A Study of Drug–Carrier Interactions in Dry Powder Inhaler Formulations Using the Andersen Cascade Impactor, X-Ray Microanalysis and Time of Flight Aerosol Beam Spectrometry (TOFABS)

Teerapol SRICHANA,*[,a] Anthony BRAIN,[b] Christopher MARRIOTT,[c] and Gary Peter MARTIN[c]

Department of Pharmaceutical Technology, Faculty of Pharmacy, Prince of Songkla Univeristy,[a] Hat Yai, Songkhla 90112, Thailand, Electron Microscope Unit, King's College London,[b] Camden Hill, London W8 7AH, UK, and Department of Pharmacy, King's College London,[c] Manresa Road, London SW3 6LX, UK.
Received May 12, 1999; accepted October 21, 1999

The purpose of this study was to determine the *in vitro* deposition of both drug (albuterol sulfate) and carrier (lactose) particles in relation to each other from a dry powder inhaler formulation using an Andersen cascade impactor (ACI) and time of flight aerosol beam spectrometry (TOFABS). In addition, scanning electron microscopy (SEM) combined with X-ray microanalysis was employed to distinguish albuterol sulfate from lactose. Drug particles apparently penetrated deeper into the impactor than lactose particles contained in the formulation. In some certain stages of impactor, drug particles were separated from lactose particles. Although the TOFABS cannot distinguish between albuterol sulfate and lactose, the TOF spectra obtained from the Aerosizer would appear to be partly indicative of the interactions which exist between drug and carrier. One symmetrical TOF peak was obtained from drug or lactose alone. The TOF peak of the drug was always lower than the TOF of lactose. The times obtained for each powder between experiments were highly reproducible and typical of material and particle size. The use of SEM–X-ray microanalysis also allowed some qualitative characterization of shape and state of association of the two components.

Key words albuterol sulfate; lactose; Andersen cascade impactor; X-ray microanalysis; time of flight aerosol beam spectrometry; dry powder aerosol

Dry powder inhaler formulations generally comprise micronized drug particles with a mean aerodynamic diameter (D_a) of 2—5 μm blended with an inert carrier (30—60 μm), usually lactose, to form an interactive mixture of the two components. A carrier is included in the formulation to act as a bulking agent and to aid aerosolization of the drug,[1)] and it should be deposited in the upper airways with only the drug particles being liberated into the inspired air, ideally reaching the lower airways.[2)] Despite the use of impactor data to assess the effect of formulation variables on aerosol cloud characteristics,[3,4)] there is limited knowledge of drug-carrier interactions and drug release from the carrier during aerosolization. French *et al*.[5)] proposed that the active drug in carrier formulations can exist in a variety of possible states following aerosolization, and these include: a) individual active drug particles, b) active-active drug particle aggregates, c) active drug bound to individual carrier particles in mono- or multi-layers, and d) combined active drug and carrier aggregates. Few previous studies have focused on the characteristics of the carrier counterpart during drug deposition *in vitro* or considered the relative depositions of the drug and carrier. A relatively recent technique, based on the aerodynamic time of flight (TOF), has been used to analyze the particle size distribution in pharmaceutical powders.[6)] In this method, particles are accelerated by the drag forces generated by an accelerating air stream, and while very small particles almost attain sonic velocity, larger particles experience a lower acceleration because of their greater mass. As particles pass through two laser beams in the measuring region spaced at a set distance, the light interception is detected and converted into electronic signals by two photomultiplier tubes. The time required for individual particles to pass between the beams is measured to a precision of 25 nanoseconds and is termed the TOF. Since TOF is dependent upon particle size it is possible to obtain a particle size distribution for any powder, including, for example, the lactose and drug deposition on individual plates of an ACI after a dry powder formulation has been aerosolized into the impactor. The size distribution produced by the software of any instrument which measures TOF assumes, as with most particle sizing techniques, sphericity of shape. This, of course, is seldom the case for pharmaceutical powders, and hence the use of scanning electron microscopy (SEM) together with X-ray microanalysis, can be employed to determine the appearance and to distinguish the drug from carrier particles. X-rays are produced whenever an electron beam interacts with matter, as in the use of SEM[7)] for example, and these can be used very effectively to provide information about the chemical composition of the specimens examined. X-ray microanalysis can be regarded as a qualitative non-destructive technique that provides a means of detecting most elements *in situ*, sometimes at levels as low as 10^{-19} g.[8)] The nature of the interaction between lactose and drugs has not been completely characterized. Hence, it was the purpose of this study to determine the interaction between drug and carrier in relation to each other after aerosolization using the ACI. TOF was used to further characterize the samples deposited on each stage of the ACI, and SEM combined with X-ray microanalysis was employed to distinguish albuterol from lactose.

Materials and Methods

Micronized albuterol sulfate (median diameter 2.8 μm) was supplied by Glaxo Wellcome, Ware, UK. Lactochem lactose (medium grade) was obtained from Borculo Whey, Ltd., Chester, UK. Micronized lactose was obtained from Meggle, Wasserburg, Germany. The ISF® (Cyclohaler®) device was obtained from Pharbita BV, Zaandam, the Netherlands. Capsules (size 3) were obtained from Farillon Limited, Essex, UK. The formulation was

* To whom correspondence should be addressed.

prepared by mixing albuterol sulfate (0.2 g) with lactose (13.5 g) in a Turbula® mixer (Basel, Switzerland) for 2 h. Two size ranges of lactose, medium grade Lactochem® (with a multimodal particle size distribution and a volume median diameter (VMD) of 20.10 μm and geometric standard deviation (GSD) of 1.86) and micronized lactose (with a monomodal distribution and VMD of 8.60 and GSD of 1.71, measured by laser diffraction (Malvern Mastersizer, Worcester, UK)), were used as carriers in the powder blend. 27.4 mg of each blend, equivalent to 400 μg drug, was weighed into each capsule. The uniformity of both blends was 102.2±1.4 and 102.8±2.4%, respectively. Other capsules were prepared containing either 27 mg albuterol sulfate alone or 27 mg of either Lactochem lactose or micronized lactose alone.

