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MEMBRANES & CRYSTALLIZATION PROCESSES: STATE OF THE ART & PROSPECTS

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ABSTRACT

Crystallization is one of the major unit operations of chemical process industries and plays a key role for particulate solids production in the pharmaceutical, chemical, electronic, minerals sectors. Most of the current crystallization processes are performed under batch or continuous mode based on a stirred tank process; the need for breakthrough technologies has been highlighted by numerous authors and reports. Membranes are one of the potentially attracting strategies in order to achieve this target. Nevertheless, a relatively limited number of publications have been reported on membranes and crystallization processes, compared to other unit operations. This study intends to provide a state-of-the-art review of the different approaches combining membranes and crystallization processes. Hybrid and integrated systems are discussed and the different role and function potentially provided by dedicated membrane materials are analyzed. Based on the results and analyses gained through the different approaches that have been tested, unexplored issues and open questions have been listed. The research efforts which are required in order to make membranes processes for crystallization/precipitation an industrial reality are finally discussed.

KEYWORDS:

Membranes, Crystallization/Precipitation, Contactors, Process Intensification, Quality.

INTRODUCTION

Crystallization is one of the oldest chemical operations to produce, purify or separate the solid products but it is only since the 70's that it has been considered as a unit operation [1]. Nowadays, crystallization and precipitation (solids produced from a chemical reaction) are major processes used in the chemicals, pharmaceuticals, food and electronics industries due the high level of product purity required and the need for low energy requirement [2]. Regardless the crystallizer technology, the crystallization process or the operating conditions, crystallization occurs by a change of the temperature and/or the composition (solvent evaporation, antisolvent added, seeding...) of a saturated solution. Hence, heat and/or mass transfer processes are key issues for the crystallization/precipitation processes.

Membrane processes have recently been proposed in order to improve performance of crystallization operations and are considered as one of the most promising strategies [3–5]. The number of publications dedicated to crystallization / precipitation [6,7] processes using a membrane have effectively increased these last years (cf. Fig. 1). Generally speaking, membrane processes make use of a porous or a dense material acting as a physical semi-permeable barrier between two phases. In terms of mass transfer, the use of a membrane logically adds a supplementary resistance [5] which has to be taken into account in the process analysis. Similarly, from the heat transfer point of view, the thermal conductivity of membrane materials is usually low [8]. These two disadvantages are however potentially counterbalanced by the unique possibilities offered by membranes such as selective mass transfer, improved fluid distribution and extremely high interfacial area (a) leading to intensified heat and mass transfer fluxes [5,8]. These characteristics can be of interest for enhanced process productivities and/or product quality purposes.

In crystallization/precipitation processes, the solid products are indeed characterized by their purity level, polymorphic form, crystal shape and crystal size distribution (CSD) which has usually to be as narrow as possible [9]. These features define the product quality and are governed by the supersaturation which is the process driving force. Hence, for crystallization/precipitation processes, the control of the supersaturation appears as being of primary importance and membranes are one promising way to fulfill that aim [9–11].

This study intends to provide a state-of-art review of the different approaches combining membranes and crystallization processes which have been reported so far. Hybrid and integrated systems are discussed and the different roles and functions potentially provided by dedicated membrane materials are analyzed. Based on the results and analyses gained through the different approaches that have been tested, unexplored issues and open questions have been listed. The research efforts which are required in order to make membranes processes for crystallization/precipitation an industrial reality are finally discussed.

CRYSTALLIZATION /PRECIPITATION PROCESSES: FRAMEWORK

Crystallization/precipitation processes have long been used in the pharmaceutical, food, chemicals and materials sectors as a means to isolate, to purify and to control the solid products materials regarding the crystal shape, the polymorphic form and the CSD. Industrial applications of large scale continuous processes are available for commodity chemicals (ammonium nitrate, urea, ammonium sulphate, phosphoric acid, sodium chloride, adipic acid, xylenes...) and for specialty chemicals (e.g. pharmaceutical, food, fine chemicals). For materials, batch processes are more often employed.

Several reports and reviews have addressed the challenges of crystallization processes for these different industrial applications and, schematically, two types of developments are often cited as of high priority:

- i) *Product quality* issues (quality by design), aims the polymorphic form, the CSD and the crystal shape factor to be mastered [4,12–15].
- ii) *Process issues* include batch to continuous breakthrough approaches, scale up challenges, intensification and green engineering developments [14,16].

In both cases, new crystallizer concepts are expected to replace the reference technology, namely the stirred tank. For instance, the transition from batch to continuous and the ease of scale up has been attempted by a strategy in which the number of smaller unit operations is increased. This is the case of microstructured reactors [4]. Unfortunately, channel blocking issues limit, for the moment, the industrial application [4].

From a more fundamental point of view, the complex interaction of the physical chemistry (nucleation, crystal growth rates) and chemical engineering (hydrodynamics, transport processes, scale up), which controls the polymorphic form, crystal stability and CSD, is a key topic. More specifically, studies, coupling hydrodynamics thanks to Computational Fluid Dynamics (CFD) and population balances [17], would be of major interest in order to offer an improved understanding of the crystallization process and the technology. However, both targets still remain very challenging from the computing and the mechanisms quantitative description point of view.

The specific feature of crystallization as a separation process is that it involves a phase change from liquid to solid (e.g. ions or molecules). Fig. 2 shows a classical temperature/concentration diagram where the supersaturation, i.e. the driving force of the liquid/solid phase change, is represented. In terms of process, different possibilities, listed in Table 1 are offered in order to generate supersaturation. Basically, two major means, corresponding to the two axes of Fig. 2, can be applied:

- i) a change in concentration (in red, i.e. solute concentration by solvent removal or dilution through adding an antisolvent)
- ii) and/or a change in temperature (in green)

Interestingly, it will be shown and discussed hereafter that each of the supersaturation generation method shown in Table 1 can be performed thanks to different membrane processes.

MEMBRANE & CRYSTALLIZATION / PRECIPITATION PROCESSES: A SHORT HISTORICAL OVERVIEW

Like many scientific discoveries, the use of a membrane material to crystallize is due to an unexpected observation. Hence, the first notification can be dated back to almost a century. Kober [18] indeed reported in 1917 in a pioneering study of using a dense polymeric membrane, i.e. a nitrocellulose bag, to evaporate water from an aqueous solution of ammonium sulfate or hydrochloric acid. In both cases, the evaporation of water induces the increase of the supersaturation level of salts until their spontaneous nucleation and crystallization (in red in Fig. 2). Kober named the phenomenon percrystallization. The general concept of inserting a membrane

material between two phases (gas-liquid or liquid-liquid) in order to produce a solid by crystallization/precipitation was born.

