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Effects of carriers and storage of formulation on the lung deposition of a hydrophobic and hydrophilic drug from a DPI

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Abstract

The effects of carriers, the drug:carrier ratio and a 1 month storage period of a formulation in permeable polystyrene tube at 40 °C/75% RH on the in vitro pulmonary deposition of model drugs from dry powder inhaler (DPI) were evaluated. Budesonide (hydrophobic) and salbutamol sulphate (hydrophilic) were used as model drugs. Mannitol and glucose were used as the carriers. In addition, lactose 110 M was used as the carrier for budesonide. The novel multiple dose Taifun® was used as a DPI; Taifun® is a breath-actuated inhaler that contains the powder formulation in a reservoir chamber. The respirable fractions (RF%) values of the drugs were determined by the "Andersen" sampler. The RF% values of salbutamol sulphate increased with an increase in the drug:carrier ratio before storage, whereas the drug:carrier ratio did not affect the RF% values after storage. In the case of budesonide, the drug:carrier ratio did not affect the RF% values before storage, instead the RF% values of budesonide increased with an increase in the drug:carrier ratio after storage. The RF% values of salbutamol sulphate decreased after storage of the formulation, this was not dependent on the carrier and the drug:carrier ratio. However, with budesonide the effect of the storage on its RF% values was dependent on which carrier was used and also the drug:carrier ratio. Overall, storage had less effect on the RF% values of budesonide than those of salbutamol sulphate. The highest RF% values of budesonide were obtained when mannitol was used as the carrier. Furthermore, the RF% values of salbutamol sulphate tended to be higher when mannitol was used as the carrier instead of glucose.

Keywords: Inhalation powder; Lactose; Mannitol; Glucose; Budesonide; Salbutamol sulphate

1. Introduction

In comparison to metered dose inhalers (MDI) which have to be pressurised, dry powder inhalers (DPIs) offer several advantages, e.g. DPIs are propellant-free, and co-ordination of actuation and inhalation may be easier with a DPI. On the other hand, it must be remembered that DPIs are usually breath actuated and a high inspiratory effect may be required for successful therapy (Hindle and Byron, 1995). In addition to the patient's inspiratory effort, the formulation (Vanderbist et al., 1999; Tee et al., 2000; Bosquillon et al., 2001) and the device (Hindle and Byron, 1995; Steckel and Müller, 1997a) can affect performance of the DPI.

A DPI formulation may consist of a drug alone or a drug blended with some carrier material (Prime et al., 1997). The aerodynamic diameter of a drug particle

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needs to be between 1 and 5 μm to be suitable for deep lung deposition. Due to the poor flow and dispersion properties of micronized drug particles, a coarse carrier is typically used in the DPI to aid in filling and emptying of the device (Braun et al., 1996; Zeng et al., 2000; Clarke et al., 2001). The adhesion of the drug particles to the carrier particles has to be strong enough to hinder deaggregation during packing and storage but must permit deaggregation during inhalation. Recent studies have revealed that major improvements may be achieved in pulmonary drug delivery by incorporating drug particles that have a low mass density and a large geometric diameter, since large, porous particles penetrate easily into the lungs and increase the pulmonary residence time of the drug (Edwards et al., 1998; Ben-Jebria et al., 1999).

Carrier particles are typically the main component in inhalation powders and thus, any change in the physicochemical properties of the carrier particles may affect lung deposition of drug (Staniforth, 1996; Tee et al., 2000; Clarke et al., 2001; Iida et al., 2001; Zeng et al., 2001b). Lactose is the material most frequently employed as a carrier in DPIs. Also glucose is used as a carrier in commercial DPIs (Steckel and Müller, 1997a). However, other carriers are also needed, e.g. lactose and glucose may not be the best carriers for protein drugs, since these compounds are reducing sugars. Promising alternative carriers are polyols, such as mannitol (Chan et al., 1997; Tee et al., 2000).

The effects of carrier on pulmonary deposition of a drug have been studied typically using a single-unit-dose DPI (Braun et al., 1996; Steckel and Müller, 1997b; Zeng et al., 2000; Clarke et al., 2001; Zeng et al., 2001b) or a multiple-unit-dose DPI (Steckel and Müller, 1997b). The aim of this work was to investigate how the physicochemical properties of a carrier, the drug:carrier ratio and the storage of the formulation at a high humidity can affect in vitro lung deposition of a hydrophobic and hydrophilic drug from a multi-dose reservoir-based DPI. Thus, pulmonary depositions of budesonide (hydrophobic) and salbutamol sulphate (hydrophilic) (Venthoye, 1997) from Taifun® were studied. Taifun® is a novel multi-dose reservoir-based powder inhaler. The device has a relatively high resistance to airflow, so that with a pressure drop of 4 kPa across the device, the air flow is approximately 30 l/min (Focus Inhalation Ltd., data on file). Earlier studies have suggested that Taifun® may be a superior form of DPI compared to other inhalers, in terms of the amount of drug deposited in the lungs, the reproducibility of lung dosage, and the relative flow-independence of lung deposition (Pitcairn et al., 1995, 2000). The carriers selected were lactose, glucose and mannitol.

2. Materials and methods

2.1. Materials

α-Lactose monohydrate (Pharmatose 110 M, DMV, The Netherlands), mannitol, glucose anhydrate, micronised budesonide ($d_{50\%}$ 0.9–1.3 μm), micronized salbutamol sulphate ($d_{50\%}$ 1.4 μm) and Taifun® were kindly supplied by Focus Inhalation Ltd., Finland. The degree of crystallinity of the materials was determined by isothermal calorimetry and X-ray diffraction (XRD) studies. All carriers and budesonide were ca. 100% crystalline. The initial amorphous content of salbutamol sulphate was 10.5%, but the amorphous content was crystallised during formulation (see Section 2.6).

