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Review

Applications of ultrasound to chiral crystallization, resolution and deracemization

Christos Xiouras[a], Antonios Fytopoulos[a,b], Jeroen Jordens[a], Andreas G. Boudouvis[b], Tom Van Gerven[a], Georgios D. Stefanidis[a,*]

[a] Process Engineering for Sustainable Systems (ProcESS), Department of Chemical Engineering KU Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium
[b] Process Analysis and Plant Design, School of Chemical Engineering NTUA, 9 Heroon Polytechniou, Zografou, 15780 Athens, Greece

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ABSTRACT

Industrial synthesis of enantiopure compounds is nowadays heavily based on the separation of racemates through crystallization processes. Although the application of ultrasound in solution crystallization processes (sonocrystallization) has become a promising emerging technology, offering several benefits (*e.g.* reduction of the induction time and narrowing of the metastable zone width, control over the product size, shape and polymorphic modification), little attention has been paid so far to the effects of ultrasound on chiral crystallization processes. Several recent studies have reported on the application of acoustic energy to crystallization processes that separate enantiomers, ranging from classical (diastereomeric) resolution and preferential crystallization to new and emerging processes such as attrition-enhanced deracemization (Viedma ripening). A variety of interesting effects have been observed, which include among others, enhanced crystallization yield with higher enantiomeric purity crystals, spontaneous mirror symmetry breaking crystallization, formation of metastable conglomerate crystals and enhanced deracemization rates. The objective of this review is to provide an overview of the effects of ultrasound on chiral crystallization and outline several aspects of interest in this emerging field.

1. Introduction

Enantiomers of chiral molecules are a specific class of stereoisomers that can exist as non-superimposable mirror images of one another. Although enantiomers share the same physical properties, their chemical behavior can differ substantially in an asymmetric medium, such as the human body (enzymes, DNA, hormones *etc*. are often chiral) [1,2]. This in turn has great consequences for the pharmaceutical industry, where more than half of the drugs manufactured are chiral compounds and their enantiomers often differ markedly in their biological activity, such as pharmacology, toxicology, pharmacokinetics and metabolism [3]. Indeed, growing awareness of the importance of chirality has led regulatory bodies, *e.g.* European Medicines Agency (EMA) to treat unwanted enantiomers as impurities and exercise pressure on marketing chiral pharmaceuticals as single enantiomers [4]. As a result, eight of the top ten selling chiral drugs are nowadays marketed as pure enantiomers (*e.g.* clopidogrel). This commercial tendency has in turn increased the demand for economic processes to obtain enantiopure compounds giving rise to the “chirotechnology” industry [5].

However, the synthesis or separation of enantiomers at high purities and yields remains a difficult task and up to date no standardized processes exist. Various classes of methods are used, such as asymmetric syntheses, chromatography, kinetic resolution and crystallization [6]. The latter approach, being relatively cheaper and simpler is the most frequently used one at industrial scales, accounting for approximately 70% of all industrial enantiomer separations in Europe [7]. Depending on the crystallization behavior of the racemate, different crystallization techniques are applicable [8]. The three possible crystallization pathways for enantiomers in racemic solutions are visualized in Fig. 1. Most racemates will crystallize as racemic compound crystals (both enantiomers are present in the crystal lattice at an equimolar ratio) and thus require the addition of a resolving agent prior to crystallization (*diastereomeric resolution*). Alternatively, racemates may also form conglomerate crystals (individual crystals contain only one enantiomer in the crystal lattice) for which *preferential crystallization*, *total spontaneous resolution* or *deracemization* processes are possible, without the addition of resolving agents. Finally, in rare occasions, enantiomers may also crystallize as a solid solution (individual crystals contain both enantiomers in the crystal lattice in a random manner), which require chemical intervention for their separation prior to crystallization.

* Corresponding author.
E-mail address: Georgios.Stefanidis@kuleuven.be (G.D. Stefanidis).

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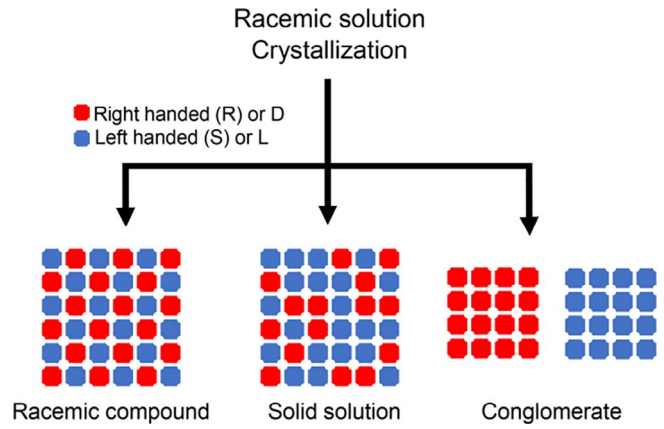


Fig. 1. Possible crystallization behavior of enantiomers from racemic solutions. Left: Racemic crystals are formed in which both enantiomers are present in the crystal lattice at an equimolar ratio (~90% of the cases). Middle: Solid solution is formed in which both enantiomers are present in the crystal lattice at random amounts (less than 1% of the cases). Right: Conglomerate crystals are formed in which individual crystals contain only one enantiomer in the crystal lattice (5–10% of the cases).

The application of ultrasound to solution crystallization processes (sonocrystallization) has been shown to have several beneficial effects, such as reduction of the induction time and narrowing of the metastable zone width, control over the product size, shape and polymorphic modification, among others [9–13]. In addition, ultrasound can also induce secondary effects to already formed particles in a crystallization process; for example breakage (sonofragmentation) and secondary nucleation, surface/shape modification and deagglomeration [14,15]. Although the exact mechanisms of sonocrystallization and sonofragmentation are still rather unclear, it is currently believed that most effects arise from the acoustic cavitation phenomenon, which includes the generation, growth and implosive collapse of μm-sized cavitation bubbles when high power ultrasound waves (20–100 kHz) propagate in a liquid medium. Upon collapse, the bubbles locally release high amounts of energy, leading to high local temperatures (~5000 K) and pressures (~10 kPa) [16,17], intense shock waves [18], enhanced mixing [19], particle collisions [20] and liquid microjets [21,22].

Although the general scientific consensus is that ultrasound irradiation cannot provide a direct chiral bias to a racemic mixture undergoing a crystallization/deracemization process, the aforementioned mechanical and kinetic effects may greatly enhance chiral crystallization [23,24]. These enhancements are complementary to the benefits reported for sonocrystallization and may allow modification of the final product chirality. In the following sections, we discuss several studies that have recently been carried out where ultrasound has been applied to 1) diastereomeric resolution, 2) preferential crystallization, 3) total spontaneous resolution and 4) deracemization. In light of the interesting results obtained in many of these studies, we anticipate that this emerging field will occupy the scope of many more studies in the near future.

2. Ultrasound facilitated diastereomeric resolution

Diastereomeric resolution, also termed as “classical” resolution is up to date the most widely applied chiral resolution technique at large scales [6]. During this process, a suitably chosen enantiomerically pure resolving agent (usually base or acid) is added to the racemate to provide two diastereomeric salts that have different solubilities and can be separated by fractional crystallization. It is the most suitable crystallization technique for chiral compounds that upon crystallization from the racemic mixture form racemic crystals.

Even though the influence of ultrasound on diastereoselective and enantioselective reactions has been relatively well studied in the context of sonochemistry [25], only a few studies focus on the effects of ultrasound on diastereomeric crystallization. Barve et al. [26] studied the ultrasound-facilitated diastereomeric salt resolution of an intermediate of silodosin, a clinically approved drug for the treatment of human prostate problems, using *(S)*-mandelic acid as chiral resolving agent. In their study, ultrasound (bath at 37 kHz, 100 W nominal electrical power) was applied during the crystallization step in 300 mL of solution for 30 min leading to increase in the yield of the diastereomeric salt from 10% to 34%. The authors attributed the crystallization yield increase to the faster nucleation rate attained with ultrasound. By including this sonocrystallization step, the authors were able to decrease the number of synthetic steps required to obtain the final product at the same yield.

