Quantification of the Surface Morphologies of Lactose Carriers and Their Effect on the *in Vitro* Deposition of Salbutamol Sulphate

Paul Wan Sia HENG,* Lai Wah CHAN, and Liang Theng LIM

Department of Pharmacy, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260.
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Application of the scanning probe microscopy technique for quantitative measurement of the surface roughness of lactose carriers was evaluated. The roughness values of four different lactose carriers were related to the *in vitro* deposition results of the drug, salbutamol sulphate. The rugosity values of the lactose carriers were represented by *R*a values which were in the order of DCL-40>DCL-11>lactose 325M>lactose 200 M. *In vitro* deposition results using a twin impinger showed that rougher carrier surfaces generally allowed more drug particles to be emitted from the capsules and inhaler but the availability of the drug to stage 2 was reduced, as detachment of drug particles from the carrier surfaces was more hindered. There was an optimum *R*a value for greater delivery of the drug particles to stage 2 of the twin impinger. A balance between adherence and detachment of the drug from the carrier surface was needed in order to optimize the delivery of a drug to the desired target sites using a dry powder inhaler.

Key words surface roughness; lactose carrier; salbutamol sulphate; scanning probe microscopy; twin impinger

Dry powder inhalers are generally formulated by mixing cohesive, micronized drug with larger carrier particles. This is done to improve the dispersion and flow of the drug particles. In such a formulation, the size, shape and surface properties of the carrier and the drug-carrier ratio may affect the respiratory deposition pattern of the inhaled drug-carrier mixture.[1] In more recent years, *in vitro* studies have shown that the addition of ternary components, such as fine lactose particles[2] or magnesium stearate[3] enhanced the detachment of drug from the carrier lactose particles.

The detachment of the drug from the carrier surface is dependent on the adhesive forces between the drug and carrier particles, which are in turn determined by the surface properties of the carrier. This is because adhesion of particles is a surface phenomenon and therefore, the surface morphology of carrier particles will have a significant effect on the adhesion of drug particles to them.[3] The coarser the particles, the higher the proportion of drug adhering to them. The coarser carrier particles apparently have a greater number of active sites which are capable of binding the adherent drug particles more strongly.[4]

There is limited information on the quantification of surface roughness of particles as this is difficult to achieve, especially when the size of the particle approaches micrometer dimensions.[5] Researchers have attempted to characterize the surface roughness of carrier lactose particles and other materials by various means. Iida *et al.*[6] examined the surfaces of glass substrates using the scanning tunneling microscope. Podczeck[7] attempted to assess the surface roughness of lactose particles using a laser profilometer over a 20 μm by 20 μm scan area. The rugosities (surface roughness) of regular, spray-dried and recrystallized lactose were studied by Kassem and Ganderton.[8] The rugosity was assessed by the ratio of the surface area derived from air permeability over that obtained when the particles were considered as spheres. Ganderton[9] reported that decreased rugosity increased the respiratory fraction of salbutamol sulphate. Kawashima *et al.*[10] determined the specific surface area of various lactose grades by air permeametry and Brunauer, Emmett and Teller (BET) adsorption methods.

The scanning probe microscope can be used for evaluating the physical surface features of particles. Unlike the scanning tunneling microscope which is more suitable for conducting materials,[11] the scanning probe microscope can be used for a greater variety of substances since it can be used for both conducting and insulating materials.[12] The scanning probe microscope quantifies directly the surface textures of the particles by the surface parameters, *R*a (arithmetic mean roughness), *R*y (maximum height) and *R*z (10-point mean roughness). For other methods like air permeametry and BET adsorption techniques, the surface characteristics are determined indirectly from surface area measurements. Therefore, the scanning probe microscope was chosen in this study due to the minimal sample preparation required, its suitability in scanning the type of material used in this study and its ability to provide direct quantitative roughness values. The aim of this study was to develop a method to quantify the surface roughness of lactose carrier particles using the scanning probe microscope and to relate this physical parameter to the inhalant performance of salbutamol sulphate and lactose mixtures in the twin impinger. Salbutamol sulphate was selected because it is a commonly used drug in asthma therapy and could be used as a good representative drug for determining the *in vitro* performance of dry powder inhalers.

