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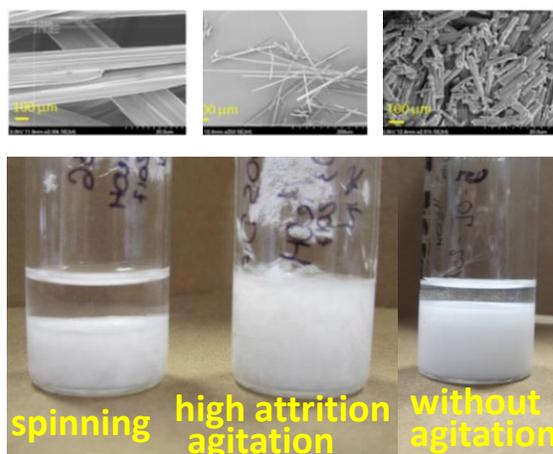
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ABSTRACT

We demonstrate the first examples of the transformation of gel-forming crystal needles into easily processable more equant crystals by accelerated Ostwald ripening without detectable crystal attrition. Using high solution shearing to accelerate mass transfer diflunisal and isonicotinohydrazide gels are transformed into easily filterable crystals. High-shear-ultra-low-attrition agitation conditions are generated by spinning with rapid reversal of the spinning direction every three seconds.

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Needle type crystals pose problems for pharmaceutical processing. [1,2] Difficulties arise in the handling of needle crystals due to their poor flow properties and the ease with which they can break leading to the generation of fines. It was the anticipation of difficulties with needles in the crystallization of ibuprofen that led the Upjohn Company to patent the crystallization of ibuprofen from hydroxylic solvents from which it was isolated as more equant shaped crystals.[3] We have found that isonicotinohydrazide (INH) and diflunisal, 2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid, (DIF) both give rise to stable gel formation when crystallized rapidly from solution. When gel-sample containers are spun with rapid reversal of the spinning direction every three seconds accelerated Ostwald ripening is observed. A stepper motor driven by a microprocessor was used to spin the sample vials about their axes and the direction of rotation was reversed every three seconds (Fig. S1, Supporting Information, SI).
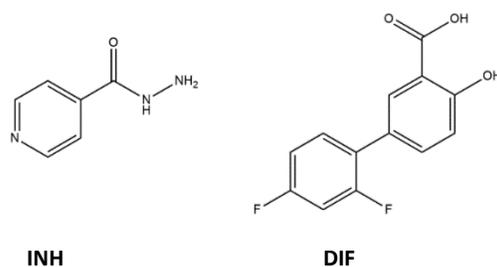

Figure 1. Structures of INH and DIF.

The crystal needles can be observed to gradually adopt a more equant shape and become easily filterable without the generation of crystal fines (Figs. S2 and S3, SI). Experimental details are described in the SI. Powder X-ray diffraction patterns rule out any polymorph change of INH and DIF during the process (Figs. S4 and S5, SI). We describe this process as high-shear-ultra-low-attrition-agitation (HSULAA) because the liquid shear generated in the spinning reversal due to the density difference between the crystals and the solution enhances the rate of material transfer from the needle tips to other crystal faces.

Samples that were subjected to the spinning process (HSULAA) have been compared to reference samples (REF) which were not agitated and to samples that were stirred with a magnetic stirrer bar, high attrition agitation (HA). All samples were held at room temperature. In Fig. 2 SEM pictures of reference samples, HA and HSULAA samples taken at different times over 14 days are shown. Over the 14 days the reference samples show little change, the HA samples show evidence of crystal fines and the HSULAA samples show progression to a more equant crystal shape. Plots of the change in the smallest crystal dimension with time are in Fig. 2(d). The corresponding results for DIF are in the SI, Figs. S6 and S7. The crystals in the 14 day HSULAA sample are of good quality and an INH crystal was indexed on a diffractometer, Fig. 3(a). Thus the HSULAA process can accelerate the transformation of micro crystals to good quality single crystals.
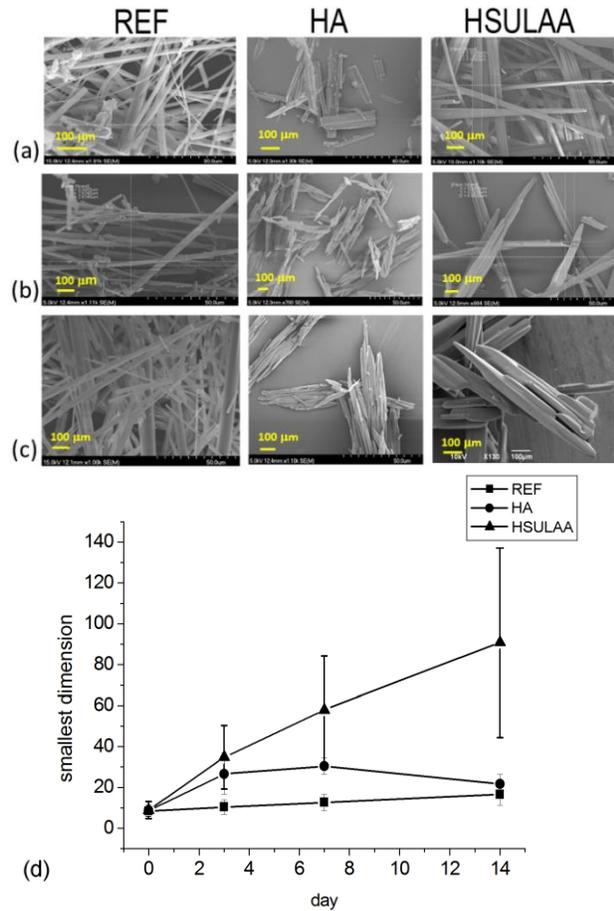
Figure 2. INH REF, HA and HSULAA samples at (a) day 3, (b) day 7, (c) day 14; (d) plot of the mean smallest crystal dimension with time.

