ELSEVIER

International Journal of Pharmaceutics 168 (1998) 59–68

international journal of pharmaceutics

Particle design of Wogon extract dry powder for inhalation aerosols with granulation method

Tomoaki Hino [1], Takanori Serigano, Hiromitsu Yamamoto, Hirofumi Takeuchi, Toshiyuki Niwa [2], Yoshiaki Kawashima *

Gifu Pharmaceutical University, 5-6-1, Mitahora-higashi, Gifu 502, Japan

Received 18 November 1997; received in revised form 14 January 1998; accepted 7 February 1998

Abstract

Aerosolization of Wogon extract powder (WEP) is difficult due to its strong adhesiveness to the inhalation device (Spinhaler®) on emitting. To improve inhalation property, WEP was granulated by slugging, tumbling and agitation methods. The inhalation properties were measured in vitro with a cascade impactor and a twin impinger. The inhalation behaviors of granules were determined by granulation method employed and inhalation conditions such as inhaled air flow rate. It was found that a key factor determining the inhalation property was the mechanical strength and the particle size of the granules. Soft granules were easily dispersed into air stream and were disintegrated to fine respirable particles. Whereas they adhered strongly to the inside wall of the device on inhalation. Consequently, a proportional correlation between the residual fraction in the inhalation device and the respirable fraction (*RF*) of the cascade impactor or the twin impinger was observed. A new inhalation index, effective index (*EI*), was proposed to evaluate the overall inhalation property by taking the residual fraction and *RF* into account. Tumbling granulation method provided the largest *EI*, and improved the inhalation property of original WEP. The *EI*s of granules prepared by tumbling granulation and slugging granulation with lower compaction pressure were larger than that of marketed disodium cromoglycate inhalation powder, Intal®.

Keywords: Aerosol; Dry powder inhalation; In vitro evaluation; Lung deposition patterns; Granulation

1. Introduction

Inhalation aerosols have been used in the asthmatic and bronchial therapies because good clinical effects and reductions of systemic side effects are achieved by delivering moderate amount of drugs directly to the affected parts. Further, the

* Corresponding author.

[1] Present address: Faculty of Pharmaceutical Science, University of Tokushima, 1-78-1, Sho-machi, Tokushima 770, Japan.

[2] Present address: Formulation Development Laboratory, Pfizer Pharmaceuticals Inc., 5-gochi, Taketoyo-cho, Chita-gun, Aichi 470-23, Japan.

0378-5173/98/$19.00
PII S0378-5173(98)00083-0

possibilities of administration of peptides and proteins via alveoli into systemic circulation have been demonstrated (Komada et al., 1994; Niwa et al., 1995). Among the aerosol inhalation systems, much attention has been paid to dry powder inhalation aerosols (DPIs) as alternatives to pressurized metered dose inhalation aerosols, because: (1) DPIs use no propellants; and (2) the inhaled dose of active component is easily controled with synchronized emission from the device with inhalation. Such advantages have been stimulating to develop new formulations and inhalation devices of DPIs.

It has been reported that the particle size of aerosols is one of the key factors that determines the deposition site of inhaled particles in the human respiratory tract on inhalation. In literatures, inhaled particles with diameters of 1.0–6.0 μm (Timsina et al., 1994), under 7 μm (Newman et al., 1994) or 0.5–8.0 μm (Davies et al., 1976) defined as 'respirable particles' are assumed to be deposited on the bronchi or alveoli. Particles larger than respirable sizes are generally deposited on the upper respiratory tracts such as throats by the inertial impaction and then expelled from the respiratory pathway. Therefore, micronized drug powders are formulated in DPIs. However, micronization leads to the difficulty in the handling (e.g. dispensing and filling) of drug particles caused by their strong adhesive and cohesive properties. Moreover, a large amount of the drug is adhered and remains in a capsule and in an inhalation device on inhalation. This results in unreliable and unstable dosing. To solve these problems, physical properties of drug particles are modified by granulation (granulation method) such as Intal® and agglomerated isoprenaline sulphate (Kassem et al., 1991) or depositing fine drug particles on coarse carrier particles, e.g. lactose (carrier method; Timsina et al., 1994). These modified drugs are designed to play as 'respirable particles' when dispersed with an inhalation device.

In the granulation method, the relationship between the physical properties of DPI granules and the inhalation properties have not been fully understood. In the present paper, we aimed to find key parameters to improve handling and inhalation properties of Wogon extract powder (WEP), used as a model inhalation dry powder. This material has been expected to develop as anti-asthmatic agent originated to natural products (Koda et al., 1970), by means of DPI. The WEP is indispersible fine powder as found generally with dried extract powder.

