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Powder specific active dispersion for generation of pharmaceutical aerosols

T. Crowder [a,*], A. Hickey [a,b]

[a] Department of Biomedical Engineering, School of Medicine, University of North Carolina at Chapel Hill, NC 27599, USA
[b] Division of Molecular Pharmaceutics, School of Pharmacy, University of North Carolina at Chapel Hill, NC 27599, USA

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Abstract

Dry powder inhalers are increasingly employed to deliver pharmaceutical aerosols. Efficient mechanisms of particle dispersion are central to their success in disease therapy. Creation of a powder aerosol requires the input of energy to transition the static powder bed into an entrained aerosol.

The purpose of this study was to investigate the effects of input of vibrational energy into a powder on aerosol entrainment. Rotating drum characterization of powder flow was performed on lactose and maltodextrin excipients blended with albuterol sulfate. Dispersion experiments were conducted using an entrainment tube and a vibration actuator, vibrational energy input being derived from analysis of powder flow data from rotating drum analysis.

Results of analysis of the rotating drum data showed that with increasing rotational speed powders reached a constant state of fluidization with a mean avalanche time dependent on the powder. Dispersion experiments demonstrated that the input of vibrational energy increased the dose emission while the input of frequencies specific to the powders improved the reproducibility. Frequency analysis of the vibration signals indicated that the reproducibility was determined by the bandwidth of the signal.

This work suggests that an ability to tailor energy input to match the flow properties of a given powder formulation may significantly improve reproducibility of dose delivery from active dry powder inhalers.

Keywords: Inhalation drug delivery; Active dry powder inhaler; Powder flow; Powder avalanching; Vertical vibration

1. Introduction

Withdrawal of atmospheric ozone depleting propellants and the development of biotechnology products that cannot be delivered by conventional routes of administration emphasize the need for improved inhaler design based on novel mechanisms of aerosol dispersion. Dry powder inhalers (DPIs) have become prominent alternatives to pressurized metered dose inhalers (MDIs) (Crowder et al., 2003) for pharmaceutical aerosol drug delivery since the ratification of the Montreal protocol in 1987 which prescribed the phase out of chlorofluorocarbons and eventual termination of use in the US by 2009 (Hickey and Dunbar, 1997; Montreal Protocol, 1987; Prime et al., 1997; US Food and Drug Administration, 2005). Research in the DPI field has focused on both particle engineering based on the physics of aerosolization (Peart and Clarke, 2001) and inhaler design to achieve desired delivery performance (Crowder et al., 2001). Creation of a powder aerosol requires the transition of the powder from a static to a suspended state achieved by the input of energy (Castellanos et al., 1999). Powder flow properties are a critical determinant of both efficiency and variability of aerosolization. Current inhaler designs in use or in development are either passive, relying solely upon the pneumatic forces created by the user's inhalation to generate the aerosol, or active, using an external energy source to impart motion, independently of inspiratory airflow, and efficiently aerosolize the powdered drug (Atkins and Crowder, 2004). The available mechanisms of dispersion energy input are limited to mechanical, electrical or pneumatic energy sources (Crowder et al., 2001). For DPIs, variability of dose delivery could potentially be reduced through the use of an active mechanism

* Corresponding author at: Oriel Therapeutics Inc., P.O. Box 14087, Research Triangle Park, NC 27707, USA. Tel.: +1 919 313 1290; fax: +1 919 313 1295.
E-mail address: tcrowder@orieltherapeutics.com (T. Crowder).

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that allowed for the controlled input of stored energy to the powder.

A key factor in regulatory approval, as well as patient outcomes, is the ability to reproducibly deliver drug doses independently of a broad range of inspiratory flow rates, environmental conditions and through-life conditions of the inhaler. Dose delivery is inherently variable when pneumatic forces alone create the aerosol (Auty et al., 1987; Clark and Hollingworth, 1993; Hindle and Byron, 1995).

Powder flow properties are a prime consideration in the development of a powder drug formulation and it has been demonstrated that in vitro and in vivo performance of a passive DPI could be predicted through rotating drum analysis of powder flow (Concessio et al., 1999). The capacity dimension, a measure of the divergence of trajectories of rotating drum avalanche angles and angle rate of change in phase space, was correlated with the in vitro fine particle fraction (the portion of an aerosol less than 5 μm and suitable for lung deposition) delivered from a commercially available DPI device and with reduction in peak inspiratory pressure in an in vivo guinea pig model of bronchoconstriction.

The purpose of the current study was to investigate the effect of the input of vibrational energy into a powder on aerosol entrainment and test the postulate that rotating drum analysis could be used to predict a powder specific vibrational energy input to control dispersion efficiency.