Deposition Studies Using the ACI A cascade impactor comprising a pre-separator, eight stages and collection plates (Andersen Sampler, Inc., Atlanta, U.S.A.) was prepared for use by rinsing the cleaned component parts with deionized water. The stages and plates were dried in a hot air oven before being employed in deposition studies, conducted at 28.3 l/min and 60 l/min for 2 l and 10 s, respectively. Two formulations, one containing Lactochem lactose and the other micronized lactose as a carrier, were aerosolized into the ACI using a Cyclohaler® device.[9] After actuating a single dose into the ACI, the glass throat,[10] pre-separator and each stage were rinsed with 50 ml of mobile phase containing the internal standards before determining drug and lactose, as previously described.[11] Detection limits of drug and lactose were 0.1 and 2 μg/ml, respectively. The drug and lactose deposition were expressed as a percentage of the nominal dose. The mass median aerodynamic diameter (MMAD) and GSD of drug and lactose was calculated based on the mass distribution of the respective particles deposited on stages 0 to 7 of the ACI,[12,13] excluding those particles deposited on the pre-separator and throat part. The drug fine particle fraction (FPF) and the amount of fine particle lactose (FPL) of a formulation were defined by the amounts deposited on stages 2 to 7 after aerosolization at a flow rate of 28.3 l/min, and when the flow rate is changed to 60 l/min, the FPF and FPL was defined by the amounts deposited on stages 1 to 7. The data were analyzed for statistical significance using an analysis of variance, and $p<0.05$ was considered to be significant.

SEM–X-Ray Microanalysis of Deposited Samples on Each Stage of the ACI The localization of drug relative to carrier particles on each stage of the ACI was assessed qualitatively using SEM and energy dispersive X-ray microanalysis. Recovered particles were mounted on an aluminium stub before coating them with carbon (Polaron E-500, Watford, UK). The coated samples were viewed by a Philips EM501B (Philips Analytical, Einhoven, The Netherlands) scanning electron microscope. X-ray microanalysis was used to identify the presence of the sulfur atom in albuterol sulfate, enabling a distinction to be made between drug and carrier particles on the basis of X-ray spectra. Such spectra in combination with the electron micrographs, allowed the determination of drug–carrier and carrier–carrier interactions in the powders deposited on each stage of the ACI.

Time of Flight Determination of Dry Powders Deposited on Each Stage of the ACI The ACI was operated as described above except that three doses of each formulation were aerosolized sequentially into the impactor at two flow rates (28.3 or 60 l/min). The empty capsule was removed from the device after aerosolization of each dose, to be replaced by a full capsule, and the device was not washed between doses. The particles retained on each stage of the ACI were carefully removed by scraping each plate with a thin sheet of paper, and were then loaded into the sample cup of the Aerodisperser connected to the Aerosizer Mach 2 (Amherst Process Instruments, Amherst, MA, U.S.A.). The optimum sample run time was 200—500 s, depending upon the sample count rate, and when the feed rate reached 100%, the run was considered complete. In particular, it is essential that no selective sampling of the smaller particles occurs due to larger particles being unsampled. The amount of powder recovered from the lower impaction plates (*i.e.* stages 4 and 5) provided sufficient data for statistical analysis (>100000 particles). Powder build up and electrostatic charge effects within the Aerodisperser were not found to occur using run times ≤500 s.[14] The shear force was set at 3 psi, as specified by the manufacturer, because the particle size was known to be lower than 10 μm (the powder having been recovered from stages 0—7 on the ACI). The deagglomeration was set at 14 l/min to prevent excessive impaction energy on the particles, and the feed rate was set at 5000 particles/s. Although this flow rate is lower than that employed in the ACI (28.3 l/min). It has to be appreciated that the air flow of the Aerosizer represents linear velocity rather than flow rate. All parameters set were kept constant in each experiment, and the results are displayed as TOF. The photomultiplier tube (PMT) voltage was set at 1100 V in order not only to provide maximum sensitivity but also to allow the detection of particles with a size greater than 0.5 μm. A higher PMT voltage setting resulted in increased noise pulses and required a longer run time (>300 s). Both the Aerosizer and the Aerodisperser have been comprehensively described by both Niven[6] and Hindle and Byron.[14] The TOF of pure albuterol sulfate and pure carriers were determined as a marker for drug and carrier TOF spectra. The TOF results were gained as a normalized frequency distribution by number.[15] Each experiment was carried out in triplicate.