Experimental

Materials Salbutamol sulphate was obtained from Fine Drugs and Chemicals (India). The geometric mean diameter for the supplied drug was 10.91 μm while that after milling was 2.55 μm. Lactose 325M (Pharmatose® 325M), lactose 200M (Pharmatose® 200M), DCL-11 (spray-dried hydrous lactose) and DCL-40 (mixture of 95% anhydrous lactose and 5% lactitol) were supplied by DMV (The Netherlands). All the lactose and salbutamol sulphate samples were stored in airtight containers at 20 °C.

Preparation of Lactose Carrier and Salbutamol Sulphate Lactose 325M was used as supplied. Lactose 200M, DCL-11, and DCL-40 were sieved to obtain the same mean diameter as lactose 325M (about 40—60 μm). This was carried out using the Micron Air Jet Sieve® (Hosokawa Micron, United States) with sieves of aperture sizes 38 and 63 μm. The sieving time for each sieve was 120 s and the vacuum pressure was 30—35 cm water.

Micronized salbutamol sulphate was prepared by subjecting the supplied drug to a jet mill (Hosokawa, AFG100, Japan) operated at a pressure of 0.4 MPa and a classifying speed of 15000 rpm.

* To whom correspondence should be addressed.

Scanning Electron Microscopy The size of the particles used was determined using a scanning electron microscope (JEOL, JSM-5200, Japan). The particles were gold-coated under an argon atmosphere (Bio-Rad, SC502, United Kingdom) and examined under the scanning electron microscope. From the photomicrographs, the diameters of at least four hundred particles were measured using a pair of digital vernier callipers (Mitutoyo, CD-6″BS, Japan) and the actual size calculated by multiplying with the respective magnification factors. For each particle, two diameters, at right angles to each other were measured and the average diameter calculated. The surface morphologies of the lactose particles were assessed qualitatively from the photomicrographs taken.

Scanning Probe Microscopy The lactose carrier particles were first sprinkled on a clean glass slide and the sample holder with double-sided adhesive tape (Scotch® 3M, United States) attached was pressed lightly on the particles to adhere the particles to the tape. The sample holder was inverted and knocked along its side several times to remove any loose particles. It was then placed under the microscope for scanning by the cantilever, using both the contact and dynamic modes.

The lactose particles were scanned over an area of 64 μm by 64 μm to observe the whole lactose particle before zooming down to an area of 8 μm by 8 μm. Other scan areas, for example, 5 μm by 5 μm and 10 μm by 10 μm were also attempted. The depth of scan, Z range, was also varied to obtain the best representative image. Scans of the same image were performed at various frequencies of 1, 2, 3, 5 and 8 Hz. Sample size of ten, fifteen and thirty lactose particles were scanned consecutively. This was repeated and the mean roughness values (Ra) obtained for each sample size were compared.

Compression of Lactose 325M Lactose 325M was manually compressed lightly into compacts of about 0.26 g using a single-punch tabletting machine (Manesty, E2, England) with 9 mm flat-faced punches. The surface of the compact was scanned and the roughness values of the constituent lactose particles were determined.

Preparation of Powder Blend Mixtures consisting of about 2% w/w salbutamol sulphate were prepared by weighing 0.10 g drug and 4.90 g lactose into a cylindrical glass container (diameter 4.8 cm, height 4.6 cm) and premixed in a vortex mixer (Ika, VX9/VXR, Germany) for 5 min. The mixture was then passed through a sieve of aperture size 125 μm to break up any large agglomerates. It was returned to the container and mixing continued for another 15 min. Twenty milligrams of each type of lactose-salbutamol sulphate mixture was weighed into three sets of ten gelatin capsules each (size no. 3) and stored in glass bottles in a desiccator at 20 °C.