Absolute ethanol (Aa) was obtained from Primalco, Finland. Hexane (HPLC grade) and methanol were purchased from Rathburn (Scotland). Sodium dihydrogen phosphate was purchased from Riedel-de Haën (Germany) and acetonitrile (HPLC grade) was purchased from Merck (Germany). All other used materials were of analytical grade and used as received.

2.2. Particle size measurement

The particle sizes of carriers were measured by laser diffraction (Malvern Mastersizer S, Malvern Instruments Ltd., Malvern, UK) using an independent particle size model and an obscuration between 12 and 20%. A small amount of sample (about 10 mg) was dispersed in 10 ml of 2-propanol. Each sample was measured at least three times.

2.3. The surface areas measurement

The Brunauer–Emmet–Teller (BET)-specific surface areas were measured with a FlowSorb II 2300 (Micromeritics, Norcross, GA) instrument determin-

ing the qualitative amount of N_2 adsorption as a single-point measurement.

2.4. Determination of amorphous content

The amorphous content of carriers and drugs was measured with an isothermal heat-conduction microcalorimeter TAM 2277 (Thermometric AB, Sweden). The miniature humidity chamber technique (Angberg et al. 1992a,b) was employed to detect the thermal response for the recrystallisation of the amorphous material. The baseline corrected evolved heat during recrystallisation was taken as to be directly proportional to the degree of the amorphicity. Lactose, mannitol, glucose and budesonide were ca. 100% crystalline, as verified with XRD measurements (Philips PW 1820, The Netherlands). The initial amorphous content of salbutamol sulphate was 10.5%. The reference value for the totally amorphous salbutamol sulphate was 27.6 J/g. This reference value was taken from the literature (Buckton et al., 1995).

2.5. Scanning electron microscopy (SEM)

The surface roughness and shape of single carrier particles were evaluated in the absence and presence of drugs by a scanning electron microscope (SEM) (JSM-35 scanning microscope, Joel Tokyo, Japan or XL 30 ESEM TMP microscope, FEI/Philips, the Czech Republic). Samples were coated with gold under vacuum (Sputter Coater II-E 5100, Polaron Equipment, England), and all micrographs were taken at an acceleration voltage of 15 kV.

2.6. Preparation of formulations

The budesonide:carrier ratio was 1:160.3 (w/w) (10 μg dose), 1:31.3 (w/w) (50 μg dose) and 1: 15.1 (w/w) (100 μg dose). The budesonide formulations were prepared in suspension as described earlier (Harjunen et al., 2002). Briefly, micronized budesonide (0.31–3.1 g) was dispersed for 5 min in *n*-hexane (100 ml) by ultrasonication (Ultrasonic cleaner, Laborette 17, 170 W, Fritsch GmbH, Germany) and the suspension was mixed at 300–400 rpm. Subsequently *n*-hexane (100 ml) and carrier were added while mixing continued for 10 min without ultrasound. The suspensions were filtered through a Büchner funnel (GF 52 Ref. No. 428248, Schleicher & Schuell). The budesonide inhalation powder was dried in a rotary evaporator for 1.5 h, rotating at 10 rpm under a vacuum of about 100 mbar at 40–50 °C.

The salbutamol sulphate:carrier ratios were 1:296.6 (w/w) (5 μg dose) and 1:58.5 (w/w) (25 μg dose). Micronized salbutamol sulphate, 0.168 g (5 μg dose) or 0.840 g (25 μg dose), was mixed for 30 min at 55 °C (200–400 rpm) in 4% (v/v) ethanol/*n*-hexane solution (35 ml) and after that, *n*-hexane (35 ml) and carrier were added while mixing continued for 10 min by ultrasound (30 s). Salbutamol sulphate was mixed at 55 °C in order to crystallise its amorphous content. The suspensions were filtered through a Büchner funnel (GF 52 Ref. No. 428248, Schleicher & Schuell). The salbutamol sulphate inhalation powder was dried in a rotary evaporator for 2.5 h, and the powder was rotated a few rounds at intervals of 30 min under a vacuum of about 100 mbar at 40–50 °C.

Finally the budesonide and salbutamol sulphate formulations were manually sieved (Ø 1.0 mm) and packed into tightly closed plastic bottles, then stored for 5–7 days in a desiccator (33% RH at room temperature). After storage, the formulation (0.5 g) was accurately measured into the two Taifun® inhalers and stored for 1 day in a test chamber at 25 °C/60% RH (WK 11-180/40, Weiss Tecnik GmbH) prior to the studies.

All formulations were also placed in the stability chamber at 40 °C/75% RH, in permeable polystyrene tubes (Brennan et al., 1974; Bellamy et al., 1980), for 1 month for later evaluation. This means that the inhalation powders were exposed to more moisture vapour in the polystyrene tubes than would be the case if they were stored inside Taifun® inhalers (Focus Inhalation Ltd., data on file). Thus, the effect of moisture on the performance of the inhalation powder could be evaluated more rapidly via the use of the polystyrene tubes.

2.7. HPLC analysis of drugs

Budesonide and salbutamol sulphate were analysed by HPLC. In the case of budesonide, a mobile phase of methanol, acetonitrile and 0.017 M sodium dihydrogen phosphate buffer (pH 3.2) (30:30:40, v/v/v) at a flow rate of 1.0 ml/min was used. In the case of salbutamol sulphate, a mobile phase of acetonitrile and 0.025 M sodium dihydrogen phosphate buffer (pH

3.0) (4:96, v/v) at a flow rate of 1.0 ml/min was used. The HPLC system consisted of a Spectra System® detector, a Spectra Series® pump, a Spectra Series® autosampler, a Spectra Series® solvent degasser (Thermo Separation Products, USA). Budesonide and salbutamol sulphate were analysed by a 150 mm × 4.0 mm i.d. column packed with 5 μm Inertsil C-8 (GL Sciences Inc.) and by a 125 mm × 4.0 mm guard column packed with 5 μm LiChrosphere 60 RP-Select B, respectively. The retention times of budesonide and salbutamol sulphate were about 6 and 5 min, these being monitored at wavelengths of 249 and 224 nm, respectively. The precision of the HPLC method was tested daily by analysing the appropriate budesonide or salbutamol sulphate standard solution five times in a row and the R.S.D. of the peak area was always <2%.

