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Comparative Investigation of Membrane Systems for Crystallization and Spherical Agglomeration †

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Abstract: In this study, two novel spherical agglomeration processes based on membrane systems were successfully implemented to produce spherical agglomerates of benzoic acid crystals obtained by antisolvent crystallization. Two membrane configurations were implemented; a flat disc mounted in a dispersion cell equipped with a mixing impeller, and a second one which uses a cylindrical membrane equipped with a vibrating module which created shear with upward-downward vibration. To optimize the performance of the spherical agglomeration process, the impact of the bridging liquid flowrate, membrane pore size and pore arrangement, as well as agitation rate were investigated. Both systems were successfully used to generate spherical agglomerates with enhanced quality and size distribution at comparable flux conditions. In near future, the membrane systems will be scaled-up to investigate the scalability of the proposed spherical agglomeration system under the optimized operating conditions identified from the current study.

Keywords: crystallization; spherical agglomeration; membrane system; oscillating; vibrating membrane; bridging liquid; benzoic acid.

1. Introduction

Crystallization is a key purification technology adopted in more than 80% of all pharmaceutical products. However, the control of crystal shape and size can be very challenging particularly in the case of needle-like and plate-like crystals [1,2]. The control of crystal shape and size distribution is critical to improve processability and physical properties of active pharmaceutical ingredients, such as dissolution, downstream processability and flowability [3]. In recent years, spherical agglomeration (SA) received growing interest in the pharmaceutical industry as a shape modification technique, as an alternative to temperature cycling, shape modifiers, or wet milling. SA is commonly achieved in batch systems by adding a suitable bridging liquid (BL) to a system containing fully formed (after equilibrium) or growing crystals (spherical crystallization). One of the major challenges in spherical agglomeration is to fine-tune particle size distribution, as most of the SA processes suffer from poor scalability and poor control of the droplet size of the bridging liquid.

Spherical agglomeration is a key process intensification technique which can increase the efficiency of the crystallization step in pharmaceutical processing. It has been possible to achieve spherical agglomerates mainly in batch systems [4] but also in continuous flow reactors [5,6], in series mixed suspension mixed product removal systems (MSMPRs) [7] and microfluidic systems [8] with the aid of glass capillaries or T-junctions. It is achieved by adding droplets of a binding or bridging liquid to a bath of already formed crystals, therefore it is a 2-step process. Agglomerate formation highly depends on the binding liquid affinity, which depends on the relative polarity, interfacial tension and viscosity of the dissolved active pharmaceutical ingredient (API) in a solvent,

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antisolvent and binding liquid [9]. In order to achieve spherical agglomerates, the binding liquid must be added during or after crystallization [10], but some studies pre-mix a low amount of BL in the solvent with the API and form droplets through capillaries [11,12]. The method of addition, and size of droplet injected will dictate the size of agglomerate formed and the mechanism by which it forms. The mechanisms discussed in spherical agglomeration by which agglomerates are formed are the immersion and distribution [13,14]. Droplet introduction and properties will influence agglomerate formation, size, and solidity.

The immersion mechanism occurs when large droplets, compared to the crystal size, are introduced to the suspension. The crystals first form at the surface of the droplet which results in smooth agglomerates with high sphericity [15]. The distribution mechanism occurs when small droplets are introduced in relation to the size of crystals and the droplets bring the crystals together to form large, non-uniform, and irregular agglomerates. In batch systems, the number of crystals available decreases over time, therefore the agglomerates formed at the beginning will be solid, whereas the agglomerates formed at the end may be hollow shells. Nevertheless, certain applications require hollow spherical API particles [16].

Additional factors that influence agglomerates formed in membrane systems include membrane pore diameter, binding liquid injection flow rate, agitation rate, mixing conditions, bridging liquid to solids ratio (BSR) (ratio between the volume bridging liquid and mass of crystals), vibration frequency and amplitude (only in vibrating module).

In both membrane systems, antisolvent crystallization is performed in the mixing vessel prior to agglomeration, the bridging liquid is then added through the membrane to the suspension of crystals. Depending on the concentration of crystals and their affinity with the binding liquid, they will adsorb onto the droplets due to their affinity of adsorption to the binding liquid compared to the mixture solvent antisolvent.

