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Improvement in the variation of inhalation properties of an FK888 dry powder inhaler using an E-haler, by adding coarse lactose in spherical soft agglomerates of fine drug particles, and its absorption in healthy volunteers

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FK888 is a candidate selective NK1 receptor antagonist that exhibits poor absorption from the gastro-intestinal tract. In our previous study, it was found that pulmonary application was effective in achieving systemic absorption of the drug in healthy volunteers. In this study inhalation powder formulations, which were carrier-free spherical soft agglomerates of FK888 fine particles, were evaluated using an E-haler. A proportional fine particle dose (FPD defined as the dose deposited less than 4.9 μm) was obtained from 10, 20 and 40-mg formulations (10, 20 and 40 mg as FK888, respectively) after discharging into a cascade impactor using an E-haler. However, poorer reproducibility of FPD was observed when five different lots of active ingredient were used in the 40-mg formulation (14.3 ± 2.7 mg for FPD, 35.8 ± 6.7% for the fine particle fraction; FPF defined as a percentage of FPD compared with the nominal dose defined as the quantity of FK888 loaded in a capsule, and a CV of 18.7%). It was found that the BET surface area of the fine drug particles was closely related to the in vitro *aerodynamic properties, and the addition of 25% (w/w) coarse lactose (Pharmatose 325M) was very effective in improving the variability (17.7 ± 0.9 mg for FPD, 44.2 ± 2.2% for FPF, and a CV of 4.9%, $p < 0.05$ compared with the carrier-free 40-mg formulation). It was considered that the higher BET surface area reflected a higher amount of finer drug particles, and the 325M lactose acted as a fixative agent allowing the finer drug particles to adhere to the lactose surface, resulting in a reduced adhesive force between the drug particles. In the formulation containing 325M lactose using an E-haler, an improvement in systemic absorption was also obtained in healthy volunteers.*

Key words: Dry powder inhaler – E-haler – Cascade impactor – Pulmonary absorption – Soft pellets – Lactose.

Dry powder inhalers (DPIs) have been developed for the treatment of respiratory diseases such as asthma or other localized lung diseases. In addition to localized lung diseases, the pulmonary route has attracted attention as a potential way of delivering drugs to the systemic circulation [1], especially drugs with a low membrane permeability in the gastro-intestinal tract [2, 3]. When the pulmonary route is considered as an alternative pathway for systemic application, the aerodynamic particle size range of the drug should be 1 to 5 μm after inhalation to allow the drug particles to reach the alveolus [4, 5]. Although pressurized metered dose inhalers (pMDIs) have been also popular for this purpose, there has been much interest in employing DPIs because of the ease of co-ordination with the respiratory cycle [6], less drug is trapped in the oropharynx [7], and, being free of chlorofluorocarbons (CFCs), they are much more environmentally friendly [8]. In the case of pMDIs, since the solubility of a drug in an appropriate propellant is limited, a suspension type of formulation has to be generally used when a high dose is required. In previous studies, we reported that the aerodynamic particle size distribution of pMDI was greater than that of DPI when suspension type pMDI and DPI were compared. The agglomerates of fine drug particles settle as the result of volatilization of the propellant after discharging small mists of the liquid suspension containing the fine drug particles from the pMDI [9].

FK888(4R)-4-hydroxy-1-[(1-methyl-1H-indol-3-yl)carbonyl]-L-prolyl-N-benzyl-N-methyl-3-(2-naphthyl)-L-alaninamide is a candidate selective NK1 receptor antagonist which exhibits poor absorption from the gastro-intestinal tract in healthy volunteers. In previous studies, we investigated DPI formulations with carrier lactose using a Spinhaler for systemic application of FK888, and a proportional absorption was obtained up to a 5 mg (5 mg fine FK888 particles were blended with 35 mg Pharmatose 200M) nominal dose in healthy volunteers [10]. There have been some studies of the influence of the physicochemical properties of carrier lactose and the blended ratio of drug in formulations on the aerodynamic drug particle size distribution [11-14]. Pharmatose 200M, originally with fine lactose particles, was selected as the most suitable carrier for FK888 dry powders using a Spinhaler. However, the percentage of fine drug particles after inhalation was dramatically reduced due to the insufficient surface area of lactose as a carrier in formulations over 5 mg [10]. In addition to the DPI formulations using Spinhaler, the DPI formulations of carrier-free powder using an E-haler were also investigated for doses over 5 mg (up to 40 mg) as the unit dose. As far as the carrier-free formulation is concerned, it is generally known that fine drug particles are very cohesive and have a poor flowability [15]. In order to improve this, the pulverized drug particles were agglomerated into soft pellets, which then disintegrated into primary particles by the air stream after inhalation. In the DPI formulations using an E-haler, a proportional fine particle dose evaluated by a cascade impactor (FPD) was obtained from 10, 20 and 40 mg formulations as shown in this study. However, it was also observed that there was a variability in the FPD after discharging from the DPI system when different lots of active

ingredient were used. Thus, the DPI formulation was required to improve the variability of the commercial product, because good reproducibility is essential for obtaining the desired effectiveness and preventing unexpected side effects. In particular, in the case of dosage forms for the pulmonary route, as far as the content uniformity of the unit dose is concerned, not only the nominal dose but also the FPD should be controlled because the FPD is the dose involved in absorption. As far as the formulations of carrier-free powder aerosols are concerned, there have been some attempts to improve the flow properties of powders [16] and the aerodynamic particle size distribution using particle engineering involving porous particles with a low particle density [17]. However, there seems to be no established theory to explain the improvement in the variability of FPD in carrier-free DPI formulations.