The percrystallization process was then investigated, 15 years later, by Tauber and Kleiner [19], who confirmed Kober's results and obtained needle shape crystals of NaCl. However, the high thickness of the membrane material and the difficulty to control the operating conditions were the major limitations of this innovative process which remained unexplored for a long time.

The crystallization process using a membrane was relaunched in the 80's due to the development of microporous membrane materials and of water treatments mainly by reverse osmosis (RO). In fact, a series of studies addressed the interest of RO in order to achieve crystallization [20]. Nevertheless, numerous publications reported, in the same period, issues about membrane fouling due to the precipitation of mostly minerals (CaCO_3 , CaSO_4 , SiO_2 ...) but also organic matters on the retentate side of reverse osmosis membranes [20,21]. However, it is interesting to note that these two types of investigations share the same scientific framework, with two opposite targets (induce crystal formation for the former, prevent it for the latter).

From 1989, another membrane process, membrane distillation, was proposed for crystallization operation [22–24]. Since that time, several attempts have been reported on different solid systems, most often through membrane distillation. Membrane contactors [25–27] have been also tested for reactant mixing or anti-solvent dilution effects. The membrane contactor concept was recently adapted to the specific case of gas induced crystallization operations [28–30]. Other membrane processes (such as ion exchange, pervaporation, pressure retarded osmosis...) have been also occasionally reported for crystallization, but through a very limited number of studies.

It should be noted that, apart from the studies dedicated to membrane crystallization or membrane fouling due to precipitates, other research topics, listed in Table 2, could be of interest within the overall framework of the incidence of a solid material surface and crystal formation. For instance, a large number of publications can be found on inorganic membrane preparation, where precipitates or crystals have to be formed on the surface of a microporous support [29,31,32]. Similarly, several

fundamental studies have reported on the influence of a specific polymeric surface on crystal formation [29,31–35].

The increase of the interfacial area and non uniform surfaces is considered to promote the heterogeneous nucleation by reducing the induction time (i.e. time elapse between reaching the supersaturation and the first detection of the crystals) [36]. Moreover, Curcio et al. [37] also highlight that the nature of the membrane material plays a key role on the crystallization process as the surface tension can affect the nucleation rate.

In-situ crystallization into polymeric matrices has been also investigated for controlled release purposes or hybrid materials preparation [38]. Finally, the occurrence of crystals in kidneys (kidney stones) as a consequence of metabolic effects or the occasional deficiencies of biological membranes functions or due to fluid maldistribution effects, can also be seen as the same type of situation [39].

In summary, the interplay between solid surfaces and crystallization processes is a generic problem which is of interest for several situations, including membrane crystallizers. The interplay between operating conditions (concentration, temperature, hydrodynamic), solid material properties (permeability, selective mass transfer, heat transfer...) and interfacial effects (surface tension, rugosity..) is expected to give rise to a large number of possibilities and behaviors. A systematic analysis of the different materials and processes which have been investigated for crystallization purposes is proposed in the next section.

MEMBRANES AND CRYSTALLIZATION PROCESSES: STATE OF THE ART & CRITICAL REVIEW

Coming back to the different possibilities which can be applied in order to generate supersaturation (cf. Table 1), it is first important to notice that each method is potentially achievable thanks to a membrane function and/or associated process (cf. Table 3). Fig. 3 illustrates the different roles that membranes can play for heat transfer (Heat exchanger HX), selective mass transfer (Ultrafiltration UF, Nanofiltration NF, Reverse Osmosis RO, Ions Exchanger IE), combined heat and mass transfer (Thermal Membrane Distillation TMD, Pervaporation PV) or non selective mass transfer for reactants mixing purposes (Membrane Contactor MC).

From a process design point of view, the membrane functions shown in Fig. 3 can be applied for a membrane assisted operation (i.e. on a mixture recirculating loop), or directly for in situ crystallization purposes (cf. Table 3). The first case can be seen as a typical hybrid process approach and it is shown on Fig. 4.a. The membrane module is here used to generate the supersaturation, or simply to concentrate the solid phase, but the nucleation and the crystal growth take place in the crystallizer (e.g. [40–42]). The second strategy aims to develop novel crystallizers with a potential technological breakthrough (cf. Fig. 4.b.). In this case, the crystallization takes place directly in the membrane module where the supersaturation is generated. Consequently, this situation can be considered as an integrated membrane crystallization process [25,26,37,43].

Based on the double typology sketched in Fig. 3 and Fig. 4, a state-of-the-art review is proposed in Table 4. Membrane assisted and *in-situ* crystallizers studies are listed respectively in Table 4.a) and 4.b). Each membrane process, membrane material and structure, but also system type are detailed for the different studies reported up to now. Integrated membrane crystallization process is the most represented but studies are focused on the crystallization or precipitation of a few model compounds (such as lysozyme, NaCl, carbonates...) using mainly a limited number of membrane materials (Polypropylene PP, Polyvinylidene fluoride PVDF, Polyamide...).

Several authors point out one or several advantages of membranes for crystallization purposes but a systematic comparison to the reference technology (e.g. stirred tank reactor) is lacking. Hence, it clearly appears that several questions, discussed hereafter, regarding the crystallization/precipitation mechanism knowledge but also the interest of membrane processes for crystallization/precipitation operations are still open. Additionally, most of the studies reported are largely descriptive. In fact, only few authors report modelling attempts and no literature dedicated to the development of a generic modelling approach is available as it could be the case in a more mature technology.

A selection of some unsolved questions of major importance and the associated prospects are detailed hereafter.

Do membranes offer heat transfer intensification possibilities for crystallization/precipitation processes?

Membranes are commonly considered to improve heat and/or mass transfer performance, which are the key parameters of the crystallization/precipitation processes. However, it is important to understand that membrane material and structure, regarding the process involved, play an important role on performance. In both cases (heat or mass transfer), the aim of the membrane contactor is to offer a fine control of the supersaturation by locally controlling the heat and/or the mass transfer, and thus the nucleation, on a large area located at the interface between the membrane and the supersaturated liquid phase.

Dense and impermeable polymer materials are logically selected to improve the heat transfer only [44–46] when it is wanted to prevent mass transfer (cf. Fig. 3). In that case, the supersaturation mode is cooling. Although these polymer materials are not membrane; their form, such as hollow fiber, are membrane inspired.