***In vitro* Deposition of Salbutamol Sulphate** The dispersing behaviour of the different types of lactose-salbutamol sulphate mixtures was assessed in a Rotahaler® (Glaxo, United Kingdom) coupled to a twin impinger (Apparatus A, British Pharmacopoeia 1993, Erweka, Germany). Stages 1 and 2 contained 7 and 30 ml of filtered deionized water respectively to collect the drug deposited in these two stages. After the Rotahaler® was connected to the mouthpiece of the twin impinger, a capsule was placed in the holder of the Rotahaler®, which was twisted to break the capsule. An air stream of 60 l/min was produced throughout the system by attaching the outlet of the twin impinger to a vacuum pump. For each capsule, an actuation time of 30 s was given to allow enough time for complete emptying of the capsule. This test was repeated for 10 capsules. On completion, the drug deposited in the inhaler, mouthpiece, stages 1 and 2 was collected by rinsing with filtered deionized water and made up to 50 ml each in volumetric flasks using the same solvent. The drug content was determined by HPLC using a mobile phase consisting of methanol and acetate buffer pH 5 in the ratio of 55 : 45, a 3.3 cm C18 column (Perkin Elmer, HS-3, United States) and a UV detector (Waters, Lambda-Max 481, United States) at 276 nm. For each type of lactose-drug mixture, three determinations were carried out and the average results calculated. All determinations were carried out under a controlled temperature of 20 °C and humidity of 45% relative humidity.

In this study, the respirable fraction (RF) referred to the fraction (%) of drug deposited in stage 2 of the twin impinger, with regard to the loaded amount of drug. The effective index (EI) proposed by Hino *et al.*[13] to evaluate inhalation behaviour was expressed as :

$$\mathrm{EI}=\sqrt{(100-\mathrm{DF})\times\mathrm{RF}}=\sqrt{\mathrm{Em}\times\mathrm{RF}} \quad (1)$$

where DF is the fraction (%) of drug remaining in the inhaler and capsules and Em is the fraction (%) of drug emitted from the inhaler and capsules.

Respirable particle percent of emitted particles (RP) was used to express the percentage of drug deposited in stage 2 with regard to the emitted amount.

$$\mathrm{RP}=\left(\frac{\mathrm{RF}}{\mathrm{Em}}\right)\times 100 \quad (2)$$

Results and Discussion

Size Distribution and Surface Morphologies of Lactose Carriers All four lactose batches were prepared by jet-sieving to obtain lactose particles of similar size. Hence, the effects of differences in the size of carrier on the inhalation property, as reported by Steckel and Müller,[14] were likely to be limited in this study.

Under the scanning electron microscope, both lactose 325M and 200M particles appeared to show similar surface textures. On closer examination, very small particles were found to adhere to the surfaces of the larger carrier particles (Fig. 1(a), (b)). The presence of such smaller particles may enhance the detachment of drug particles from the carrier particles.[2] Both DCL-11 and DCL-40 appeared to be rougher (Fig. 1(c), (d)). There were large crevices interspersing with smooth areas for DCL-11 while the whole surface of DCL-40 particles appeared rough with small crevices, suggesting that the DCL-40 particles resembled aggregates of very small agglomerated sub-units. Since the surfaces of DCL-11 and DCL-40 appeared to be quite rough, small drug particles in the formulation of dry powder for inhalation can be embedded into the crevices on the surfaces of these carrier particles, such that their detachment from the carrier particles upon inspiration and subsequent delivery of the drug to the lower reaches of the lungs would be reduced.

Evaluation of the Scanning Probe Microscope Technique to Quantify Surface Morphologies Substrates for Mounting of Lactose Particles on Metal Sample Holder: Different substrates (Table 1) for the mounting of lactose particles for examination using the scanning probe microscope were assessed. All the surfaces appeared similar to that of the lactose particles and could not be easily distinguishable from the lactose surfaces. Only one substrate, Scotch® 3M single-sided adhesive tape showed a different surface texture from the lactose particles when scanned. The adhesive tape surface consisted of very even and regular lines that could be differentiated from images of the surfaces of lactose particles. Therefore, the Scotch® 3M single-sided tape was chosen as the substrate for mounting of the lactose particles on the metal sample holder for scanning probe microscopy.

Mode of Scan: The scanning probe microscope has two operational modes, contact and dynamic modes. In the contact mode, repulsion between the cantilever tip and sample is detected with an optical lever detection method. When this mode of scanning was attemped in this study, the contact made by the cantilever tip with the edges of the particles during the scan made it difficult to scan images without breaking the cantilevers. In the dynamic mode, there is no contact between the cantilever tip and the particle surface. Instead, the cantilever tip vibrates near the resonance frequency of the cantilever. When the vibrating cantilever approaches the sample surface, the resonance frequency of the cantilever shifts due to the force between the cantilever and sample. This shift in the resonance frequency is then detected from a change in the amplitude of the cantilever tip, thus converting to changes in displacement. Both modes were able to pro-

