European Roadmap of Process Intensification

-Technology Report –

Technology: ***Membrane Crystallization Technology***

Technology Code:

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1. Technology

1.1 Description of technology / working principle

(Feel free to modify/extent the short technology description below)

Membrane Crystallization (MCr) is an innovative crystallization concept, put into operation by using membrane technology, by which crystals nucleation and growth is carried out in a well-controlled pathway, starting from a under-saturated solution. The working principle of a membrane crystallizer can be considered as an extension of the Membrane Distillation (MD) concept. In fact, in its typical configuration, it is a device in which a solution containing a non-volatile solute that is likely to be crystallized (defined as the crystallizing solution or feed or retentate), is "contacted" by means, generally, of a hydrophobic microporous membrane, with a stripping solution or pure water or the vacuum, on the distillate side, on the principle of the membrane contactors. The physical-chemical properties of the membrane impede the contacted solution(s) to pass through its porous structure directly in the liquid state. As the feed is stopped at the mouth of each pore on the one side of the membrane, a liquid/vapor interface is generated by the solvent molecules evaporating over and in dynamic equilibrium with the solution. These solvent molecules in the vapor state leave the interface, going towards the distillate side, under the action of a driving force. Upon arrival on the distillate compartment, the solvent molecules re-condensate in the liquid phase generating a second vapor/liquid interface. The driving force is a gradient of chemical potential and is generated by means of a concentration and/or temperature between the two sides of the membrane. Under this mechanism, as the driving force is kept active, the crystallizing solution progressively concentrates reaching the thermodynamic conditions required for crystals' nucleation and/or growth. In MCr, although the membrane put in contact the crystallizing solution with the distillate side, the two compartments are independent. This means that external manipulation on the crystallization kinetics, by tuning some of the operative parameters, can be carried out without disturbing the crystallizing solution, by acting *e.g.* on the distillate side. The effect would be the control of the rate and the extent on nucleation over the crystal growth thus investigating a broad set of kinetic trajectories for crystal nucleation and growth, that are not readily achievable in conventional crystallization formats, and which would lead to the production of specific crystalline morphologies and structures.

As in a membrane crystallizer the crystallizing solution is in direct contact with the membrane, a heterogeneous contribution to the crystallization mechanism, arising by solute-membrane interaction, might occur. As a consequence, the lowering of the activation energy for nucleation allows crystallization in that conditions which would not be adequate for spontaneous nucleation and/or to induces an enhancement of the crystallization kinetics with respect to conventional evaporative crystallization methodologies. Furthermore, the solute-membrane interaction can provide specific solute-solute interaction pathways which would lead to

the formation of specific crystal forms. This effect can be due to both the structural and chemical properties of the membrane surface: *(1)* the porous nature of the surface might achieve cavities where solute molecules are physically entrapped leading, locally, to high supersaturation values suitable for nucleation; *(2)* the non-specific chemical interaction between the membrane and the solute molecules can lead to molecular orientation and hence to the facilitated effective interaction proper for crystallization.

1.2 Types and "versions"

(Describe the most important forms/versions of technology under consideration, including their characteristic features, differences and similarities)

Crystallization occurrence in membrane operation have been observed by various researchers. A common issue was the observation of crystal formation on the surface of polymeric reverse osmosis (RO) membranes used in water desalination . Moreover, the interest in this phenomena was primarily to avoid it, as to prevent crystal formation would preserve the system from flux decline during the operation *(1,2)*.

The first study aiming to use a membrane unit properly as a crystallizer dates back to 1986, when Azoury *et al*. *(3-6)* studied the precipitation of calcium oxalate in hollow fiber reverse osmosis modules to simulate the early stages of stone formation in the renal tubules. Protein crystallization was also tested by using RO membranes in an osmotic dewatering technique *(7)*.

In membrane distillation, crystallization phenomena have been observed by various researchers as well *(8-13)*. In some studies *(11,13)* crystallization was merely a hindering factor introducing flux decline due to fouling, while in others *(9,10,12)* membrane distillation accompanied by crystallization served simply as a polishing step of wastewater streams followed by downstream recovery of the crystallizing solute.

In spite of the first experiences of crystallization in membrane operations in which crystallization was considered at best a secondary phenomenon if not a side effect, the use of the membrane technology to design a well-controlled crystallization processes is quite recent as also the terms *Membrane Crystallizer (14-16)*. This technique was first used by Drioli's group even to growth single protein crystals suitable for X-ray diffraction analysis *(17)*. Several following papers described the advantages, over conventional evaporative techniques, of MCr *(18-32)*.

