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European Journal of Pharmaceutics and Biopharmaceutics 59 (2005) 25–33
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Formulation development of inhalation powders for FK888 using the E-haler® to improve the inhalation performance at a high dose, and its absorption in healthy volunteers

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Received 22 December 2003; accepted in revised form 10 August 2004
Available online 7 October 2004

Abstract

FK888 is a candidate selective NK1 receptor antagonist, and it exhibits poor absorption from the gastrointestinal tract in healthy volunteers. In a previous study, the optimized dry powder inhaler (DPI) formulation with carrier lactose using the Spinhaler® was developed, although the maximum dose per capsule was only 5 mg because the fine particle fraction (FPF) was reduced at doses over 5 mg. The objective of this study was to develop an optimized DPI formulation for higher doses, such as 40 mg, with proportional systemic absorption. The Spinhaler® and E-haler® were used as the inhalation devices, and the in vitro deposition was evaluated using a multistage cascade impactor at different flow rates (28.3 and 60 l/min). When hydroxypropyl methylcellulose (HPMC) capsules were used as the container, and spherical soft agglomerates of fine FK888 particles (soft pellets) and the E-haler® were used, the fraction of particles emitted from the inhalation system (Em) was significantly improved, to over 80% of the nominal dose, and no significant difference was found between the airflow rates (84.3 ± 2.3% for 28.3 l/min, 88.1 ± 3.6% for 60 l/min). It was also found that the E-haler® was an extremely suitable device for obtaining the higher respirable particle percentage of emitted particles (RP) in the 40 mg formulation with the soft pellets contained in HPMC capsules (35.0 ± 1.8% for 28.3 l/min and 42.5 ± 3.5% for 60 l/min), compared with the Spinhaler® (13.8 ± 3.0% for 28.3 l/min and 28.9 ± 1.0% for 60 l/min). Using the formulations with the E-haler®, proportional systemic absorption was achieved up to 40 mg FK888 in healthy volunteers (62.91 ± 27.58, 103.70 ± 40.19 and 254.79 ± 85.01 ng h/ml as AUCs for 10, 20 and 40 mg FK888, respectively; $R^2 = 0.9641$). It is also expected that the E-haler® will act as an efficient device when a higher dose, such as 40 mg, is required in clinical situations.

Keywords: Dry powder inhaler; E-haler; Multistage cascade impactor; Pulmonary absorption; Soft pellets, HPMC capsule

1. Introduction

Dry powder inhalers (DPIs) have been developed for the treatment of respiratory diseases such as asthma or other localized lung conditions. Although pMDIs have also been popular for this purpose, there has been much interest in employing DPIs because of the ease of co-ordination with the respiratory cycle compared with pMDIs [1], less drug trapped in the oropharynx [2], and formulations without chlorofluorocarbons (CFCs) are more environmentally friendly [3]. In addition to localized lung diseases, the pulmonary route has attracted attention as a potential way of delivering drugs to the systemic circulation [4], especially drugs exhibiting a low membrane permeability in the gastrointestinal tract [5,6].

FK888(4R)-4-hydroxy-l-[(l-methyl-lH-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 gastrointestinal tract in

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0939-6411/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2004.08.004

healthy volunteers [7]. In a previous study, it was reported that a DPI formulation with carrier lactose using the Spinhaler® was developed in order to achieve systemic absorption. However, it was also found that the loading dose was limited to 5 mg as the maximum dose in a capsule for the Spinhaler® when the fine particle fraction, defined as the percentage delivered to stage two of the twin impinger (FPF), required to be maintained at different doses. The main reasons for the reduction in FPF at a higher loading dose in a capsule, were reductions in the fraction of particles emitted from the inhalation system (Em) and the respirable particle percentage of emitted particles (RP). It was considered that the reductions in Em and RP were caused by an increase in the excess amount of FK888 in relation to the entire surface of the carrier lactose. Because the excess fine drug particles form agglomerates, this results in a higher adhesive force than the force between the fine FK888 particles and carrier lactose. In the present study, a new DPI formulation was investigated for unit doses over 5 mg FK888, with proportional systemic absorption in healthy volunteers. In order to improve the Em, there were two options, namely, reducing the amount adhering to the surface of the inside wall of a capsule, and improving the flowability of the powder, as Kawashima et al. demonstrated that a drug/carrier mixture, which flowed and packed easily into a capsule, was emitted efficiently [8]. As far as the first option is concerned, the material of the capsule shell could influence drug adhesion [9]. In the DPI formulation with the Spinhaler®, a conventional gelatin capsule was adopted as the container for the unit dose. As far as the adhesive force of the particles is concerned, there are some reports describing the relationship between the adhesive force and the moisture content of a polymer film, whereby a higher moisture content results in a higher amount of adhering particles [10,11]. HPMC capsules have been recently developed as an alternative material to gelatin for hygroscopic and moisture-sensitive drugs, in the expectation that the fine drug particles will be less affected by moisture. A hard gelatin capsule usually contains 13–15% water as a weight ratio, and it is hard to reduce the water below 10% because this makes the capsule very brittle. In contrast, the HPMC capsule contains much less water compared with a hard gelatin capsule, 2–5%, and it retains the designated hardness even at moisture levels of 2% [12]. As far as the second option for improving the Em is concerned, a spherical soft agglomerate form of fine drug particles has been evaluated [13]. It was also considered that the use of an efficient inhalation device would be an appropriate way of obtaining a better RP as Steckel et al. reported [14]. The E-haler® was investigated as an efficient inhalation device, and compared with the Spinhaler® to improve the dispersion of unit doses over 5 mg. The pulmonary absorption of FK888 with the developed formulations using the E-haler® was evaluated in healthy volunteers.

