Enhanced control of particle size with microfluidization and membrane microfiltration

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Summary

Background: Particle size (PS) and particle size distribution (PSD) are two of the most important attributes when designing an inhalation drug product. A fine control of both these parameters is not easily achieved by current available technologies. The new method herein presented consists in combining a microfluidization step with a cross-flow microfiltration step. The combination of these technologies allows the production of particles with stricter limits in terms of size and distribution and therefore enables a more efficient delivery to the lung.
Methods: A microfluidizer and two hydrophilic flat sheet track-etched polycarbonate membranes (30 and 20 µm pore sizes) were used. The permeability critical flux (Jv_{crit}) and critical transmembrane pressure (TMP_{crit}) were determined. Filtration tests were conducted below the Jv_{crit}, using, as model system, a 5% (w/w) aqueous suspension of fluticasone propionate. The effects of the addition of surfactant and ultrasound were also assessed. PS and PSD of the particles in the feed and permeate were monitored by focused beam reflectance measurement (FBRM). Laser diffraction was also used for comparison purposes.
Results: The proof of concept work shows that the selected membranes are capable of efficiently classifying the feed suspension according to membrane pore size, narrowing the PSD of permeates.
Conclusions: The combination of these two technologies - microfluidization and cross-flow microfiltration - provides a greater control of PS and PSD and, therefore, it is expected to result in particles with enhanced performance for inhalation delivery.

Introduction

Particle size (PS) and particle size distribution (PSD) are two important attributes when developing an inhalation active pharmaceutical ingredient (API). The higher the fraction of API particles that reaches the deeper lung, the lower is the dose needed per actuation, minimizing the API manufacturing costs and reducing side effects **[1]**. One of the main challenges is to keep the particle size distribution (PSD) as narrow as possible, since too large or too small particles may not be adequately administered. Monodisperse or near-monodispersed particles are extremely interesting for this purpose since the physical and chemical characteristics of a single particle can be extrapolated to the whole particle population **[2]**. The routine production of monodisperse particles in the pharmaceutical industry is still being hindered by limitations and challenges related to current technologies for particle size control. Jet milling and controlled crystallization are some of the most widely used, but both show modest control of PSD. Microfluidization allows the production of narrower PSD with a good control over particle size but still limited in terms of the resulting span of the particle size distribution.
A novel technology was developed **[3]** to meet the objective of reducing the span resulting from a microfluidization process by combining the latter with a cross-flow membrane filtration step (see **Figure 1**). The suspension in the feed tank (T1) is fed simultaneously to a membrane filtration unit (MF1), where particles smaller than the membrane pore radius are allowed to permeate to tank T2. The permeate stream of the membrane unit will therefore be comprised of a quasi-monodisperse size distribution, dictated by the pore size of the membrane. A second membrane filtration step (MF2) enables the recovering and recycling of the solvent to T1, and may also be used to remove fines from T2.