The WEP granules with various mechanical strength were prepared to disperse them in different manners when emitted from inhalers. The residual drug percent in the inhalation device and respirable fraction (*RF*), expected to reach bronchi and lung after actuation of the loaded drug amount, were used as indices to describe inhalation properties. The desirable formulation provides a low percentage of the residual drug in the device and a high percentage of *RF*. A new index was proposed by taking the above two parameters into account to evaluate the inhalation properties of granules, depending on the granulation method. Micromeritic properties influencing the inhalation properties were clarified to develop ideal DPI formulations.

2. Materials and methods

2.1. Materials

The WEP was supplied from Ichimaru Pharcos (Japan), which was a ground product of ethanol-extracted powder from the root of *Scutellaria baicalensis Georgi (Labiatae)*, having particle diameter of 0.6–9.3 μm, weight-averaged diameter, $D_{50} = 3.6$ μm and geometric standard deviation (GSD) = 1.89 as shown in Table 1. The WEP contains flavonoids, i.e. baicalein (58.6%) and wogonin (13.5%) etc. Disodium cromoglycate inhalation powder (Intal®, Fisons Pharmaceuticals, UK) and its inhalation device (Spinhaler®, Fisons Pharmaceuticals, UK) were obtained from commercial sources. Other chemicals used were of analytical grade.

2.2. Preparation of WEP granules

The WEP granules were prepared, following three ways to have various mechanical strength.

Slugging granules were prepared by compressing WEP (2 g) in a die with diameter of 20 mm at 5, 10 and 30 kgf/cm^2 using Autograph AG-5000D® (Shimadzu, Japan) followed by crushing the resultant slugs with a rotary disintegrator (TG2S and KU-1, Erweka, Germany). Referred to compaction pressures employed, the granules were named SG 5, SG 10 and SG 30, respectively.

Tumbled granules (TG) of WEP were prepared by tumbling method. Five hundred milligrams of WEP were weighed on a lidded dish with diameter of 8 cm, and the dish was shaken with a row tap shaker for 3 min. During tumbling, WEP was uniformly agglomerated and spheronized.

Agitation granules (AG) were prepared with a high speed agitation granulator (Super mixer type, Toyo Packing, Japan). Eighteen milliliters of distilled water as binder, was added slowly to 30 g of WEP with agitating and the product was dried with an oven at 60°C for 6 h.

The SG 5, SG 10, SG 30, TG and AG were sieved and the particles fractionated between 180 and 500 μm were used as standard test samples for inhalation. The mean diameters of granules were almost the same irrespective of the preparation method of granules, and their GSDs were reasonably small (Table 1). To evaluate the effect of granule size on inhalation property, SG 5 was further fractionated into three ranges, i.e. 74–180, 180–500 and 500–840 μm.

Table 1
Micromeritic properties of WEP granules

Sample	D_{50} (μm)	GSD[a] (——)	Angle of repose[b] (°)
Original powder	3.6	1.89	47.1 ± 0.1
SG 5	293	1.33	38.2 ± 0.8*
SG 10	301	1.45	39.3 ± 0.7*
SG 30	307	1.38	40.6 ± 0.9*
TG	311	1.38	37.8 ± 1.0*
AG	302	1.40	30.3 ± 0.3*

[a] Geometric standard deviation.
[b] Mean $\pm$ S.D. ($n = 6$).
Statistical significance: *$p < 0.001$ compared with original powder.

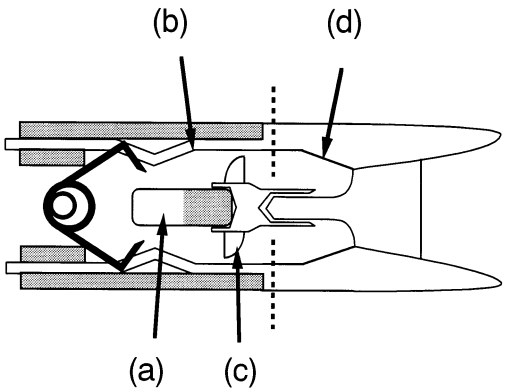

Fig. 1. Composition of the Spinhaler®: (a) Capsule; (b) Body; (c) Propeller; and (d) Mouthpiece.