In its current general conception, what is defined as a *membrane crystallizer* is a system comprised by a solid hydrophobic (for hydrophilic crystallizing solution) or hydrophilic (for hydrophobic crystallizing solutions) (micro)porous membrane. The membrane might be made by polymeric or inorganic materials or by a combination of both type in a hybrid or composite configuration. Hollow fibers as well as flat membranes can be used in the system. When the driving force of the evaporation-migration-condensation mechanism is generated by a temperature gradient the system is named *thermal membrane crystallizer*, whilst if the driving force arises by an osmotic potential difference, the system is said *osmotic membrane crystallizer*. In the

different cases, the crystallizing solution can be re-circulated generating a condition of forced solution convection in a dynamic MCr or might be kept quiescent in a static configuration.

The concept of the osmotic membrane crystallizer has been used in the very last years by several authors to produce *microfluidic* system for proteins crystallization *(33, 41)*. These systems consist in traditional vapor diffusion apparatus where a polymeric membrane, generally made by poly(dimethylsiloxane) (PDMS), is used to separate the crystallizing and the reservoir solutions. The control in the solvent evaporation rate from the macromolecular solution towards the reservoir, in dependence of several operative parameters, lead to the production of high quality crystals and/or with particular morphologies, suitable for X-ray diffraction.

If considering crystallization carried-out by using similar apparatus, a solid hollow fiber cooling crystallization system have been proposed by Sirkar and Zarkadas *(34, 36)*. This system consists in a solid non-porous hollow fiber mounted within a shell where the feed solution flows through the lumen side of the hollow fibers and a cooling solution flows through the shell side to induce nucleation and crystals' growth in the feed solution at a temperature below its saturation temperature.

In an additional embodiment of a membrane-based crystallization device, a crystallizing solution is forced trough a membrane in one or more anti-solvents for the specie which is likely to be crystallized or that one ore more anti-solvents are forced trough the membrane in the solution comprising the specie to be crystallized. *(37,39,35)*.

Overall, the several versions of the crystallization systems described above can be therefore classified according with the different working principle:

1) Diffusion of solvent molecules in vapor phase through the pores of a (generally) microporous membrane under the action of a gradient of chemical potential as driving force; this is the working principle of a membrane crystallization in its current and more general definition.

2) Solid hollow fibers as heat exchanger for supersaturation generation by cooling.

3) Anti-solvent (crystallizing solution) forced directly into the crystallizing solution (anti-solvent) through the pores of a membrane under a pressure gradient.

1.3 Potency for Process Intensification: possible benefits

(In Table 1 describe the most important documented and expected benefits offered by the technology under consideration, focusing primarily on energy; CO_2 emission and costs, providing quantitative data, whenever possible. Add other benefits, if needed).

Table 1: Documented and expected benefits resulting from technology application

Benefit	Magnitude	Remarks
High control of the crystallization process.	-	See below.
Low energy demand.	-	See below.
Facilitated crystallization processes.	-	See below.
Mild operating conditions.	-	See below.
Improved crystal quality.	-	See below.
Possibility of scale-up and scale-down.	-	See below.
Easy incorporation in integrated membrane processes.	-	See below.

High control of the crystallization process. The thermodynamic driving force for crystallization is supersaturation, *i.e.* that condition of non-equilibrium in which the concentration of solute molecules in solution is above its solubility limit. As all the stages comprising the crystallization mechanism, *i.e.* nucleation, growth and growth cessation are governed by supersaturation, controlling supersaturation will means to control the crystallization kinetics and, at the end, the final properties of the crystalline materials produced. In other words, morphological (crystal size, size distribution, shape and habit) and structural (polymorphism) crystal properties can be behaved by acting on supersaturation. These properties are fundamental in industry for several downstream processes like filtering, drying, compression in tablets, *etc.* as well as for product utilization by end-users (effect on solubility, rate of dissolution, thermal stability, *etc.*). In a membrane crystallizer, the membrane acts as physical support modulating the rate of solvent evaporation from the crystallizing solution towards the distillate side. The rate of solvent extraction (driving force) can be well-controlled, in a very gentle mode, by acting both on membrane and process parameters. Therefore, in a membrane crystallizer, control of supersaturation is feasible and allows to modulate the final crystals' properties with important effects in terms of production costs and product effectiveness.

