

Method to Evaluate the Dustiness of Pharmaceutical Powders

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The trend among pharmaceutical companies to develop selective drugs of high potency has pushed the industry to consider the potential of each hazardous ingredient to become airborne. Dustiness issues are not unique to the pharmaceutical industry, but are relevant to any industry where powdered materials are mixed, transferred and handled. Interest in dustiness is also driven by concerns for worker health, the potential for plant explosions and the prevention of product loss. Unlike other industries, the pharmaceutical industry is limited by the milligram quantity of powdered material available for testing during product development. These needs have led to the development of a bench-top dustiness tester that requires only 10 mg of powder and fully contains the generated aerosol. The powder is dispersed within a 5.7 liter glass chamber that contains a respirable mass sampler and a closed-face sampler to quantify the respirable and total dust that are generated with a given energy input. The tester distinguished differences in dustiness levels of five different powders. Finer powders were dustier, and the respirable dust percentage was always less than that for total dust. Four testers have been built and evaluated using pharmaceutical grade lactose. Dustiness measurements determined using all four testers were comparable. The pharmaceutical industry uses surrogates such as lactose to represent active compounds in tests that estimate the dust concentration likely to occur in a new manufacturing operation. Differences between the dustiness of the active compound and its surrogate challenge the relevance of the surrogate tests to represent true exposures in the workplace. The tester can determine the dustiness of both the active compound and its surrogate, and the resultant ratio can help to interpret dust concentrations from surrogate tests. Further, dustiness information may allow the pharmaceutical researcher to select powder formulations that present low airborne concentrations in the workplace.

Keywords: dustiness measurement; pharmaceuticals; toxic powders

INTRODUCTION

Pharmaceutical powders contain biologically active components that are soluble in moist environments and are designed to produce biological effects at very low dosages. These capabilities are beneficial to the patient but can result in undesirable effects to the worker. Such health hazards have been recognized since at least the early eighteenth century when Ramazzini noted with irony that apothecary workers often became seriously ill while 'compounding remedies that would restore others to health' (Ramazzini, 1713).

Health risks to pharmaceutical workers are complicated by new drug formulations that target specific cells, interact at the gene level and express their biological activity through altered protein synthesis (Binks, 2003). The enhanced specificity of these formulations increases their potency and emphasizes the need to protect pharmaceutical workers. During the research stage of drug development, small teams of scientists and workers involved in small batch production may be exposed to novel therapeutics (Heron and Pickering, 2003). Because these compounds are unique to one company, occupational exposure limits (OELs), threshold limit values (TLVs) and biological exposure indices (BEIs) are not available from external authorities to guide the pharmaceutical industry in limiting occupational exposures.

Historically, pharmaceutical industries have derived their own OELs for active ingredients by

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assigning exposure control limits (ECLs) based on a no-effect level for the most sensitive endpoint after considering informations such as animal studies, bioavailability and pharmacokinetic data (McHattie *et al.*, 1988; Sargent and Kirk, 1988; Agius, 1989). Difficulties in identifying an unambiguous no-effect level on which to base an ECL for these formulations have led the industry to develop a performance-based approach and to set exposure limits based on engineering and containment principles referred to as 'control bands' (Naumann *et al.*, 1996; Heidel, 2001; Binks, 2003). Performance-based ECLs provide a systematic approach that involves assigning pharmaceutical active ingredients to one of five control bands based on their potency, pharmacological and toxicological effects (Heidel, 2001). Each control band corresponds to certain facility and process containment strategies that are known to provide exposure control sufficient to protect the worker (Heidel, 2001). In addition to the exposure limits, highly sensitive analytical methods are needed to measure workplace concentrations. Without this information, pharmaceutical industries must rely upon surrogates or existing monitoring data for other compounds to represent workplace exposures to new formulations.

Although toxicological effects are important to consider when establishing exposure controls, factors associated with the material may also affect exposure and should be considered. For example, physical properties will affect material dispersion. If the compound is a liquid and vapor inhalation is a concern, then volatility is important; volatility relates directly to vapor pressure which can be predicted using well-established theory.