2. Materials and methods

2.1. Powders

Powders for aerosol drug delivery typically consist of drug particles in a size suitable for lung delivery (1–5 μm diameter) blended at low concentration with excipient particles typically 50–150 μm in diameter. One purpose of the excipient particles is to serve to increase the flowability of the drug particles by reducing the van der Waals force between them (Hickey et al., 1994). They also serve as a bulking agent as aerosol drug therapeutic doses are typically less than 500 μg.

As the purpose of this study was to determine if dispersion performance could be improved through input of appropriate frequencies of vibration, no attempt was made to optimize the powder formulations, i.e. the aim was to optimize dispersion efficiency by modulating energy input for a given powder as compared to the standard approach for passive DPIs, where powder properties are modulated (through optimization of formulation/process) for a given energy regime (determined by the inhaler design). Micronized albuterol sulfate (Cirrus Pharmaceuticals, RTP, NC) of median particle size 1.34 μm was blended (2%, w/w) with sieved fractions of bulk lactose (Meggle, Wasserburg, Germany), a common inhalation excipient, and maltodextrin (Grain Processing Corp., Muscatine, IA), chosen for its distinctly different flow properties relative to lactose. The sieve fractions were 45–75 μm for lactose and 75–125 μm for maltodextrin. Mean particle size measured by laser diffraction (Sympatec GmbH, Clausthal-Zellerfeld, Germany) was 50.4 μm for lactose and 81.6 μm for maltodextrin. Blends were prepared in a Turbula mixer (Glen Mills Inc., Clifton, NJ) and had a blend content uniformity of 3% or less. When dispersed by the Rotahaler™, a passive DPI, the emitted doses were similar for each blend (emitted dose ∼64% for maltodextrin and ∼59% for lactose), though deaggregation by the Rotahaler™ was different (fine particle fraction as a percent of loaded dose 2% for maltodextrin and 10% for lactose) (Concessio et al., 1999). The laboratory ambient relative humidity was not controlled and varied from 42 to 51%. Albuterol recovered from the cascade impactor stages was determined by fluorescence spectroscopy (Perkin-Elmer LS50B; excitation wavelength of 220 nm and emission at 310 nm; LOD 0.27 μg/ml; LOQ 0.82 mcg/ml; all sample dilutions kept in linear range).

2.2. Rotating drum characterization

Rotating drum experiments were performed on an early prototype model Aeroflow (TSI, Shoreview, MN) loaded with 30 mL of test material (Crowder et al., 1999). This apparatus consists of a clear cylinder approximately 20% loaded with powder that rotates around an axis parallel to the horizontal (Fig. 1). The powder bed rises with the drum until the angle of the bed surpasses the powder's angle of repose, at which point it avalanches, repeating the process as the drum continues to rotate. The intensity of a light source at the bottom of one side of the drum is measured on other side of the drum by a photocell that is more or less obscured by the powder depending on the angle of the powder in the drum. A sudden change in intensity of light measured by the photocell occurs with an avalanche and is used to detect the time of the avalanche. In addition to times between avalanches, the size of avalanches can be measured through a direct correlation with the voltage change of the photocell output (Crowder et al., 1999). The rotation rate of the drum can be altered and here testing was performed at 0.25 rpm increments up to 2 rpm (Fig. 2). At low drug concentration, the avalanching behavior was dominated by the excipient particles. It has

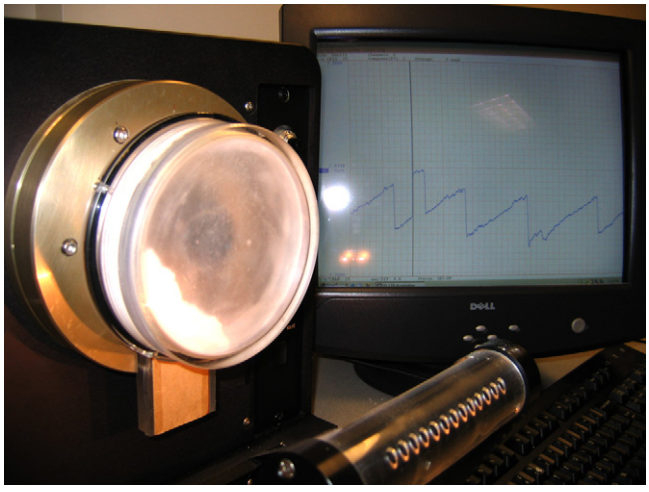

Fig. 1. Photograph of rotating drum apparatus. Powder can be seen in the drum as can the voltage response of the photocell on the associated computer. An abrupt change in the photocell voltage mark the occurrence of an avalanche.

