Influence of Heat Treatment on Dissolution and Masking Degree of Bitter Taste for a Novel Fine Granule System[1]

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The influence of heat treatments on the dissolution and the masking degree of the bitter taste for the coated fine granules with water-insoluble film composed of ethylcellulose, hydroxypropylmethylcellulose, titanium dioxide and sucrose fatty acid ester (SS) (4:2:1:1), containing sparfloxacin (SPFX) and low-substituted hydroxypropylcellulose in the cores was investigated.

The dissolution rate of SPFX from the coated fine granules in water was increased by heat treatment of the granules. Dissolution percentage at 30 min in water after heat treatment at 70 °C for more than 4 h reached almost 100%, whereas it was about 90% before the heat treatment. The masking degree of the bitter taste for the coated fine granules was improved by the heat treatment. Differential scanning calorimetry (DSC) analysis of the coating film indicates that the endothermic peak due to melting of SS in the film disappeared with the heat treatment at 70 °C for 4 h, and also that the tensile strength of the film was reduced to one-half of the initial value after the heat treatment.

It is thought that heat treatment caused changes of film properties, *i.e.* that tensile strength and wettability are attributable to the melting and diffusing of SS in the film, resulting in the dissolution level being increased to about 100% and the masking degree of the bitter taste being greatly improved.

Key words sparfloxacin; film-coated fine granule; heat treatment; bitter taste masking; rapid dissolution

We developed a novel fine granule system containing sparfloxacin (SPFX) with a bitter taste,[2] which showed excellent properties; masking of the bitter taste and rapid release of SPFX. This is a coated fine granule system that consists of core fine granules containing SPFX and 52% low-substituted hydroxypropylcellulose (L-HPC) as a highly water swellable polymer, and a water-insoluble film layer primarily composed of ethylcellulose around the core to mask the bitter taste. The mechanism of dissolution of SPFX from the coated fine granules is assumed to be: the water is first taken up by L-HPC in the core through the film, after a short lag time the film is cracked and broken by the swellable force of L-HPC, and this releases SPFX rapidly.

It is also known, however, that the granulating, coating and aging temperature for several dosage preparations containing wax materials such as hydrogenated castor oil, stearic acid and so on is an important factor determining their dissolution characteristics.[3-8] The film of this SPFX fine granule system contained sucrose fatty acid ester with a melting point of 55 °C, to prevent the aggregation of granules during the coating process. It was thought that the heat treatment of these film coated fine granules would affect the characteristics of the film.

The purpose of the present work was thus to examine the influence of the heat treatment on the dissolution behavior and the degree of masking of bitter taste, and also to clarify the mechanisms of these phenomena through differential scanning calorimetry (DSC) analysis and measurement of the tensile strength of the film.

Experimental

Materials SPFX (Dainippon Pharmaceutical Co., Ltd.) with a mean diameter of about 15 μm was used. L-HPC (LH31) and hydroxypropylmethylcellulose (HPMC, 3 cps) were purchased from Shin-Etsu Chemical Co., Ltd. ethylcellulose (EC, 10 cps), hydroxypropylcellulose (HPC, HPC L), titanium dioxide, lactose, sucrose fatty acid ester (mainly sucrose stearate, SS, Ryoto Sugar Ester, S-370 (hydrophile lipohile balance 3 (HLB 3)), S-770 (HLB 7), S-1170 (HLB 11)) and polyethylene glycol 6000 (PEG 6000) were purchased from Dow Chemical Co., Ltd., Nippon Soda Co., Ltd., Ishihara Sangyo Kaisha Co., Ltd., B.V. Hollandsche, Mitsubishi-Kasei Foods Co., Ltd. and Taihei Kagaku Co., Ltd.

Test Preparations The coated fine granule formula are shown in Table 1.

The preparation method was as follows[2]: core fine granules were prepared by wet granulation method with ethanol in a high speed mixer (Vertical Granulator, VG-25, Powrex Co., Ltd.). After drying at 70 °C for 12 h, those granules were coated with film suspension dispersing titanium dioxide and dissolving other additives in dichloromethane–ethanol (15:2, w/w), using Spir-a-Flow Mini (Freund Industrial Co., Ltd.).

Heat Treatment The coated fine granules were heated for 4 h at 40—70 °C or for 1—12 h at 70 °C in an oven (Mini Jet Oven, MO-92, Toyama Sangyou Co., Ltd.).