2. Materials and methods

2.1. Materials

FK888 was provided by Fujisawa Pharmaceutical Co., Ltd (Osaka, Japan). α-Lactose (Phamatose® 200M, abbreviated 200M) was supplied by DMV (The Netherlands). Hard capsule shells (No. 2 in size), produced from gelatin and HPMC capsules, were purchased from Shionogi Qualicaps (Osaka, Japan). Ethanol (analytical grade) was purchased from Hayashi Pure Chemical Industries Ltd (Tokyo, Japan). Diethyl ether (agricultural test grade) was obtained from Wako Pure Chemical Industries Ltd (Osaka, Japan). The chemicals were used as received.

A Spinhaler®, and an E-haler® which had been developed as a successor to the Spinhaler® for INTAL® by Aventis Pharma (as shown in Fig. 1), were used as the inhalation devices.

2.2. Preparation of inhalation powders

In order to investigate the effectiveness of HPMC capsules and soft pellets on the in vitro deposition of drug particles, the following formulations were prepared. FK888 drug substance was pulverized using an air-jet mill (JM-80, M and M Fryma). Then, 100 g fine drug 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 (Soft pellets). The soft pellets were then passed through sieves of mesh size 810 and 75 μm to control the pellet size distribution. *Fine particles in gelatin capsules:* 40 mg fine drug particles was transferred to a No. 2 size gelatin capsule manually. *Fine particles in HPMC capsules:* 40 mg fine drug particles was transferred to a No. 2 size HPMC capsule manually.

Fig. 1. Photograph of E-haler®.

Soft pellets in HPMC capsules: 40 mg soft pellets was transferred to a No. 2 size HPMC capsule manually.

For pulmonary absorption studies using the E-haler® in healthy volunteers, the following formulations, which contained lactose as a bulking agent, were also prepared. The FK888 drug substance was blended with 200M lactose as supplied at a 50:50 weight ratio. The blended powder was then pulverized using an air-jet mill into fine particles of FK888 and 200M lactose. The pellets were prepared using the pulverized mixture in the same manner as the 40 mg formulations without the lactose. Aliquots (20 and 40 mg) of the pellets were transferred to a No. 2 size HPMC capsule manually, as for the 10 and 20 mg formulations of FK888. An E-haler® was used as the inhalation device.

The particle size distribution of the fine drug particles was measured with a laser diffraction size analyzer (LA-920, Horiba, Japan). The fine drug particles were dispersed in purified water which was pre-saturated with FK888 following sonication for 1 min. The suspension was then added drop-wise 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. In the case of the pulverized mixture, the mixture of FK888 and lactose was dispersed in the FK888 saturated water solution to dissolve the lactose in advance of the measurements. The median particle sizes were 2.1 ± 0.2 and 2.3 ± 0.1 μm (as the mean ± SD of three runs) respectively. As far as the particle size of the pulverized lactose was concerned, the pulverized mixture of FK888 and lactose was dispersed in ethanol saturated with lactose to dissolve the drug particles in advance of the measurements. The lactose particle size was measured as for FK888. The median particle size was 7.2 ± 0.8 μm (as the mean ± SD of three runs).

2.3. 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, UK). In order to investigate the influence of the airflow rate on the in vitro deposition, two flow rates of 28.3 and 60 l/min. were selected. Capsules containing each formulation were loaded into the Spinhaler® and the E-haler®, which were fitted with a moulded rubber mouthpiece. *Spinhaler®*: The capsule was pierced to produce two emitting pores for dispersing the particles. The Spinhaler® was attached to the throat of the Cascade Impactor immediately after piercing. The experiments were conducted at air flow rates of 28.3 and 60 l/min. for 8 and 4 s, respectively. *E-haler®*: The capsule body was cut to disperse the particles. The E-haler® was attached to the throat of the Cascade Impactor immediately after cutting. The experiments were conducted at air flow rates of 28.3 and 60 l/min. for 8 and 4 s, respectively. The flow rate of 40 l/min. for 6 s, which produced a pressure drop of 4 kPa over the E-haler®, was also measured.