Low energy demand. Membrane crystallization technique requires low energy input for its operation. As an instance, in a thermal membrane crystallizer small temperature gradients between the feed and the distillate sides, in the order of 15 *°C*, is enough to produce trans-membrane fluxes as high as 15-20 $L/m^2\ h$. This means that a membrane crystallizer can be driven by using heat generated by other industrial processes (as *e.g.* in co-generation plants) and that would, in normal cases, be lost in the surrounding with high operating costs. On these bases, also non-conventional alternative energy sources, like wind – solar – geothermal – *etc.*, might be potentially used to operate a membrane crystallization installation.

Facilitated crystallization processes. In a membrane crystallizer, working in both static and dynamic configuration, the membrane surface acts as a promoter of crystallization in that conditions of supersaturation that would not be adequate for spontaneous nucleation. The special effect of the heterogeneous contribution allows crystals to be grown faster and/or by using lower initial amount of substance with respect to usual comparable techniques. Moreover, particular surface-assisted pathways for solute-solute interaction, can allow the obtainment of specific crystalline habits of the same structure or specific polymorphs. This would be of extreme importance *e.g.* in pharmaceutics, microelectronics and other nanotechnology areas where crystals' structure and morphology have an important impact on the properties of the crystals produced in regards to their specific applications.

Mild operating conditions. In a thermal MCr low feed temperature is sufficient to operate at high trans-membrane fluxes. In an osmotic system, the supersaturation inside the crystallizing solution can be generated by using a stripping agent, which normally consist in a solution of an inert inorganic salt (NaCl, $MgCl_2$, $CaCl_2$, etc.). In both cases, the concentration of the feed is carried out in gentle conditions, without the solution experiencing thermal or mechanical stress. This means that with the membrane-based system, labile or thermal-sensitive molecules, like *e.g.* proteins, viruses or other macromolecules, can be crystallized in large amount, in very mild conditions, thus avoiding degradation and/or denaturation.

Improved crystal quality. Two molecules that have to form a crystalline contact are brought together by translational diffusion and may be adjusted spatially by a subsequent rotational diffusion. In this way, the chance for fine-tuning of the proper spatial positioning of the crystallization patches on the two molecules is increased. It is straightforward that the random rotations of molecules, which even slows down very fast with larger complexes, leads to a reduced chance for the proper and effective molecular interaction. In the membrane-assisted interaction among the solute molecules, the induction of the proper orientation would allows to form crystalline clusters with well-ordered organization of the crystal building blocks. Furthermore, a condition of laminar flow in laminar regime, typical of a dynamic membrane crystallizer, would improve the rectification of the thermal motion of the growing clusters in solution. These effects, in turn, allow to generate high ordered crystals by improving first stage aggregation and aggregate growth. This

would be a fundamental improvement in the field of *e.g.* protein crystallization, in which high diffracting (ordered) single crystal is required for X-ray diffraction analysis for medical advancement.

Possibility of scale-up and scale-down. As for every membrane operations, modularity might allow to scale-up or scale-down a process by simply adding or removing membrane modules. A similar case is for membrane crystallization techniques. In fact, this system would not suffer to any limitations for industrial-scale purposes by using well designed multi module system approach. On the other side, the simple working principle of the system allows to produce as small crystallization devices as micro-fluidic systems for the crystallization of little amounts of high-expensive materials, usually macromolecules, in high-throughput screening apparatus.

Easy incorporation in integrated membrane processes. As environmental protection laws become more and more stringent, high-impact wastes arising from industrial productions cannot be anymore discharged in around without preventive specific purification steps. This is the case of several industrial sectors where wastewaters containing high polluting and/or high value substances (fine chemicals, heavy-metals, agro-food, tannery, desalination, petrol-chemical, *etc.*) dispersed in the productive cycle must be processed before being discharged in the environment. In this sense, membrane crystallization might be introduced in a integrated membrane systems in which, after specific separation steps, the selective crystallization and removal of specific components might be achieved. In this way, on the one side, the treated wastes can be purified by several pollutants thus reaching the right characteristics for direct discharge and, on the other side, valuable materials with commercial implications can be recovered in crystalline state, and hence with high purity, to be used for other purposes. Crystallization of marine salts from the brines of nanofiltration and/or reverse osmosis in seawater desalination is a typical example of such a strategy.

