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Powder Properties and Their Influence on Dry Powder Inhaler Delivery of an Antitubercular Drug

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ABSTRACT The purpose of this study was to determine if aerosol delivery of drug loaded microparticles to lungs infected with *Mycobacterium tuberculosis* may be achieved by predicting dispersion of dry powders through knowledge of particle surface properties. Particle sizes of rifampicin-loaded poly(lactide-co-glycolide) microparticles (R-PLGA), rifampicin alone, and lactose and maltodextrin carrier particles (bulk and 75-125-µm sieved fractions) were determined by electron microscopy for the projected area diameter (D_p) and laser diffraction for the volume diameter (D_v). Surface energies (γ) of R-PLGA, rifampicin alone, lactose, and maltodextrin were obtained by inverse phase gas chromatography, surface areas (S_a) by N_2 adsorption, and cohesive energy densities by calculation. Particle dispersion was evaluated (Andersen nonviable impactor) for 10% blends of R-PLGA and rifampicin alone with bulk and sieved fractions of the carriers. D_p for R-PLGA and rifampicin alone was 3.02 and 2.83 µm, respectively. D_v was 13 ± 1 and 2 ± 1 µm for R-PLGA and rifampicin alone, respectively, indicating that R-PLGA was more aggregated. This was evident in γ of 35 ± 1 and 19 ± 6 mJ/m ^{2} for R-PLGA and rifampicin alone. D_p for lactose and maltodextrin (sieved and bulk) was approximately 40 mm. Bulk maltodextrin (D_v = 119 ± 6 mm) was more aggregated than bulk lactose (D_v = 54 ± 2 mm). This was a result of the higher S_a for maltodextrin (0.54 m^2/g) than for lactose (0.21 m^2/g). The γ of bulk lactose and maltodextrin was 40 ± 4 and 60 ± 6 mJ/m ^{2} and of sieved lactose and maltodextrin was 39 ± 1 and 50 ± 1 mJ/m^2. Impaction studies yielded higher fine particle fractions of R-PLGA from sieved lactose, 13% ± 3%, than from sieved maltodextrin, 7% ± 1%, at 90 L/min. An expression, based on these data, is proposed as a predictor of drug dispersion from carrier particles. Delivery of dry powder formulations can be achieved by characterizing particle surfaces and predicting impact on dispersion.

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INTRODUCTION Tuberculosis (TB) is the leading cause of infectious disease in the world today. Each year, about 2 million people in the world die as a result of the infectious disease caused by *Mycobacterium tuberculosis* (MTB) [1]. TB is most commonly caused by deposition of the bacteria in the lungs [2]. MTB are typically about 2 to 5 µm in length [3], making them suitable to enter the lower airways. Respirable poly(lactide-co-glycolide) (PLGA) microspheres containing rifampicin have been developed [4]. The potential of aerosol therapy for tuberculosis with these microspheres was investigated and shown to decrease the bacterial counts in the lungs [5,6]. There is a need to understand powder performance for inhaler development and delivery to humans. This work is intended to determine if aerosol delivery to lungs infected with MTB may be achieved by predicting dispersion of dry powders through knowledge of particle surface properties.

The 3 types of inhalers include metered-dose inhalers (MDIs), nebulizers, and dry powder inhalers (DPIs). DPIs have the advantage of providing automatic coordination between a patient's inhalation and actuation of the dose. In addition, powders are often easier to formulate [7]. To deliver particles from MDIs or nebulizers, the particles must be placed in solution or suspension. This can affect the stability of the particles. In addition, there has been a phaseout of the chlorofluorocarbon propellants used in MDIs of the past [8]. Therefore, the use of DPIs may be advantageous in the delivery of many particles to the respiratory tract.

DPIs consist of 3 components: the formulation, the metering system, and the aerosol dispersion mechanism [9]. In this study, a commercial device and metering system have been adapted to evaluate aerosol dispersion and the relationship to powder surface and physico-

chemical properties. The dispersion of dry powders from DPIs was previously described as a process involving fluidization of a powder bed followed by deaggregation of the powder [9]. In these studies, the deaggregation process was investigated by studying the surface properties of powders.

The primary powder properties that were evaluated in these studies were surface area, surface free energy, and cohesive energy density (CED). Surface area, S_a, is a measure of surface geometry. Particle size is a primary determinant of surface area. As the number of irregularities in the surfaces of particles increases and the particle size decreases, the surface area increases [10]. Surface free energy, γ, can be used to represent the physical nature of particle surfaces or the amount of energy needed to separate particles or surfaces [11]. CED, equivalent to the solubility parameter (δ) squared, is a measure of the chemical functionality or intermolecular forces of particles [12]. CED is related to dissolution and can thus affect moisture association and capillary forces between particles.

The relationship between CED and surface free energy has previously been described; V_m is the molar volume and n is a constant related to the number and arrangement of atoms or molecules in space [13]:

$$\delta^2 = \left(\frac{\gamma}{V_m^{1/3}} \right)^n \quad (1)$$

It is proposed that the surface area, surface energy, and CED can be related to dispersion in an attempt to improve aerosol delivery to the respiratory tract (**Figure 1**).

