal membrane, and is now undergoing a phase 2 clinical study for the treatment of inflammatory bowel disease in Korea (Kim et al., 1999; Chung et al., 2006). Recently, DA-6034 was also found to have local a gastroprotective effect in a pharmacological study conducted in a gastric ulcer-induced rat model (Choi et al., 2007). However, the pharmacological effect of DA-6034 is limited due to its low solubility in the acidic gastric region.

Gastroretentive systems have been studied to increase bioavailabilities of drugs with narrow absorption window, or to enhance the local effects of drugs in the gastric region by delaying their gastric emptying (Davis, 2005). Many types of systems have been devised, e.g., high density, expandable, superporous hydrogel, bioadhesive, mucoadhesive, magnetic, and floating systems, to increase drug gastric residence times (Streubel et al., 2006). Of these the floating system, one of the most widely applied concepts for developing gastroretentive systems, causes tablets to become buoyant in the stomach and to continuously releases pharmacologic agents (Singh and Kim, 2000). Several types of floating systems have been devised, e.g., the hydrodynamically balanced system (HBS®), the gas generating system, the raft forming system, and the low density system (Bardonnet et al., 2006).

The objective of this study was to develop a gastroretentive drug delivery system for DA-6034 utilizing a floating mechanism to maximize its local gastroprotective effect. Initially, the solubility of DA-6034 was screened at various pH values and the effect of drug solubility on its oral gastroprotective effect was evaluated by administrating DA-6034 in the form of a

* Corresponding author. Tel.: +82 31 290 7704; fax: +82 31 290 7724.
E-mail address: kclee@skku.edu (K.C. Lee).

0378-5173/$ – see front matter © 2008 Published by Elsevier B.V.
doi:10.1016/j.ijpharm.2007.12.042

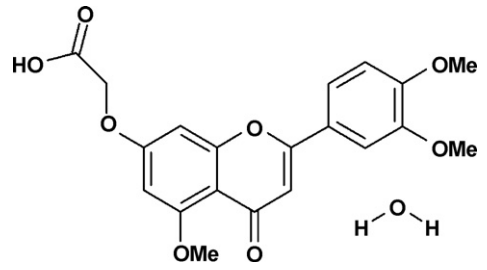

Fig. 1. Chemical structure of DA-6034 (7-Carboxymethyloxy-3′,4′,5-trimethoxyflavone monohydrate, MW 404.37, $C_{20}H_{18}O_8 \cdot H_2O$).

solution or suspension to rats with alcohol-induced ulcers (Mizui and Doteuchi, 1983). The effervescent floating matrix system (EFMS) was formulated using swelling polymers, a gas generating agent, erosion polymers, and solubilizers, and this mixture was pressed to form tablets by adding a lubricant. The formulation was optimized and its local gastroprotective effect was evaluated in a gastric ulcer-induced beagle dog model by gastric endoscopy.

2. Materials and methods

2.1. Materials

DA-6034 was synthesized by the Dong-A Pharmaceutical Company (Yongin, Korea). Hydroxypropylmethylcelluloses, HPMC 2208 (Metolose 90 SH-100,000) and HPMC 2910 (Pharmacoat 606), were purchased from Shin-Etsu Chemical (Tokyo, Japan). Kollidon CL and Poloxamer F68 were obtained from BASF (Florham Park, NJ), and Carbopol 934P was supplied by Noveon (Clevelend, OH). Eudragit L100-55 and Aerosil 200 were purchased from Degusa (Parsippany, NJ). Avicel PH 101 and magnesium stearate were obtained from Asahi Kasei (Tokyo, Japan) and Taihei Chemical (Kawaguchi, Japan), respectively. All other chemicals were of analytical grade.

2.2. Animals

Male Sprague–Dawley rats (Orient Co. Ltd., Seoul, Korea) weighing 230–300 g and female beagle dogs (Central Lab. Animal Inc., Gyeonggi-do, Korea) weighing 7–8 kg were used in this study. Animals were kept under standard laboratory conditions and given access to a standard diet and water ad libitum. All experiments were carried out in accordance with the Standard Operation Procedure for Animal Care and Experiments (SOP-ANC) of the Dong-A Pharmaceutical Company. All the experimental protocols using animals was approved by the Animal Ethical Committee of Dong-A Pharmaceutical Company.