Dissolution Test The dissolution test was carried out according to the JP XII paddle method at 50 rpm in 900 ml distilled water at 37 °C. The fine granules containing 50 mg of SPFX were tested. At appropriate time intervals, 10 ml aliquots of the test mediums were filtered through a membrane filter (FM-45; pore size 0.45 μm, Fuji Film Co., Ltd.) and diluted with 0.1 N NaOH solution. Concentrations of SPFX in the samples were determined spectrophotometrically at 291 nm.

Table 1. Formulas of Coated Fine Granules

Formula		1	2	3	4
Core	SPFX	20 parts			
	L-HPC	52			
	Lactose	13			
	HPC	5			
Film	EC	4.45	4.45	4.45	4.45
	HPMC	2.22	2.22	2.22	2.22
	TiO_2	2.22	2.22	2.22	2.22
	SS (HLB3)	1.11	—	—	—
	SS (HLB7)	—	1.11	—	—
	SS (HLB11)	—	—	1.11	—
	PEG 6000	—	—	—	1.11
Total		100 parts			

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Simplified Dissolution Test Simplified dissolution test was performed as an *in vitro* test to evaluate the degree of masking of the bitter taste of the fine granules under the assumption that the fine granules were held in the mouth with 10 ml of distilled water, with weak mixing by the tongue for 30 s. The method was as follows: Fine granules containing 50 mg of SPFX were mixed with 10 ml of the distilled water in a 10 ml syringe by revolving the syringe end to end five times within 30 s. Thereafter, the concentrations ($D_{30\,\mathrm{s}}$) of SPFX in the filtrate with a membrane filter with a 0.45 μm pore size were determined spectrophotometrically at 291 nm after being diluted with 0.1 N NaOH solution. Each test was carried out five times. The coated fine granules, whose $D_{30\,\mathrm{s}}$ values on the simplified dissolution test were below the 100 μg/ml threshold concentration of bitter taste defined from a sensory test for SPFX by healthy volunteers,[2] could be masked *in vivo*.

Bursting Time of Coated Fine Granules in Water In groups of 10 coated fine granules sieved through 42 to 60 mesh sieves were carefully spread over the surface of distilled water (10 ml, at 25 °C). At a fixed time the number of granules which had burst on the surface were counted. Bursting time was defined as the time the film of the granule began to crack. Cumulative number in 10 experiments were determined on each sample.

DSC of Film Films were prepared by a technique in which a film suspension dispersing film additives (formula 2 in Table 1) in dichloromethane–ethanol (15 : 2, w/w) was sprayed onto small polyethylene tips (2 × 2 × 0.5 cm) and placebo core granules with Spir-a-Flow Mini under the same conditions as used to coat the fine granules. The films were peeled off the tips and 10 mg of film was thermocalorimetrically analyzed by DSC (TAS-1000, Rigaku Denki Co., Ltd.) at a heating rate of 10 °C/min.

Tensile Strength of Film Films were again prepared by a technique in which a film solution dissolving film additives (formula 2 in Table 1) without titanium dioxide in dichloromethane–ethanol (15 : 2, w/w) was sprayed onto polyethylene tips (3 × 3 × 1 cm) and suitable placebo tablets with a spray coating pan (High Coater, Freund Industrial Co., Ltd.). The films were peeled from polyethylene tips, and their thickness and width were measured with a micrometer dial gage. The peeled films were fixed with clips, and their tensile strengths were measured using a Rheo Meter (NRM-3002D, Fudoh Kogyo Co., Ltd.). The tensile strength was expressed as kg/cross section area.

Results and Discussion

Influence of Heat Treatment on Dissolution Profiles of SPFX from Coated Fine Granules The dissolution profiles of SPFX in distilled water from the coated fine granules (formula 2) after 4 h of heat treatment at 40—70 °C, or at 70 °C for 1—12 h are shown in Fig. 1a and 1b, respectively. The profiles were not influenced by the treatment at 40 °C for 4 h, however, the profiles improved either with an increase of the temperature between 50 °C and 70 °C for 4 h in Fig. 1a, or with an increase in heating time between 1 and 4 h at 70 °C (Fig. 1b). The dissolution percentage in water from the coated fine granules at 30 min ($D_{30\,\mathrm{min}}$) was about 90% that before the heat treatment, but reached almost 100% after the heat treatment at 70 °C for more than 4 h. As previously reported,[9] it became clear from DSC observation that SPFX in the precipitates in the dissolution process of the coated fine granules was partially transformed to trihydrates with lower solubility before release. Therefore, the improved dissolution of SPFX from the fine granules by the heat treatment was thought to be due to the increased fragility and rapid burst of the films in water. This may account for the complete release of SPFX.