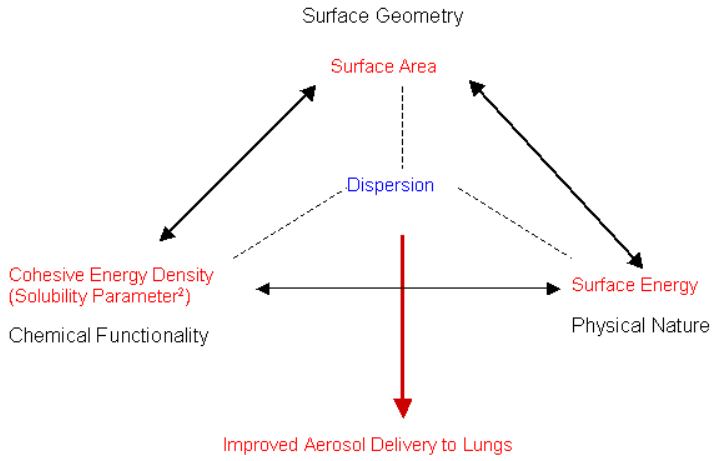

Figure 1. The surface properties of particles may be used to optimize the dry powder formulation for improved dispersion and aerosol delivery to the lungs.

MATERIALS AND METHODS

Powder Preparation

A solvent evaporation technique was used to manufacture biodegradable microspheres containing rifampicin (Sigma Chemical, St Louis, MO). The technique was based on a method developed using experimental design procedures to optimize the drug load and reduce particle size [4]. PLGA (Birmingham Polymers, Birmingham, AL) with a 75:25 lactide-to-glycolide ratio, a molecular weight of 85 200 Da, and a glass transition temperature of 50 to 55°C was selected as the polymer based on the dissolution profiles over 11 days for the particles produced in the previous studies [4]. The dispersed phase consisted of polymer and rifampicin dissolved in 3 mL of methylene chloride. The continuous phase was formed by dissolving ≤ 0.10% Pluronic-F68 (Sigma Chemical) in a mixture of 70% glycerol (Fisher Scientific, Fair Lawn, NJ) and 30% phosphate buffer of pH 5.2. The continuous phase was cooled to < 10°C in an ice bath and stirred at 5000 to 6000 rpm with a high-speed dispersator (Premier Mills, Reading, PA). A syringe pump (Model 100, KD Scientific, Boston, MA) was used with a glass syringe and a 10", 22-gauge stainless steel needle (Aldrich Chemical, Milwaukee, WI) to inject 3.5 mL of dispersed phase into the continuous phase. Stirring was continued for 15 minutes at the reduced temperature of <10°C, followed by removal of the ice bath and stirring at 22 to 25°C for 45 minutes to allow evaporation of methylene chloride. The emulsion was then filtered with filter paper of 0.45-μm pore size (Durapore, Millipore, Bedford, MA) for particle collection. The rifampicin-loaded poly(lactide-co-glycolide) microparticles (R-PLGA) were washed with 150 to 200 mL of deionized water and dried in a vacuum oven (Napco Model 5890, Precision Scientific, Chicago, IL) at 10 in Hg and 30 to 35°C overnight. To ensure dispersion of R-PLGA and rifampicin particles in a cascade impactor, micronization by jet milling was employed (Gem T Research Model Jet Mill, Garlock, Plastomer Products, Newton, PA). The particles were stored in a dessicator at room temperature until they were needed for experimental studies.

Non-spray-dried crystalline lactose monohydrate (Mallinckrodt Baker, Paris, KY) and maltodextrin 500M (Grain Processing Corporation, Muscatine, IA) were sieved with sieve mesh sizes of 45, 75, 125, 180, and 300 μm using a vibrating 3-inch sieve shaker (Model No. SS-5, Gilson Company, Worthington, OH) until sufficient amounts of the 75- to 125-μm fractions were available for experimental studies.

Particle Sizing

Projected area diameters, D_p, were obtained by scanning electron microscopy followed by image analysis. The powders were adhered to double-sided adhesive carbon tabs (Ted Pella, Redding, CA) on aluminum stubs (Ernest F. Fullam, Latham, NY). A Polaron sputter

coater (model E-5200, Electron Beam Services, Agawan, MA) was used to coat the samples with gold-palladium. A scanning electron microscope (JEOL 6300, JEOL Corp, Peabody, MA) was used with an electron beam at an acceleration voltage of 15 kV and a working distance of approximately 15 mm. Photomicrographs were taken of several different areas of the powder on each stub. Representative areas of the stub were photographed. Image analysis software (Sigma Scan version 4.0, Jandel Scientific, Corte Madera, CA) was utilized to estimate the particle size distributions for a minimum of 500 particles for each powder in a minimum of 10 fields of view. The particle sizes obtained were D_p, in the form of count distributions, where d_{50} were the count median diameters. The geometric standard deviations (GSD) were calculated as $(d_{84}/d_{16})^{1/2}$ based on these log normal distributions.