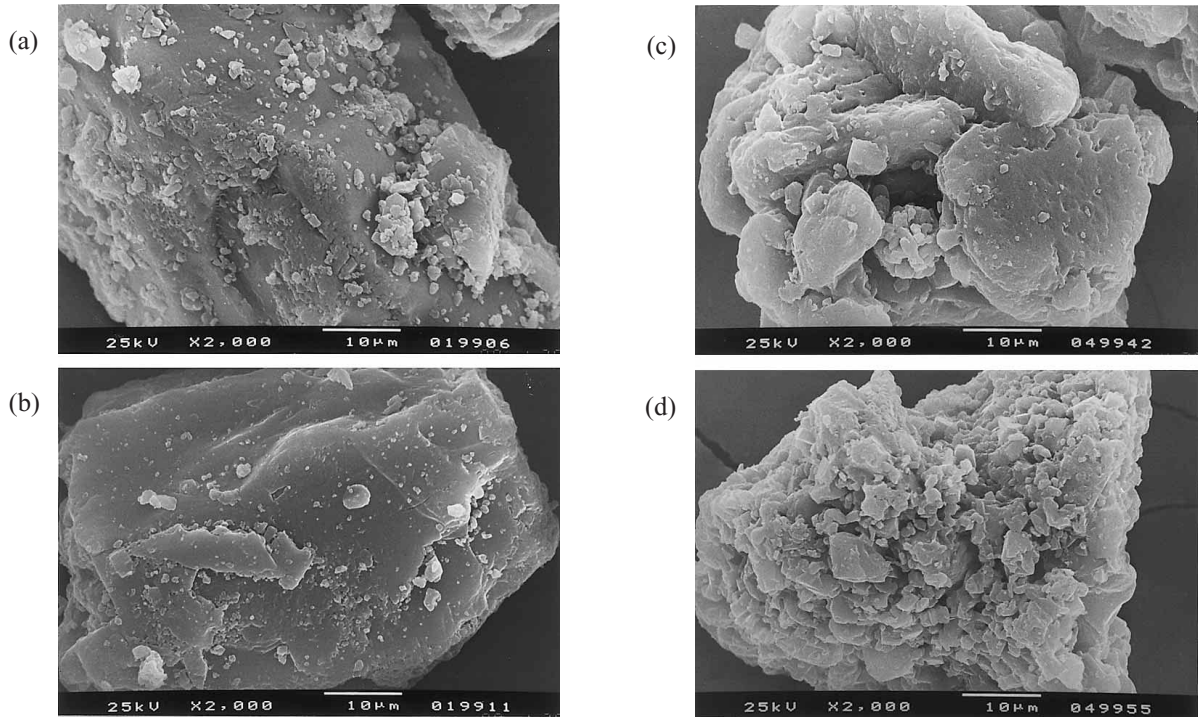

Fig. 1. Scanning Electron Micrographs of (a) Lactose 325M, (b) Lactose 200M (38—63 μm), (c) DCL-11 (38—63 μm) and (d) DCL-40 (38—63 μm)

Table 1. Substrates for Mounting Lactose Particles on Metal Sample Holder

Substrates	Observations
Adhesive glue on metal sample holder Adhesive glue on plastic materials Adhesive glue on paper materials Adhesive glue on glass coverslip Scotch® 3M double-sided stick tape on metal sample holder Itotape® double-sided stick tape on metal sample holder	Surface with irregularities that were similar to lactose surface
Scotch® 3M single-sided stick tape attached to metal sample holder by Scotch® 3M double-sided stick tape	Surface with very regular and even lines

Table 2. Roughness Values of Lactose 325M and Lactose 200M (38—63 μm) at Z Ranges of 2 and 5 μm (n=30)

	Lactose 325M		Lactose 200M (38—63 μm)	
	Z=2 μm	Z=5 μm	Z=2 μm	Z=5 μm
Ra (nm)	199.182	197.473	155.733	158.703
Ry (μm)	1.594	1.582	1.218	1.389
Rz (μm)	1.112	1.006	0.711	0.868

duce reasonably good images. However, the dynamic mode was chosen as the likelihood of damage to the cantilever was lower. In addition, it was felt that using the dynamic mode, the cantilever tip exerts less effect on the sample surface and may provide a higher sensitivity.