After discharging, the capsule was removed from the inhaler device. The drug remaining in the capsule, adhering to the device, and the deposits at eight stages, preseparator and filter were collected with solvents (50% V/V ethanol) for analysis. The rinsed solutions were then diluted to suitable volumes and the drug contents were determined by HPLC under the following conditions: TSK gel ODS-80TM CTR column 5 μm C18-100 Å (Waters, 10 cm × 4.6 mm I.D.), with methanol: pH 6.5 phosphate buffer (70:30, V/V) as a mobile phase at a flow rate of 1.4 ml/min and a detection wavelength of 225 nm.

The aerodynamic cut-off diameter of stage 1 of the Cascade Impactor was 5.8, 4.9 and 4.0 μm at 28.3, 40 and 60 l/min., respectively [15]. The particles captured in stages 1–7 and the filter were expected to be deposited in the lung lobe or trachea after inhalation. This was defined as the fine particle dose (FPD).

The percentages of the FPD compared with the nominal dose and the emitted dose from the inhalation system were defined as FPF and RP, respectively, and used to describe the inhalation properties of DPIs by means of the following equations:

$$\mathrm{FPF}(\%) = \frac{\mathrm{FPD\ (mg)}}{\mathrm{Nominal\ Dose\ (mg)}} 100 \quad (1)$$

$$\mathrm{RP}(\%) = \frac{\mathrm{FPD\ (mg)}}{\mathrm{Em\ (mg)}} 100 \quad (2)$$

2.4. Pulmonary absorption studies in healthy volunteers

Sixteen male volunteers in total, aged 20 to 24 years (mean age 22 years) with a body weight ranging from 52.5 to 69.1 kg (mean weight 60.2 kg), were given 10, 20 or 40 mg FK888 by the pulmonary route using HPMC capsules containing the pellets via an E-haler®. In order to investigate the pulmonary absorption using the E-haler®, the 5 mg formulation using the Spinhaler® (the mixture of 5 mg fine drug particles and 35 mg 200M lactose was used to fill a No. 2 size gelatin capsule) was also used for a comparison. Six male volunteers, aged 21 to 44 years (mean age 29 years) with a body weight ranging from 55.5 to 82.7 kg (mean weight 69.2 kg), were given 10 or 20 mg FK888 by the pulmonary route using two or four capsules via Spinhaler®. All subjects were required to practice the correct inhaler technique using the Spinhaler® and E-haler® with placebo in advance of the studies.

After application, blood samples were collected from an arm vein at designated time-periods. Plasma levels of FK888 were determined by a sensitive enzyme immunoassay (EIA). The EIA method involved extracting FK888 from plasma with diethyl ether under basic conditions

(1/10 M sodium tetraborate adjusted to pH 8.2 with hydrochloric acid), followed by purification by solid-phase extraction with silica sorbent. The determination limit of FK888 was 0.1 ng/ml plasma. The area under the concentration/time curve ($AUC_{0-24\ h}$) was calculated by the trapezoidal method.

2.5. SEM photographs

SEM photographs of fine FK888 particles were taken with a Hitachi S-800 electron microscope (Hitachi, Japan). Each sample was mounted on a metal plate, and sputtered with gold to a thickness of 10–30 nm under 6×10^{-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-3000 N (Hitachi, Japan).

2.6. Statistical tests

The in vitro deposition data were examined for statistically significance differences by Student's unpaired *t*-test. A *P*-value of <0.05 was considered significant.

3. Results and discussion

3.1. Improvement in the emitted dose (Em)

Fig. 2A shows the percentage of Em discharged from a capsule and that remaining in a capsule with each formulation of 40 mg FK888 given by Spinhaler®, measured using a Cascade Impactor. The Em of fine drug particles was slightly improved on average by using HPMC capsules at both flow rates of 28.3 and 60 l/min., from