1.4 Stage of Development

At moment, the stage of development of the membrane crystallization technology is at laboratory or at pilot-plants scale.

2. Applications

2.1 Existing technology (currently used)

(Describe technology (-ies) that are conventionally used to perform the same or similar operations as the PI-technology under consideration)

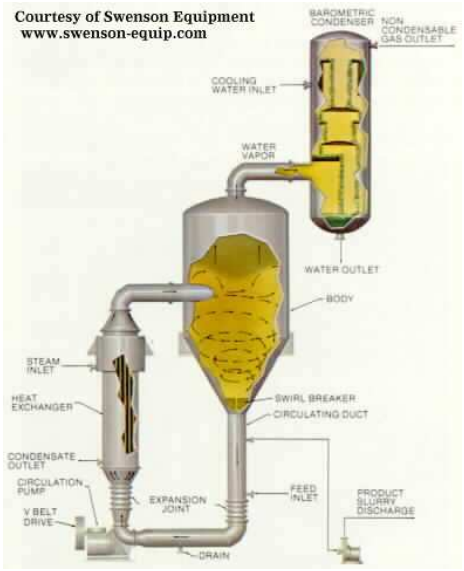
Currently industrial crystallization is carried out by one of the following methods.

Tank Crystallizers. This is probably the oldest and most basic method of crystallization. In fact, the "pot of salt water" is a good example of tank crystallization. In this system, hot, saturated solutions are allowed to cool in open tanks. After crystallization, the mother liquor is drained and the crystals are collected. Controlling nucleation and the size of the crystals is difficult. The crystallization is essentially just "allowed to happen". Heat transfer coils and agitation can be used. Labor costs are high, thus this type of crystallization is typically used only in the fine chemical or pharmaceutical industries where the product value and preservation can justify the high operating costs.

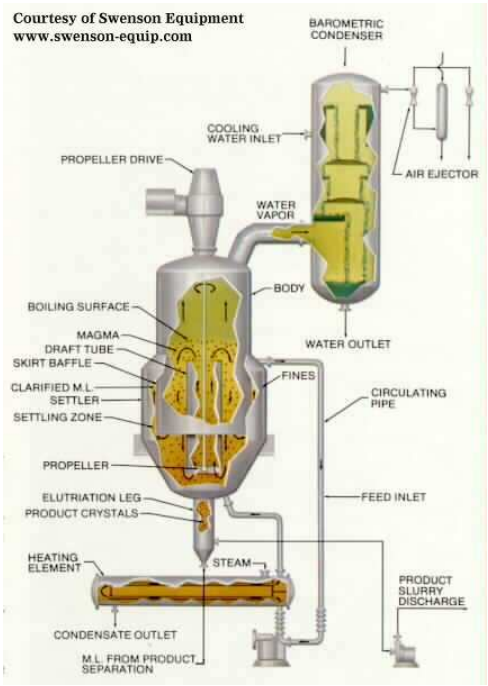
Scraped Surface Crystallizers. An example may be the Swenson-Walker crystallizer consisting of a trough about 2 feet wide with a semi-circular bottom. The outside is jacketed with cooling coils and an agitator blade gently passes close to the trough wall removing crystals that grow on the vessel wall.

Forced Circulating Liquid Evaporator-Crystallizer. Just as the name implies, these crystallizers combine crystallization and evaporation, thus the driving forces toward supersaturation. The circulating liquid is forced through the tubeside of a steam heater. The heated liquid flows into the vapor space of the crystallization vessel. Here, flash evaporation occurs, reducing the amount of solvent in the solution (increasing solute concentration), thus driving the mother liquor towards supersaturation. The supersaturated liquor flows down through a tube, then up through a fluidized area of crystals and liquor where

crystallization takes place via secondary nucleation. Larger product crystals are withdrawn while the liquor is recycled, mixed with the feed, and reheated.



Circulating Magma Vacuum Crystallizer. In this type of crystallizer, the crystal/solution mixture (magma) is circulated out of the vessel body. The magma is heated gently and mixed back into the vessel. A vacuum in the vapor space causes boiling at the surface of the liquid. The evaporation causes crystallization and the crystals are drawn off near the bottom of the vessel body.



