An experimental method to measure APIs residence time distribution in the jet mill micronization process

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INTRODUCTION

Micronization by jet mill technology is a method of improving the bioavailability of poorly soluble APIs (Active Pharmaceutical Ingredient). The particle's residence time distribution (RTD) is a key factor on which the number of particle impacts depends, hence, the achievable particle size reduction and the amorphization state, the so called mechano-chemical activation (MCA). To date, just a few attempts have been made to quantify the particles RTD in jet mill micronization processes, the most relevant are:

- Direct measurement by radioactive tracers, method developed by Müller F. et al. [1] in 1996;
- Indirect measurement by means of RT's particle size dependence with probability functions, study performed by Gommeren H.J.C. et al. [2] in 1996.

The state of the art of the existent methods present some limitations, the first because of technological complexity, the second being inaccurate (based on probability functions and assumptions).

This work deals with the development and testing of a robust, safe and affordable experimental measuring technique suitable to quantify the particles mean residence time (MRT) in micronization processes. The developed method, based on phosphorescent tracer particles emitting green afterglow light, is a partial adaptation of the method developed by Harris et al. [3]. The application of the measurement system is thought for spiral jet mills, however it is applicable to any other solid-gas multi-phase flow process.

RESIDENCE TIME

Given a sample of material, which undergoes a process, the RTD is defined as the average amount of time spent by each single particle of material inside the process apparatus. The MRT measurement in short time scale systems provides vital information for system designers and operators and is critical for the process performance enhancement.

Moreover, the MRT could be used as a parameter to identify the best operating conditions to either minimize amorphization effects of API'-s, or the other way around , to obtain maximized amorphization of particles through the mechano-chemical activation (MCA) process. One of the advantages of the MCA process is the enhancement of the dissolution rate of particles which, in case of API, results in a bioavailability enhancement [4].

MEASURING PROCESS

The tracer is injected into the plant at a known time and its passage is detected at the outlet of the process. The time difference (**Δ**T) between the injection and the detection represents the residence time.

The working principle is based on the differentiation of a sample of tracer particles via luminescence, conferred to the particles by a light pulse train during the injection into the plant. The light pulse activation command can be used as reference time point since it corresponds to the tracer introduction in the process. At the outlet of the process the tracer passage is detected with three light sensitive photodiodes. The light intensity over time curve, measured by the sensors, is correlated to the tracer mass flow rate. Thus, the **Δ**T between the injection and the luminosity peak measured corresponds to the MRT.

The advantages of this technique are:

(i) Immediate activation of the tracer with a light pulse with no disturbance to the process;

(ii) Detection of the tracer online by light sensitive photodiodes with no disturbance to the process;

(iii) Wide range of phosphorescent tracers with different chemical and physical properties;

(iv) Low cost, compared with radioactive techniques;

(v) Tracer undergoes micronization process.

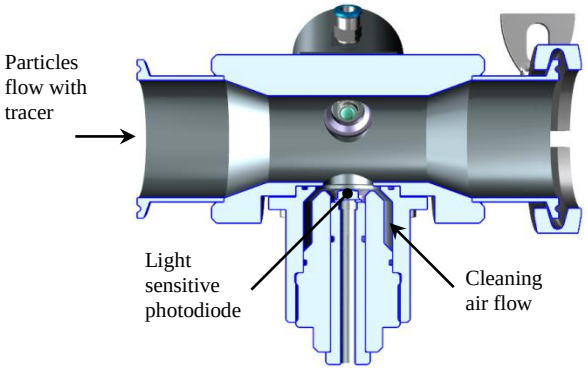

Figure 1. Pipeline section with the sensor detection system

MATERIAL AND METHODS

Tests were performed in a prototype pipeline with a diameter of 35mm, reproducing the outlet pipeline of a MC-150 spiral jet mill (Micromacinazione SA, Switzerland). A sample of 1g of phosphorescent tracer was excited for 1s and injected immediately in the pipeline. The sample was accelerated up to a velocity of 4m/s in proximity to the detection zone.

Detection system

The detection system (Figure 1) is composed of three photodiodes (Vishay model BPW-21R) radially oriented on a support with an interval of 120°. Those are semiconductor devices that absorb photons to produce an electrical current. A trans-impedance amplifier based on an operational amplifier (Analog devices model AD823A) converts and amplifies the current signal to a voltage signal. The voltage signal is input to a PC for analysis via a prototype acquisition board based on the PIC-32MX microcontroller.

A pneumatic cleaning system has been implemented in order to maintain the pressure on the sensor surface positive and avoid the particles deposition on the sensor.

Phosphorescent tracer

A commercial phosphorescent pigment MHG-6B (rare earth doped strontium aluminate) provided by Zhejiang Minhui Luminous Technology Co., Ltd, China, has been studied and characterized for the experimental tests. The emitted wavelength corresponds to 520 nm, the particle size distribution (PSD) measured with a HELOS/KF laser diffractometer equipped Rodos dispersion unit (Sympatec GmbH, Germany), resulted equal to 89.36µm (x_{50}).

Calculations

The calculation for the luminous intensity (E_A) and current (I_P) produced by the photodiodes are based on basic electrical circuit laws and the device characteristic curve. There is a proportional relation between the measured luminous intensity and the current produced by a photodiode (K parameter). The voltage (U) signal measured by the sensors is treated as follows to obtain the luminous intensity:

$$I_{produced} = \frac{U_{measured}}{R_{circuit}} \quad (1)$$

$$E_A = K \cdot I \quad (2)$$

The data signals measured by the sensors were analyzed and elaborated using MATLAB r2016a (The MathWorks, Inc., Natick, Massachusetts, United States.).

RESULTS

Figure 2 show the results of the executed test, the X-axis represents the time at which data were obtained, while the Y-axis represents the luminous intensity measured by the three sensors during the test. Each sensor measured a curve which corresponds to the tracer passage in the detection zone.

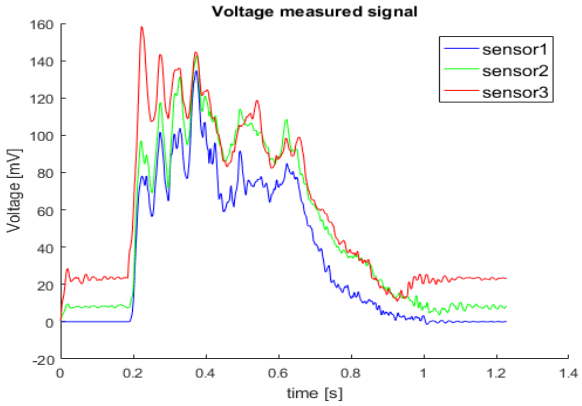

Figure 2. tracer passage detection

The curves measured by the sensors are not comparable between each other, because the sample tracer particles are not homogeneously distributed over the pipeline's cross section area. Nevertheless, the peak value measured corresponds to the highest tracer concentration passage over time measured the three sensors measured their local maximum of luminous intensity at the same instants of time.

CONCLUSION

A novel technique for the powder mean residence time measurement in solid-gas multi-phase flow processes has been developed and experimentally tested. The device permit to analyze the effect of geometric jet mill variations on the micronization process.

Based on the test results, the developed technique could represent a cost accessible and safe alternative to radioactive tracer techniques. The technique can be used for the mean residence time measurement and is particularly suitable for micronization processes.

ACKNOLEDGMENT

The Authors want to thank the Commission for Technology and Innovation CTI, Switzerland for financial support.

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