Volume diameters, D_v, were obtained using a RODOS dry powder disperser and VIBRI vibrating powder feeder with a HELOS laser diffraction system (with software version 1.2, Sympatec, GmbH, Clausthal-Zellerfeld, Germany). The powders analyzed were placed on the vibrating feeder operated at a feed rate of 35% of the maximum rate. The powder was passed into an air stream, where it was subjected to high shear forces (3.0 bar). A vacuum (90-100 mbar) was used to draw the particles into the path of a He-Ne laser beam. The diffraction of the laser beam by the particles created a pattern measured by an array of 32 detectors that was a function of size. Software provided with the HELOS was used to obtain the particle size distributions. Based on these distributions, the GSD could be calculated. Replicate measurements were obtained for the powders (n = 5).

Physicochemical Characterization

The equilibrium moisture content of drug and carrier particles was assessed by thermogravimetric analysis (TGA). A titanium pan was tared with the balance of the TGA system (Hi-Res TGA 2950 Thermogravimetric Analyser, TA Instruments, New Castle, DE). Known masses of powder were placed on the pan, which was then equilibrated to 35°C. The powder samples were heated at a rate of 10°C/min with a nitrogen gas until all powder was burned off and 0% of the starting material remained on the pan. Since the temperature at which water evaporates is 100°C, the weight loss that occurred by 150°C was determined. This ensured that all free and bound water had evaporated. The percent weight loss at 150°C was thus recorded as the equilibrium moisture content.

Differential scanning calorimetry (DSC) was used to study the thermal stability and changes in crystallinity over a range of temperatures. The carriers and manufactured drug particles were studied by this method. A known mass of powder was placed in an aluminum pan, and a lid was crimped onto the pan. The pan was then placed in the sample cell of a DSC module (DSC 2010 Differential Scanning Calorimeter, TA Instruments). The temperature of the DSC module was equilibrated at 35°C and then increased at a rate of 10°C/min under a N_2 gas purge until the material began to degrade. The temperatures were obtained for each peak in the resulting curve and provided indications of temperature stability and phase transitions.

The moisture uptake of the carrier and drug powders at elevated relative humidity (RH) was determined with a dynamic vapor sorption apparatus (DVS-1, automated water sorption analyzer, Surface Measurement Systems, Coopersberg, PA). The RH of the sample and reference were maintained by the mixing of wet and dry N2 gas streams at a total gas flow of 200 cm^3/min and a temperature of 25°C. Prior to each run, the balance of the DVS was calibrated with a 100-mg weight and a quartz pan was tared at 10% RH and 25°C. Known masses of powder were placed in the quartz pan and rapidly placed on the DVS balance to minimize exposure to moisture. Time was allowed for the initial weight of the powder to equilibrate at 10% RH and 25°C. Two ramped cycles from 10% to 80% to 10% RH were used for the RH, while the temperature remained constant.

Surface Characterization

The surface area was measured by nitrogen adsorption for carrier and drug particles. Prior to surface area measurement, known masses of the sample powders were placed in sample tubes and outgassed overnight (Flow Prep 060 outgasser, Micromeritics, Atlanta, GA) at a temperature of 35°C to remove any adsorbed gases from the surfaces of the particles. The sample tubes were then connected to a surface area apparatus interfaced to a computer (TriStar 3000, Micromeritics). The masses of powder in each tube were input to the computer. Liquid nitrogen was used to keep the powder samples at a low temperature to allow for the formation of a gas monolayer during the measurements, allowing accurate determination of specific surface area. With this apparatus, the pressure, volume, and temperature of the nitrogen gas were determined. The saturation vapor pressure could then be calculated. Nitrogen was allowed to adsorb onto the surface of the powder. When the pressure, temperature, and volume reached equilibrium, the volume of gas adsorbed was calculated by subtracting the volume of unadsorbed gas from the initially measured volume. More nitrogen was then allowed to adsorb, and when equilibrium was reached, the volume of adsorbed gas was calculated again [10,14]. These measurements were made at 10 different pressures. The Brunauer-Emmett-Teller (BET) plot was then generated, and the slope and intercept were used to calculate the specific surface area.

Inverse phase gas chromatography (IGC) was used to obtain the surface energy of carrier and drug powders. The method incorporated was based on previous work [15-17]. A straight column 23 cm in length and 3 mm in-

