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Development of an easily swallowed film formulation

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Abstract

We have developed an easily swallowed film formulation that swells and turns into a jelly instantaneously upon absorption of a small amount of saliva. The formulation's structure comprises a gelating layer on both faces of a drug-containing layer, and this structure restrains the elution of a drug in the mouth. Swelling experiments confirmed the instantaneous gelation when the gelating layer absorbs purified water. Fifteen seconds after immersion in purified water, the bulk modulus of the film formulation was less than 500 N/m^2, which is an appropriate value for easy swallowing by elderly people. A dissolution study confirmed the delayed dissolution of glimepiride as a model drug. In a clinical study, although the stagnation at the upper esophagus was observed with a gelatin capsule, the film formulation passed the esophagus and reached the stomach quickly.

Keywords: Film formulation; Gelation; Swallowing; Delayed dissolution; Video fluoroscopy

1. Introduction

According to the National Institute of Population and Social Security Research, aged citizens older than 65 years of age will comprise more than 25% of the population in Japan by 2013. Many elderly people have difficulty taking medicines because of their reduced swallowing capability (Palmer et al., 2000). Commercially available swallowing-assistive jelly has been developed as a functional food to help people swallow medicines (Morita, 2003), and is used by children, the elderly, and those who have a difficulty taking medicine.

To improve patient compliance, recently developed medicines have been produced as a jelly formulation (Hanawa et al., 2003) or disintegrating oral tablet (Corveleyn and Remon, 1997, 1998; Seager, 1998; Kuno et al., 2005; Harada et al., 2006). Although the jelly formulation is favored by people who have difficulty taking medicine, it lacks versatility in terms of stability because of its high moisture and the added cost. Some researchers focus on taste masking in a design of the oral disintegrating tablet. It was reported that the bitterness of pirenzepine hydrochloride and oxybutynin hydrochloride was taste-masked by the preparation of granules using aminoalkyl methacrylate copolymer (Ishikawa et al., 1999). The masking of the bitterness of triethyl citrate as an additive was achieved by means of the enteric coating with macrogol 6000 (Shimizu et al., 2003). Although the disintegrating oral tablet is an ideal formulation, there remains a problem of masking the bitterness of bitter-tasting drugs because the drug spreads within the mouth and remains in the cavity until it is swallowed (Fu et al., 2004).

The aim of this study was to develop a new type of oral formulation that would be useful for people who have difficulty swallowing and versatile for use with many drugs. We prepared a film formulation that was a dry film and easy to swallow. This formulation turns into a jelly instantaneously by absorbing a small amount of water. Elution of a drug inside the mouth is restrained by its structure with a gelating layer provided on both faces of a drug-containing layer, as shown in Fig. 1.

We evaluated the swelling property, the texture of the gelating layer, and the dissolution property of glimepiride as a model drug in the film formulation. We also used video fluoroscopy to investigate the motion of the film formulation in the throat and esophagus after the film formulation was swallowed by healthy

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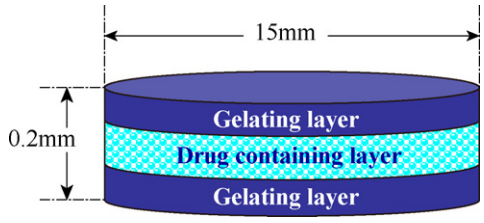

Fig. 1. Schematic structure of the film formulation.

subjects (Jones and Donner, 1991; Palmer et al., 2000; Morita, 2003).

2. Experimental

2.1. Materials

Polyvinyl alcohol (PVA, Gohsenol EG05T, Nippon Synthetic Chemical Industry Co., Ltd., Osaka, Japan), carboxyvinyl (CV) polymer (Carbopol 974P, CBC Co., Ltd., Tokyo, Japan) and polyvinylpyrrolidone (PVP, Kollidon K90, ISP Japan Ltd., Tokyo, Japan) were purchased. Acesulfame potassium was purchased from Maruzen Pharmaceuticals Co., Ltd., Hiroshima, Japan and used as a sweetener. Barium sulfate was kindly supplied by the Department of Rehabilitation Medicine, School of Medicine, Fujita Health University, Aichi, Japan. Titanium oxide (CR-EL, Ishihara Sangyo Kaisha, Ltd., Osaka, Japan) and calcium chloride (Tomita Pharmaceutical Co., Ltd., Tokushima, Japan) were purchased. Glycerin was purchased from ADEKA Corporation, Tokyo, Japan and used as a softener. Purified water was purchased from Kozakai Pharmaceuticals Co., Ltd., Tokyo, Japan. All excipients used in the film formulation are specified in the *Japanese Pharmacopoeia* (Hirokawa-shoten, 2006) and *Japanese Pharmaceutical Excipients* (Yakuji Nippo, 1998).

