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Pulmonary deposition of lactose carriers used in inhalation powders

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Abstract

Dry powder dosage forms are generally formulated by mixing the micronized drug particles with the larger carrier particles. Lactose is a commonly used carrier. Carriers enhance the flowability of powder mixtures and therefore enable low dosing of active substances. During inhalation, the drug particles are dispersed from the surface of carrier particles. The aim of this study was to compare how different qualities of ^{99m}Tc-labelled lactose carrier systems deposit in the lungs. The sizes of the labelled and unlabelled α-lactose monohydrate particles were compared by using a laser diffraction method. Distribution of radiolabel between different particle size fractions was determined using the Andersen cascade impactor. The in vivo depositions of lactose carrier systems were investigated in ten healthy men using the technique of gammascintigraphy. In addition, redispersion of budesonide from the carrier materials was evaluated by using the Andersen cascade impactor. According to the validation data the particle size of the lactose carriers remained unchanged during the labelling process. Low pulmonary deposition varying between 2.5 and 3.3% was detected. Only a small amount of lactose was deposited in the lungs, thus pulmonary deposition is not a limiting factor for lactose selection. According to in vitro redispersion data the fine particle fraction of the delivered dose in the impactor varied between 10.3 and 26.0%. Thus, the redispersion of the budesonide particles can be altered by the properties of the carrier system.

Keywords: Inhalation powders; Carrier systems; Lactose; ^{99m}Tc-labelling; Gamma scintigraphy; Pulmonary deposition

1. Introduction

Metered dose inhalers (MDIs) have been the most commonly used drug delivery system in the treatment of bronchial asthma. MDIs are small, portable and relatively unaffected by the external environment. Although MDIs are apparently easy to use, many patients found it difficult to release the aerosol dose in co-ordination with their respiratory cycle (Wetterlin, 1988; Vidgren et al., 1991). Furthermore, MDIs contain CFCs (chlorofluorocarbons), which will limit their use. Several dry powder inhalers (DPIs) have been introduced to overcome the co-ordination problems of the MDIs (Borgström and Newman, 1993).

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Novel approaches (compressed gases, battery operated motors or impellers, etc.) have been suggested to create energy into the powder dose by the device (Dalby et al., 1996). However, most of the commercially available DPIs are breath actuated, and thus patient's inspiration disperses a drug dose into the inspired air stream. Most of the patients, who are unable to use their MDIs correctly, can use the DPIs without difficulty (Hartley et al., 1977). In addition the amount of drug which impacts in the oropharynx is lower using the DPIs than using the MDIs (Selroos et al., 1996). Delivery efficiency of the DPIs is dependent upon the inhalation manoeuvre, design of an inhaler device and formulation of an inhalation powder (Ganderton, 1992). Because micronized drug particles are very cohesive and their flow properties are poor, the larger carrier particles, which are usually lactose, are most often incorporated with the micronized drug powder to make the powder blend less cohesive and freer flowing. These powder mixtures are often called ordered or interactive mixtures, which are commonly easier to handle during manufacturing processes. Furthermore, it ensures accurate dosing of active ingredients and improves emptying of the micronized materials from a delivery system (Timsina et al., 1994; Vidgren et al., 1994).

During inhalation the drug particles are dispersed from the surface of the carrier particles by the energy of the inspired air flow. The larger carrier particles should impact in the upper airways, whereas the small drug particles should penetrate into the lungs. Thus, if the drug particles adhere strongly to the lactose particles, it may reduce pulmonary deposition of the drug. The relatively strong bonding of drug to carrier particles tends to exacerbate free drug particle liberation, thereby reducing deep lung penetration (Staniforth, 1996). To avoid this problem several interactive powder formulations, with effective drug release properties, have been developed. For example, carrier systems with broad particle size distribution are used. In addition, finer carrier particles are mixed with coarser carrier particles. In both cases the finest carrier particles occupy the highest energy binding sites of coarser carrier size fraction. This leaves the lower energy sites available for adhesion of drug particles, which would be expected to be yielded up more efficiently and completely under any given inspiratory effort. Besides altering the size distribution of the carrier, drug particle adhesion to carrier lactose surfaces can be modified too, by alteration of shape, texture and density of the carrier (Yeung and Hersey, 1979; Staniforth, 1996). The inclusion of the small carrier particles would increase the concentration of the aerosol in the inhaled air stream and may cause irritation, coughing and even bronchoconstriction.

