Review Article

Melt Sonocrystallization A Novel Technique of Solubility Enhancement: A Review

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ABSTRACT

Oral bioavailability drugs are depends on several factors such as aqueous solubility, drug permeability and dissolution rate. The most frequent causes of low oral bioavailability are because poor solubility and low permeability. Solubility is one of the important parameters to achieve desired concentration of drug in plasma for achieving required pharmacological response. It has been investigated that new chemical entities currently being discovered most of them have poor water solubility, which limits its therapeutic efficacy. Melt sonocryatallization is newer particle engineering technique involved utilization of ultra sound energy to generate fine particles of drugs that helps to improve aqueous solubility and bioavailability. Melt sonocrystallization offers solvent and carrier less technique for the formation of fine particles which makes this technique more promising for the enhancement drug solubility in water.

Keywords: Sonocrystallization, Melt Sonocrystallization, BCS, Ultra sound.

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INTRODUCTION

Absorption of a drug through the oral route involves dissolution of drug from the delivery system into gastric or intestinal fluids followed by its permeation through gastrointestinal cell membranes. Bioavailability of drugs from oral route depends on their solubility as well as permeability. Solubility is one of the important parameter to achieve desired concentration of drug in plasma for desired pharmacological response. [1-2]

It has been investigated that most of new chemical entities currently being discovered most of them have poor water solubility, which limits the therapeutic efficacy of that drug. Poor solubility results in higher dose and repeated administration causes higher incidences of side-effects. Hence, major challenges in front of pharmaceutical scientist are to improve the oral bioavailability of poorly water-soluble drugs by improving their solubility, dissolution rate and membrane permeability. [3-6]

The low solubility and low dissolution rate of poorly aqueous soluble drugs in gastro-intestinal fluids often shows insufficient bioavailability. The idea of permeability and solubility characteristics had been helpful to classify the drug under four classes prescribed by Biopharmaceutics Classification System (BCS). The BCS is a scientific framework for classifying a drug substance based on its solubility in water and intestinal permeability. According to BCS, class II and IV drugs are rate limiting step is drug release from the dosage form and solubility in gastrointestinal fluid, so improving the solubility of such drugs will enhance the bioavailability.[7-10] The details of BCS Classification System are shown in Table 1.

Table 1: Biopharmaceutical Classification System

Class 1	High Solubility – High Permeability
Class 2	Low Solubility – High Permeability
Class 3	High Solubility – Low Permeability
Class 4	Low Solubility – Low Permeability

Techniques of solubility enhancement

Solubility enhancement techniques can be categorized in to three types like physical modification techniques, chemical modifications techniques and other techniques.[11-23] The details of solubility enhancement techniques are summarized in table 2.

Sonocrystallization

Sonocrystallization is crystallization induced by ultrasound (US). In 1927 Richards and Loomis firstly reported the effects of US on crystallization.[24] The research in this field was delayed owing to inconsistent results and the lack of proper US devices. In the period of 1950s to the 1970s, sonocrystallization was actively studied in the former Soviet Union.[25-28] From that time, sonocrystallization of various materials have been reported.[29-31] The industrial use of sonocrystallization increased during the 1980s due to advances in ultrasonic equipment, and, currently,

sonocrystallization is common for generating crystals in the pharmaceutical and fine chemicals sectors.[32-34] Sonocrystallization is the technique based on the use of ultrasound (US) to produce smaller particle size and particle size distribution (PSD) and to generate of the desired morphology.

