

Can Systemic Drug Delivery via the Pulmonary Route be Achieved Effectively with a Dry Powder Inhaler? Lessons Learned from Exubera

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Summary

Pfizer introduced the first insulin dry powder inhaler (Exubera) to the market in 2006 and terminated the sales less than two years later, claiming a failing marketing success. It can be questioned whether the real reasons for termination have been given and whether the Exubera system was appropriate for systemic drug delivery through the respiratory tract. Therefore, the performance of the Exubera was tested in comparison with that of a highly efficient dry powder inhaler (Twincer). The results suggest that the delivered fine particle dose from the Exubera may have been insufficiently consistent for a drug like insulin. The results also show that the bioavailability of insulin can be increased from 10% (with the Exubera) to at least 20% (with the Twincer).

Introduction

In the past two decades an increasing interest has been developed in the administration of systemically acting drugs via the pulmonary route (Patton et al., 2004A). Animal studies have been presented on a large variety of relatively small peptides and proteins to show the feasibility of inhaled biopharmaceuticals (e.g. Adjei, 1997). In many of these studies instillation techniques or exposure to wet aerosols were applied. Although in most cases bioavailability could be proved, only a few of the studies have shown a promising result, for various reasons (Sakagami, 2002; Heinemann and Heise, 2004). For larger molecules the bioavailability is mostly limited to only a few percent of the dose administered due to a low rate and efficacy of the transport mechanisms proposed, which include passage either through or between the cells (Patton, 1996). Transport occurs particularly in the alveoli where the barriers are thin and there exists a large surface area for absorption. The conditions needed for alveolar deposition have been studied and discussed extensively. Deposition modelling studies suggest that particles in the aerodynamic size range between 1 and 3 micron are most appropriate. Within this size range the predominant deposition mechanism changes from inertial deposition (for 3 µm particles) to sedimentation (for 1 µm particles) and therefore the inspiratory manoeuvre is extremely relevant. For particles of 3 micron, substantial losses in mouth and throat may occur already at a moderate flow rate of 60 l/min, ranging from 5 to 40% depending on the empirical model used (eg. DeHaan and Finlay, 2004). Additional losses may be expected in the conducting and transitional airways. Therefore, part of the inhaled dose does not reach the alveoli. For 1 µm particles, theoretically 8.5 s are needed to travel only 50% of the 0.5 mm diameter of a bronchiole or alveolar sac by settling. Particles of this size may have a fair chance of entering the alveoli, but they require a long breath holding period to yield an acceptable deposition fraction in situ. When using dry powder inhalers, particles in the aerosol are polydisperse and part of the dose may not be within the desired size range from 1 to 3 micron. This depends on the primary drug particle size distribution in the formulation and the efficacy with which this formulation can be dispersed during inhalation. Most inhalers, like the Exubera, have a low air flow resistance which enables the patient to generate flow rates higher than 60 l/min. Patients using the Exubera were instructed to stand or sit up straight and breathe out before taking one slow, deep breath in through the mouth and holding the breath subsequently for 5 seconds. This does not guarantee transport of the aerosol into the alveoli however. Considering a total lung capacity of 6 l with a residual volume of 1.2 l, the maximal volume to be inhaled (vital capacity) is 4.8 l (80% of total lung capacity: TLC). The alveolar contribution to total lung volume is approximately 35% (2.1 l for a lung with a TLC of 6 l). Therefore, at least 3.9 l has to be inhaled for direct aerosol transport into the alveoli, which is approx. 80% of the vital capacity. And even after exhalation to residual volume and subsequent inhalation to TLC, only part (0.9 l, equals 43%) of the alveolar volume is refreshed. For adequate alveolar deposition, it is required that the aerosol is within this 43%. At a flow rate of 60 l/min this requires that the aerosol emission is confined to the first 0.9 s of inhalation.

