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In vitro evaluation of dry powder inhalers II: influence of carrier particle size and concentration on in vitro deposition

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Abstract

Dry powders and their delivery devices are an alternative to pressurized metered-dose inhalers (pMDI) for the administration of aerosols to the lungs. Generally dry powder aerosols are formulated by mixing a cohesive micronized drug with larger carrier particles resulting in an interactive powder mixture. Redispersion of the drug from agglomerates or the carrier surface during inhalation is a critical factor which greatly influences the fine particle fraction (particles < 6.4 μm) to be achieved. Two devices, the single-unit-dose Spinhaler™ (Fisons) and the multiple-unit-dose Easyhaler™ (Orion Pharma) were used to investigate the influence of dry powder formulation on the deposition of interactive mixtures. Following the scheme of a 3^2-factorial design budesonide was mixed with lactose-α-monohydrate varying the lactose sieve fractions and the drug to carrier proportion. The in vitro deposition of these mixtures was determined using a Twin Stage Impinger (Apparatus A, BP 93) and compared to control experiments performed with unsieved drug carrier. Deposition was found to be highly dependent on the dry powder formulation. Fine particle fractions from 10 up to 50% were observed. The Easyhaler™ shows little differences compared to the Spinhaler™ device. © 1997 Elsevier Science B.V.

Keywords: Dry powder inhaler; Lactose; Budesonide; Twin Impinger; Fine particle fraction; Factorial design

1. Introduction

In the last 10 years inhalation therapy using powdered drugs has become an established alternative to pressurized metered-dose inhalers (pMDI) (Timsina et al., 1994). An in vitro evaluation of dry powder inhalers (DPI) available on the German market has shown that most of the delivery systems were able to generate an aerosol cloud containing about 20–30% of particles < 6.4 μm (Steckel and Müller, 1997). For drug delivery via a dry powder inhaler the quality of the aerosol

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cloud produced is dependent on three key factors-inspiratory effort of the patient, device performance and dry powder formulation (Ganderton, 1992; Zanen et al., 1992 and Bell, 1994).

The inspiratory flow could not be imitated but only kept constant in in-vitro deposition studies, except where the use of an 'Electronic Lung' is possible (Brindley et al., 1994). The adjusted air flow through the impinger should be in accordance to the dry powder device resistance (Clark and Hollingworth, 1993). Powder deaggregation is further dependent on inhaler design (Vidgren et al., 1988). Several devices are commercially available and each of them proved to generate an aerosol cloud sufficient for inhalation therapy. The first dry powder inhaler on the market was the Spinhaler™ (Bell et al., 1971). In this device a gelatine capsule is connected with a rotor and pierced with metal needles. During inhalation the rotor begins to move and drug is dispersed out of the rotating capsule into an inhalation channel (Fig. 1). Another recently developed dry powder inhaler is the Easyhaler™, a multiple-unit dose inhaler of very simple construction (Fig. 2). Both the Spinhaler™ and the Easyhaler™ were conspicuous in a previous study (Steckel and Müller, 1997): The Spinhaler™ was found to generate an aerosol cloud with only 10% of drug in the range $< 6.4\ \mu$m using the standard flow rate of 60 l min^{-1}. The Easyhaler™ showed differences in the fine particle fractions for beclomethasone dipropionate and salbutamol sulphate formulations at the same flow rate. This is why these devices were taken as model inhalers for the dispersion of the performed interactive mixes.

The third but most important factor influencing the fine particle fraction is the powder formulation itself which has to meet two different criteria: coarse particles are required for satisfactory metering and flow properties but the same time particles have to be smaller than 5 μm in order to penetrate into deeper lung regions (Ganderton, 1992). The mixing of micronized drug particles with a coarse carrier seems to be a way out of this contrast but is linked with several problems: a good powder dispersion is dependent on particle size (French et al., 1996) and particle shape or rugosity (Wong and Pilpel, 1990). The smaller the particle rugosity the smaller is the particle surface and the surface free energy (Kassem and Ganderton, 1990). Furthermore the type of micronization may have influence on flow properties (Hickey et al., 1994), interparticulate cohesive forces and particle-surface-forces as adhesion of drug onto the capsule surface or onto the device wall. All these forces affect the powder aerosolization (Staniforth et al., 1981, 1982; Visser, 1989). The