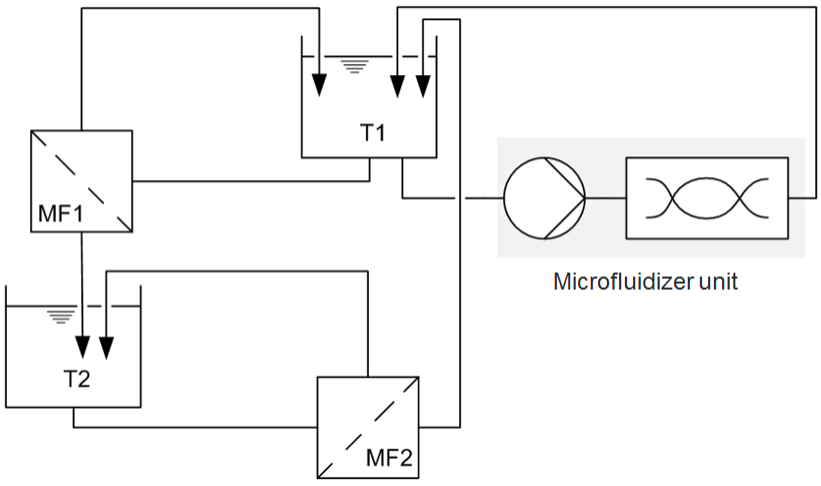
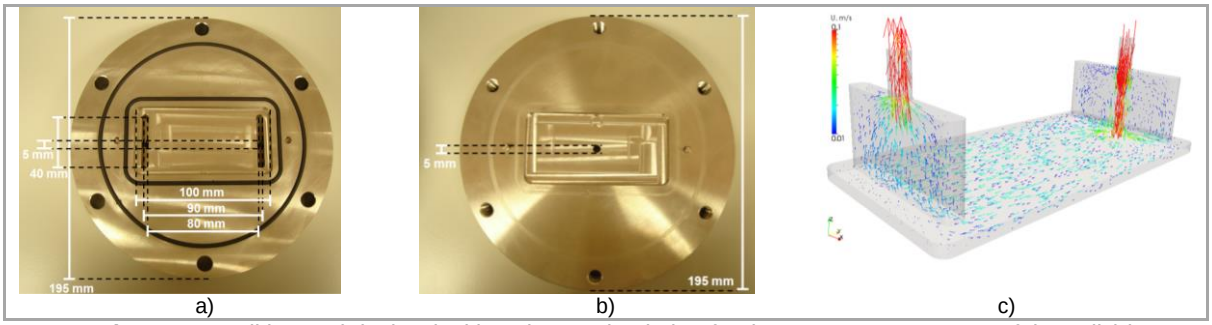


Figure 1 – Process diagram of the combination of microfluidization with membrane filtration.

Case Study

The combination of microfluidization with membrane separation is anticipated to enable a tighter control of PS and PSD by a careful selection of the membrane pore sizes. It is therefore of extreme importance to evaluate the efficiency of the membrane in terms of its permeability and particle size sieving capacity since this will determine the outcome of the combined process. In this initial proof of concept work, the separation efficiencies of two different membranes were evaluated using an aqueous suspension of non-micronized fluticasone propionate (FP). Two hydrophilic flat sheet track-etched polycarbonate membranes were used, with pore sizes of 30 and 20 µm - separation in the inhalation particle size range of 1 to 5 µm is expected to be significantly more challenging and will be considered at a later stage of development.
The microfiltration cross flow unit used in this work is shown in **Figure 2**. This figure also includes the results for a Computational Fluid Dynamics (CFD) simulation to assess the flow profile and mass transfer performance of the unit.



a) b) c)

Figure 2 – Cell internal design (a, b) and CFD simulation for the upper compartment of the cell (c).

The process was controlled by manipulating the transmembrane pressure (TMP) and monitoring the permeate flux (Jv). **Figure 3** shows the typical particle size and shape of the particles used in the feed suspension, being possible to identify both spherical and non-spherical particles with a wide PSD. The presence of non-spherical particles in the feed suspension, especially the most elongated crystals, is expected to impact the accuracy of the PSD determination by the analytical methods, since these typically assume spherical geometry.

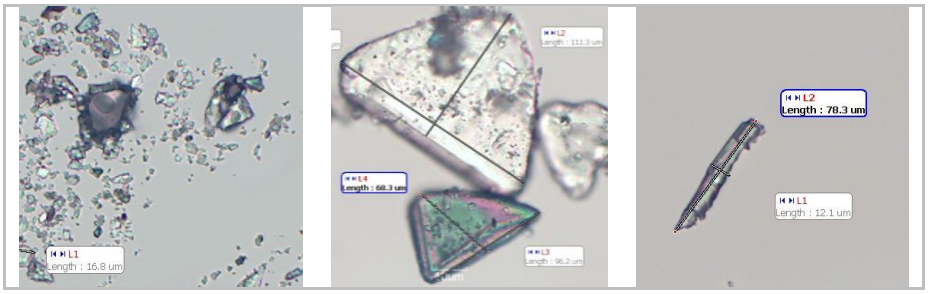


Figure 3 – Microscopy images of FP particles in the feed suspension.