Taking all these aspects in consideration, it may be questioned whether dry powder inhalers, delivering the dose in a single inhalation manoeuvre, are appropriate for effective systemic drug delivery indeed. Concern about the performance of the Exubera inhaler in this respect was based particularly on the lack of in vitro data released for this device. Therefore, the objective of this study was to test the in vitro and in vivo performance of this system in comparison with that of the Twincer high dose dry powder inhaler using the Exubera formulation. This, to investigate whether the relatively low bioavailability of inhaled insulin (10%) can be explained and also whether further improvement is possible by optimising all the conditions that are relevant to respiratory drug deposition.

Materials and methods

Exubera inhalers and blister packs were purchased from EuroCept pharmaceuticals (The Netherlands). One of the Exubera inhalers was instrumented with a differential pressure gauge to measure the inhalation manoeuvres in vivo (Fig. 1A). Injection moulded Twincer dry powder inhalers (Fig. 1C) were used with unsealed (open) blisters filled manually with Exubera powder derived from 3 mg blister packs. Also one Twincer was instrumented for the in vivo experiments. Both inhalers have been described previously (e.g. de Boer et al., 2006; White et al., 2005).

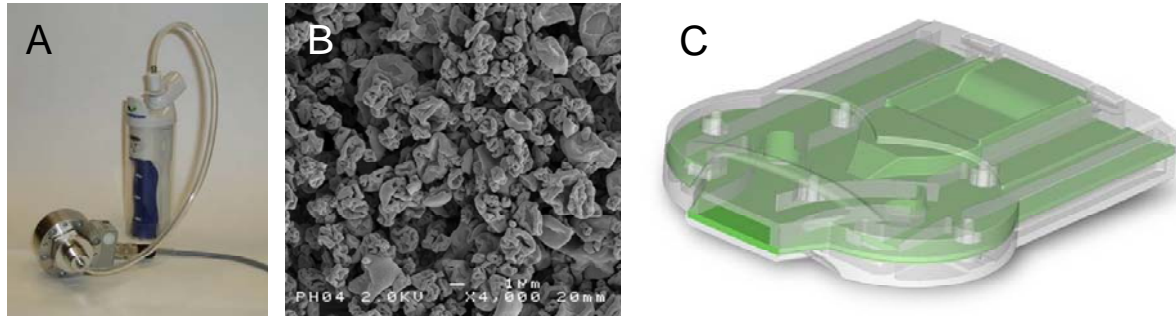


Figure 1: Instrumented Exubera inhaler (A), Exubera formulation (B) and Twincer high dose dry powder inhaler (C)

Scanning electron micrographs (Fig. 1B) and moisture isotherms of the Exubera formulation were obtained from using a Jeol 6301F microscope (Jeol, Japan) and a DVS-1000 dynamic vapour sorption apparatus (SMS, UK). Fill masses in the Exubera blister packs, mass fractions deposited on impactor stages and inhaler retentions were determined with chemical analysis using the Lowry assay and a spectrophotometer Unicam UV 500 (ThermoSpectronic, UK).

Particle size distributions (psd's) were measured with a Sympatec HELOS BF Magic laser diffraction apparatus (Sympatec, Germany) using a 100 mm lens and the Fraunhofer theory for the calculations. The primary psd of the Exubera formulation was obtained from dispersion with a RODOS dry powder disperser at 3 bar. For measurement of the psd's in the aerosols from the Exubera and Twincer, the inhalers were connected to an Inhaler 2000 adapter. Flow rates were adjusted to be 20, 40 or 60 l/min through the Exubera inhaler and 35 l/min (2 kPa) respectively 50 l/min (4 kPa) through the Twincer. For measurement of the emission times, time sliced measurements were applied using the same laser diffraction equipment.

For assessment of the delivered fine particle doses from both inhalers cascade impactors (apparatus 4 described by the USP/NF 2007; Erweka, Germany) were used in combination with a standard USP induction port. Both inhalers were used (alternately) for the administration of insulin doses to a young (age 12) diabetes type 1 patient diagnosed with severe subcutaneous insulin resistance.