2.3. Evaluation of inhalation property

Inhalation properties of the WEP granules were evaluated with a cascade impactor (Andersen sampler AN-200, Andersen, USA) and a twin impinger (COPLEY instruments, UK). These instruments for characterization of DPIs were validated in the previous paper (Hino et al., 1997). Twenty milligrams of each sample was loaded in a No. 2 gelatin hard capsule (Japan Elanco, Japan), and the capsule was placed to a Spinhaler®. On the wall of the capsule, two pinholes were pierced with a needle equipped in the Spinhaler®. The Spinhaler® was attached to the cascade impactor or the twin impinger via a mouthpiece. Then, the system was connected to a vacuum pump and the dry powder aerosols were emitted from the Spinhaler® for proper period under the required air flow rate. After emission, inside of the Spinhaler®, mouthpiece and each stage of the apparatus were rinsed with proper solvent (methanol and distilled water for WEP and Intal®, respectively). On characterizing the deposition of residual drug in the inhalation device, the device fraction was divided into four fractions, i.e. capsule, body, propeller and mouthpiece, as shown in Fig. 1. The rinsed solutions were diluted to suitable volumes with the rinsing solvent and the drug contents in the solutions were determined spectrophotometrically with a spectrophotometer (UV-160A, Shimadzu, Japan). The wavelength for the determination of WEP and Intal® were 275 and 328 nm, respectively.

The air flow rates of the cascade impactor were 30, 40 or 60 l/min and the actuation time was 30 s. The 50% cut-off diameter of each stage of the cascade impactor was determined by converting from the nominal size ($Dp_{50(28.3\ \mathrm{l/min})}$) to the corresponding size under the tested air flow rate of Q l/min ($Dp_{50(Q\ \mathrm{l/min})}$) with Eq. (1) (Biddiscombe et al., 1993).

$$Dp_{50(Q\ \mathrm{l/min})} = Dp_{50(28.3\ \mathrm{l/min})} \times \sqrt{\frac{28.3}{Q}} \quad (1)$$

In the characterization of inhalation property by cascade impactor under the air flow rate of 30 l/min, the *RF* was defined as the summation of percentages of drug deposited on the 1.1–6.8 μm fractions.

The flow rate and actuation time of the twin impinger were 60 l/min and 5 s, respectively. The volumes of capturing solvents in the upper (stage 1) and lower (stage 2) stages of the impinger were 7 and 30 ml, respectively. The *RF* was defined as the percentage of drug deposited in the stage 2 fraction.

The inhalation property were evaluated with the residual drug percent in the inhalation device and the *RF*%.

In all trials, measurement was carried out more than three times and the mean values are represented in the figures and tables in the text.

2.4. Physical properties of WEP granules

The flowability of the WEP granules was evaluated by means of angle of repose. The powder sample was piled on a plate by pouring through a funnel positioned at a fixed height (75.5 mm) over the plate. The angle of repose was directly measured with the photograph taken of the heap formed. The angle of repose of original WEP was relatively large (47.1°), which was decreased by granulation, resulting in the improvement of flowability of WEP as shown in Table 1.

The particle size distributions of the granules dispersed with a dry disperser (PD-10S, Tohnichi Computer, Japan) were measured with a laser diffraction method (LDSA-2400A, Tohnichi Computer, Japan; Nozzle dispersion method). The dry disperser was operated with the compressed air of 0.5, 1.1 and 1.9 kgf/cm^2 (corresponding air flow rate; 20, 30 and 40 l/min, respectively).

The hardness of WEP granules was measured with a particle hardness tester (GRANO®, Okada Seiko, Japan). The SG 5, SG 10, SG 30 and AG granules fractionated to 16–32 mesh (500–1000 μm) were used for measurement. Granule hardness (H (Pa)) was calculated with Eq. (2) (Hiramatsu et al., 1965).

$$H = \frac{2.8P}{\pi D^2} \quad (2)$$

where, P and D are the load required to break the granule (N) and the particle diameter (m), respectively.

3. Results and discussion

3.1. Inhalation properties characterized by cascade impactor and twin impinger

The inhalation properties of WEP granules evaluated with the cascade impactor are shown in Fig. 2. The fraction of residual drug in the inhalation device and the *RF* are shown in Fig. 3.

Large amounts of original WEP (48.1 ± 14.8%) were remained in the device with large standard deviation. This problem was solved by granulation. The TG had a slightly smaller value of residual drug in the inhalation device. The SGs and AG had significantly ($p < 0.01$) smaller values than the original powder. The *RF*s of WEP granules except AG were similar (SG 10, SG 30) or significantly larger ($P < 0.01$; SG 5, TG) than that of commercially accepted inhalation powder, Intal®, indicating that the WEP granules are acceptable as possible candidates for DPIs. With regard to SGs, the *RF* and device fraction decreased with increasing compaction pressure to prepare the slug.