Membrane emulsification systems have proven effective in many applications including droplet generation [17], drug formulation for sustained delivery [18], encapsulation [19], colloidal emulsions [20,21]. In this work, membrane configurations are used for droplet formation of bridging liquid to enhance spherical agglomeration of benzoic acid.

The main motivation behind this study is that the oscillating module is a scale-up of the dispersion cell, however they are both fed-bath systems, and do not currently have continuous processing, or in-situ PAT analytical techniques implemented. This work employs a comparative investigation of spherical agglomerate formation in two different membrane configurations. Both systems were successfully used to form spherical agglomerates, however they both require optimization to ensure higher mixing efficiency and enhanced spherical agglomerates.

2. Methods

2.1 Dispersion Cell

The dispersion cell consists of a membrane holder, glass chamber and a two-blade impeller which can be fitted on top of the glass chamber. Agitation rate can be adjusted with a voltage knob on a BBH Power Products 24V Motor. Two 11 Elite Pumps (Harvard Apparatus) were used to feed the solvent and bridging liquid to the crystallization chamber. Benzoic acid dissolved in ethanol was added through the top of the chamber into the water, and the bridging liquid was fed through the bottom of the membrane connected to the chamber with Teflon tubing.

Figure 1 shows the structure of the chamber with its dimensions: membrane diameter, D_m, which is equal to chamber inner width, T, impeller diameter, D, impeller height, b, height from membrane to impeller, h, number of impeller blades, n_b, volume below membrane, V_b.

2.2 Oscillating Module

The oscillating module involves a cylindrical membrane attached to a module that moves up and down and is connected to a control panel. The frequency, amplitude distance from peak to peak and voltage can be adjusted on the control panel. Figure 1 shows the different configurations of the dispersion cell (a) and vibrating membrane module (b). For the vibrating module: c is the baffle width, H_b baffle height submerged in the bath, H_v is height of membrane, W_v is the cylinder membrane diameter, D_p is the pore radius, S_L and S_W is the stirrer length and width respectively, T_v is the beaker diameter, n is number of baffles.

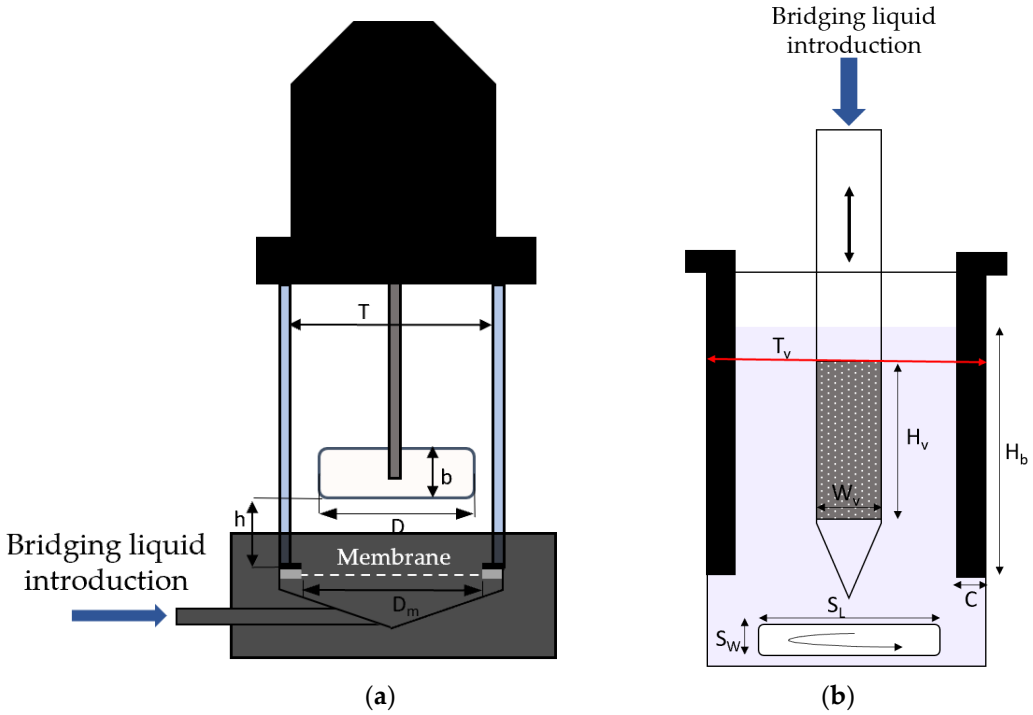


Figure 1. Schematic of (a) dispersion cell with a flat-blade impeller above a flat-disc membrane, with dimensions: D_m = 3.45cm, T = 3.75 cm, D = 2.95cm, b = 1.2 cm, h = 0.5 cm, n_b = 2, V_b = 4.33mL; (b) vibrating membrane module with dimensions: Wv = 1.3 cm, Hv = 6.5cm, Tv = 4.3 cm, Hb = 3.75 cm, c =0.7 cm, Sw = 1.05 cm, S_L = 3.8 cm.