ner diameter (ID) was used for all measurements. Prior to each measurement, the column was deactivated by a silanation process [18]. This was performed by sequentially washing the column with distilled water, methanol, and toluene (Mallinckrodt-Baker, Paris, KY). The column was then soaked in 5% dichloromethylsilane (Mallinckrodt-Baker) in toluene solution for 12 hours. The column was then washed sequentially with toluene, methanol, and distilled water. The column was dried overnight in a vacuum oven (Napco Model 5890, Precision Scientific) at 10 inHg and 40°C. The powder was dried in the vacuum oven for 16 hours before a known mass was packed into the column using repetitive tapping and a vacuum. This was a critical step, as voids in the column can have considerable effects on the measurement. Therefore, great caution was used to pack the columns, and a light microscope was used to inspect the packing. Tapping of the column was continued until no voids were present in the packing. Silanated glass wool (Sigma Chemical) was used to plug the end of the column and prevent powder from falling out. The column was then attached to a gas chromatograph (GC, 5890 Series II GC Chromatograph with 7673 auto-injector, Hewlett-Packard, Avondale, PA). The oven temperature for the GC was set to 30°C (this corresponded to a column temperature of 35°C), and dry nitrogen was passed through the column at a flow rate of about 20 to 30 mL/min overnight to allow the powder to reach an equilibrium state. Prior to the measurement, the nitrogen carrier gas flow rate was measured with a soap-bubble flowmeter (Sigma Chemical). For the surface energy measurement, the inlet and detector temperatures were set to 200°C (greater than the boiling point of the probes). A flame ionization detector was lighted with hydrogen and compressed air at flow rates of 30 and 300 mL/min, respectively. The detector was used to determine the retention times of probes on the column. All probes were injected at infinite dilution into the column with a 10-mL syringe (Hamilton Company, Reno, NV) and the auto-injector. A volume of 1 mL was used for each probe. The ambient temperature and RH were recorded for each measurement, as these can affect the surface energy determined [19]. The temperature was in the range of 22 to 25°C, and the RH was in the range of 35% to 50%. The probes were vaporized at the inlet temperature of 200°C before passing through the column. All probes had a purity of > 99%. The carrier gas holdup time was determined using a series of homologous alkanes as probes [20]: decane, nonane (Sigma Chemical), octane (Spectrum Quality Products, Gardena, CA), heptane, and hexane (Sigma Chemical). The retention times of the alkane probes were also used to calculate the dispersive surface energy of the powder in the column.

The CEDs were calculated for lactose and maltodextrin. These calculations were based on a group contributions method previously described by Fedors [21,22]. The CEDs were also calculated for rifampicin and PLGA. The value for 75:25 PLGA was used as an approximation of the CED for R-PLGA.

Aerosol Dispersion

Blends of the R-PLGA and rifampicin particles with lactose monohydrate and maltodextrin carrier powders (10% wt/wt) were prepared for use in the in vitro dispersion studies. A Turbula shaker-mixer (Model T2C, GlenMills, Clifton, NJ) was used for preparation of all blends. Blends were prepared at 20 rpm for 10 minutes in 8-mL glass vials. Ample space (>50%) was retained in the vial with the powder for proper mixing. A calibration curve with rifampicin concentrations ranging from 0.5 to 50 µg/mL was obtained by UV spectrophotometry (Model UV160U, Shimadzu Scientific Instruments, Columbia, MD) with an absorbance maximum wavelength of 480 nm. Rifampicin contents in samples obtained from the blends were then determined and used to calculate the fine particle fractions from the cascade impaction data.

Powder dispersion was performed with each blend using an Inhalator (Boehringer Ingelheim, Ingelheim,Germany) as the device and an 8-stage Andersen MKII nonviable cascade impactor (Graseby Andersen, Smyrna, GA). The Inhalator is a high-resistance inhaler that would be expected to overcome a high level of interparticulate forces [23]. The mouthpiece of the inhaler was inserted into a rubber adapter to achieve a tight seal. The adapter was then connected to the induction port of the cascade impactor. Dispersion was studied at 2 flow rates, 60 and 90 L/min, with each blend (n = 3). The selected coating method for the preseparator of the impactor involved coating with 1% silicon oil (Fisher Scientific) in hexane (Sigma-Aldrich, St Louis, MO). The same coating procedure was used for the collection plates below each stage to prevent particle bounce and reentrainment. Glass fiber filters with a pore size of 0.22 µm (Graseby Andersen) were used below the last stage of the impactor. Six gelatin capsules (size 3, Eli Lilly and Co, Indianapolis, IN) were filled with 20 mg of a blend. The capsules were then placed in the Inhalator. A vacuum pump was used to draw air through the impactor at the 2 flow rates. Following piercing of each capsule, sampling was continued for 10 seconds. For the washing procedure, the inhaler was washed with 10 mL of deionized water containing ascorbic acid (1% wt/vol) (Aldrich Chemical) to prevent the degradation of rifampicin. The throat and preseparator of the cascade impactor were washed with 10 mL of chloroform and the impaction plates with 5 mL into glass test tubes. The inhaler could not be washed with chloroform because of degradation of the plastic components. The chloroform samples were placed in an evaporator (Speed Vac Plus SC110A evaporator, Savant, Holbrook, NY) to evaporate the solvent. These samples were then reconstituted in a volume of 0.5-mL chloroform. A volume of 4.5 mL of methanol was added to each tube to precipitate the

Table 1. Particle Size and Distribution of the Various Powders as Determined by Scanning Electron Microscopy/Image Analysis and Laser Diffraction*