The aim of this study was to compare how different qualities of radiolabelled lactose carriers deposit in the lungs. In addition, the influence of the carrier to the redispersion of the budesonide powder blends was investigated.

2. Materials and methods

2.1. Labelling of lactose particles

A total of three α-lactose monohydrate carrier systems, Pharmatose® Mesh 325 (DMV, Holland), a mixture of Pharmatose® Mesh 325 (80%) and Pharmatose® Mesh 450 (20%) (DMV, Holland), and Granulac® 200 (Meggle, Germany), were chosen for this study. Mesh 325 has a narrow particle size distribution whereas Granulac 200 has a wide particle size distribution containing many fine lactose particles (Fig. 1). Mixed lactose is a combination of two lactose qualities (Mesh 325 80% + Mesh 450 20%). Fine lactose particles (Mesh 450) in mixed lactose and Granulac 200 are supposed to occupy the highest energy binding sites of coarse lactose particles.

These lactose qualities were labelled with ^{99m}Tc using a labelling method based on that described by Newman et al. (1989). Briefly, the radionuclide was eluated from a radionuclide generator as pertechnetate ($^{99m}TcO_4^-$) and 3 ml of the eluate was placed in a glass test tube. The radionuclide was then extracted out of the aqueous phase in chloroform. Then, one drop of ammonia and one drop of tetraphenylarsenium chloride (TPAC, 5% aqueous solution) were added to the eluate. Chloroform (3 ml) was then added and the test tube

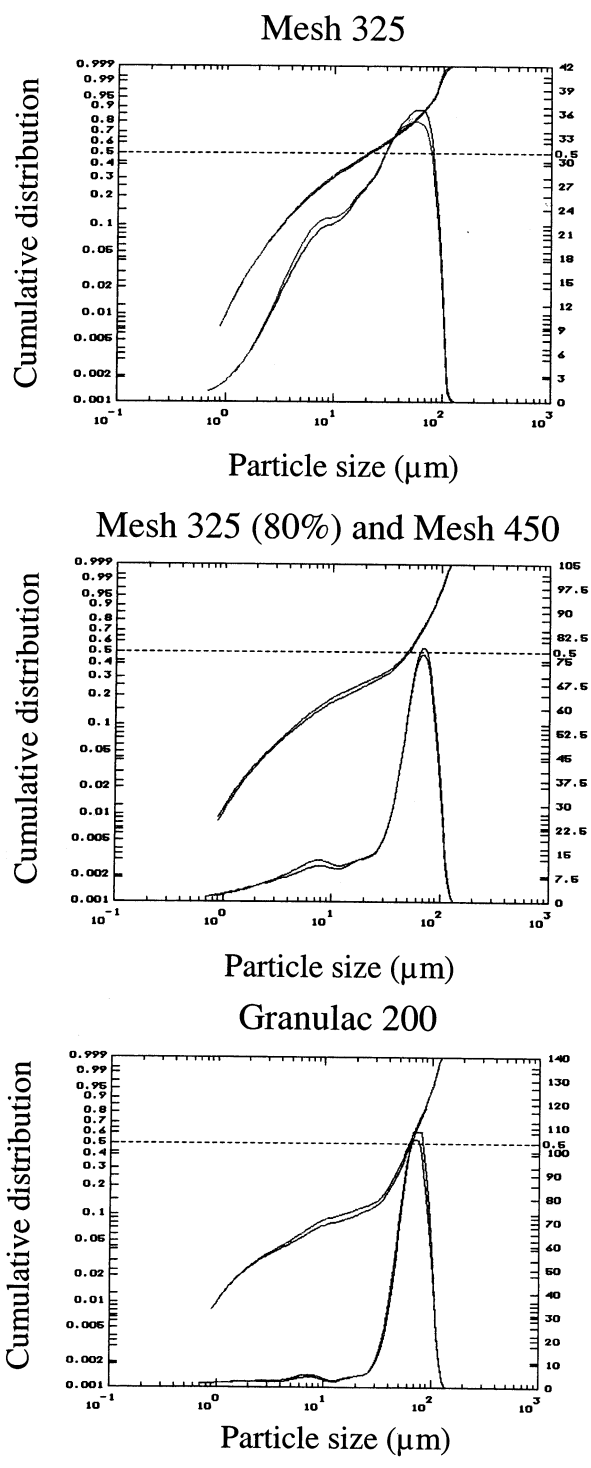

Fig. 1. Cumulative (volume) and frequency (volume) particle size distributions of the labelled and unlabelled lactose samples determined by using the laser diffraction method ($n = 3$).