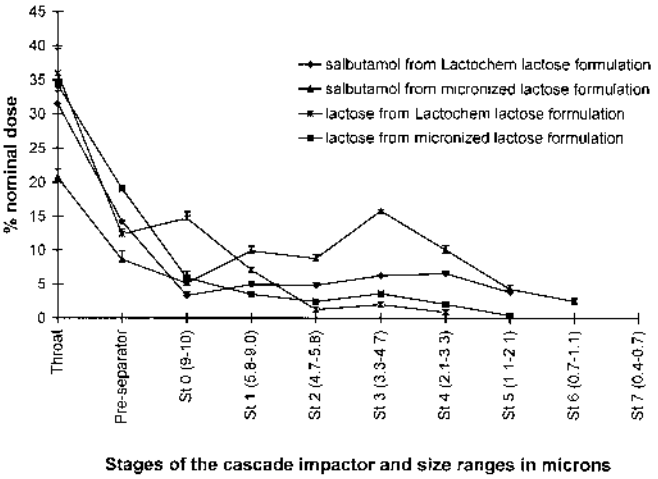

Fig. 1. The Deposition of Albuterol Sulfate and Lactose from Two Formulations of Albuterol Sulfate Containing Either Lactochem or Micronized Lactose as Diluent after Aerosolization into an ACI at 28.3 l/min (mean±S.D., $n=5$)

Results

Deposition Studies Using the ACI The stage cut-off diameters of each stage of the ACI, based on calibration of uncoated plates at 28.3 l/min, are 9, 5.8, 4.7, 3.3, 2.1, 1.1, 0.7, 0.4 μm, for stage 0, 1, 2, 3, 4, 5, 6 and 7, respectively.[12] The cut-off diameters at 60 l/min have not been previously reported, however, according to Eqs. 1 and 2, these values can be calculated.[16]

$$d_{50}=\sqrt{\frac{9Stk_{50}\eta\pi D_j^3 N}{4\rho FC}} \quad (1)$$

where F=total flow rate through the jets, N=total number of jets, d_{50}=effective cut-off diameter, ρ= density of particle (g cm^{-3}), C=Cunningham slip correction factor, Stk_{50}=Stokes number for 50% collection efficiency, η=fluid viscosity (dyne·s cm^{-2}), D_j=jet width (cm).

All parameters are constant if the same impactor and operating conditions are used, therefore, the simplified Eq. 2 is obtained.

$$d_{50} \propto \left(\frac{1}{F}\right)^{1/2} \quad (2)$$

From the known d_{50} at 28.3 l/min, the cut-off diameter at 60 l/min is calculated based on Eq. 2, and the values are 6.2, 4.0, 3.2, 2.3, 1.4, 0.8, 0.5, 0.3 μm for stage 0, 1, 2, 3, 4, 5, 6 and 7, respectively. The size distributions of the fine lactose and drug delivered from the two formulations at 28.3 and 60 l/min, are presented in Figs. 1 and 2. Drug particles were detected as low as stage 5 of the ACI when the Lactochem lactose formulation was aerosolized at 28.3 l/min, but with the same formulation at 60 l/min, some drug penetrated as far as stage 6 (Figs. 1, 2). After aerosolization of the Lactochem

lactose formulation at 28.3 l/min lactose could also be detected as having been deposited as far as stage 4 of the ACI (Fig. 1), whereas at the higher flow rate, carrier particles could only be determined as reaching stage 3 (Fig. 2). Drug particles were found to be deposited as far as stage 6 when the micronized lactose formulation was aerosolized at 28.3 l/min, and since no lactose was detected on stage 6 from this formulation, it can be assumed that the drug on this stage was separated from carrier particles (Fig. 1). When the flow rate was increased to 60 l/min, drug particles penetrated to stage 7, whereas carrier particles reached only stage 4. Drug particles were entrained into the airstream in higher quantities at the higher flow rate (the percent fine particle fraction of drug increasing ($p<0.01$) from 21.6 to 29.7% for the Lactochem lactose formulation and 41.3 to 44.3% for the micronized lactose formulation). However, at a flow rate of 60 l/min, the amount of drug which completely detached from the lactose particles was 8.8% (particles deposited on stages 4, 5 and 6) for the Lactochem lactose formulation whereas the comparable value for the micronized lactose formulation was only 2.3% (particles depositing on stages 5, 6 and 7) (Fig. 2). When the micronized lactose formulation was aerosolized at 28.3 l/min, it would appear that the FPL was much higher than that derived from the Lactochem lactose formulation at the same flow rate (8.5% and 4.2%), respectively. At the higher flow rate, the amount of FPL increased to a greater extent from the micronized lactose formulation (8.5% at 28.3 l/min to 15.0% at 60 l/min) than from the Lactochem lactose formulation (4.2 to 4.3%). When the particle size was plotted as a log-probability distribution, as described in the USP XXIII,[13] it was found that the MMAD of albuterol sulfate in the Lactochem lactose formulation at 28.3 l/min was 4.89 μm, while in the micronized lactose formulation it was 4.07 μm (Table 1), although these two values were not statistically different ($p>0.05$). Aerosolization of the drug at the higher flow rate (60 l/min) resulted in a lower MMAD of the drug, a value of 2.8 μm being obtained irrespective of formulation (Table 1). The MMAD of lactose deposited within the impactor from the Lactochem lactose containing formulation was not surprisingly higher than that of the drug particles, although the MMAD did not change significantly ($p>0.05$) when the flow rate was increased. Despite the MMAD of lactose from the formulation containing the micronized excipient being smaller (5.10 μm at 28.3 l/min) than that in the formulation containing Lactochem lactose, it again did not change significantly as a function of flow rate. The GSD of both drug and carrier particle size was approximately 2 in all experiments.