Depth of Scan: The depth of scanning, as measured by the Z range, is important for ensuring that the scan can cover a large surface with indentations or undulations that determines the depth of the particle. A Z range with insufficient depth will result in some parts of the images being cut off and thereby causing inaccuracies in the roughness measurements. When the Z range is set too high, there will be a compromise in the clarity and sharpness of the image produced. For this study, thirty images of 8 μm by 8 μm were captured with Z ranges set at 2 and 5 μm. The roughness values obtained for lactose 325M were compared and found to be similar (Table 2). The Ra values for lactose 200M at a Z range of 2 and 5 μm were similar, while the Ry and Rz values differed by 14.0% and 22.1%, respectively. A Z range of 5 μm was chosen in subsequent studies as any unusually large protrusions on the lactose surface could be captured without loss of the image due to insufficient Z range. The Ra value was also chosen to represent surface roughness in the subsequent discussion because it was a calculated average reading based on a reference length across the surface scanned. On the other hand, Ry was a value obtained from the distance between the crest line and trough line and Rz was the average of ten points along the reference length. Ry and Rz would be less representative of the whole surface roughness compared to Ra as they were calculated based on selected points only.

Size of Scan: Although the size of the lactose particles is 40—60 μm, it is not easy for the cantilever to land on a flat surface with sufficient length and width for scanning due to the random orientation of the particles on the adhesive tape. Various scan sizes of 5 μm by 5 μm, 8 μm by 8 μm and 10 μm by 10 μm were attempted. It was generally difficult to locate a particle with the correct orientation to present a surface suitable for a scan size of 10 μm by 10 μm. A scan size of 8 μm by 8 μm was chosen as 5 μm by 5 μm appeared to be too small to adequately represent the whole surface of the lactose particle.

Frequency of Scan: The rate of scan is important as a faster scan rate with an acceptable resolution would be more

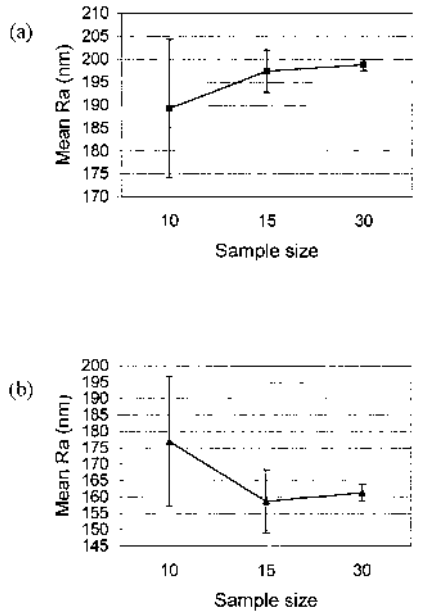

Fig. 2. Effect of Sample Size on the Range of Mean *R*a values for (a) Lactose 325M and (b) Lactose 200M (38—63 μm)

efficient. Scans at frequencies of 1, 2, 3, 5 and 8 Hz were made. The times needed to scan an image of 8 μm by 8 μm were 256, 128, 86, 52 and 33 s at 1, 2, 3, 5, and 8 Hz respectively. It was found that as the frequency increased, the images were less well resolved and some small features on the surfaces were not captured. Based on the clarity of the image obtained, a slow scan frequency of 1 Hz was chosen as the sharpest image was desired.

Determination of Sample Size: Figures 2(a) and 2(b) show the mean *R*a values for lactose 325M and lactose 200M respectively with sample sizes of ten, fifteen and thirty particles. Two sets of data were obtained for each sample size and the mean *R*a values and their range were compared. Since the range for the sample size of 30 was very small, this sample size was used for subsequent roughness determinations.

Comparison of the Surface Characteristics of Lactose 325M, Lactose 200M, DCL-11 and DCL-40 The roughness values obtained for both lactose 325M and 200M showed that the 325M lactose particles had rougher surfaces than 200M lactose particles since the *R*a, *R*y and *R*z values were all higher (Table 3). Roughness values for DCL-11 and DCL-40 were much higher than those for lactose 200M and 325M. From this finding, it could be inferred that the interactive force between the drug and DCL-11 or DCL-40 would be higher than that of lactose 325M and 200M.