shaken in a Vortex shaker for 5 s before filtering through a silicone-treated phase-separating filter paper (Schleicher and Schull, D-Dussel). The filtrate contained $\sim 60\%$ of the original activity in the form of tetraphenylarsenium pertechnetate. Lactose monohydrate was suspended in the chloroform phase. Chloroform was removed by evaporating in an ultrasonic bath. The ^{99m}Tc- labelled lactose powders were dispensed into hard gelatine capsules. Each capsule contained 20 mg of α-lactose monohydrate and an average 60 MBq of radioactivity.

2.2. Assessment of the labelling process

The particle size distributions of the labelled and unlabelled lactose monohydrate particles were compared by using a laser diffraction method (Lazer-Particle Sizer, Sucell, Germany). Three parallel measurements were carried out.

To ensure reliable monitoring of inhaled lactose particles within the respiratory tract the amounts of lactose and radioactivity in different particle size fractions were assessed by using the Andersen cascade impactor (Sierra Andersen 1 CFM Ambient Sampler, USA). A total of 20 mg of the labelled and unlabelled lactose monohydrate was delivered from hard gelatine capsules to the air stream (56.8 l/min) by using the Aerolizer™ (Novartis) powder inhaler. The stages of the impactor, the preseparator and the imitation throat (USP) as well as the inhaler were washed with purified water and both the radioactivity (Capintec Radioisotope Calibrator CRC-120, USA) and the lactose contents (HPLC) of the samples were determined. Three parallel measurements were carried out. The HPLC system used for lactose monohydrate analysis consisted of a Dionex series 4000i pump, the CarboPac PA-1 column (4×250 mm) and a pulsed amperometric detector (Dionex Corporation, USA). The following pulse potentials were used for detection: $E_1 = 0.1$ V ($t_1 = 300$ ms), $E_2 = 0.6$ V ($t_2 = 120$ ms) and $E_3 = -0.8$ V ($t_3 = 300$ ms). The elutions were carried out in 0.15 M sodium hydroxide under isocratic conditions over 7 min at the flow rate of 1.0 ml/min. Reproducibility of the assay is shown to be better than 3% (Rocklin and Pohl, 1983; Bao et al.,

1996), the linear range of determination is up to 10 nmol in a single injection, and the detection limit 50 pmol (Bao et al., 1996).

2.3. Administration of ^{99m}Tc-labelled lactose carrier systems

A total of ten healthy male volunteers took part in the open, controlled, non-randomized, cross-over study. Their mean age was 26 years (range 21–31 years), the mean height was 179 cm (range 172–198 cm), and the mean weight was 77 kg (range 62–112 kg). The lung functions of the subjects were within the normal values (Viljanen et al., 1982). Mean FEV_1 was $109 \pm 13\%$ (mean $\pm$ S.D.) of the predicted value (Medikro 202®, Finland).

In order to document the mode of inhalation the Aerolizer™ powder device was inserted in a specially designed cover. The cover was connected to the pneumotachograph of a spirometer (Medikro 202®, Finland) from which the signals of the air flow (l/min) were detected and from which the volunteers saw their own inspiratory air flows during inhalations. The inspiratory air flow and inhalation volume was documented and printed out. The volunteers were instructed to exhale normally, place the mouthpiece tightly between lips, inhale rapidly and deeply with a inspiratory flow of 60 l/min to the total lung capacity, hold the breath at least for 5 s and exhale normally.