The inhalation properties of WEP granules evaluated with the twin impinger are shown in Fig. 4. Significantly smaller ($p < 0.05$) amounts of SG 10, SG 30 and AG were remained in the

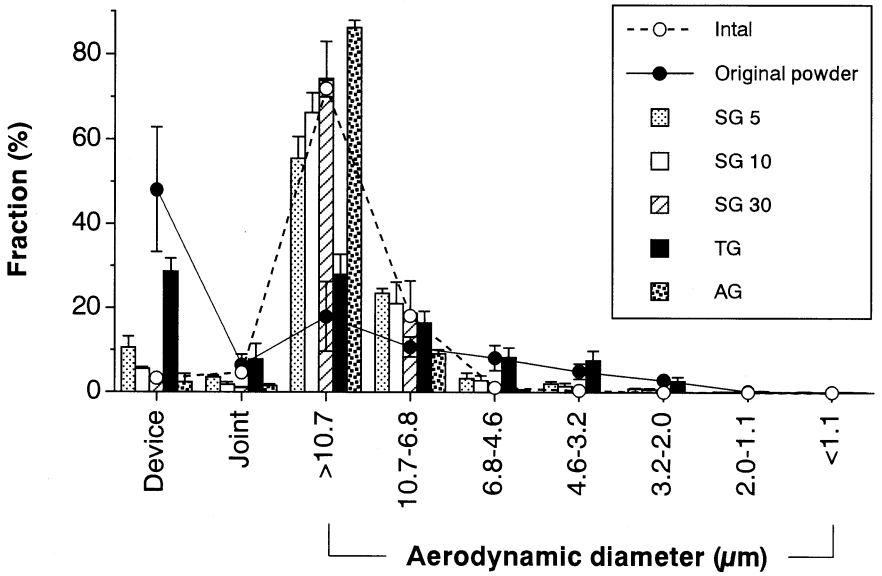

Fig. 2. Inhalation properties of WEP granules evaluated with cascade impactor. The values are represented as mean ± S.D. ($n = 3–5$).

device than that of original WEP as well as found with the cascade impactor. The residual drug in the inhalation device of original WEP determined by the twin impinger was lower than that by the cascade impactor. The SGs and TG showed higher residual drug percentage in the inhalation device with the twin impinger than the cascade impactor. Consequently, it was found that the SG 5 and TG did not significantly decrease in the residual drug fractions compared with original WEP.

The *RF* values of granules evaluated with the twin impinger (stage 2) were much higher than those with the cascade impactor. The granules except TG reduced the *RF* values significantly compared with original WEP.

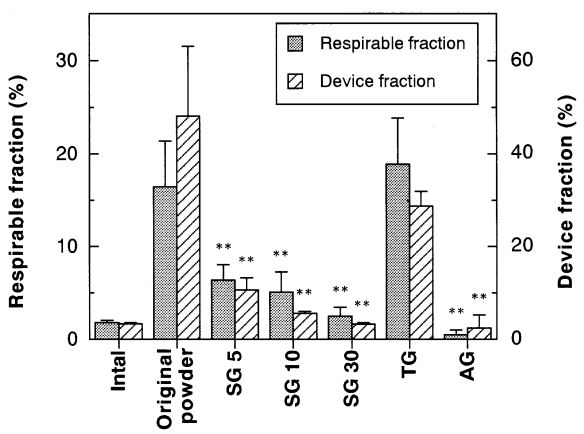

Fig. 3. Inhalation indices of WEP granules evaluated with cascade impactor. The values are represented as mean ± S.D. ($n = 3–5$). Statistical significance: $^{**}p < 0.01$ compared with the original powder.

3.2. Effect of air flow rate on the inhalation properties of WEP granules

The residual fraction in the inhalation device of original WEP determined by the twin impinger was smaller than that by the cascade impactor. The air flow rates were 60 and 30 l/min for the former and latter methods, respectively. The former rate was specified in British Pharmacopoeia (1993), and the latter rate was used because the cascade impactor was originally designed to operate at the rate of 28.3 l/min ($\approx$ 30 l/min; Hinds, 1982). The small value of the fraction remained in the device with the former method was due to the easier desorption of adhered drug on the inner walls of the capsule and device under higher flow rate than the latter method. The granules except