Table 2: Various solubility enhancement techniques

Physical Modification Technique				
1. Reduction of particle size	**2. Drug dispersion in carrier**	**3. Modification of crystal habit**	**4. Complexation**	**5. Solubilisation by surfactant**
a. Micronization b. Nanosuspension c. Sono crystallization d. Supercritical fluid process e. Spray Drying	a. Solid solution b. Eutectic Mixture c. Solid dispersion	a. Polymorph	a. Use of complexing agent • Inorganic • Coordination • Chelates • Metal Olefin • Inclusion • Molecular complexes	a. Microemulsion b. Self emulsifying drug delivery system
Chemical Modification Technique				
a.Co-solvency	b.Co-crystallization	c.Salt formation	d.Solubalizing agent	e.Hydrotrophy
Other Technique				
a.Hot melt extrusion	b.Supercritical fluid method	c.Solvent evaporation	d.Lyophylization Technique	e.Polymeric alteration

Ultrasound (US) is an oscillating sound pressure wave over a frequency range of 15 kHz to 10 MHz.[35] When ultrasonic waves pass through a liquid with sufficient amplitude, the negative pressure exceeds the local tensile strength of the liquid and bubbles are created. Bubbles are generated near pre-existing impurities (e.g., gas-filled crevices in dust motes), which oscillate and grow during cycles of compression and expansion. When the developing bubbles reach to a resonant size, they efficiently absorb energy from ultrasound waves during a single compression expansion cycle. The resonant size depends on the frequency of the irradiated ultrasound, and is approximately 170 µm for a 20 kHz ultrasound. At the resonant size, bubbles grow rapidly during a single cycle of ultrasound waves due to efficient energy absorption. Thought the bubbles cannot be sustained without absorption of energy, they implosively breakdown after reaching the resonant size. This process is referred to as acoustic cavitation.[36]

The collapse of bubbles produces hot spots, which have intense local temperatures (~5000 K) and pressures (~1000 atm) and a rapid heating and cooling rate (>10^{10} Ks^{-1}) and shockwaves. Shockwaves have velocities as high as ~4000 m/s and high-pressure amplitudes of 10^6.kPa.[37]

The physical effects of ultrasound are more diverse in heterogeneous systems than in homogeneous systems. At the point when a bubble collapses near larger surface or particle, the bubble no longer collapses spherically and because of that high-speed liquid stream with a velocity >100 m/s is generated. The liquid moves toward the surface of the solid material, which deforms it or changes its chemical composition. Furthermore, shockwaves produced from acoustic cavitation cause high-velocity collisions between micron-sized solid particles (i.e., interparticle collisions). Shockwaves can also directly interact with particles and induce breakage this phenomena is also called as sonofragmentation.[38]

Crystallization is a universal operation for formation of fine chemicals, pharmaceuticals or intermediates whether derived from chemical or biochemical processing. Nucleation and crystallization can be mediated by acoustic cavitation and streaming.[39] Sonocrystallization is mediated by the bubbles caused by such acoustic effects. These bubbles are temporary micro reactors that allow faster chemical reaction and crystallization. Sonocrystallization is involved in one or all of the key steps in the nucleation and crystallization process.

The sonocrystallization process involves:

- Improved mass transport which improves clustering and templating
- Fast cooling after cavitation collapse
- Temporary high super saturation close to the collapsing bubble
- Pressure increases which reduce the temperature for crystallization
- Shock waves to assist in nucleation
- Overcoming energy barriers for nucleation

Mechanism of Sonocrystallization

Widely accepted explanation is the so-called “hot spot” theory, which attributes nucleation to local hot spots, created by the concentration of kinetic energy in the collapsing cavity or due to rapid cooling afterwards. Another well-known mechanism is based on the fact that the pressure shockwave caused by cavity collapse creates locally high pressures. There are substances for which the

solubility reduces with pressure, this increases the local super saturation and could induce nucleation. A theory related to the shockwave effect states that nucleation is initiated due to separation of the solute and solvent near the bubble wall. This is due to high pressures occurring in the ultimate phase of bubble collapse. One more theory suggests that nucleation occurs during bubble expansion. Solvent evaporating into the bubble or cooling of the liquid interface layer increases local super saturation, which could lead to nucleation around the cavity. Also of interest is the electrical theory, which proposes the consequences of cavitation are caused by electrical charges on the cavity interface layer.[40]