If the compound is a powder and dust inhalation is a concern, then dustiness is important. Dustiness can be defined as the tendency of a powder to form an aerosol after it receives a given energy input. Powder dustiness depends on many factors that affect interparticle binding forces. These factors involve the size and shape of the powder particles, the powder moisture content and the powder surface chemistry. Even recent history is important as powders that have been compressed can be more cohesive than uncompressed powders, and powders that have been dried to reach a certain moisture content may be more cohesive than those with the same moisture content that have not been dried (Plinke *et al.*, 1994a). Because the factors that affect interparticle binding forces are complex, dustiness cannot be predicted reliably using theory and must be measured.

Concern arises when pharmaceutical powders are processed using operations that impart energy such as mixing and grinding. The ability to measure dustiness could allow the option to select or formulate powders that generate less dust. Further, the ability to predict dustiness could allow better interpretation of processing tests that use a surrogate such as lactose,

whose dustiness may differ from that of the active compound it represents.

Hamelmann and Schmidt (2004) note that more than 65 devices have been described to measure the dustiness of powders. These devices generally employ one of four methods to generate separation forces between the particles in the powder and make a dust. These methods include mechanical dispersion such as vibration or use of a rotating drum with baffles (Stauber and Beutel, 1984; British Occupational Hygiene Society, 1985), gravity dispersion such as a drop test (Cowherd *et al.*, 1989; Plinke *et al.*, 1991; Cawley and Leith, 1993), gas dispersion in which a pulse of gas suspends the test material in a turbulent flow or fluidized bed (Schofield *et al.*, 1979) and a resuspension chamber that simulates a continuous dumping operation (Visser, 1992; Hamelmann and Schmidt, 2003).

The goal of all these methods is to produce results that relate the mass of dust produced to the mass of the original powder. Some of these devices are applicable to one type of material (e.g. coal, dyes, pigments and fillers) or to one specific application (e.g. dumping operations); some devices have been tested with several types of powders and a few have been recommended as a standard method for specific industries (e.g. agriculture; Pujara and Kildsig, 2001). However, none can be used with most pharmaceutical powders because they all require, at a minimum, many grams of powder to test. Further, some devices have the potential to expose the operator to the powder or to the dust generated in the test.

The objective of this work was to develop a method to determine the dustiness of pharmaceutical powders to predict potential exposures to workers. The test device should use <50 mg of powder, contain the generated aerosol, measure something related to exposure, be quick and easy to use, and provide reproducible results.

METHODS

The dustiness tester developed to meet these objectives is shown in Fig. 1. It employs a 5.7 liter (1.5 gallon) wide-mouth glass jar into which the dust is generated. Two clamps keep an aluminum header plate sealed tightly against the jar mouth.

Dust is injected into the jar through a nozzle that consists of a stainless steel tube (10 cm long, 0.44 cm inside diameter) bent at 90° angle, an attached funnel with a removable cap and a smaller secondary tube. The funnel measures 1.0 cm in length, 1.4 cm in diameter tapering to 0.44 cm and is attached to one end of the primary tube. The exterior of the funnel holds an O-ring so that a cap with a central 0.11 cm hole can seal the contents of the funnel. To help empty the funnel, a secondary stainless steel tube 3 cm long and 0.19 cm in outside diameter is attached

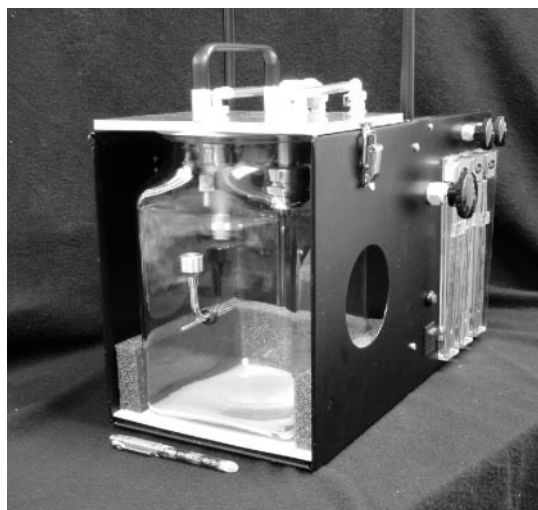
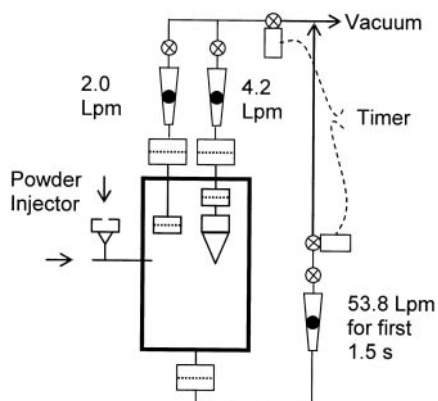


