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Original Research Paper

Mixing effectiveness of a new pneumatic PTS-Batchmixer® with an in-line sampling device

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ABSTRACT

The aim of this paper is to define the range of utilisation of a new pneumatic pilot plant mixer. We report the validation of the mixing performances and efficiency for a binary mixture of cohesive powders, lactose monohydrate as excipient and salicylic acid as tracer. We studied the effect of the fill levels (25%, 50% and 90%) and tracer concentrations (0.01%, 0.1%, 1% and 10% w/w) obtained without pre-blending on the blend homogeneity (relative standard deviation) and the mixing time. We also investigated the effect of the sampling size (30 g vs 1 g) on the stochastic homogeneity of 2% (w/w) salicylic acid blends with an automatic sampling device.

The fill level has only a slight effect on the mixing performances of the mixer with 30 g samples. Moreover the different target concentrations were obtained in a single blending step in less than 6 min. Most of the related RSD were beneath 7%. A smaller sample size of 1 g showed a greater variation in the limits of ±10% of the target value.

This mixer is a good alternative to most batch mixers used at the time in the pharmaceutical industry. Nevertheless, as assumed, we confirmed the crucial impact of the scale of scrutiny.

1. Introduction

In pharmaceutical formulations as well as in the cosmetic, chemical or food industry, the need for a homogenous mixture (statistically dispersed) is critical. The main problems encountered until now were unsuited sampling procedures (off-line, thief probe), which could not guarantee the accurate concentration, especially for very small product units like pharmaceutical pills, which represent about 80% of the market [1–3]. Are we sure to find the exact same concentration in each tablet, as declared on the notice? [4]. This problem is even more acute for high [5] or very high dilutions, because according to the FDA guidance for industry on powder blends [6], each individual sample should fall within the range of 75–125% of target concentration, which is not very restrictive.

The quality control of a blend is characterized by a statistical approach, comparing the actual homogeneity with the ideal homogeneity (stochastic ordering of the grain). The result is influenced by the mixing mechanisms occurring in the mixer (convection, diffusion, shearing, segregation) in relation with the formulation of the mix. In the pharmaceutical industry, the quality of a blend must fulfill the GMP procedures defined by the EU Pharmacopoeia or by the FDA [6]. Berthiaux et al. [7] discussed and summarized this problem perfectly.

Considering the wide choice of powder blenders, each of them has its own advantages and disadvantages [8–10]. Most powder mixers include mechanical moving elements, which can induce particle attrition for some applications. The efficiency of those mixers has generally been achieved only thanks to binary mixes or related blends. Moreover, very few studies are dealing with highly diluted mixes [5,11,12]. To our knowledge, even though pneumatic transport of powders is being widely used and studied in the industry [13–24] due to its gentle effect on particles (attrition, heat transfer, etc.) [17,18,24], this technology has never been directly used for mixing purposes, as it is in this paper. Our new mixer builds a link between dense phase pneumatic transport of powders and pneumatic mixing systems while minimizing the attrition phenomenon.

Sampling is a crucial operation that should guarantee a good representativeness of the sample for the whole population. The results of a mixing process are highly dependent on the sampling procedure, such as off-line and in-line sampling devices. It needs to be made sure that the results are representative of the mixing state and that there is no bias due to a bad sampling process.

Off-line methods are still commonly used, either with scoops or thief probes [3,25]. The main disadvantage of this method is the local disturbance of the mixing stage by thrusting the thief into

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the powder [3,6,26,27]. Moreover, the machine should be switched off during sampling, which could lead to segregation phenomena.

Concerning the in-line methods, two different processes are used.

Generally, the first method consists in taking the samples during the discharge of the powder. Most of the time, samples are taken at the beginning, in the middle and at the end of the process, often followed by sub-sampling. Therefore, when the target homogeneity of the mix is not achieved, Good Manufacturing Practice in the pharmaceutical industry dictates that the entire batch be destroyed if a second and less restrictive set of analysis fails. This means a loss of time and money for companies, specifically for very expensive drugs [7,28].

The second in-line sampling process takes samples during the mixing process, allowing the powder components to be mixed until the target tracer concentration is achieved, as done in this paper. The mixing time can then be optimized, which reduces the production costs.

Last but not least, another critical aspect of sampling is sample size. Most of the previous publications on this subject deal with bigger samples than the actual dose taken by the patients. In this paper, we use an in-line sampling device to pump the flowing powder directly from a circulation pipe into a glass bottle or a test tube using a MPTS® (*Mini-Powder Transfer System*) or a Powderflex®, respectively. Samples could then be taken from the moving powder at different times. These sampling devices can be used to study the effect of sample size (~30–300 g and ~0.5–5 g, respectively) on the estimation of the powder homogeneity. Thus, the scale of scrutiny can be easily adapted to the actual unit size and no sub-sampling is necessary. If we assume that the final product package will be 1 g, it is better to take samples of that size for homogeneity analysis, as this represents exactly the dose that will be sent to the tabletting machine. We can then measure the actual concentration beforehand and adjust the mixing time if needed, thus reducing the risk of throwing the whole batch away.