The influence of heat treatment on the dissolution of SPFX from coated fine granules containing other SS of HLB 3 and 11 in films (formulae No. 1, 3) were also investigated. The dissolution profiles were improved by the heat treatment at 70 °C for 4 h, and their $D_{30\,\mathrm{min}}$ reached almost 100%, as did those of fine granules containing SS of HLB 7 in film as shown in Fig. 2a and 2b, respectively. Profiles of the coated fine granules containing PEG 6000 in the film (formula 4) instead of SS, however, were not improved with the heat treatment as shown in Fig. 2c.

These results suggested that the effect of the heat treatment on the dissolution profiles was attributable to change of the SS state in the film.

Influence of Heat Treatment on Simplified Dissolution Test Results We also performed a simplified dissolution test to determine the masking degree of the bitter taste of SPFX. As shown in Fig. 3, the percentage dissolved from the coated fine granules containing SS of HLB 3 or 7 in film at 30 s in this test ($D_{30\,\mathrm{s}}$) was decreased by heat treatment at 70 °C for 4 h. These findings imply that the heat treatment strengthens the masking degree of the bitter taste for these fine granules. However, $D_{30\,\mathrm{s}}$ of the coated fine granules with SS of HLB 11 and PEG 6000 were little influenced by the heat treatment even at 70 °C for 4 h. $D_{30\,\mathrm{s}}$ of the fine granules with PEG 6000 was over 100 μg/ml, the target value for masking the bitter SPFX taste.

Similar phenomena reflecting the results of the simplified dissolution test were observed when the influence of heat treatment at 70 °C for 4 h on the bursting time of the

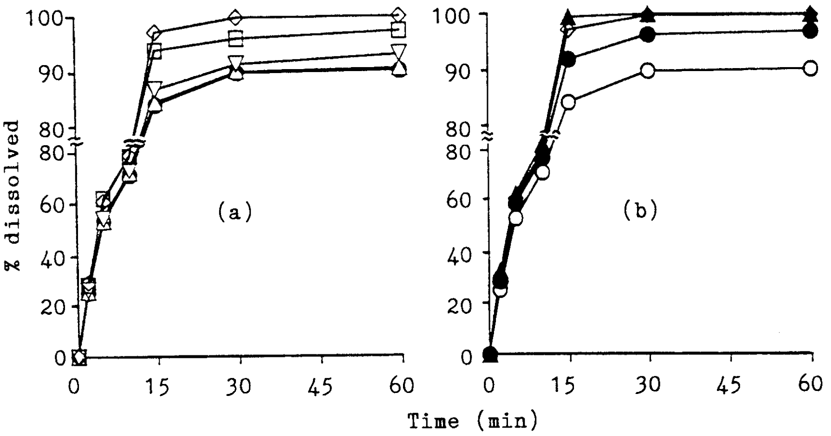

Fig. 1. Influence of Heat Treatment (Temperature, a; Time, b) on Dissolution Profiles of SPFX from Coated Fine Granules

Temp. ○, initial; △, 40 °C—4 h; ▽, 50 °C—4 h; □, 60 °C—4 h; ◇, 70 °C—4 h. Time ○, initial; ●, 70 °C—1 h; ◇, 70 °C—4 h; ▲, 70 °C—12 h.

