EUROPEAN ROADMAP OF PROCESS INTENSIFICATION

- TECHNOLOGY REPORT -

TECHNOLOGY: ULTRASOUND ENHANCED CRYSTALLISATION

TECHNOLOGY CODE: 3.2.6

AUTHOR: Herman J.M. Kramer, Delft University of Technology

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1. Technology

1.1 Description of technology / working principle

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

Power ultrasound usually operates at frequencies around 20kHz, higher than the audible range. The interaction of the pressure wave with the media containing liquids, generates chemical or physical changes due to acoustic cavitation. Acoustically induced cavitations are particularly effective at inducing nucleation in liquids. Application of the ultrasound enhances the nucleation rate up to a factor 20 and moreover nucleation can be induced at a lower supersaturation, by the reduction of the so called “meta-stable band width”. The effect of power ultrasound on crystal suspensions is complex, but strong effects have been reported on the growth, secondary nucleation and agglomeration rates. In addition less defined effects have been found on properties of the crystalline product, like particle size, and shape, surface properties type of polymorph.

Therefore power ultrasound seems a suitable technique to control crystallisation and precipitation processes of especially organic compounds, which often have difficulty to nucleate. In addition however power ultrasound can be used as a tool in crystal engineering to affect additional properties of the crystalline product, like particle size, and shape, surface properties type of polymorph etc. There have been reports on the formation of ultra-fine, nano-structured materials.

1.2 Types and “versions

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

The technique can be applied in two different way

1: In crystal free supersaturated solution. Primary nucleation is promoted, avoiding high supersaturation levels needed to produce enough crystals nuclei, which gives rise to kinetic roughening, agglomeration impurity take up etc.

2: Prolonged application of power ultrasound to crystal suspensions is used to tune the product properties of the produced crystals

Application in both cases is mostly done in a recycle loop containing a Ultrasonic cell.

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, wherever possible. Add other benefits, if needed).

Table 1: Documented and expected benefits resulting from technology application

Benefit	Magnitude	Remarks
Energy saving		Power ultrasound enables the formation of ultra-fine materials which are very difficult to produce with traditional crystallisation or precipitation techniques, avoiding the energy spilling milling steps which are now applied to produce the fine powder
Cost saving		Faster processing due to better particle quality no Avoiding milling steps Smaller equipment
Improved product properties		Making fine particles or single crystals, which cannot be achieved otherwise

1.4 Stage of development

Most applications are still in the laboratory phase of development although recently a number of industrial applications are reported by Prosonic, which offers laboratory and pilot scale equipment.

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)

The current technology is the use of crystallisation and/ or precipitation processes. In many cases time consuming Oswald ripening steps have to be used to enhance the crystallinity and/or filterability of the product. In case the polymorphism, re-crystallisation steps might be needed to obtain the desired product properties. Finally sieving and/or milling might be needed to meet the product specifications

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
Hydro-metallurgical	Aughinish Alumina	Impurity removal		2006	Increase plant capacity and efficiency
Aluminum production	Alcoa	Product property improvement		2007	

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
				•

2.4 Potential applications discussed in literature

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

The use of ultrasound as alternative for addition of seed crystals
Sono-crystallisation in late phase of Active Pharmaceutical Ingredient (API) to improve shape , size and type of polymorph
Catalyst production when ultra fine or nano-structured materials are needed.
Application fields of interest are pharmaceutical products food products (sugars, fats, oils) and fine powders which are difficult to crystallise.

3. What are the development and application issues?

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?
Engineering and design	A number of power ultrasound applications have been developed mainly for laboratory scale. Procedures are needed to design of the application of power ultrasound for a application without extensive test programs. In addition much effort must be put in the design of the ultrasound equipment to optimize the desired effects on the crystallisation process. Finally scale up issues must be investigated.	Research project in university centers in cooperation with manufactures of ultrasound devices and process or pharmaceutical companies
Modeling and scale up issues	Research to describe and quantify the effects of ultrasound on the different kinetic phenomena in crystallisation and precipitation processes to develop models for optimization and scale up pf the sono-crystallisation.	Research project in university centers in cooperation with manufactures and process or pharmaceutical companies
Equipment development	Investigation how cavitation can be controlled and manipulated to control desired effect on the crystallisation phenomena/crystal properties. Development of new equipment in which this technology is applied and which will enable to generate specific interaction of the applied ultrasound field with the liquid or suspension to yield the desirable effect on the crystallisation process or the product properties.	R&D projects in university centers with expertise on ultrasounds and crystallisation in cooperation with manufacturers.