2.8. Uniformity of emitted drug dose

The uniformity of the emitted dose dosage was investigated in the test chamber (25 °C/60% RH). The first 25 doses were individually emitted by Taifun® into the dosage unit sampling apparatus (Ph. Eur. 3rd ed., 1997). The first five doses were omitted from the calculations (i.e. only doses from 6 to 25 were included). The test was performed at a flow rate of 30 l/min, at a flow time of 8 s. Each budesonide dosage unit sampling apparatus was carefully washed with 10 ml of methanol:sodium dihydrogen phosphate buffer (0.017 M, pH 3.2) mixture (50:50, v/v). In the case of salbutamol sulphate, the dosage unit sampling apparatus was washed with 10 ml of sodium dihydrogen phosphate buffer (0.025 M, pH 3.0). The concentrations of the drugs were determined by HPLC, as described above. The emitted drug doses were measured from two inhalers before and after a storage period of 1 month at 40 °C/75% RH.

2.9. In vitro deposition of drugs

The pulmonary deposition of drugs was evaluated by the "Andersen" sampler (Ph. Eur.) (the impactor stages were not coated with a viscous liquid), using a vacuum pump and three-way valve, operated at a flow rate of 28.3 l/min, at a flow time of 8 s. The Andersen sampler consists of a throat, a pre-separator, eight stages and a final filter. The test was carried out on the same DPIs described in Section 2.8. A total of 20 doses were released from the Taifun® DPI to a cascade impactor at intervals of 1 min. The deposition of drug from each inhaler was determined twice, i.e. depositions of doses from 26 to 45 and from 46 to 65 were studied. The budesonide formulation was washed from the collection stages of the impactor, the pre-separator and throat with methanol:sodium dihydrogen phosphate buffer (0.017 M, pH 3.2) mixture (50:50, v/v). In the case of salbutamol sulphate, the collection stages of the impactor, the pre-separator and throat were washed with sodium dihydrogen phosphate buffer (0.025 M, pH 3.0). The drug concentrations in these samples were analysed by HPLC.

A variety of parameters were employed to characterise the deposition profiles of the drugs. The recovered mass (RM) was the sum of the drug from each of the cascade impactor stages (plates+frame 0–7 and filter), metal throat, which included the DPI adapter, and from the pre-separator. The fine particle mass (FPM) (particle size < 5.8 μm) was the sum of the amount of the drug recovered from stages 2–7 and the filter. The respirable fraction (RF%) was calculated as the ratio of FPM to RM. The mass median aerodynamic diameter (MMAD) was calculated with the cumulative drug percentages at each stage, from filter to stage 0. The MMAD value was taken as the particle size at a cumulative percentage value of 50%.

2.10. Data analysis

A non-parametric Kruskal–Wallis test was used to test the differences between multiple groups; significance in the differences in the means was tested using the Games–Howell's multiple range test. The Mann–Whitney *U*-test was used to test the differences between means of two independent groups. The level of significance was taken as $P < 0.05$.

3. Results and discussion

3.1. Characterisation of the carriers

Table 1 shows crystallinity, particle size distribution and specific surface area of the carriers before storage. All carriers were 100% crystalline. All carriers had approximately the same mean particle size ($d_{50\%}$ ranged

Table 1
Degree of crystallinity (%), particle size distribution (μm) and surface area (m^2/g) of the carriers before storage

Carriers	Degree of crystallinity (%)	Particle size (μm) ($n = 3$)			Surface area (m^2/g) ($n = 4$)
		$d_{10\%}$	$d_{50\%}$	$d_{90\%}$	
Lactose 110 M	100	51.6 (1.1)	133.6 (1.7)	240.1 (6.6)	0.17 (0.01)
Mannitol	100	42.6 (0.4)	116.0 (1.1)	295.5 (2.3)	0.30 (0.01)
Glucose	100	29.7 (0.6)	106.2 (3.3)	207.6 (4.5)	0.16 (0.01)

Mean values (±S.D.) are shown.

from 106.0 to 133.6 μm), whereas specific surface area of mannitol was about two times greater than that of lactose 110 M and glucose (Table 1). Fig. 1 shows the morphology of the carriers. The lactose 110 M exhibited the tomahawk shape, which is typical of α-lactose monohydrate (Fig. 1A). Mannitol particles (Fig. 1B) appeared to be more elongated and showed more surface asperities than lactose 110 M and glucose. The glucose particles (Fig. 1C) were more symmetrical and more spherical than lactose or mannitol particles.

3.2. The emitted drug dose

The effects of carrier, the drug:carrier ratio and the storage period on the emitted drug dose are shown in Tables 2 and 3.

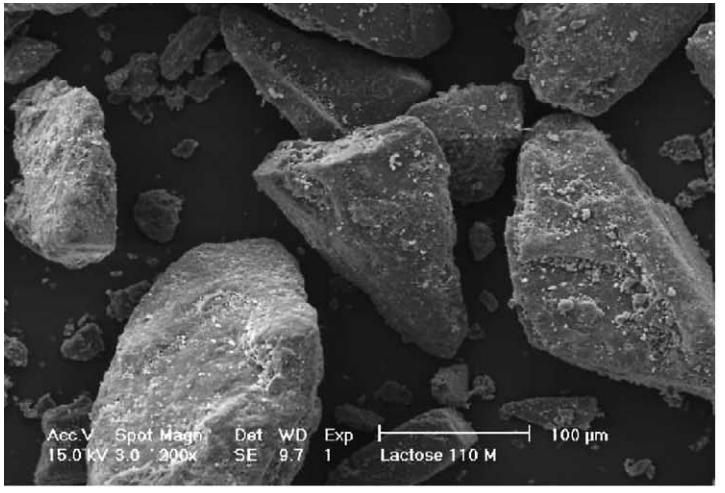
Overall, the ratio of the emitted budesonide dose to the theoretical dose (10–100 μg) varied from 84 to 106% before and after storage when mannitol, glucose or lactose was used as the carrier (Table 2). When compared to mannitol at the corresponding dose and time, the emitted budesonide dose tended to be higher when either glucose or lactose 110 M was used as the carrier. When compared to the corresponding carrier before storage, the emitted budesonide dose was significantly lower after storage at the budesonide dose of 10 μg. This trend was not observed at higher budesonide doses.