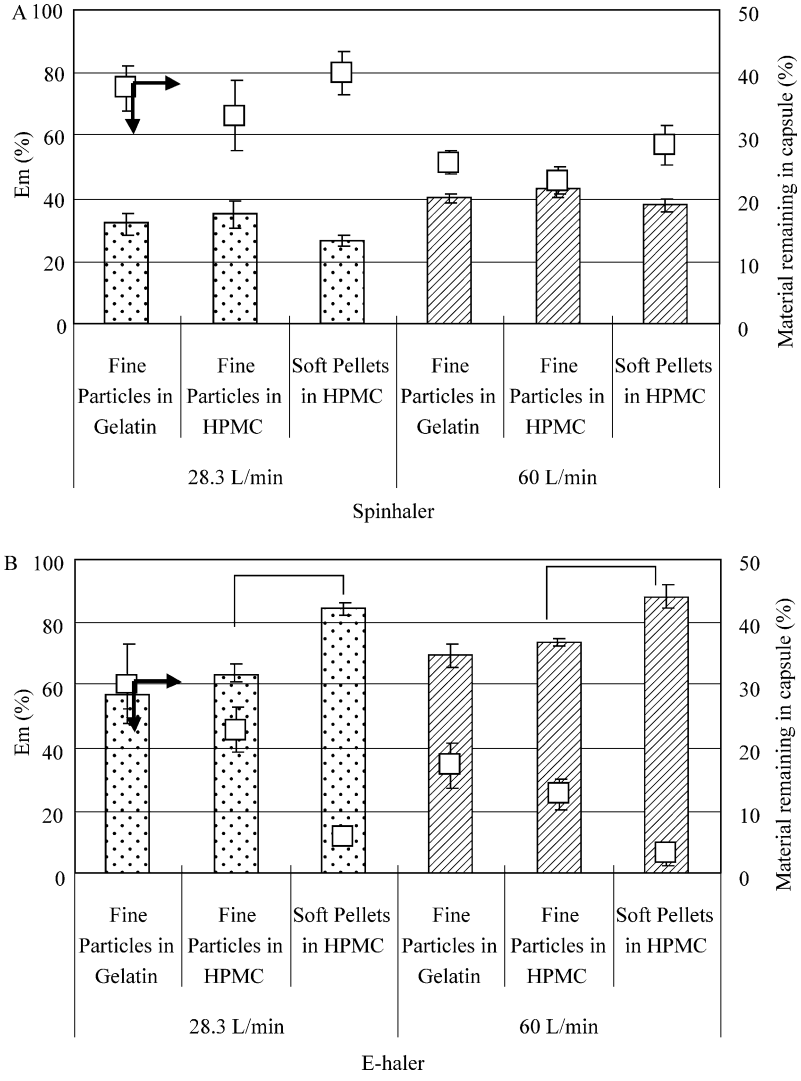

Fig. 2. Comparison of the Em and material remaining in a capsule after discharging from a Spinhaler® (A) and E-haler® (B) with the formulations of fine FK888 particles in a gelatin capsule, fine drug particles in an HPMC capsule, and soft pellets in an HPMC capsule. Data are expressed as the mean ± SD of three determinations. $^{*}P<0.01$.

31.9±3.64 to 34.9±4.23% and from 41.1±2.76 to 43.1±2.67%, respectively. When the soft pellet dosage form was used, the Em was reduced at both flow rates. The values of Em were 26.5±1.70 and 37.7±1.93% for 28.3 and 60 l/min., respectively. The results of the material remaining in capsules also indicated that this was reduced by using HPMC capsules, although the improvement was not statistically significant. As far as the soft pellet formulation was concerned, it appeared that the powder fluidization using soft pellets did not affect the enhancement of the emitted dose because the emission force, which was the pressure drop across the capsule walls towards the perforations, was not great enough. In the case of the Spinhaler®, the formulation containing 40 mg fine drug particles in an HPMC capsule showed the highest Em at both flow rates, and the values of Em showed a significant difference between the flow rates ($P < 0.05$). Fig. 2B shows the percentages of Em discharged from a capsule and the material remaining in a capsule with each formulation of 40 mg FK888 given by E-haler®, measured using a Cascade Impactor. The Em using the E-haler® was also slightly improved on average by using an HPMC capsule at both flow rates of 28.3 and 60 l/min., from 56.7±4.39 to 63.7±2.61% and from 69.2±3.90 to 73.7±1.16%, respectively. When the soft pellet dosage form was applied, the Em was significantly increased compared with the fine drug particles at both flow rates. The values of Em were 84.3±2.25 and 88.1±3.55% for 28.3 and 60 l/min., respectively. The results of material remaining in the capsules also indicated that the Em was increased by using an HPMC capsule. As far as the soft pellet formulation using the E-haler® was concerned, the soft pellets appeared to be easily fluidized from the capsule because of the better flowability compared with the fine drug particles. It is generally accepted that smaller particles exhibit a lower flowability [16]. In order to obtain an improved flowability of the fine drug particles, spherical agglomerates were used in an attempt to obtain apparently bigger particles as shown in Fig. 3. The flowability of the soft pellets was compared with that of fine drug particles using Carr's Index, when an improvement was found (data are not presented). It was also considered that the mechanism of the E-haler® for discharging the powders might be better than that of the Spinhaler® because part of the capsule was cut, and then tilted when discharged as shown in Fig. 4. In the case of the E-haler®, the formulation containing 40 mg soft pellets in an HPMC capsule showed the highest Em at both flow rates, and no significant difference was observed between the flow rates.

