

Micro-Flow Imaging: spotlight on PLGA microparticle agglomeration

Since the 1980s, engineers are capable of precisely controlling fluids inside channels of a few microliter or less. Recent advances in microfluidics have led to the development of powerful analytical techniques. One of those techniques is Micro-Flow Imaging (MFI), which combines digital microscopy with small sample volumes and high throughput. A digital camera collects microscopic images of microparticles (i.e., particles in the size range between about 1-100 micrometer, or 0.001-0.1 mm) that are suspended in a fluid that flows through a micro-channel (Fig. 1).

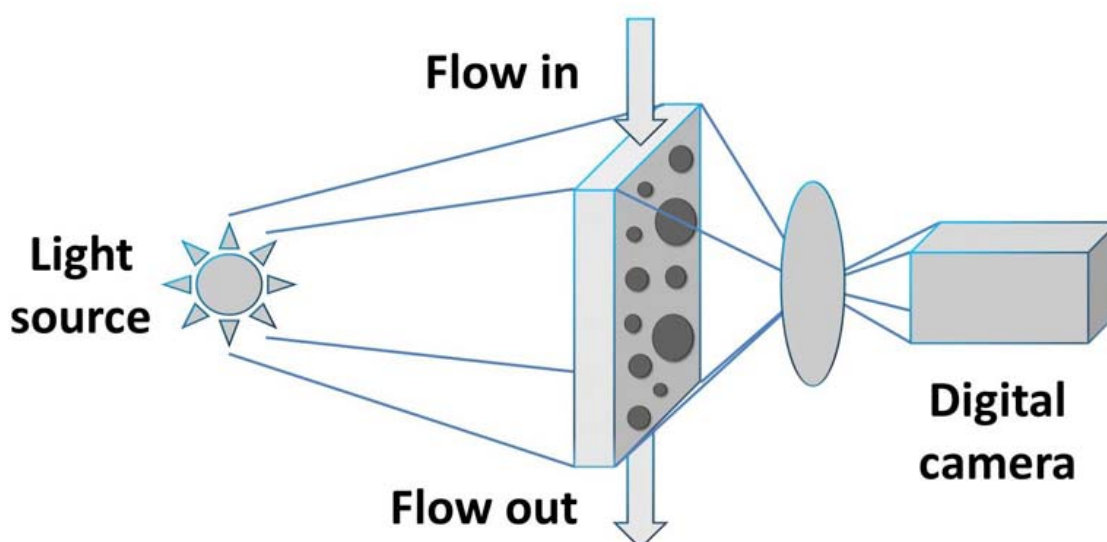


Fig. 1. Measurement principle of a Micro-Flow Imaging instrument.

MFI has found many applications, which are primarily focused on the detection of *undesired* microparticles in protein pharmaceuticals. In our research, we have evaluated the applicability of MFI to characterize *desired* microparticles that are used for drug delivery. We conclude that MFI is particularly useful to quantitate the percentage of agglomerated drug microparticles.

One of the most successful injectable drug delivery systems are microparticles composed of poly(lactic-co-glycolic acid) (PLGA) polymers. Degradable PLGA microparticles slowly release the encapsulated drug after administration, overcome the need of frequent injections and improve patient compliance and comfort. Size and agglomeration of PLGA microparticles are of critical importance for polymer degradation and drug release rates. The presence of agglomerated microparticles may shorten the duration of action and hamper the injectability of the drug.

Currently, the most common technique to evaluate the size distribution of PLGA microparticles is laser diffraction. However, this technique does not provide information on microparticle

agglomeration. The aim of this study was to explore the potential of MFI to quantitatively assess size and agglomeration of PLGA microparticles.

We performed a unique side-by-side comparison between MFI (using a MFI 5100) and laser diffraction (using a Mastersizer 2000) for the particle size analysis of two commercial PLGA microparticle products, i.e., Risperdal Consta and Sandostatin LAR. Risperdal Consta consists of PLGA microparticles that are loaded with risperidone, an antipsychotic drug that is used to treat schizophrenia and bipolar disorder. After administration, risperidone is released in about two weeks. Sandostatin LAR consists of PLGA-glucose microparticles that are loaded with octreotide acetate. This drug is used to treat acromegaly, a hormonal disorder that results from overproduction of growth hormone, and is released in about 1 month.

MFI and Mastersizer gave similar results regarding the size distribution of the main particle population in the two commercial products (28 – 220 μm for Risperdal Consta; 16 – 124 μm for Sandostatin LAR). MFI additionally detected a ‘fines’ population (<28 μm for Risperdal Consta; <16 μm for Sandostatin LAR), which was overlooked by Mastersizer. Moreover, MFI was able to distinguish ‘monospheres’ and ‘agglomerates’ within the main population based on particle morphology, and to count the number of particles in each sub-population (Fig. 2).

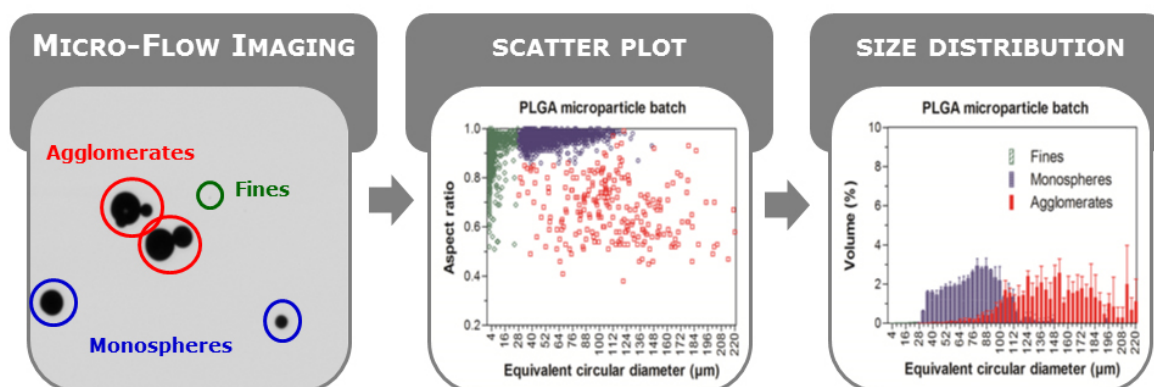


Fig. 2. Workflow to quantitatively assess size and agglomeration of PLGA microparticles.

From our data we conclude that MFI can be a valuable tool to support development and manufacturing of PLGA microparticles. It helps to achieve the correct particle size and prevent agglomeration, in order to deliver drugs that are safe to the patient, suitable for injection, and show an efficacious drug release profile.

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