2.3 Membrane

The membranes have been supplied by Micropore Technologies Ltd. (Teesside, UK) and were fabricated by galvanic deposition of nickel into a template formed by photolithographic technique [17]. The membrane with an annular ring membrane is fabricated using laser interference lithography. The cylindrical membrane for the oscillating module made from the same material, first as a flat sheet, then rolled and welded on the edge. Both were supplied by Micropore Technologies Ltd. Both types of membranes contain uniform, cylindrical pores with a diameter of $d_p = 18$ and a hexagonal array spacing of $L = 212\ \mu m$. The cylindrical membrane had pores with $d_p = 17\ \mu m$ *and* $L = 210\ \mu m$, where the membrane porosity, ε, is given by equation 1 [17]. The porosity calculated for the flat disc membrane $(d_p = 18\ \mu m)$ was 0.65 and for the cylindrical membrane $(d_p = 17\ \mu m)$ it was 0.59.

$$\varepsilon = \frac{\pi}{2\sqrt{3}}\left(\frac{d_p}{L}\right)^2 \quad (1)$$

2.4 Materials

Benzoic acid (C6H5COOH) (Sigma Aldrich) (density (ρ_{BA}) = 1316 kg/m^3 [22]) was used as a model active pharmaceutical ingredient (API) at a concentration of 30wt.%, dissolved in ethanol (99.8% purity; company), and de-ionised water was used as anti-solvent.

Toluene (Lab Grade; Fisher Chemical) was used as bridging liquid at a bridging liquid to crystal solids ratio (BSR, eq. 2) of 0.7g/mL.

$$BSR = \frac{Volume\ bridging\ liquid}{Mass\ of\ crystals}\left(\frac{mL}{g}\right) \quad (2)$$

PTFE tubing is used to connect the inlet to the membrane with the injection syringe (SGE), that injects the bridging liquid through the membrane using glass plunger 25mL SGE needle syringe mounted on top of an 11 Elite Syringe Pump (Harvard Apparatus).

2.5 Procedure

Spherical agglomeration in the membrane system was achieved in three main steps. In both the DC and oscillating membrane module (Figure 2), (step 1) antisolvent crystallization was first performed in the mixing vessel, either a beaker or the DC glass chamber during mixing: the solvent (S: benzoic acid in ethanol) was added to the antisolvent (AS) in a ratio of 1:9 (S:AS) in both systems. Then (step 2), the bridging liquid (toluene) was pumped to reach a BSR of 0.8mL/g at the corresponding flow rate (Q=V/t). Finally, (step 3) the spherical agglomerates were allowed to grow and consolidate as the mixing continued. Shortly after, the spherical agglomerates were removed and separated in petri dishes for observation (Nikon Eclipse TE300) and drying for observation after 24 hrs. For DC, the given flux corresponds to 0.025-0.05 mL/min and for the oscillating module it is 0.02-0.05 mL/min. After the antisolvent crystallization step, the crystals formed were mainly needle-shaped and plate-like ranging in the size of 10-100 μm. The oscillating module frequency and amplitude were started at the beginning of the experiment, and were varied from 30-70 Hz and 1-3, respectively.

To be able to compare the results from the DC membrane and the oscillating membrane, the flux, *J,* through the membrane needed to be calculated and ensure to be equal at each membrane type with the adjustment of the flow rate of bridging liquid through the membrane. The filter area can be found by using the porosity value obtained from equation 1.

$$J = \frac{Flow\ rate\ through\ membrane}{Filter\ surface\ area}\left(\frac{L}{m^2 h}\right) \quad (3)$$

3. Results and Discussion

Spherical agglomeration occurs in three main steps (shown in Figure 2) which are aided by the membrane technology. The membrane pore radius ensures that there are multiple droplets of the same diameter formed simultaneously, which makes it a scale-up solution to microfluidic or single capillary systems [11].