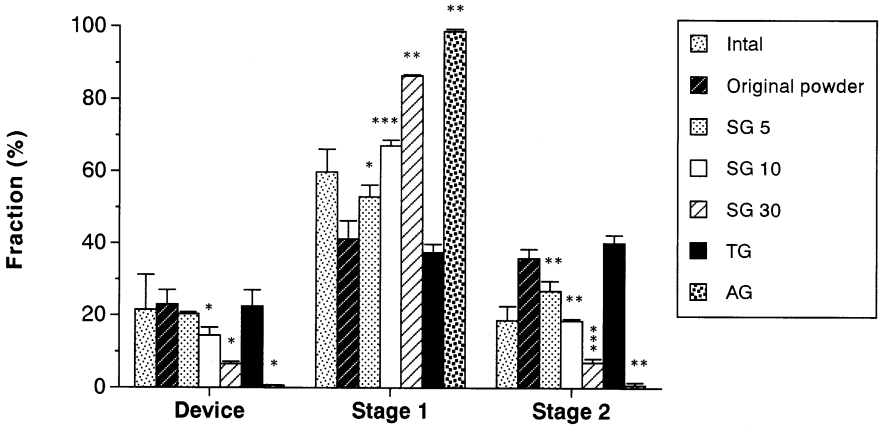

Fig. 4. Inhalation properties of WEP granules evaluated with twin impinger. The values are represented as mean ± S.D. ($n = 3$). Statistical significance: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ compared with the original powder.

SGs showed similar results. The SGs had larger residual drug percentages in the inhalation device with the twin impinger than the cascade impactor. This finding was caused by the degradation of granules into adhesive fine particles occurred before the emission from the capsule under the rapid rotation of the propeller and capsule.

The *RF* values evaluated with the twin impinger were much larger than those with cascade impactor. These results were also explained by the larger dispersion force of Spinhaler® produced with a rapid rotation of the propeller, which disintegrated the granules to fine particles under the larger shear stress.

To clarify the effect of inhalation air flow rate as indicated above on the inhalation behaviors of WEP granules, the inhalation properties of SG 5 were evaluated with the cascade impactor under various flow rates, e.g. 30, 40 and 60 l/min as shown in Fig. 5. The *RF* ranges obtained are shown in the footnote of the figure, calculated as a function of air flow rate.

The *RF* increased with increasing the air flow rate as expected. This was explained by the increased disintegration of granules caused by the increasing in fluid force of air applied to the granules. The residual drug in the capsule increased significantly with increase in the flow rate. This was caused by the adhesion of the fine particles produced by the collision of granules in the capsule rotated under the intensified air flow. The data of SG 5 at 60 l/min in Fig. 5 almost coincided with those of SG 5 in Fig. 4, i.e. the stage 2 and device fractions with the twin impinger being 26.8 ± 2.7 and $20.3 \pm 0.6\%$, respectively and the corresponding values of the cascade impactor being 29.8 ± 3.3 and $16.9 \pm 3.1\%$, respectively. Therefore, the difference of the inhalation properties of Figs. 3 and 4 were considered to be due to the difference in the flow rates.

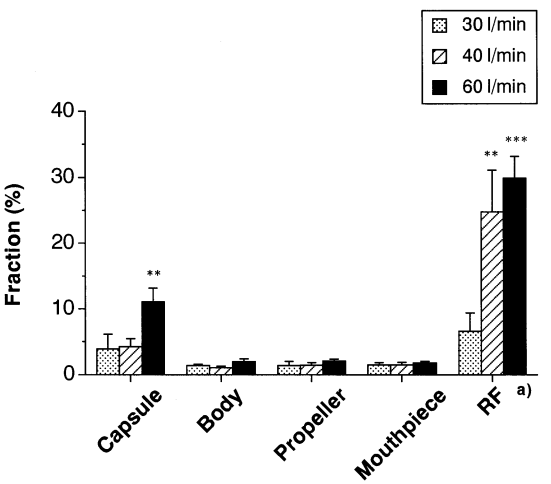

Fig. 5. Effect of air flow rate on *RF* or residual drug fractions in the Spinhaler evaluated with cascade impactor (SG 5). The values are represented as mean ± S.D. ($n = 3$–5). (a) *RF* range; 1.1–6.8 μm (30 l/min), 0.92–5.9 μm (40 l/min), 1.4–4.8 μm (60 l/min). Statistical significance: $**p < 0.01$, $***p < 0.001$ compared with 30 l/min.

To clarify the mechanism of increase in *RF* under higher air flow rate, the following dispersion process of the granules into the air stream was assumed; (1) disintegration of granules in the rotated capsule; (2) discharge of the fractured granules from the capsule into the air stream by the centrifugal force and hydrodynamic negative pressure of air stream; (3) further disintegration of granules by their collisions to the wall of the body; and (4) by their collisions to the propellers when they flow through the narrow space between rotating propellers. If the contributions of steps (3) and (4) were dominant, the fractions in the device should increase with the increase in the flow rate. As the amount of residual drug in the body, propeller and mouthpiece were not varied by the air flow rates as shown in Fig. 5, suggesting that the contributions of steps (3) and (4) were not significant. The increase in the fraction of capsule with the increase in the flow rate might be caused by the disintegration of the granules in the capsule, resulting in depositing of fine particles on the inside wall of the capsule. It was found that once the fracture granules were emitted from the capsule into the air stream, they successfully flew into the capture device, i.e. cascade impactor and twin impinger.