2.4. Measurement of the pulmonary deposition

The pulmonary deposition of the ^{99m}Tc labelled lactose monohydrates, was acquired into two dynamic data sets by a two head gamma camera (Siemens E.Cam, USA) equipped with low energy all-purpose collimators (Kuikka et al., 1998). The first set of data was based on 12×5 s (60 s) and the second set on 14×60 s (14 min). Anteroposterior and posteroanterior views of the whole lung area with the same measurement geometry were obtained in the sitting position. The amount of lactose monohydrate retained in the inhaler was also determined with the gamma camera. The data analysis was made by Hermes Software (Nuclear Diagnostics AB, Sweden). Primary counts were corrected for background radiation, radioactive decay of ^{99m}Tc and individual attenuation of the radiation. To obtain individual attenuation coefficients and edges of the lungs, a flat ^{57}Co source was used. The lung area was determined by drawing regions of interest (ROIs) around the lungs on the transmission images which were then superimposed on the lactose deposition images. The attenuation coefficients were determined by comparing transmission count rates on count rate of ^{57}Co source.

2.5. Ethical aspects

The trial plan was accepted by the ethical committee of Kuopio University Hospital. All the volunteers gave a written informed consent and the study protocol was completely explained before attending the trial. The radiation exposure to the lungs was less than 0.1 mGy/study.

2.6. Statistical testing

Statistical significance between pairs of scintigraphy data was examined using the Wilcoxon matched-pairs signed-ranks test.

2.7. In vitro deposition of budesonide

The cascade impactor study (Sierra Andersen 1 CFM Ambient sampler, USA) was carried out to investigate how the lactose carrier systems included in the in vivo study affect to the redispersion of the drug particles. The powder mixtures were prepared using a Turbula mixer (T 2 C, Switzerland). A total of 100 mg of budesonide was mixed with 9.9 g of lactose. Lactose was added in three portions and power blend was mixed for 10 min after each step with a speed of 60 rpm. To determine powder blend homogeneity, 20 250-mg samples were analysed by using an HPLC method based on the monograph of Budesonide in Ph.Eur. (European Pharmacopoeia, 1997). The linear range of determination of budesonide using the Ph.Eur. method is 5–120 μg/ml. Using an air flow of 56.8 l/min, 20 mg of the powder mixture, containing 200 μg of budes-

onide (Astra Draco AB, Sweden) and 19.8 mg of the carrier was delivered from hard gelatine capsules to the impactor. The Aerolizer™ powder inhaler was used as a delivery device. The collection stages of the impactor, the preseparator, the USP-throat and the inhaler were washed with 75% methanol solution. The drug concentrations were analysed by using the HPLC method based on Ph.Eur. Three parallel measurements were carried out.

3. Results

3.1. Assessment of the labelling process

According to the laser diffraction data (Fig. 1) the size of the lactose particles remained unchanged during the labelling process. Thus, the labelling process did not cause any changes in the particle size distributions of the carrier materials.

Aerodynamic particle size distribution of the unlabelled and labelled lactoses as well as the radiolabel as assayed with the Andersen cascade impactor are given in Fig. 2. The distributions of labelled lactose, unlabelled lactose (determined using HPLC method) and radioactivity (determined using radio isotobe calibrator) within the cascade impactor were virtually the same. Thus, ^{99m}Tc-label was a valid marker for the lactose carriers.

3.2. Pulmonary deposition

All of the volunteers completed mixed lactose and Granulac 200 lactose studies. Of the ten volunteers, three did not complete Mesh 325 gamma scintigraphy study, because the gelatine capsules were not pierced properly. True peak inspiratory flow rates during inhalations as well as duration of inhalations are presented in Table 1. Only small part (2.5–3.3%) of lactose samples deposited in the lungs (Table 1). Most of the lactose deposited in the lungs was located in the central lung area. The major site of deposition was in the oropharynx from where the deposited lactose was swallowed (Fig. 3).

Pulmonary deposition of Mesh 325 was slightly smaller than deposition of mixed lactose and Granulac 200 containing small lactose particles. There was a statistically significant ($P < 0.05$) difference between Mesh 325 and mixed lactose but there was no statistically significant difference between Mesh 325 and Granulac 200 or between mixed formulation and Granulac 200. In addition, compared to the Mesh 325 (10.0%) and the mixed formulation (9.9%), a significantly higher fraction of the Granulac 200 were retained in the device (16.9%). Thus, the small lactose particles of the Granulac 200 seemed to be intensively retained in the plastic device.

3.3. In vitro deposition of budesonide

Homogeneity of the budesonide powders was good. Relative standard deviation of 20 samples varied from 0.3% (Mesh 325 lactose carrier) to 1.0% (mixed lactose carrier). According to the cascade impactor data, the fine particle fraction of the delivered dose (stages 2–7) was $10.3 \pm 3.5\%$ for the Mesh 325 lactose and $17.0 \pm 1.0\%$ and $26.0 \pm 8.0\%$ for the mixed lactose and Granulac 200, respectively (Fig. 4). Thus, the redispersion of the drug particles can be affected by the properties of the carrier system.