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?
Quantification and scale up of the nucleation effect	The control of the number of crystals is essential in to control the product quality Quantification and control of the nucleation rate using ultrasound is needed to reach that goal.	Research in university research centers in cooperation with manufacturers of

		ultrasonic equipment
Understanding the interaction of cavities and the crystals	Cavity formation in liquids can be described by the Raleigh Plesset theory. To understand the formation in the vicinity of crystals and the interaction with these crystals research is needed to be able to quantify and optimize these effects	Research in university research centers in cooperation with manufacturers of ultrasonic equipment
Optimization of the different effects without compromising the others.	Are the different effects of ultrasound really caused by different mechanisms or are they the result of the complex interactions and phenomena of crystallisation processes. Can the effects be isolated and optimized separately by the proper choice of the process conditions?	Research in university research centers in cooperation with manufacturers of ultrasonic equipment

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
B.Ratsimba and B. Biscans, Sonocrystallisation: The end of empirism?, 1999,KONA,17, pp.38-47	Review	
John Dodds, Fabienne Espitalier,Olivier Louisnard, RomainGrossier, René David, Myriam Hassoun, Fabien Baillon, Cendrine Gatumel, Nathalie Lyczko, The Effect of Ultrasound on Crystallisation-Precipitation Processes: Some Examples and a New Segregation Model, Part. Part. Syst. Charact. 24 (2007) 18–28		Scientific paper discussing possible mechanisms
C. Virone, H.J.M. Kramer, G.M. van Rosmalen, A.H. Stoop and T.W. Bakker, 2006, Primary nucleation induced by ultrasonic cavitation Journal of Crystal Growth, Volume 294, pp. 9-15		Scientific paper discussing possible mechanisms
R.K. Bund, A.B. Pandit Sonocrystallisation: Effect on lactose recovery and crystal habit Ultrasonics Sonochemistry 14 (2007) 143–152		Application in lactose
G. Ruecroft, D. Hipkiss, T. Ly, N. Maxted, P. W. Caims, Sonocrystallisation: the use of ultraound for improved industrial crystallisation, Organic Process Research & Development, 2005, 9, 923–932, 12–14		Technical paper about applications
Linda McCausland and Peter Cains Ultrasound to make crystals, Chemistry & Industry, 2003, No 9, 15-17		Technical paper
Z. Guoa, M. Zhangb, H. Lib, J. Wangb, E. Kougoulos, Effect of ultrasound on anti-solvent crystallisation process Journal of		

Crystal Growth 273 (2005) 555–563.		

4.2 Relevant patents 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
WO03/10157	ACCENTUS PLC (GB)	production of crystalline materials by using high intensity ultrasound
WO03057717	ABBOTT GMBH & CO KG	Crystallisation of amino acid, e.g., L-thyroxine
WO03101578	ACCENTUS PLC	Production of crystalline material useful in pharmaceuticals and foods
WO2004034943,	BOEHRINGER INGELHEIM PHARMA GMBH & CO KG	Production of powders of inhalable medicaments
WO0044468	BRISTOL-MYERS SQUIBB CO	Crystallisation of pharmaceutical compound by impact of jet streams in presence of sonicator probe
WO0200200	GLAXO GROUP LTD	New preparation of crystalline particles
WO0205921 ds	LIPTON DIV CONOPCO INC	Solid phase crystallisation from liquid

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
Ecole des Mines D'Albi-Carmaux, Albi	France.	
Dep of applied chemistry of the Waseda Univ	Japan	
Department of Chemical Engineering, University College London,	United Kingdom	
Delft University of Technology, Dep. of Process and Energy Technology	The Netherlands	
Chemical Engineering Division, Institute of Chemical Technology, University of Mumbai, Mumbai	India	
Prosonix Ltd	United Kingdom	

5. Stakeholders

5.1 Suppliers and developers

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

Table 9. Supplier and developers

Institute/Company	Country	Remarks
Prosonix Ltd	United Kingdom	

5.2 End users

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

6. Expert's brief final judgment on the technology

(maximum 5 sentences)

Power ultrasound is a promising technology which can play, when further developed an important role in crystallisation and precipitation processes for the production of solid materials with special properties or in cases where traditional control mechanisms fail. The technology is still in an early stage of development and interdisciplinary research is needed to extend the number of industrial applications and to improve the fundamental knowledge, the design and engineering of the applications and the equipment. On the longer term the technology could be applied in a more broader range of applications become a key technology in novel crystallisation designs.