2.3. Determination of the solubility of DA-6034 at different pH values

DA-6034 (200 mg) was added to vials containing 20 mL of deionized water and USP buffer solutions: hydrochloric acid buffers at pH 1.2 and 2.0, acid phthalate buffer at pH 3.0, acetate buffer at pH 4.0, and phosphate buffers at pH 6.0, 6.8 and 7.4. Vials were incubated at 37 °C and rotated using a dialysis tester at 40 rpm for 24 h. Solutions were then filtered through 0.45 μm membrane filters and the solubilized DA-6034 was analyzed by high-performance liquid chromatography (HPLC).

2.4. HPLC analysis

HPLC analysis of the above-mentioned DA-6034 solutions was performed using a Hitachi L2200 HPLC system (Tokyo, Japan), which consisted of an L2130 pump, an L2400 UV–vis detector and an Ezchrom Elite integrator (version 3.1.3). Samples (20 μL) were applied to an Inertsil ODS-II column (4.6 mm × 150 mm, 5 μm; GL Science, Tokyo, Japan) and isocratically eluted using a mobile phase consisting of 10 mM KH_2PO_4 (pH 2.5) and acetonitrile (75:25, v/v) at a flow rate 1 mL/min. UV absorbance was monitored at 330 nm.

The calibration curve was plotted from 0.1 to 200 μg/mL with a correlation coefficient greater than 0.999. Intra- and inter-day precision values were determined as the coefficient of variations (each $n = 3$). The intra-day precision ranged from 0.6 to 7.7%, and the accuracy was 96.0–100.5%. The inter-day precision was 0.7–5.8% with an accuracy of 98.4 to 102.6%.

2.5. Gastroprotective effect of DA-6034 in rats

Gastroprotective effects of oral DA-6034 were evaluated in an alcohol-induced ulcer rat model ($n = 5$) in order to compare the pharmacological efficacy of DA-6034 in solution and in suspension. DA-6034 solutions were prepared by dissolving DA-6034 in 0.1% (w/v) NaOH solution, and then the solution was adjusted to pH 7 by adding some of 0.1N HCl solution. DA-6034 was very soluble in 0.1% NaOH solution and there was no precipitation when the pH was adjusted to 7. DA-6034 suspensions were prepared in 1% HPMC solution. Solutions (0, 3, 10 mg/kg) and suspensions (0, 10, 100, 300 mg/kg) of DA-6034 were administered orally to rats that had been fasted for 24 h prior to the experiment. After 1 h, acute gastric damage was induced with 60% ethanol (in 150 mM HCl) administered intragastrically at 5 mL/kg (Choi et al., 2007). Stomachs were then removed to measure areas of gastric lesions. Rats were sacrificed by cervical dislocation.

2.6. Preparation of DA-6034 EFMS tablets

Effervescent floating matrix was formulated using HPMC, Carbopol 934P and Kollidon CL as a swelling polymer, sodium bicarbonate as a gas generating agent, Eudragit L100-55 or alginic acid as an erosion polymer, and Poloxamer F68 and SLS as a solubilizer. Before mixing, DA-6034 and other excipients were treated by being suitably size reduced using the sieve with the mesh number of 40. DA-6034 was mixed with the swelling polymers, gas generating agent, erosion polymers and solubilizers, and tablets were produced from this mix by pressing after adding lubricant using the wet granulation method with water as granulating solvent. In detail, mixtures of DA-6034, Avicel and calcium silicate were kneaded with water using a high-speed mixer and granulated by drying and sieving. Gran-

Table 1
Compositions of EFMS tablets used to study the effect of different ingredients on the dissolution of DA-6034 (mg/tablet)