Powder	Sieved Size Range	Particle Size and Distribution			
		Image Analysis†		Laser Diffraction, mean (SD)	
		D_p (µm)	GSD	D_v (µm)	GSD
Lactose	Bulk	40.81	1.56	54 (2)	2.8 (0.1)
	75-125 µm	38.48	1.92	81 (1)	2.1 (0.1)
Maltodextrin	Bulk	34.63	2.05	119 (6)	1.9 (0.1)
	75-125 µm	42.10	1.82	83 (1)	1.6 (0.1)
R-PLGA		3.02	1.76	13 (1)	2.1 (0.1)
Rifampicin		2.83	1.50	2 (1)	1.9 (0.1)

*D_p indicates projected area diameter; D_u, volume diameter; GSD, geometric standard deviations; R-PLGA, rifampicin-loaded poly(lactide-co-glycolide) microparticles.

†The diameters of a minimum of 500 particles were measured.

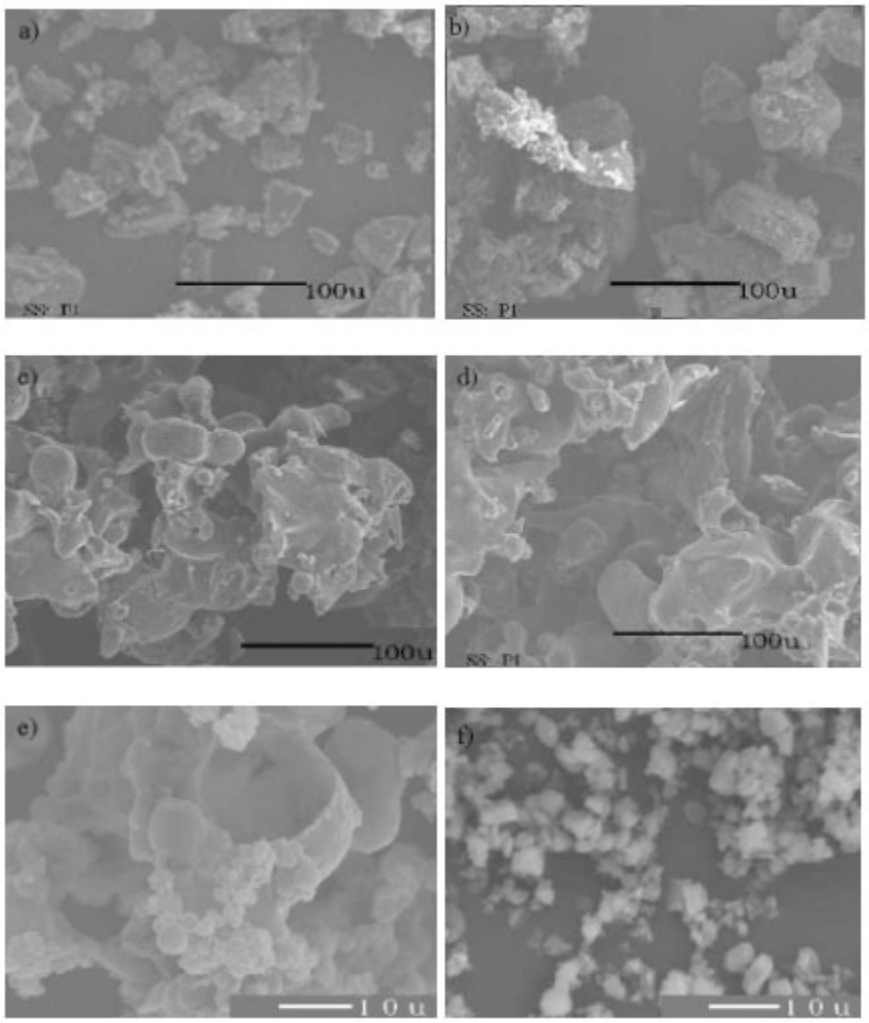

Figure 2. Scanning electron micrographs of carrier particles (a) bulk lactose, (b) sieved lactose (75-125 µm), (c) bulk maltodextrin, and (d) sieved maltodextrin (75-125 µm) and drug particles (e) R-PLGA and (f) rifampicin alone.

Table 2. Equilibrium Moisture Content, Thermal Transitions, and Moisture Adsorbed for the Powders Evaluated*

Powder	Equilibrium Moisture Content,† %	Thermal Transitions‡	Moisture Adsorbed,§ %
Lactose	3.5	142°C—monohydrate to anhydrous form 221°C—melting	0.6 (recrystallized at 55% RH)
Maltodextrin	2.8	Thermally unstable	10.7
R-PLGA	0.7	55°C—glass transition for PLGA	2.8
Rifampicin	1.0	187°C—melting 197°C—recrystallization	1.8

*RH indicates relative humidity; R-PLGA, rifampicin-loaded poly(lactide-co-glycolide) microparticles; PLGA, poly(lactide-co-glycolide).

†Weight loss during heating to 150°C.

‡Thermal transitions prior to decomposition of the powder.

§Total moisture adsorbed when the powder was exposed to 80% RH.