The most accepted explanation of the small size particle achieved by Sonocrystallization is related to the characteristic effects of ultra sound (US), the stirring effect causes a reduction in thickness of the diffusion layers in the vicinity of the crystal surfaces by the high-energy shockwaves impinging on the particle surface. This can create high-velocity inter particle collisions that can alter the particle morphology and size dramatically. It was reported that these inter particle collisions occur with such a great force that even metal particles tend to melt together.[41] As the exact mechanisms behind US-assisted crystallization are not known yet, the following hypotheses seem to be the most accepted.[42]

1. The effect of US is not directly caused by vibrations of the US waves but by the cavitation bubbles formed by the US field.
2. Both the amount and the size of the cavitation bubbles affect the nucleation rate.
3. Higher US intensities produce more cavitation bubbles and nucleation increases.
4. Larger US frequencies produce smaller cavitation bubbles which have a smaller impact on the nucleation rate.
5. The segregation and cavitation bubble theories link the nucleation rate to the size of the cavitation bubbles.

Melt Sonocrystallization

Melt sonocryatallization technique is a novel particle engineering technique involves the application of ultra sound (US) energy to the soft or viscous molten mass dispersed in an immiscible liquid. Solidification/ crystallization from emulsified melt is carried out under the influence of US energy. The technique was initially used for production of sintered crystals and a porous glassy bead which allows extending the US energy received by the melt in the emulsified state and determines the properties of the resultant particles, which are dependent on US energy input and frequency, and solidification rate of the melt. In turn, this last variable depends on the temperatures of glass transition of the material and that of the medium. Application of US at temperatures above the transition temperature favors crystallization, whereas processing below the transition temperature results in an amorphous state. The mechanical stress due to ultra-sonication results in sintered crystals or porous beads. The porous nature and potential for producing crystalline particles as well as amorphous particles offer flexibility to the technology and are looked upon for improving the solubility of poorly soluble pharmaceuticals.[43-45]

Melt sonocrystallization offers solvent and carrier less technique for the formation of fine particles of drug with enhanced solubility in water. This technique has also been reported to improve solubility, micromeritics properties and rheological properties of drugs.

Process of Melt sonocrystallization

The generalized method/process of melt sonocrystallization is as follows

1. The required amount of drug was melted in a vessel on a paraffin oil bath maintained at temperature range of 190°C to 193°C.
2. Molten drug was then poured in a vessel containing deionized water maintained at 50 to 60°C.
3. The mixture was sonicated for 15 to 20 minutes using probe ultrasonicator at different amplitude.
4. The product obtained after solidification of dispersed droplet was separate by filtration and dried at room temperature. [46-52]

Variables affecting sonocrystallization

1. Frequency of Ultrasound

Changes in ultrasound frequencies affect the bubble dynamics.[53] At low ultrasonic frequencies (<100 kHz), cavitation bubbles experience positive and negative pressure ultrasound waves for extended periods of time because wavelengths increase as frequencies decrease. Thus, the bubble oscillation amplitude is large since the size of the bubble differs substantially during compression and expansion periods. While, high ultrasonic frequencies (>200 kHz) shorten the wavelength of the ultrasound and the life of the cavity is reduced. In all cases, there are generally dense clouds of cavitation bubbles, and the power of collapse from each bubble is dependent on their size: stronger for large bubbles at low frequencies, weaker for small bubbles at high frequencies.[54-56] Yamaguchi et al. prepared the liposomes under different ultrasonic irradiation frequency and studied the effects of irradiation frequency on their size. Three different frequencies (43, 143, and 480 kHz) were applied at a fixed intensity (8 W/cm2). It was observed that the size of the liposomes decreased as the sonication frequency decreased, due to changes in bubble dynamics.[57]

2. Intensity of Ultrasound

As ultrasound intensities increase the size of generated crystals decreases and vice versa. Increased sonication intensities cause more vigorous micro scale mixing and turbulence, which cause solutes to diffuse more rapidly.