Process	Object	Ingredient	NGR52 O1	NGR52 P1	NGR52 E4	NGR52 I6
Granulation	Active	DA-6034	30	30	30	30
	Filler	Avicel	80	80	80	80
		Ca silicate	20	20	20	20
	Total		130	130	130	130
Mixing	Solubilizer	SLS	20	0	0	20
		Poloxamer F68	30	30	0	30
	Gas generating agent	$NaHCO_3$	60	60	60	60
	Swelling polymer	Carbopol 934P	15	15	15	15
		HPMC 2208	50	50	50	50
		HPMC 2910	5	5	5	5
	Erosion polymer	Eudragit L100-55	40	40	40	–
		Alginic acid	–	–	–	40
	Lubricant	Aerosil 200	5	5	5	5
		Mg. stearate	5	5	5	5
Total (mg)			360	340	320	310

ules were mixed with additives, i.e., the gas generating agent, swelling polymers, erosion polymers, solubilizers and lubricants, and then pressed to form tablets by using single-punch tablet pressing machine (EK0, Korsch AG, Berlin, Germany). The EFMS tablet formulation was optimized by adjusting the levels of ingredients (Table 1).

2.7. Drug release study of DA-6034 EFMS tablets

Drug release study of EFMS DA-6034 tablets was performed using the USP paddle method with 900 mL of acidic buffer solutions at pH values of 1.2 (hydrochloric acid buffer), 2.0 (hydrochloric acid buffer), 3.0 (acid phthalate buffer) and 4.0 (acetate buffer) at $37.0 \pm 0.2\,^{\circ}C$ and a rotation speed of 50 rpm ($n = 6$). The DA-6034 EFMS tablet was putted into the dissolution medium without any other device for sinking, so the tablet floated on the surface of the medium after some lag time. The lag time to float, disintegration time and percentages of drug released were determined from the drug release study in order to optimize the tablet formulation. One milliliter of medium was withdrawn from the middle depth in the medium and it was centrifuged. Amounts of drug released on 15, 30, 45, 60, 90, 120 and 180 min after beginning of the study were determined by HPLC.

The in vitro release rates of different formulations were compared by calculating the similarity factors (f_2), which was calculated by the following formula:

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

n is the number of the time points, R_t is the value of the dissolution rate of reference tablet at time t, and T_t is the value of the dissolution rate of the test batch at time t. The f_2 value greater than 50 ensures sameness or equivalence of two curves (Shah et al., 1998).

2.8. Stability of DA-6034 EFMS tablets

The stability test was conducted according to the guideline of Korea Food and Drug Administration. Tablet stability was tested by evaluating dissolution rates using the dissolution test of samples contained in high-density polyethylene bottles at $40 \pm 2\,^{\circ}C$ and $75 \pm 5\%$ relative humidity for 4 months.

2.9. Gastroprotective effect of DA-6034 EFMS tablet in gastric ulcer-induced beagle dogs

The gastroprotective effect of DA-6034 EFMS tablet was evaluated using six female beagle dogs weighing 7–8 kg with gastric ulcers, which were produced as described below. The dogs were anesthetized as follows: atropine sulfate (0.04 mg/kg) was injected subcutaneously, and after 30 min, meditomidine (0.02 mg/kg) was injected intravenously, and midazolam (0.30 mg/kg) intramuscularly. Stomach walls were confirmed to be normal by gastric endoscopy and then ulcer was induced by making injury of uniform size, 3 mm in diameter and 3 mm in depth, using biopsy forceps. The region of injury was selected from the region of fundus, which could be easily inspected by endoscopic inspections. DA-6034 EFMS tablet or control tablet was orally administered to the dogs three times per day after meals for 16 days. Ulcer healing effects were evaluated using a 10-mm gastric endoscope (Olympus CLV-E). Gastric endoscopy was performed 0, 4, 8, 12 and 16 days after the procedures. On the mornings of inspection days, dogs were allowed only water and drug. Gastric endoscopy was performed 1–2 h after drug administration. Ulcer healing effects were estimated by grade ulcers from 0 to 5, where '0' indicated a normal gastric wall, '1' a scar with similar to normal gastric wall, '2' insignificant erosion with flare, '3' severe erosion with flare and swelling, '4' a gastric ulcer with a blood spot, and grade '5' a bleeding gastric ulcer. 'Erosion' means that inflammation was restricted in the mucosal membrane, and an 'ulcer' means that an inflammation invaded up to the muscular region. The statistical treatment was performed using Student t-test using

