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Establishment of powder dustiness evaluation method by dustmeter with small amount of pharmaceutical ingredients

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ABSTRACT

The ratio of high potent materials in the new chemical entities has recently increased in the pharmaceutical industry. Generally, most of them are highly hazardous, but there is little toxicity information about the active pharmaceutical ingredients in the early development period. Even if their handling amount is quite small, the dustiness of high potent powder generated in the manufacturing process has an important impact on worker health; thus, it is important to understand the powder dustiness.

The purpose of this study was to establish a method to evaluate the powder dustiness by the consumption of small amount of samples. The optimized measurement conditions for a commercially available dustmeter were confirmed using lactose monohydrate and naproxen sodium.

The optimized test conditions were determined: the dustmeter mode, the flow rate, the drum rotation speed, the total measurement time, and sample loaded weight were type I mode, 4 L/min, 10 rpm, 1 min and 1–10 g, respectively. The setup conditions of the dustmeter are considerably valuable to pharmaceutical industries, especially, at the early development stage and especially for expensive materials, because the amount of air-borne dust can be evaluated with accuracy by the consumption of small amount of samples.

1. Introduction

The ratio of high potent materials in the new chemical entities has increased recently, and a variety of research and development regarding the potent materials as typified by steroidal drugs and anticancer drugs are moving forward in the pharmaceutical industry. Generally, most of these potent materials are highly hazardous, but there is little toxicity information about the active pharmaceutical ingredients (APIs) in the early development stage. The dustiness of high potent powder generated in the manufacturing process has an important impact on worker health even if their handling amount is quite small.

It is necessary to use dedicated or containment equipments for the handling of the potent materials for the purpose of the prevention of cross-contamination and exposure to operators (Gurney-Read and Koch, 2002). In Europe and the United States, the review of containment restrictions or the publication of the baseline guide (ISPE Good Practice Guide, 2012) has become more active in particular.

In the International Society for Pharmaceutical Engineering Inc. (ISPE) baseline guide, lactose monohydrate, naproxen sodium, D-mannitol, acetaminophen, insulin, riboflavin, and sucrose are introduced as industry accepted test materials "surrogates" to evaluate the containment capability of equipments. For evaluating of the performance of containment equipments, safe surrogates are often used in place of high potent materials, and the exposure concentration of the surrogate collected on the filter is evaluated during the simulation with the surrogate. From the evaluation results, the air conditions and process room pressure control are verified to contain the dust of the high potent powder more effectively (Yamagami et al., 2002), and an appropriate personal protect equipment (PPE) like an air-supplied respirator (Raymond, 2008) or an air-fed protective ensemble (Edwards et al., 2009; Tesch et al., 2009) is used for the purpose of ensuring safety and reliability of operators as necessary.

In the early development stage, however, there are insufficient amounts of potent API to confirm the containment capability because the API is quite expensive and the amount of API is small. So, it is necessary to understand the degree of dustiness of the

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potent API in small amounts. The proposal of the laborsaving estimation method of the exposure risk may be valuable to pharmaceutical industries that handle extremely high potent powders.

The methods of preventing dust generation are of increasing importance in handling of powders, due to the growing emphasis on health and safety by the Food and Drug Administration. Powder dustiness is widely investigated (Wells and Alexander, 1978; Bach and Schmidt, 2008; Petavratzi et al., 2007; Plinke et al., 1992), but dustiness studies on pharmaceutical powders are relatively sparse in the literature (Boundy et al., 2006; Pratap, 1997), and there is little effective way to evaluate the dustiness easily in small amounts of sample (O'Shaughnessy et al., 2012).

Powder dustiness is defined as the tendency of a powder to emit dust during handling operations (Liden, 2006). The Heubach dustmeter, a commercially available instrument, was used to measure powder dustiness (Hamelmann and Schmidt, 2004; Plinke et al., 1992), but it is reported that the dustmeter test parameters should be carefully controlled to have reproducible powder dustiness evaluation (Heitbrink, 1990). Lactose monohydrate and naproxen sodium were selected for this study, and these powder dustiness were evaluated in appropriate conditions.