The flow rates inhaled by human subjects are variable, which depend on the anatomical structure and pathological conditions, etc. (Ralph and David, 1996). Therefore, the desirable granules for DPIs should be: (1) easily discharged from the capsule under any air flow rate; and (2) easily dispersed (disintegrated) to fine particles in the air stream even under a moderate rate. These two factors are further considered in the following sections.

3.3. Micromeritic properties of granules required for DPIs

3.3.1. Dispersibility of granule in the air stream

To characterize dispersibility of WEP granules into the air stream, particle size distribution of granules dispersed in the air was measured with the nozzle dispersion method under various dispersion pressures. The relationships between the *RF* evaluated with the cascade impactor and the mean particle diameter (D_{50}) of the granule dispersed with the nozzle dispersion method are shown in Fig. 6. The size of the dispersed granule size decreased with the increase in dispersion air pressure, resulting in an inversely proportional correlation between *RF* and D_{50} is observed. The nozzle dispersion method was found to be useful to measure the dispersibility to predict the inhalation behavior of granules.

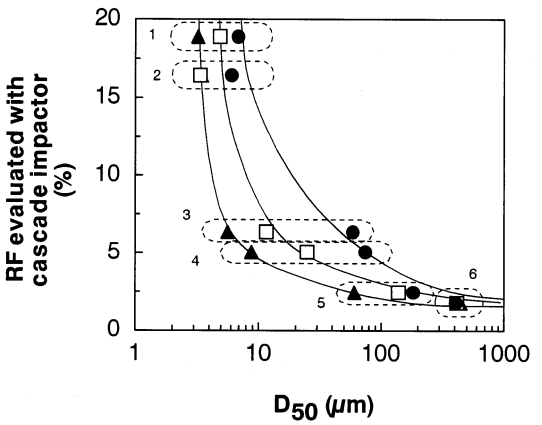

Fig. 6. Relationship between *RF* evaluated with cascade impactor and D_{50} of dispersed granule size of WEP under various dispersion pressures. The values are represented as mean of three runs. ●: 0.5 kgf/cm^2, □: 1.1 kgf/cm^2, ▲: 1.9 kgf/cm^2. 1: TG, 2: original powder, 3: SG 5, 4: SG 10, 5: SG 30, 6: AG.

3.3.2. Granule hardness

The mechanical strength of SG 5, SG 10, SG 30 and AG granules was investigated by the particle hardness tester. The relationship between the granule hardness and the *RF* and residual device fraction evaluated with the cascade impactor is shown in Fig. 7. An inversely proportional correlation between the *RF* and the hardness was observed, indicating that the soft granules with small hardness were easily broken into primary particles by the shear stress applied on emitting them from the device on inhalation. Some resultant particles adhered on the inner walls of the capsule and device and the emitted particles reached to the respirable stages in the cascade impactor. The values of *RF* and device fraction of SGs decreased with increasing compaction pressure applied to prepare the slug (Figs. 3 and 4) were explained by the increase in hardness of granules.

In conclusion, it was found that the hardness of the granule was an important factor to determine the inhalation behavior of granules.

3.3.3. Granule size

Original WEP showed large values of residual drug percentage in the inhalation device due to the adhesion to the capsule and device wall, which were decreased by granulation (Figs. 3 and 4). The decrease in the device fraction by granulation could be due to the increase in inertial force applied to the granules when emitted from the device. Therefore, the granule size was assumed to be one of the most important factors for the formulation design. The inhalation properties of large (500–840 μm), medium (180–500 μm) and small (74–180 μm) fractions of SG 5 were compared with the original WEP by using the cascade impactor as shown in Fig. 8. The device fraction and the *RF* decreased significantly with the increase in granule size. It was reported that the force required to break the granule increased with the particle size of the granule (Newitt and Conway-Jones, 1958). Consequently, large granules decreased the device fraction and the *RF* values.

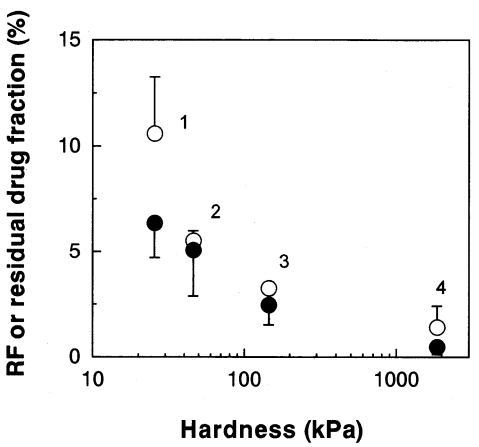

Fig. 7. Relationship between (●) *RF* or (○) residual drug fraction in the Spinhaler evaluted with cascade impactor and hardness of WEP granules evaluated with particle hardness tester. The values are represented as mean ± S.D. ($n = 3$–4 for *RF* and residual drug fraction, $n = 35$ for hardness). 1: SG 5, 2: SG 10, 3: SG 30, 4: AG.