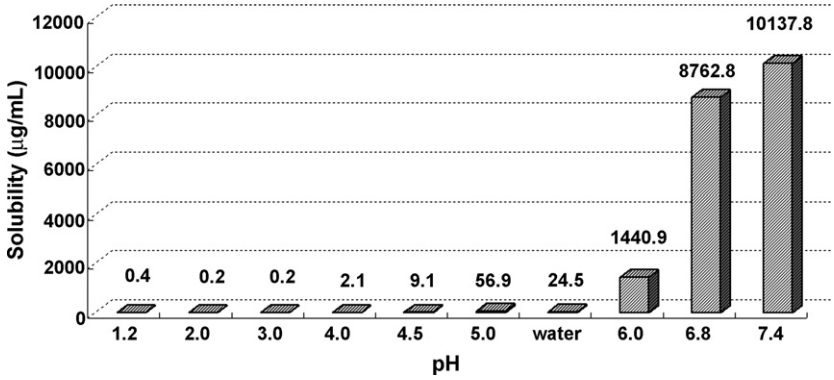

Fig. 2. Solubility of DA-6034 in buffer solutions at pH values of 1.2–7.4. The numbers above to the bar mean the amount of solubilized DA-6034 (μg)/mL of each medium.

Microsoft Excel Software. A p value <0.05 was considered as significant.

3. Results and discussion

The solubility of DA-6034 was studied in buffer solutions with pH values ranging from 1.2 to 7.4 (Fig. 2). While DA-6034 showed favorable solubility (>8 mg/mL) in neutral pH buffers, it showed poor solubility (<10 μg/mL) in the buffers with pH values of less than 5. Its poor solubility in acidic media indicates that DA-6034 would have a limited gastroprotective effect if it was administered in a conventional tablet formulation.

In order to investigate the relationship between the pharmacological efficacy and solubility of DA-6034, the oral gastroprotective effects of DA-6034 solutions and suspensions were evaluated using an alcohol-induced ulcer rat model ($n = 5$). DA-6034 solution was prepared by dissolving DA-6034 in 0.1% (w/v) NaOH solution, then the pH of the solution was adjusted to 7 by adding some of 0.1 M HCl solution, and suspensions were prepared by dispersing DA-6034 in 1% HPMC solution. As shown in Fig. 3, DA-6034 in solution showed a favorable gastroprotective effect at 10 mg/kg, whereas DA-6034 suspension did not have a significant effect at this dose as compared with control group. When 300 mg/kg was administered it was found to have the same effect as the above solution. This result indicates that the presence of soluble DA-6034 is required for its gastroprotective effect. Moreover, the use of gastroretentive system that releases drugs in a sustained manner is likely to enhance this effect.

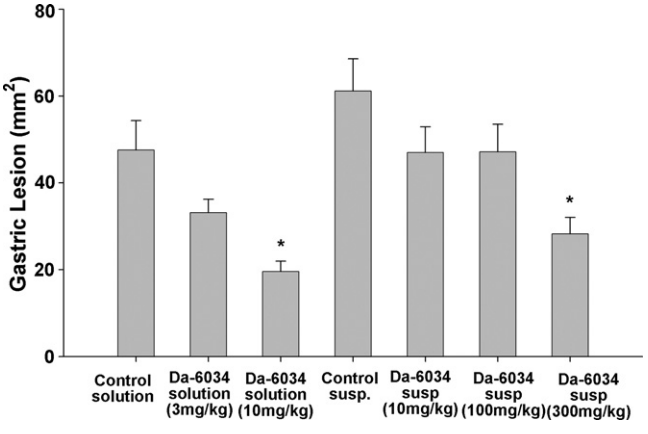

Fig. 3. Gastroprotective effects orally administered DA-6034 solution and suspension in the alcohol-induced rat ulcer model ($n = 5$). Doses of 0, 3 and 10 mg/kg were administered to solution group animals, and doses of 0, 10, 100 and 300 mg/kg were administered to suspension group animals. Gastroprotective effects were evaluated by assessing gastric legions as described in Section 2. Asterisk (*) indicates statistically significant difference with negative control ($p < 0.05$).