Results and discussion

The primary psd of the Exubera formulation seems tailor made for respiratory deposition and is the same for the formulations in the 1 and 3 mg blister pack. The volume median diameter from RODOS dispersion (laser diffraction analysis) is 1.92 μm and more than 95% of the volume is in particles < 5 μm (Fig 2A).

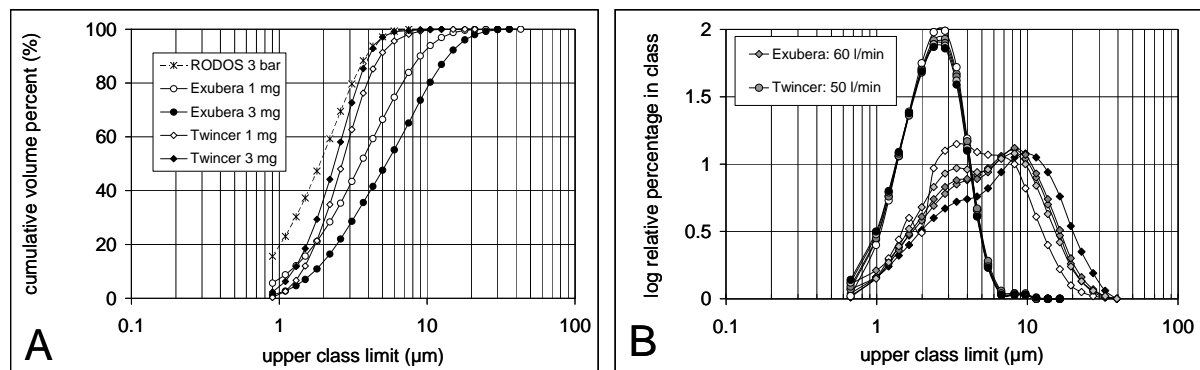


Figure 2: Size distributions in the aerosols from the Twincer (50 l/min) and Exubera inhaler (60 l/min) compared with the primary particle size distribution of the Exubera formulation from RODOS dispersion at 3 bar (A) and the reproducibility in dispersion between both devices for 5 subsequent doses from the same inhalers at the same flow rates (B)

The formulation has been spray dried and contains insulin, mannitol, glycine, sodium citrate and sodium hydroxide. The amorphous powder is hygroscopic and absorbs more than 15% of water after exposure to 50% relative humidity. The hygroscopic nature is a risk as retained particles (in the inhaler) may stick to the inhaler wall firmly by capillary and solid bridges and hinder following inhalations. A high moisture content in adhering particles may also promote microbial growth. The size distribution in the aerosol from the Exubera inhaler is different for the 1 and 3 mg blister pack (Fig. 2A). This difference is independent of the flow rate (Fig. 3A) and seems to explain at least partially why one single 3 mg blister (equivalent to 8 IU of subcutaneously injected fast-acting human insulin) does not give the same insulin plasma level as three 1 mg blisters (each being equivalent to 3 IU of subcutaneous insulin). Not only the dispersion efficacy is different between the 1 and 3 mg blister pack for the Exubera inhaler, this device also has a low reproducibility for the 3 mg blister, as shown in Fig. 2B. The relative standard deviation in volume median diameter (vmd: five subsequent doses) is 22% versus only 6% for the Twincer.