2.2. Preparation of the film formulations

2.2.1. The solution for the gelating layer (solution A)

The formulation is shown in Table 1. Into 85.8 g of purified water, 0.1 g of calcium chloride was added and then dissolved by stirring for 2 min, and 3.2 g of CV was then added slowly with stirring, and the stirring was continued for 15 min. Next, 3.2 g of PVA was added slowly with stirring and then dissolved completely by stirring for 1 h at 70 °C. The solution was returned to room temperature, and 0.1 g of acesulfame potassium and 1.1 g of glycerin were added, and stirring was continued for another 5 min.

Table 1
The formula of the film formulation

(A) Gelating layer (mg)	
Polyvinyl alcohol (partially hydrolyzed)	9.7
Carboxyvinyl polymer	3.2
Glycerin	1.1
Accesulfame potassium	0.1
Calcium cholide	0.1
Purified water[a]	85.8
Total	100.0
(B) Drug-containing layer (mg)	
Gurimepiride	4.1
Polyvinyl pyroridone	20.7
Glycerin	4.5
Titanium oxide	0.6
Purified water[a]	70.1
Total	100.0

[a] Removed during drying process.

2.2.2. The solution for the drug-containing layer (solution B)

This formulation is shown in Table 1. Into 70.1 g of purified water, 0.6 g of titanium oxide was added and then dispersed by stirring with a homogenizer for 5 min. Thereafter, 20.7 g of PVP was added slowly with stirring and then dissolved completely by stirring for 30 min. Next, 4.1 g of glimepiride and 4.5 g of glycerin were added, and the stirring was continued for 5 min.

2.2.3. Preparation of the film formulation

Solution A was degassed and coated on the siliconized surface of a 38 μm-thick polyethylene terephthalate film (S-PET) and heated at 80 °C for 5 min to prepare the gelating layer of about 5 μm thickness. Next, solution B was degassed and coated on the gelating layer and then dried for 5 min at 70 °C. A drug layer of about 50 μm thickness was prepared on the gelating layer, producing in sequential layers the drug-containing layer, gelating layer, and S-PET. Next, the sequence of S-PET, the gelating layer, the drug-containing layer, the gelating layer, and S-PET was prepared by laminating two pieces of the above double-layered sheet and heating at 100 °C. Finally, S-PET was removed from both sides, and the multilayered sheet was cut to a round shape with a diameter of 15 mm.

Using this method, the film formulation shown in Fig. 1 was prepared.

2.3. Swelling property of the gelating layer

2.3.1. Linear expansion coefficient in purified water

The gelating layer (1 cm × 1 cm square) was immersed in purified water. Specimens were taken 2, 4, 6, 8, 10, 15, 30, and 60 s after immersion, and the size of the side length was measured. The linear expansion coefficient (L) was defined as

$$L\,(\%) = \left[\frac{(L_1 - L_0)}{L_0}\right] \times 100,$$

where L_1: the side length of the gelating layer after immersion and L_0: the side length of the gelating layer before immersion.

2.3.2. Amount absorbed in purified water

The gelating layer (2 cm × 4 cm square) was weighed (W_1) and put into the stainless steel mesh basket. The weight after immersion in purified water in the basket was measured (W_2). Similarly, the weight after immersion was measured without the gelating layer (W_3). The amount absorbed in purified water was determined by the difference in weight with and without the

gelating layer. The absorbed amount (W) was defined as

$$W\,(\mathrm{g/g}) = \frac{(W_2 - W_1 - W_3)}{W_1}$$

2.4. Texture of the gelating layer during swallowing

The texture was determined by texture profile analysis (Bourne, 1978; Pons and Fizman, 1996; Shiozawa et al., 2002). The jelly was prepared by letting the gelating layer swell with an arbitrary amount of purified water. The stainless steel container (inner diameter, 20 mm; height, 15 mm) to measure the specimen in a creepmeter (RE2-33005B, Yamaden Co., Ltd., Tokyo, Japan) was filled up with the jelly described above. Each specimen was compressed twice using a plunger (20 mmØ, 13 mm height) at a constant speed of 10 mm/s. The output data were analyzed using software for texture analysis (TAS-3305, Yamaden Co., Ltd.).

