A Novel Fine Granule System for Masking Bitter Taste

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In order to prepare fine granules of sparfoxacin (SPFX), a new quinolone anti-bacterial drug that shows masking of the bitter taste of SPFX and dissolves at a rapid rate, various film-coated fine granules containing 20% SPFX and 0—52% low-substituted hydroxypropylcellulose (L-HPC) in the cores, were prepared by a spray method. Mixtures of ethyl cellulose (EC), hydroxypropylmethylcellulose (HPMC), titanium dioxide and sucrose stearate in weight ratios of X:Y:Z:1 (X + Y = 6) were used as film materials.

The degree of masking of the bitter taste by water-insoluble film, mainly consisting of EC and HPMC, increased by increasing the content ratio of EC to HPMC and the amount of films, but was also slightly affected by the amount of L-HPC in the cores, which were coated with either EC or EC/HPMC (4/2). On the other hand, the dissolution rate increased with an increased amount of L-HPC in the cores and with a decreasing ratio of EC to HPMC in the films. Increasing the amount of L-HPC in the cores, which induced a considerable expansion of the fine granules owing to their taking up of water from the dissolution medium, resulted in bursting of the film after a short lag time. The bioavailability of the film-coated fine granules containing 20% SPFX and 52% L-HPC in the cores and 10% EC/HPMC (4/2) in the coating film, which masked the bitter taste of SPFX and showed the optimal release characteristics, was equivalent to that of conventional tablets containing 100 mg SPFX in beagle dogs.

Keywords film-coated fine granule; bitter taste masking; rapid dissolution; microcapsule; sparfoxacin; bioavailability

Introduction

As a pharmaceutical dosage form, fine granules, which are convenient for controlling the dose and mixing with other fine granules and powders, have been widely used for various drugs. However, the designing of fine granules for drugs with an unpleasant taste is difficult because of the usual need to incorporate two contradictory characteristics, masking of the unpleasant taste for compliance of patients taking the drug, and rapid and complete releasing of the drug from the fine granules to avoid lowering of bioavailability.

Recently, several techniques for masking the unpleasant taste of fine granules and powders have been reported, that is, the water-insoluble matrix fine granules, 2) and fine granules and powders coated with pH-dependent watersoluble films 3—7) and so on. Fine granules and powders coated with water-insoluble films composed of ethylcellulose are probably the most orthodox way of ensuring masking of unpleasant tastes. However, this technique is mainly used for prolonged release preparations 8—17) and is unsuitable for rapid-release preparations.

New quinolone anti-bacterial drugs are usually administered in tablets for the treatment of various infectious diseases. Fine granule preparations of new quinolones are not yet commercially available. This may be mainly due to their severely bitter taste.

Sparfoxacin (SPFX), 18) a new quinolone drug which shows superior anti-bacterial activity, 19) also has a bitter taste. This paper describes and evaluates a novel design of fine granules containing SPFX in the cores, coated with water-insoluble film, so as to mask the bitter taste without lowering the dissolution rate.

Experimental

Materials

SPFX (Dainippon Pharmaceutical Co., Ltd.) of mean diameter about 15 μm, measured by the air-permeability method on a Specific Surface Area Meter, Model SS-100 (Shimadzu Seisakusho Co., Ltd.). Low-substituted hydroxypropylcellulose (L-HPC, LH31) and hydroxypropylmethylcellulose (HPMC, 3cps) were purchased from Shin-etsu Chemical Co., Ltd. Ethyl cellulose (EC, 10 cps), sucrose stearate (SS, Ryoto Sugar Ester, S-770), hydroxypropylcellulose (HPC, HPC L), titanium dioxide and lactose were purchased from Dow Chemical Co., Ltd., Mitsubishi-Kasei Foods Corp., Ltd., Nippon Soda Co., Ltd., Ishihara Sangyo Kaisha Co., Ltd., and B. V. Hollandsche, respectively. Tablets containing 100 mg of SPFX were rapidly releasing ones which disintegrated within 2 min in the JP XII disintegration test, and SPFX was dissolved almost 95% from the tablets in 30 min.