Comparison of Surface of Compact with that of Lactose 325M Particles The use of lactose particles mounted on adhesive tape for scanning probe microscopy can pose various problems. Care must be taken to dust just sufficient particles for measurement and to distinguish lactose particles from the tape material. In addition, the particles may shift during measurements, resulting in an unsuccessful scan. The possibility of preparing lactose particles as lightly compacted particles for surface measurements appeared to be an attractive alternative.

The *R*a value obtained from scanning the surface of compact prepared using lactose 325M was about half of the uncompacted lactose particles (Table 3). This could be due to fragmentation of the protrusions on the particles and surface remoulding under the forces of compaction, thus resulting in smoother surfaces. In one literature study, it was reported that fragmentation of crystalline lactose occurred during compaction even when the mean particle size was small, around 32—45 μm.[15] In another study, it was suggested that surface deformability of the particles occurred due to fragmentation during compaction.[16] Thus, surface roughness values of compacted lactose particles obtained by scanning compacts might not be representative of the actual particle surface.

Table 3. Roughness Values of Lactose 325M, Lactose 200M (38—63 μm), DCL-11 (38—63 μm), DCL-40 (38—63 μm) and Compacted Lactose 325M (n=30)

	Lactose 325M	Compacted lactose 325M	Lactose 200M (38—63 μm)	DCL-11 (38—63 μm)	DCL-40 (38—63 μm)
*R*a (nm)	197.473	111.733	158.703	290.907	346.623
*R*y (μm)	1.582	1.108	1.389	2.164	2.564
*R*z (μm)	1.006	0.642	0.868	1.437	1.732

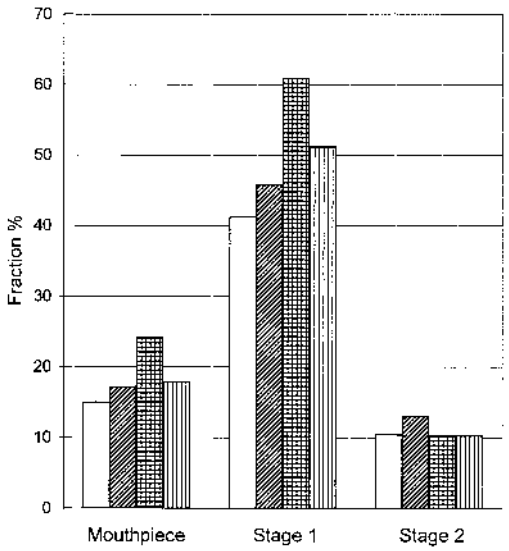

Fig. 3. *In vitro* Deposition of Salbutamol Sulphate in the Twin Impinger with Different Types of Lactose

□, Lactose 200M; ▨, lactose 325M; ▦, DCL-11; ▥, DCL-40.

***In vitro* Deposition of Salbutamol Sulphate** The deposition patterns of salbutamol sulphate by the various types of lactose are shown in Fig. 3 while the calculated inhalation indices are presented in Table 4.

There was a significant difference in the emission of drug particles (% Em) between DCL-11 and the other three lactose carriers (p=0.004, one-way ANOVA at 95% confidence level). DCL-11 was more effective in emitting the drug from the inhaler and capsules, resulting in a large amount of drug deposited in the mouthpiece and stage 1 of the twin impinger (Fig. 3). The % Em for DCL-40 was also significantly higher than that for lactose 200M. This could be due to a higher accommodation of the drug particles in the crevices found on the surfaces of both DCL-11 and DCL-40. However, the fraction (% RF) of drug found in stage 2 of the twin impinger was significantly higher for lactose 325M compared to the

Table 4. *In vitro* Deposition Results for Salbutamol Sulphate with Different Types of Lactose (Represented by Mean±S.D., $n=3$)

	Em (%)	RF (%)	EI (%)	RP
Lactose 200M (38—63 μm)	66.62±6.14	10.43±0.61	26.36±1.92	15.70±0.83
Lactose 325M	75.98±5.91	13.01±1.44[a)]	31.44±2.94	17.10±0.62
DCL-11 (38—63 μm)	95.36±4.13[b)]	10.31±1.06	31.34±2.05	10.81±0.95[c)]
DCL-40 (38—63 μm)	79.29±9.13[d)]	10.25±0.13	28.47±1.57	13.06±1.71[e)]

a) $p<0.05$, significant difference compared to lactose 200M, DCL-11 and DCL-40. *b*) $p<0.05$, significant difference compared to lactose 200M, lactose 325M and DCL-40. *c*) $p<0.05$, significant difference compared to lactose 200M, lactose 325M and DCL-40. *d*) $p<0.05$, significant difference compared to lactose 200M and DCL-11. e) $p<0.05$, significant difference compared to lactose 200M, lactose 325M and DCL-11.