Fig. 1. Drawing and photograph of the UNC dustiness tester designed for evaluating the dustiness of pharmaceutical powders.

to the primary tube at the base of the right angle. The delivery end of the injection nozzle is inserted through an O-ring in a 5.0 mm hole centered in one side of the glass jar. Dry powder (5 ± 0.1 mg) is then weighed and placed in the funnel, and the funnel cap is attached. Although the nozzle was not electrically grounded in the present work, it could be grounded if particle charging is a problem. Air is drawn from the jar at 60 l min^{-1} for 1.5 s; replacement air passes through the injection nozzle and disperses the powder into the jar. The 60 l min^{-1} is composed of 6.2 l min^{-1} through the samplers as described below, and 53.8 l min^{-1} through an auxiliary extraction port. Although the moisture content of the dispersed powder is probably an important determinant of its dustiness, the humidity of the dispersing air is probably unimportant because the air and powder are in close contact for only 1.5 s.

Two devices sample the resultant aerosol: (i) a respirable mass cyclone (BGI, Inc., Waltham, MA, USA) followed by a filter cassette that collects the respirable dust, and (ii) either an open-face or a

closed-face filter cassette that collects the total suspended dust. Both samplers are electrically grounded to the header plate and the inlets to both are vertically aligned in the jar. The respirable dust sampler and the total dust sampler operate for 4 min at flows of 4.2 and 2.0 l min^{-1} , respectively, beginning when the powder is dispersed. Thus, the total volume of air sampled over 4 min provides more than four air changes to the jar. To increase sensitivity, the cycle of injection and sampling is then repeated with an additional 5 mg of powder so that 10 mg of powder are dispersed in all.

HEPA capsules (Whatman Inc., Clifton, NJ, USA), located immediately downstream of both the respirable mass sampler and the total dust sampler, collect any dust that accidentally bypasses the filters used for sample collection. From these capsules, air passes through calibrated flowmeters (Dwyer, Michigan City, IN, USA) and needle valves to a vacuum source.

At 4.2 l min^{-1} , the performance of the respirable mass cyclone conforms to the US and European respirable dust curve which has a 50% cut point at $4 \mu\text{m}$ (Kenny and Gussman, 1997). A closed-face Slaton cassette (BGI, Inc.), made from nickel-plated aluminum, is used downstream of the cyclone to collect respirable dust; either an open-face or a closed-face Slaton cassette is used alone to sample for total dust. Both cassettes hold 37 mm PTFE filters with $2 \mu\text{m}$ pore size (SKC Inc., Eighty Four, PA, USA) that are supported by stainless steel screens (BGI, Inc.). The filters are equilibrated to room conditions before sampling. The sampling times are controlled by two time-delay relay switches (Dayton Electrical Manf. Co., Niles, IL, USA).

After sampling, the header plate is unclamped and removed from the jar. The filters are removed from the two samplers and re-weighed immediately on a microbalance (Mettler MT-5, Mettler-Toledo, Inc., Columbus, OH, USA). Two blank filters are carried for each run.

To determine the percentage of respirable aerosol, the mass of dust collected on the filter behind the respirable mass cyclone corrected by the average of the two blanks, $M_{\text{respirable filter}}$, is divided by the total amount of material dispersed, $M_{\text{total dispersed}}$, and then adjusted to account for the fraction of total sampling flow drawn through the respirable mass sampler.

$$\begin{aligned} \% \text{Respirable} &= \frac{M_{\text{respirable filter}}}{M_{\text{total dispersed}}} \\ &\times \frac{\text{total sampling flow}}{\text{respirable mass flow}} \times 100 \\ &= \frac{M_{\text{respirable filter}}}{M_{\text{total dispersed}}} \times \frac{6.2}{4.2} \times 100 \quad (1) \end{aligned}$$