In order to assess the performance of the membrane system, the permeability (Lp), critical flux (Jv_{crit}) and critical TMP (TMP_{crit}) were determined using the model system. **Figure 4** compiles the results for both membranes, where the typical linear relation between flux and pressure is observed (at the critical flux the linear relationship breaks apart and a steep change in slope occurs **[4]**). The critical flux obtained is well below the typical values for an industrial-capable microfiltration process and reveals the need for additional design work to minimize the formation of a thick layer of product on the top of the membrane.

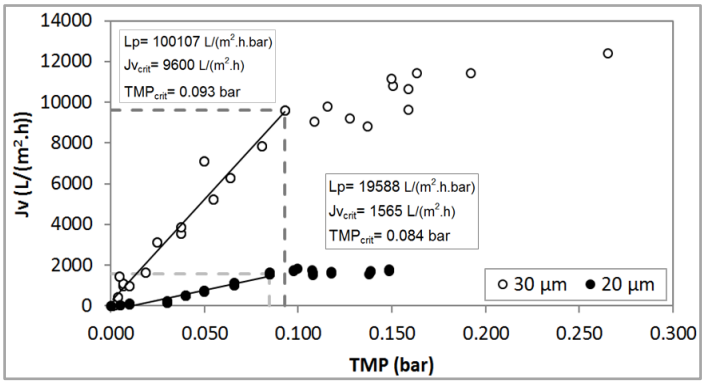
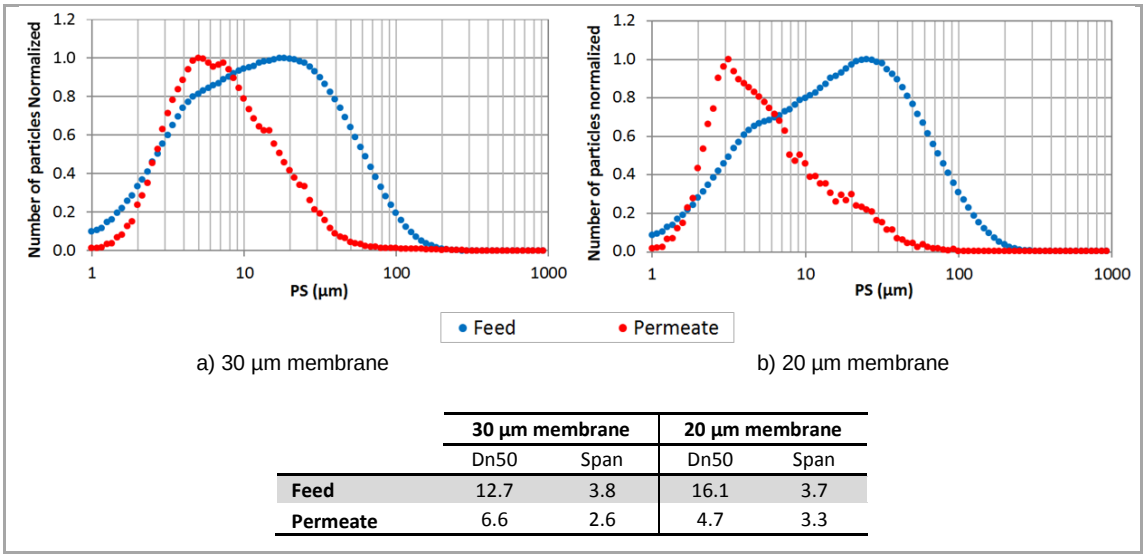


Figure 4 – Permeate flux versus TMP for the 30 and 20 µm membranes.

The subsequent permeation trials using both membranes were ran slightly below the critical flux conditions in order to prevent cake buildup and to enhance the process selectivity **[4]**. Particle size was monitored by focused beam reflectance measurement (FBRM) and several strategies were used to overcome particle agglomeration challenges including the addition of surfactants (sodium lauryl sulfate) and application of ultrasounds. The results shown that particle deagglomeration was more efficient through the use of ultrasounds.