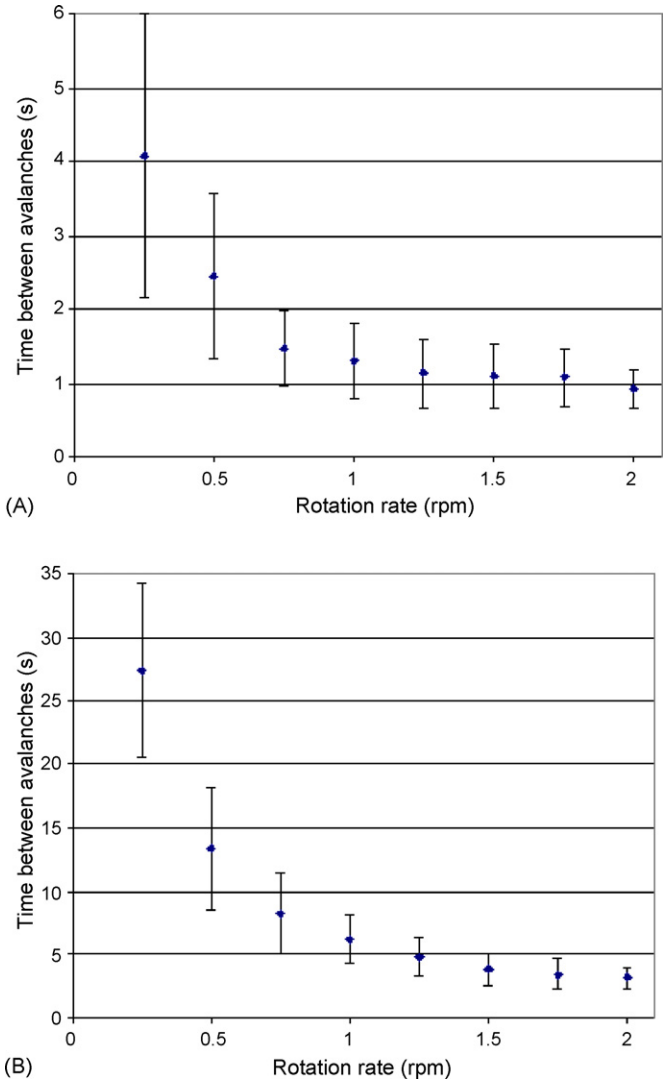

Fig. 2. Time between avalanches as a function of drum rotation rate for: (A) lactose and (B) maltodextrin with 50 avalanches measured for each. Each powder demonstrates a linear region with the more cohesive maltodextrin having the higher average time between avalanches. The existence of a region of relatively constant avalanche rate is used to justify the input of energy at a highly scaled vibration frequency.

been observed that ∼10% (w/w) typically independent of drug properties, is the limit at which the avalanche size distribution begins to be perceptibly modified by the presence of the binary component (Crowder et al., 1999).

2.3. Vibration signal derivation

Simulations of granular materials in the rotating drum have exhibited complex periodicity in surface angle (Baumann et al., 1995). A stochastic relationship between the avalanche initiation and termination angle was observed experimentally (Morales-Gamboa et al., 1993). Distributions of avalanche sizes have also been described for pharmaceutical excipients (Alexander et al., 2006; Crowder et al., 1999). Crowder et al. found avalanche size to be a discriminating measurement of free or poor flow in the rotating drum and Alexander et al. attributed this to the nature and intensity of cohesive forces. Importantly, Alexander et al. measured the effect of dilation of the powder bed on the avalanche statistics and determined that avalanching was a history dependent process, i.e. the dilation state of the powder at a given time determined the avalanche statistics at subsequent time. Castellanos et al. (1999) described dilation as the first step in transition of powder from a static bed to either flowing or aerosolized states.

The concept of the role of dilation in dispersion and the measurement of dilation governed distributions of avalanche statistics with complex periodicity were combined to conclude that application of appropriate perturbations to a fluidized powder could drive the system into a quasi-linear fluidization state. Vibration is a convenient and well-known method for powder fluidization. Visually evident patterns have been demonstrated in the surface of vertically vibrated granular materials at subharmonics of the vibration frequency (Aranson et al., 1999; Duran, 2000; Melo et al., 1994, 1995; Pak and Behringer, 1993). An open control loop approach was required since closed loop control is impractical for a DPI device. From the observations above, it was further postulated that vibration driven fluidization of a powder could be made more uniform by inclusion of subharmonic frequencies determined from the distribution of rotating drum avalanche frequencies. The experiment described below tested this postulate and the vibration signal analysis suggests a mechanism for the effect.

Modifying previous approaches (Morales-Gamboa et al., 1993), the discrete time distribution of avalanche times for rotation speeds was analyzed in the linear regime. Taking the most frequently occurring avalanche times (typically 4) and converting to frequency space, a signal was calculated by multiplying sinuosoids using the equation $x_n = \sum_{n=1}^{m} a_n \sin(2\pi f_n/f_1 + n\pi/m)$ where m is the number of frequencies selected, a_n the relative frequency of occurrence of the avalanche times, and f_n is the avalanche times converted to frequency. This signal was applied as an amplitude modulation to a carrier frequency determined by the actuator resonance (Fig. 3). A deeper understanding of the signal and its mechanism of action require detailed mathematical treatment; further information is provided in Appendix A.