2.2 Known commercial applications

(Is the technology broadly applied on commercial scale? In which process industry sectors is the technology most often applied: large volume chemicals – specialty chemicals & pharma – consumer products – ingredients based on agro feedstocks? What is the estimated number of existing applications? In Table 2 provide the most prominent examples of realized applications and provide their short characteristics)

Table 2. Industrial-scale applications of the Technology (existing and under realization)

Sector	Company – Process/Product name/type	Short characteristic of application	Production capacity/Plant size	Year of application	Reported effects

No commercial applications of the membrane crystallization technology are known.

2.3 Known demonstration projects

(Are there any demonstration projects known related to the technology under consideration? In which process industry sectors are those projects carried out: large volume chemicals – specialty chemicals & pharma – consumer products – ingredients based on agro feedstocks? In Table 3 provide the short characteristics of those projects.)

Table 3. Demonstration projects related to the technology (existing and under realization)

Sector	Who is carrying out the project	Short characteristic of application investigated, including product name/type	Aimed year of application	Reported effects
Desalination	Co-ordinator: Prof. Enrico Drioli, University of Calabria	Title: MEmbrane-based Desalination: an INtegrated Approach The strategy proposed in the project is the integration of different membrane operations in pre-treatment and post-treatment stages. In particular, membrane crystallization is used to approach the concept of Zero Liquid Discharge (increasing the water recovery factor up to 95% bringing concentrates to solids and to reduce the brine disposal environmental impact and cost.	Duration: 36 months	N.A.

N.A.	Middle East Desalination Research Center, Muscat, Oman.	N.A.	N.A.	N.A.
N.A.	National Technological Department of China 973 (N. 2003CB615700) .	N.A.	N.A.	N.A.
N.A.	College of Life Science and Technology, Beijing University of Chemical Technology, Beijing, China	N.A.	N.A.	N.A.
N.A.	Pfizer Inc., Global Research & Development, Groton CT, USA.	N.A.	N.A.	N.A.
N.A.	Center for Membrane Technologies at New Jersey Institute of Technology.	N.A.	N.A.	N.A.
N.A.	Akzo Nobel, The Netherlands	N.A.	N.A.	N.A.
N.A.	TNO, The Netherlands	N.A.	N.A.	N.A.
N.A.	Universität Erlangen-Nürnberg, Germany.	N.A.	N.A.	N.A.

2.4 Potential applications discussed in literature

(Provide a short review, including, whenever possible, the types/example of products that can be manufactured with this technology)

Membrane crystallization has been used to growth crystals characterized by narrow crystal size distribution. This was the case of inorganic *(16,21)*, small organic *(18)* and macromolecular *(22,23)* materials.

Some applications demonstrated as membrane crystallization is a versatile technique to control sovrassaturation, thus inducing polymorph selection in the crystallization of organic materials *(29,31,32)*.

Enhanced crystallization kinetics were obtained in the crystallization of proteins thank to the heterogeneous contribution to nucleation provided by the membrane surface *(20,26)*.

Membrane crystallization has been tested for the recovery of crystalline materials from the brine of nanofiltration and/or reverse osmosis in integrated membrane operations for seawater desalination *(21,25,28,30)*.

3. What are the development and application issue?

3.1 Technology development issues

(In Table 4 list and characterize the essential development issues, both technical and non-technical, of the technology under consideration. Pay also attention to "boundary" issues, such as instrumentation and control equipment, models, etc.) Also, provide your opinion on how and by whom these issues should be addressed)

Table 4. Technology development issues

Issue	**Description**	**How and by whom should be addressed?**
Increase of the membrane life with constant hydrophobic character.	Development of new materials/preparation methods for membrane with extended life and particularly with stable hydrophobic character to be used in the technology.	These issues should be addressed at basic as well as at applied-scale research through a close collaboration among public/private research centers and industries. A multidisciplinary approach, involving chemists, materials scientists, chemical engineers, process engineers, and biologists should be put in operation.
Improvement of the membrane performances.	Development of new materials/preparation methods for the production of membranes with tailored properties (pore size and morphology, overall porosity, thickness, thermal conductivity, *etc.*) to be used in the technology.	
Avoidance of crystals growth on the membrane surface.	Development of new materials/preparation methods for the production of membranes with specific surface properties to be used in the technology.	
Control of the membrane surface roughness and hydrophobic character.	Development of new materials/preparation methods for the production of membranes with specific surface roughness and hydrophobic character.	
Efficient products separation.	Development of new process design in integrated systems aiming to selectively produce crystals of various type.	
Process optimization.	Development of the technology for an efficient process design and crystallization kinetics control.	