The ratio of the emitted salbutamol sulphate dose to the theoretical dose (5 or 25 μg) varied from 77 to 99% before and after storage when mannitol or glucose was used as the carrier (Table 3). When compared

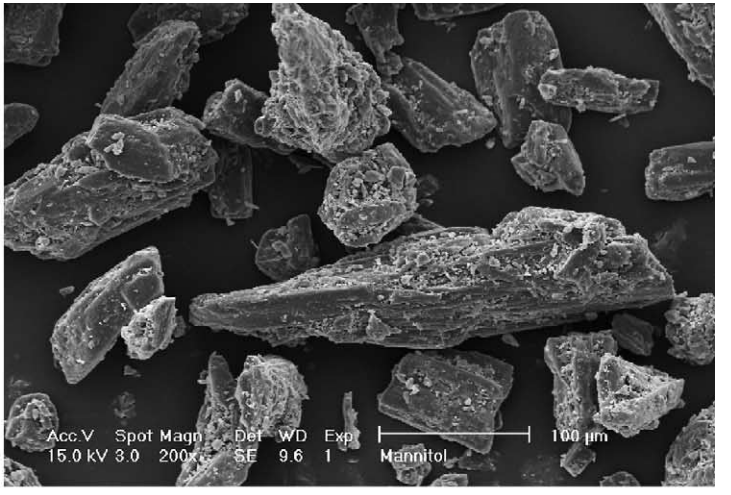
Table 2
Influence of carrier on the emitted dose (the theoretical dose 10–100 μg), mass median aerodynamic diameter (MMAD) and respirable fraction of the emitted dose (RF%) of budesonide particles initially and after a 1 month storage period (40 °C/75% RH)

Dose and carrier	Dose (μg) ($n = 40$)		MMAD (μm) ($n = 4$)		RF% ($n = 4$)	
	Initial	Storage	Initial	Storage	Initial	Storage
10 μg						
Mannitol	9.4 (0.5)	8.4[b] (0.8)	3.5 (0.1)	3.9[b] (0.3)	44.4 (0.7)	37.3[b] (3.0)
Glucose	10.6[a] (1.3)	9.7[a,b] (1.2)	4.0 (0.5)	5.9[a,b] (0.3)	33.7[a] (5.0)	15.8[a,b] (1.2)
50 μg						
Mannitol	46.5 (4.7)	45.8 (3.7)	3.2[c] (0.1)	3.0[c] (0.1)	43.9 (0.5)	51.5[b,c] (3.8)
Glucose	48.2 (3.1)	48.2[a] (3.6)	3.6[a] (0.2)	3.7[a,d] (0.0)	36.4[a] (2.8)	32.2[a,b,d] (0.6)
100 μg						
Mannitol	85.0 (7.2)	88.2 (11.2)	3.3 (0.1)	3.3 (0.1)	52.6[c] (1.4)	51.1[c] (3.3)
Glucose	97.4[a] (11.0)	98.8[a] (5.7)	3.0[a,d] (0.1)	3.0[a,d] (0.0)	37.4[a] (2.3)	41.2[a,b,d] (1.9)
Lactose 110 M	88.5[a] (10.0)	97.9[a,b] (6.3)	2.9[a] (0.1)	2.7[a] (0.1)	35.3[a] (2.2)	39.7[a,b] (3.2)

Taifun® was used as the DPI. Mean values (±S.D.) are shown.
[a] Significantly different from the values of mannitol at the corresponding dose and time ($P < 0.05$).
[b] Significantly different from the values of the corresponding carrier before storage ($P < 0.05$).
[c] Significantly different from the values of mannitol at the dose of 10 μg at the corresponding time ($P < 0.05$).
[d] Significantly different from the values of glucose at the dose of 10 μg at the corresponding time ($P < 0.05$).



(A)



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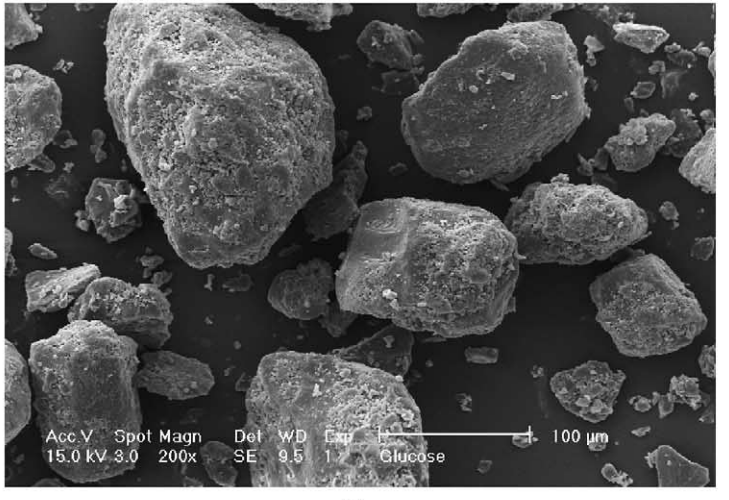


(C)

Fig. 1. Scanning electron micrographs of lactose 110 M (A), mannitol (B) and glucose (C) before storage. Scale bars are 100 μm.