Because of accelerated diffusion of solute, the induction time and metastable zone width (MZW) are reduced and nucleation rate increases. The vigorous micro scale mixing and turbulence helps to prevent crystals from agglomeration.[58-59] Park et al. studied the effect of ultrasound intensity on roxithromycin during sonocrystallization. The intensity was adjusted from 5 to 15 W/cm2, crystal length was decreased from ~60 µm to ~15 µm during 10 min sonication.[60]

3. Sonication Time

As sonication time increases, crystal sizes decrease and also size become more uniform. In case of short sonication times, solution and precipitants are not mixed uniformly due to that irregular shaped and size of crystals generated. Prolonged sonication time improves mixing and prevents crystals from aggregating.[61] Narducci et al. studied the effects of sonication time on crystal size using Adipic acid and found a significant difference in crystal size. Crystal size was reduced as sonication duration increased.[62]

4. Types of Ultrasound Generator

Multiple types of ultrasonic generators are exists and which provide different experimental configurations for sonocrystallization. Ultrasound generators are typically ultrasonic baths, ultrasonic horns/probe, and plate transducers.

Sonicating baths are standard laboratory equipment and are typically used to disperse particles in Liquid.[63-64] Ultrasonic horns also called as probe sonicator are also used to perform sonocrystallization and offer batch or flow-through configurations.[65-70] The plate transducer generates a wide range of ultrasound frequencies. It is important for sonocrystallization when high frequencies are needed (>100 kHz). With an ultrasonic plate transducer a batch configuration usually used for crystallization.[71]

CONCLUSION

Melt sonocryatallization is newer particle engineering technique involved utilization of ultra sound energy on soft or viscous molten mass to create fine particles of drugs that helps to improve aqueous solubility and bioavailability. Melt sonocrystallization offers solvent and carrier less technique for the formation of fine particles which makes this technique more promising for the enhancement drug solubility in water.