Technology transfer to industry	Application of the technology on industrial-scale and valuation of benefits/advantages obtained in the logic of the process intensification strategy, with respect conventional processes.	

3.2 Challenges in developing processes based on the technology

(In Table 5 list and characterize the essential challenges, both technical and non-technical, in developing commercial processes based on the technology under consideration. Also, provide your opinion on how and by whom these challenges should be addressed)

Table 5. Challenges in developing processes based on the technology

Challenge	**Description**	**How and by whom should the challenge be addressed?**
High control of the crystallization process.	See Section 1.3.	These issues should be addressed at basic as well as at applied-scale research through a close collaboration among public/private research centers and industries. A multidisciplinary approach, involving chemists, materials scientists, chemical engineers, process engineers, and biologists should be put in operation.
Low energy demand.	See Section 1.3.	
Facilitated crystallization processes.	See Section 1.3.	
Mild operating conditions.	See Section 1.3.	
Improved crystal quality.	See Section 1.3.	
Possibility of scale-up and scale-down.	See Section 1.3.	
Easy incorporation in integrated processes.	See Section 1.3.	

4. Where can information be found?

4.1 Key publications

(Provide the list of key publications in Table 6)

Table 6. Key publications on the technology

Publication	Publication type (research paper/review/book/report)	Remarks
(1) Boerlage, S.F.E.; Kennedy, M.D.; Bremere, I.; Witkamp, G.J.; Van der Hoek, J.P.; Schippers, J.C. J. Membr. Sci. 2000, 179, 53.	Research paper	N.A.
(2) Boerlage, S.F.E.; Kennedy, M.D.; Bremere, I.; Witkamp, G.J.; Van der Hoek, J.P.; Schippers, J.C. J. Membr. Sci. 2002, 197, 251.	Research paper	N.A.
(3) Azoury, R.; Garside, J.; Robertson, W.G. J. Cryst. Growth 1986, 79, 654.	Research paper	N.A.
(4) Azoury, R.; Garside, J.; Robertson, W.G. J. Cryst. Growth 1986, 76, 259.	Research paper	N.A.
(5) Azoury, R.; Garside, J.; Robertson, W.G. J. Urol. 1986, 136 (1), 150.	Research paper	N.A.
(6) Azoury, R.; Robertson, W.G.; Garside, Chem. Eng. Res. Des. 1987, 65, 342.	Research paper	N.A.
(7) Todd, P.; Sikdar, S.K.; Walker, C.; Korzun, Z. R. J. Cryst. Growth 1991, 110, 283.	Research paper	N.A.
(8) Wu, Y.; Drioli, E. Water Treat. 1989, 4, 399.	Research paper	N.A.
(9) Wu, Y.; Kong, Y.; Liu, J.; Zhang, J.; Xu, J. Desalination 1991, 80, 235.	Research paper	N.A.
(10) Wu, Y.; Kong, Y.; Liu, J.; Xu, J. Water Treat. 1991, 6, 253.	Research paper	N.A.
(11) Tomaszewska, M. J. Membr. Sci. 1993, 78, 277.	Research paper	N.A.
(12) Gryta, M. Desalination 2000, 129, 35.	Research paper	N.A.
(13) Gryta, M.; Tomaszewska, M.; Grzechulska, J.; Morawski, A.W. J. Membr. Sci. 2001, 181, 279.	Research paper	N.A.