In a recent study, Szeleczky et al. [27] studied the effect of ultrasound power and duration (horn-type transducer at 20 kHz, 4.3–11 W calorimetric power for 1–30 min) on the diastereomeric salt resolution of tetramisole enantiomers in 32 mL of a biphasic solvent mixture (75%/25% dichloromethane-water). Similarly to the previous study, the authors found that the application of ultrasound led to faster crystallization of the desired diastereomeric salt. Their best result (54–64% enantiomeric purity at 78–93% yield) was attained for 15 min of ultrasound irradiation at a low calorimetric power of 4.3 W. In addition, ultrasound irradiation allowed for the preservation of a high enantiomeric excess even for prolonged crystallization times, an effect not present at silent conditions (Fig. 2). The authors attributed this effect to the ultrasound preventing the co-precipitation of racemic compound forming salts, which reduce the enantiomeric purity.

3. Ultrasound-facilitated preferential crystallization and total spontaneous resolution

Unlike diastereomeric resolution, preferential crystallization involves the direct (seeded) crystallization of a single enantiomer from a racemic supersaturated solution without the addition of resolving agents. It is a kinetically-driven process that depends on differences in the crystallization rates between the enantiomers and is only feasible when the enantiomers crystallize as conglomerate crystals, *i.e.* individual crystals that contain only one enantiomer [28,29]. Coupling preferential crystallization with in-situ racemization (interconversion of the enantiomers via a chemical equilibrium) allows for total spontaneous resolution, *i.e.* total conversion of the racemic mixture into a single enantiomer [8].

Recently, several studies have been published in which the application of ultrasound in preferential crystallization and total spontaneous resolution processes is investigated [30–42]. In the following sections, we discuss the studies that have applied ultrasound to preferential crystallization using single- or multiple-vessel configuration as well as to total spontaneous resolution.

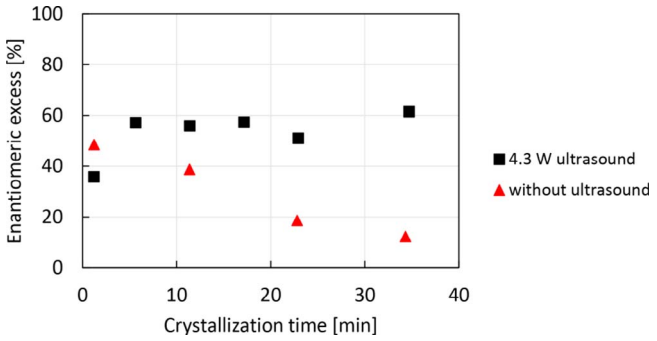


Fig. 2. Enantiomeric excess of tetramisole mixture obtained through the diastereomeric salt under ultrasound (horn-type transducer) at 20 kHz and 4.3 W calorimetric power in 32 mL solution compared to silent conditions at different crystallization times [27].

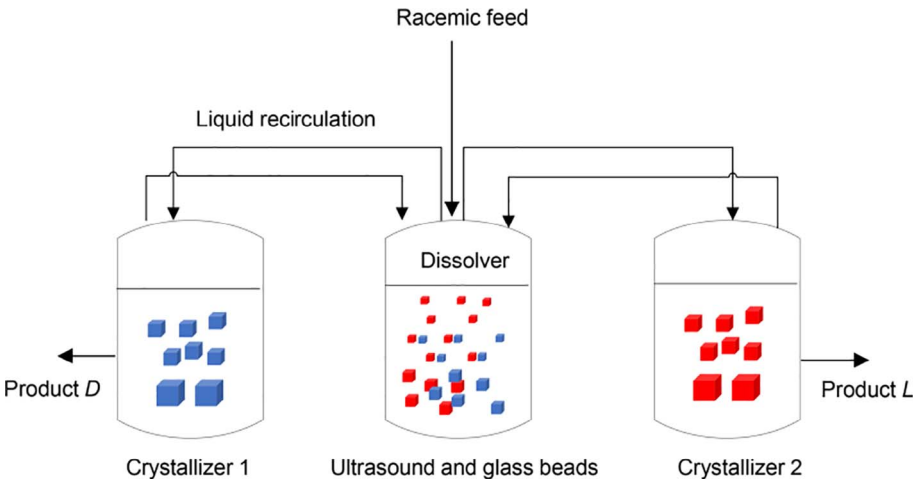


Fig. 3. Schematic of the experimental setup used by Hein et al. [33] to separate the enantiomers of threonine. Ultrasound together with glass beads were used in the dissolver vessel (35 mL) to break down the crystals of both enantiomers and increase their solubility.

3.1. Preferential crystallization using ultrasound in single-vessel configuration

Recent studies have reported significant enantiomeric enrichment in the solids during preferential crystallization under the presence of ultrasound. Medina et al. [30] applied pulsed ultrasound irradiation (horn-type transducer at 20 kHz, 40 W nominal electrical power, on/off time of 1 s) during the unseeded preferential crystallization of *DL*-threonine, a non-racemizable, conglomerate-forming chiral amino acid, starting from nearly racemic supersaturated aqueous solutions of 10 mL. The authors reported faster crystallization, smaller crystal size and enantiomeric enrichments of up to 34% for the sonicated experiments at short times (180–210 s), starting from 0.25% enantiomeric enrichment in the liquid, while vigorously stirred control experiments at silent conditions showed no enantiomeric enrichment. However, it was found that enantiomeric purity decreases with crystallization time. By a slight bias (5%) of one enantiomer in the liquid, the authors could, upon sonocrystallization, obtain a final enrichment in the solid phase of up to about 87% of the same enantiomer. The authors postulated that under ultrasound irradiation, a large population of chiral clusters is formed for both enantiomers prior to nucleation, but since the system is slightly biased toward one enantiomer, a difference in cluster population will be generated. The clusters continuously grow/agglomerate and dissociate, but for the enantiomer in excess the clusters survive longer giving birth to more initial crystal nuclei of the same chirality. Further chiral amplification takes place through cavitation-induced secondary nucleation, but since threonine does not undergo solution phase racemization, total resolution for that compound was not possible.

The application of ultrasound during crystallization may also affect the final crystal form obtained, which can have strong implications for chiral resolution. As an example, Zhou et al. [31] showed that upon unseeded sonocrystallization (bath at 40 kHz, 5 W nominal electrical power) of *DL*-glutamic acid from a supersaturated aqueous racemic solution (10 mL), the conglomerate crystal form was obtained, while for silent experiments at the same conditions the racemic crystal form was always obtained. For glutamic acid, the conglomerate crystal form is metastable with respect to the racemic compound [43]. For the unseeded experiments, the conglomerate crystals formed were from both chiralities at equal amounts. However, the addition of a small amount of seeds, or an initial enrichment in the liquid phase of the preferred enantiomer, resulted in enrichment of 10–55% in the solid phase by using a single sonocrystallization step. The authors also showed that by applying sequential dissolution/re-crystallization steps using ultrasound, enantiomeric purities of up to ~97% could be achieved. In another study, Shiau et al. [32] employed stripping crystallization from the melt (1 g liquid feed) for the separation of *(S)*-ibuprofen from ibuprofen enantiomers in combination with seeding and ultrasound. While ibuprofen forms a stable racemic compound rather than a conglomerate, preferential crystallization is still possible if a sufficiently enriched mixture is available (> 0.82 mass fraction for *(S)*-ibuprofen). The authors showed that controlled application of ultrasound or magnetic stirring with seeding (0.01 g seeds of *(S)*-ibuprofen with size 15–60 μm) could suppress the nucleation of *rac*-ibuprofen leading to enhanced final purity of the produced crystals. However, the type of ultrasound equipment and the operating frequency and power used were not reported.