3.1 Agglomerate Formation Mechanism

From off-line observations, and previously studied model, it can be inferred that the immersion mechanism is at play in the DC, where the droplets introduced are larger than the crystals, allowing them to adsorb onto the surface and consolidate after the addition of toluene is finished. The distribution mechanism might be more prominent in the oscillating module, where the introduced droplet size much smaller than the size of initial crystals, which then adsorb onto the surface of the crystal, acting like a glue to bring the crystals together into non-smooth spherical agglomerates. The adsorption of the crystals onto the droplet depends on the properties of the interfacial tension of the solvent to antisolvent and the polar affinity of benzoic acid to toluene, which aids it to adsorb onto the toluene droplet.

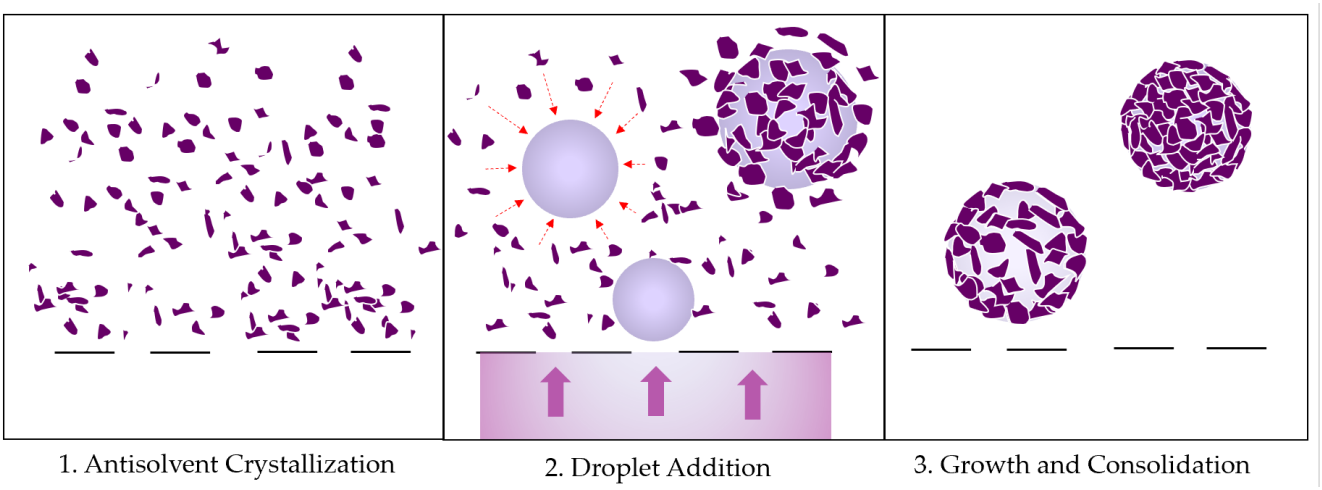


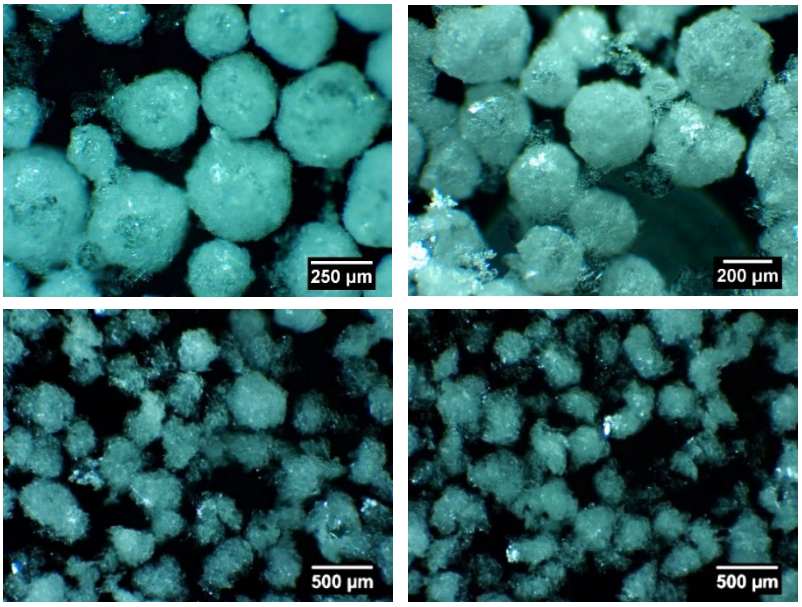
Figure 2. Spherical Agglomeration Steps: 1. API dissolved in solvent added to antisolvent to create supersaturation and cause nucleation and growth of crystals. 2. Bridging liquid droplets are introduced through the membrane to allow for crystals to adsorb onto the droplet surface. 3. Droplet addition ends, and spherical agglomerates are still mixed to allow for consolidation and growth of agglomerates.