Figure 5 compares the PSD of the feed suspension (blue dots) with that of the permeate obtained with a 30 µm and 20 µm membrane. The results show that the selected membranes efficiently sieved the feed suspension to particle sizes that are dependent on the selected membrane pore size, consequently reducing the span. It should be noted that the PSD presented in Figure 5 was determined in a number basis and not in a volume basis as is more frequently used, which leads to relatively higher span values that for volume based distributions since particles from all sizes have the same relative weight in the distribution.



a) 30 µm membrane b) 20 µm membrane

	30 µm membrane		20 µm membrane	
	Dn50	Span	Dn50	Span
Feed	12.7	3.8	16.1	3.7
Permeate	6.6	2.6	4.7	3.3

Figure 5 – PSD curves of the feed and permeates for the 30 µm (a) and 20 µm (b) pore-sized membranes.

It can be seen that the proportion factor (ratio between the membrane pore size and the Dn50 of the permeate) was about 4.4 for the two membranes. This indicates a consistent separation efficiency of both membranes on the basis of their pore size and such ratio can be used for selecting the membrane pore to meet a target particle size. On **Figure 6,** particles from the permeate obtained from the 30 and 20 µm membrane are presented. The permeated particles are for the most part smaller than the membrane pore size but a number of elongated particles did pass through the pores, most probably by assuming certain orientations in relation to the pores. This way, the elongated particles are expected to contribute to a misrepresentation of the PSD measured by most analytical techniques contributing to larger PS values and broader PSD.

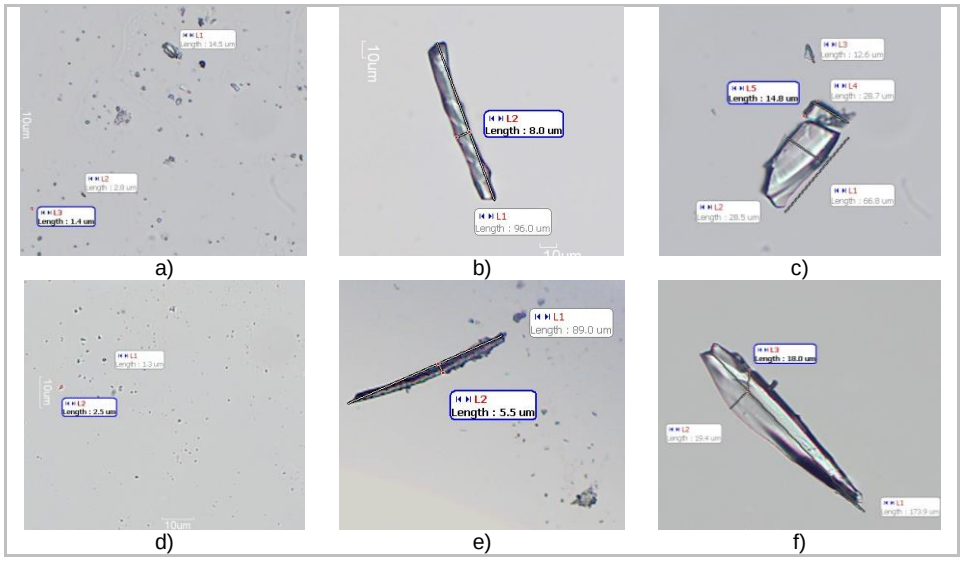
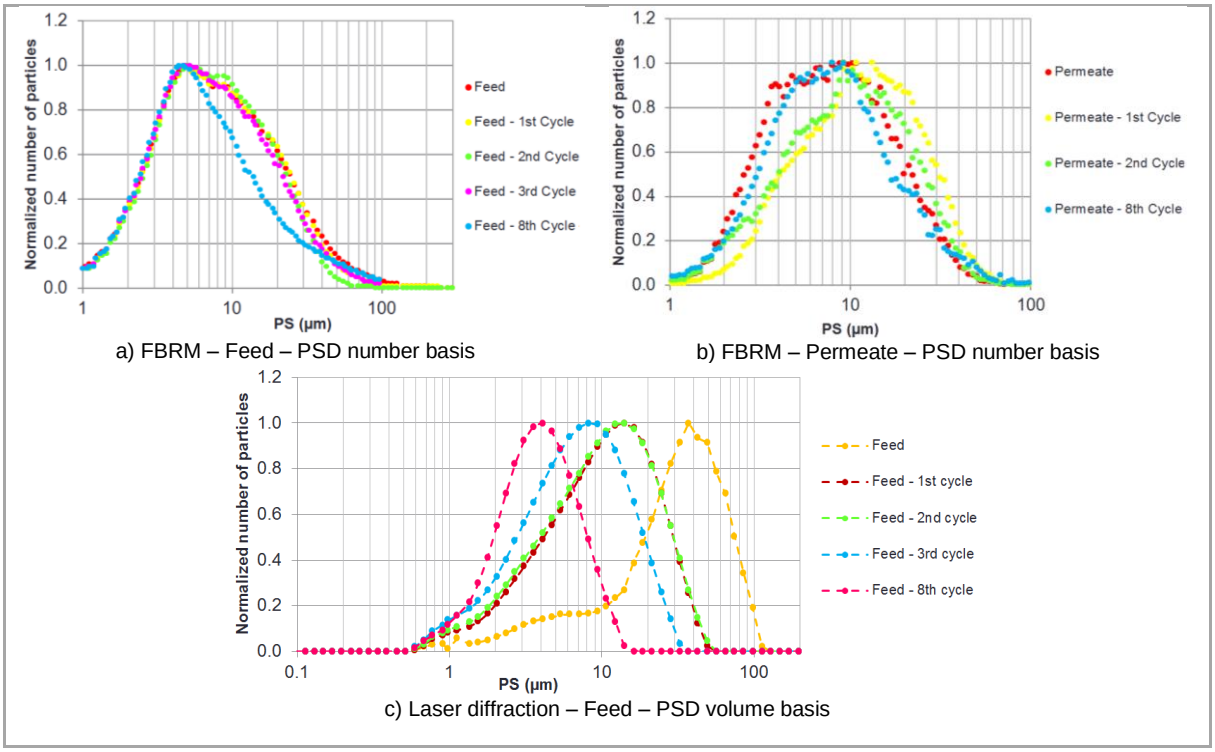