3.2. Preferential crystallization using ultrasound in multiple-vessel configuration

Ultrasound technology has also been applied for preferential crystallization in multiple, usually three-vessel configuration. One of the vessels usually functions as the feed tank of racemic solution at a higher temperature, which can also be a dissolver, (continuously) fed with racemic solids. The other two vessels are seeded with enantiopure crystals and parallel preferential crystallization of both enantiomers takes place in their respective vessel. Circulating the liquid phase between the crystallizers serves to equalize their concentration and to avoid primary nucleation of the antipode, enhancing also the productivity of the process [44]. In such schemes, ultrasound has been applied both in the dissolver tank, in order to enhance the solubility and dissolution of the racemic solids, and in the crystallizer vessels to enable the in-situ generation of seeds through breakage of larger crystals.

Hein et al. [33] demonstrated such an approach, using three vessels, for the preferential crystallization of threonine enantiomers. Two of the vessels contained seeds of *D*-threonine and *L*-threonine, respectively, only mildly stirred at 20 °C. As shown in Fig. 3, the liquid phase of each vessel was recirculated (1 mL/min) between a third vessel (feed vessel), which contained an aqueous slurry (35 mL) of the racemic *D* and *L* solids at a higher temperature (35 °C) under sonication (bath, frequency and power not reported) and glass beads to enhance the attrition of the racemic solids. In such a scheme, the racemic solution entering the seeded vessels is supersaturated with respect to both enantiomers, but only crystal growth of the seeds of the respective enantiomer takes place in each vessel, since the liquid is recirculated back to the feed vessel before primary nucleation of the antipode occurs. The application of ultrasound-assisted grinding creates smaller crystals that have

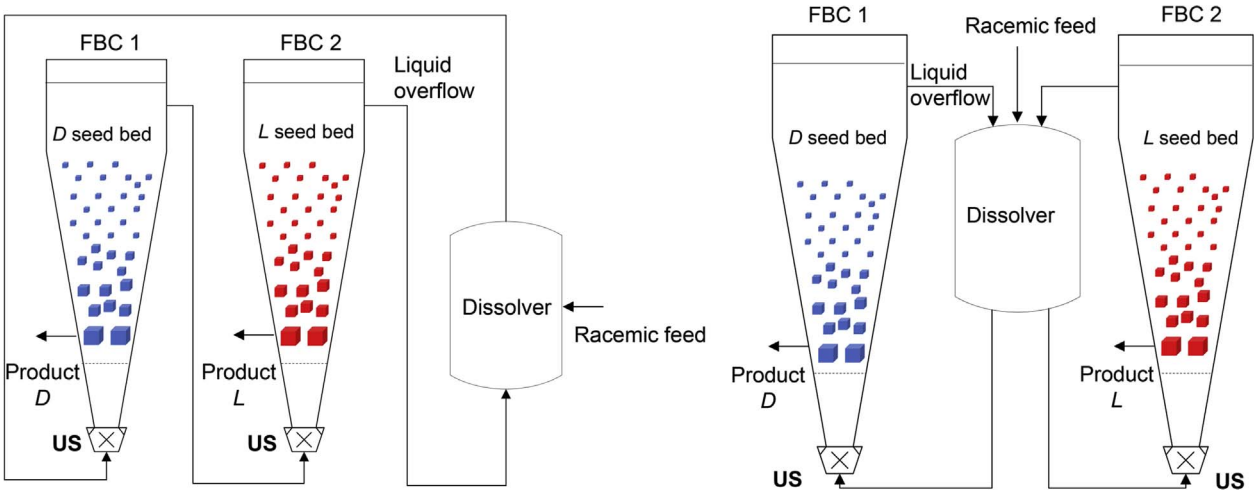


Fig. 4. Left: Schematic of the coupled FBCs (7–160 L) in series employed by Midler [34–36] for the separation of the enantiomers of a precursor of methyldopa. Right: Schematic of the coupled fluidized bed crystallizers (0.8 L) in parallel employed by Binev et al. [38] to separate the enantiomers of asparagine monohydrate. In both cases, ultrasound was applied in both FBCs at the conical bottom for the in-situ generation of seeds through breakage of larger crystals and agglomerates.

higher solubility (Gibbs-Thomson effect), providing an even larger driving force for crystallization in the two seed vessels. Based on this approach, the authors showed that both threonine enantiomers can be continuously recovered at high purity (> 97%) and yield (~76%) by gradually adding racemic solids in the feed vessels.

Ultrasound technology has also been utilized at a larger scale (7–160 L crystallizers) for the in-situ generation of seeds through breakage in continuous preferential crystallization processes in coupled fluidized bed crystallizers (FBCs). Midler [34–36] was the first to investigate this approach in a series of patents released in the early 70 s. Several conglomerate-forming chiral molecules were separated in that way, including a precursor to *L*-methyldopa, an antihypertensive agent, at an average productivity of 2 kg/h of enantiopure (> 97%) material per crystallizer. In this approach, as shown in Fig. 4 (left), a slightly supersaturated racemic solution from a dissolver at a higher temperature enters the first FBC, where crystallization of the *D*-enantiomer takes place by growth of the *D* seeds present. Subsequently, the solids-free overflow enters the second FBC, where *L* seeds are present and crystallization of the *L*-enantiomer takes place. High intensity ultrasound (4.3–37.5 W/cm^2 ultrasound power per crystallizer bottom area), supplied by a horn-type transducer (19.5 kHz) serves to produce seeds by the comminution of the larger particles that settle on the bottom of the FBCs. The smaller fragments are carried upwards in the fluidized bed, maintaining a large surface area to facilitate fast crystal growth and prevent nucleation of the counter-enantiomer in each crystallizer. An additional advantage of such a process is that even if nucleation of the counter-enantiomer occurs in one of the FBC, purification is possible by temporarily raising its temperature above that of the dissolver. That way, the racemic part will preferentially dissolve from the FBC and re-crystallize in the dissolver without the need to shut down the process and replace the seed bed. A similar setup was also used at lab scale by Grabowski [37] for the resolution of 3-fluoroalanine-2-d benzenesulfonate salt, but the ultrasound equipment, power and frequency used were not reported.

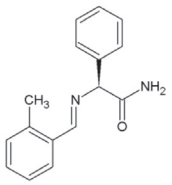
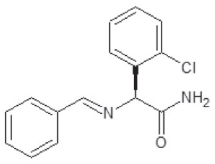
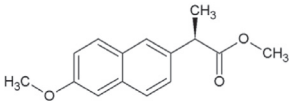
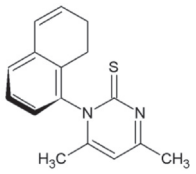
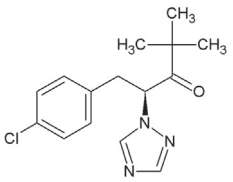
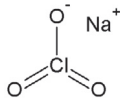
Binev et al. [38,39] recently published a related approach. The authors used FBCs (0.8 L each) and a dissolver, but this time the FBCs were connected in parallel [38]. A simplified representation of this process is shown in Fig. 4 (right). In this setup, the enantiomers of *DL*-asparagine monohydrate were continuously separated at high purities (> 97%). From the bottom of each crystallizer vessel, part of the suspension was recirculated through an ultrasonic bath, operated at 35 kHz and 48 W nominal electrical power, in order to break the larger crystals and agglomerates. The resulting smaller fragments were subsequently mixed with the inlet flow from the bottom of each crystallizer. The authors showed that the coupled fluidized bed crystallizers could deliver constant crystal size with narrow crystal size distribution of the preferred enantiomer at a productivity of 14 g/(L h) per enantiomer of asparagine monohydrate.