(14) Curcio E. , Criscuoli A. , Drioli E. , "EUROMEMBRANE 2000", Hills of Jerusalem (Israel), 24-27 Settembre, 2000, p. 393.	Conference proceedings	N.A.
(15) Curcio E. , Criscuoli A. , Drioli E. , "3rd Italy-Korea Workshop on Membrane Processes for Clean Energy and Clean Environment", Cetraro (Italy), 23-27 Settembre, 2001.	Conference proceedings	N.A.
(16) E. Curcio, A. Criscuoli, E. Drioli, Ind. Eng. Chem. Res., 2001, 40, 2679.	Research paper	N.A.
(17) E. Curcio, G. Di Profio, E. Drioli, Desalination, 2002, 145, 173.	Research paper	N.A.
(18) E. Curcio, G. Di Profio, E. Drioli, Sep. Pur. Tech., 2003, 33, 63.	Research paper	N.A.
(19) Curcio, E.; Di Profio, G.; Drioli, E. J. Cryst. Growth 2003, 247, 166.	Research paper	N.A.
(20) Di Profio, G.; Curcio, E.; Cassetta, A.; Lamba, D.; Drioli, E. J. Cryst. Growth 2003, 257, 359.	Research paper	N.A.
(21) E. Drioli, E. Curcio, A. Criscuoli, G. Di Profio, J. Memb. Sci., 2004, 239, 27.	Research paper	N.A.
(22) Di Profio, G.; Curcio, E.; Drioli, E. J. Struct. Biol. 2005, 150, 41.	Research paper	N.A.
(23) Di Profio, G.; Perrone, G.; Curcio, E.; Cassetta, A.; Lamba, D.; Drioli, E. Ind. Eng. Chem. Res. 2005, 44, 10005.	Research paper	N.A.
(24) E. Curcio, S. Simone, G. Di Profio, E. Drioli, A. Cassetta, D. Lamba, J. Memb. Sci., 2005, 257, 134.	Research paper	N.A.
(25) C. M. Tuna, A. G. Fane, J. T. Matheickal, R. Sheikholeslami, Journal of Membrane Science 257 (2005) 144.	Research paper	N.A.
(26) Curcio, E.; Fontananova, E.; Di Profio, G.; Drioli, E. J. Phys. Chem. B 2006, 110, 12438.	Research paper	N.A.
(27) E. Drioli, A. Criscuoli, E. Curcio, Membrane Contactors: Fundamentals, Applications and Potentialities, Elsevier, Amsterdam, 2006.	Book	N.A.
(28) E. Drioli, E. Curcio, G. Di Profio, F. Macedonio, A. Criscuoli, Chem. Eng. Res. Des., 2006, 84, 209.	Research paper	N.A.
(29) S. Simone, E. Curcio, G. Di Profio, M. Ferraroni, E. Drioli, Journal	Research paper	N.A.

of Membrane Science 283 (2006) 123.		
(30) L. Mariah, C.A. Buckley, C.J. Brouckaert, E. Curcio, E. Drioli, D. Jaganyi, D. Ramjugernath, Journal of Membrane Science 280 (2006) 937.	Research paper	N.A.
(31) Di Profio, G.; Tucci, S.; Curcio, E.; Drioli, E. Cryst. Growth Des. 2007, 7, 526.	Research paper	N.A.
(32) G. Di Profio, S. Tucci, E. Curcio, E. Drioli, Chem. Mater. 2007, 19, 2386.	Research paper	N.A.
(33) Hansen, C.L.; Classen, S.; Berger, J.M.; Quake, S.R. J. Am. Chem. Soc. 2006, 128, 3142.	Research paper	N.A.
(34) D.M. Zarkadas, K.K. Sirkar, Ind. Eng. Chem. Res. 2004, 43, 7163.	Research paper	N.A.
(35) D.M. Zarkadas, K.K. Sirkar, Chemical Engineering Science 61 (2006) 5030.	Research paper	N.A.

4.2 Relevant patens and patent holders

(Provide the list of relevant patents in Table 7. Under "remarks" provide, where applicable, the names/types of products targeted by the given patent.)

Table 7. Relevant patents

Patent	**Patent holder**	**Remarks, including names/types of products targeted by the patent**
(36) Solid Hollow Fiber Cooling Crystallization System and Methods US2006/0096525A1	K.K. Sirkar, D. Zarkadas	Highly uniform in size crystals of: KNO_3, Salicylic Acid, Paracetamol.
(37) Antisolvent Solidification Process WO2004/096405A1	Akzo Nobel N.V., Arnhem (NL)	Higly uniform in size crystals of: NaCl, 3-Ketodesogestrel, Progesteron
(38) Method for Crystallizing Soluble Salts of Divalent Anions from Brine WO2006/045718A1	Akzo Nobel N.V., Arnhem (NL)	Removing alkali metal or ammonium salts of divalent anions from brine by membrane filtration
(39) Process Involving the Use of Antisolvent Crystallisation WO2004/096404A1	Akzo Nobel N.V., Arnhem (NL)	Process involving the use of antisolvent crystallization of salts comprising

		crystallization and filtration units
(40) Method of Increasing Concentration of Salt Solutions by Membrane Distillation Combined With Crystallization of Salt and System There for. PL346481	Politechnika Szczecinska (PL)	-
(41) Microfluidic Protein Crystallography Techniques WO2005/056813A3	California Institute of Technology; The Regent of the University of California	-