By using a combination of HPMC capsules, soft pellets and the E-haler® as the delivery device, it was found that an Em of over 80% was achieved for the dose loaded in a capsule, and the effect of the airflow rate on Em was also improved compared with that of the Spinhaler®.

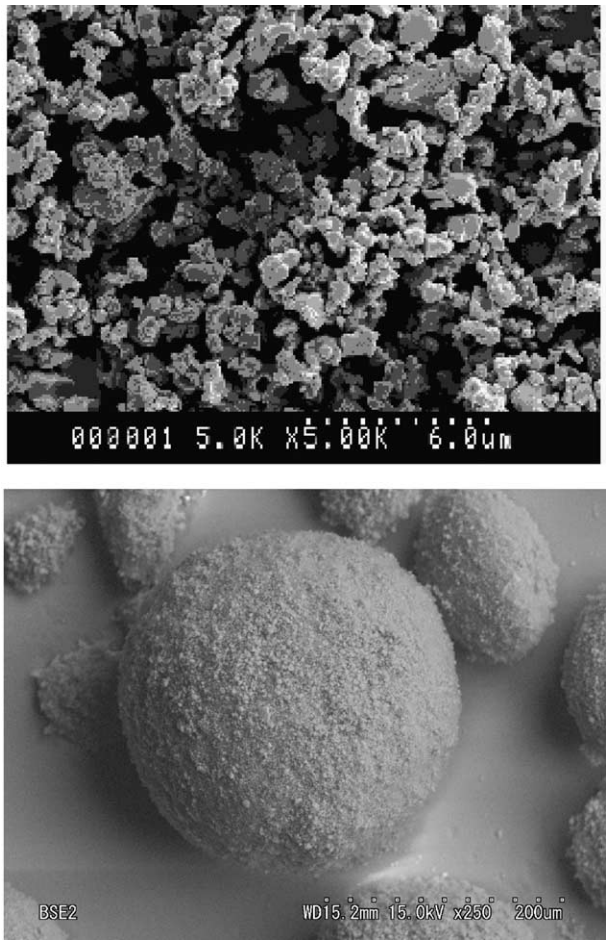

Fig. 3. Scanning electron microscope images of fine FK888 particles (A) and FK888 pellets (B). Scale bars are 6 μm (A) and 200 μm (B).

3.2. Improvement in the respirable particle fraction (RP)

Fig. 5A shows the percentages of RP with each formulation of 40 mg FK888 given by Spinhaler®, measured using a Cascade Impactor. It was observed that 13.8–17.7% was only de-agglomerated and distributed as fine drug particles at 28.3 l/min. At 60 l/min., a higher RP than 28.3 l/min was observed for all formulations tested, and the values were 27.2–29.0%. Consequently, a significant

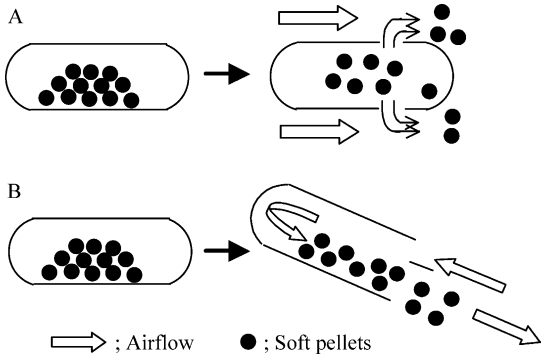

Fig. 4. Mechanism for the soft pellets emitted from the capsule using the Spinhaler® (A) and E-haler® (B). Scale bars are 6 μm (A) and 200 μm (B).