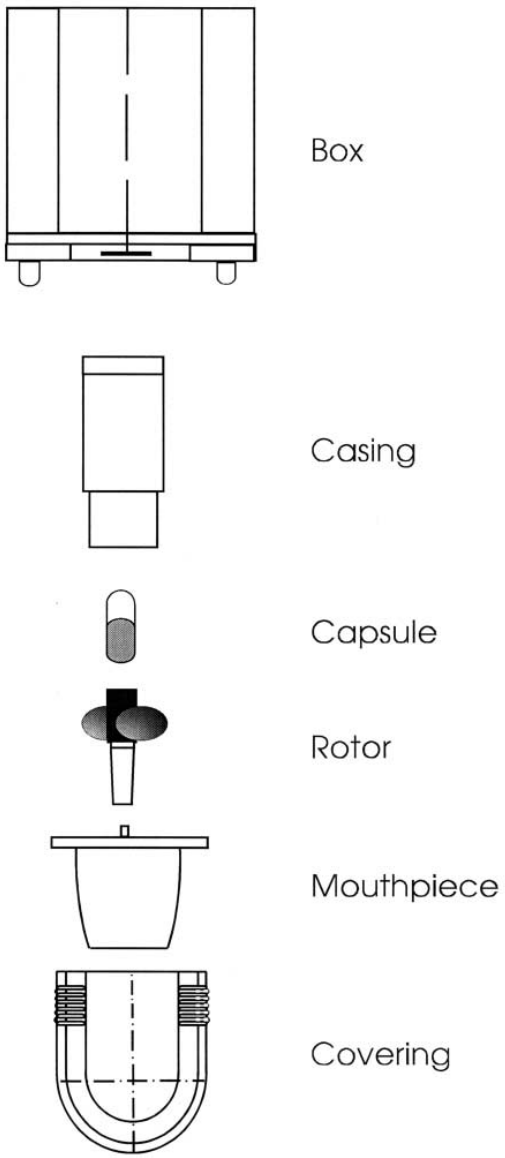

Fig. 1. The Spinhaler™.

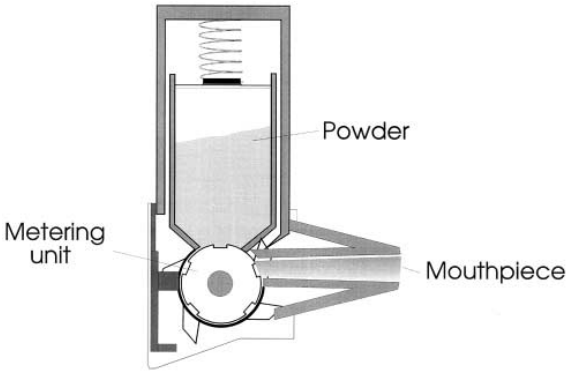

Fig. 2. The Easyhaler™.

properties of pharmaceutical powders, however, which are critical for improved deaggregation and lung deposition have not been yet evaluated.

The objective of the presented study was to identify the formulation characteristics responsible for an efficient lung deposition. The application of two different inhalers should give information on the influence of the inhaler design upon in vitro deposition.

2. Materials and methods

The Spinhaler™ and the Easyhaler™ device are commercially available devices. α-lactose monohydrate was supplied as Granulac 200 from Meggle (Wasserburg, Germany). Acetonitrile and methanol (HPLC grade) were obtained from Merck (Darmstadt, Germany). Budesonide with a mass median diameter of 3.1 μm was supplied from Farmabios (Gipello Cairoli, Italy). Cellulose acetate filters were from Sartorius (Göttingen, Germany).