SEM–X-Ray Microanalysis of Samples Deposited on Each Stage of the ACI X-ray microanalysis enabled drug particles to be distinguished from lactose, as shown in Fig. 3. Sulfur atoms present in albuterol are capable of being de-

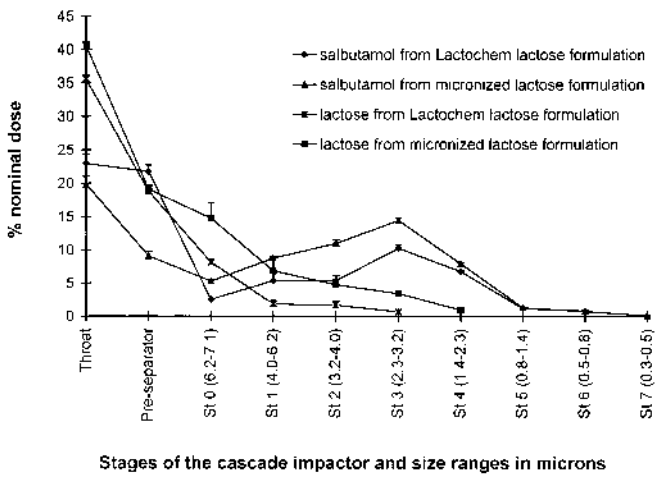

Fig. 2. The Deposition of Albuterol Sulfate and Lactose from Two Formulations of Albuterol Sulfate Containing Either Lactochem or Micronized Lactose as Diluent after Aerosolization into an ACI at 60 l/min (mean±S.D., $n=5$)

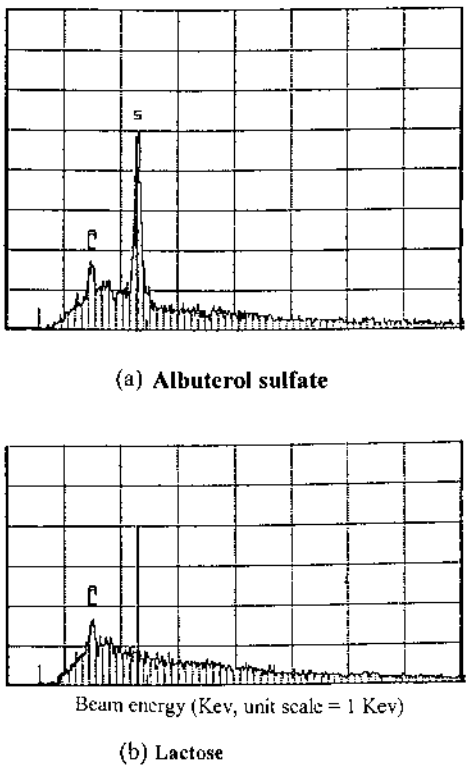

Fig. 3. The X-Ray Spectrum of a) Albuterol Sulfate (S) and b) Lactose

The peak (s) is indicative of the sulfur atom present in albuterol sulfate, which is absent from the X-ray spectrum of a lactose particle. (Al=aluminium, unit scale of x-axis=1 KeV)

Table 1. MMAD of Albuterol Sulfate and Lactose Carrier Obtained from ACI Data (mean±S.D., $n=5$)

Formulation	Flow rate (l/min)	MMAD (μm) of drug	GSD of drug	MMAD (μm) of lactose	GSD of lactose
Lactochem lactose	28.3	4.89±0.11	1.74±0.03	6.94±0.05	1.95±0.01
	60	2.81±0.04	2.00±0.02	4.48±0.11	1.65±0.10
Micronized lactose	28.3	4.07±0.09	2.01±0.10	5.10±0.11	2.02±0.03
	60	2.80±0.02	1.86±0.04	4.42±0.22	2.30±0.04