Polymeric materials are actively investigated as heat exchangers due to their high chemical stability, their corrosion resistance but also their fouling resistance [46]. However, they have a low strength, a poor creep resistance, a large thermal expansion and a relatively poor thermal conductivity [45]. This last property is indeed usually 100 to 1 000 times lower than metals [8,45,47]: $0.11 \text{ W}\cdot\text{m}^{-1}\cdot\text{K}^{-1}$ for PP, $0.27 \text{ W}\cdot\text{m}^{-1}\cdot\text{K}^{-1}$ for Polytetrafluoroethylene (PTFE) [44] versus $401 \text{ W}\cdot\text{m}^{-1}\cdot\text{K}^{-1}$ for copper. It is assumed to be partially counterbalanced by the higher surface area developed by hollow fibers thanks to their lowest diameter, their smallest fiber thickness, and their lowest cost. The development, during the last decades, of new polymer matrix composites materials offers possibility to enhance the thermal conductivity of polymer materials by including for instance conductive metals and/or ceramic particles. Fibrous fillers made of glass, carbon or aramid fibers [44] are also used in matrix polymer to reinforce the elastic modulus and/or strength and the fatigue resistance properties [44]. If the results reported, in the best case, allow thinking that the performance could be in the same order of magnitude as metals usually employed, their use stays, until now, limited to few specific areas such as aerospace or high corrosive systems...

Finally, regarding the supersaturation mode, only integrated membrane processes (cf. Fig.4.b.) can be selected in crystallization process by cooling because the

temperature of the supersaturated phase is of key importance to regulate and control the nucleation and crystals growth rates.

Do membranes offer Process Intensification possibilities for crystallization/precipitation processes?

While dense impermeable membrane-like devices are needed for heat transfer purposes, porous [10,23,27,29,42,48], composite [20,48–50] or dense [18,32,51,52] membranes are used to control and intensify mass transfer applications. Coupled heat and mass transfer can occur in some case [52], and the mass transfer can be purely convective or with an additional selectivity effect [18,19,53]. In any case, permeable materials, most often polymeric, are used. Several supersaturation modes are conceivable regarding Fig. 3: Concentration, Dilution, Evaporation, and Reaction. In two modes, concentration and evaporation, heat and mass transfer are coupled. Differences take place depending on the membrane structure and function. In the Evaporation supersaturation mode, the selectivity of the process can be ensured by the membrane itself (such as through a selective solvent extraction by pervaporation), or due to vapor liquid equilibria properties (such as membrane distillation of salt containing mixtures). Thus, dense or porous membrane materials are potentially of interest.

In the dilution or reaction mode, a selective solute transfer is aimed thanks to the membrane. Controlled addition of a reactant or an antisolvent to the fluid mixture can be achieved under a liquid or a vapor or a gaseous state. Mixing can be in principle prevented before the transferred reactant reaches the fluid solution due to the membrane selectivity effect (e.g. solution diffusion mechanism for dense materials or size rejection for nanofiltration). Depending on the membrane, system and operating conditions, a very broad range of situations can result and the evaluation of the incidence on the process characteristic performance is not obvious. Similarly to gas-liquid absorption processes [54], one first indicator of the intensification effect would be the comparison, between the membrane crystallizer and the stirred tank, of the system volumetric productivity ratio.

To our knowledge however, no systematic comparison of the crystallization/precipitation process using a stirred tank reactor to one using a

membrane reactor is available in the literature. Consequently, major efforts should be performed in order to experimentally quantify the expected increased productivity of membrane processes for crystallization operations. Di Profio et al. [36,55] experimentally observed that the membrane surface, more specifically the pores and the roughness of the polymer, promotes heterogenous nucleation which reduces the induction time [9,10,29,36,37,56–59]. By increasing the nucleation rates, the nuclei amount in the solution is sufficiently important to increase the crystal growth rate [53,60]. However, the roughness of the membrane polymer but also the interactions between the membrane surface and the liquid phase are responsible for boosting the deposit of crystals on the membrane surface, i.e. fouling, which is discussed hereafter [3,25,61].

Finally, contrary to the cooling supersaturation mode, if the aim of the membrane is to favour the heat and/or mass transfer then the module can be used either in a membrane hybrid process (cf. Fig. 4.a.) or an integrated membrane process (cf. Fig. 4.b).

What is the impact of fouling on process performance?

Solid formation or impact on a porous or dense surface is prone to generate unwanted phenomena such as particulate deposit accumulation leading to so called surface fouling. More generally, fouling is responsible for the significant decrease of the permeate (and heat) fluxes through the membrane material. In membrane operations, porous or dense materials are well known to be potentially exposed to fouling effects which result from the deposition of suspended or dissolved matters. The deposit can be organic or inorganic, and accumulation can take place on the membrane surface (cf. Fig. 5.a), until blocking the flow, and/or inside the pores (cf. Fig. 5.b) [62]. Fouling is reported in most membrane processes [46,62–64] having at least one liquid phase in contact with the surface and is one of the major operating issues.

Integrated membrane crystallization processes [3,25,50,65,66] are likely to be more sensitive to fouling than the hybrid processes. This can be explained by the fact that supersaturation, nucleation and growth take place in the membrane module of the integrated process while only the supersaturation and probably the beginning of the nucleation occur in the membrane module of the hybrid process. Until now, no

comparison of the two processes on the same system has been carried out. It would be interesting to do it, especially on induction time and fouling.

Nevertheless, several studies are reported in the literature regarding the influence of the operating parameters on the fouling. Kieffer et al. [25] show that, in their experimental conditions, the increase of the inner diameter of the hollow fibers is sufficient to reduce fouling but no experiments on long time have been achieved. Most of the studies investigated pretreatment to limit fouling [62] based on the fact that, as the wetting of porous polymer material, fouling will necessarily occur at one time or another. Hence, Gryta et al. [67] recommends to heat the salt solution to the boiling point before a filtration step in order to eliminate most of the organic matters. Baker et al. [49] investigate magnetic pretreatment in order to prevent fouling by CaCO_3 crystals. However, they show that magnetic pretreatment is useful only in recirculating RO where the increase of the particle size, on the membrane, and the deposit growth, on the prefilter, are observed but not correlated to the improved performance of their reverse osmosis system.

In summary, there is a crucial lack of studies on membrane crystallizers performed over a long time scale, in order to evaluate the stability of performance of the membrane system. The rate of flux decline due to surface fouling or pore blocking effects, which is of major importance in microfiltration and ultrafiltration, remains relatively unexplored in membrane crystallization studies. Apart from the impact of fouling on process performance, the fouling mechanisms have not been investigated up to now. It is expected that the interactions between fluid conditions, crystal properties and membrane characteristics affect the importance of fouling phenomena.

Modelling of membrane crystallizers: possibilities and limitations

The general problem of modelling combining mass transfer, by diffusion or convection mechanism, and chemical reaction leading to solid formation is a major challenge [17]. Complex phenomena such as dissolution/precipitation fronts [68] or spatial changes of the diffusion/reaction front [69] have been already reported. It has been discussed before that the modelling attempts applied on membrane crystallizers are scarce [25,29]. A general framework showing the possibilities and bottlenecks is discussed hereafter.