2.5. Dissolution property

The dissolution of the model drug glimepiride from the film formulation was evaluated in accordance with USP 24 Dissolution 711 and Drug release 724 using the paddle method. The dissolution test was performed in 900 ml of phosphate buffer (pH 7.5) at 37 °C. The paddle was driven at 50 rpm. Samples of the dissolution medium were withdrawn 15, 30, 60, 120, 180, and 300 s after starting the experiment. The amount dissolved in the dissolution medium was determined by a high-performance liquid chromatography method after filtration through a membrane filter (5 μm, Mighty Sill RP-18 GP150-4.6, Kanto Chemical Co., Inc., Tokyo, Japan).

2.6. Clinical study of the swallowing property

This study was performed under the management of a doctor after institutional review board approval by Lintec Corporation. Ten healthy volunteers (one man and nine women), whose mean age was 47.5 (SD, 12.1) years, participated after providing both oral and written informed consent. The volunteers took the film formulation and the gelatin capsule containing barium sulfate with or without water. The motion of the film formulation and the gelatin capsule during swallowing and the movement afterwards were investigated using video fluorography (Jones and Donner, 1991). The maximum time of the video fluorography was limited to 30 s to minimize the exposure dose of X-rays. The volunteers were assigned to one of two groups of five each. In the first group, the responses to swallowing of the film formulation and gelatin capsule were compared, and the amount of barium sulfate and the surface area of the film formulation were adjusted to equal those of the gelatin capsule. In the second group, the effect of film formulation size (1.14 cm × 1.2 cm, 1.4 cm × 1.46 cm, and 1.67 cm × 1.7 cm) was studied. In the second group, the surface area of the film was adjusted to equal to the surface area of one, two, or three capsules.

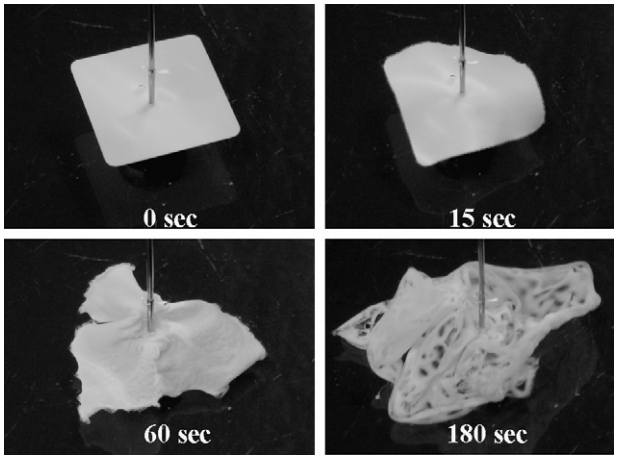

Fig. 2. The swelling behavior of the film formulation in the purified water.

3. Results and discussion

3.1. Gelation of the gelating layer

Gelation occurs through the interaction of the carboxyl group of a polymer and a calcium ion (Miyazaki et al., 2000; Kubo et al., 2004). In the present study, CV polymer was used as the polymer with a carboxyl group. CV polymer in the gelating layer interacts with calcium ions and forms a three-dimensional cross-linked structure. The gelation occurs by this structure after absorbing water. The appearance of the film formulation changed markedly and rapidly in purified water, as shown in Fig. 2. The speed of the gelation must have been very fast because the linear expansion coefficient increased instantaneously up to about 170% and was saturated in purified water, as shown in Fig. 3.

3.2. Texture of the gelating layer during swallowing

Because the film formulation was swallowed smoothly 10–15 s after taking it by mouth, we investigated its water-absorbing property and texture during swallowing. Purified water was absorbed up to five to six times the weight of the gelating layer in 10–15 s, as shown in Fig. 4. Fig. 5 shows

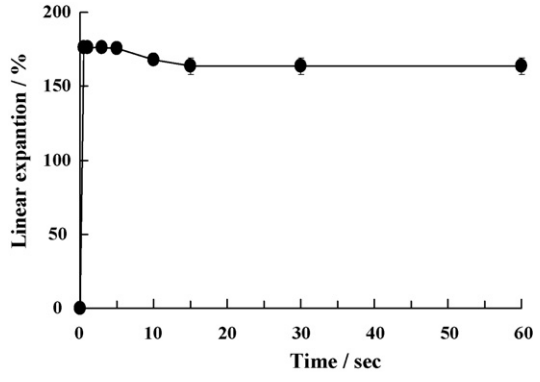

Fig. 3. The linear expansion profile of the gelating layer in the purified water. Data represent the mean ± SD of three sample determinations.