3.3. Total spontaneous resolution using ultrasound

Total spontaneous resolution, or crystallization-induced second order asymmetric transformation (SOAT), may occur for chiral molecules, when fast racemization takes place concurrently with the (seeded) preferential crystallization [8,45,46]. In this manner, the decrease in the concentration of the preferred enantiomer, due to its preferential crystallization, will immediately be counterbalanced by the conversion of the counter-enantiomer to the preferred enantiomer through the racemization. This effect can suppress the nucleation of the counter-enantiomer and lead to its complete conversion to the preferred enantiomer. Although this technique has not yet been combined with ultrasound for intrinsically chiral compounds, there are a few studies that investigated total spontaneous resolution for achiral compounds (*e.g.* $NaClO_3$) that upon crystallization form chiral conglomerate crystals [40–42]. Upon dissolution, these compounds, instantly lose chiral identity and can re-crystallize as crystals of both chiralities (this situation can be thought of as equivalent to instantaneous in-situ racemization for intrinsically chiral molecules).

Chen and co-workers [40] were the first to show that $NaClO_3$ crystals that were nucleated and grown from 100 mL of supersaturated aqueous solution under an ultrasonic field (bath, 40 kHz and 50 W nominal electrical power) consisted mainly of a single chirality (> 96%). The final chirality was random for unseeded experiments, but it could be controlled by the addition of a single large (0.5–1 mm) right- or left-handed seed. The authors attributed this symmetry breaking phenomenon to cavitation-induced secondary nucleation, in which an initial stochastically-formed nucleus (or a deliberately added homochiral seed) is instantly broken to several bits of the same chirality, which act as secondary nuclei and transfer their chirality to the entire system. The results were in accordance with the older work of

Table 1
List of molecules that have successfully been deracemized using Viedma ripening in the presence of ultrasound-enhanced grinding with or without grinding media.

Compound	US equipment	Grinding media (g)	Catalyst (g)	Solvent (mL)	T (°C)	Refs.
 A) N-(2-methylbenzylidene)-phenylglycine amide	Standard Ultrasonic Bath, 45 kHz, no power reported	Yes 5–15	DBU 0.12–1.33	MeCN 4.5–45	20	[55–58]
 B) 2-(benzylideneamino)-2-(2-chlorophenyl)acetamide	Standard Ultrasonic Bath, 40 kHz, no power reported	Yes 1–10	DBU 0.10–0.15	MeCN 4.5–32	20	[33,59,60]
 C) methyl 2-(6-methoxynaphthalen-2-yl) propanoate	Standard Ultrasonic Bath, 35 kHz, no power reported	Yes 8.7	NaOMe 0.86	MeOH 8	23	[61]
 D) 4,6-dimethyl- 1-(naphthalen-1-yl)pyrimidine-2(1H)-thione	Standard Ultrasonic Bath, 35 kHz, 320 W nominal electrical power	Yes 5	None	Toluene 10	60	[62]
 F) 1-(4- chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl) pentan-3- one	Ultrasonic horn 20 kHz 13.9 – 90.3 W nominal electrical power	No	NaOH 1	MeOH/ Water 80/20 wt% 120	25	[63]
 G) Sodium Chlorate	Ultrasonic transducer 41 kHz 35 W ultrasound power	No	None (achiral)	Water 20	30	[64]

Kondepudi et al. [46,47] who observed the exact same phenomenon for $NaClO_3$, using vigorous magnetic stirring to induce secondary nucleation. In a follow-up study, Chen et al. [41] used sequential seeding of single $NaClO_3$ crystals of both chiralities in a supersaturated solution (100 mL) under the presence of ultrasound (bath 40 kHz and 50 W nominal electrical power). The single crystals used for seeding were prepared as rectangular prisms with smooth surfaces ranging from 0.5 to 4 mm in size giving surface areas between 7.5 and 53.9 mm^2. It was found that the first added chiral seeds dominated the chiral outcome, while in the simultaneous addition of seeds of both chiralities, the chirality of the seed with the larger surface area generally prevailed, although the relative proportion of clusters for the two enantiomers was also found to play an important role. The authors suggested that chiral symmetry breaking occurs in an ultrasonic field due to competition between secondary and primary nucleation rate; the seeded (or first-formed) enantiomer propagates its chirality through faster secondary nucleation, while the unseeded enantiomer forms mostly through the slower primary nucleation step. Once enough secondary nuclei are present, they grow consuming the supersaturation; thus effectively prohibiting the formation of additional counter-enantiomer nuclei. Similar observations were made by Azeroual et al. [42], who studied the mirror symmetry breaking in foldamer-based supramolecular helical aggregates of a pyridine/pyridazine strand. The authors found that a dilute sonicated (bath, 35 kHz, no power level reported) sample of this compound evolved to a homochiral fibrous structure. The authors attributed this symmetry breaking event, to ultrasound-induced break-up of mother fibers, with sequential gradual growth of daughter fibers of the same chirality.

Although the resolution of the achiral model compounds used in the aforementioned studies is not of industrial relevance, their use can still offer several insights into the mechanisms of chiral crystallization and also more generally into the mechanisms of sonocrystallization itself. For instance, one of the theories for sonocrystallization states that a secondary nucleation pathway could be responsible for the nucleation

rate enhancements and the smaller crystals generally obtained [10]. More specifically, it is often stated that the cavitation and acoustic streaming processes could result in transport of matter from growing nuclei and crystals (at their very early stage) to the bulk of the solution where they can become new nuclei [9]. This effect should amplify with an increasing number of growing nuclei, effectively leading to an autocatalytic increase in the total number of nuclei. For achiral molecules that form achiral crystal structures, it is very difficult to estimate the origin of the new nuclei and to distinguish between primary and secondary nucleation during sonocrystallization. However, studying achiral molecules that form chiral crystal structures may circumvent this limitation. In primary nucleation, crystals of both chiralities will be formed stochastically for these compounds, whereas in secondary nucleation, the parent nucleus or crystal will transfer its chirality to new nuclei. That way, any initial chiral asymmetry (formed stochastically) will be amplified autocatalytically by secondary nucleation, as shown in the work of Kondepudi at al. [46,47]. The fact that this effect is also observed in the presence of ultrasound, as shown in the studies discussed here, could support a secondary nucleation-dominated mechanism for sonocrystallization processes in general.

4. Ultrasound-facilitated deracemization under near-equilibrium conditions

An alternative approach to preferential crystallization for obtaining enantiopure compounds is based on the pioneering work of Viedma: attrition-enhanced deracemization or Viedma ripening [48]. During this process, a racemic population of conglomerate crystals in contact with their saturated solution, where racemization takes place, completely transforms to a single chirality upon continuous grinding of the crystals (usually achieved by stirring the suspension in the presence of grinding media) [49]. Grinding reduces the crystal size and yields a broad crystal size distribution (CSD). Under these conditions, small chiral fragments can preferentially dissolve (Gibbs-Thomson effect) contributing to the growth of larger crystals via Ostwald ripening, or they can agglomerate with larger crystals of the same chirality. These two effects in combination with racemization act to amplify even a minute excess of one enantiomer in the solid phase leading to enantiopurity in an autocatalytic fashion [50]. Recent studies have also shown that the application of small spatial thermal gradients [51] or temporal temperature variations (thermal cycles as low as ± 2 °C) [52], rather than grinding, can have a similar deracemization effect as Viedma ripening. Temperature variations induce cycles of partial crystal dissolution (in hot zones or periods) followed by crystal growth (in cold zones or periods), which combined with the solution-phase racemization also lead to deracemization. Whether the exact mechanisms of deracemization through temperature variations are the same as Viedma ripening is still a subject of ongoing scientific debate.