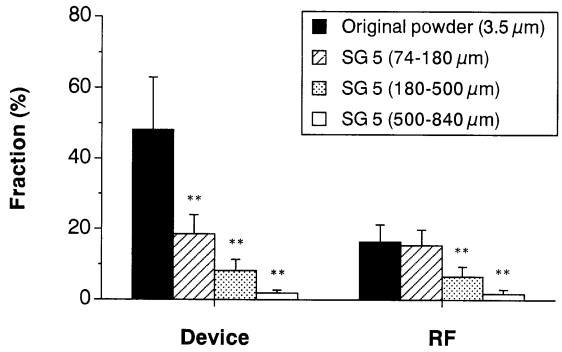

Fig. 8. Effect of granule size of SG 5 on *RF* or residual drug in the Spinhaler evaluated with cascade impactor. The values are represented as mean ± S.D. ($n = 3$–4). Statistical significance: $^{**}p < 0.01$ compared with the original powder.

3.4. Effective index to evaluate DPIs properties

Ideal formulation of DPIs should provide: (1) small device fraction (effective emission from the device); and (2) large *RF* when inhaled. Granulation of WEP in this study reduced both values. The relationship between *RF* and device fraction evaluated by the cascade impactor and the twin impinger are shown in Fig. 9. Proportional correlations between the two factors were observed ($r = 0.974$ and 0.893 for cascade impactor and twin impinger, respectively), indicating that the granule with the large *RF* value revealed a large value of residual drug fraction.

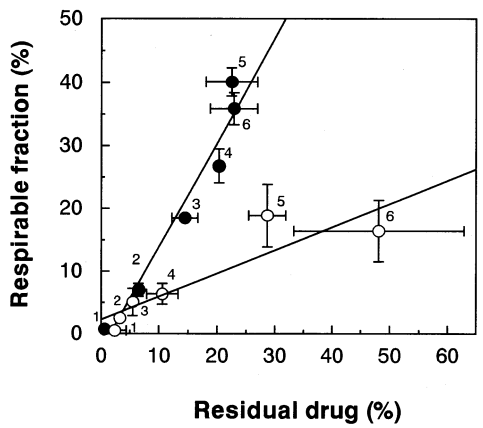

Fig. 9. Relationship between residual drug in the Spinhaler and *RF*. The values are represented as mean ± S.D. ($n = 3$–4). ●: cascade impactor, ○: twin impinger. 1: AG, 2: SG 30, 3: SG 10, 4: SG 5, 5: TG, 6: original powder.

Table 2
Effective index and hardness of WEP granules

Sample	Effective index[a]		Hardness[b] (kPa)
	Cascade impactor	Twin impinger	
Intal	13.0 ± 0.7*	38.3 ± 6.2*	N.D.[c]
Original powder	29.2 ± 8.5***	52.6 ± 2.2***	N.D.
SG 5	23.7 ± 3.0****	46.2 ± 1.5*	25.5 ± 9.8
SG 10	21.4 ± 4.9***	39.8 ± 0.8**	46.1 ± 20.6
SG 30	15.2 ± 3.2*	25.5 ± 1.4**	145.0 ± 87.2
TG	36.4 ± 4.3****	55.7 ± 2.2***	N.D.
AG	6.4 ± 2.8**	8.0 ± 3.4**,****	1854.2 ± 1247.5

[a] Mean ± S.D. ($n = 3$–5).
[b] Mean ± S.D. ($n = 35$).
[c] Not determined.
Statistical significance: *$p < 0.05$; **$p < 0.01$ compared with original powder; ***$p < 0.05$, ****$p < 0.01$ compared with Intal.

To evaluate reasonably the inhalation behaviors, we proposed an effective index (*EI*), which is the geometric mean of the emission fraction and *RF*, as represented by Eq. (3).

$$EI = \sqrt{(100 - DF) \times RF} \quad (3)$$

where, *DF* is the device fraction.

For ideal formulation, *EI* becomes 100%. When the powder is not emitted from the device, nor is reached to the *RF* stage, the *EI* becomes 0%.