2.1. Preparation of interactive mixtures

Lactose and budesonide were weighed in the calculated proportion as shown in Table 1 using an analytical balance. Mixtures of 10.0 g were made by mixing for 1 h with a Turbula Blender (Type T 10 B, W.A. Bachhofen AG, Basel, Switzerland). The resulting mixture was filled into capsules of size two for the Spinhaler™ experiments (20.0 mg $\pm$ 1.0 mg per capsule). The Easyhaler™ was filled with 2.0 g of the binary mixture.

2.2. Particle size analysis

A Twin Impinger (Apparatus A, British Pharmacopeia (1993) Appendix XVII) was used at a continuous air flow of 60 l min^{-1}. For each determination 7 ml of water were placed in stage 1 and 30 ml in stage 2. The powder devices were attached to the glass inlet and as many doses as necessary for quantitative drug analysis (5–10 doses) were released into the impinger. The washing solutions were diluted to volume and filtered through a 0.2 μm cellulose acetate filter. For each powder mixture and each inhaler device three determinations were performed. The drug recovered in the second stage of the impinger is similar to the amount of particles smaller than 6.4 μm and is termed fine particle fraction.

2.3. HPLC method

The HPLC system consisted of a Gynkotek High Precision Pump Model 300 (Gynkotek, Munich, Germany), a Kontron HPLC Autosampler 360 (Kontron Instruments, Milan, Italy), a Shimadzu UV spectrophotometric detector, a Shimadzu Chromatopak C-R 3A Integrator (Shimadzu, Kyoto, Japan) and a LiChrospher 100 RP-18 column (4.0 $\times$ 125 mm) obtained from Merck (Darmstadt, Germany). Samples of 100 μl were injected. The mobile phase was an acetonitrile/water-mixture (45:55). Flow rate was 1.2 ml/min resulting in a pressure of about 9.0 MPa. Budesonide was detected at a wavelength of 254 nm. The amount of drug was calculated using an external standard.

2.4. Statistical design

A factorial design serves as test of the influence of certain factors on one or several responses. To perform a general factorial design, the investigator selects a fixed number of levels for each factor and then runs experiments with all possible combinations (Box et al., 1978). In this study, two variables (lactose sieve fraction and drug-to-car-

Table 1
Influencing factors in the 3^2-factorial design

Code	Experimental setting (% drug in the mixture)	Code	Experimental setting: particle size of lactose (μm)
−1	1	−1	<32
0	5	−1	<32
+1	9	−1	<32
−1	1	0	63–90
0	5	0	63–90
+1	9	0	63–90
−1	1	+1	125–180
0	5	+1	125–180
+1	9	+1	125–180

rier proportion) on three levels were chosen resulting in a 3^2-factorial design. Table 1 shows the code variables and the experimental settings for the performed design. All experiments were performed in a randomized order.

2.5. Lactose sieve fractions

To achieve the lactose fractions in the desired particle size range a Retsch Sieve Tower, Type Vibro (Retsch, Haan, Germany) with the following sieve plates was used: 180, 125, 90, 63 and 32 μm.

2.6. BET surface area

The BET-surface area of the resulting lactose sieve fractions was measured using a Gemini 2360 Surface Analyzer (Micromeretics Instruments, Neuss, Germany) calculating the surface area with BET multi-point measurement (Table 2).

Table 2
BET surface areas of lactose sieve fractions

Sieve fraction (μm)	BET surface area (m^2/g)	RSD[a] [%]
0–32	0.6812	1.72
63–90	0.3606	1.67
125–180	0.1889	0.41
Unsieved	0.3336	0.47

[a] Relative standard deviation, $n = 3$.

2.7. SEM photographs

SEM photographs were taken by a Philips XL 20 (Philips, Eindhoven, Netherlands). A sample of the interactive mixture was fixed on a mutual conductive adhesive tape (Leittabs, Plano, Marburg, Germany) on an aluminium sample disk. These samples were sputtered with gold for 3 min choosing a current of 50 mA under argon atmosphere at 5×10^{-4} mbar using a Sputter Coater SCD 005 (Balzers Union, Balzers, Liechtenstein).