REFERENCES

1. Naseem A, Olliff CJ, Martini LG, Lloyd AW, Effects of plasma irradiation on the wettability and dissolution of compacts of griseofluvin, Int J Pharm, 269(2), 443-50.
2. Singh G, Kaur I, Gupta D, Sharma S, Enhancement of the Solubility of Poorly Water Soluble Drugs through Solid Dispersion: A Comprehensive Review, Indian J Pharm Sci, 79(5), 2017, 674-687.
3. Aulton ME, Pharmaceutics: The science of dosage form design, 1st ed, London: Churchill Livingstone, 1996.
4. Dhirendra K, Lewis S, Udupa N, Atin K, Solid dispersions: A Review, Pak J Pharm Sci, 22, 2009, 234-46.
5. Tiwari R, Tiwari G, Srivastava B, Rai AK, Singh P, Solid Dispersions: An overview to modify bioavailability of poorly water soluble drugs, Int J Pharm Tech Res, 1, 2009, 1338-49.
6. Serajuddin AT, Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems and recent breakthroughs, J Pharm Sci, 88, 1999, 1058-66.
7. Amidon GL, Lunnernas H, Shah VP, Crison JR, A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, Pharmaceutical Research, 12, 1995, 413–420.
8. Helga M, The Biopharmaceutical Classification System (BCS) and its usage, Drugs Made in Germany, 45, 2002, 63-5.
9. Dressman J, Butler J, Hempenstall J, Reppas C, The BCS: Where do we go from here, Pharmaceut Technol, 25, 2001, 68-76.
10. Chavda HV, Patel CN, Anand IS, Biopharmaceutics Classification System, Sys Rev Pharm, 1(1), 2010, 62-69.
11. Kumar S, Singh P, Various techniques for solubility enhancement: An overview, The Pharma Innovation, 5(1), 2016, 23-28.
12. Patil SK, Wagh KS, Parik VB, Akarte AM, Baviskar DT, Strategies for solubility enhancement of poorly soluble drugs, Int J Pharm Sci Rev Res, 8(2), 2011, 74-80.
13. Alam MA, Ali R, Al-Jenoobi FI, Al-Mohizea AM, Solid Dispersions: A Strategy for Poorly Aqueous Soluble Drugs and Technology Updates, Expert Opin Drug Deliv, 9(11), 2012, 1419-1440.
14. Blagden N, Matas M, Gavan PT, York P, Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, Advanced Drug Delivery Reviews, (59)7, 2007, 617- 630.
15. Vemula VR, Lagishetty V, Lingala S, Solubility enhancement techniques, Int J Phar Sci Rev Res, 5(1), 2010, 41-51.
16. Vogt M, Kunath K, Dressman JB, Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: comparison with commercial preparations, Eur J Pharma Biopharm, 68(2), 2008, 283-288.
17. Ahmad Z, Maurya N, Mishra KS, Khan I, Solubility Enhancement of Poorly Water Soluble Drugs: A Review, International Journal of Pharmacy & Technology, 3(1), 2011, 807-823.
18. Riehemann K, Fuchs H, Schneider SW, Luger TA, Godin B, Farrari M, Nanomedicine-Challenge and Perspectives, Chem Int Ed Engl, 48, 2009, 872-897.
19. Phillips EM, Stella VJ, Rapid expansion from supercritical solutions, application to pharmaceutical processes, Int J Pharmaceutics, 94, 1993, 1-10.
20. Subramaniam B, Rajewski R,A, Snavely K, Pharmaceutical processing with supercritical carbon dioxide, J Pharm Sci, 86, 1997, 885-890.
21. Manna L, Banchero M, Solta D, Ferri A, Ronchetii S, Sicrdi S, Impregnation of PVP microparticles with ketoprofen in the

presence of supercritical CO2, J Supercritical Fluids, 78, 2006, 67-69.

22. Furqan maulvi VTT, Soni TG , Gohel MC, Gandhi TR, Supercritical fluid technology: A promising approach to enhance the drug solubility, J, Pharm, Sci, & Res, 1(4), 2009, 1-14.

23. Devil NKD, Rani AP, Javed M, Kumar KS, Kaushik J, Sowjanya, Cyclodextrins in pharmacy-An overview, Pharmacophore, 1(3), 2010, 155-165.

24. Richards WT, Loomis AL, The chemical effects of high frequency sound waves, A preliminary survey, J Am Chem Soc , 49, 1927, 3086–3100.

25. Vasilev BP, Vinograd KN, Amplification of high-intensity ultrasound in cadmium sulfide single crystals, Sov Phys Solid Stat, 9, 167, 1052–1054.

26. Kapustin, A, The Effects of Ultrasound on the Kinetics of Crystallization; Springer Science & Business Media: Berlin, Germany, 2012.

27. Polotski IG, Ovsiyenk DY, Khodov ZL, Sosnina YG, Baselyuk GY, Kushnir VK, Effect of an ultrasound on perfection of melt-grown aluminium single crystals, Phys Met Metallogr, 21, 1966, 81.

28. Belyaev VK, Reshetny II, Effect of ultrasound on growth and dissolution of single crystals in a drop of solution, Sov Phys Acoust, 12, 1967, 312.

29. De Castro ML, Priego-Capote F, Ultrasound-assisted crystallization (sonocrystallization), Ultrason Sonochem, 14, 2007, 717-724.

30. Sander JRG, Zeiger BW, Suslick KS, Sonocrystallization and sonofragmentation, Ultrason Sonochem, 21, 2014, 1908–1915.

31. Gajendragadkar CN, Gogate PR , Intensified recovery of valuable products from whey by use of ultrasound in processing steps—A review, Ultrason Sonochem, 32, 2016, 102-118.