Preparation of Fine Granules

The core additives, weighing 1.8—2.0 kg according to the core formulas in Table I, were mixed at 390 rpm for 1 min in a high speed mixer (Vertical Granulator MV-25, Powrex Co., Ltd.). Subsequently, ethanol was added to dissolve HPC as a binder under successive mixing of powders for 3 min. The wet granulated powder was dried at 70°C for 12 h and sieved using JIS standard sieves with 150—32 mesh to obtain the core fine granules. These were coated with dichloromethane—ethanol (15:2 weight ratio) dispersing EC, HPMC, titanium dioxide, and SS (X:Y:Z:1, X + Y = 6, weight ratio) according to the film formulas in Table I, using a Spira-A-Flow MINI (Freund Industrial Co., Ltd.) equipped with a tangential spray gun. The basic composition of the experimental fine granules was 90% cores and 10% coating film, except in the study of a varying amount of film in the range of 4 to 20%.

Dissolution Test

The dissolution tests were carried out by the JP XII paddle method at 50 rpm and in 900 ml distilled water at 37°C. The fine granules containing 50 mg of SPFX were tested. At appropriate time intervals, the test mediums were filtered through a membrane filter (FM-45, pore size 0.45 μm, Fuji Film Co., Ltd.) using a syringe. The concentrations of the SPFX in the samples were determined spectrophotometrically at 291 nm after being diluted with 0.1 N NaOH solution. In this study the

| TABLE I. Formulas of Cores and Films |
| No. of formula of cores | No. of formula of films |
| 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| SPFX | 20 | 20 | 20 | 20 | parts | EC | 6 | 4 | 3 | 0 | parts |
| L-HPC | 0 | 25 | 40 | 52 | HPMC | 0 | 2 | 3 | 6 |
| Lactose | 65 | 40 | 25 | 13 | TiO_2 | 2 | 2 | 2 | 2 |
| SS | 1 | 1 | 1 | 1 | CH_3Cl | 1 | 5 | 1 |
| EtOH | 1 | 1 | 1 | 1 | 15 | 1 | 20 |

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dissolved percentage of the so-called rapid releasing preparation at 30 min (D30s min) was defined as greater than 90%.

The Sensory Test on Threshold Value of Bitter Taste for SPFX. Ten healthy volunteers held 10 ml of aqueous solution of SPFX 0, 25, 50, 75, 100, 150 and 200 μg/ml of water, respectively, in their mouths for 10s and then washed their mouths with 30 ml of distilled water following each test. The bitterness threshold concentration was judged to be 100 μg/ml.

Simplified Dissolution Test. A simplified dissolution test for evaluation of the degree of bitterness of the experimental coated fine granules was performed as an *in vitro* test under the assumption that the fine granules were held in the mouth with 10 ml of water, with weak mixing by the tongue for 30s. The method was as follows. The fine granules, each containing 50 mg of SPFX, were mixed with 10 ml of distilled water in a 10 ml glass tube by revolving the syringe end to end five times in 30s. Thereafter, the test medium was filtered through a membrane filter (pore size of 0.45 μm). The concentration of SPFX in the filtrate was determined spectrophotometrically at 291 nm after being diluted with 0.1 N NaOH solution. Each test was carried out five times. Thus, the coated fine granules, whose D30s values on the simplified dissolution test were below 100 μg/ml, the threshold concentration of bitter taste, could be masked *in vitro*.

Study of Fine Granule Structure. The surface of the intact core fine granules and the coated fine granules were observed using a scanning electron microscope (Nihon Densi; Model JSM-T20).

Measurement of Apparent Swelled Ratio of Fine Granules. 15 g of fine granules were carefully poured into a 100 ml graduated cylinder (i.d. 2.8 cm, height 25 cm) from a height 5 cm above the cylinder. 80 ml of distilled water was gently added to the vertical cylinder and the swelled percentage of fine granules calculated from the difference in their apparent volume before and after the addition of water using the following equation.

\[
\text{swelled ratio } \% = \frac{V(s) - V(i)}{V(i)} \times 100
\]

\(V(s)\), apparent volume of fine granules before addition of water
\(V(i)\), apparent volume of fine granules at a steady state in water

Measurement of Physicochemical Properties of Prepared Fine Granules. The size distribution of fine granules was determined by sieve analysis with a row-tap shaker (Iida Seisakusho Co., Ltd.). The shaking time was 3 min and the charged amount was 10 g. A mass median was used as a mean diameter.