The objective of this work was to establish a method to evaluate the powder dustiness by the consumption of small amount of samples to be able to estimate the powder dispersion risk of high potent materials which characteristics are poorly informed from the early development stage. The optimized measurement conditions for Heubach dustmeter were confirmed using lactose monohydrate and naproxen sodium.

2. Materials and methods

2.1. Materials

Lactose monohydrate complied with all ICH regions (Pharmatose® 100M and Pharmatose® 200M from DMV-Fonterra Excipients, Japan) and naproxen sodium from Dr. Reddy's, India, were purchased as the sample of powder dustiness measurement.

2.2. Methods

2.2.1. Powder property measurement

Powder properties of all materials used were evaluated. Imaging analyses of the materials were conducted using an automated particle imaging system Morphologi G3 (Malvern Instruments, UK) for the measurement of particle size distribution. The standard operation procedure details used in the analyses are shown in Table 1. The volume distribution circle equivalent diameters (10%, 50% and 90%) were compared among the materials.

Loose bulk densities were measured with a Powder Tester PT-R (Hosokawa Micron, Japan). The sample volume, the vibration level, and the vibration time were 50 mL, 3 and 30 s, respectively. Tapped bulk densities were also measured with the same equipment and the same sample volume. Tapping number was 180 times. Compressibilities were calculated from both densities using the following Eq. (1):

$$\text{Compressibility}(\%) = \frac{T - A}{T} \times 100 \quad (1)$$

where T refers to the tapped bulk density and A refers to the loose bulk density.

2.2.2. Aerosol concentration monitoring

To evaluate actual powder dustiness in weighing operation of Pharmatose® 200M and naproxen sodium, a preliminary study was conducted in a mc6 fume hood BP-F182 (ITOKI, Japan) and the aerosol concentration of each compound was monitored using a handheld aerosol monitor DustTrak™ DRX 8534 (TSI Incorporated, the United State).

The 10 mL glass beaker was set on a magnetic stirrer HSD-6 (As One Corporation, Japan) after the sample of approximately 5 g was weighed in the glass beaker and a Tygon® sampling tube attached to the sample inlet nozzle of the aerosol monitor was set upper center of the glass beaker. The aerosol monitor was started after a few seconds from the initiation of rotating. The pump run time, the test interval, and the flow rate were set at 1 min, 1 s and 3 L/min, respectively. After the measurement was finished, the total aerosol concentration recorded at the individual data points was compared between Pharmatose® 200M and naproxen sodium. Total three times of measurement were conducted. The area under the average aerosol concentration approximated by trapezoidal rule was calculated using the following Eq. (2) and compared between Pharmatose® 200M and naproxen sodium.

$$S(\text{mg/m}^3 \times \text{s}) = \frac{C_1}{2} + \sum_{n=1}^{59}\left(\frac{C_n + C_{n+1}}{2}\right) \quad (2)$$

where S, C_1, and C_n refer to the area under the curve, the aerosol concentration after 1 s and the aerosol concentration after n s, respectively.

Table 1
Standard operation procedure details used in the image analysis by Morphologi G3.

Measurement control	Minimum number of particles: 50,000
Sample carrier	Sample dispersion unit (SDU) glass plate (180 × 110 mm)
SDU settings	Foil type: 25 μm foil
	Injection pressure: 5.0 bar
	Injection time: 10 ms
	Setting time: 180 s
Compensation for tilt	Enabled
Illumination settings	Diascopic (bottom light)
Automatic light calibration	Calibration intensity: 80.00
	Intensity tolerance: 0.20
Optics selection	5 x (6.5–420 μm)
Overlap	40.00%
Focus	Manual
Threshold	105 Grey scale
Scan area	Circular-radius 42.00 mm
Trash size	Minimum number of pixels: 10
Filters	Solidity: less than 0.9 (to remove images of touching particles)
	Pixel area: less than 100 (to remove images with limited shape information)

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