There is high potential for power ultrasound technology in deracemization applications, since the mechanical actions of ultrasound in suspensions have been known to result in substantial particle fragmentation, but also in the formation of hot spots [16,17] that could lead to many local temperature variations and temperature gradients. The mechanisms of sonofragmentation in slurries are not entirely understood, but several studies report that the physical properties of the cavitation medium (*e.g.* viscosity and vapor pressure), the mechanical properties of the particles (*e.g.* hardness and elasticity) [14,53], as well as the ultrasound process parameters (*e.g.* frequency and power) [54] influence particle breakage to a large extent. Since many of these studies have been discussed in detail elsewhere [14], it is not our intention to expand on these here. Instead, in the following sections, we discuss studies that have applied ultrasound technology to Viedma deracemization, either in the presence, or in the absence of grinding media. A list of molecules that have been shown to undergo deracemization using ultrasound is provided in Table 1. Several molecules have been shown to undergo ultrasound-facilitated deracemization, including precursors to actual pharmaceutical compounds (*e.g.* compounds B and C, are precursors to blockbuster drugs clopidogrel and naproxen, respectively). However, not all studies were conducted using the same ultrasound equipment and often power levels were not reported at all, which hinders a precise comparison between the results reported by the different authors.

4.1. Deracemization using ultrasound in the presence of grinding media

A number of studies have reported enhancements in the deracemization rate through Viedma ripening when sonication was applied simultaneously with grinding media. Noorduin et al. [55,56] were the first to apply ultrasound using a standard ultrasonic bath (45 kHz, no power level reported) for the solid phase deracemization of conglomerate forming N-(2-methylbenzylidene)-phenylglycine amide (compound A, Table 1) in MeCn (45 mL) using the organic base DBU as racemization catalyst. In their experiments, the authors compared magnetic stirring against ultrasound (15 g of glass beads were present in both cases) and reported ~5 times faster deracemization rate in the sonicated experiments, which reduced the total deracemization time from a week to less than a day [55]. The authors attributed the rate enhancement to the additional crystal attrition enabled by ultrasound, generating smaller particles and therefore enhancing the Ostwald ripening mechanism of the process. In later studies, the same group successfully applied ultrasound-assisted grinding in the presence of grinding media for the deracemization of actual pharmaceuticals on the lab scale (10 mL), such as the imine of 2-chlorophenyl glycine, an intermediate to the blockbuster drug clopidogrel (compound B, Table 1) [59,60], and the conglomerate forming derivatives of Naproxen (compound C, Table 1) [61]. In addition, the method was also combined with circularly polarized light, in which a small initial asymmetry, generated due to the rotation direction of the polarized light, was further amplified to enantiopurity using ultrasound in the presence of grinding media [57]. Engwerda et al. [62] also investigated Viedma deracemization of an atropisomer (compound D, Table 1) at 60 °C, using ultrasound (bath, 35 kHz, 320 W nominal electrical power), or magnetic stirring, in the presence of grinding media in 10 mL toluene and found that the time required to reach an enantiomeric excess of 80%, starting from a nearly racemic mixture, was reduced from ~ 13 days to ~ 9 days when sonication was applied. Comparing their results with those of Noorduin et al. [55], the authors claimed that a less pronounced enhancement of the deracemization rate could ensue due to a different hardness of the studied crystals, which could hinder their efficient break-up during ultrasonication. Another reason for the discrepancy could be the difference in the properties of the solvents at the respective experimental conditions. Engwerda et al. carried out the sonication experiments in toluene at 60 °C, whereas Noorduin et al. used MeCN at 20 °C. While the kinematic viscosity of the two solvents is comparable at the respective temperatures of the experiments, the vapor pressure of toluene at 60 °C is ~2 times higher compared to MeCN at 20 °C. Thus, in the case of toluene more gas molecules are present and can diffuse inside the cavitation bubbles prior to their collapse [54]. The gases will absorb energy upon collapse, potentially leading to less violent collapse and subsequently less resultant crystal breakage.

The concurrent application of ultrasound with grinding media has also been shown to suppress, to a certain extent, the effect of chiral impurities in a Viedma ripening process. Such (trace) chiral impurities are almost always present and have been shown to lead to a non-stochastic outcome of the deracemization by influencing the growth rate of one of the enantiomers, especially when starting the process from (nearly) racemic mixtures [65]. Steendam et al. [58] showed that the application of ultrasound (45 mL MeCN) with glass beads (bath at 45 kHz, no power level reported) could suppress the effect of chiral

impurities giving access to both enantiomers of N-(2-methylbenzylidene)-phenylglycine amide (compound A, Table 1) in a stochastic manner. This was not possible at silent conditions and lower attrition intensities, where only the *(R)* enantiomer could be obtained, indicating the potential presence of an *(S)* type impurity. The authors attributed this phenomenon to the enhanced attrition of the needle-shaped initial crystals with ultrasound, which leads to smaller particles (up to 10 μm for ultrasound versus up to 100 μm for glass beads). For smaller particles the total surface area is higher, thus the surface density of chiral impurities becomes smaller, and therefore, their influence on the crystal growth decreases. Similar observations were made by Hein et al. [33] for the deracemization of needle-shaped crystals of an imine of 2-chlorophenyl glycine (compound B, Table 1) using ultrasound (bath, frequency and power not reported) and glass beads in 32 mL of MeCN, where 24 identical experiments starting from racemic crystals led to both enantiomers in almost equal numbers with some experiments remaining racemic for > 22 h. Final particle size was found to be below 5 μm for most cases, but experiments that reached enantiopurity fast, exhibited a broader crystal size distribution as compared to slower ones that exhibited a narrow crystal size distribution. The rate of deracemization was also found to vary substantially between the experiments, demonstrating an "apparent randomness" of the process. It is at present unclear whether this effect is due to ultrasound or it is inherent to the deracemization process.

4.2. Deracemization using ultrasound in the absence of grinding media

All studies mentioned so far investigated the application of ultrasound in deracemization where grinding media were also present. The results of these studies have undoubtedly shown that the presence of ultrasound influences the deracemization process. However, it is difficult to discern the exact nature of the effect when grinding media are also present, since the latter will also cause breakage of crystals. In addition, the presence of grinding media complicates scale-up and downstream processing for Viedma ripening processes because the grinding media have to be separated from the solid product and they can also introduce impurities into the system.

To this end, our research group recently investigated the application of ultrasound-assisted grinding as an alternative method to glass bead grinding for carrying out attrition-enhanced deracemization in the absence of grinding media [64]. It was found that ultrasound treatments of chiral cubic $NaClO_3$ crystals (~200 μm) in water (20 mL) using a transducer glued on a glass plate and attached to the bottom of the reactor at 41 kHz, 35 W ultrasound power, resulted in significant particle size reduction (~30 μm) and narrow crystal size distribution (CSD). In addition, ultrasound-assisted grinding resulted in faster initial rate of deracemization compared to the glass bead grinding; however, after prolonged ultrasonication times enantiomeric excess levelled off contrary to the glass bead grinding experiments. The reason for this effect was that the hard $NaClO_3$ crystals reached a similar minimum size at the uniform sonication-attrition conditions of these experiments. It was further shown that the combination of an initial ultrasonication time followed by bead grinding without ultrasound, or the combination of continuous ultrasound and periodic seeding with enantiopure crystals, could resume the deracemization process and lead to homochirality.