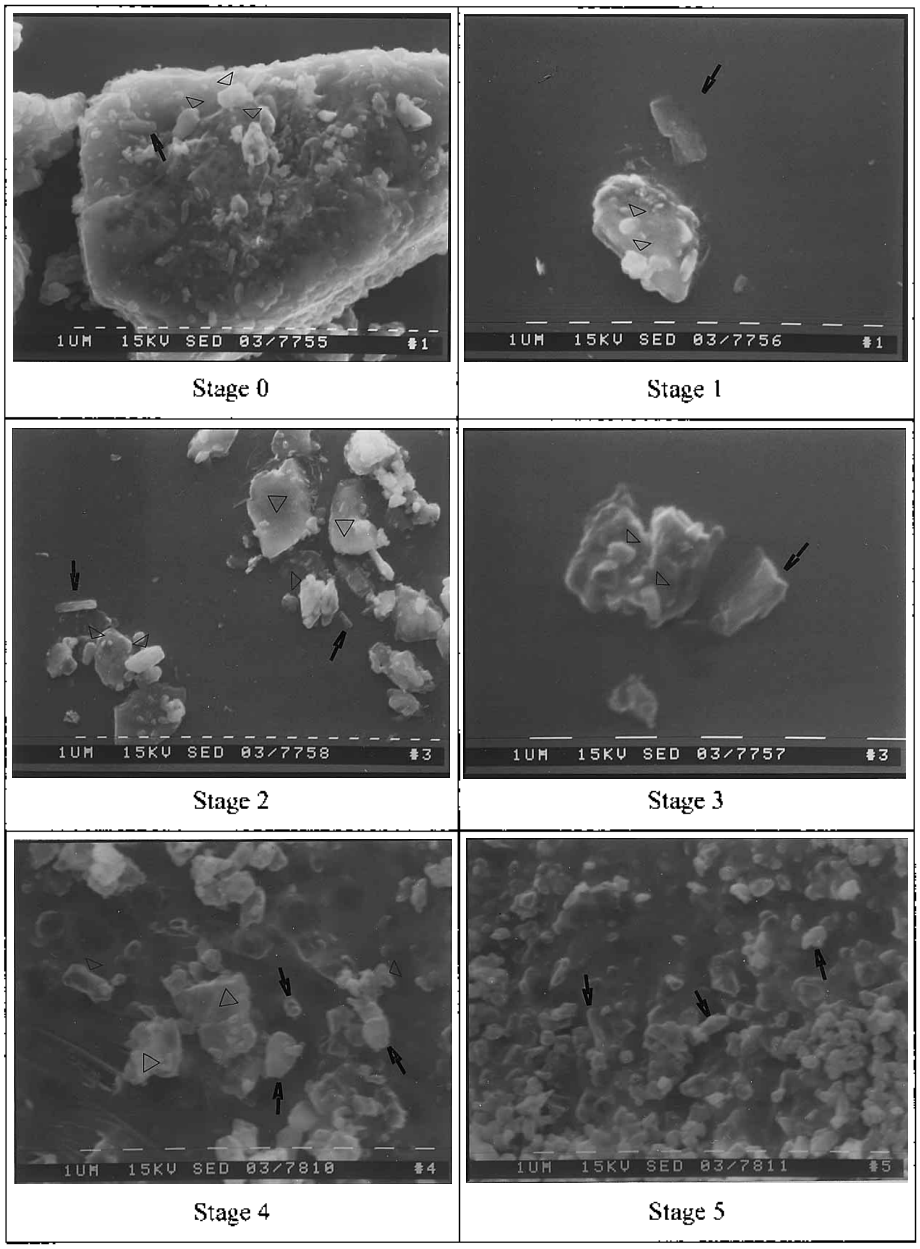

Fig. 4. Electron Micrographs of Albuterol Sulfate (Black Arrows) and Lactose (Empty Deltas) on Each Stage of the ACI after Aerosolization of the Lactochem Lactose Formulation at 28.3 l/min (Bars Correspond to a Distance of 1 μm)

tected as an X-ray peak, even in a single crystal. The electron micrographs, together with X-ray microanalysis, show how drug and lactose orientate on each stage of the ACI. In addition, as the electron beam from the microscope tracked across the surface of the particles, it was found that while the lactose crystals changed visibly, possibly as a result of localized heating, this did not occur for albuterol. Such *in situ* observations enabled an accurate and reproducible identification of the two materials. Figure 4 shows an electron micrograph of particles derived from stages 0 to 5 of the ACI for the Lactochem lactose formulation aerosolized at 28.3 l/min. Stage 0 indicated clearly that both fine drug and lactose particles adhered on the surface of coarse lactose particles. The numbers of adhered drug particles were found to be markedly lower than the fine lactose particles, being present in an approximate ratio of 1 : 4. The same trends were apparent for powder deposited from the micronized lactose formulation, although the number of drug particles was even lower in comparison to the fine lactose particles. The electron micrographs obtained for powder depositing on stage 1 showed the presence of drug particles which did not adhere to the surface of lactose. Not surprisingly, the size of lactose particles on stage 1 were smaller than those seen on stage 0. Powder derived from stages 2 and 3 showed that free drug particles were found in combination with aggregates of drug particles, and sometimes these aggregates were found in association with lactose particles. However, on stages 4 and 5 of the ACI, with the Lactochem lactose formulation aerosolized at 28.3 l/min, free drug particles were seen more frequently (in the ratio of approximately 4 : 1) than lactose particles. The higher the stage number of the ACI (stages 3—6), the easier it was to find drug particles either in the aggregated or