PLGA out of solution for a 10:90 chloroform-to-methanol ratio. Although there was no polymer present in the impactions with micronized rifampicin, the same washing procedure was used for these control studies. For the analysis of the samples, UV spectroscopy with a maximum absorbance wavelength of 480 nm was incorporated. A standard curve was prepared, with rifampicin concentrations ranging from 10 to 50 µg/mL in deionized water with ascorbic acid (1% wt/vol). This standard curve was used for the detection of rifampicin remaining in the inhaler after sampling. An additional standard curve was prepared with rifampicin concentrations from 0.5 to 50 µg/mL in 10:90 chloroform:methanol. This standard curve was used for the detection of rifampicin on all impaction plates.

RESULTS AND DISCUSSION

Particle Sizing

Table 1 shows the particle sizes and distributions obtained by image analysis and laser diffraction. There are deviations between the values obtained by image analysis or microscopy and laser diffraction. The deviations are due to the different measurements obtained with each method. Image analysis of scanning electron micrographs (**Figure 2**) can be used to determine D_p and laser diffraction to obtain D_v. The low diameters obtained by microscopy indicate that there was some aggregation of the powders during the sieving process. This is evident in the comparison of D_p to D_v. In the laser diffraction measurements, if the shear force exerted on the aggregated particles was not sufficient to overcome the interparticulate forces, the resulting size distribution included primary particles and aggregates. Lactose appeared to be a crystalline powder with smaller particles adhering to the surfaces of larger particles (**Figures 2a and 2b**). In comparison, maltodextrin did not appear to be crystalline. The micrographs (**Figures 2c and 2d**) show a high degree of particle interaction for maltodextrin. The D_v obtained for R-PLGA microspheres and rifampicin alone indicate that the microspheres were aggregated and rifampicin alone was broken down to primary particles. Microscopy also revealed that there was a greater degree of particle interaction for the R-PLGA microspheres than for rifampicin alone (**Figures 2e and 2f**).

Physicochemical Characterization

The physicochemical properties of the powders were investigated to reveal the influence on particle interactions (**Table 2**). The weight loss up to 150°C, a temperature at which free and bound water would evaporate, was obtained as a measure of the initial moisture content of the powder. Lactose had slightly greater moisture content than maltodextrin. R-PLGA and rifampicin alone had similar weight losses. The thermal transitions of the powders were investigated to determine melting and recrystallization temperatures. Lactose exhibited an endothermic peak at 142°C that can be attributed to the conversion from a monohydrate to an anhydrous form. This corresponded with the 3.5% weight loss observed by TGA. Maltodextrin appeared to be a thermally unstable powder. Analysis of R-PLGA revealed an endothermic peak at 55°C that was attributed to the glass transition of PLGA. Upon heating to 187°C, rifampicin experienced an endothermic transition immediately followed by an exothermic transition. This was previously described as melting followed by recrystallization [24]. Dynamic vapor sorption revealed that lactose adsorbed little moisture when exposed to relative humidities up to 80%. However, a recrystallization event occurred at 55% RH. In contrast, maltodextrin adsorbed a large amount of moisture, 10.7%, when exposed to the elevated RH. R-PLGA and rifampicin alone adsorbed 2.8% and 1.8% moisture, respectively.

Table 3. Surface Area, Dispersive Surface Energy, and Cohesive Energy Density for the Powders Evaluated*

		Surface Area, m^2/g	Dispersive Surface Energy, mJ/m^2 (SD)	Cohesive Energy Density, cal/cm^3
Lactose	Bulk	0.21	40 (4)	392
	75-125 µm	0.18†	39 (1)	392
Maltodextrin	Bulk	0.54‡	60 (6)	384
	75-125 µm	0.17†	50 (1)	384
R-PLGA		3.13	35 (1)	174
Rifampicin		6.42	19 (6)	174

*R-PLGA, XXX.

†Surface areas obtained from Concessio et al [27].

‡Surface area obtained from *Handbook of Pharmaceutical Excipients* [28].

Surface Characterization

Table 3 shows the surface areas and dispersive surface energies of the carrier and drug particles. Bulk lactose had a much lower surface area than bulk maltodextrin. This was a result of the broader particle size distribution for maltodextrin, as indicated by D_p and the corresponding GSD (**Table 1**). The surface energies of bulk and sieved maltodextrin were greater than the surface energies of bulk and sieved lactose, respectively. This could be correlated to the particle sizes obtained by laser diffraction, which indicated that maltodextrin was more aggregated than lactose, as the shear forces exerted on the particles did not overcome the surface energy of maltodextrin to break the particles down to the primary particle size. The surface area for rifampicin alone was greater than the surface area for R-PLGA. This was because of the broader distribution for R-PLGA, which included more large particles. The surface energy for rifampicin was lower than the surface energy for R-PLGA. This could also be correlated to the laser diffraction data, which indicated that R-PLGA was more aggregated because of the higher surface energy. It is important to note that the dispersive component of surface energy due to van der Waals forces is not the only component of surface energy. The total surface energy consists of the dispersive component plus a component due to acid-base effects [25]. However, the acid-base component is difficult to measure by IGC [16]. CEDs for lactose and maltodextrin were similar, 392 and 384 cal/cm^3, respectively. This corresponds to solubility parameters of 19.8 and 19.6 $(cal/cm^3)^{1/2}$. Powders used as carriers for inhaled dosage forms are selected based on appreciable water solubility. The solubility parameter for water is 23.4 $(cal/cm^3)^{1/2}$. For a solid to dissolve in a liquid, the solubility parameters must be similar [26]. Therefore, most suitable carriers have similar solubility parameters or CEDs that allow them to be soluble in physiologic fluids.