4.3 Institutes/companies working on the technology

(Provide the list of most important research centers and companies in Table 8)

Table 8. Institutes and Companies working on the technology

Institute/Company	**Country**	**Remarks**
Institute on Membrane Technology (ITM-CNR), Rende	Italy	N.A.
Department of Chemical Engineering and Materials, University of Calabria, Rende	Italy	N.A.
Center For Membrane Technologies, Otto H. York Department of Chemical Engineering, New Jersey Institute of Technology.	USA	N.A.
College of Life Science and Technology, Beijing University of Chemical Technology, Beijing.	China	N.A.
UNESCO Centre for Membrane Science and Technology, School of Chemical Engineering and Industrial Chemistry, University of New South Wales, Sydney	Australia	N.A.
Institute of Environmental Science and Engineering, Nanyang Technological University	Singapore	N.A.
TNO	The Netherlands	N.A.

5. Stakeholders

5.1 Suppliers and developers

(Provide the list of key suppliers/developers in Table 9)

Membranes used for Membrane Crystallization are currently the same as for membrane distillation. Therefore, potential suppliers are all that involved in the production and distribution of MD modules and membranes.

Table 9. Suppliers and developers

Institute/Company	Country	Remarks
Institute on Membrane Technology (ITM-CNR), Rende	Italy	Developer of MCr.
Department of Chemical Engineering and Materials, University of Calabria, Rende	Italy	Developer of MCr.
Center For Membrane Technologies, Otto H. York Department of Chemical Engineering, New Jersey Institute of Technology.	USA	Developer of MCr.
College of Life Science and Technology, Beijing University of Chemical Technology, Beijing.	China	Developer of MCr.
UNESCO Centre for Membrane Science and Technology, School of Chemical Engineering and Industrial Chemistry, University of New South Wales, Sydney	Australia	Developer of MCr.
Institute of Environmental Science and Engineering, Nanyang Technological University	Singapore	Developer of MCr.
TNO	The Netherlands	Potential Developer of MCr.

5.2 End users

(Describe the existing and potential end-users, other than those already listed in Table 2)

As the membrane crystallization technology has not yet experienced visible commercial applications, currently end-users are not yet visible. Potential end-users would be:

- ✓ All the industries involving crystallization and/or a crystallization steps in the productive cycles. As an instance, around to 90% of all the product from the pharmaceutical industry are delivered in crystalline state or involve, in their production a crystallization step. As a second instance, fabrication of microelectronic devices requires single semiconductor crystals with high purity. In the agro-food field, a great number of product are produced as crystalline powders.
- ✓ In every industrial field where wastewater purification prior to discharge and/or re-use, might be operated by extracting solutes as crystals. In this sense, sea and brackish water desalination industry might receive great benefit from this technology.
- ✓ Research centers involved in medical advancement by macromolecular single crystal X-ray diffraction analysis. The possibility to produce high ordered crystals of proteins and/or viruses can lead to higher resolution patterns for a better understanding of the molecular structure and functions. The use of membrane crystallization techniques might also allow to use little amount of materials for high-throughput screening.

6. Expert's brief final judgment on the technology

(Maximum 5 sentences)

1) A crystallizer based on microporous hydrophobic membrane can be considered a new membrane unit operation well consistent with the requirements of the process intensification.
2) The possibility of improving significantly the crystallization velocity exists as well also the crystallization of specific polymorphs by acting on the trans-membrane fluxes, axial flow rates, temperature, membrane morphology and chemical properties, *etc.*.
3) The use of membrane crystallization combined with all membrane operations might offer solutions in various industrial fields minimizing the problem *e.g.* of the brine disposal of RO and NF systems used in desalination.
4) The control of the various parameters characterizing the membrane crystallization process (pore size, porosity, thickness, hydrophobic character, *etc.*) can offer interesting new opportunities for the final formulation of crystalline drugs, proteins and other bio-active species. Specific enantiomeric forms or polymorphs might be obtained.
5) Energy consumption and both capital and running costs might be lower than that characterizing traditional crystallization systems.