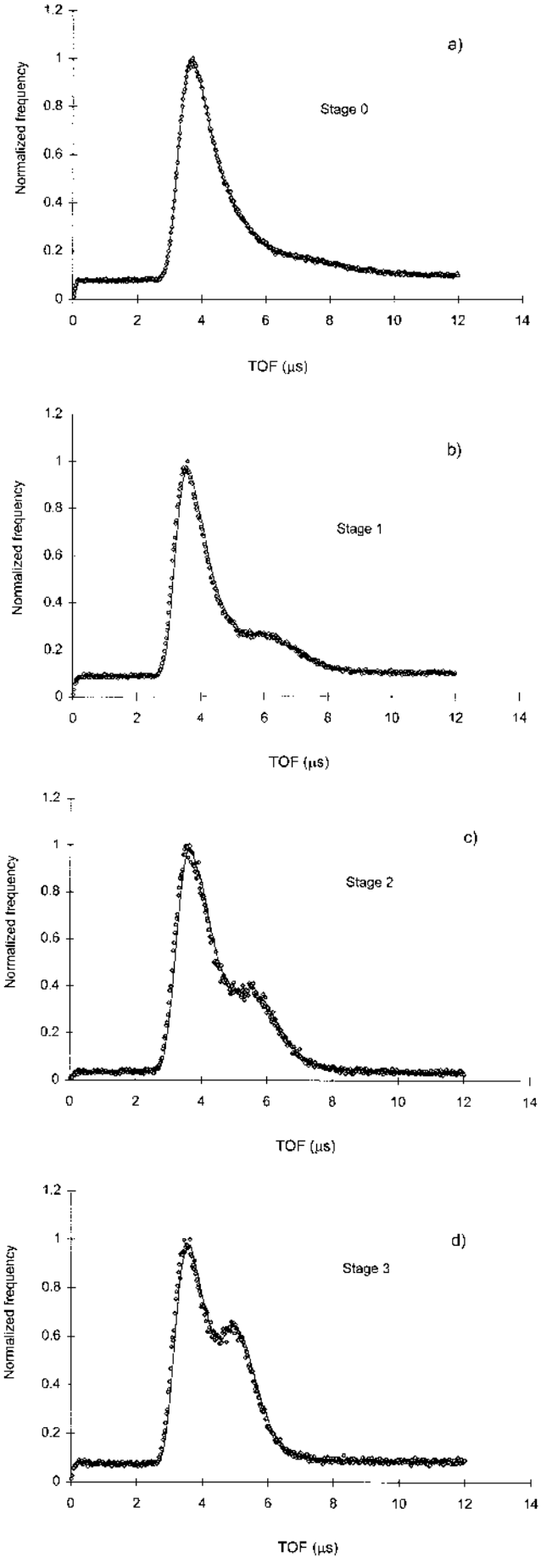

Fig. 5. The TOF of Albuterol and Lactose Particles Recovered from Various Stages of the ACI after Aerosolization of the Lactochem Lactose Formulation at 28.3 l/min

individual form, as such particles rarely adhered to lactose. When the flow rate was increased to 60 l/min for the Lactochem lactose formulation, the drug particles were found to be adhered to lactose on stage 0, whereas on stages 1 and 2, individual drug particles could be identified, separate from the lactose particles. On stage 3 and 4 of the ACI, free and aggregated drug particles were found, and by stage 5 over 90% of the particles could be characterized as free drug. In general, when the micronized lactose formulation was aerosolized at 28.3 and 60 l/min, the state of aggregation and deposition characteristics of drug and lactose particles was qualitatively not different from the Lactochem lactose formulation for powder deposition on stages 0 to 5 of the ACI. The only readily observable difference was that the mean particle size of lactose in the micronized lactose formulation was relatively smaller than that of the Lactochem lactose formulation.

TOF Analysis of Dry Powder Formulations Recovered from Each Stage of the ACI Figure 5a shows the results of TOF measurements carried out on particles deposited on stage 0 of the ACI from the Lactochem lactose formulation aerosolized at 28.3 l/min. The frequency distribution indicated that the TOF for the majority of the particles deposited on this stage was 3.725 μs, but the curve tailed, indicating that some particles had a TOF greater than 5.5 μs. The particles deposited on stage 1 (Fig. 5b) of the ACI from the same

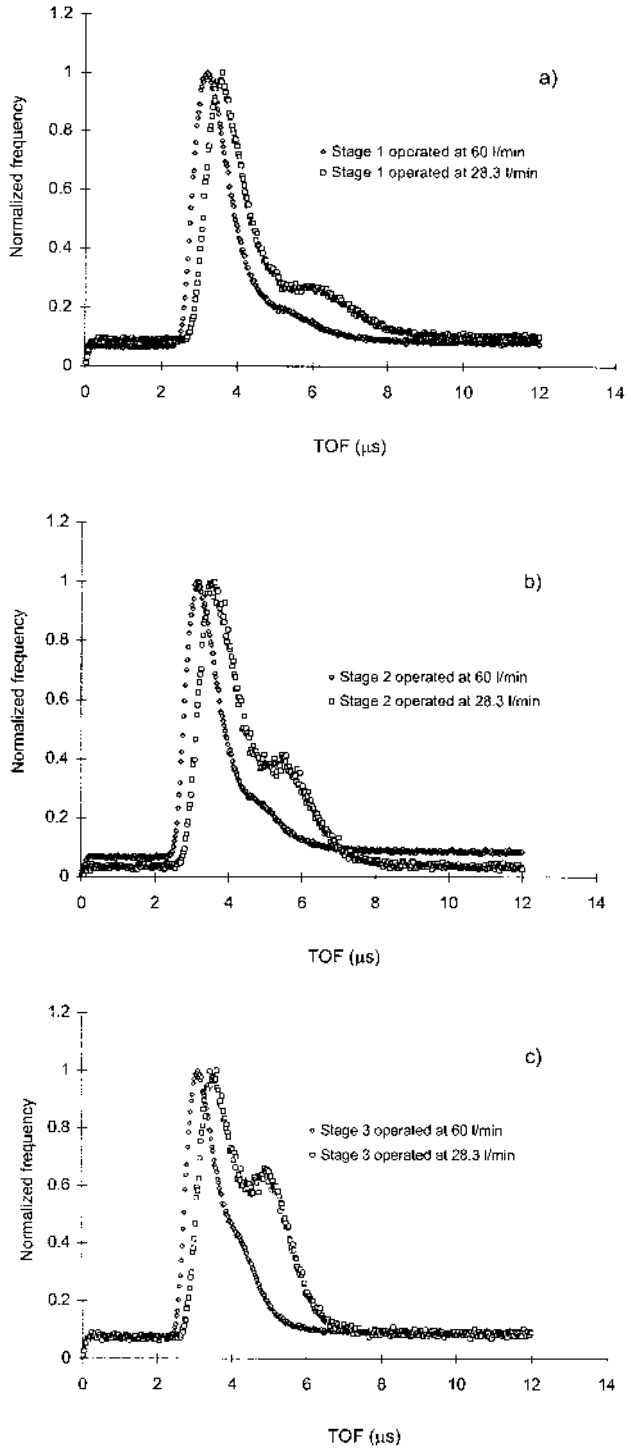

Fig. 6. The TOF of Albuterol and Lactose Particles Recovered from Various Stages of the ACI after Aerosolization of the Lactochem Lactose Formulation at 28.3 and 60 l/min