Table 3
Influence of carrier on the emitted dose (the theoretical dose 5–25 μg), mass median aerodynamic diameter (MMAD) and respirable fraction of the emitted dose (RF%) of salbutamol sulphate particles initially and after a 1 month storage period (40 °C/75% RH)

Dose and carrier	Dose (μg) ($n = 40$)		MMAD (μm) ($n = 4$)		RF% ($n = 4$)	
	Initial	Storage	Initial	Storage	Initial	Storage
5 μg						
Mannitol	4.5 (0.3)	4.8[b] (0.3)	5.7 (0.3)	8.6 (0.3)	21.9 (1.3)	11.6[b] (0.6)
Glucose	4.7[a] (0.3)	4.1[a,b] (0.3)	6.0 (0.3)	>9 (ND)	18.2[a] (0.9)	6.5[a,b] (2.7)
25 μg						
Mannitol	23.4 (1.3)	23.5 (1.1)	3.7[c] (0.5)	7.7[b,c] (0.3)	31.0[c] (2.6)	12.9[b] (1.0)
Glucose	24.7[a] (1.4)	19.2[a,b] (2.1)	3.1[d] (0.1)	8.8[a,b] (0.2)	32.8[d] (1.2)	7.3[a,b] (0.4)

Taifun® was used as the DPI. Mean values (±S.D.) are shown.
[a] Significantly different from the values of mannitol at the corresponding dose and time ($P < 0.05$).
[b] Significantly different from the values of the corresponding carrier before storage ($P < 0.05$).
[c] Significantly different from the values of mannitol at the dose of 5 μg at the corresponding time ($P < 0.05$).
[d] Significantly different from the values of glucose at the dose of 5 μg at the corresponding time ($P < 0.05$).

to mannitol at the corresponding dose before storage, the emitted salbutamol sulphate dose was higher when glucose was used as the carrier. However, when compared to mannitol at the corresponding dose after storage, the emitted salbutamol sulphate dose was lower when glucose was used as the carrier. When compared to the corresponding carrier before storage, the emitted salbutamol sulphate dose was significantly lower after storage at both studied doses when the carrier was glucose. In contrast, storage did not decrease the emitted salbutamol sulphate dose when mannitol was the carrier.

Table 1 shows that surface area of the mannitol was higher than that of glucose and lactose 110 M. Kawashima et al. (1998) demonstrated the relationship between the specific surface area of carrier lactose and the fraction of pranlukast hydrate particles emitted from the single-unit-dose DPI. In the present study, this correlation was not observed (Tables 2 and 3). Our earlier study showed that the emitted drug dose from Taifun® increased as a function of bulk density of formulation (Harjunen et al., 2002).

Interestingly, when glucose was used as the carrier, the emitted salbutamol sulphate dose decreased during storage whereas the emitted budesonide dose did not change (except at the budesonide dose of 10 μg). Salbutamol sulphate and glucose were observed to form large, tight agglomerates during the storage (data not shown), which probably decreased the flow properties of the formulation. Budesonide and glucose did not form these kinds of agglomerates. With mannitol salbutamol sulphate did not form any agglomerates. These results can be explained by the fact that glucose can absorb a significant amount of moisture at 40 °C and 75% RH humidity while the moisture sorption capacity of mannitol is less (Callahan et al., 1982; Kibbe, 2000). The sorption of water vapour by the solid material increases the interparticulate forces via liquid bridging and fusion among the particles (Zeng et al., 2001a). When glucose was used as the carrier, the agglomerates were formed in the presence of the hydrophilic drug, salbutamol sulphate, whereas no agglomerates were observed in the presence of the hydrophobic compound, budesonide.

3.3. The RF% values of the drugs

The effects of carrier, the drug:carrier ratio and the storage period on the RF% values of the drugs are shown in Tables 2–3 and in Fig. 2. The effects of lactose 110 M, mannitol and glucose on the pulmonary deposition of budesonide were studied. In the case of salbutamol sulphate, mannitol and glucose were used as the carrier.

In the case of budesonide (dose 100 μg), the formulation containing mannitol showed the highest RF% values before and after storage (Table 2). When mannitol was used as the carrier at the budesonide dose of 100 μg, the RF% values remained practically unchanged after storage. In contrast, the RF% values significantly increased after storage with either lactose 110 M or glucose used as the carrier (Table 2).