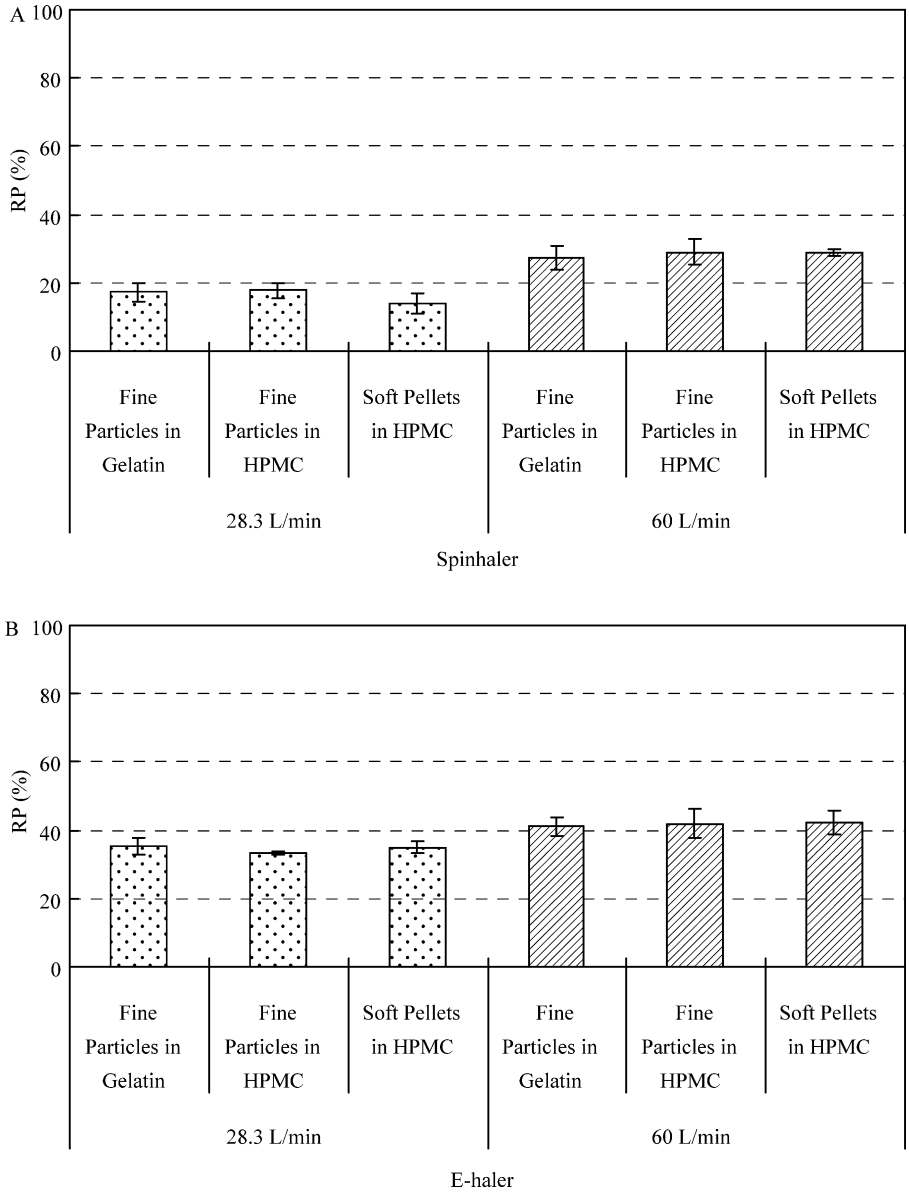

Fig. 5. Comparison of the RP after discharging from a Spinhaler® (A) and an E-haler® (B) with the formulations of fine FK888 particles in a gelatin capsule, fine drug particles in an HPMC capsule, and soft pellets in an HPMC capsule. Data are expressed as the mean ± SD of three determinations.

difference was found between the airflow rates ($P < 0.05$). As far as the dosage type was concerned, no significant differences were observed among the three formulations of fine drug particles in gelatin or HPMC capsules, and the soft pellets in HPMC capsules at each airflow rate. The soft pellets in HPMC capsules showed a slightly poorer RP than the fine drug particles in both gelatin and HPMC capsules at 28.3 l/min. Fig. 5B shows the percentage of RP with each formulation of 40 mg FK888 given by E-haler®, measured using a Cascade Impactor. It was observed that there were no significant differences among the dosage formulations at each airflow rate. It was also observed that the values at 60 l/min. were significantly higher than those at 28.3 l/min., although the difference was smaller than that using the Spinhaler®. As far as differences in the inhalation device were concerned, it was found that the RP using the E-haler® was significantly higher than that using the Spinhaler® at both airflow rates. In the case of the soft pellets in HPMC capsules, the values using the E-haler® were approximately 2.5 and 1.5 times higher than that using the Spinhaler® at 28.3 and 60 l/min., respectively. Consequently, it was found that the airflow rate was less affected by using the E-haler®.

3.3. Improvement in the fine particle fraction (FPF)

Fig. 6A shows the percentages of FPF with each formulation of 40 mg FK888 given by Spinhaler®, measured using a Cascade Impactor. It was observed that only 3.7–6.2% was distributed as fine drug particles at