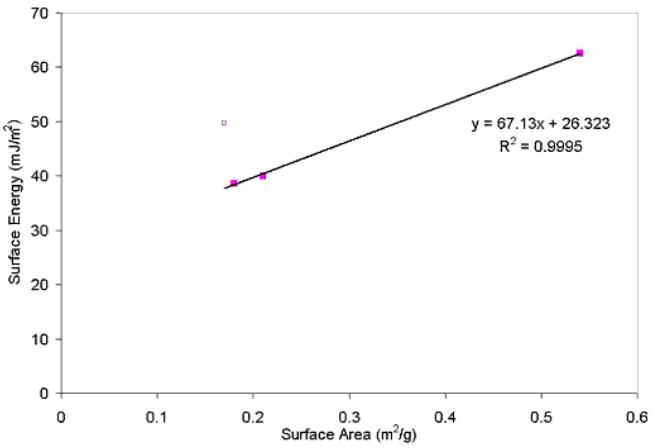

Figure 3. Surface energy of the carrier particles versus the surface area.

For this reason, the effect of CED on dispersion was not studied. When the dispersive surface energy of the carrier particles was plotted against the surface area, a linear curve resulted (**Figure 3**). This curve would be expected to have a slope of 0 for the same batch of powder with no contamination. This is the case for lactose, but not for maltodextrin, as the sieved maltodextrin has a lower surface energy than the bulk powder. Thus, the sieved maltodextrin was not included in the plot, as contamination may have occurred during the sieving process. The linearity between the maltodextrin and the lactose suggests a correlation between the surface area that is representative of the surface geometry of particles and the surface energy that is representative of the physical nature of particle surfaces.

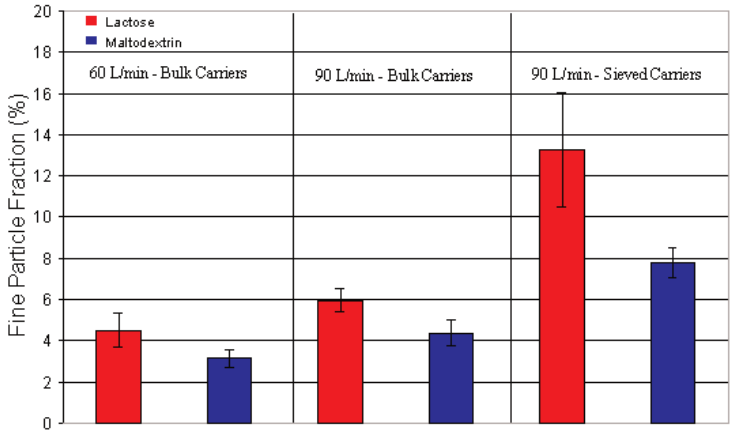

Figure 4. Fine particle fractions of R-PLGA with bulk carriers at 60 and 90 L/min and sieved carriers at 90 L/min.

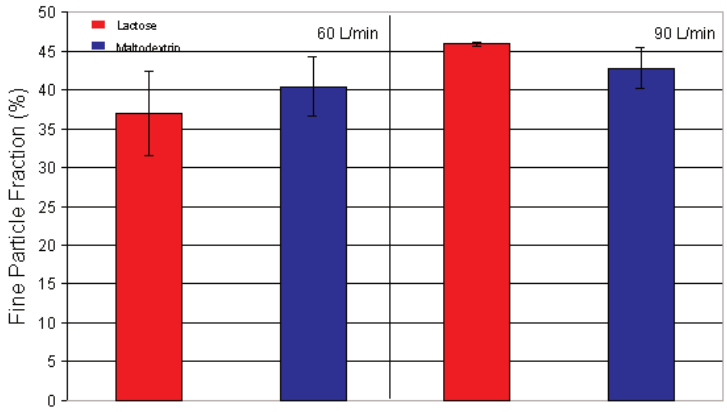

Figure 5. Fine particle fractions of micronized rifampicin with bulk carriers at 60 and 90 L/min.

Aerosol Dispersion

The initial dispersion studies were performed with the bulk carriers at flow rates of 60 and 90 L/min through the inertial impactor for R-PLGA and rifampicin alone. **Figure 4** shows that for R-PLGA at a flow rate of 90 L/min, the fine particle fractions were greater than at 60 L/min. At the higher flow rate, greater shear forces were exerted on the particles to overcome interparticulate forces. At both flow rates with the bulk carriers, the fine particle fraction obtained for R-PLGA was greater with lactose than maltodextrin. This was because of the broader particle size distribution for maltodextrin, which included a greater proportion of fine particles. The interparticulate forces between the R-PLGA particles and fine maltodextrin particles were not overcome, and these aggregates were deposited in the preseparator of the impactor.