2.4. Dispersion testing

The effect of various vibrations on the fluidization and aerosol entrainment of the particles was tested by use of a simple tube with a cross sectional area of 1.2 cm^2. The design was intended to be low resistance so that little energy was provided by the tube for pneumatic deaggregation of drug from excipient. The specific airflow resistance of the tube was measured using a manometer and found to be 0.031 (cm $H_2O)^{0.5}$/Lpm. For comparison, the low resistance Rotahaler™ has a specific airflow resistance of 0.04 (cm $H_2O)^{0.5}$/Lpm (Clark and Hollingworth, 1993). A vibration actuator was attached to bottom of the tube in the form of a curved section of polyvinylidene fluoride (PVDF, Measurement Specialties Inc., Hampton, VA), a piezoelectric polymer material. PVDF was chosen over a ceramic piezoelectric actuator since it could potentially be incorporated into DPI

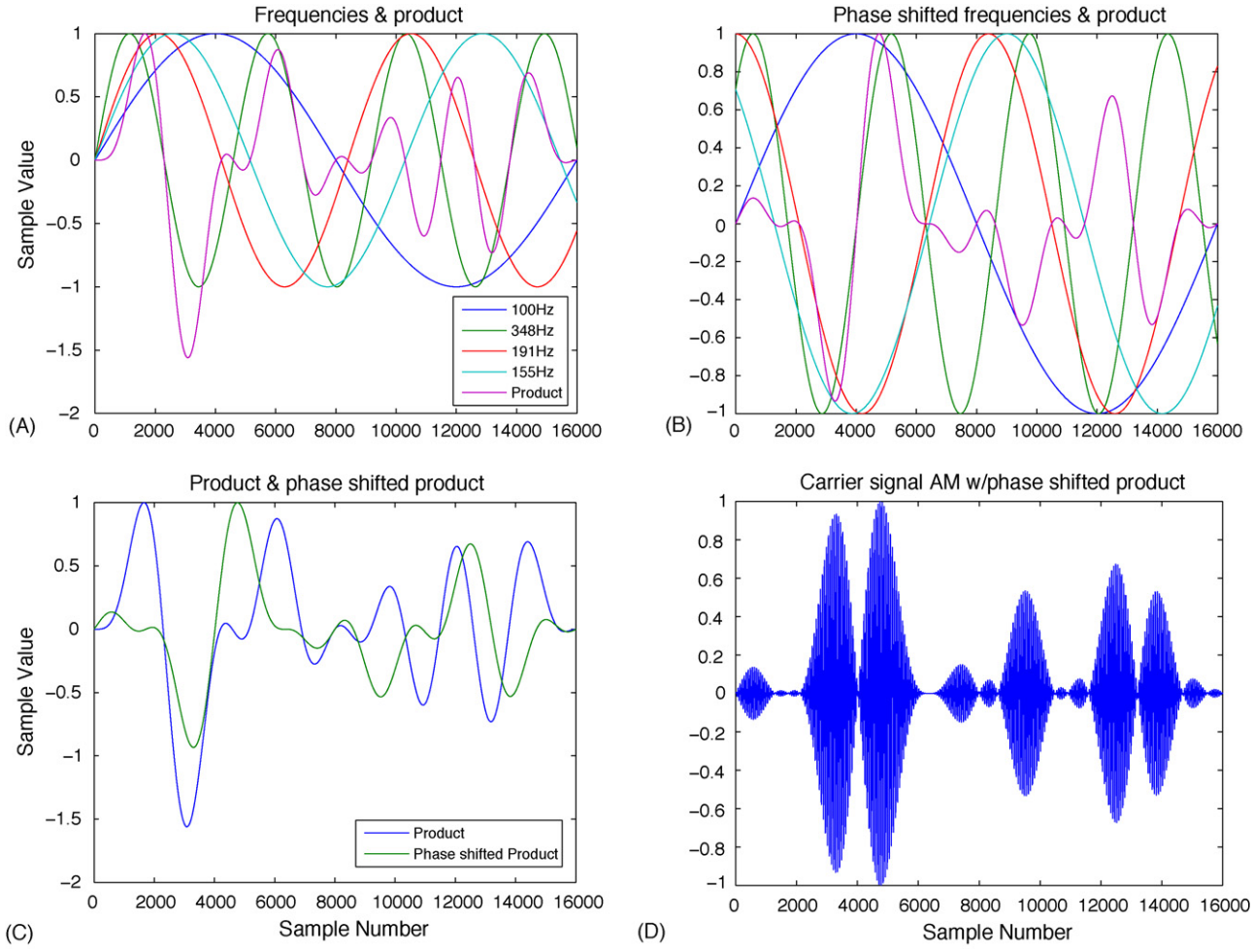

Fig. 3. Implementation of the powder specific vibration frequencies. Frequencies derived from the rotating drum analysis are normalized to the lowest frequency (A) and then phase shifted (B). The process of phase shifting reduces the destructive interference due to small differences in the frequencies (C). The product signal is applied as an amplitude modulation to a carrier frequency (D).