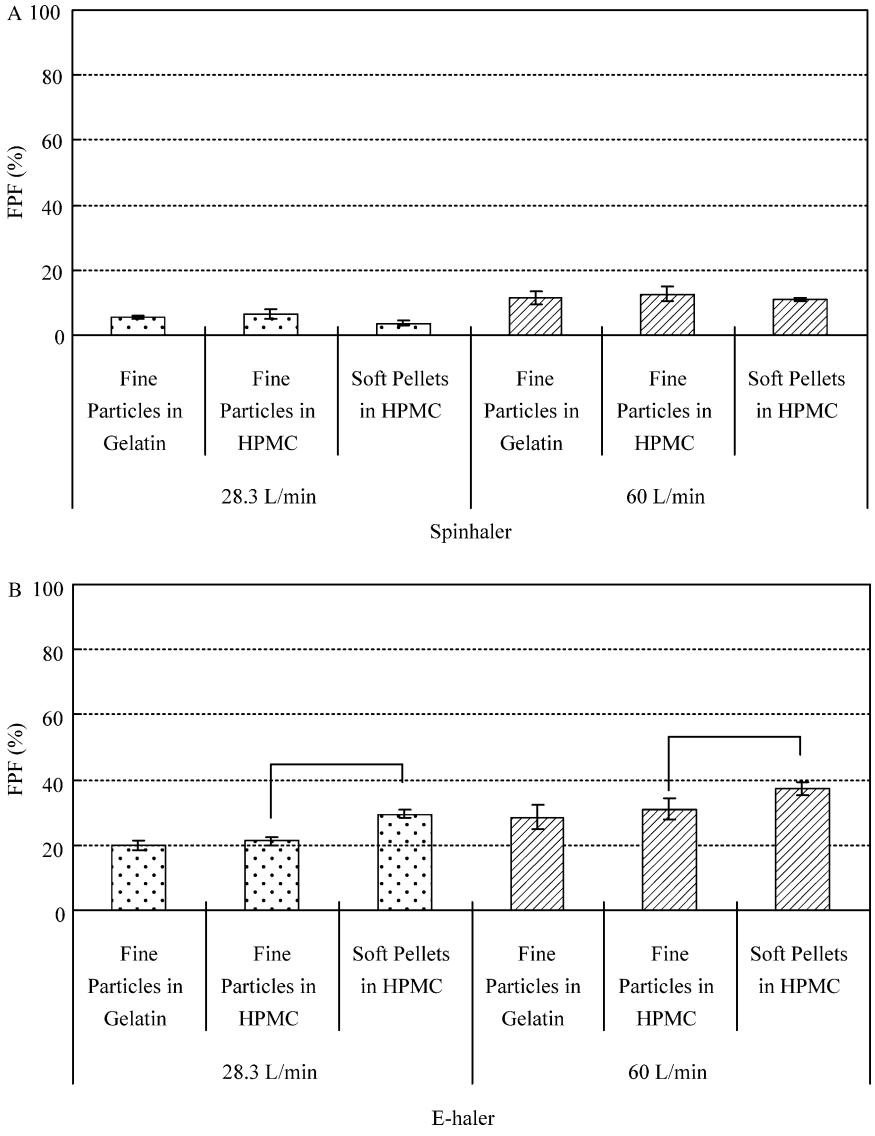

Fig. 6. Comparison of the FPF after discharging from a Spinhaler® (A) and an E-haler® (B) with the formulations of fine FK888 particles in a gelatin capsule, fine drug particles in an HPMC capsule, and soft pellets in an HPMC capsule. Data are expressed as the mean ± SD of three determinations. $*P < 0.01$, $**P < 0.05$.

28.3 l/min. At 60 l/min., a higher FPF than 28.3 l/min was observed for all formulations tested, and the values of the material remaining were only 10.9–12.6%. The differences between the airflow rates were approximately 2–3 times higher at 60 l/min. As far as the dosage type is concerned, no significant differences were observed among the three formulations of the fine drug particles in gelatin or HPMC capsules, and the soft pellets in HPMC capsules at each airflow rate, while the soft pellet formulation had the lowest FPF due to the lowest Em at both airflow rates. Fig. 6B shows the percentage of FPF with each formulation of 40 mg FK888 given by E-haler®, measured using a Cascade Impactor. It was observed that there were no significant differences between the fine drug particle formulation in gelatin or HPMC at each airflow rate. The pellet formulation had the highest FPF because it had the highest

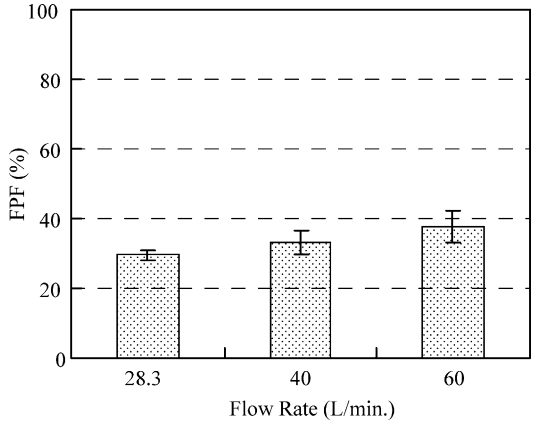

Fig. 7. Comparison of the FPF after discharging from the E-haler® with FK888 soft pellets in an HPMC capsule at different airflow rates. Data are expressed as the mean ± SD of three determinations.

