Powder Technology 209 (2011) 152–157

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Short Communication

PowderPicking: An inexpensive, manual, medium-throughput method for powder dispensing

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ARTICLE INFO

Article history:
Received 26 February 2010
Received in revised form 7 February 2011
Accepted 11 February 2011
Available online 18 February 2011

Keywords:
Powder dispensing
Volumetric
Medium throughput screening
Preformulation
Solids
Pharmaceuticals

ABSTRACT

Many applications in late discovery/early stage formulation require repetitive accurate dispensing of solid powders. This is often performed manually using spatula and micro balance since existing automated dispensing systems are too expensive or the required starting mass is not available. In this study, commercially available Gilson MICROMAN® positive displacement pipettes with disposable capillary piston tips were used for manual, volumetric dispensing of solid powders. Tips were filled with powder by pushing them several times into the powder (PowderPicking) and powder was expelled with the push button into target vessels. Results obtained with 10 solid drug and excipient powders with largely different size and shape indicate that the technique can be employed for repetitive powder dispensing in the 0.6 mg to 25 mg range with acceptable accuracy (average %CV in delivered mass for all dispenses was 6%). The technique is easy to calibrate and perform, rapid, inexpensive, and compound-saving, adapted to the daily demands in laboratories, and can help to close the gap for powder dispensing between labor-intense, manual weighing and expensive, high-end automated systems.

1. Introduction

The early measurement of distinct physicochemical properties influencing ADMET characteristics has become standard in most discovery and development screening programs [1,2]. The most common properties addressed in these screens are solubility, permeability, lipohilicity and metabolic stability since they are regarded as crucial for reducing attrition rates of compounds in later stages. Most pharmaceutical companies progressively automate theses assays and adapt them to high throughput (HT) technologies to cope with the increasing number of new chemical entities coming from combinatorial chemistry. The need to distribute compounds and solvents is common to all HT assays. Since the handling of liquids by robotic systems is usually straight forward, many HT assays in early phases are run with compounds predissolved in an organic solvent, typically in DMSO [3]. However, for a number of assays this solvent-based approach cannot be used since the original, unchanged solid is required as starting material. Typical examples are polymorph and cocrystal screening [4], salt selection, thermodynamic solubility testing [5,6], compatibility studies [7] or formulation development. In many companies these activities are now shifted to earlier stages to address development related issues early on and to focus time and resources on the potentially most successful candidates. Consequently, there is an increasing demand for simple, rapid solid compound dispensing technologies in these stages that can handle diverse sets of compounds that are available only in limited amounts, often less than 100 mg.

Manual dispensing of compounds with a micro-balance is certainly still an option for handling only a few samples. However, this is too tedious and time-consuming if larger numbers of solid samples need to be distributed, for example for microplate-based assays. Therefore, a number of companies offer automated powder dispensing systems with different technologies most of them having a gravimetric (weighing) component. Solid is transported by different mechanisms (e.g., volumetric, Archimedes screw, tapping, shaking) from a storage container to the target vessel and the increase in weight in the destination vessel or weight-loss in the storage container is monitored (e.g., Zinser Analytic, Symix. Chemspeed) [3,8]. Another principle is the use of statically-charged collector pins for powder distribution (Innovative Engineering and Design) [9]. None of these techniques is universal and applicable to all requirements. If not focused exclusively on HT screening and continuous use, many of the automated powder dispensing systems are often overkill for the intended application, are too difficult to calibrate, require too much compound and/or need an investment that is too high to justify the purchase. As a consequence, end-users constantly seek for alternatives for low-to-medium throughput powder dispensing methods that do not cost a fortune and serve the purpose. Recent examples are the distribution of compounds to 96-well plates with a Titan resin

Abbreviations: HTS, high throughput screening.

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doi:10.1016/j.powtec.2011.02.014

loader [7] or compound distribution as a suspension in a non-solvent [5]. This Technical Note describes a manual, rapid, volumetric, low-cost distribution method for powders with equipment that is often already available in pharmaceutical laboratories.

2. Materials and methods

2.1. Materials

Glucose, Sulfinpyrazone, Phenylbutazone, Furosemide, Glibenclamide, Carboxymethyl-cellulose sodium salt (CMC-Na), Sulfaphenazole, L-Leucine, and Pyrimethamine were purchased from Sigma-Aldrich (Buchs, Switzerland). Sodium chloride was from Merck (Darmstadt, Germany). Microscopic pictures of the different powders are presented in Fig. 1. Gilson MICROMAN® positive displacement pipettes models M10, M25, M50, and M100 and corresponding disposable capillary piston tips CP10, CP25, CP50, and CP100 (CP10 and CP100 pre-assembled racked) were from Gilson, Inc (Middleton, US). 1.5 ml polypropylene Safe-Lock® microcentrifugation tubes were purchased from Eppendorf AG (Hamburg, Germany). The balance was a model AT201 from Mettler-Toledo GmbH (Greifensee, Switzerland).

2.2. Powder properties

The bulk and tapped density of each powder was determined using Stampfvolumeter model STAV 2003 (JEL, Germany). The test conditions according to USP 24-NF 19 were modified in respect of the limited availability of some powders [10]. Ten milliliter graduated cylinders (readable to 0.1 ml) were filled with powder and the weight of 10 ml powder (poured volume) was recorded. After tapping 1250 times, the powder volume (tapped volume) was recorded and poured and tapped density was calculated from the weight of the powder divided by the volume of the powder. Carr's index (CI) and Hausner ratio (H) were calculated according to the following equations [11,12]:

$$CI(\%) = 100\ (\text{tapped density} - \text{poured density})\ /\ \text{tapped density}$$

$$H = \text{poured volume}\ /\ \text{tapped volume}$$

Measured and calculated powder properties and the predicted flowability are summarized in Table 1.