Similarly, the percentage of total dust aerosol is determined from the mass on the open-face or

closed-face sampler corrected by the average of two blanks, $M_{\text{total dust filter}}$, divided by the total amount of material dispersed, and adjusted to account for the fraction of total sampling flow that passed through the total mass sampler.

$$\begin{aligned} \% \text{Total dust} &= \frac{M_{\text{total dust filter}}}{M_{\text{total dispersed}}} \\ &\times \frac{\text{total sampling flow}}{\text{total mass flow}} \times 100 \\ &= \frac{M_{\text{total dust filter}}}{M_{\text{total dispersed}}} \times \frac{6.2}{2.0} \times 100 \quad (2) \end{aligned}$$

Following completion of a test, the glass jar with its sampling components are easily disengaged and removed for cleaning. Decontamination of the jar, cyclones, cassettes, dispersion nozzle and resulting effluent should be handled in accordance with the standard protocol for the test material. All components are compatible with oven drying.

Experiments

Experiments were conducted using five test powders to determine if the tester could distinguish differences in dustiness among these powders and to determine whether an open-face or closed-face sampler would best characterize generation of total dust. Titanium dioxide and glass beads were each classified into two aerodynamic size fractions, 5–25 μm and >25 μm , using a Donaldson Accucut classifier (Plinke *et al.*, 1994b). Lactose, supplied by a Pfizer plant in Holland, MI, USA, was used as the fifth test powder. The size-classified materials were kept in

desiccators prior to use; the sample of pharmaceutical lactose was not desiccated. Eighteen dustiness tests were conducted with each of the five powders: nine using the respirable mass sampler and an open-face sampler, and nine with the respirable mass sampler and a closed-face sampler.

Once the best method (i.e. open-face or closed-face sampler) to measure total dust was determined, four dustiness testers were built according to these specifications. Twelve tests were then conducted with each of the four devices in random order using lactose as a test powder to determine reproducibility of the method and variability from tester to tester. Analysis of variance (ANOVA) and paired-difference *t*-tests were performed to determine the level of significance in the data.

RESULTS

Tests with five test powders

Results of the tests to characterize the percentage of respirable and total dust generated by dispersion of the five powders are shown in Fig. 2; the error bars in this figure represent 1 SD. Overall, Fig. 2 shows that dustiness measurements determined by this test method had good precision and that they differed substantially and significantly from powder to powder ($P < 0.001$). Titanium dioxide proved to be somewhat dustier than glass beads ($P < 0.001$), and for respirable as well as total dust ($P < 0.001$). As expected, the finer grades of both test powders were dustier than the coarser ($P < 0.001$). Logarithms of the data were taken before statistical analyses.

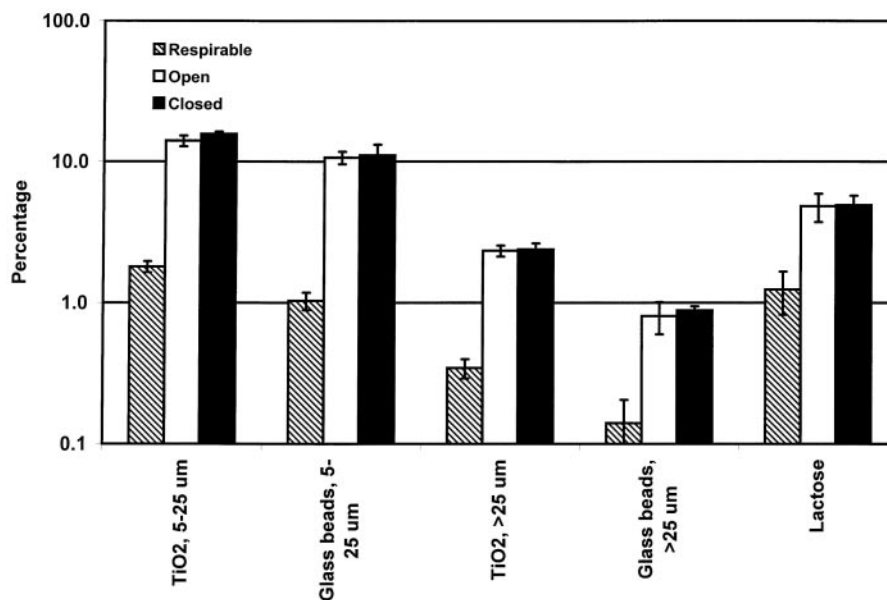


Fig. 2. Dustiness of five powders expressed as percentage respirable and as percentage total dust where total dust is determined using both open-face and closed-face samplers. Error bars represent 1 SD.