drug packaging. A radius of curvature 1 cm was selected to give operating frequencies above 20 kHz, above the audible range (according to the manufacturer, curved PVDF operating frequency is determined according to 21 kHz/radius of curvature in cm). A quantity of 20 ± 1 mg of powder was weighed and placed upon the actuator, air pulled through the tube and the resulting aerosol entrained into a cascade impactor (Thermo-Andersen, Roswell, GA) for measurement of the distribution of the drug particles (Fig. 4). The impactor was fitted with a USP throat, preseparator and 60 Lpm modification. Silicon oil (1%) in hexane was used to coat the plates to prevent particle bounce.

For each powder, three conditions were utilised to demonstrate the effect of various vibration signals, all tests being performed at a fixed flow rate: (a) a 'no vibration' control to determine the intrinsic pneumatic dispersion efficiency of the tube, (b) a single frequency vibration (24 kHz sinusoid) equivalent to the resonant frequency of the actuator and (c) a 24 kHz signal, amplitude modulated (AM) with the powder specific frequencies derived from rotating drum analysis. Four replicates were performed for each condition. A function generator (HP 33120A, Agilent Technologies, Palo Alto, CA) with arbitrary waveform storage was used to generate the vibration signal and amplified with a piezo amplifier (PiezoSystems EPA104, Cambridge, MA). The root mean square (rms) voltage for the 24 kHz signal was 141 V and 105 V for the AM signal. The lower V_{rms} for the AM signal is a result of reduced voltage values for portions of the signal due to amplitude modulation. Since the amplifier did not provide fine tuning of the excitation voltage, no attempt was made to normalize the rms level of the excitation.

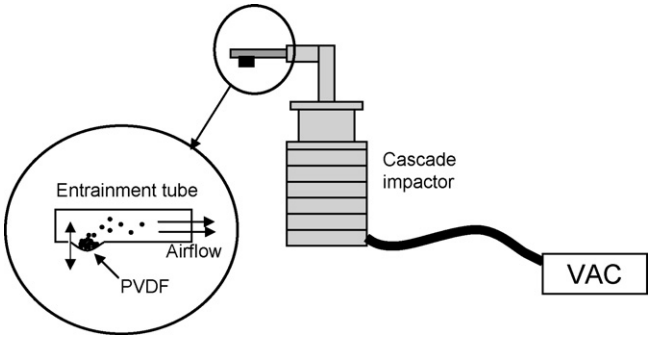

Fig. 4. Powder dispersion characterization apparatus.

Table 1
Dispersion performance measures of lactose and maltodextrin excipient formulations for three test conditions

Performance measure (S.D.)	Formulation excipient	Test condition		
		No vibration	24 kHz	24 kHz + AM
ED (% loaded)	Lactose	56.9 (11.4)	65.3 (13.1)	81.2 (2.4)
	Maltodextrin	38.5 (11.6)	83.0 (16.6)	94.7 (0.9)
FPF (% loaded)	Lactose	8.8 (3.5)	9.1 (0.9)	13.0 (1.3)
	Maltodextrin	3.6 (1.8)	7.8 (1.6)	8.1 (0.8)

3. Results

3.1. Rotating drum characterization

Times between avalanches as a function of rotation rate for lactose and maltodextrin are shown in Fig. 2. At low rotation speeds, times between avalanches are longer as the drum must rotate through an angle sufficiently beyond the powder's angle of repose. As the rotation rate increases, the angle of repose is reached more quickly until the powder reaches a point at which it is constantly fluidized and the time between avalanches plateaus. This condition persists until the rotation rate increases into a centrifugal regime where the powder remains on the walls through the vertical.

The avalanching data for lactose and maltodextrin were compared using a two-factor ANOVA without replication. The mean times to avalanche as a function of rotation rate were significantly different with a p-value of 0.026. The maltodextrin had a larger average time between avalanches indicating it was less free flowing than lactose. This correlates with direct observation of the flow of these powders where maltodextrin is visibly less free flowing.