Dispersion studies were performed with rifampicin alone and bulk carriers. All fine particle fractions obtained for rifampicin were greater than for R-PLGA because of the lower surface energy of rifampicin (**Figure 5**). There were no statistical differences observed between the fine particle fractions obtained with the bulk carriers at 60 or 90 L/min. Since the surface energy of rifampicin was low, the interparticulate forces with any of the carriers were overcome at these flow rates.

Once these studies had been completed, the effect of carrier particle size on dispersion was minimized by us-ing similar sieved fractions of lactose and maltodextrin. This allowed for the effect of the surface properties of carriers on dispersion to be studied. A flow rate of 90 L/min was used to increase the shear forces exerted on the aggregated particles. It was revealed that the fine particle fraction for R-PLGA was statistically greater with lactose as the carrier than with maltodextrin ($P<.05$).

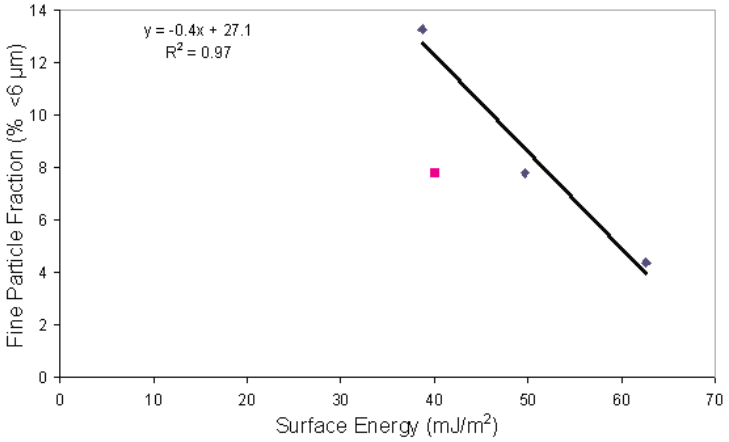

Figure 6. Fine particle fraction of rifampicin microspheres versus the dispersive surface energy of the carriers.

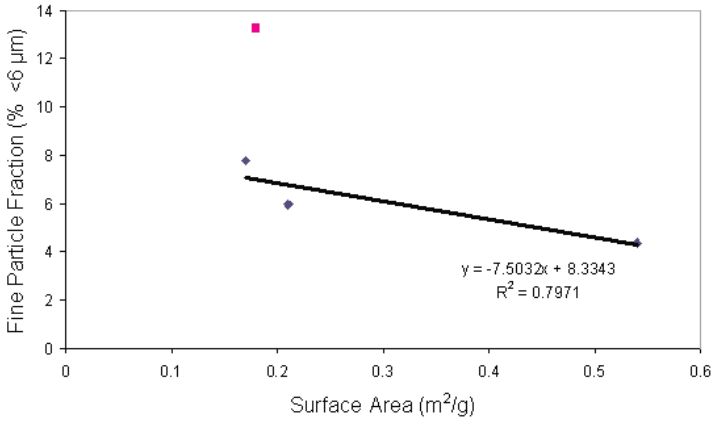

Figure 7. Fine particle fraction of rifampicin microspheres versus the surface area of the carriers.

This correlated with the surface energies of the carriers. The interparticulate forces between R-PLGA were greater with maltodextrin as the carrier because of the higher surface energy of maltodextrin than lactose. A plot of the dispersive surface energy of the carrier particles versus fine particle fraction showed a linear relationship (**Figure 6**). A plot of surface area versus fine particle fraction also showed a linear relationship (**Figure 7**). The sieved lactose yielded a higher fine par-ticle fraction and was excluded from the plot.

Based on the results obtained in these studies, an expression is proposed that relates surface area, surface energy, and CED of carrier particles to aerosol dispersion:

$$\text{Dispersion} = k\,\frac{(\delta^2)^j}{S_a{}^l \gamma^m} \qquad (2)$$

where k is dependent on the molar volume of the carrier and the number of molecules present at the surfaces of the carrier particles. The exponents l and m have been shown to be approximately 1 in these studies. The exponent j is dependent on the arrangement of atoms or molecules in space. The relationships proposed here are first approximations, and substantial additional data are required to fully elucidate the nature of these relationships. This dispersion value can be determined for a number of different carriers and used to predict how well given drug particles may disperse from the carriers. Carriers with higher dispersion values would be expected to yield higher fine particle fractions.

CONCLUSION An expression has been developed that allows for the calculation of a dispersion value for carrier particles in dry powder inhaler formulations. The dispersion value allows for the prediction of how well given drug particles will disperse from carriers. This approach has been used to optimize the dispersion of rifampicin-loaded microspheres from a commercial dry powder inhaler.

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