4. Discussion

Interactive mixtures are commonly used in DPI systems (Timsina et al., 1994). Several different carrier systems have been either introduced onto the market or are under development. There are two main concerns as the carrier formulations are designed. First, the main target of the pharmaceutical and biopharmaceutical research of the new DPI systems is to obtain as reproducible and high pulmonary deposition as possible. This could be achieved by successful carrier selection and careful process optimisation. Second, the selected carrier system should not cause local side-effects in the upper airways, e.g. irritation, cough and hoarseness. Furthermore, it would be a clear disadvantage if the carrier particles penetrated deep into the lungs causing irritation of pulmonary mucosa.

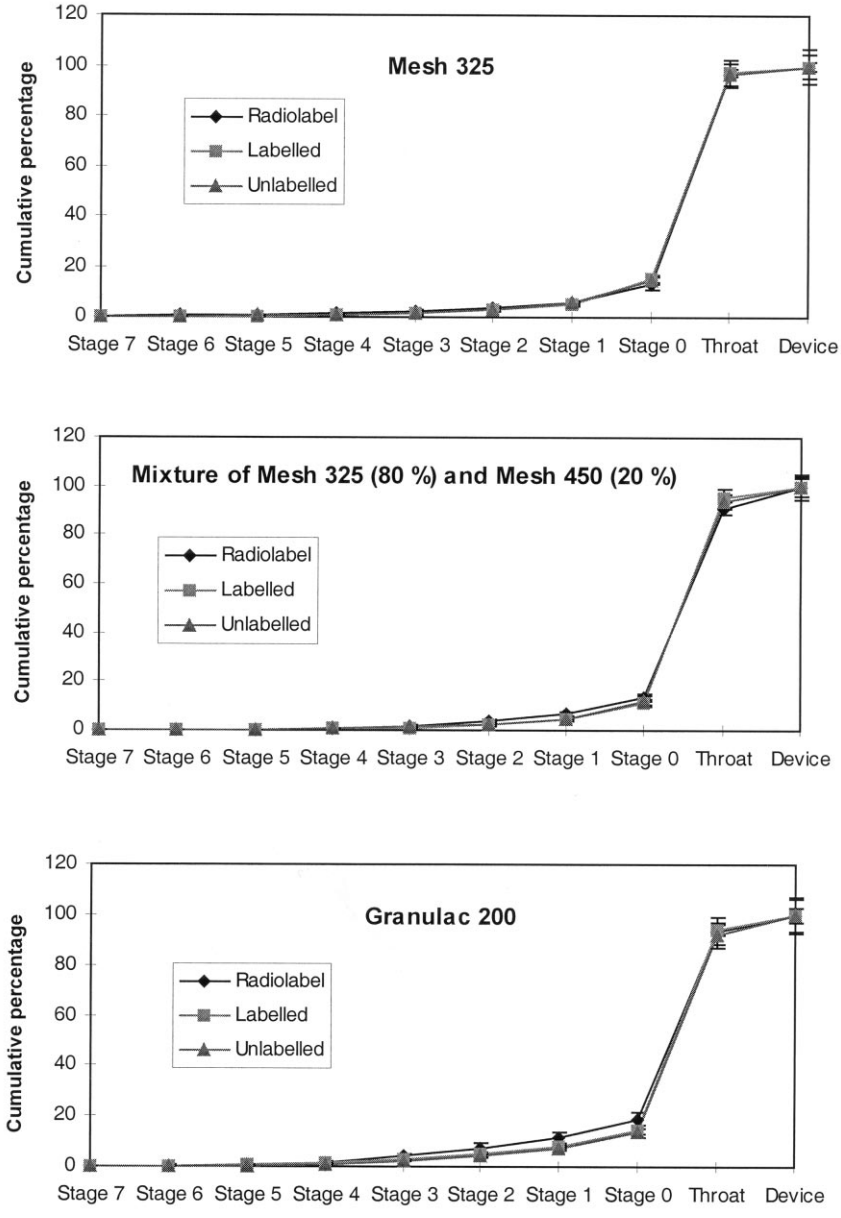

Fig. 2. Cumulative deposition of radiolabel, labelled and unlabelled lactose in the device, in USP-throat and on the different stages of the Andersen cascade impactor ($n = 3$).