The schematic diagram on Fig. 6 shows mass and heat transfer phenomena for a typical membrane module using hollow fibers. A resistance-in-series approach is proposed taking into account the convection and diffusion contributions. Hence, three layers (shell, membrane and lumen) are treated separately. The differential energy and mass balances in the radial and the axial directions over a single fiber (due to the symmetry of the module) are:

- Shell side: Diffusion, convection and reaction

$$D_i^{shell} \left[\frac{\partial^2 c_i^{shell}}{\partial r^2} + \frac{1}{r} \frac{\partial c_i^{shell}}{\partial r} \right] - v_z^{shell} \frac{\partial c_i^{shell}}{\partial z} + R_i^{shell} = 0 \quad (1)$$

$$\kappa^{shell} \left[\frac{\partial^2 T^{shell}}{\partial r^2} + \frac{1}{r} \frac{\partial T^{shell}}{\partial r} \right] - \rho C_p v_z^{shell} \frac{\partial T^{shell}}{\partial z} + \rho \sum H_i^{shell} = 0 \quad (2)$$

- Membrane: Diffusion only

$$D_i^{mem} \left[\frac{\partial^2 c_i^{mem}}{\partial r^2} + \frac{1}{r} \frac{\partial c_i^{mem}}{\partial r} \right] = 0 \quad (3)$$

$$\kappa^{mem} \left[\frac{\partial^2 T^{mem}}{\partial r^2} + \frac{1}{r} \frac{\partial T^{mem}}{\partial r} \right] = 0 \quad (4)$$

- Lumen side: Diffusion and convection

$$D_i^{lumen} \left[\frac{\partial^2 c_i^{lumen}}{\partial r^2} + \frac{1}{r} \frac{\partial c_i^{lumen}}{\partial r} \right] - v_z^{lumen} \frac{\partial c_i^{lumen}}{\partial z} + R_i^{lumen} = 0 \quad (5)$$

$$\kappa^{lumen} \left[\frac{\partial^2 T^{lumen}}{\partial r^2} + \frac{1}{r} \frac{\partial T^{lumen}}{\partial r} \right] - \rho C_p v_z^{lumen} \frac{\partial T^{lumen}}{\partial z} + \rho \sum H_i^{lumen} = 0 \quad (6)$$

With, D_i the diffusion coefficient of the species i in each layer ($\text{m}^2 \cdot \text{s}^{-1}$), c_i the concentration of the species i in each layer ($\text{mol} \cdot \text{m}^{-3}$), v the interstitial velocity defined as below ($\text{m} \cdot \text{s}^{-1}$), R the reaction rate ($\text{mol} \cdot \text{m}^{-3} \cdot \text{s}^{-1}$), r the radial coordinate (m), z the axial coordinate (m), T the temperature (K), ρ the density ($\text{kg} \cdot \text{m}^{-3}$), κ the thermal conductivity of each layer ($\text{W} \cdot \text{m}^{-1} \cdot \text{K}^{-1}$), H_i the enthalpy of reaction of the species i ($\text{J} \cdot \text{mol}^{-1}$), and C_p the thermal capacity ($\text{J} \cdot \text{K}^{-1} \cdot \text{kg}^{-1}$).

If heat and mass transfers occur simultaneously as for the concentration and evaporation supersaturation modes, then temperature and mass polarization effects have to be considered [62] :

$$TP = \frac{T_h - T_c}{T_{h,mean} - T_{c,mean}} \quad (7)$$

$$CP = \frac{c_{i,m}}{c_i} \quad (8)$$

With TP the temperature polarization (-) and CP the concentration polarization (-), T_h and T_c the temperature respectively of the hot fluid and the cold fluid (K), $T_{h,mean}$ and $T_{c,mean}$ the logarithmic mean temperature of the hot and the cold fluid (K), $c_{i,m}$ the concentration of i at the membrane surface ($\text{mol} \cdot \text{m}^{-3}$).

This set of equation highlights the numerous variables which are expected to affect the behavior of a mass and energy exchanger, such as a membrane crystallizer. It should be stressed that the crystal formation phenomena are not included in this equation set. The objective is first to evaluate temperature and concentration axial and radial profiles under steady state conditions, in order to identify the locations of crystal formation zones. Even if this representation is far to be complete, it would be of interest to apply it to the different systems, operating conditions and membrane types in order to better understand membrane module behavior. We notice that this type of approach has almost not been investigated in the studies listed in Table 4 [25] and the convection contribution is generally neglected. This matter of fact shows the efforts which are required in order to build a quantitative understanding of membrane crystallizers.

Regarding the Process Robustness and the Scale-up possibilities

A key question regarding any new process is the robustness and the scale-up possibilities. One of the main advantages of membrane processes is the scale-up ability [5,27]. Indeed, the inlet feed flow rate (capacity) can be easily increased by increasing the number of membrane modules used in parallel [60] or the number of fiber in the membrane. This strategy completely differs from the stirred tank approach, where scale-up often leads to trade off due to the impossibility to get the same hydrodynamic conditions when the size of the tank is increased.

However, if the scale up of membrane systems seems to be easy, the robustness of the process stays relatively unexplored. In fact, whatever the membrane materials used critical issues are reported in the literature. Regarding dense polymeric material, particulate deposits on the membrane surface, i.e. fouling, are commonly reported [46,65,70,71]. Porous polymeric materials are often preferred because of the better mass transfer performance. For instance, polypropylene is the most referenced material for membrane contactors applications for aqueous solutions. But, as in gas-liquid process where porous membrane materials are used, critical issues are reported in the literature [3,62]. The first issue is due to the pores wetting by the liquid. This phenomenon is often reported in gas-liquid and liquid-liquid processes using a membrane contactor [42,62,72,73]. It is expected to occur when evaporation is applied for crystallization purposes, thanks to a membrane distillation effect. The second issue is about fouling [3,25,62,74,75]. Both phenomena induce a decrease of

the transmembrane flux and an increased mass transfer resistance which is responsible for the decrease of the process performance over time. Several studies are reported about cleaning solutions or antifouling additive [46,63,64,76] but finding again the initial performance of the process is usually time consuming and harsh chemicals may be needed.

What about Product Quality?

The preferential crystallization/precipitation of a polymorphic, crystal shape and CSD is governed by the kinetics of the mechanisms involved [13,77].

Several studies have reported about the influence of the operating conditions and the membrane properties on the crystal shape.

Hence, Gugliuzza et al. [3] used a porous membrane contactor in PVDF to nucleate lysozymes and formed micro-size crystals. They also reported that the attractive interfacial forces between lysozyme and modified PVDF have an influence on the agglomeration of the protein crystals on the membrane surface, i.e. fouling which reduces the induction time. They confirmed that the membrane hydrophobic property is required in order to be used in a crystallization/precipitation process. Lin et al. [32] quantified this observation by measuring the kinetics of gypsum surface crystallization on several polyamide surfaces (Polysodium 4-styrenesulfonate PSS, Polyacrylic acid PAA, Polyethyleneimine PEI, Polyallylaminehydrochloride PAH). They concluded that mineral scaling or mineral crystallization is reduced on smoother surfaces and also suggested that the surface crystallization is influenced by the surface chemical functionality [31,32].