3.2 Optical Microscopy Results

Figure 3 shows the optical microscopy results of benzoic acid spherical agglomerates obtained from (a) the oscillating membrane and (b) the flat membrane in the dispersion cell. Visually, the DC agglomerates appear smooth and have a clear spherical shape with a greater level of consolidation that the agglomerates from the oscillating module. The poor consolidating with the vibrating module may be a result of poor mixing conditions due to the magnetic stirrer and formation of vortex in the vessel. To aid this, a unit of 4 baffles was 3D printed using Polypropylene (PP) as material, as it is resistant to corrosive chemicals, such as toluene or acetone (used for cleaning). This has prevented the formation of a vortex and has improved the mixing and formation of monodisperse spherical agglomerates. Since the DC has a built-in 2-blade paddle and covers most of the membrane surface and is placed at a distance of 0.5 cm to the membrane, the mixing in the DC is much better and more efficient.

The agglomerates from the oscillating module are more uniformly sized and shaped overall, and have a smaller mean size, 212 μm as opposed to 285 μm mean agglomerate size obtained from the DC. This is a result of a larger surface area of the oscillating membrane available for droplet addition than the surface area of the flat membrane where droplet detachment is subject to a uniform level of shear. The shear in the DC is mainly generated by the rotation of the impeller, whereas in the oscillating membrane, it is generated by the vibrating movement of the module, and as it shakes, it releases the droplets from the surface of the membrane. Gravity may also play a role in the visual results of the agglomerates, as the crystals have not the same density as the continuous phase (DI water), they will preferentially sink to the bottom of the vessel. In the DC unit, the membrane is at the bottom, so the agglomerates will form preferentially at the bottom during droplet addition. However, the oscillating unit has a vertical membrane set in the middle of the vessel, with corresponds to where the vortex forms at high mixing rates. Because of this, the crystals would be mostly found at the bottom and sides of the vessel rather than in the middle where the droplet introduction occurs. Because of this, there will be less crystals

available for agglomerate formation at a time than in the DC, and it will require more time and mixing, as well as baffles to obtain smooth and spherical agglomerates such as the ones obtained from the DC.



The DC also has a substantial dead-zone area which may exist in the right-angle corner between the flat membrane and the vertical chamber wall. This can be aided by a curved membrane to mimic a curved bottom of CSRT optimal design, or a membrane that has pores arranged in an annulus ring at the radial distance of the membrane where highest shear occurs due to agitation.

3.3 Agglomerate Size Ditribution

The mechanism of shear generation and droplet formation is different in both systems, which will affect the final shape and size of the agglomerates. In the flat DC membrane, shear is generated by the agitation of the impeller and is assumed to be constant across the membrane. However, studies show, that it is highest about ¾ distance from the center of the membrane in the radial direction [25]. There is a critical point under the blade, where the shear is at its highest, where the droplets will be smallest, and therefore the agglomerates formed there will be the smallest. The shear in the vibrating module is generated by the frequency, amplitude, and mixing conditions, which cause the droplets to detach from the membrane, and fall into the bath of crystals to form agglomerates. Other factors influencing the droplet size are the interfacial tension, viscosity, and density of the continuous phase (water), Reynolds number and dimensions of the tank.

Figure 5 shows the comparison between agglomerate size distribution (ASD) obtained from the flat membrane and the oscillating module based on number %. The agglomerates obtained from the oscillating membrane have a mean size of around 290 µm compared to the 350 µm from the flat membrane. Both modules can have a similar volume, therefore a similar yield of monodisperse agglomerates can be obtained of 70 and 80% for the flat and vibrating membranes respectively. ASD mean size measurements were done in ImageJ, without considering the roughness of the agglomerate crystal surface.