In the present study, a 40 mg formulation (40 mg fine FK888 particles in the soft pellet form in No. 2 size capsules) using an E-haler was investigated to improve the variability of FPD in formulations using different lots of active ingredient. The possible reasons for the variability in FPD are also discussed in this study. The pulmonary absorption of 40 mg FK888 with the improved formulation was compared with that of earlier formulations in healthy volunteers.

I. MATERIALS AND METHODS

1. Materials

FK888 was provided by Fujisawa Pharmaceutical Co., Ltd. (Osaka Japan). α-Lactose of Pharmatose 200M and 325M (abbreviated 200M and 325M lactose, respectively), was supplied by DMV (The Netherlands). Pharmatose 200M has a wide particle size distribution including fine lactose particles (milled lactoses) while Pharmatose 325M has a narrow particle size distribution (sieved lactoses). These were used as supplied. Hard capsule shells (size No.2), produced from hydroxypropyl methylcellulose (HPMC), were purchased from Shionogi Qualicaps (Osaka Japan). Ethanol (analytical grade) was purchased from Hayashi Pure Chemical Industries Ltd (Tokyo, Japan) and used as received. An E-haler (Aventis Pharma) was used as the inhalation device.

2. Physicochemical properties of fine FK888 particles and lactose

The particle size distribution was measured with a laser diffraction size analyzer (LA-920, Horiba, Japan). Fine drug particles were dispersed in purified water which was pre-saturated with FK888 following sonication for 1 min. The suspension was then added dropwise to the measuring cell containing approximately 5 ml water pre-saturated with FK888 at a transmittance of around 0.8. The suspension was stirred during the measurements. Lactose particles were dispersed in ethanol pre-saturated with lactose, and the particle size distribution was measured as for FK888. Each sample was measured in triplicate.

The specific surface area of fine drug particles, 200M lactose, 325M lactose, and a mixture of fine drug particles and 325M lactose before pelletizing, was measured by the BET adsorption method with nitrogen gas using a Gemini surface analyzer (Gemini 2375, United States), and calculating the surface area by BET multi-point measurement.

3. Preparation of soft pellets

Lactose-free FK888 soft pellets: FK888 drug substance was pulverized into fine particles using an air-jet mill (JM-80, M&M Fryma). Then, 100 g fine FK888 particles was weighed in a 500-ml stainless-steel container, and the container was rotated at 30 rpm for 60 min in order to obtain spherical agglomerates. The spherical agglomerates were formed without any solvents for granulation, but using the nature of the fine particles in aggregates. The pellets were then passed through sieves of mesh size 810 and 75 μm to control the pellet size distribution. Five different samples of FK888 pellets were prepared using five different lots of bulk drug powders (FK888 bulk lot A, B, C, D and E). Following this, 10, 20 and 40 mg lactose-free FK888 pellets were transferred to No. 2 size HPMC capsules as formulations of 10, 20 and 40 mg FK888, respectively. The pellets were weighed accurately by hand to prevent the loaded quantity affecting the FPD. As far as FK888 pellets prepared using lot D with the lowest FPD of the five samples were concerned, in order to investigate the influence of the pellet size on the in vitro particle deposition, the pellets were also passed through 180-250 μm and 500-810 μm sieves to obtain two samples with different pellet size distributions.

FK888 soft pellets containing lactose: FK888 fine particles pulverized from FK888 bulk lot D, which showed the lowest in vitro aerodynamic performance in five samples of FK888 pellets with five different FK888 bulk lots, were selected in order to investigate the formulation improvement. Then, 12.5 or 25% of each lactose (200M or 325M lactose) as a weight ratio was added to the fine FK888 particles in advance of preparation of the soft pellets. Following this, 87.5 or 75 g of the fine FK888 particles and 12.5 or 25 g of each lactose were weighed in a 500-ml stainless-steel container and pelletized by rotation under the same conditions as for the lactose-free FK888 pellets preparation (abbreviated e.g. 12.5%-200M lactose pellets). The pellets were also passed through sieves of mesh size 75 and 810 μm. As far as the 25%-325M lactose pellets were concerned, five different samples were prepared using five different lots of bulk ingredients to evaluate the improvement.

In total, 45.7 and 53.3 mg of 12.5% lactose pellets and 25% lactose pellets were manually transferred to No. 2 size HPMC capsules as the formulation of 40 mg FK888. The particle size distribution of each sample of pellets was measured by passing through sieves with mesh sizes of 75, 180, 250, 350, 500 and 810 μm.

4. SEM photographs

SEM photographs of fine FK888 particles were taken with a Hitachi S-800 (Hitachi, Japan). Each sample was mounted on a metal plate, and sputtered with gold to a thickness of 10-30 nm under 6 x 10^{-2} mbar using an Ion Sputter E-1010 (Hitachi, Japan). SEM photographs of the pellets were taken by backscattered electron imaging using a Hitachi S-3000N (Hitachi, Japan).

5. *In vitro* deposition

The aerodynamic particle deposition of FK888 was measured using a Multistage Cascade Impactor consisting of eight stages with a preseparator and final filter (Copley, United Kingdom).