32. Cains PW, Martin PD, Price CJ, The use of ultrasound in industrial chemical synthesis and crystallization Applications to synthetic chemistry, Org Process Res Dev, 2, 1998, 34-48.

33. Ruecroft G, Hipkiss D, Maxted N, Cains PW, Sonocrystallization: The use of ultrasound for improved industrial crystallization, Org Process Res Dev, 9, 2005, 923-932.

34. Castillo-Peinado LD, de Castro MDL, The role of ultrasound in pharmaceutical production: Sonocrystallization, J Pharm Pharmacol, 68, 2016, 1249-1267.

35. Suslick KS, Sonochemistry, Science, 247, 1990, 1439-1445.

36. Leighton TG, The Acoustic Bubble, Cambridge, MD, USA: Academic Press, 1994.

37. Pecha R, Gompf B, Microimplosions: Cavitation collapse and shock wave emission on a nanosecond time scale, Phys Rev Lett, 84, 2000, 1328-1330.

38. Zeiger BW, Suslick KS, Sonofragmentation of molecular crystals, J Am Chem Soc, 133, 2011, 14530-14533.

39. Graham Ruecroft, Tylan Lu, David Hipkiss, Sonocrystallization: The Use of Ultrasound for Improved Industrial Crystallization, Organic Process Res Dev, 2005, 923-931.

40. Suresh C, Rakshit Ameta, Garima Ameta, Sonochemistry: An Emerging Green Technology, 1st ed, Florida: Apple Academic Press, 2018.

41. Doktycz SJ, Suslik KS, Interparticle collision driven by ultrasound, Science, 247, 1990, 1067-1069.

42. Dodds John, Espitalier Fabienne, Louisnard Olivier, Grossier Romain, The effect of ultrasound on crystallisation-precipitation processes: some examples and a new segregation model, Particle & Particle System Characterization, 24(1), 2007, 18– 28.

43. Deshmukh V, Deshmukh T, Design and development of melt sonocrystallization technique for carbamazepine, Ind J Pharm Edu Res, 47, 2017, 199 – 205.

44. Ruecroft G, Sonocrystallization: The use of ultrasound for improved industrial crystallization, Org Process Res Dev, 9, 2005, 923-932.

45. Chaudhari PD, Uttekar PS, Melt-sonocrystallization: A novel particle engineering technique for solubility enhancement, Int J Pharm Tech Res, 1(1), 2009, 111-120.

46. Jagtap VA, Vidyasagar G, Dvivedi SC, Solubility enhancement of rosiglitazone by using melt sonocrystallization technique, J Ultrasound, 17, 2014, 27–32.

47. Deshmukh V, Deshmukh T, Deshmukh M, Jadhav P, Design and Development of Melt Sonocrystallization Technique, Ind J Pharm Edu Res, 2(2), 2010, 19-25.

48. Mohammad AK, Akhtar N, Sharma V, Pathak K, Product Development Studies on Sonocrystallized Curcumin for the Treatment of Gastric Cancer, Pharmaceutics, 7, 2015, 43-63.

49. Tripathi R, Biradar SV, Mishra B, Paradkar AR, Study of polymorphs of progesterone by novel melt sonocrystallization technique: A technical note, AAPS Pharm Sci Tech, 11, 2010, 1493-1498.

50. Dhumal RS, Biradar SV, Yamamura S, Paradkar A, York P, Preparation of amorphous cefuroxime axetil nanoparticles by sonoprecipitation for enhancement of bioavailability, Eur J Pharm Biopharm, 70, 2008, 109-115.

51. Maheshwari M, Jahagirdar H, Paradkar A, Melt sonocrystallization of ibuprofen: Effect on crystal properties, Eur J Pharm Sci, 25, 2005, 41-48.

52. Paradkar A, Maheshwari M, Ketkar AR, Chauhan B, Preparation and evaluation ibuprofen beads melt solidification technique, Inten J Pharma, 255(1-2), 2003, 33-42.