As the novel DPI systems are evaluated, most often the main attention is paid to careful analysis of the pharmaceutical, technical and biopharmaceutical properties of the drug delivery system (device and formulation). This means, that, for example, technical function, dose reproducibility, delivered drug dose as well as fine particle fraction and fine particle dose, are analysed. However, less attention is paid to obtaining the data of deposition of inhaled carrier particles.

We have now investigated pulmonary deposition of three different lactose carrier systems by

Table 1
Fractional deposition (mean ± S.D.) of ^{99m}Tc-labelled lactose carriers, peak inhalation flow (PIF) and forced inspiratory vital capacity (FIVC) during inhalation of lactose samples

Lactose	Pulmonary deposition (%)	Device deposition (%)	PIF (l/s)	FIVC (l)
Mesh 325	2.5 ± 0.7*	10.0 ± 6.7	1.09 ± 0.17	3.6 ± 1.0
Mixed[a]	3.3 ± 1.2*	9.9 ± 4.2	1.05 ± 0.08	3.9 ± 0.7
Granulac 200	3.2 ± 1.1	16.9 ± 2.3	1.08 ± 0.09	4.1 ± 0.9

[a] Mixed, mixture of Mesh 325 (80%) + Mesh 450 (20%).
* There was a statistically significant difference between Mesh 325 and mixed lactose on pulmonary deposition ($P < 0.05$).

using a gamma camera. Before entering the in vivo gamma camera study the labelling process was validated using the Andersen cascade impactor. The in vitro validation study showed, that the amount of radioactivity corresponds to the amount of lactose in the different particle size fractions (Fig. 2). In addition, the particle size distributions of the labelled and unlabelled lactoses were similar. However, the amounts of radioactivity in the finest lactose particle fractions were slightly higher than the amounts of radioactivity in the larger lactose particles. This might be due to the fact, that small lactose particles have larger surface area versus mass than the large lactose particles. Thus, the results of gamma scintigraphy study slightly overestimate the amount of lactose deposited in the lungs; the real lung deposition of lactose is even lower than our results indicate.

According to the gamma camera data only a small amount of lactose was deposited into the lungs (2.5–3.3%). The effect of the particle size distribution of the carrier systems on the lung deposition was the main object of this study. Mesh 325 lactose has narrow particle size distribution with a mean particle size of 62.1 μm. Mixed lactose (mean particle size 49.0 μm) is mixture of two lactose qualities having a wider particle size distribution. Granulac 200 (mean particle size 20.5 μm) has the widest particle size distribution of carrier systems. Theoretically, higher lung deposition should be expected for carrier systems containing a larger fraction of fine lactose particles. The in vivo lung deposition study showed somewhat higher pulmonary dose as the carrier systems containing small lactose particles were inhaled. However, this difference was not as large as predicted according to the particle size data. This finding indicates that small lactose particles in mixed lactose and in Granulac 200 occupy highest energy binding sites on the surface of coarse lactose particles forming a stable system, which does not break down during inhalation. Since fine lactose particles adhere on the surface of coarse lactose particles, fine lactose particles are not free for lung deposition.

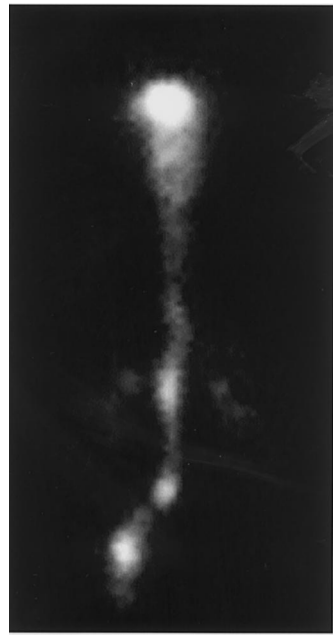

Fig. 3. Typical posteroanterior gamma camera image of the inhaled lactose carrier (Granulac 200) delivered from the Aerolizer™ powder inhaler. Only a small amount of the lactose is deposited in the lungs, whereas most of the lactose is deposited in the oropharyngeal region and is then swallowed into the stomach.