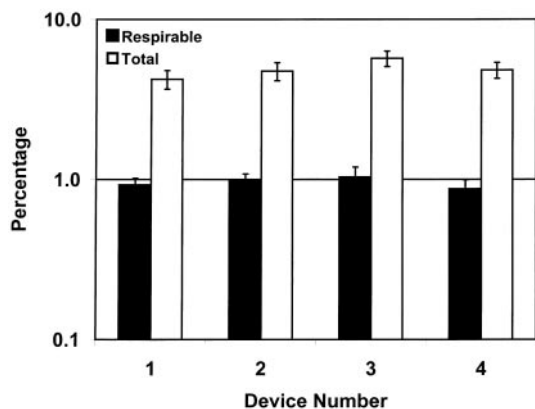


Fig. 3. The percentages of respirable and total dust determined using each of four dustiness testers. The test powder was pharmaceutical grade lactose. Error bars represent 1 SD.

The percentage of dust collected by the respirable mass sampler was always less than that collected by the total dust sampling method. For a particular powder, the difference between the respirable and the total mass measurements gives some insight into the size distribution of the aerosol produced. If the dust is all fine enough to be respirable, then results from the respirable mass and total mass measurements would be the same; however, if the dust is relatively coarse then the respirable mass results would be less than the total mass results.

For all five powders, the results for open-face and closed-face sampling were similar and were not significantly different ($P = 0.232$). Because of the potential to dislodge collected dust from the surface of an open-faced sampler, the closed-face sampler was chosen as the total dust sampler of choice and was used in all further tests.

Evaluation of the four dustiness testers

Figure 3 presents results of tests to compare the four dustiness testers; the error bars in this figure represent 1 SD for the variability in the tests. For these evaluations, the test powder was pharmaceutical grade lactose. The figure shows that the four testers each measured comparable percentages of respirable dust and total dust as determined using a closed-face sampler.

DISCUSSION

Because dustiness is measured empirically and no standard method has been established to characterize it, results from any dustiness tester will depend in part on the inherent characteristics of the test device. Thus, the most practical approach for characterizing dustiness with a given device involves dividing a measurement for a given powder by the corresponding measurement of a reference powder. The resulting

ratio can then be used to estimate the extent to which the new powder will be more or less dusty than the reference. With this information, informed judgments may be made about dust exposures that can be expected, and about the level of dust control required, when the new powder is used. Data for the dustiness of lactose given in Figs 2 and 3 show good reproducibility and suggest that lactose might be used as an appropriate reference compound in the pharmaceutical industry.

Routine tests with lactose might also be used for quality assurance. A test with standard lactose might be performed at the same time as each test of a new powder, both to facilitate calculation of a dustiness ratio and to be sure that lactose results remain consistent. In this way, the relative dustiness of the new powder can be determined and the continued efficacy of the test method and device can both be assured.

CONCLUSIONS

No dustiness tester designed for pharmaceutical work has been reported in the literature previously. The present device fits on a bench-top, requires only 10 mg of powder per test, fully contains the generated dust and is relatively easy to use. Each test characterizes the dustiness of the test powder in terms of (i) the respirable dust and (ii) the total suspended dust; differences between these values give insight into the dust size distribution. The relative dustiness of a new powder can be characterized by taking the ratio of dustiness for that powder to the dustiness of a reference powder such as pharmaceutical grade lactose.

Results presented here show that this tester seems to work as intended. It could distinguish an 18-fold difference in dustiness among five test powders. The closed-face sampling method yielded similar concentrations of total dust compared to the open-face method. Closed-face sampling is preferred because it seems more likely to preserve sample integrity. Measurements of respirable dust and total dust from four identical testers were reproducible within and between the devices.

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