As surfactant was not used to stabilize the toluene droplets, it is not possible to measure the original droplet mean size *in situ* before they form agglomerates. They may be prone to deformation due to impeller or magnetic stirrer mixing. However, since the suspension is saturated with crystals of benzoic acid, it can be assumed that as soon as the

droplet forms, it is met with a crystal. As the droplet forms, the crystals first adsorb onto the surface of the droplet and then continue to grow on top, resulting in hollow shell agglomerates that are much larger than the initial droplet size. Hollow agglomerates formed in the DC, with a clear shell that did not deform after drying, which could have some potential uses, if their formation can be predicted. In contrast, the oscillating membrane did not form any fully solid agglomerates such as the ones in the DC. They do not have a clear spherical shape and sometimes, they are difficult to tell apart, as sometimes they form larger agglomerates.

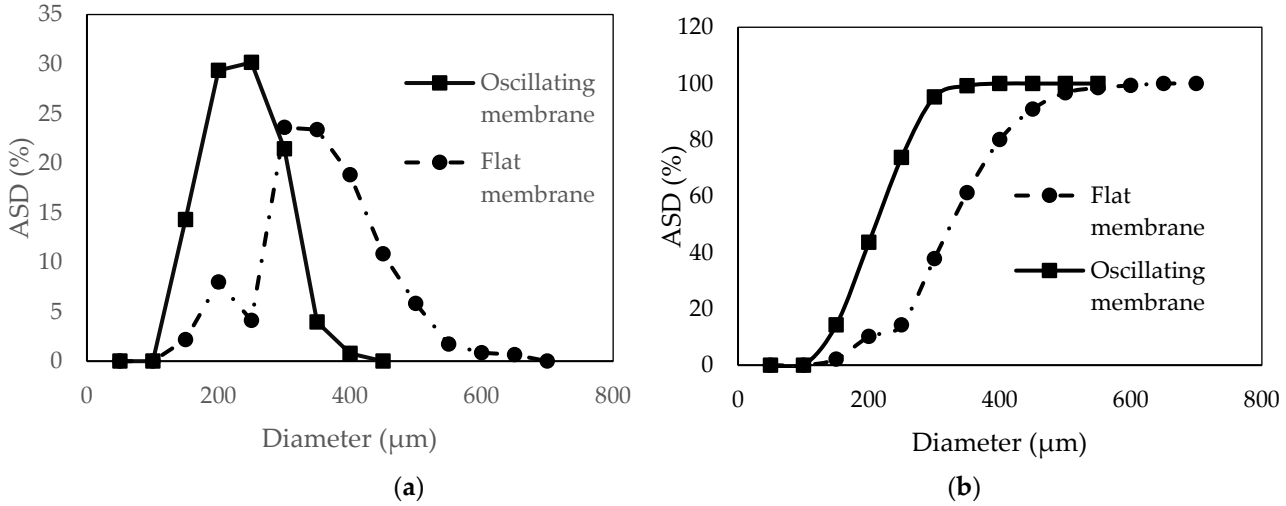


Figure 1. (a) Agglomerate size distribution (ASD) and (b) cumulative size distribution, based on number, of spherical agglomerates formed at Flux = 240Lm^{-2}h^{-1}, at 800RPM, nickel membrane d_P = 18μm.

4. Conclusions

Spherical agglomeration has been investigated as a technique that can potentially reduce the number of required stages commonly adopted in pharmaceutical manufacturing such granulation and wet milling, making it an effecting process intensification technique. Two membrane technologies were used to aid the formation of evenly distributed droplets of bridging liquid to help achieve consistent spherical agglomerates. Both membrane systems used in this study, the dispersion cell and the oscillating module were successful at forming spherical agglomerates, however, the DC offered better mixing conditions. The oscillating module was improved with the use of baffles, but the vessel must be optimized to offer better contact of crystals to membrane surface.

Scale-up opportunities include fed-batch mixed suspension mixed product removal (MSMPR) continuous crystallizers with an inbuilt membrane so that it can perform a crystallization and binding liquid addition in the same vessel in a sequence. Future work will investigate scale-up opportunities of using membranes for spherical agglomeration in continuous crystallization and *in-situ* PAT incorporation.

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