Effervescent floating matrix was formulated using sodium bicarbonate as gas generating agent, Carbopol and Kollidon CL as a swelling polymer, Eudragit L100-55 as erosion polymer, and Poloxamer and SLS as solubilizer. DA-6034 EFMS tablets could be produced by direct compression or wet granulation. However, the direct compression method was problematic due to a mix flowability problem attributed to the low density of DA-6034 (<0.3 g/mL), and thus, the wet granulation method was applied using water as the tablet binding solution. Any other granulating agent was not used. In the determination of flowability, Hausner's ratio and Carr's index of DA-6034 itself were 1.505 and 33.562%, respectively, whereas those of the DA-6034 granule were 1.108 and 9.714%, respectively. The value of Hausner's ratio less than 1.2 indicates good flowability of the material, whereas the value more than 1.2 indicates poor flowability. The Carr's index values of 5–10, 12–16, 18–21, and 23–28 indicates excellent, good, fair, and poor flow properties of the material, respectively (Schüssele and Bauer-Brandl, 2003).

The formulation of DA-6034 EFMS tablets was optimized by adjusting the types or amounts of gas generating agent, solubilizers, and erosion polymers (Table 1). The physico-chemical characteristics of DA-6034 EFMS tablets were summarized in Table 2. To optimize the amount of a gas generating agent,

Table 2
The physico-chemical properties of DA-6034 EFMS tablets

	NGR52-O1	NGR52-P1	NGR52-E4	NGR52-I6
Weight (mg)	0.10	0.07	0.04	0.06
Friability (%)	7.8	8.5	10.1	8.3
Thickness (mm)	4.6	4.4	4.2	4.1
Content (%)	98.7	101.5	99.3	99.0
Lag time[a] (min)	8.7	8.1	7.6	8.5

[a] The lag time was measured at pH 3.0.

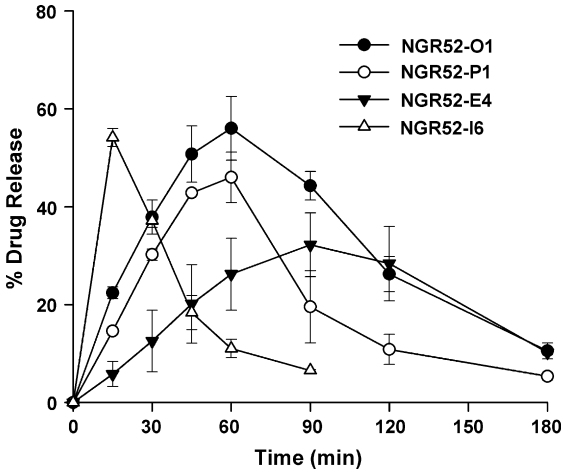

Fig. 4. Dissolution rates of DA-6034 EFMS tablets containing different amounts of solubilizers and erosion polymers at pH 3.0 ($n = 6$). The formulations used are detailed in Table 1.

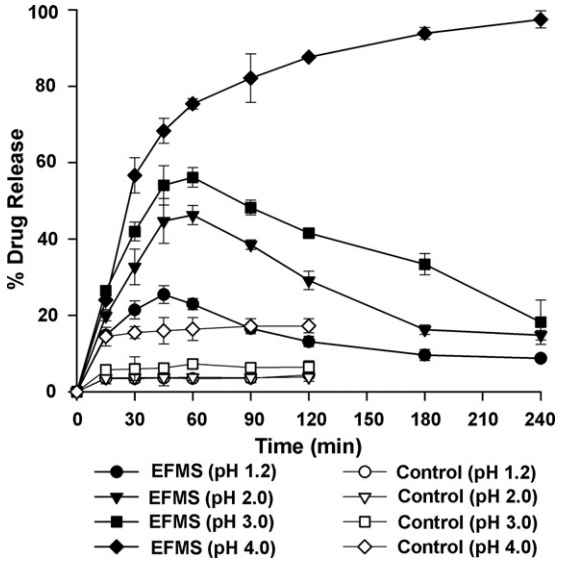

Fig. 5. Dissolution rates of DA-6034 EFMS tablets (NGR52-O1) in acidic buffer solutions (pH 1.2–4.0; $n = 6$).