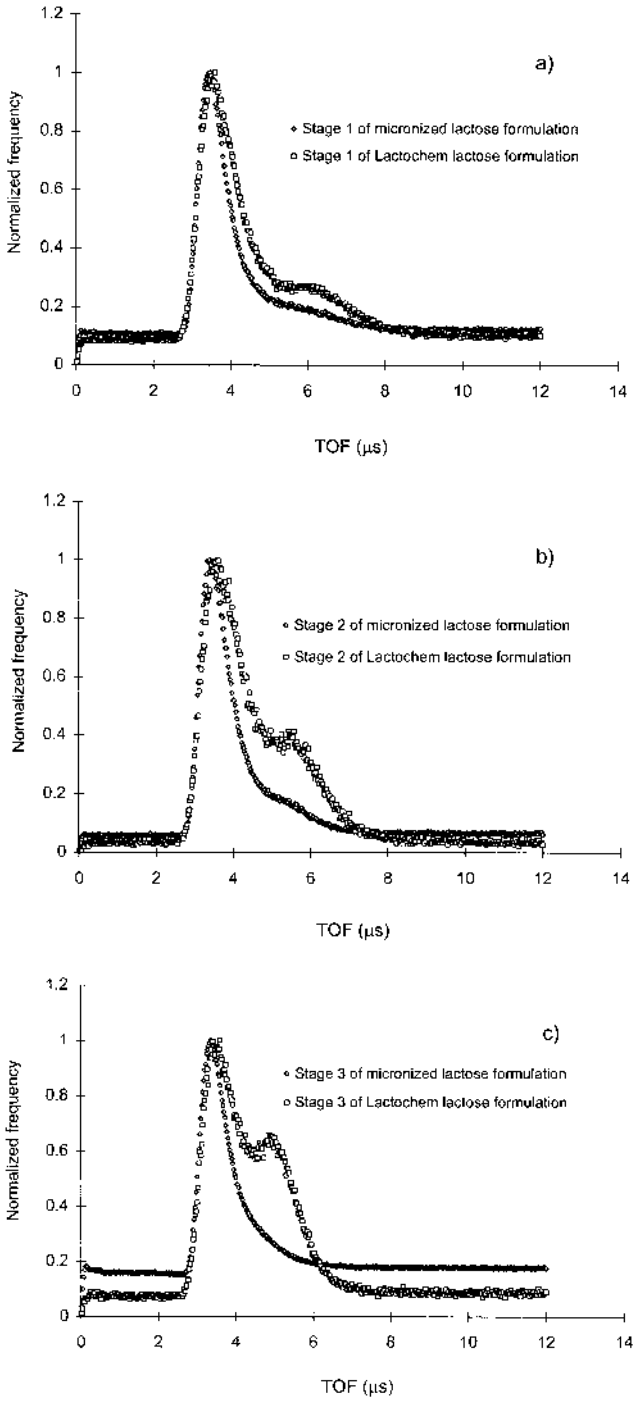

Fig. 7. The TOF of Albuterol and Lactose Particles from Two Formulations of Albuterol Sulfate Containing Either Lactochem or Micronized Lactose as Diluent Recovered from Different Stages of the ACI after Aerosolization at 28.3 l/min

formulation, when re-aerosolized into the Aerosizer, produced two peaks in the TOF spectra, one corresponding to 3.600 μs but also a second indicating a proportion of the particles with a TOF of about 6.2 μs. Powder collected from stages 2 and 3 (Figs. 5c, 5d) also exhibited split peaks at 5.5 and 5.0 μs, respectively, the second peak not being fully separated from the common first peak found at 3.600 μs. However, when the powder deposited on stage 4 (Fig. 5e) was analyzed, the second peak was no longer apparent, leaving only a broad single peak with a TOF for the particles of 4.025 μs. Meanwhile, for particles deposited on stage 5 (Fig. 5f), a sharp single peak in the TOF spectrum was obtained at 3.425 μs. When the flow rate was increased to 60 l/min, the TOF spectrum for particles from the Lactochem lactose formulation, which was deposited on stages 1, 2 and 3, showed less tailing of the principal peak compared to those obtained at 28.3 l/min (Fig. 6), and the peak in the TOF spectra appeared at a shorter time. For example, the maximum in the TOF profile for particles collected from stage 1 of the ACI after

aerosolization at 60 l/min was after 3.2 μs, compared to after 3.5 μs when the same formulation was aerosolized at 28.3 l/min. In addition, for the powder collected from stages 2 and 3 after aerosolization at 60 l/min, although a slight shoulder appeared in the TOF profile after 4.5 and 4.0 μs, respectively, a distinct split peak was not obtained (Figs. 6b, 6c), as was the case when the powder collected from the same plates after aerosolization at 28.3 l/min was analyzed. The particles from the micronized lactose formulation, collected from plates 1, 2 and 3 of the ACI operated at 28.3 l/min, showed tailing of the sole peak in the TOF spectrum of the re-aerosolized powder, in contrast to the distinct shoulders and split peaks found for particles from the Lactochem formulation deposited on the same plates (Fig. 7). The TOF spectra obtained for pure drug or lactose was found to produce a single symmetrical peak. Shorter TOF peaks were obtained for albuterol (3.425—3.475 μs) compared with those for lactose particles (>4 μs). Different size ranges of lactose (Lactochem and micronized) also gave different TOF peaks ($p<0.01$). The relevant densities of lactose and albuterol sulfate are 1.54 g/ml[17] and 1.32 g/ml,[18] respectively. Therefore, the TOF obtained depended on the type and size of materials analyzed.