(a)

(b)

(c)

(d)
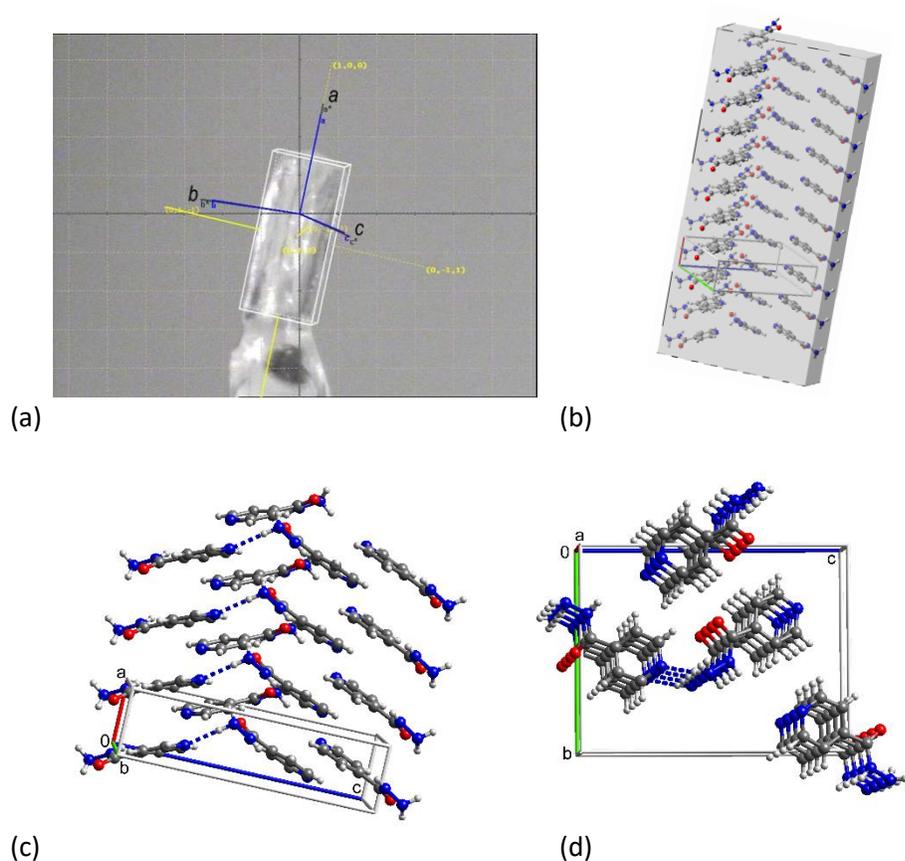
Figure 3. (a) INH crystal from the HSULAA day 14 sample indexed on a diffractometer, (b) crystal structure fitted into the observed crystal shape, (c) Top section of the structure in (b) from approximately the same viewpoint and the 4 unit cells in (c) showing the stacking down the *a* axis.