It is of primary importance, especially in pharmaceuticals, to characterize all polymorphs and to be able to only produce the desired polymorphic form. According to several pioneering studies, membrane processes appear as a tool to reach that aim [36,55,78]. This possibility remains to be systematically explored, because it offers attractive possibilities for major industrial applications. Due to its ability to control local supersaturation and temperature, membrane crystallizer could also be used to favor a given polymorph formation. The research scope in this area is very large.

Finally, the fine control of mass transfer across a membrane allows directly influencing and controlling the crystal size distribution and thus offers the possibility

to reach a narrower CSD than in the batch crystallizers [20,40,42,43,47] but, to our knowledge, no experimental comparison with the batch reactor is available until now in the literature.

In summary, in terms of product quality targets, membrane processes have been occasionally reported to offer specific polymorph production and narrow CSD [53,55,78]. Given the importance of product quality indicators in solid production, these qualitative observations suggest to be more systematically investigated and quantitatively described in membrane crystallizers [53,55,78].

CONCLUSION: FORTHCOMING ISSUES & PROSPECTS

This review paper analyzes the state of the art, challenges and major issues of membrane processes for an important, largely unexplored field of industrial interest, namely crystallization and precipitation processes.

At this point, we want to suggest several prospective issues which call for exploratory approaches:

i. Membrane materials : polymeric vs inorganic

The review highlights that, surprisingly, the main absentee, in terms of membrane materials, are the inorganic materials. Except very rare publications [79], the problem of crystal formation on a porous inorganic material is indeed unexplored. Given the differences between polymeric and inorganic membrane materials (surface properties, adhesion effects, rugosity...), the evaluation of inorganic membranes for crystallization applications should be performed. This could be of major interest, for instance, to crystallize under high or very low temperature.

ii. Membrane materials : porous vs dense

The second point underlined in the review is about the effects of membrane surface and structure. In fact, the use of membrane material is commonly accepted to promote the transfer of heat and/or mass and thus offering an optimal control of the supersaturation which induces an increase of the nucleation rate and the crystal growth. Thanks to the membrane, the crystal size distribution is narrower than in the reference process (batch) and could be easier to control as the choice of the polymorphic form of the compound.

However, the choice of the membrane material is of major importance as it is the first responsible for the life expectancy of the process. Until now, porous polymeric materials have been mainly reported in the literature to intensify mass transfer. However, the surface tension and the rugosity of the polymer play a key role on the adhesion of crystals on the membrane surface which will be responsible for the membrane fouling. This phenomenon is a critical issue to the process development. Dense membranes are little investigated, probably because of the higher membrane mass transfer resistance of the polymer, however this kind of material offers the possibility to avoid the pore blocking due to intra pore crystal growth. Composite material, i.e. a dense skin supported by a macroporous support could allow avoiding the entering of the crystals inside the porous support which reduce the membrane mass transfer performance. Low surface energy materials, such as perfluorinated polymers which offer interesting permeability levels towards small molecules, could be of interest to that respect.

iii. Development of modelling approaches for improved understanding

The third point which could be of major interest is the study of the concentration/reaction profiles of the process into porous or dense membranes in order to understand/elucidate where crystals formation takes place. Is it at the membrane surface or inside the membrane (inside the pores or the free volume)? The two types of situations have been reported; for instance *in-situ* crystal formation into dense polymeric membranes has been observed by McLeod et al.[29] and Zhang et al. [80]). Unfortunately, there is no understanding of the conditions which will induce crystal formation into the membrane, be it porous or dense, or at the surface. For membrane crystallizer operation, crystal formation at the membrane surface is an absolute necessity. In order to better understand, simulations should ideally be done the first time in order to identify the system behavior and, the second time, by experimental proof of concept studies, with *in-situ* measurements and, if possible, visualization methods. From a broader point of view, the possibility to achieve *in situ* crystal formation in a given matrix could also be of interest for different purposes. Hybrid materials combining a continuous polymeric matrix

with a solid dispersed phase, such as shown on Fig. 5 could offer applications in medicine to deliver drugs for example [38].

iv. Membrane module modelling and design

Finally, it is suggested that coupling, at the membrane module scale, kinetics, by using population balance, and fluid mechanics (CFD) is still required to obtain a fine modelling of the processes and thus to elucidate and/or predict the incidence of operating and geometric properties on the polymorphic form of the solid product, the local supersaturation conditions, the nucleation kinetics, the crystal size distribution and the crystal growth rate [25]. This target is clearly a major challenge but it should be attempted so that membrane crystallizers can be definitely considered as a mature and liable unit operation.

We hope that the ideas and prospects reported in this study, and summarized on Fig. 7, will stimulate research in a challenging area, which could open new promising applications for membrane processes in different industrial sectors.

SYMBOLS & ABBREVIATION

a	:	Interfacial area ($\text{m}^2 \cdot \text{m}^{-3}$)
c_i	:	Concentration of i ($\text{mol} \cdot \text{m}^{-3}$)
$c_{i,m}$:	Concentration of i at the membrane surface ($\text{mol} \cdot \text{m}^{-3}$)
C_p	:	Thermal capacity ($\text{J} \cdot \text{kg}^{-1} \cdot \text{K}^{-1}$)
CP	:	Concentration polarization (-)
D_i	:	Diffusion coefficient of i ($\text{m}^2 \cdot \text{s}^{-1}$)
H_i	:	Enthalpy of reaction of i ($\text{J} \cdot \text{mol}^{-1}$)
HX	:	Heat Exchanger
IE	:	Ion Exchanger
L	:	Fiber length (m)
MC	:	Membrane Contactor
NF	:	Nanofiltration
PA6,6	:	Polyamide 6,6
PAA	:	Polyacrylic acid
PAH	:	Polyallylaminehydrochloride
PDMS	:	Polydimethylsiloxane

PEI	:	Polyethyleneimine
PES	:	Polyethersulfone
PP	:	Polypropylene
PSS	:	Polysodium 4-styrenesulfonate
PTFE	:	Polytetrafluoroethylene
PV	:	Pervaporation
PVDF	:	Polyvinylidene Fluoride
R	:	Reaction rate ($\text{mol.m}^{-3}.\text{s}^{-1}$)
r	:	Radial coordinate (m)
r_i	:	Inner radius of the fiber (m)
r_e	:	External radius of the fiber (m)
r_s	:	Shell side radius (m)
RO	:	Reverse Osmosis
SiO_2	:	Silicon dioxide
T	:	Temperature (K)
T_c	:	Temperature of the cold fluid (K)
$T_{c,\text{mean}}$:	Logarithmic mean temperature of the cold fluid (K)
T_h	:	Temperature of the hot fluid (K)
$T_{h,\text{mean}}$:	Logarithmic mean temperature of the hot fluid (K)
TMD	:	Thermal Membrane Distillation
TP	:	Temperature polarization (-)
UF	:	Ultrafiltration
v	:	Interstitial velocity (m.s^{-1})
z	:	Axial coordinate (m)