3. Results and discussion

3.1. Evaluation of Spinhaler™ data

Generally, the fine particle fraction measured in-vitro (FPF, particles < 6.4 μm) could be increased using binary interactive mixtures compared to the proprietary product Intal™ capsules (10% FPF, Steckel and Müller, 1997). Table 3 shows the results of all experiments of the factorial design. A low carrier particle size (< 32 μm) resulted in the highest fine particle fractions. Nevertheless, it has to be taken in consideration that lactose within this particle range is reaching the alveolar region, too, but can certainly be neglected from toxicological view (Bell, 1994). Increasing the amount of budesonide in the mixture leads to a continuous decrease in fine particle fraction: agglomerates of pure drug will build up which can not be redispersed. The same trend

Table 3
Fine particle fractions (FPF) of all experiments performed with Spinhaler™ and Easyhaler™

Experimental settings		FPF [%][a] Spinhaler	FPF [%][a] Easyhaler
% Drug in the mixture	Particle size of lactose (μm)		
1	<32	37.46 (0.15)	48.67 (2.72)
5	<32	30.36 (0.59)	26.79 (1.71)
9	<32	27.48 (0.2)	28.43 (1.97)
1	63–90	28.40 (0.74)	37.25 (0.41)
5	63–90	22.93 (0.42)	37.75 (1.33)
9	63–90	23.69 (0.46)	25.96 (2.19)
1	125–180	26.36 (0.79)	32.99 (1.33)
5	125–180	17.23 (0.56)	19.69 (1.34)
9	125–180	10.36 (0.43)	22.02 (1.44)

[a] Mean value (standard deviation), $n = 3$.

could be observed with the mixes with the medium sized lactose (63–90 μm) as well as with the coarse lactose fraction (125–180 μm).

Fig. 3 shows a SEM-photograph of the binary mixture of 1% budesonide with the medium sized lactose. Drug particles strongly adhere to the carrier surface. The adsorption of drug seems to be higher at sites of higher rugosity as suggested by Wong and Pilpel (1990). Furthermore it is obvious that the lactose crystal is nearly saturated with drug: if an even higher amount of budesonide is added to the mixture the drug cannot adhere onto the carrier surface completely and will form drug agglomerates. If the carrier particle size is increased and the drug content in the mixture is kept constant the fine particle fraction will decrease. This seems to be contradictory at first sight because decreasing free surface and surface free energy due to increasing carrier particle size (Table 2) should result in lower adhesive forces between drug and carrier. This is the point where the design of the powder inhaler should be considered. With the Spinhaler™ generating an aerosol cloud facilitated by the rotation of the rotor within the device particles of higher particle size and, with it, higher mass will impact on the inhaler wall (inhalation channel) due to their high inertia force. This is why the undelivered dose is increased with increasing carrier particle size. Using a higher drug-to-carrier proportion results in a higher fraction remaining within device and mouthpiece, too (Fig. 4).

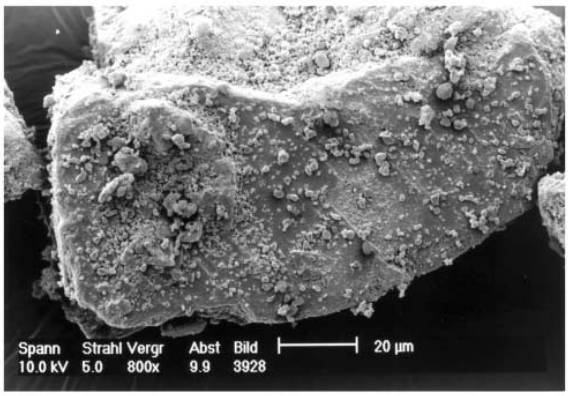

Fig. 3. SEM photograph of an interactive mixture with medium-sized lactose (63–90 μm) containing 1% budesonide.