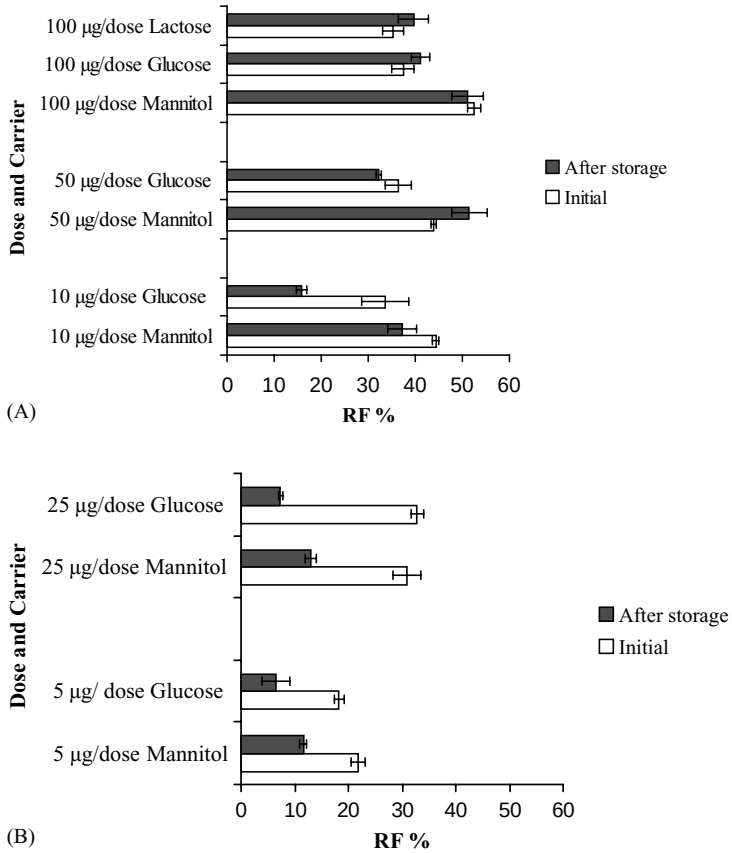
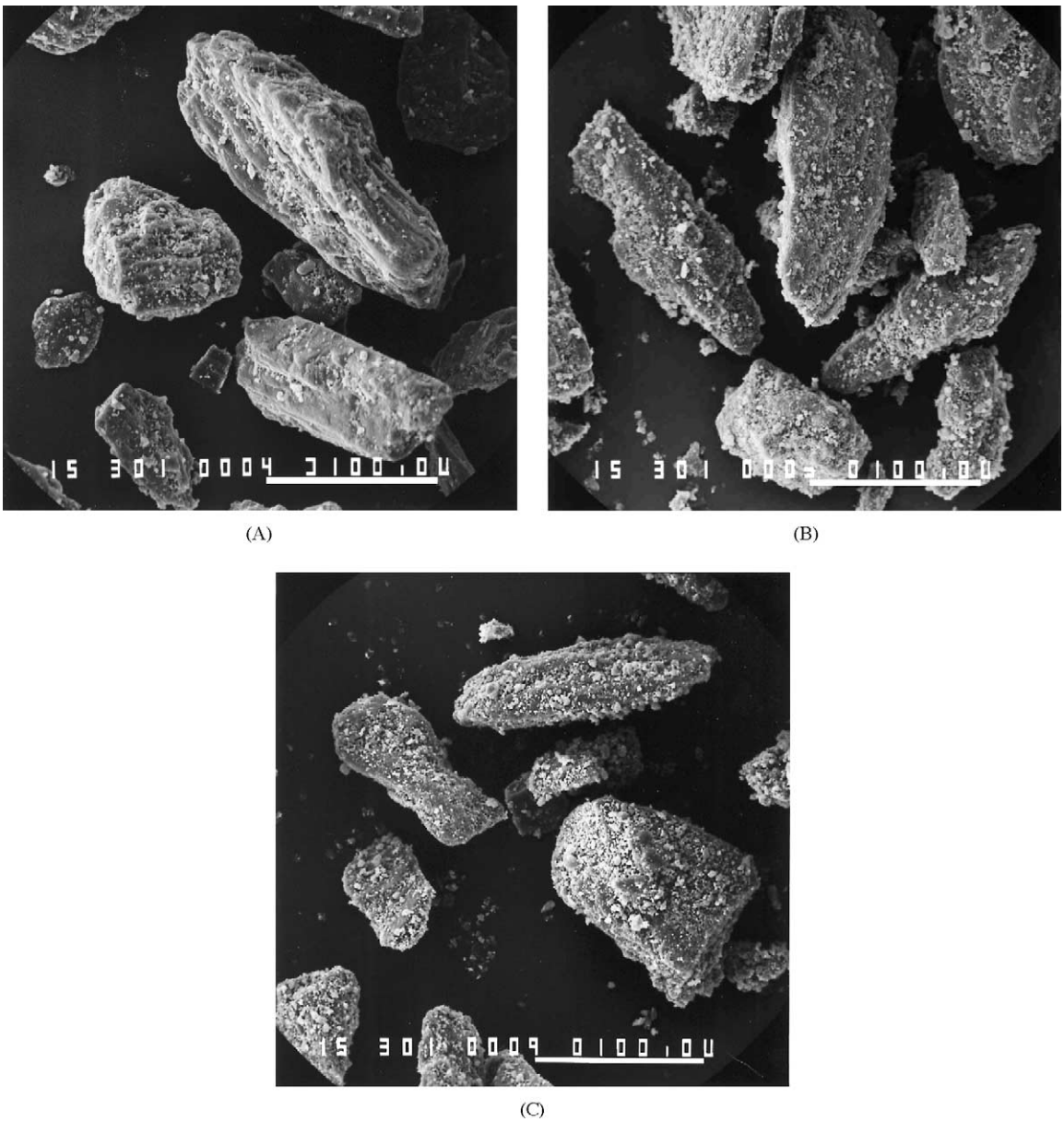


Fig. 2. Respirable fraction (RF%) pattern of budesonide (A) and salbutamol sulphate (B) before and after storage (1 month at 40 °C and 75% RH).

One explanation for the increased RF% values of budesonide particles after storage could be that surface electrostatic properties of budesonide and the carrier may have decreased due to moisture sorption on the particle surfaces during storage. As a result, fine budesonide particles were easier to become detached from the surface of the carriers during inhalation (Zeng et al., 2001a). The capacity of the moisture sorption of glucose is higher than that of mannitol and lactose (Callahan et al., 1982; Kibbe, 2000). However, it must be noted that effects of storage on the RF% values of budesonide were not straightforward but depended on the carrier and the drug:carrier ratio (Table 2). For example, irrespective of the carrier, storage decreased the RF% values of budesonide at the dose of 10 μg, suggesting that the moisture sorption increased the interparticulate forces due to capillary forces (Price et al., 2002). This explanation is supported by the fact that the MMAD values of budesonide particles increased during storage at the dose of 10 μg.