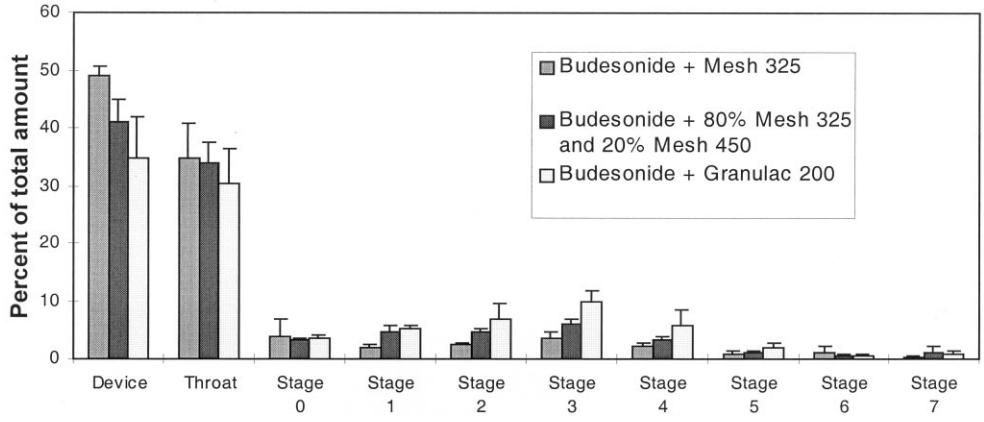

Fig. 4. Deposition of budesonide inhalation powders (% ± S.D.) in the Andersen cascade impactor ($n = 3$).

The gamma camera study showed high oropharyngeal deposition of the inhaled lactose formulations (Table 1 and Fig. 3). This might be one of the reasons why asthmatic patients, who have used the DPI systems, have more caries than for example MDI users (Ginty, 1997). Thus, it reasonable to rinse the mouth with water after administration of the inhalation powders. In addition, the swallowed lactose may cause unpleasant adverse events to the most sensitive lactose intolerant patients.

In our study, we have also investigated fine particle fractions of budesonide inhalation powders using the Andersen cascade impactor. Budesonide was mixed with the carrier systems used in gamma scintigraphy study. The results showed that higher fine particle fraction could be achieved as the carrier systems with broader particle size distribution containing fine lactose particles are used (Fig. 4). These results are supported by Staniforth (1996), who described the theory for the interactive carrier systems used in the inhalation powders. Accordingly, most of the high energy binding sites of the large carrier particles (Mesh 325) are unoccupied allowing budesonide particles to adhere strongly on the surface of lactose. The fine particle fraction of budesonide was increased as the mixed lactose and Granulac 200 carrier systems were used. Small lactose particles have occupied high energy binding sites on the surface of the coarse lactose particles, and thus less high energy binding sites are available for the micronized budesonide particles.

As Granulac 200 was used as a carrier the fine particle fraction of budesonide inhalation powder was further increased. This might be caused by the different particle size distribution or surface properties of the Granulac 200 lactose particles. The number of high energy binding sites is apparently related to the surface porosity and roughness of the carrier particles (Staniforth et al., 1982; Staniforth and Rees, 1983). According to Lucas et al. (1998) there is an alternative explanation for the use of fine lactose as a carrier. First, fine lactose particles have occupied high energy binding sites of coarse lactose particles. Secondly, during mixing fine particle multiplets, which are combinations of fine lactose particles and drug particles, are produced. Drug particles are more effectively liberated from these multiplets. This would be expected as smaller particles have a lower degree of surface roughness, which restricts opportunities for contacts at clefts and aspirates on the substrate surface.

As pointed out in the in vivo study the lung deposition of the lactose carriers with wide particle size distribution (mixed lactose and Granulac 200) did not differ greatly from lung deposition of coarse lactose carrier. Therefore, it can be concluded that the benefits from using carrier systems with wide particle side distribution are greater than disadvantages of higher lung deposition.

In conclusion, according to gamma scintigraphy study, pulmonary deposition of inhaled lac-

tose carriers remained relatively small. Thus, the interactive lactose blends remained stable during inhalation. In addition, the selection of lactose carrier has great influence on the biopharmaceutical properties, e.g. fine particle fraction, of the inhalation powder formulations.

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