Rougeot et al. [63] also studied the application of ultrasound-assisted grinding in the absence of grinding media for the deracemization of a precursor of Paclobutrazol (compound F, Table 1), a plant growth inhibitor, in a methanol/water mixture using NaOH as racemizing agent. The authors treated the prepared needle-shaped conglomerate crystals (10–200 μm) of both chiralities with a horn-type transducer at 20 kHz in 120 mL of a methanol-water mixture varying the nominal electrical power (13.9 – 90.3 W). It was found that the ultrasound treated crystals reached enantiopurity faster than the ones ground with glass beads at similar conditions (Fig. 5), even though the final crystal size was larger in the event of ultrasound at all power levels (~1–10 μm for glass beads versus ~5–20 μm for ultrasound using 90.3 W). An increase in the power output of the ultrasonic horn resulted in smaller particles and a concomitant increase in the deracemization rate, as shown in Fig. 5. However, since the attrition effect was less pronounced using ultrasound compared to bead grinding, the authors suggested that the mechanical effects of ultrasound alone are not sufficient to explain the faster deracemization.

The discrepancies between studies [63,64], can be partly explained if one considers the different materials and cavitation media used. For example, $NaClO_3$ is expected to be much harder than the needle-shaped crystals of the organic compound used in study [63], while methanol/water (80/20 wt%) mixture is easier to cavitate compared to pure water due to its lower kinematic viscosity. Consequently, breakage was more pronounced for the latter study, as evidenced from the minimum particle sizes that were attained for the different compounds (~30 μm for $NaClO_3$ versus ~5 μm for the compound in study [63]). Another point of concern is the type of ultrasound equipment used in the two studies (horn versus transducer) leading to different ultrasound intensities and potentially different type of cavitation. In a previous study, we characterized the type of cavitation bubbles obtained when ultrasonic transducers are used versus ultrasonic horns through sonoluminescence experiments for a wide range of operating frequencies and power levels [54]. In the latter case, transient bubbles are dominant, whereas in the former case mostly stable bubbles are obtained due to the lower intensity attained. Transient bubbles are short-lived and expand very rapidly to large sizes, collapsing before dissolved gasses diffuse through the bubble-liquid interface. On the other hand, stable bubbles survive many acoustic cycles allowing more time for the gases to diffuse through the bubble-liquid interface. Since gases inside the bubbles absorb energy upon collapse, transient bubbles will release more energy and generate stronger shockwaves, possibly resulting in more particle breakage and/or different breakage mechanisms.

The intriguing observations and differences in the aforementioned studies demonstrate that the exact mechanisms behind ultrasound-enhanced deracemization are not fully understood. Most authors attribute the deracemization rate enhancements to ultrasound enhanced attrition. However, it should be noted that in all studies of Viedma ripening using ultrasound, temperature increase was observed after sonication, thus efforts were made to maintain the temperature of the suspension constant by cooling in order to minimize the effect of temperature variations on deracemization. Yet, this may not exclude the presence of local hot spots [16,17], which could lead to local temperature variations and partial cycles of dissolution/re-crystallization eventually leading to deracemization [51]. The contribution of this phenomenon to ultrasound-enhanced deracemization remains for the moment unexplored.

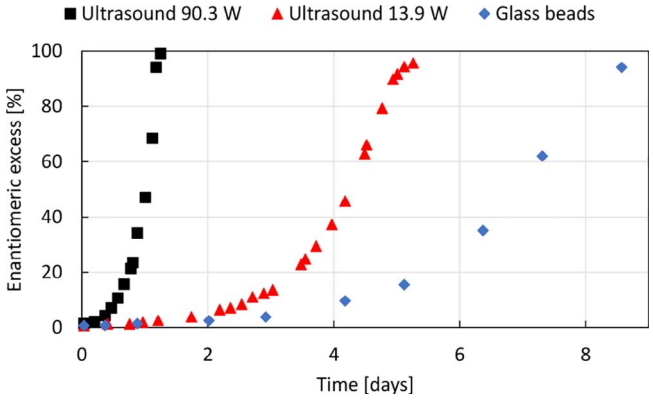


Fig. 5. Comparison of ultrasound-assisted grinding (120 mL) at different nominal electrical power using an ultrasonic probe (20 kHz) versus bead grinding at similar conditions for the deracemization of compound F in Table 1 [63].

5. Scale-up of ultrasound technology

Even though ultrasound technology can offer several benefits in chiral crystallization processes, the scale of application could pose a barrier for the adoption of the technology in manufacturing. Indeed most studies reviewed here were conducted at scales < 1 L with laboratory probe or bath systems, utilizing mostly a single transducer attached to a delivery tip (horn) or to the bottom of a cylindrical vessel (bath). The size of this equipment fundamentally limits the system size to which ultrasound can be applied. Furthermore, upon scale-up, these systems have to deal with nonhomogeneous distribution and strong attenuation of the acoustic field with distance. Additional limitations include tip erosion and possible contamination of the reaction mixture for probe systems and large stresses on the materials of construction for transducer systems. All these aspects can potentially hinder the application of power ultrasound technology for chiral crystallization in the pharmaceutical industry, whereby reliable operation and contamination-free environments at kg-ton scales is often required.

However, scale-up of ultrasound technology depends on the desired ultrasound effect and should be studied on a case-by-case basis. For instance, it was already shown in studies [34–36] that ultrasound technology could be applied at a larger scale (7–160 L) for the chiral resolution of several pharmaceuticals via preferential crystallization. In these studies, although homogeneous insonation of the suspension was not achieved, it was found that local ultrasound irradiation combined with appropriate reactor geometry could already produce the desired effect (secondary nucleation) enhancing the productivity of the preferred enantiomer crystals. For cases where homogeneous sonication of larger volumes at high power intensities and long residence times is required (*e.g.* deracemization), larger insonation cells fitted with multiple transducer systems, such as those described elsewhere [11] may be considered. The recent development of such systems also allows the combination of several modules to achieve longer residence times in continuous operation. The further development of such novel processing equipment is expected to increase the potential of ultrasound technology in the pharmaceutical industry.

6. Summary, conclusions and future perspectives

Although the application of ultrasound is known to influence solution crystallization processes to a large extent (sonocrystallization), little attention was paid so far on its effect on chiral crystallization, resolution and deracemization. In this paper, we provide an overview of the relatively few studies ultrasound technology has been applied to diastereomeric resolution, preferential crystallization and the recently discovered process of attrition-enhanced deracemization (Viedma ripening). Up to now, there is no scientific evidence that ultrasonic fields can directly induce stereodiscrimination in any of the aforementioned processes, as opposed to chiral fields (circularly polarized light). However, the mechanical and kinetic effects arising from the acoustic cavitation phenomenon, *i.e.* the development, growth and collapse of μm-sized bubbles, when a solution or a suspension is irradiated with high intensity low frequency ultrasound (20–100 kHz) can induce various benefits in such processes. In diastereomeric resolution, ultrasound greatly enhances the crystallization kinetics and yield of the diastereomeric salt, while preventing the co-precipitation of racemic compound salts that can lower the enantiomeric purity. In (seeded) preferential crystallization, ultrasound can promote the secondary nucleation of a single enantiomer (in slight excess) leading to highly enantiomerically-enriched final products. In some cases, ultrasound might also promote the precipitation of metastable conglomerate crystal forms, which are favorable for separation via crystallization. In Viedma ripening, ultrasound (with or without grinding media) has been shown to dramatically reduce the deracemization time, possibly due to the sonofragmentation of the irradiated crystals in the suspension.