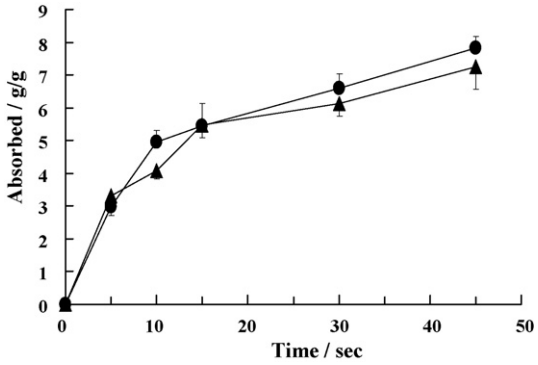

Fig. 4. The swelling profiles of the gelating layer in the purified water and synthetic saliva. (●) Purified water; (▲) synthetic saliva. Data represent the mean ± SD of three sample determinations.

the relationship between the amount of water absorbed and the bulk modulus in the gelating layer. The bulk modulus decreased exponentially with an increasing amount of water absorbed ($y = 1.1 \times 10^5\, e^{-0.9548}\ N/m^2$, $R^2 = 0.9623$) and was 400–500 N/m^2 after absorbing of purified water of five to six times its weight. The regulation for indicated food for the elderly by the Ministry of Health, Labor, and Welfare defines the modulus of food that can be taken without biting as less than 500 N/m^2 (Ei-shin No.15, 1994). The physical property of the gelating layer within 10–15 s after taking by mouth will be optimized for swallowing by elderly people. Therefore, patients should take the film formulation after swelling by saliva or water in advance. The bulk modulus of the commercial swallowing-assistive jelly (OKUSURI-NOMETAYO, Ryukakusan Co., Ltd., Tokyo, Japan) was 400 N/m^2.

3.3. Delayed dissolution

The dissolution property of glimepiride as a model drug was evaluated, and the results are shown in Fig. 6. Although no drug was detected 1 min after the start of the experiment with the film formulation, about 20% of the glimepiride dissolved in amaryl (Sanofi-Aventis K.K.), a commercial tablet formulation. Therefore, the film formulation can be taken without releasing the drug in the mouth by delayed dissolution. In particular, the film formulation would be advantageous for formulations containing bitter-tasting drugs because of its masking performance. In

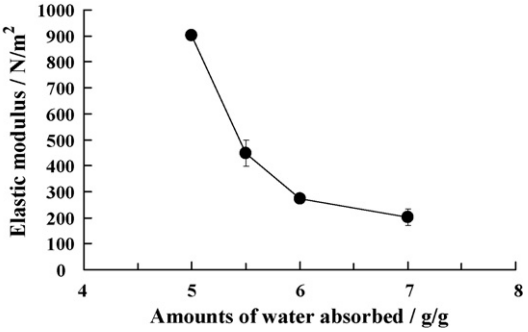

Fig. 5. The relationship between absorbed water and bulk modulus in the gelating layer. Data represent the mean ± SD of three sample determinations.

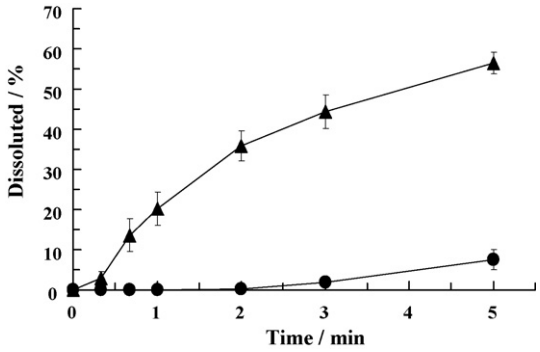

Fig. 6. The dissolution profiles of grimepiride from the film formulation in the buffer solution. (●) Film formulation; (▲) gelatin capsule. Data represent the mean ± SD of three sample determinations.

addition, the dissolution ratio of glimepiride 15 min after the start of the dissolution experiment was more than 85% (data not shown). Although the taste-masking of a drug occurs because of the delayed dissolution in the initial stage, the bioequivalence of the film formulation can be adjusted to equal that of the conventional formulation.