Table 1
Summary of the pharmacokinetics parameters (mean ± SD) of FK888 after inhalation using Spinhaler or E-haler in normal healthy volunteers

Nominal dose (mg/body)	Device	No. of volunteers	T_{max} [a] (h)	C_{max} [a] (ng/ml)	$AUC_{0\text{-}24\ hr}$ [a] (ng h/ml)
10(5×2)[b]	Spinhaler	6	0.19 ± 0.09	41.41 ± 20.51	73.94 ± 28.19
20(5×4)[b]	Spinhaler	6	0.17 ± 0.09	95.13 ± 38.09	141.70 ± 19.25
10	E-haler	8	0.25 ± 0.00	31.19 ± 13.08	62.91 ± 27.58
20	E-haler	8	0.31 ± 0.12	49.71 ± 27.87	103.84 ± 40.19
40	E-haler	8	0.17 ± 0.09	172.70 ± 101.30	254.79 ± 85.01

[a] Data are presented as mean ± SD
[b] 5 mg formulation was applied two or four times.

Em. It was also observed that the values at 60 l/min. were significantly higher than those at 28.3 l/min., although the difference was smaller than that obtained using the Spinhaler®. As far as differences with respect to the inhalation device were concerned, it was found that the RP using the E-haler® was significantly higher than that using the Spinhaler® at both airflow rates. In the case of the soft pellets in HPMC capsules, the values using the E-haler® were approximately 8.1 and 3.4 times higher than that using the Spinhaler® at 28.3 and 60 l/min, respectively. As shown in Fig. 7, no significant difference was obtained between 28.3 and 40 l/min., and 40 and 60 l/min. ($P = 0.165$, and 0.116, respectively), although a significant difference was observed between 28.3 and 60 l/min ($P = 0.004$). In the case of the E-haler®, the airflow rate of 40 l/min produces a pressure drop of 4 kPa. When the FPF at 40 l/min was considered as the standard inhalation condition because of a pressure drop of 4 kPa, the FPF at 28.3 l/min was 89.4% that at 40 l/min, and the FPF at 60 l/min was 113.2% that at 40 l/min. It was considered that the variability in the airflow rate would have less effect on the FPF when using the E-haler®, compared with the Spinhaler®.

3.4. Pulmonary absorption in healthy volunteers

The PK parameters after pulmonary administration of FK888 with the developed formulations using the E-haler® are listed in Table 1. When the drug was given by the pulmonary route as a dose of 10, 20 or 40 mg in a single capsule to healthy volunteers, the Cmax was 31.19 ± 13.08, 49.71 ± 27.87 and 172.70 ± 101.30 ng/ml, and the $AUC_{0\text{–}24\ h}$ was 62.91 ± 27.58, 103.84 ± 40.19, and 254.79 ± 85.01 ng h/ml respectively. On the other hand, when the drug was given as two or four capsules of 5 mg lactose-carrier formulation for single doses of 10 and 20 mg, the Cmax was 41.41 ± 20.51 and 95.13 ± 38.09 ng/ml, and the $AUC_{0\text{–}24\ h}$ was 73.94 ± 28.19 and 141.70 ± 19.25 ng h/ml, respectively. The AUC was increased in relation to the loaded dose, as expected from the in vitro aerodynamic properties in formulations with soft pellets using the E-haler®. When the AUC values obtained by the Spinhaler® were compared, both AUCs were located on the same proportional line as those obtained by the E-haler® (the correlation coefficient was 0.9641). This confirmed that the new formulation obtained by the E-haler® resulted in the proportional systemic absorption of FK888 when using a single capsule even at high doses of 10 to 40 mg. At all doses, rapid absorption was observed with T_{max} values ranging from 0.17 to 0.31 h.

4. Conclusion

The E-haler® is an extremely efficient device for obtaining a high RP at a high dose range of 10–40 mg FK888 in a single capsule, even for formulations without carrier lactose, although the Spinhaler® led to a limit on the RP in the dose range used due to greater adhesion between the fine drug particles. The use of HPMC capsule shells, and the soft pellet form of fine drug particles are effective approaches to obtain a better Em as far as FK888 is concerned. Using the formulation with the E-haler®, proportional systemic absorption was achieved up to 40 mg FK888 for a single capsule application in healthy volunteers. It is also expected that the DPI using the E-haler® offers an alternative way of delivering poorly absorbed oral drugs at higher doses such as 40 mg.

Acknowledgements

We wish to thank David Shadwell for providing the E-haler®.

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