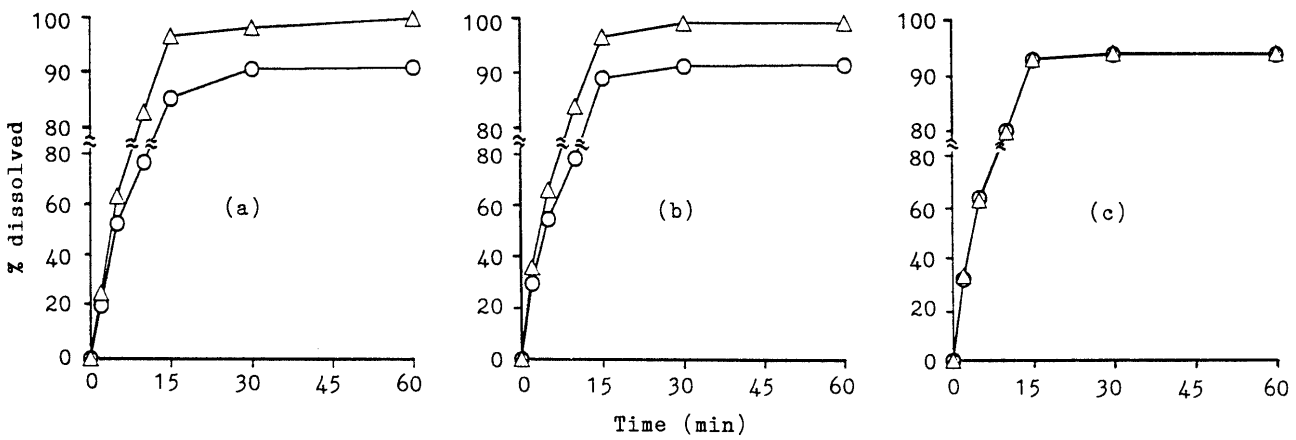

Fig. 2. Influence of Heat Treatment at 70 °C for 4 h on Dissolution Profiles of SPFX from Coated Fine Granules Containing SS of HLB 3 (a), HLB 11 (b) and PEG 6000 (c)

Temp. ○, initial; △, 70 °C—4 h.

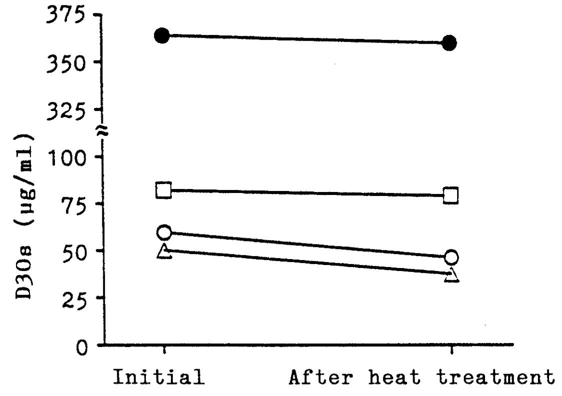

Fig. 3. Influence of Heat Treatment at 70 °C for 4 h on Simplified Dissolution Test Results of Coated Fine Granules

△, SS of HLB 3; ○, HLB 7; □, HLB 11; ●, PEG 6000.

coated fine granules in distilled water was studied. As shown in Fig. 4, the burst of the fine granules containing SS of HLB 3 or 7 was remarkably delayed by this treatment, while the burst of those containing SS of HLB 11 was only slightly delayed by the treatment, and that of the fine granules containing PEG 6000 was not influenced at all.

Bursting time is probably strongly influenced by the wettability of the film coating. Therefore, the wettability of the coated fine granules containing SS of HLB 3 and 7 was thought to be decreased by the heat treatment, and in consequence the permeability rate of water through the film into the fine granules was lowered.

The coated fine granules with SS of HLB 3 and 7 showed superior ability to mask the bitter taste and were successfully influenced by the heat treatment, although those containing SS of HLB 3 electrostatically adhered to a chamber wall of Spir-a-flow during the coating process. The film containing SS of HLB 7 (formula 2) was thus superior considering productivity.

Influence of Heat Treatment on Characteristics of Film These results showed that the heat treatment leads to far superior characteristics of the coated fine granules, *i.e.* allowing them to rapidly and completely release SPFX and masking the bitter taste. To elucidate these beneficial phenomena, the film characteristics were investigated using a free film prepared by a spraying method.

As shown in Fig. 5, the DSC curve of the film showed an endothermic peak due to melting of SS. The peak was still visible after heat treatment of the film at 40 °C for 4 h, but disappeared after the treatment at 70 °C. It did not reappear thereafter, even after storage at room temperature. These results suggest that the crystalline SS was melted by the heat treatment and homogeneously diffused in the coating film, and even after cooling amorphous SS was not transformed again into crystal form. Thus, when the coated fine granules came in contact with water, the wettability of the film decreased and early permeability of water through the film declined.

Table 2 shows the tensile strengths of film without titanium dioxide before and after the heat treatment for 4 h at 40 °C or 70 °C. The film of formula 2 was too fragile to measure the tensile strength, so to compare the tensile strengths of the free film before and after the heat treatment, titanium dioxide was omitted from this formula. The tensile strength of the free film was little influenced by the heat treatment at 40 °C for 4 h, however, that after the treatment at 70 °C for 4 h was less. Thus, it was thought that the diffusion of melted SS in the film cased by the heat treatment lowered the film tensile strength due to the poor film formability of SS. To boost the dissolution level of SPFX before its transformation to the trihydrate with lower solubility in the coated fine granules in the dissolution process, probably required intense destruction of coating film. It was thought possible that decline in the tensile strength was one reason that the heat treatment caused the complete dissolution.