3.2. Dispersion testing

The emitted dose (ED, percentage of loaded dose removed from entrainment tube) was calculated using the cascade impactor (Table 1). For both powders, the efficiency of aerosol delivery from the tube was increased through use of a single frequency vibration compared to the control with no applied vibration, while the variability was unchanged; the ED increased from 57–65% to 39–83% for lactose and maltodextrin, respectively. The powder specific AM vibration increased the ED further to 81% for lactose and 95% for maltodextrin. Also, in both cases, the variability was significantly reduced ($p < 0.05$, by one-tailed t-test) by the powder specific signal component (Fig. 5). The powder specific vibration influenced dispersion reproducibility with a range of powder blends with different excipient particle sizes and distributions. The fine particle mass (FPM) is defined here as the mass on and below stage 1 of the impactor (i.e. mass contained in particles with aerodynamic diameter less than 6.2 μm) and the fine particle fraction (FPF) is the ratio of the FPM to the loaded mass. FPF was also increased by the vibration but only to the degree that the ED was increased (increased 47% for lactose and 224% for maltodextrin) with a concomitant decrease in variability. The low energy vibration does not significantly deaggregate the drug from excipient.

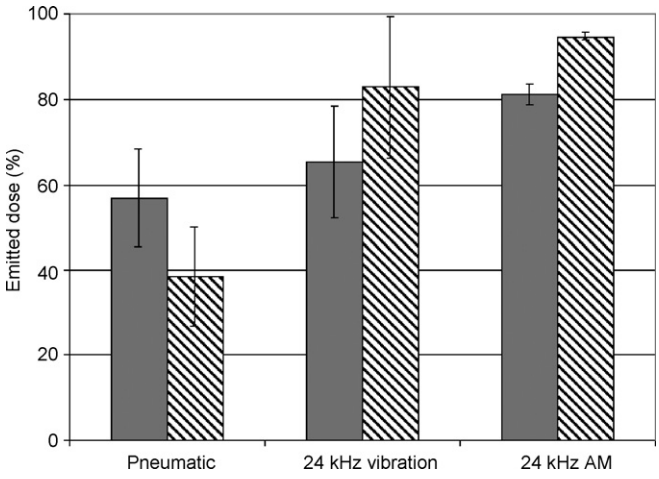

Fig. 5. Dose emitted from the dispersion tube for three conditions: pneumatic dispersion with no vibration, vibration at the actuator resonance and vibration using the described powder specific signal. Lactose blends (solid) were compared with more cohesive maltodextrin blends (diagonal hatch). In each case the powder specific signal decreased the variation.

The maltodextrin blend, which had a very low intrinsic pneumatic ED (39%), responded more strongly to the input of single frequency vibration energy than the lactose blend (116% increase versus 15% increase). Lactose was more freely flowing in the rotating drum tests and was dispersed more readily by pneumatic forces (ED 57%). The maltodextrin results demonstrate the performance increase that can be achieved by vibrational fluidization of a poorly flowing powder. For the more freely flowing lactose, single frequency vibrational fluidization did not provide the same impact as for maltodextrin but performance was increased by the use of powder specific AM frequencies. Importantly, the use of powder specific AM frequencies provided similar ED results for both excipients.

4. Discussion

The bandwidth of the vibration frequency that affects fluidization is directly correlated to the breadth of the distribution of avalanche frequencies, which in turn is determined by the cohesiveness of the powder (see Appendix A for further details). This was demonstrated here with a comparison of lactose and maltodextrin rotating drum flow data where the visibly more cohesive maltodextrin powder had a longer mean and larger standard deviation around the mean time between avalanches. The poor flow properties of a cohesive powder result in a gen-

eral tendency of the powder to rise to a higher angle before avalanching (related to the static angle of repose) but with variation when large clumps of powder spontaneously avalanche at lower angles. A freely flowing powder exhibits a narrow distribution of avalanche times and can be efficiently fluidized with narrowband or single vibration. A more cohesive powder, with its broad distribution of frequencies governed by more complex forces of interaction (Hickey and Concessio, 1997) is more efficiently fluidized when a broadband vibration signal is applied. Efficiency is determined by the degree of fluidization since creation of an aerosol for particles of diameters in the 50–150 μm range used here requires fludization (Castellanos et al., 1999). The carrier frequency is non-specific to powder but, rather, to the resonance of the actuator since the low piezo coefficient (weak piezoelectric effect) of PVDF provides small amplitudes of vibration. Resonance is required to achieve visible fluidization. But the observation of a plateau in avalanche time once the rotation rate is sufficient to support continual fluidization suggests that fluidization for entrainment from vertical vibration for the thin bed may also be insensitive to frequency provided the fluidization is constant, i.e. the frequency of the vibration is faster than the relaxation time of the powder. In any case, the reproducibility effect is provided by the bandwidth around the carrier. This width is independent of carrier frequency just as the width of the avalanche distribution is independent of rotation rate in the range described.