The flowability of fine granules was measured by the angle of repose using a fixed-bottom method. The apparent density was determined in the method reported by Aoki. 20

**In Vivo Study.** A cross-over experimental design with an interval of one week was used with eight male beagle dogs weighing from 10.3 to 13.9 kg. All dogs were fasted overnight and preparations containing 100 mg of SPFX were orally administered with 60 ml of water. Subsequently, all dogs were freely allowed water but were not fed until 10 h after drug administration. Blood specimens from the cephalic vein in the front legs were drawn up to 24 h following drug administration, using a heparinized syringe. The plasma concentrations of SPFX were assayed by HPLC following the method reported by Yamaguchi. 21

Results and Discussion

Coating of Fine Granules. Coating was applied using a Spir-a-Flow with a tangential spray gun. Coating process parameters are listed in Table II. The coating solution was sprayed tangentially to the flow of fine granules in the chamber. These moved in a spiral current generated by the combined actions of the fluidizing air, centrifugal force, and gravity. Accordingly, a more densely coated film can be formed onto the fine granules in contrast with the coating process in an ordinary fluidized bed granulator with a top spray. 22,23 The coating conditions, which are tabulated in Table II, were almost the same throughout this study. The core fine granules under a 32 mesh sieve and on a 150 mesh sieve were used for the coating process so as to obtain a homogeneous coating film. The mean diameters of all core fine granules ranged from 261 to 280 μm. Such small differences in diameter would not affect the characteristics of the fine granules in this study. The yields of the sieved core fine granules ranged from 92 to 94%, demonstrating the advantage of the applied apparatus, a high speed mixer, in the granulation process.

SS and titanium dioxide were used in a constant ratio in all of the prepared films in order to prevent agglomeration of the fine granules and adhesion to the inner wall of the chamber and filter due to electrostatic charges during the coating process. Typical scanning electron microscope (SEM) photographs of the core fine granules containing 52% L-HPC and the coated fine granules with 10% film of EC/HPMC = 4/2 are shown in Fig. 1. The coated fine granules form microcapsules whose surface is smooth due to tangential spraying, however, small pores are observed in their surface.

**Effect of Film Components on D30s Values and Dissolution Behaviors of SPFX from Coated Fine Granules.** The relationship between the D30s values and the amount of film of the coated fine granules lacking L-HPC in the cores are shown in Fig. 2. The D30s values decreased with increasing amounts of film and became less than 100 μg/ml, the target value for masking the bitter taste on the coated fine granules, with EC and EC/HPMC (4/2 and 3/3) films whose amounts were more than 4, 6 and 10%, respectively. However, on the coated fine granules with HPMC the D30s value was more than six times the target value, even when the amount of coated film was increased to 20%, indicating that HPMC film cannot be used to mask the bitter taste of fine granules with a huge specific surface area in contrast with tablets.

The dissolution behaviors of SPFX from the film-coated fine granules lacking L-HPC in the cores are shown in Fig.
3. The film components are 4, 6, or 10% EC, EC/HPMC (4/2 or 3/3), respectively, which are minimum amounts for masking bitter taste. It was apparent that these coating fine granules do not rapidly release SPFX, unlike the core fine granules.

Effect of L-HPC in the Cores on Dissolution Behaviors of SPFX from Coated Fine Granules. With the intention of increasing the dissolution rate of the coated fine granules showing low D30's values, the addition of L-HPC to the cores was carried out in expectation of a rapid release following disruption of the film due to extremely large expansion of the cores caused by water uptake. The dissolution behaviors of SPFX from the 10% coated fine granules with EC/HPMC (4/2), containing various amounts of L-HPC in the cores are shown in Fig. 4. When the amount of L-HPC in the cores was increased, the dissolution rate also increased remarkably. As shown in Fig. 5, regarding the 10% coated fine granules with EC and EC/HPMC (4/2 and 3/3), the D30 min values increased with an increase in the amount of L-HPC, irrespective of the film components. Nevertheless, the D30 min value of the fine granules coated with EC remained less than 90%, even with 52% L-HPC in the cores.

Although, as shown in Fig. 6, the D30's values largely depended upon the film components, they also depended slightly upon the amount of L-HPC in fine granules coated with 10% of EC or EC/HPMC (4/2), being less than 100 μg/ml.

Figure 7 shows the relationships between the amount of L-HPC in the cores and the amount of film with respect to the masking ability of the bitter taste (D30's values:...
<100 µg/ml) and to the rapid dissolution rate (D30 min values: >90%). The cross-hatched area of Fig. 7(b) (D30 min values above 90% and D30 s values below 100 µg/ml) indicates the composition range of fine granules having desirable properties regarding both dissolution rate and masking bitter taste. It was found that the ratio of EC to HPMC in the film and the amount of L-HPC in the cores play an important role in the above aspects. Clearly, the fine granules containing about 50% of L-HPC in the cores and coated with 10% EC/HPMC (4/2), satisfy the pharmaceutical requirement of masking the bitter taste without lowering the rapid dissolution. By the way, preparations showing D30 min values above 90% are considered as rapid releasing. However, even when the fine granules exceed this target value, all of them could not run up to 100% as shown in Fig. 4. This point is undergoing further study.