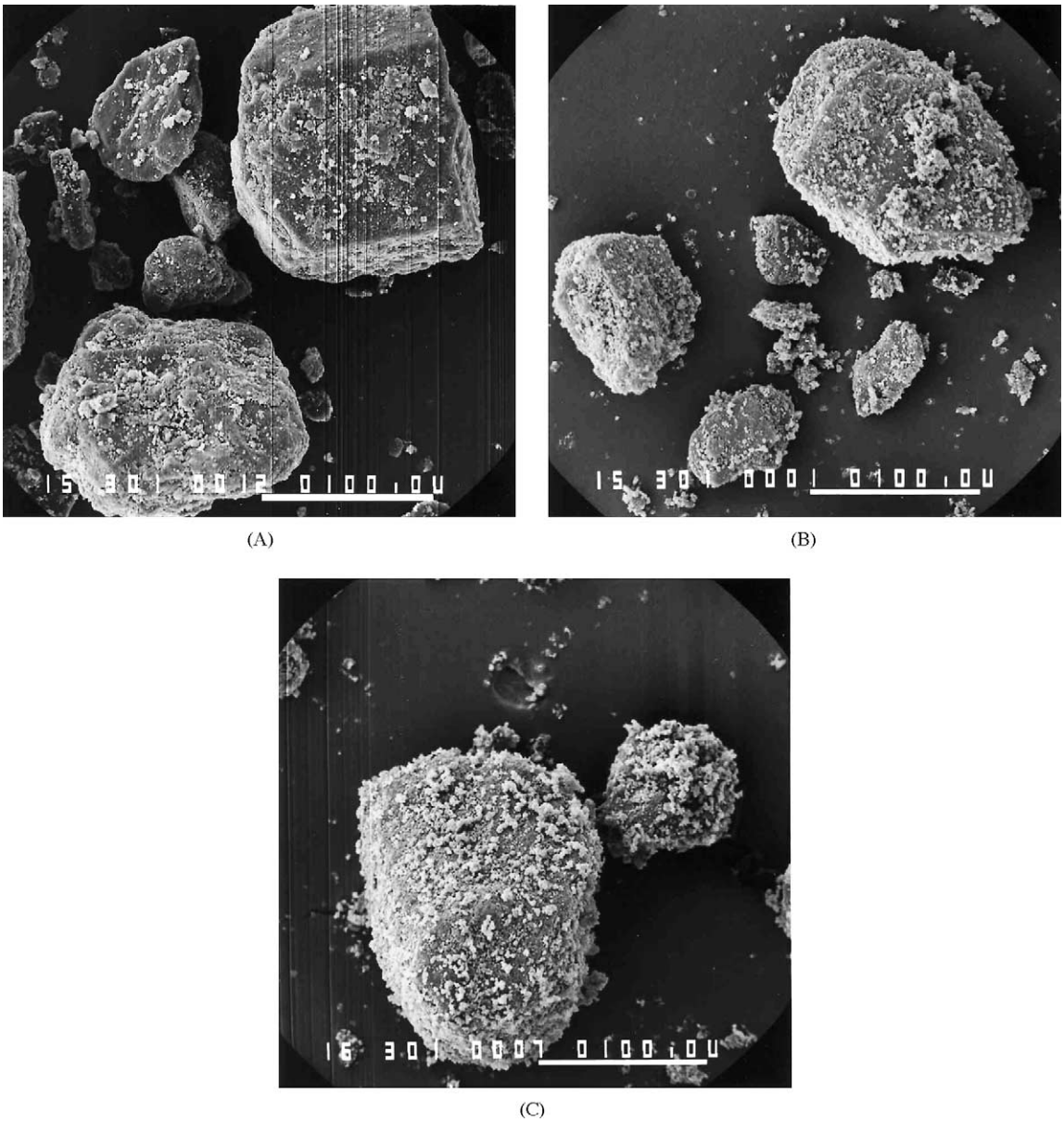
Table 3 indicates that when compared to mannitol at the corresponding salbutamol sulphate dose, the glucose containing formulations tended to have lower RF% values (except for the formulation with the salbutamol sulphate dose of 25 μg before storage). The RF% values of salbutamol sulphate decreased and the MMAD values increased strongly during storage irrespective of whether mannitol or glucose were used as the carrier. These results indicate that interparticulate forces increased during storage. Thus, water sorption on the particle surface increased the attractive forces between particles through capillary forces (Zeng et al., 2001a; Price et al., 2002; Young et al., 2003).

The effects of the drug:carrier ratio on pulmonary deposition of budesonide was evaluated using mannitol and glucose as carriers (Table 2). The ratio of budesonide to the carrier was 1:160.3 (dose 10 μg), 1:31.3 (dose 50 μg) and 1:15.1 (dose 100 μg) (Figs. 3 and 4). Table 2 shows that the drug:carrier ratio did not affect significantly the RF% values of budesonide before storage of the formulation. The only exception was that the RF% values of budesonide increased when there was an increase in the ratio of budesonide to mannitol from 1:160.3 to 1:15.1. However, the RF% values of budesonide increased with an increase in the



(A) (B) (C)

Fig. 3. Scanning electron micrographs of formulation before storage when the budesonide:mannitol ratio was 1:160.3 (w/w) (A), 1:32.3 (w/w) (B), 1:15.1 (w/w) (C). Scale bars are 100 μm.



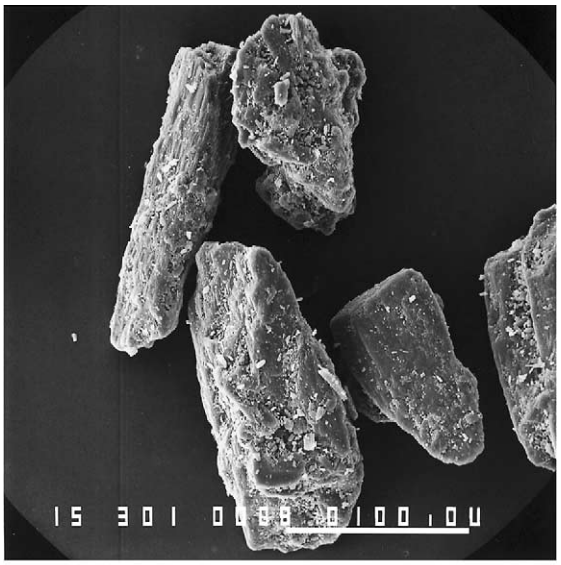
(A) (B)

(C)

Fig. 4. Scanning electron micrographs of formulation before storage when the budesonide:glucose ratio was 1:160.3 (w/w) (A), 1:32.3 (w/w) (B), 1:15.1 (w/w) (C). Scale bars are 100 μm.

drug:carrier ratio after storage with both mannitol and glucose used as the carrier.