The rotating drum method is a useful tool for formulation screening since the freely flowing or cohesive nature of a powder will clearly determine its aerosolization potential in pneumatic entrainment from passive DPIs. The use of a bulk powder characterization method such as a rotating drum to predict fluidization of small (20 mg) quantities of powder is supported by the observation that active flow in the drum occurs in a relatively thin surface layer (Boateng, 1998). It is believed that particle interactions, at the powder surface, control the avalanching time and would thus act similarly upon fluidized powder.

The relationship between the rotating drum characterization method and the vibration's impact on fluidization can be explained by the following thought experiment. In the rotating drum, the powder responds to an input of energy (increase in potential energy gained by the powder bed as the drum rotates) by initiating flow in an avalanche. The rate of input of energy is the drum rotation rate, ω. If one were to perturb the system through an impulse, the powder would be expected to avalanche provided the powder bed was sufficiently close to its angle of repose. If one desired to control the system by causing the powder to avalanche once the powder had reached a given angle α, then the period of the impulse would vary based on the size of the preceding avalanche according to $T_{n+1} = (\alpha - \beta_n)/\omega$, where β_n is the angle of the powder bed after the nth avalanche. A feedback control system would require instrumentation to measure the avalanche termination angle and calculate the time to the next impulse from the relation above. The periods for each discrete impulse would fall into a distribution determined by the size of the avalanches. Note that the β_n distribution would be expected to have the same shape as the distribution of the times between avalanches. The β_n (or time between avalanches) distribution would be unique for a given powder and would be largely determined by the cohesive properties of the powder. In this imagined control system, if the angle β_n could not be measured, then open loop control using the most frequently occurring β_n to calculate the impulse period would provide the greatest likelihood of success in controlling the avalanching. Small impulse perturbations using the β_n distribution would provide energy to the powder when susceptible to avalanching and would be expected to reduce the overall variability in avalanche angle or time between avalanches. Switching to the vibration system, the powder gains kinetic energy from the vibratory motion of the actuator. The carrier frequency is the rate of input of energy, which is analogous to the rotation rate of the drum though clearly shifted to a much higher frequency. The frequencies contained in the amplitude modulation are analogous to the impulses described above as they are derived from the powder flow properties and act as small perturbations to the fluidized powder. Thus, by using the distribution of times between avalanches to achieve open loop control similar to that described above, an "impulse" is input to the system in a manner most likely to result in reduction in variability of fluidization. Reduced variability in fluidization would be expected to reduce variability in dispersion.

5. Conclusion

Rotating drum avalanche statistics were measured for two powder formulations and provided a set of frequencies of vibration used to fluidize the powders for dispersion in an entrainment tube. The use of these powder specific frequencies was compared to non-specific vibration and pneumatic dispersion as a control. The powder specific vibration frequencies provided increased dispersion performance and improved reproducibility of dispersion performance parameters (ED, FPF). A rationale was provided for the linkage between the measurement of rotating drum flow and fluidization for aerosol entrainment based on the dependence of the rotating drum on powder cohesiveness. A constraint of the method is that the vibration is not solely powder dependent, i.e. the carrier frequency was determined by the actuator resonance rather than the powder characterization. Subsequent work will focus on alternative actuators that eliminate this dependence. The reproducibility demonstrated by the powder specific vibrations with this system is promising with regards to meeting or exceeding current regulatory requirements of DPI devices (CDER, 1998). Understanding powder flow properties in the absence and presence of applied energy, particularly powder specific vibrational frequencies may provide a useful tool in achieving desired performance characteristics in inhaled drug delivery and may simplify the formulation process for inhaled product development.