2.3. PowderPicking

About one-third of a 1.5 ml Safe-Lock® Eppendorf tube was filled with powder. The tube was closed and tapped on a solid surface to slightly compact the powder in the lower part of the tube (Fig. 2A). A disposable capillary piston tip (Fig. 2B left) was mounted to a Gilson MICROMAN® positive displacement pipette, the volume adjusted to the desired volume and then the tip was rapidly pushed 10–15-times into the powder bed without pressing the push-button of the pipette. This staccato-like insertion ("picking") into the powder (PowderPicking) pressed powder particles into the tip until the cylindrical volume of the disposable tip formed by the capillary and the piston was filled (Fig. 2B right). The tip was withdrawn from the powder and powder particles sticking to the outside of the tip were removed with a paper tissue. The powder collected inside the tip was then pushed out of the capillary onto a piece of paper in a balance by pressing the push button of the pipette and the weight of the resulting powder pellet (Fig. 2C) was recorded. PowderPicking was repeated 10-times for each powder and each tip size/adjusted volume combination and the average amount of transferred powder, the standard deviation (SD), and the percent coefficient of variation (%CV) was calculated (Table 2).

The capillary piston tips CP10, CP25, and CP50 were used as delivered for powder transfer. In contrast, the opening of the 100 µl Gilson capillary piston tip (CP100) is narrower than its upper part and hence a small part of the tip opening had to be cut-off with a scalpel (at the position where the conical part of the tip opening starts) to obtain a wider tip opening and a tip cylinder with a constant diameter from top to bottom. Electrostatic powders, fine, flyaway, and powders significantly sticking to the outside of the tip (e.g. Sulfaphenazole) were difficult to handle with the originally used 1.5 ml Safe-Lock® Eppendorf tubes (Fig. 2A). Their wide opening allowed unrestricted release of dust when the tip was pushed into the powder and resulted in larger losses of powder. Therefore, they were replaced by 1.8 ml Waters HPLC Screw top vials with cap and pre-slit PTFE/Silicone septa (Waters GmbH, Eschborn, Germany) (Fig. 2A insert, left hand side) or by 1 ml glass vials (Schmidlin Labor & Service AG, Neuheim, Switzerland) with pre-slit SepraSeal™ caps (Thermo Fisher Scientific, Hudson, US) (Fig. 2A insert, right hand side). In this set-up, the capillary piston tip was first pushed through the seal and then the powder was collected as described before. This significantly reduced raised dust and powder losses and stripped of most of the powder particles sticking to the outside of the tip when the tip was pulled out of the vial.

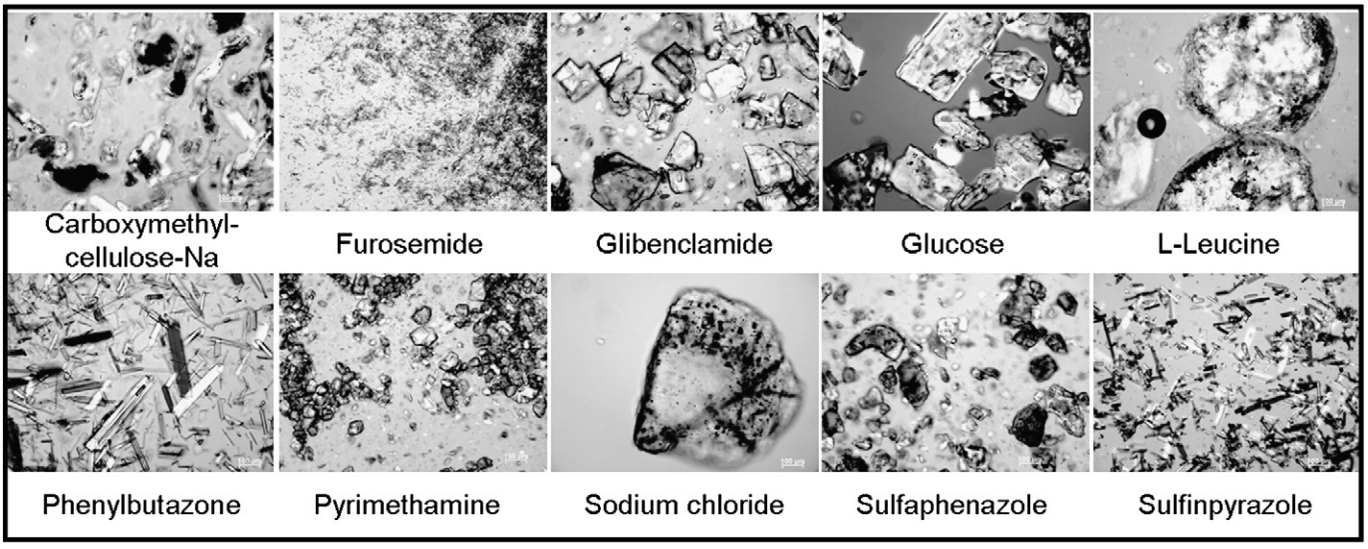

Fig. 1. Microscopic pictures of powders studied (200× magnification).