Discussion

There was a clear indication that the interactions (which existed) between the particles of lactose and drug were different in the Lactochem and micronized lactose formulations from data derived using the ACI operated at 28.3 and 60 l/min. At higher flow rates more drug particles were separated from the lactose carrier, irrespective of the formulation. The separation of drug particles from lactose particles was not complete for powder deposited on stage 0 when the Lactochem lactose formulation was aerosolized at 28.3 l/min. The electron micrographs confirmed that large numbers of fine drug particles had adhered to the coarse lactose particles present on this stage. Also, the TOF spectra of particles collected from stage 0 showed tailing because the drug had not been separated from the lactose carrier on this impactor plate. If the shear force from the aerosolization process was sufficient to overcome the adhesive forces between the drug and lactose, the spectra would be predicted to split into a doublet peak. Individual drug particles, aggregates of drug and some aggregates of drug with lactose were apparent from electron micrographs taken of powder deposited on stages 1—4, which showed peak splitting in their TOF spectra. The TOF spectrum for powder from the Lactochem lactose formulation recovered from stage 4, after aerosolization at 28.3 l/min (Fig. 5e), contained a single but broader peak than that found on stage 5 (Fig. 5f), and this was due to the contribution of small lactose particles present together with drug particles. The sharp TOF peak on stage 5 appeared to be due to only drug particles being present, and this was supported by HPLC analysis as well as electron microscopy studies. The surface of lactose particles was damaged by the X-ray beam, while this phenomenon was not apparent when the beam passed over the drug particles. It is possible that the change in appearance of the lactose was due to the loss of water, which occurs due to localized heating.

This study employed an ACI without the plates being coated, usually carried out to reduce the possibility of particle bounce and re-entrainment in the airstream. If the plates were coated, then difficulties would have arisen when attempting to recover powder from the plates due to adherance of the powder to the plate. It was also thought that the coating material might interfere with HPLC analysis and X-ray microanalysis. In addition, it was considered that the aerosolized powders (lactose and albuterol sulfate) employed in this study, which are both plastic materials,[17,18] were not likely to bounce which would have a marked influence on the results obtained.

Conclusions

Deposition studies carried out using an ACI required a large number of chemical analyzes to be carried out by HPLC, for both drug and lactose, and thus proved to be a very time consuming exercise. Nevertheless, the results obtained by this technique were quantitative in nature and certain conclusions could be derived in relation to the strength of the interaction between the drug and carrier. However, the results of this study show that TOFABS can be employed in conjunction with the ACI to validate the deposition profiles obtained by HPLC analysis if the components of the formulation possess different physical properties (*i.e.* density and size). In the case of a binary mixture, after aerosolization of powder into the ACI, the TOF will give only a single symmetrical peak if a single component (either drug or carrier) is present on an individual plate. When split peaks are obtained, then both components are present. Use of TOFABS does not require a prolonged analytical procedure, therefore, once set up, the influence of subtle changes in formulation on the detachment of drug from carrier can be investigated relatively rapidly. SEM–X-ray microanalysis, which is also a time consuming method to carry out, is useful to view the shape and orientation of particles. In the case of albuterol sulfate and lactose, the X-ray spectra can clearly distinguish between drug and lactose particles. On the basis of the results from study it is concluded that TOFABS studies carried out on powder deposition on individual plates within an impactor can provide useful information on particle–particle interaction. If a difference in particle size and density exists between drug and excipient, then it is apparent that the particles, upon re-aerosolization with sufficient force to disrupt particulate interactions, exhibit measurable differences in their TOF. During formulation development, determining the TOF of the particles after deposition on impactor plates would provide an indication of whether a drug remains associated with lactose, is deposited as an aggregate or is primarily in individual particles. Should a drug remain extensively associated with a lactose of large particle size, then large amount of drug that would be detected in samples taken from low numbered stages. Such a drug is unlikely to be respirable. Obviously, the TOFABS data are strengthened by the analysis of the relative amounts of drug and lactose deposited on each plate, as carried out in this study. However, TOFABS studies alone would allow some prediction to be made as to whether the interactions between particles might change as a function of air flow or change in the nature (*e.g.* particle size, shape, crystallinity, processing, *etc*.) of drug and/or vehicle. X-ray microanalysis provides excellent supporting qualitative data of adherence between particles, providing that one of the particles contains an atom with an appropriate absorbing

spectrum. In conclusion, TOF, SEM–X-ray microanalysis and drug–carrier analysis from the ACI all proved to be useful tools in studying the interaction of drug and carrier in dry powder inhalers. It may be possible to relate those results to the possible states of interaction which exist between drug and carrier particles during passage through the airways after aerosolization.

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