other three lactose carriers ($p=0.019$, one-way ANOVA at 95% confidence level). This was seen even though the amount of drug emitted by lactose 325M was not as high as that compared to DCL-11. This finding indicated that the roughness of the carrier surface can affect drug particle detachment. Although the presence of crevices like those found in DCL-11 and DCL-40 (Fig. 1(c), (d)) allowed more drug particles to be attached and delivered to stage 1 of the twin impinger, they also cause drug particle entrapment. Thus, as the separation of the drug from the carrier in the air stream was more hindered, a relatively smaller amount of drug was deposited in stage 2. There was no significant difference at the 95% confidence level between the EI value of DCL-11 and lactose 325M as the high Em compromised for the drop in RF for DCL-11 (Table 4).

The process of inhalation of a drug-carrier mixture involves the emission of drug on a carrier from the inhaler, the separation of drug from the carrier, the dispersion of the separated drug in the air-stream and the delivery of the dispersed drug to the targeted site of the lung. An effective formulation should consist of a drug and a carrier of a suitable surface morphology such that the adhesion force between the carrier and the drug is strong enough for drug particles on the carrier particles to be emitted from the inhaler, but yet not too strong so that a large proportion of the emitted drug could be detached from the carrier and be deposited in stage 2 of the twin impinger. For *in vitro* studies, a high EI alone may not necessarily represent an effective dry powder formulation. This is because a high EI may be a result of an exceptionally large Em which compromises the low RF. EI is affected by Em and RF. In a reported study,[10] the EI for a formulation without a carrier was significantly lower than that of a formulation with lactose 325M. This was due to the relatively lower Em of the formulation without a carrier. However, the EI of the formulation without a carrier was similar to that of a formulation with fluidized bed granulated lactose. This was because of the relatively higher RF value of the formulation without a carrier. Therefore, in assessing the performance of a dry powder formulation using EI, the RP of a formulation should also be taken into account. A low RP would indicate poor performance in spite of a high EI. In this study, although the EI of DCL-11-drug mixture is equivalent to the EI of lactose 325M-drug mixture, the latter is a more effective formulation because of the much higher RP. The EI of DCL-11 is higher than that of DCL-40 due to the higher Em

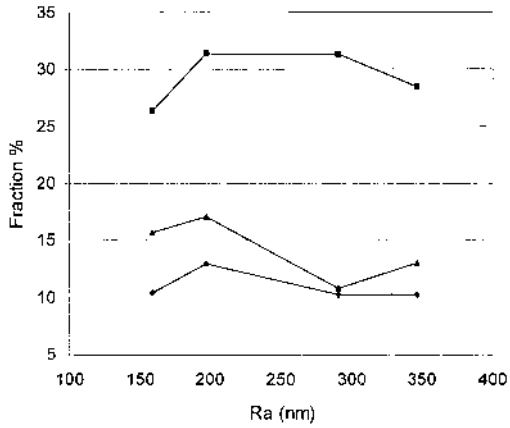

Fig. 4. EI, RP and RF Values of Salbutamol Sulphate with Lactose of Different Roughness Values (*R*a)

■, EI; ▲, RP; ◆, RF.

for DCL-11, suggesting greater drug emission ability of DCL-11. As a result of the higher Em but similar RF for DCL-11 compared to DCL-40, the RP of DCL-11 is lower. This indirectly indicates that the drug releasing property of DCL-11 is lower than that of DCL-40.