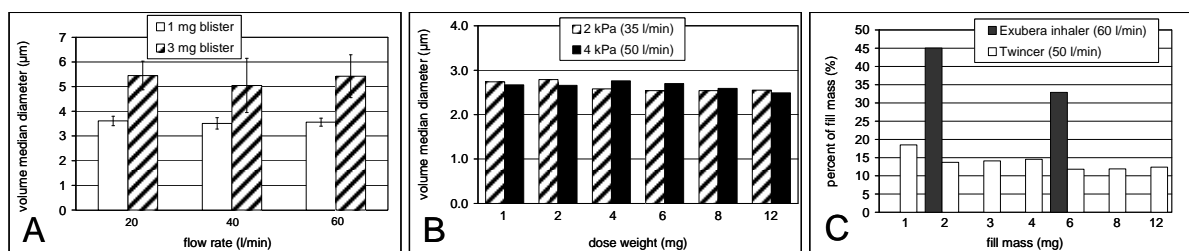


Figure 3: The difference in volume median diameter (in the aerosol) between the 1 and 3 mg blister pack as function of the flow rate through the Exubera inhaler (A); the volume median diameter in the aerosol from the Twincer at two different flow rates (35 and 50 l/min) for the range of dose weights between 1 and 12 mg (B) and the inhaler retentions in the Twincer (50 l/min) and Exubera inhaler (60 l/min) (C). For the Exubera inhaler the 1 mg blister pack corresponds with 1.8 mg powder; the 3 mg blister contains 5.5 mg powder

The Figs. 2A-B show that the aerosol from the Twincer is much finer and much more consistent for a 1 and 3 mg dose (vmd is 2.67 and 2.37 µm versus 3.56 and 5.42 µm for the Exubera inhaler). Also for the Twincer the particle size distribution is largely independent of the flow rate (Fig. 3B). Within the range of dose weights from 1 to 12 mg, the variation in volume median diameter is only between 2.5 and 2.8 µm and the overall mean values at 2 and 4 kPa are practically the same (respectively 2.62 and 2.65 micron). In Fig. 3B it can be seen that the powder retention in the Twincer (at 50 l/min) is less than 50% of the losses that occur in the Exubera inhaler.

The differences in dispersion efficacy and inhaler retention (Figs. 2-3) are reflected in the delivered fine particle doses from the Twincer and Exubera inhaler as measured with cascade impactor analysis. The fine particle dose in the aerodynamic size range 1-5 µm is on average 34% (as percent of the fill mass) for the Exubera inhaler (mean of both blister packs) versus 57% for the Twincer (mean of fill masses between 2 and 6 mg). Within these fine particle fractions the subfractions 1-3 µm are most relevant to alveolar deposition however. Therefore, equivalent fill masses in the Twincer have been calculated on the basis of the difference in these subfractions, being (on average) 22% (21.2-22.6) for the Exubera and 38% (36.7-40.3) for the Twincer inhaler (Table 1).

Table 1: comparison of estimated maximal fractions of the fine particle dose (1-3 micron) that can be transported to the alveoli for the Exubera inhaler and the Twincer on the basis of recorded emission times (and equivalent doses for the Twincer)

| Blister pack | Fill mass | Emission time from Exubera inhaler ¹ | Estimated fraction in alveoli from Exubera ² | Equivalent fill mass in Twincer | Emission time for equivalent fill mass from Twincer ¹ | Estimated fraction in alveoli from Twincer ² |
|--------------|-----------|---|---|---------------------------------|--|---|
| (mg) | (mg) | (s) | (-) | (mg) | (s) | (%) |
| 1 | 1.80 | 1.65 | 0.85 | 1.12 | 0.79 | 1.00 |
| 3 | 5.52 | 2.60 | 0.69 | 2.96 | 1.15 | 0.97 |

¹Recorded emission time at 60 l/min through Exubera inhaler and 50 l/min through the Twincer

²Estimated fraction of the delivered dose in the first 0.9 s of inhalation, corresponding (at 60 l/min) with the first 0.9 l of air inhaled, which is theoretically the volume entering the alveoli after exhalation to residual volume (20% of TLC) followed by maximal inhalation (inhaled volume is 80% of TLC), assuming that the alveolar volume is 35% of TLC (see introduction)

Table 1 also presents the measured emission times from the Exubera inhaler (60 l/min) and Twincer (50 l/min) and the estimated fractions of the delivered dose that can theoretically enter the alveoli under optimised inhalation conditions (see footnote Table 1). These estimated fractions have been derived from the optical concentration curves in the aerosol clouds as function of the inhalation time (using time sliced measurements) as the ratio of AUC from 0 to 0.9 s to AUC total. From these data the doses entering the alveoli for the Exubera inhaler and Twincer can be calculated (Table 2). Calculations in Table 2 have been made for the amount of drug

corresponding with the fill mass of a 3 mg blister pack (5.52 mg). Based on a 1.74 times higher fine particle dose from the same fill mass and a 1.41 times higher fraction of this fine particle dose entering the alveoli when the inhalation manoeuvre is fully optimised, a 2.45 times higher fine particle dose entering the alveoli may be expected from the Twincer.