53. Nalajala VS, Moholkar VS, Investigations in the physical mechanism of sonocrystallization, Ultrason Sonochem, 18, 2011, 345-355.

54. Li H, Wang JK, Bao Y, Guo ZC, Zhang MY, Rapid sonocrystallization in the salting-out process, J Cryst Growth, 247, 2003, 192-198.

55. Lee J, Ashokkumar M, Kentish SE, Influence of mixing and ultrasound frequency on antisolvent crystallisation of sodium chloride, Ultrason Sonochem, 21, 2014, 60-68.

56. Nii S, Takayanagi S, Growth and size control in anti-solvent crystallization of glycine with high frequency ultrasound, Ultrason Sonochem, 21, 2014, 1182–1186.

57. Yamaguchi T, Nomura M, Matsuoka T, Koda S, Effects of frequency and power of ultrasound on the size reduction of liposome, Chem Phys Lipids, 160, 2009, 58–62.

58. Su CS, Liao CY, Jheng WD, Particle size control and crystal habit modification of phenacetin using ultrasonic crystallization, Chem Eng Technol, 38, 2015, 181–186.

59. Nishida I, Precipitation of calcium carbonate by ultrasonic irradiation, Ultrason Sonochem, 11, 2004, 423-428.

60. Park MW, Yeo SD, Antisolvent crystallization of roxithromycin and the effect of ultrasound, Sep Sci Technol, 45, 2010, 1402-1410.

61. Belkacem N, Salem MAS, AlKhatib HS, Effect of ultrasound on the physico-chemical properties of poorly soluble drugs: Antisolvent sonocrystallization of ketoprofen, Powder Technol, 285, 2015, 16–24.

62. Narducci O, Jones AG, Kougoulos E, An assessment of the use of ultrasound in the particle engineering of micrometer-scale adipic acid crystals, Cryst Growth Des, 11, 2011, 1742–1749.

63. Crespo R, Martins PM, Gales L, Rocha F, Damas AM, Potential use of ultrasound to promote protein crystallization, J Appl Crystallogr, 43, 2010, 1419-1425.

64. Kiani H, Zhang ZH, Delgado A, Sun DW, Ultrasound assisted nucleation of some liquid and solid model foods during freezing, Food Res Int, 44, 2011, 2915-2921.

65. Hatkar UN, Gogate PR, Process intensification of anti-solvent crystallization of salicylic acid using ultrasonic irradiations, Chem Eng Process, 57, 2012, 16-24.

66. Bhoi S, Sarkar D, Modelling and experimental validation of ultrasound assisted unseeded batch cooling crystallization of L-asparagine monohydrate, Crystengcomm, 18, 2016, 4863-4874.

67. Jiang M, Papageorgiou CD, Waetzig J, Hardy A, Langston M, Braatz ,D, Indirect ultrasonication in continuous slug-flow crystallization, Cryst Growth Des, 15, 2015, 2486-2492.

68. Shirsath SR, Sonawane SH, Saini DR, Pandit AB, Continuous precipitation of calcium carbonate using sonochemical reactor, Ultrason Sonochem, 24, 2015, 132-139.

69. Jamshidi R, Rossi D, Saffari N, Gavriilidis A, Mazzei L, Investigation of the effect of ultrasound parameters on continuous sonocrystallization in a millifluidic device, Cryst Growth Des, 16, 2016, 4607-4619.

70. Ramisetty KA, Pandit AB, Gogate PR, Ultrasound-assisted antisolvent crystallization of benzoic acid: Effect of process variables supported by theoretical simulations, Ind Eng Chem Res, 52, 2013, 17573-17582.

71. Wohlgemuth K, Ruether F, Schembecker G, Sonocrystallization and crystallization with gassing of adipic acid, Chem Eng Sci, 65, 2010, 1016-1027.

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