Importantly, many of the aforementioned studies have already used actual pharmaceutical compounds or intermediates, including some blockbuster drugs with sales in the order of billion dollars (naproxen, clopidogrel *etc.*). Since particle engineering by sonocrystallization is already deemed a high potential technique [10] in developing small crystals of sparingly soluble pharmaceuticals to increase their bioavailability, the additional possibility of controlling the chiral outcome for these drugs is expected to bring much more attention to ultrasound processing for the pharmaceutical industry. Larger scale applicability of ultrasound processing, at least for preferential crystallization, has also been demonstrated leading to increased productivity of the preferred enantiomer crystals (Section 3.2).

However, while encouraging effects were observed in most of the studies, the precise mechanism and nature of the ultrasound effects in chiral crystallization processes remain rather elusive. This is also evident from several discrepancies reported among different authors. Indeed, many of the studies reviewed herein focused mostly on delivering a successful resolution/deracemization process, rather than carrying out a systematic study on the effects of ultrasound on the process. We believe that future studies should focus more on elucidating the origin of these effects, which seem to be tightly connected to the mechanisms of sonocrystallization and sonofragmentation, which are likewise to a large extent unclear.

Besides, studying the crystallization behavior of compounds that form chiral crystals could offer more insight into the mechanisms of sonocrystallization itself. In this regard, chirality serves as a means to "tag" individual crystals and identify to what extent primary or secondary nucleation is involved in the process (the former yields both chirality crystals, while the latter leads to significant enantiomeric enrichment). The fact that mirror symmetry breaking crystallization has been reported for such compounds using ultrasound supports theories for a secondary-nucleation driven mechanism of sonocrystallization (Section 3.3). Finally, we believe that further research using different types of ultrasound equipment and varying key parameters such as frequency, intensity and power for a wide range of compounds could shed more light on these aspects and enable harnessing of the full potential of ultrasound processing in chiral crystallization.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] D. Ager, Handbook of Chiral Chemicals, Second ed., CRC Press, 2005.
[2] N.M. Maier, P. Franco, W. Lindner, Separation of enantiomers: needs, challenges, perspectives, J. Chromatogr. A 906 (2001) 3–33.
[3] L.A. Nguyen, H. He, C. Pham-Huy, Chiral drugs: an overview, Int. J. Biomed. Sci. 2 (2006) 85–100.
[4] European Medicines Agency (EMEA), Reproduction 2006 (2) (November 1994) 1–15.
[5] R.A. Sheldon, Chirotechnology: designing economic chiral syntheses, J. Chem. Technol. Biotechnol. 67 (1996) 1–14.
[6] H. Lorenz, A. Seidel-Morgenstern, Processes to separate enantiomers, Angew. Chemie – Int. Ed. 53 (2014) 1218–1250.
[7] BCC Market Research, Global Markets for Chiral Technology – Focus on Europe, 2012.
[8] J. Jacques, A. Collet, S.H. Wilen, Enantiomers, Racemates, and Resolutions, Wiley, 1981.
[9] S.L. Hem, The effect of ultrasonic vibrations on crystallization processes, Ultrasonics 5 (1967) 202–207.
[10] R.D. Dennehy, Particle engineering using power ultrasound, Org. Process Res. Dev. 7 (2003) 1002–1006.