This paper presents the first part of a wider study, whose aim is to define the limits of use of a new pneumatic mixer, with regard to the loading rate, the efficiency and the performances to mix powders with different flowing properties, the effect of tracer concentration on the stochastic homogeneity in a single operation step and the blend stability when keeping the powder in circulation (e.g. before conditioning). The present article has a double purpose. The first one is to validate the mixing performance of a pilot PTS-Batchmixer®, using a single step mixing process for the blending of 0.01% to 10% (w/w) binary mixtures of salicylic acid and lactose monohydrate. The blend for this paper was selected for its difference in particle shape rather than particle density or particle diameter. The second purpose is to investigate the effect of the sample size (1g and 30 g) on the stochastic homogeneity of the blends according to the golden rules of sampling [1,6].

2. Experimental

2.1. Powder characterization

The characterization of bulk properties of salicylic acid (API, pharmaceutical grade USP, Ph. Eur. Rhodia Operations, Aubervilliers, France) and lactose monohydrate as excipient (Variolac 99 G800 Mesh 200, Biolac GmbH & Co. KG, Harbarnsen, Germany) was performed with the Hosokawa Powder Tester PT-N (Hosokawa Micron B.V., Doetichem, Holland). The angle of repose and the angle of fall were measured three times to determine the powder flowability and floodability, respectively. For this test, 200 ml powder (lactose or salicylic acid) were used. The angle of repose was determined by measuring the heap resulting from dropping the material through a vibrating screen and glass funnel onto a horizontal plate. The angle of fall was measured after the previous experiment by hammering a weight three times from a predetermined height and measuring the resulting new heap.

The particle size distribution was determined with a Malvern Mastersizer-S analyzer (Malvern Instruments Ltd, Worcestershire, United Kingdom). The lactose monohydrate was suspended in isopropanol and analyzed twice after rinsing the circulation pipe with water followed by isopropanol. As salicylic acid is soluble in isopropanol, it was dispersed in 0.2% v/v Tween 20 in deionized water, with some drops of octanol. To better fit to the actual particle size distribution of the components to blend, the samples were not sonicated before the measurement.

2.2. Mixing procedure

The mixing trials were carried out with a 100 l pilot pneumatic mixer (PTS-Batchmixer®, from DEC Group, Switzerland) with a theoretical mixing capacity varying between 10 l and 90 l (Fig. 1). The system has no moving or rotating mechanical parts and can operate under inert conditions and in a contained manner. This mixer is controlled via computer software that regulates the filling, the mixing, the emptying and the washing steps. The traceability of the procedure is achieved through the recording of the processing parameters.

The system comprises a main container with an integrated central deflector. A PTS® (*Powder Transfer System*) with two tangential inlets is installed on top of the container. The powders are introduced automatically into the PTS® and then circulated within the container for a predetermined period of time. A homogenous distribution of the mixture in the tank is guaranteed thanks to this deflector.

The mixing chamber is filled with powder via a pipe connected to the filling valve (Fig. 1). The powder is sucked by vacuum from a feed container into the PTS and ends in the mixing chamber. During the mixing process, both mixing pipes are used in parallel. The powder is sucked from the bottom of the mixing chamber through the pipes into the PTS and goes back into the mixing chamber. The mixing effect in the PTS® body, when the two jets of powder meet, allows increasing efficiency of the mixing process. Since the powder circulates in a dense phase mode, the particle velocity and, consequently, the heat production and the particle damage are limited. Therefore, the initial characteristics of the powder are maintained.

Different loading quantities were studied. The maximum quantity was set at 50 kg lactose. Different amounts of powder were then used with the inferior limit set at 15 kg. Some tests were also made with 10 and 5 kg, respectively, with good results, but they will not be presented here. A "sandwich" mode was used for loading the powders. This method consists in pneumatically pumping the first half of the excipient (lactose) into the mixer and then pouring the weighed salicylic acid on the remaining half before loading it the same way into the mixing chamber of the mixer. A complete mixing cycle consists of two sequences: pumping the powder into the PTS® through the two circulation pipes and then emptying the PTS® into the mixing chamber. One mixing cycle lasts about 10 s, depending on the powder properties and the "temporizations" chosen to open and close the different valves regulating the mixing process. Table 1 gives some relations between the fill level (25%, 50% and 90%), the number of mixing cycles, the number of product renewals and the mixing time. One product renewal means that the whole blending load has been put into circulation. It can be considered as equivalent to the residence time "*t*" described by Berthiaux et al. [7]. Each mixing trial was done in one step for all experiments, which means that no successive