3.4. Motion of the film formulation during swallowing and the movement afterwards

If the formulation stagnates in the esophagus, there is a risk of ulcer formation associated with irritating drug formulations. For this reason, we investigated both the motion of the formulation in the swallowing and movement of the formulation after the swallowing by healthy subjects using video fluoroscopy. Photographs of the video fluoroscopy 1 s after swallowing are shown in Fig. 7. Although the stagnation at the upper esophagus was observed with the swallowed capsule, the film formulation passed the esophagus quickly and reached the stomach. The passage time from the C5 superior margin to the T5 inferior margin was analyzed. Figs. 8 and 9 show the upper esophagus passage time of the film formulation taken and the gelatin capsule taken with or without water. The gelatin capsule formulation stagnated in the esophagus for more than 30 s in three of five subjects who swal-

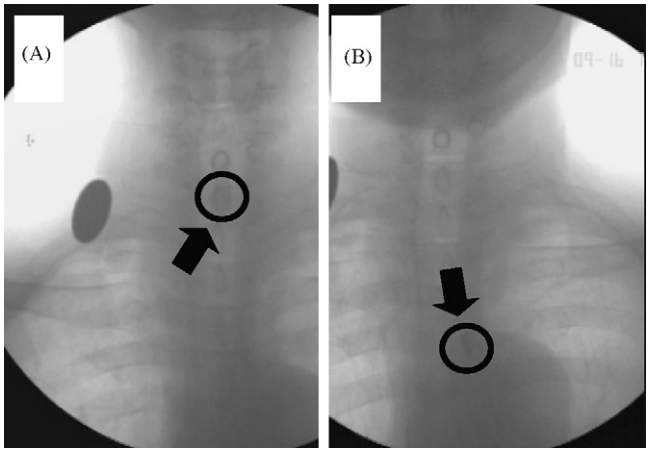

Fig. 7. Photographs from the fluoroscopic study. (A) Gelatin capsule; (B) film formulation.

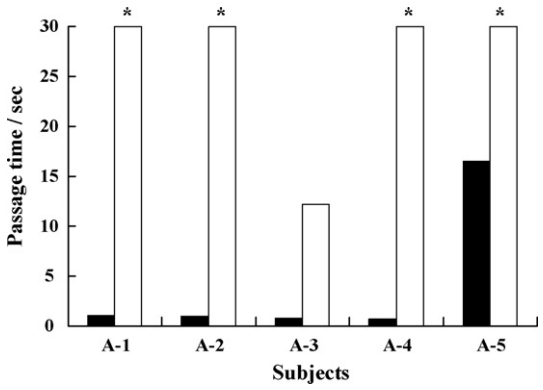

Fig. 8. The esophagus passage time when taking the film formulation and gelatin capsule without water. (*) More than 30 s; (■) film formulation; (□) gelatin capsule.

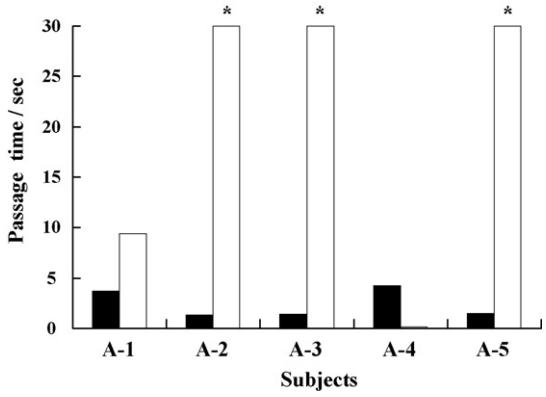

Fig. 9. The esophagus passage time when taking the film formulation and gelatin capsule with water. (*) More than 30 s; (■) film formulation; (□) gelatin capsule.

lowed without water and in two of five subjects who swallowed the capsule with water. The film formulation was delivered to the stomach within 20 s in all the subjects, regardless of whether it was taken with or without water. The delivery took place within 5 s in four of five subjects when taken with or without water. The motions in the oral stage and pharyngeal stage were incapable of being evaluated because of the quick swallowing. The influence of the size of the film formulation was not confirmed (data not shown). It was clarified that the film formulation can be taken with or without water, and delivered to the stomach without the stagnation at esophagus in this investigation.

4. Conclusion

The film formulation that we developed is a patient-friendly formulation that would be useful for people who have difficulty swallowing and those taking ordinary drugs because it turns into a jelly instantaneously upon absorption of a small amount of saliva. Another advantage of this formulation is its masking performance because of its delayed dissolution. In addition, the film formulation is so thin that it can be carried in a name card case. This film formulation technique has potential for use with many drugs, and we believe it will improve patient compliance.

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