DA-6034 EFMS tablets containing 30, 45 and 60 mg of sodium bicarbonate were prepared and their floating times were determined. Floating times of DA-6034 EFMS tablets was delayed by increasing buffer pH, because of reduced bicarbonate reaction. DA-6034 EFMS tablets floated after 1–2 min at pH 1.2, 2–3 min at pH 2, 8–9 min at pH 3, and 10 min at pH 4, but no significant differences in the lag time to float were observed after changing the amount of sodium bicarbonate (30–60 mg) within the range 10–18% on total tablet weight. EFMS tablet could not have floating property without swelling, but there was little difference in floating property with different swelling ability. So, there was no further study about the effect of various species of swelling polymer with different viscosity or molecular weight. The density of prepared formulation was 0.883 g / cm^3.

Fig. 4 shows the effects of solubilizers and erosion polymers on the dissolution of DA-6034 from DA-6034 EFMS tablets. The inclusion of Poloxamer and SLS in the matrix increased dissolution. Poloxamer (NGR52-O1 and NGR52-P1) significantly increased dissolution rates compared with tablets prepared without solubilizer (NGR52-E4) (Similarity factors, f_2, was 34.8 between NGR52-O1 and NGR52-E4, and 41.0 between NGR52-P1 and NGR52-E4, which ensure significant differences between each two tablet because of the value less than 50.). Dissolution rates were enhanced by adding SLS in the matrix with Poloxamer. As shown in the dissolution profile of NGR52-O1, SLS resulted in a delay of the recrystallization of the solubilized drug (The f_2 value was 44.1 between NGR52-O1 and NGR52-P1.). As an erosion polymer, Eudragit L100-55 appeared to be suitable for the optimal release of DA-6034. DA-6034 EFMS tablets prepared using alginic acid as erosion polymer (NGR52-I6) had the delay in floating times (8 min vs. 0.5 min with NGR52-O1), but more rapid disintegration times (18 min vs. 60 min for NGR52-O1) in acidic buffer (pH 1.2). Also, the recrystallization occurred more quickly than in EFMS tablets prepared with Eudragit (NGR52-O1, NGR52-P1 and NGR52-E4) as shown by their dissolution rate profiles (The f_2 values were 24.1 between NGR52-O1 and NGR52-I6, 28.4 between NGR52-P1 and NGR52-I6, and 27.8 between NGR52-E4 and NGR52-I6). It is believed that the rapid disintegration of DA-6034 EFMS tablets caused burst release of solubilized DA-6034 from the hydrated gel matrix, and then it was precipitated as soon as it contacted the acidic buffer solution. Consequently, NGR52-O1 prepared with Eudragit L100-55 40 mg, sodium bicarbonate 60 mg, SLS 20 mg and Poloxamer 30 mg in 360 mg tablets was chosen to be the most favorable formulation (standard tablet).

Fig. 5 shows drug release as determined by the dissolution test of standard DA-6034 EFMS (NGR52-O1) and control tablets containing DA-6034 in acidic buffer solutions with pH 1.2–4. The control tablet was prepared by the conventional wet granulation method without any solubilizers, gas generator, or swelling or tablet erosion-inducing polymers. Standard tablets swelled in the beginning of the dissolution test, and then floated within 1–2 min at pH 1.2 and 10 min at pH 4. DA-6034 was released from the hydrated gel matrix, which was continuously eroded for a period of approximately 1 h. Based on the visual obser-