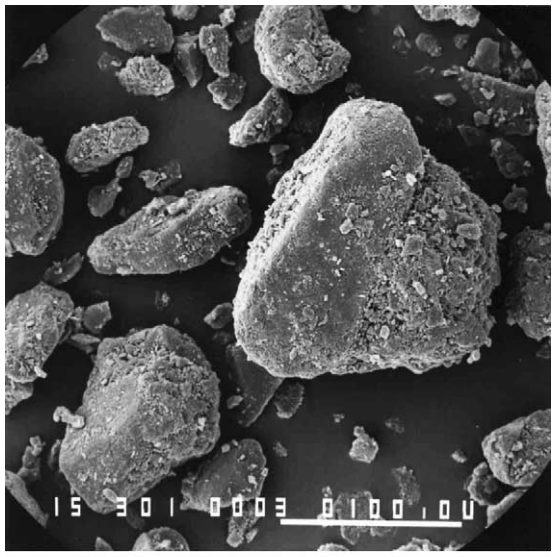
The effects of the drug:carrier ratio on pulmonary deposition of salbutamol sulphate were evaluated using mannitol and glucose as carriers. The ratio of the drug to the carrier varied from 1:296.6 (dose 5 μg) to 1:58.5 (dose 25 μg) (Figs. 5 and 6). The RF% values of salbutamol sulphate particles initially increased and the MMAD values decreased with the increase in the drug:carrier ratio (Table 3). This trend was not obvious after the storage of the formulations (Table 3).



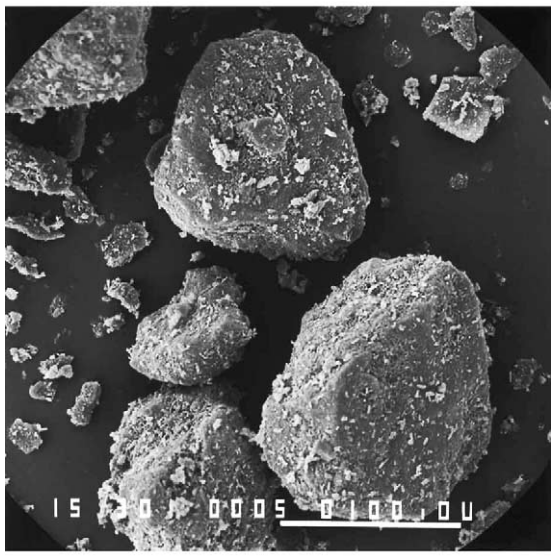
(A)

(B)

Fig. 5. Scanning electron micrographs of formulation before storage when the salbutamol sulphate:mannitol ratio was 1:296.6 (w/w) (A) and 1:58.5 (w/w) (B). Scale bars are 100 μm.



(A)



(B)

Fig. 6. Scanning electron micrographs of formulation before storage when the salbutamol sulphate:glucose ratio was 1:296.6 (w/w) (A) and 1:58.5 (w/w) (B). Scale bars are 100 μm.

Tables 2 and 3 show that the increase in the drug:carrier ratio either increased or did not affect the RF% values of the drug. The increases in the RF% values with increases in the drug:carrier ratio may be accounted for by the fact that the detachment of the drug from the carrier does not occur efficiently when the amount of the drug is low in the mixture, since the drug particles initially occupy the high energy adhesion sites on the carrier particles, as described by Staniforth (1996). As a result, the fraction of irreversible bonds between the drug particles and the

carrier particles becomes higher when the drug concentration is low. At higher drug doses, more drug particles may be adhering to sites with less strong binding affinities on the surface of carriers (Figs. 3–6). However, the effect of the drug:carrier ratio on the RF% values of the drug is not straightforward as some studies have demonstrated that the fine particle fraction of the drug can decrease when there is an increase in the ratio of drug to the carrier (Braun et al., 1996; Steckel and Müller, 1997b). Mixing and deaggregation processes depend on a competition between the adhesion and cohesion forces existing between drug–carrier, carrier–carrier or drug–drug (Bérard et al., 2002). Both cohesion and adhesion forces of solids relate to the surface energies of the interacting particles. Solids with a high surface energy have a high tendency to adsorb other materials onto their surface and form strong bonds with adhered particles. When an adherent particle is exposed to a compressed air stream, it will be detached from the adhering surface if the drag forces of the stream overcome the adhesional forces of the particle (Zeng et al., 2001a).

4. Conclusion

The effects of the carrier, the drug:carrier ratio and storage of formulation for 1 month at 40 °C/75% RH on in vitro lung deposition of budesonide and salbutamol sulphate from a novel multiple dose DPI (Taifun®) were evaluated. Lactose, mannitol and glucose were used as the carriers in the inhalation powders. The effect of the chemical composition of carrier was most apparent on the RF% values of budesonide: the highest RF% values were achieved when mannitol was used as the carrier. The increase in the drug:carrier ratio either increased or did not affect the RF% values of the drug. Irrespective of the chemical composition and the amount of carrier, the RF% values of salbutamol sulphate particles decreased after storage. Instead, the effect of the storage on the RF% values of budesonide was dependent on the carrier and the drug:carrier ratio.

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