The *EI* of original powder, granules and Intal® evaluated with the cascade impactor and the twin impinger are shown in Table 2. The rank order of *EI* was TG > original powder > SG 5 > SG 10, SG 30, Intal® > AG irrespective of the evaluation method. The *EI* was correlated with the hardness and the particle size of the granules. Soft and small granules increased the *EI* as shown in Fig. 8 and Table 3. Only TG improved the *EI* and the other granules decreased the *EI* compared with the original powder. Considering the poor handling property (flowability) of the original powder as shown in Table 1, TG, SG 5 and SG 10 are more acceptable formulations because they were superior to the Intal®. Among the granules prepared in this study, TG proved to be the best formulation for DPIs.

The *EI* defined by Eq. (3) describes the emission and *RF* with the same weights to evaluate the inhalation property. Although further experiments and considerations to the weights of two factors might be required, the *EI* was assumed to be an index characterizing the overall inhalation properties of dry powder aerosols in vitro. It was found that optimum hardness and size of granules should be provided to the granules to increase the *EI*.

Acknowledgements

The authors are grateful to M. Hashimoto and Y. Tanabe for their technical assistance in part of this work. The authors wish to thank Okada Seiko Co. for generously providing technical support for the particle hardness measurement. Part of this project was supported by a Grant in Aid

Table 3
Effective index of SG 5 evaluated with cascade impactor

Sample	Effective index[a]
Original powder	29.2 ± 8.5
SG 5	
(74–180 μm)	35.2 ± 4.8
(180–500 μm)	23.7 ± 3.0
(500–840 μm)	12.4 ± 4.1*

[a] Mean ± S.D. ($n = 3$).
Statistical significance: *$p < 0.01$ compared with original powder.

for General Scientific Research (Grant No. 08457595) from the Ministry of Education, Science, Sports and Culture, Japan.

References

Biddiscombe, M.F., Melchor, R., Mak, V.H.F., Marriott, R.J., Taylor, A.J., Short, M.D., Spiro, S.G., 1993. The lung deposition of salbutamol, directly labelled with technetium-99m, delivered by pressurised dose and dry powder inhalers. Int. J. Pharm. 91, 111–121.

British Pharmacopoeia, 1993. Her Majesty's Stationery Office, London. Appendix XVII-C, A194–A196.

Davies, P.J., Hanlon, G.W., Molyneux, A.J., 1976. An investigation into the deposition of inhalation aerosol particles as a function of air flow rate in a modified 'Kirk Lung'. J. Pharm. Pharmacol. 28, 908–911.

Hinds, W.C., 1982. Uniform particle motion. In: Hinds, W.C. (Ed.), Aerosol Technology. Wiley-Interscience, New York, pp. 38–68.

Hino, T., Serigano, T., Yamamoto, H., Takeuchi, H., Niwa, T., Kawashima, Y., 1997. Assessment of inertial separation techniques used for pressurized metered dose inhalers to evaluate respiratory deposition of aerosolized Wogon extract dry powder in vitro. STP Pharma Sci. 7, 307–314.

Hiramatsu, Y., Oka, Y., Kiyama, H., 1965. Rapid determination of the tensile strength of rocks with irregular test pieces. J. Mining Metallurgic. Inst. Jpn. 81, 1024–1030.

Kassem, N.M., Shamat, M.A., Duval, C., 1991. The inspirable properties of a carrier-free dry powder aerosol formulation. J. Pharm. Pharmacol. 43, 75P.

Koda, A., Nagai, H., Yoshida, Y., Lauw, H.K., 1970. Pharmacological actions of baicalin and baicalein III: Effects on experimental asthma. Folia Pharmacol. Jpn. 66, 471–486.

Komada, F., Iwakawa, S., Yamamoto, N., Sakakibara, H., Okumura, K., 1994. Intratracheal delivery of peptide and protein agent: Absorption from solution and fry powder by rat lung. J. Pharm. Sci. 83, 863–867.

Newman, S.P., Hollingworth, A., Clark, A.R., 1994. Effect of different modes of inhalation on drug delivery from a dry powder inhaler. Int. J. Pharm. 102, 127–132.

Newitt, D.M., Conway-Jones, J.M., 1958. A contribution to the theory and practice of granulation. Trans. Inst. Chem. Eng. 36, 422–442.

Niwa, T., Takeuchi, H., Hino, T., Kawashima, Y., 1995. Aerosolization of lactide/glycolide copolymer (PLGA) nanospheres for pulmonary delivery of peptide-drugs. J. Pharm. Soc. Jpn. 115, 732–741.

Ralph, J.A., David, C.T., 1996. Physiology and pharmacology of the airways. In: Hickey, A.J. (Ed.), Inhalation Aerosols. Marcel Dekker, New York, pp. 85–137.

Timsina, M.P., Martin, G.P., Marriott, C., Gamderton, D., Yianneskis, M., 1994. Drug delivery to the respiratory tract using dry powder inhalers. Int. J. Pharm. 101, 1–13.