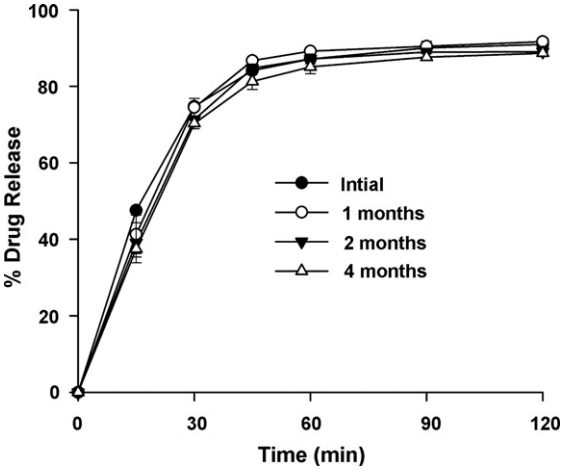

Fig. 6. Stability of DA-6034 EFMS tablets (NGR52-O1) in HDPE bottles at 75% RH and 40 °C for 4 months ($n = 6$).

vation, the release of DA-6034 from EFMS tablet appeared to be occurred by tablet disintegration in acidic pH and the disintegration was attributed to the presence of enteric polymer such as Eudragit. The presence of enteric polymer insoluble in acidic pH may lead to disruption of tablet after swelling. Maximum dissolution rate coincided with the time of complete tablet disintegration, at 1 h. At pH 1.2–3.0, dissolution rates increased up to ca. 1 h, and then decreased, due to recrystallization of DA-6034 after complete tablet disintegration, whereas no recrystallization occurred at pH 4. It was thought to be due to the pH-solubility characteristics of DA-6034, as shown in Fig. 2. In the pH from 1.2 to 3, the DA-6034 was extremely insoluble, less than 0.4 (g/mL, but the solubility became to be increased from the pH 4, more than 2.0 (g/mL. The increased solubility of drug might to be attributed to the resistance to recrystallization at pH 4.

Standard DA-6034 EFMS tablets had higher dissolution rates than control tablets in acidic buffer solutions. The standard tablets had maximum dissolutions of about 20% at pH 1.2, 50–60% at pH 2.0, 50–80% at pH 3.0, and 80–100% at pH 4. On the other hand, although control tablets completely disintegrated within 2 min, dissolution rate were only ∼5% at pH 1.2–3.0 and ∼20% at pH 4 (The f_2 values of drug releases between the standard DA-6034 EFMS tablet and the control tablet at different pH values were 39.7 at pH 1.2, 19.7 at pH 2, 16.8 at pH 3, and 10.2 at pH 4.). The improved dissolution of the standard DA-6034 EFMS tablets is believed to be due to the effect of solubilizers (Poloxamer and SLS) in the matrix and the alkalizing effect of the sodium bicarbonate.

During stability testing, standard DA-6034 EFMS tablets (NGR52-O1) showed no change in dissolution rate pattern when stored in HDPE bottles at 75% RH and 40 °C for 4 months (Fig. 6), which demonstrated the absence of an interaction between the drug and its matrix. The similarity factor (f_2) values for the dissolution rate profile of the tablet stored for 1 month, 2 months, and 4 months were 79.5, 76.9, and 70.0, respectively, which ensures equivalence of each curve (Shah et al., 1998).

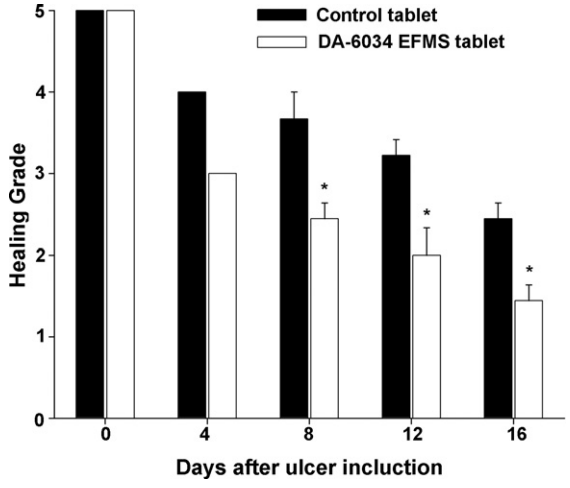

Fig. 7. Gastroprotective effect of DA-6034 EFMS tablet (NGR52-O1) in the beagle dogs. Grades indicate states of healing: grade 0: a normal gastric wall, grade 1: presence of a scar with similar to normal gastric wall, grade 2: presence of an insignificant erosion with flare, grade 3: presence of severe erosion with flare and swelling, grade 4: presence of gastric ulcer with a blood spot, grade 5: presence of a gastric ulcer with bleeding. Asterisk (*) indicates statistically significant difference with control tablet ($p < 0.05$).