Ostwald crystal ripening normally involves the transfer of material from small crystals or an amorphous phase to larger crystals. [4] The material transfer from the small crystals or amorphous phase is by their dissolution and crystal growth on the part of the larger crystals. [5] The process is based on the higher solubility of smaller crystals of the same phase of a substance relative to larger crystals.[6] The particle size dependence of solubility is due to the higher energy of molecules on a crystal surface compared to molecules in the crystal bulk. This coupled with the higher surface area per unit mass of smaller crystals compared to larger ones leads to the tendency of smaller crystals to dissolve. However, the higher solubility of small crystals only becomes effective at very small crystal sizes.[5] Ostwald ripening of

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macroscopic crystals is a very slow process. [7] This is why the recent resurgence of interest in Ostwald ripening following the work of Viedma involves the deliberate crushing of smaller crystals using glass beads to accelerate the process. [8]

The same principle of solubility difference can exist between different faces of the same crystal when highly anisotropic crystal shape is coupled with vdW contact stacking in the anisotropic growth direction. Fig. 3(b) shows the crystal structure of INH, CSD code INICAC02, inside the crystal shape indexed on the diffractometer. Needle growth is along the *a* axis and Figs. 3(c) and 3(d) show the vdW contact stacking in the needle growth direction. The higher energy of the molecules at the top of the stacks is also clear where most of the atoms in a molecule will be subject to solvent collisions in contrast to molecules along the sides of the stacks where a lower number of atoms in each molecule are exposed to solvent. This higher energy will increase the dissolution rate of the crystal tips. A movie of the dissolution of a DIF crystal in methanol clearly shows that the needle gets shorter faster than it gets thinner, SI. A similar selective dissolution from the needle tips has been observed and reproduced using molecular dynamics for carbamazepine which also has a stacked structure. [9, 10] The role of sample spinning induced liquid shear close to the crystal surface in the current work is to speed the movement of molecules from the diffusion layer[11] which surrounds the immobile saturated layer[12] at the dissolving tips to the bulk of the solution without needle attrition. This process is also favored by the general observation that growth rates are slower than dissolution rates.[13]

There have been many attempts to predict crystal shape which have met with some success. These methods range from the BFDH method which relies on unit cell dimensions alone[14] to methods based on the calculation of slice attachment energies for each crystal face[15, 16] to Monte Carlo force field based methods which have recently been extended to include both molecular crystals and covalently bonded crystals. [17, 18] The Monte Carlo based methods give the best results for anisotropic crystal growth in stacked systems and the prediction that the aspect ratio is inversely proportional to the gas phase crystallization driving force for β-phthalocyanine has been confirmed for other stacked systems which exhibit needle growth. [17, 19] It is likely that the systems most likely to benefit from the HSULAA process are those which exhibit vdW contact stacking. This type of stacking can be detected in crystal structures in an automated procedure using a molecular centroid distance matrix analysis which counts the fraction of atoms in a molecule that are in contact with their neighbours above and below them in a stack. [20] When this fraction exceeds 55%, needle growth tends to be observed in that direction. These fractions are 87 and 74% for INH and DIF respectively in the direction of needle growth.

In summary we have developed a laboratory-scale method for accelerating the Ostwald ripening of needle type crystals without detectable crystal attrition. Since vdW stacking is a frequent feature of crystal structures that show anisotropic growth the HSULAA process should be applicable to a wide range of systems and scale-up should be possible provided low-attrition agitation is used in the reactor.

ASSOCIATED CONTENT

Supporting Information

Experimental methods, sample pictures, powder X-ray diffraction patterns, scanning electron microscope images, plots of the thickness of the smallest crystal dimension of DIF samples with time.

CONFLICT OF INTEREST

There are no conflicts to declare.

ACKNOWLEDGMENTS

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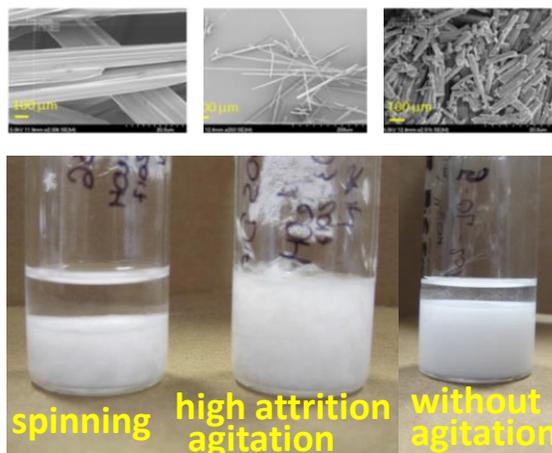
Spinning with rapid reversal of the spinning direction generates high-shear-ultra-low attrition agitation (HSULAA) conditions that accelerate Ostwald ripening of gel-forming needles into easily filterable crystals.