[11] G. Ruecroft, D. Hipkiss, T. Ly, N. Maxted, P.W. Cains, Sonocrystallization: the use of ultrasound for improved industrial crystallization, Org. Process Res. Dev. 9 (2005) 923–932.
[12] M.D. Luque de Castro, F. Priego-Capote, Ultrasound-assisted crystallization (sonocrystallization), Ultrason. Sonochem. 14 (2007) 717–724.
[13] L. de Los, S. Castillo-Peinado, M.D. Luque de Castro, The role of ultrasound in pharmaceutical production: sonocrystallization, J. Pharm. Pharmacol. 68 (2016) 1249–1267.
[14] J.R.G. Sander, B.W. Zeiger, K.S. Suslick, Sonocrystallization and sonofragmentation, Ultrason. Sonochem. 21 (2014) 1908–1915.
[15] B.W. Zeiger, K.S. Suslick, Sonofragmentation of molecular crystals, J. Am. Chem. Soc. 133 (2011) 14530–14533.
[16] E.B. Flint, K.S. Suslick, The temperature of cavitation, Science 253 (1991) 1397–1399.
[17] D.J. Flannigan, K.S. Suslick, Plasma formation and temperature measurement during single-bubble cavitation, Nature 434 (2005) 52–55.
[18] R. Pecha, B. Gompf, Microimplosions: cavitation collapse and shock wave emission on a nanosecond time scale, Phys. Rev. Lett. 84 (2000) 1328–1330.
[19] H. Monnier, A.M. Wilhelm, H. Delmas, Effects of ultrasound on micromixing in flow cell, Chem. Eng. Sci. 55 (2000) 4009–4020.
[20] S. Doktycz, K. Suslick, Interparticle collisions driven by ultrasound, Science 247 (1990) 1067–1069.
[21] V. Raman, A. Abbas, W. Zhu, Particle grinding by high-intensity ultrasound: kinetic modeling and identification of breakage mechanisms, AIChE J. 57 (2011) 2025–2035.
[22] R.M. Wagterveld, L. Boels, M.J. Mayer, G.J. Witkamp, Visualization of acoustic cavitation effects on suspended calcite crystals, Ultrason. Sonochem. 18 (2011) 216–225.
[23] M. Avalos, R. Babiano, P. Cintas, J.L. Jiménez, J.C. Palacios, L.D. Barron, Absolute asymmetric synthesis under physical fields: facts and fictions, Chem. Rev. 98 (1998) 2391–2404.
[24] P. Cintas, On cavitation and chirality: a further assessment, Cryst. Growth Des. 8 (2008) 2626–2627.
[25] B. Torok, K. Balazsik, K. Felfoldi, M. Bartok, Asymmetric reactions in sonochemistry, Ultrason. Sonochem. 8 (2001) 191–200.
[26] I.J. Barve, L.H. Chen, P.C.P. Wei, J. Te Hung, C.M. Sun, Enantioselective synthesis of (-)-(R) Silodosin by ultrasound-assisted diastereomeric crystallization, Tetrahedron 69 (2013) 2834–2843.
[27] Z. Szeleczky, E. Kis-Mihály, S. Semsey, H. Pataki, P. Bagi, E. Pálovics, G. Marosi, G. Pokol, E. Fogassy, J. Madarász, Effect of ultrasound-assisted crystallization in the diastereomeric salt resolution of tetramisole enantiomers in ternary system with O, O'-dibenzoyl-(2R,3R)-tartaric acid, Ultrason. Sonochem. 32 (2016) 8–17.
[28] G. Levilain, G. Coquerel, Pitfalls and rewards of preferential crystallization, CrystEngComm 12 (2010) 1983–1992.
[29] C. Rougeot, J.E. Hein, Application of continuous preferential crystallization to efficiently access enantiopure chemicals, Org. Process Res. Dev. 19 (2015) 1809–1819.
[30] D.D. Medina, A. Gedanken, Y. Mastai, Chiral amplification in crystallization under ultrasound radiation, Chem. – A Eur. J. 17 (2011) 11139–11142.
[31] X. Zhou, H. Wang, Q. Zeng, Chiral separation of DL-glutamic acid by ultrasonic field, CrystEngComm 19 (2017) 762–766.
[32] L.-D. Shiau, K.-F. Liu, Y.-C. Hsu, Chiral purification of S-ibuprofen from ibuprofen enantiomers by stripping crystallization, Chem. Eng. Res. Des. 117 (2017) 301–308.
[33] J.E. Hein, B. Huynh Cao, C. Viedma, R.M. Kellogg, D.G. Blackmond, Pasteur's Tweezers revisited: on the mechanism of attrition-enhanced deracemization and resolution of chiral conglomerate solids, J. Am. Chem. Soc. 134 (2012) 12629–12636.
[34] M. Midler, Production of crystals in a fluidized bed with ultrasonic vibrations, US Patent 3,510,266, May 5, 1970.
[35] M. Midler, Process for production of crystals in fluidized bed crystallizers, US Patent 3,892,539, July 1, 1975.
[36] M. Midler, Crystallization system and method using crystal fracturing external to a crystallization column, US Patent 3,996,018, Dec. 7, 1976.
[37] E.J.J. Grabowski, Enantiopure drug synthesis: from methyldopa to imipenem to efavirenz, Chirality 17 (2005) 249–259.
[38] D. Binev, A. Seidel-Morgenstern, H. Lorenz, Continuous separation of isomers in fluidized bed crystallizers, Cryst. Growth Des. 16 (2016) 1409–1419.
[39] D. Binev, A. Seidel-Morgenstern, H. Lorenz, Study of crystal size distributions in a fluidized bed crystallizer, Chem. Eng. Sci. 133 (2015) 116–124.
[40] Y. Song, W. Chen, X. Chen, Ultrasonic field induced chiral symmetry breaking of NaClO 3 crystallization, Cryst. Growth Des. 8 (2008) 1448–1450.
[41] Y. Song, W. Chen, X. Chen, Crystal chiral symmetry breaking: a self-seed inducing effect controlled by kinetics, Cryst. Growth Des. 12 (2012) 8–11.
[42] S. Azeroual, J. Surprenant, T.D. Lazzara, M. Kocun, Y. Tao, L.A. Cuccia, J.-M. Lehn, Mirror symmetry breaking and chiral amplification in foldamer-based supramolecular helical aggregates, Chem. Commun. 48 (2012) 2292–2294.
[43] C. Xiouras, E. van Cleemput, A. Kumpen, J.H. Ter Horst, T. van Gerven, G.D. Stefanidis, Towards deracemization in the absence of grinding through crystal transformation, ripening, and racemization, Cryst. Growth Des. 17 (2017) 882–890.
[44] M.P. Elsner, G. Ziomek, A. Seidel-Morgenstern, Efficient separation of enantiomers by preferential crystallization in two coupled vessels, AIChE J. 55 (2003) 3–194.
[45] E. Havinga, Spontaneous formation of optically active substances, Biochim. Biophys. Acta 13 (1954) 171–174.
[46] D.K.K. Kondepudi, R.J.J. Kaufman, N. Singh, Chiral symmetry breaking in sodium chlorate crystallisation, Science 250 (1990) 975–976.
[47] D.K. Kondepudi, C. Sabanayagam, Secondary nucleation that leads to chiral symmetry breaking in stirred crystallization, Chem. Phys. Lett. 217 (1994) 364–368.
[48] C. Viedma, Chiral symmetry breaking during crystallization: complete chiral purity induced by nonlinear autocatalysis and recycling, Phys. Rev. Lett. 94 (2005) 3–6.
[49] L.C. Sögütoglu, R.R.E. Steendam, H. Meekes, E. Vlieg, F.P.J.T. Rutjes, Viedma ripening: a reliable crystallisation method to reach single chirality, Chem. Soc. Rev. 6723–6732 (2015).
[50] W.L. Noorduin, W.J.P. van Enckevort, H. Meekes, B. Kaptein, R.M. Kellogg, J.C. Tully, J.M. McBride, E. Vlieg, The driving mechanism behind attrition-enhanced deracemization, Angew. Chemie – Int. Ed. 49 (2010) 8435–8438.
[51] C. Viedma, P. Cintas, Homochirality beyond grinding: deracemizing chiral crystals by temperature gradient under boiling, Chem. Commun. 47 (2011) 12786–12788.
[52] K. Suwannasang, A.E. Flood, C. Rougeot, G. Coquerel, Using programmed heating-cooling cycles with racemization in solution for complete symmetry breaking of a conglomerate forming system, Cryst. Growth Des. 13 (2013) 3498–3504.
[53] H.N. Kim, K.S. Suslick, Sonofragmentation of Ionic Crystals, Chem. – A Eur. J. 23 (2017) 2778–2782.
[54] J. Jordens, T. Appermont, B. Gielen, T. Van Gerven, L. Braeken, Sonofragmentation: effect of ultrasound frequency and power on particle breakage, Cryst. Growth Des. 16 (2016) 6167–6177.
[55] W.L. Noorduin, H. Meekes, W.J.P. van Enckevort, A. Millemaggi, M. Leeman, B. Kaptein, R.M. Kellogg, E. Vlieg, Complete deracemization by attrition-enhanced Ostwald ripening elucidated, Angew. Chemie – Int. Ed. 47 (2008) 6445–6447.
[56] W.L. Noorduin, H. Meekes, W.J.P. van Enckevort, B. Kaptein, R.M. Kellogg, E. Vlieg, Enantioselective symmetry breaking directed by the order of process steps, Angew. Chemie – Int. Ed. 49 (2010) 2539–2541.
[57] W.L. Noorduin, A.A.C. Bode, M. van der Meijden, H. Meekes, A.F. van Etteger, W.J.P. van Enckevort, P.C.M. Christianen, B. Kaptein, R.M. Kellogg, T. Rasing, E. Vlieg, Complete chiral symmetry breaking of an amino acid derivative directed by circularly polarized light, Nat. Chem. 1 (2009) 729–732.
[58] R.R.E. Steendam, B. Harmsen, H. Meekes, W.J.P. van Enckevort, B. Kaptein, R.M. Kellogg, J. Raap, F.P.J.T. Rutjes, E. Vlieg, Controlling the effect of chiral impurities on Viedma ripening, Cryst. Growth Des. 13 (2013) 4776–4780.
[59] R. Kellogg, M. van der Meijden, M. Leeman, E. Gelens, W. Noorduin, H. Meekes, W. van Enckevort, B. Kaptein, E. Vlieg, Attrition-enhanced deracemization in the synthesis of clopidogrel-a practical application of a new discovery, Org. Process Res. Dev. 13 (2009) 1195–1198.
[60] W.L. Noorduin, P. van Der Asdonk, A.A.C. Bode, H. Meekes, W.J.P. van Enckevort, E. Vlieg, B. Kaptein, M.W. van Der Meijden, R.M. Kellogg, G. Deroover, Scaling Up attrition-enhanced deracemization by use of an industrial bead mill in a route to clopidogrel (Plavix), Org. Process Res. Dev. 14 (2010) 908–911.
[61] W.L. Noorduin, B. Kaptein, H. Meekes, W.J.P. van Enckevort, R.M. Kellogg, E. Vlieg, Fast attrition-enhanced deracemization of naproxen by a gradual in situ feed, Angew. Chemie – Int. Ed. 48 (2009) 4581–4583.
[62] A.H.J. Engwerda, P. van Schayik, H. Jagtenberg, H. Meekes, F.P.J.T. Rutjes, E. Vlieg, Solid phase deracemization of an atropisomer, Cryst. Growth Des. 17 (2017) 5583–5585.
[63] C. Rougeot, F. Guillen, J.C. Plaquevent, G. Coquerel, Ultrasound-enhanced deracemization: toward the existence of agonist effects in the interpretation of spontaneous symmetry breaking, Cryst. Growth Des. 15 (2015) 2151–2155.
[64] C. Xiouras, J. van Aeken, J. Panis, J.H. Ter Horst, T. van Gerven, G.D. Stefanidis, Attrition-Enhanced Deracemization of NaClO3: comparison between Ultrasonic and Abrasive Grinding, Cryst. Growth Des. 15 (2015) 5476–5484.
[65] C. Viedma, Selective chiral symmetry breaking during crystallization: parity violation or cryptochiral environment in control? Cryst. Growth Des. 7 (2007) 553–556.