Conclusion

The influence of heat treatment at 70 °C over 4 h on characteristics of a particle system containing SPFX was found to be an important process, showing contradictory characteristics, masking the bitter taste of fine granules and releasing rapidly. The dissolution rate increased and the percentage dissolved reached almost 100% in the dissolution test without transforming SPFX to the trihydrate with low solubility; additionally, the masking degree of the bitter taste was greatly improved by the heat treatment. The mechanism could be thought as follows:

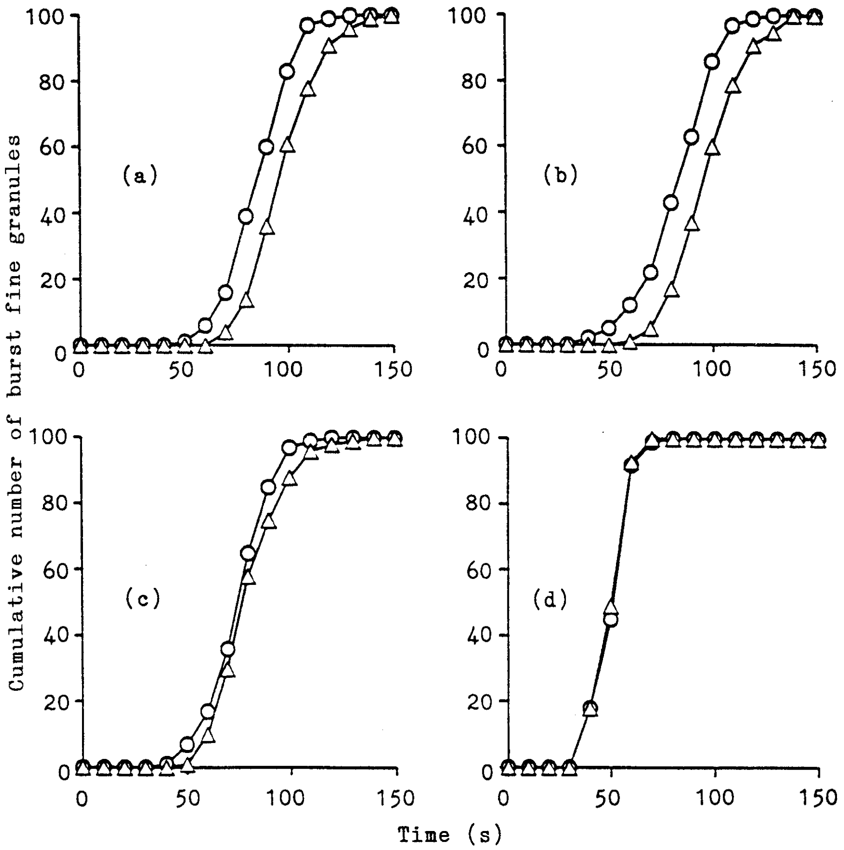

Fig. 4. Influence of Heat Treatment on Bursting Time of Coated Fine Granules Containing SS of HLB 3 (a), HLB 7 (b), HLB 11 (c) and PEG 6000 (d)

○, initial; △, after heat treatment.

1) crystalline SS in the film melted and homogeneously diffused in the coating film; 2) the wettability and the tensile strength of the film decreased, and consequently 3) the degree of masking of the bitter taste was improved and the dissolution level increased.

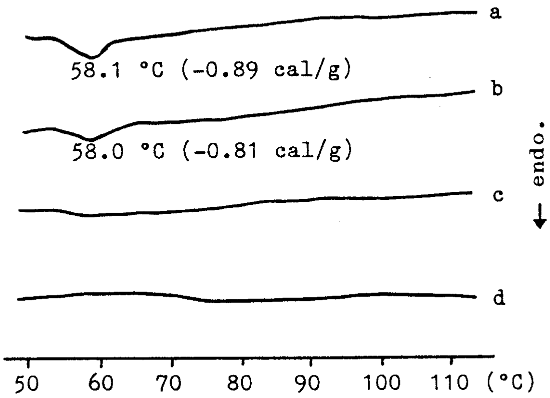

Fig. 5. DSC Curves of Free Film Prepared by Spraying Technique

a, initial; b, heat treatment at 40 °C for 4 h; c, heat treatment at 70 °C for 4 h; d, storage for 1 month at room temperature after heat treatment at 70 °C for 4 h.

Table 2. Tensile Strength of Free Film

Initial (kg/cm^2)	Heat treatment (kg/cm^2)	
	40 °C–4 h	70 °C–4 h
85.3±14.4	80.4±13.3	43.6±4.7

Mean±S.D. ($n=3$).

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