Greek symbols

ρ	:	Density (kg.m^{-3})
κ	:	Thermal conductivity ($\text{W.m}^{-1}.\text{K}^{-1}$)

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TABLE 1*Generation of supersaturation using a membrane*

Supersaturation generation method	Mode	References	
		Reference Technology (Stirred Tank Reactor)	Membranes (Breakthrough technology)
Decrease of the temperature	Cooling	[77,81,82]	[8,29,40–42,46]
Addition of antisolvent	Dilution	[83]	[27,53]
Addition of a reactant	Reaction	[84]	[26,27,32]
Removal of solvent	Evaporation		[18,36,37,43,50,59,85,86]
Flash Evaporation, Cooling	Vacuum		[51,62]

TABLE 2

Different research fields for which crystal formation in contact to a solid surface has to be taken into account

Topic	Target	References
Membrane crystallization	Novel crystallization process	[24–32,36,37,40–45,87]
Particulate deposit and fouling of membranes (RO, IE, TMD...)	Crystal formation prevention	[50,63,75,76,88]
Inorganic membrane production via in situ crystal formation (e.g. zeolite membranes)	Materials production	[89]
Incidence of surfaces on polymorphism	Fundamental studies	[29,31–35]
Hybrid matrix polymers (osmotic release systems, photo films...)	Product design	[38]
Crystal formation in kidneys	Medicine	[39]

TABLE 3

Membrane applications in precipitation/crystallization processes.

Applications	Usable membrane processes
Heat exchanger	Polymeric Hollow Fiber Heat Exchanger
Solvent evaporation	Membrane distillation Pervaporation
Concentration	Reverse Osmosis, Nanofiltration, Ultrafiltration, Microfiltration
Reactant adding	Membrane contactor Ultrafiltration, Nanofiltration, Microfiltration, Ion Exchange
Antisolvent	Membrane contactor

TABLE 4

List of publications on membrane processes applied for crystallization / precipitation operations. Membrane process, membrane material and structure, system type are detailed.

a) Hybrid membrane process

Membrane Process	Membrane Material	Membrane Structure	System Type	References
Membrane Contactor	PP	Porous	CaSO ₄ , NaCl, MgSO ₄ 7.H ₂ O	[90]
Membrane Distillation	PVDF	Porous	Na ₂ SO ₄ , NaCl	[40,42,86,91]
Microfiltration	Ceraver ZrO ₂ , PP	Porous	Ions, NaCl, MgSO ₄ 7.H ₂ O	[92,93]
Nanofiltration	PS on PE Polyamide, PP	Composite, Porous	Na ₂ SO ₄ , NaCl, MgSO ₄ 7.H ₂ O	[48,92]
Reverse Osmosis	Polyamide, PP	Composite, Porous	(NH ₄) ₂ SO ₄ , NaCl, MgSO ₄ 7.H ₂ O	[41,92]
Ultrafiltration	Polysulfone	Porous	Glutamic Acid	[94]

b) Integrated membrane process

Membrane Process	Membrane Material	Membrane Structure	System Type	References
Heat Exchanger	Nitrocellulose, PP, PP-g-MA	Dense	(NH ₄) ₂ SO ₄ , HCl, NaCl, KNO ₃	[8,18,19,46,47,71]
Membrane Contactor	PP, PTFE, PVDF, PDMS	Porous, Dense	Trypsin, Na ₂ CO ₃ , NH ₄ HCO ₃ , CaCO ₃ , NaCl, MgSO ₄ 7.H ₂ O	[29,60,90,95]
Membrane Distillation	PVDF, PP	Porous	NaCl, Taurine, CaCO ₃	[22–24,43,62]
Microfiltration	PP	Porous	NaCl, MgSO ₄ 7.H ₂ O	[92]
Membrane crystallizer	PP, PVDF, Cellulose Acetate, PES, EtOH	Porous, Liquid	Lysozyme, Fumaric acid; Paraffins, L-Asparagine, Paracetamol, L-Glutamic acid, Glycine, BaSO ₄ , Ions, Na ₂ CO ₃ , NaF	[3,25–27,30,36,37,53,55,57–59,78,96–100]
Nanofiltration	PAA, PSS, PAH, PES, PA(6,6), SiO ₂	Dense	CaSO ₄	[32]
Pervaporation	PEBA 2533	Dense	Phenols	[51]
Reverse Osmosis	PAA, PSS, PAH, PES, PA(6,6), SiO ₂ , Polyamide, Cellulose Acetate	Dense, Composite, Porous	Ca(COO) ₂ , CaCO ₃ , Lysozyme, CaSO ₄ , Si(OH) ₄ , Biofilms	[20,31,32,49,50,52,85,101]
Ultrafiltration	Cellulose Acetate	Porous	Biofilms	[85]

LIST OF CAPTIONS

Figure 1:

Evolution of the number of publications per year in scientific journals which include the keywords “Crystallization” (black diamond) and “membrane crystallization or membrane distillation” (grey diamond).

ISI Web of Science, April 2015.

Figure 2:

Classical concentration / temperature phase diagram showing the different regions of a liquid / solid phase transition & Schematic representation of the evolution of the supersaturation during Kober’s experiments [18] (in red).

Figure 3:

Schematic representation of the different functions that can potentially be offered by a membrane based on the different supersaturation methods listed in Table 1. Heat and mass transfer (selective or non selective) properties can be used, through different membrane processes listed in the last row.

Figure 4:

Schematic representation of the two process designs: a) Hybrid membrane crystallization process. b) Integrated membrane crystallization process.

Figure 5:

*Examples of hollow fiber fouling due to intramembrane crystal formation (a) and precipitate formation **on the membrane surface** (b).*

Figure 6:

Schematic diagram of a membrane fiber

Figure 7:

Summary diagram of the interactions.