**Mechanism of Release from Coated Fine Granules**

SEM photographs of the fine granules coated with 10% EC/HPMC (4/2), containing 0, 25, 40 or 52% L-HPC in the cores at 30 min in the dissolution test are shown in Fig. 8. The film surface of the coated fine granules lacking L-HPC, hardly changed in water, compared with that of the other fine granules containing L-HPC, and the degree of cracking and bursting of the films was progressively enhanced with an increase in the amount of L-HPC.

The relationship between the apparent swelled ratio of coated fine granules and the D30 min values was studied in connection with the amount of L-HPC and is shown in Fig. 9. The D30 min values was strongly dependent on the apparent swelled ratio of the coated fine granules in water. Figures 8 and 9 suggest that the increase of the dissolution rate by increasing the amount of L-HPC is caused by the bursting of films due to the extremely large expansion of the cores containing L-HPC in water.

The dissolution profiles of SPFX from the coated fine granules and from the cores at the first stage of dissolution are shown in Fig. 10. The dissolution of SPFX from the coated fine granules was almost perfectly suppressed for 30 s compared with that from the cores, and thereafter, the rapid dissolution of SPFX occurred.

Considering these findings, a diagram of the releasing process of SPFX from the coated fine granules may be proposed as shown in Fig. 11. This is based on the assumption that after a short lag time the core expansion due to water intake enhanced by L-HPC through the film caused the burst of the film at a stroke, consequently releasing SPFX. It was thought that EC film was too hard to burst perfectly by the swelling force of L-HPC due to water intake, resulting in SPFX remaining undissolved in the fine granules. The EC/HPMC (3/3) film showed high permeability of water, resulting in a slight masking of the bitter taste of SPFX. It was also thought that at the extreme first stage of the release of SPFX from the coated fine granules with EC/HPMC = 4/2 the pores of film, rather than bursting of the film, mainly contribute to the dissolution of SPFX because the D30 s values were independent upon the amount of L-HPC in the cores as shown in Fig. 6.

**Pharmaceutical Characteristics of the Fine Granules**

Physicochemical properties of the 10% coated fine granules with EC/HPMC = 4/2 containing 52% of L-HPC in
the cores and their core fine granules are shown in Table III. The particle size distribution of the coated fine granules was slightly broad relative to that of their core fine granules. This result indicates that neither defacement nor agglomeration of the fine granules occurred in the coating process. This may be mainly due to the presence of titanium dioxide and SS as lubricants in the film layer, and to the core fine granules prepared by the high speed mixer which are hard enough to resist the high spray pressure. It may be also due to the tangential spraying of the coating solution. The angle of repose less than 40° indicates good flowability of the fine granules. Moreover, the apparent density of the coated fine granules was higher than 0.5 g/ml. These characteristics of the coated fine granules are desirable for dispensing and for mixing with the other fine granules, as is reported by Fukuda.24)

Plasma Concentration Curves of SPFX Following Oral Administration of the Coated Fine Granules and the Rapid Releasing Tablets in Dogs Figure 12 shows the profiles of mean plasma concentrations of SPFX following the oral administration of the 10% coated fine granules with EC/HPMC = 4/2, containing 52% of L-HPLC in the cores, in
comparison with the tablets with rapidly releasing characteristics.

The plasma concentrations obtained from the coated fine granules at 0.5h and 1h after administration were higher than those obtained from the tablets, however, there was no significant difference in $C_{\text{max}}$ and $AUC$ between the two preparations, as shown in Table IV. These data indicating small inter-individual variations were also similar to those after oral administration of an aqueous suspension of SPFX, suggesting that in the stomach the burst of film of the coated fine granules occurred in a short time and SPFX was rapidly released in gastric juices, as expected from in vitro dissolution characteristics.

**Conclusion**

The formulation of fine granules containing drugs with bitter tastes must overcome the problem of masking the bitter taste without lowering the bioavailability. By the addition of large amounts of highly water-swellable material into the cores and by selecting a combination ratio of film components, we could design the novel coated fine granules system without the bitter taste of drugs and with rapid releasing characteristics. This design of fine granules was expected to apply to various drugs with unpleasant tastes.

**References and Notes**

1) A part of this study was presented at the 110th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, August 1990.