Acknowledgement

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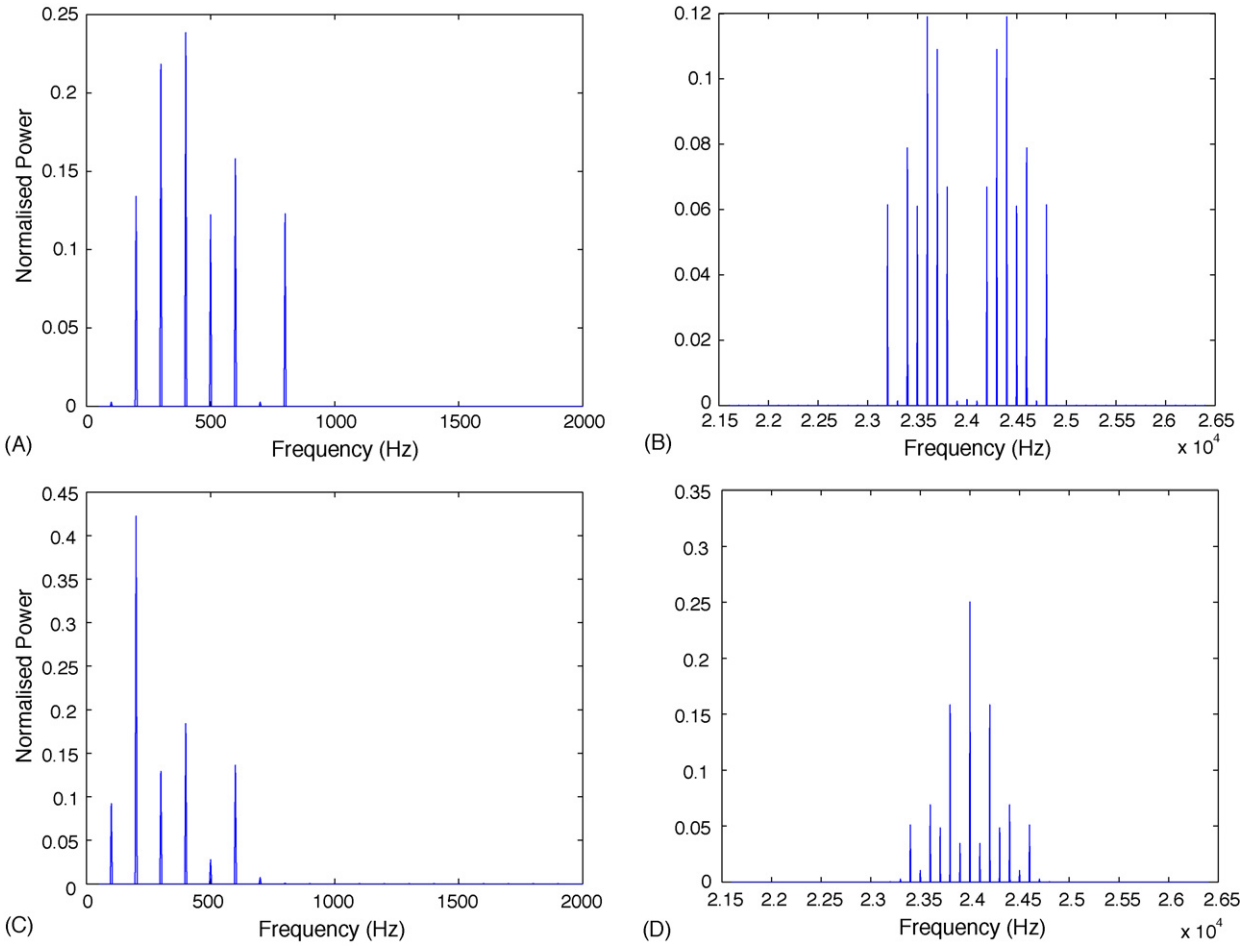

Fig. 6. Fourier transform spectral analysis of the implementation of the amplitude modulation alone shows distribution of power at multiples of 100 Hz for lactose (A) and maltodextrin (C) and when applied to a carrier frequency of 24 kHz for lactose (B) and maltodextrin (D). The bandwidth and relative amplitudes of these signals are determined from the frequencies from the rotating drum.

Appendix A. Signal analysis

A method used to determine a distribution of times between avalanches was described in the main text. A histogram plot of these distributions was used to determine the most frequently occurring avalanche times which are then inverted to provide frequencies, $f_1, \ldots, f_n$. One cycle of a sinusoid with these frequencies was generated discretely using MATLAB. All frequencies were normalized to the lowest frequency f_1. Typically, a phase shift was used to space the sinusoids based on the number of frequencies, i.e. if four frequencies were chosen the phase shifts were 0, $\pi/4$, $\pi/2$ and $3\pi/4$. These sinusoids were multiplied together (convolved). To create the vibration signal, the convolved sinusoids were stored in a function generator and applied as an amplitude modulation (AM) to a higher frequency carrier signal. The AM was repeated at 10 ms intervals, this means that the normalized frequencies were normalized to 100 Hz since one cycle of f_1 was the normalization frequency.

Fourier analysis of the AM carrier signal sheds more light on the mechanism of action. Fourier analysis is a means of taking a complex signal and representing it as a sum of sinusoids. Each sinusoid has a characteristic amplitude determined by its contribution to the signal. A Fourier transform power spectrum shows the relative contributions of the individual frequencies to the composite signal. The Fourier transform power spectrum of the AM vibration frequencies shown in Fig. 3 is presented in Fig. 6. A carrier frequency at resonance for the actuator provides the primary fluidization. As described above, the AM is repeated at 100 Hz. When the powder specific frequencies are shifted to modify the carrier and repeated at 100 Hz, power in the vibrational signal occurs at integer multiples of 100 Hz increments around the central carrier frequency. Heights of the peaks in the power spectrum are determined by the frequencies from the rotating drum characterization. The bandwidth (spread) around the carrier is directly correlated to the breadth of the avalanche distribution. Thus, a more variable avalanche distribution results in a wider bandwidth vibration signal.

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