Figure 1

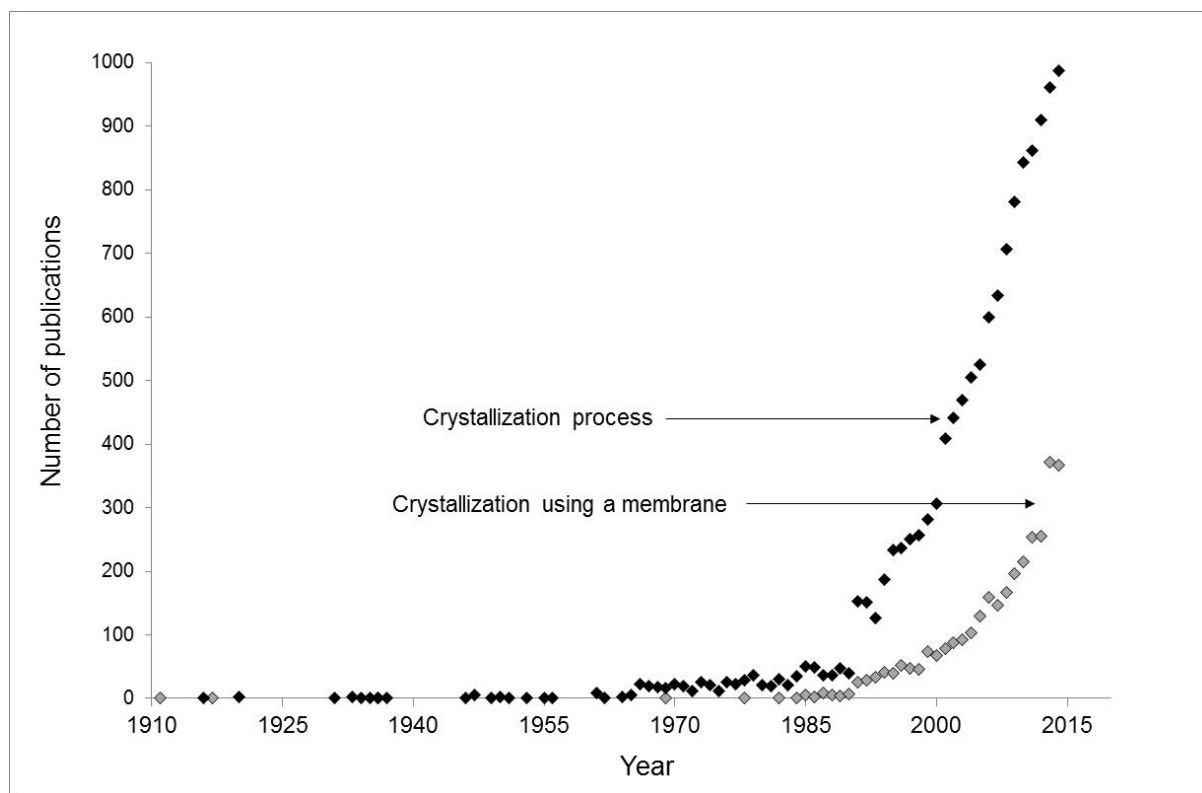


Figure 2

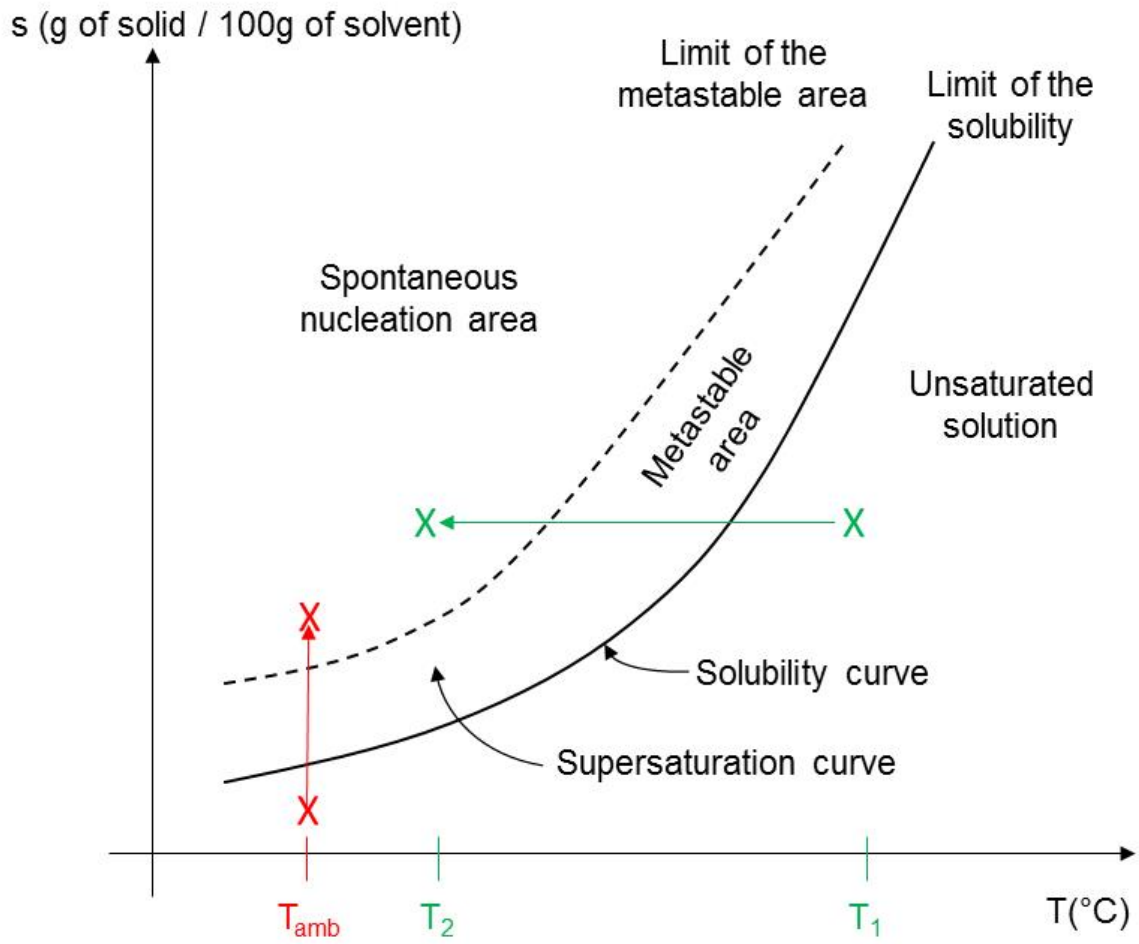


Figure 3

Supersaturation mode	Cooling	Concentration	Dilution	Evaporation	Reaction
Membrane function					
Process type	Membrane heat exchanger (HX)	Selective mass transfer for solvent removal (UF, NF, RO)	Selective mass transfer for solvent removal (UF, NF, RO)	Selective mass transfer for solvent removal by evaporation (PV, TMD)	Reactant mixing through a membrane (MC, UF, NF, RO, IE)