When the surface roughness (*R*a) of lactose particles was compared with the RF and RP of the drug-lactose mixture, there was an optimal *R*a value when a RP of 17.10% and a RF of 13.01% drug was delivered to stage 2 (Fig. 4). This could be related to the adhesion force between the drug and carrier as the higher the adhesion force, the less likely for the particle to detach from the lactose surface. From previous work,[10] the rank order of adhesion and interactive force of the lactose with drug particles is shown in Fig. 5 where performance models (i)>(ii)>(iii). The interactive force for (ii) is greater than (iii) because of the larger surface in contact with lactose resulting in higher van der Waals attractive forces. The surface roughness (*R*a) of lactose 200M was smaller than that of lactose 325M, thus resembling (ii) while lactose 325M resembled (iii). Therefore, the interactive force between the drug and lactose 200M would be higher than that between the drug and lactose 325M and a significantly lower RF value was obtained for the lactose 200M–drug mixture when compared to the lactose 325M–drug mixture.

The surface roughness (*R*a) of DCL-11 was found to be higher than lactose 325M and 200M. Deep crevices interspersing with smooth surfaces were observed for DCL-11 and drug-DCL-11 interaction was expected to be resembling performance model (i) in Fig. 5. Drug particles adhered in the deep crevices would become entrapped and become relatively immobile in the clefts and indentations.[3] Thus, the likelihood for overall drug detachment from the lactose particle would be lower, resulting in even lower RP values as compared to the values for lactose 325M and 200M. The *R*a value for DCL-40 was higher compared to that of DCL-11, indicating that the surface of DCL-40 was rougher than that of DCL-11. This could be due to the presence of microscopic projections on the surface of the DCL-40 particle, in addition to some large crevices. A possible representation is shown in Fig. 5 (iv). Therefore, the average surface roughness of DCL-40 was higher than that of DCL-11, on which the presence of smooth areas reduced the average surface roughness of the

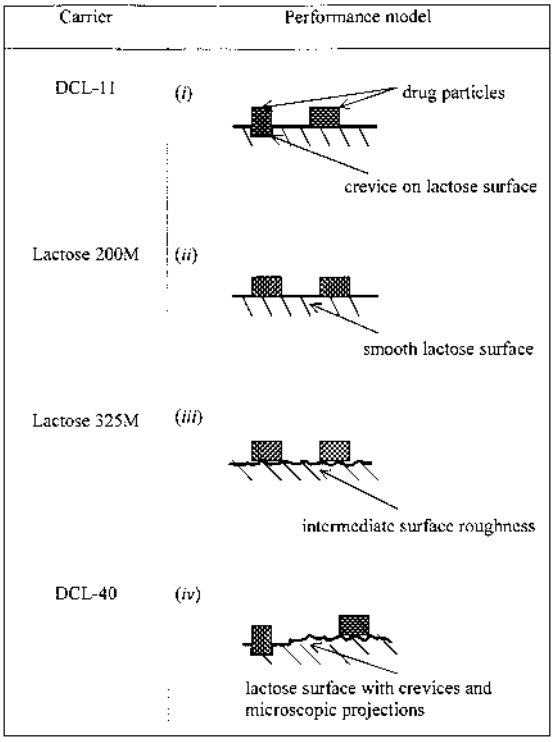

Fig. 5. Performance Model for Different Lactose Carriers

DCL-11 particle. However, although the *R*a of DCL-40 was higher than that of DCL-11, the RP value was significantly higher than that for DCL-11 while the EI and Em values were lower. A possible reason could be that the microscopic projections reduced the contact areas between the contacting drug and lactose surfaces and increased the distances between them. Due to the smaller areas of actual contact, there may be reduced drug attachment onto DCL-40, resulting in a lower Em and EI. On the other hand, the surface of DCL-11 consists of large crevices interspersing with smooth surfaces. Compared to the microscopic projections on DCL-40, the smooth surfaces allowed a relatively greater area of contact with the drug particles, thus a greater chance of drug adhesion resulting in a higher Em and EI. In addition, for drug particles adhering onto the microscopic projections, van der Waals attractive forces were reduced, resulting in easier separation of deposited drug particles from the surfaces of DCL-40 and a higher RP. Therefore, the drug-releasing property of DCL-40 with respect to the emitted dose would be higher than that of DCL-11.

Conclusion

The scanning probe microscope enabled a quantitative measure of the surface property of the lactose carriers. The ability to measure surface roughness quantitatively provided the means to evaluate carriers for their relative drug delivery efficiencies. There is an optimum roughness (*R*a) value for increased availability of drug to stage 2 of the twin impinger among the four lactose carriers studied. A balance between adhering to and detachment of the drug particles from the carrier surface is important for optimizing its delivery to the desired sites.

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