3.2. Evaluation of Easyhaler™ data

In a previous study (Steckel and Müller, 1997) the Easyhaler™ device was found to deliver about 21% of drug in the respirable range for a beclomethasone dipropionate/lactose mixture and about 30% fine particles for a salbutamol/lactose mix at the standard flow rate of 60 l min^{-1}. Using different budesonide/lactose ordered mixtures higher fine particle fractions were obtained (Table 3). The highest fine particle fraction (nearly 50%) was measured at the experimental setting with small sized lactose and a low drug load. Compared to the Spinhaler™, interactive mixtures

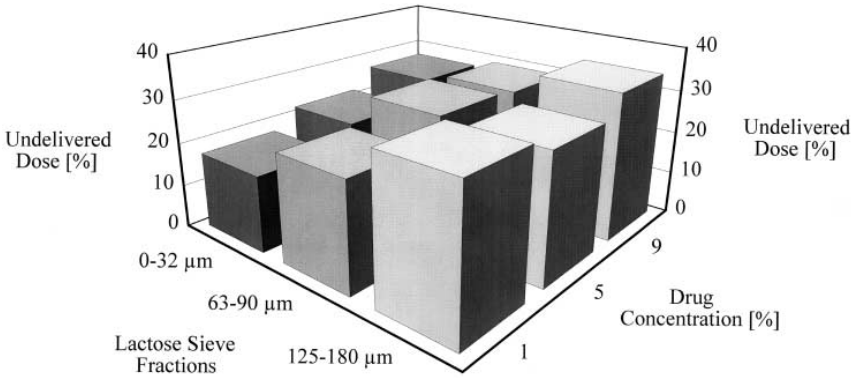

Fig. 4. Percentage of drug remaining within the device (Spinhaler™).

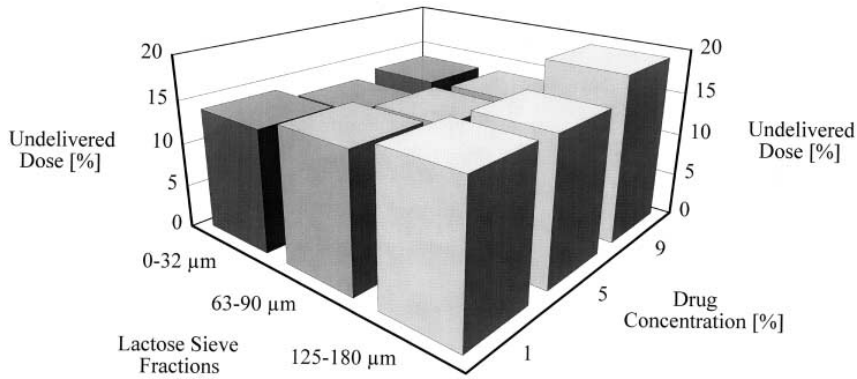

Fig. 5. Percentage of drug remaining within the device (Easyhaler™).

containing 1% Budesonide yielded significantly higher fine particle fractions ($P = 0.001$). This is again a proof for the dependence of the efficacy of the aerosol cloud generated on inhaler design.

With regard to fine particle fraction and undelivered dose the trend is similar to the Spinhaler™ experiments as depicted in Table 3 and Fig. 5. This trend shows some exceptions representing interactions between the two variables: the fine particle fraction is, e.g. not decreasing continuously with increasing drug amount but decreases at 5% drug content and slightly increases with the higher drug-to-carrier proportion of 9% for both the medium and the coarse lactose sieve fraction. These observations suggest that a high overage of drug leads to a more effective dispersion of the powder as it was postulated by Ganderton (1992). Control experiments with unsieved lactose exhibited the same tendency (Table 4) and supported this hypothesis, provided that adhesion forces between lactose and budesonide are higher than cohesion within the budesonide powder. Furthermore, the control experiments pointed out that varying the dry powder formulation is a reasonable start to increase the fine particle fraction: binary interactive mixes with unsieved lactose re-

Table 4
Fine particle fractions of control experiments with unsieved lactose (Granulac 200) using the Easyhaler™

% Drug in the mixture	Fine particle fraction (%)[a]
1	32.87 (0.49)
5	21.68 (3.45)
9	23.33 (0.34)

[a] Mean value (S.D.) $n = 3$.

sulted in fine particle fractions of about 33% whereas a variation in carrier particle size alone or in both drug content and carrier particle size could increase the fine particle fraction significantly.

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