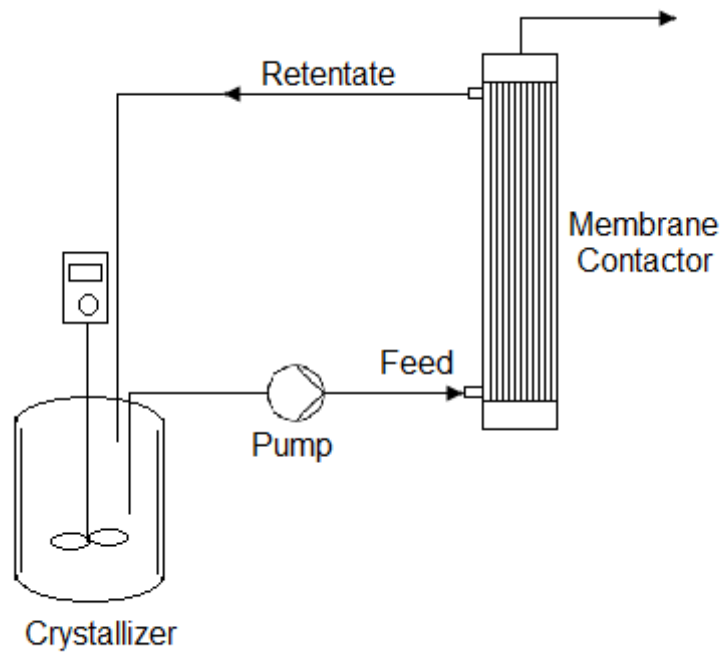
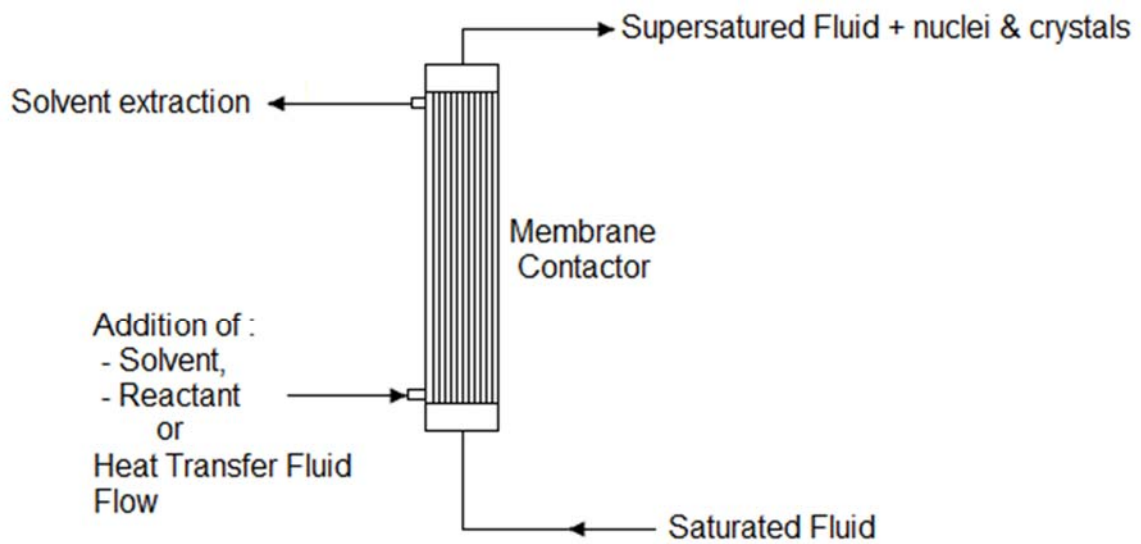
Figure 4**a)****b)**

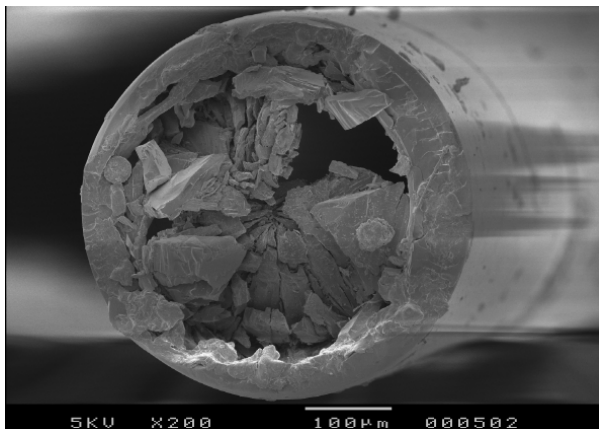
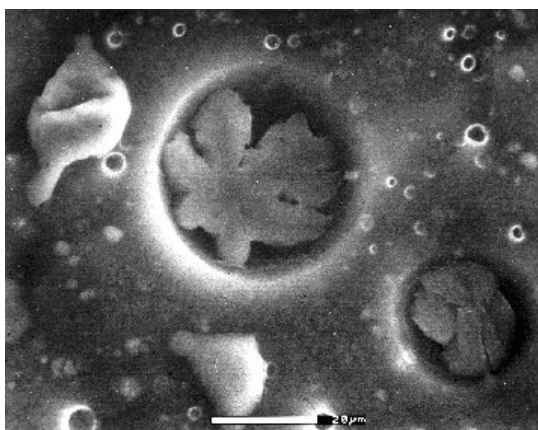
Figure 5**a)****b)**

Figure 6

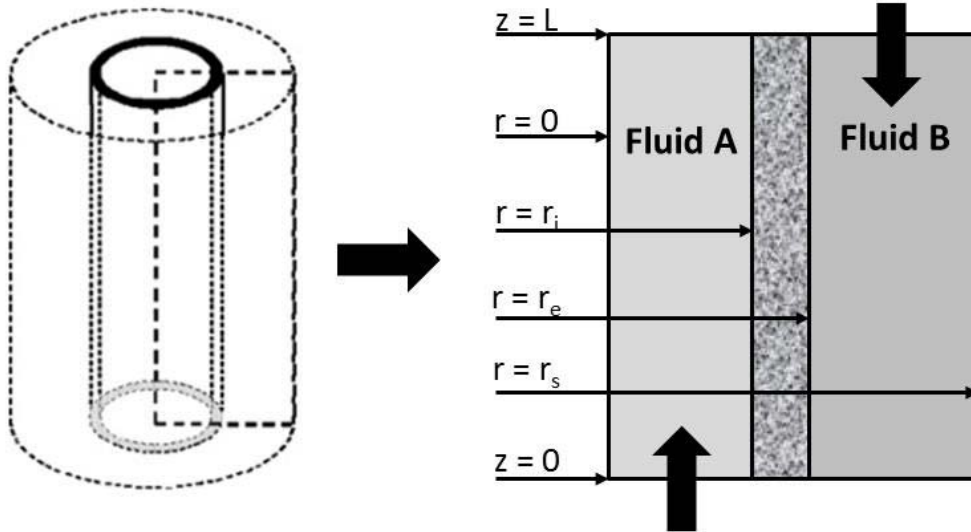


Figure 7