Figure 6 – Microscopy images taken from the 30 µm permeate a) smaller particles, b) c) elongated particles; and the 20 µm permeate d) smaller particles and e) and f) elongated particles.

A subsequent work involved the combination of microfluidization with a 30 µm microfiltration system. The process was run sequentially, meaning that the suspension was microfluidized after each microfiltration cycle. The feed obtained after each cycle was measured by FBRM and by laser diffraction (Malvern, Mastersizer 2000), whereas the permeate was analyzed by FBRM (given that the suspension concentration was not adequate for laser diffraction analysis). **Figure 7** shows the PSD data obtained by FBRM for the feed (a) and permeate (b), and that obtained by laser diffraction for the feed only (c). It was possible to observe that FBRM technology was not capable to measure and distinguish the differences on the feed and the permeate samples obtained after successive microfluidization cycles. As expected, the laser diffraction method allowed the determination of the feed suspension PSD with increasing microfluidization cycles but could not be used for the permeate samples due to the lower concentration of these (specifically, the obscuration lower limit requisite was not fulfilled). Nevertheless, optical microscopy assessment of the permeate samples indicated that particles were smaller with an increasing number of cycles.



a) FBRM – Feed – PSD number basis

b) FBRM – Permeate – PSD number basis

c) Laser diffraction – Feed – PSD volume basis

Figure 7 – PSD measurements from FBRM for a) feed and b) permeate after several microfluidization cycles and from laser diffraction for c) feed.

Conclusions and Future Work

The combination of microfluidization and membrane filtration allows the production of particles with tailored particle size and narrower particle size distribution. The method can be used in several pharmaceutical applications where these attributes are critical to the performance of the drug product. The membranes tested in this work showed to be effective in classifying the feed suspension of fluticasone propionate to a particle size range dictated by the membrane pore size narrowing the PSD. Future work will focus on the optimization of the process and its development for inhalation delivery. An additional goal is to conduct the subsequent scale-up of the process to produce monodisperse particles for inhalation purposes.

References

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