Table 2: comparison of estimated fine particle (1-3 µm) doses transported to the alveoli from the Exubera and Twincer inhaler (in vitro availability) and the mean measured serum insulin concentrations 30 min after administration per mg of fill mass (insulin C_{t=30}) in a single diabetes type 1 patient (in vivo availability)

| Inhaler | Fill mass | Fine particle fraction (fpf) (1-3 µm) | Fine particle dose (fpd) (1-3 µm) | Estimated fraction of fpd in the alveoli ¹ | Estimated dose in the alveoli ² | Insulin C _{t=30} per mg fill mass ³ |
|---------|-----------|---------------------------------------|-----------------------------------|---|--|---|
| | (mg) | (%) | (mg) | (-) | (mg) | (mU/l)/mg |
| Exubera | 5.52 | 22 | 1.21 | 0.69 | 0.83 | 6.688 |
| Twincer | 5.52 | 38 | 2.10 | 0.97 | 2.04 | 13.629 |
| Ratio | | | 1.74x | 1.41x | 2.45 x | 2.04x |

¹Values copied from Table 1: fraction entering the alveoli within the first 0.9 s of inhalation (see introduction)

²Estimated dose in the alveoli is the product of the fine particle dose and its fraction likely to enter the alveoli under fully optimised inhalation conditions (see footnote Table 1)

³Mean of 4 different doses from the Exubera inhaler (ranging from 11.04 to 22.08 mg fill mass, equals 2x3 to 4x3 mg blisters) and 5 doses from the Twincer (ranging from 3.5 to 10-7 mg fill mass)

Based on glucose levels in the blood measured immediately before inhalation, insulin doses from the Exubera inhaler and equivalent doses from the Twincer were determined for a young diabetes type 1 patient (age 12) diagnosed with severe subcutaneous insulin resistance. The patient was trained to use the inhalers correctly and to hold the breath after inhalation for at least 5 s. The patient used the Exubera inhaler (3 times) during day one, the Twincer (3 times) during day two and both inhalers alternately during day three (at 10 am, noon, and 2 pm). Serum insulin concentrations were measured at 30, 60, 90 and 120 min after inhalation and the mean (of all inhalations per inhaler) for t=30 per mg real dose (fill mass) is shown in Table 2, indicating that the difference in the in vitro availability (2.45x) is reflected by a similar difference in the in vivo availability (2.04x).

Conclusions

This study shows that systemic delivery through the respiratory tract of relatively small biomolecules is very well possible. For a drug like insulin, having a bioavailability of 10% from the Exubera inhaler, an increase to 20% is possible when a highly effective and reproducible inhaler like the Twincer is used and the inhalation manoeuvre is fully optimised. Considering this relatively high bioavailability in relation to the small fraction of the delivered fine particle dose that reaches the alveoli when the inhalation manoeuvre is not optimal, absorption via the terminal bronchioles for a drug like insulin is very likely. When less than 80% of vital capacity is inhaled, convective aerosol transport directly into the alveoli is zero. Exubera-like formulations seem appropriate for alveolar deposition, but they should be used in combination with disposable inhalers to avoid material build-up due to moisture uptake. Exubera-like inhalers are less appropriate, because they combine a moderate and inconsistent dispersion efficacy with a long emission time, a relatively high inhaler retention and a low inhaler resistance. Effective (disposable) high dose inhalers like the Twincer can increase the bioavailability of inhaled insulin at least by a factor two.

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