The pharmacological efficacy of standard DA-6034 EFMS tablets was evaluated in the gastric ulcer-induced beagle dog model (Fig. 7). Gastric endoscopies of control group animals administered control tablet showed that a tendency toward a chronic condition from 8 to 12 days after administration (healing grade >3), whereas ulcers in animals administered standard DA-6034 EFMS tablets tended to heal from 4 days after drug administration (healing grade <3). These findings suggest that the standard formulation enhanced ulcer healing as compared with the control. In particular, ulcer regions in the animals treated with standard EFMS tablets were more quickly covered by a mucus film than those in the control group. These pharmacological efficacy results encourage us to conclude that the standard DA-6034 EFMS formulation has a substantial gastroprotective effect.

4. Conclusions

This study shows that the therapeutic limitations of DA-6034 with respect to the treatment of gastritis can be overcome by using an effervescent floating matrix composed of swelling polymers, a gas generating agent, erosion polymers and solubilizers. The dissolution of DA-6034 from the tablets in acidic media was significantly improved by using EFMS. Moreover, the gastroprotective effect observed in our beagle ulcer model indicates that the developed DA-6034 EFMS tablets offer a potential treatment for gastritis.

Acknowledgements

We thank Mr. Seul Min Choi, Mr. Kyung Koo Kang and Dr. Byung Ok Ahn for help with the rat animal study, and Dr. Young Won Lee for the help with the beagle experiments.

References

Bardonnet, P.L., Faivre, V., Pugh, W.J., Piffareti, J.C., Falson, F., 2006. Gastroretentive dosage forms: overview and special case of Helicobacter pylori. J. Control. Release 111, 1–18.

Choi, S.M., Shim, J.H., Kang, K.K., Ahn, B.O., Yoo, M., 2007. Gastroprotective effects of DA-6034, a new flavonoid derivative, in various gastric mucosal damage models. Dig. Dis. Sci. 52, 3075–3080.

Chung, H.J., Choi, Y.H., Choi, H.D., Jang, J.M., Shim, H.J., Yoo, M., Kwon, J.W., Lee, M.G., 2006. Pharmacokinetics of DA-6034, an agent for inflammatory bowel disease, in rats and dogs: Contribution of intestinal first-pass effect to low bioavailability in rats. Eur. J. Pharm. Sci. 27, 363–374.

Davis, S.S., 2005. Formulation strategies for absorption windows. Drug Discov. Today 10, 249–257.

Kim, Y.S., Son, M., Ko, J.I., Cho, H., Yoo, M., Kim, W.B., Song, I.S., Kim, C.Y., 1999. Effect of DA-6034, a derivative of flavonoid, on experimental animal models of inflammatory bowel disease. Arch. Pharm. Res. 22, 354–360.

Mizui, T., Doteuchi, M., 1983. Effects of polyamines on acidified ethanol-induced gastric lesions in rats. Jpn. J. Pharmacol. 33, 939–945.

Schüssele, A., Bauer-Brandl, A., 2003. Note on the measurement of flowability according to the European Pharmacopoeia. Int. J. Pharm. 257, 301–304.

Seo, H.J., Surh, Y.J., 2001. Eupatilin, a pharmacologically active flavone derived from Artemisia plants, induces apoptosis in human promyelocytic leukemia cells. Mutat. Res. 496, 191–198.

Shah, V.P., Tsong, Y., Sathe, P., Lie, J., 1998. In vitro dissolution profile comparison-statistics and analysis of the similarity factor, f_2. Pharm. Res. 15, 889–896.

Singh, B.N., Kim, K.H., 2000. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Control. Release 63, 235–259.

Streubel, A., Siepmann, J., Bodmeier, R., 2006. Gastroretentive drug delivery systems. Expert Opin. Drug Deliv. 3, 217–233.