

Supporting Information for:

Separation and Enrichment of Enantiopure from Racemic Compounds Using Magnetic Levitation

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The Setup of MagLev Device:

The magnetic field was established in the MagLev device by aligning like poles of two NdFeB magnets (grade N50, 5 cm x 5 cm x 2.5 cm, Model #NB063-N50; Applied Magnets, Plano, TX) co-axially. Both magnets are positioned at 3.5 cm apart, equivalent to the width of the container in which the samples are suspended in the paramagnetic solution (Figure 1). With this setup, a low-density object will have a higher levitation height compared to a high-density object.

Previous work showed that tilting the MagLev device at a larger angle generates a larger separation distance between beads of different densities. Using this rationale, we conducted tilted experiments at different angles and found MagLev tilted at 30° yielded a better resolution of crystals and an easy experimental set-up.

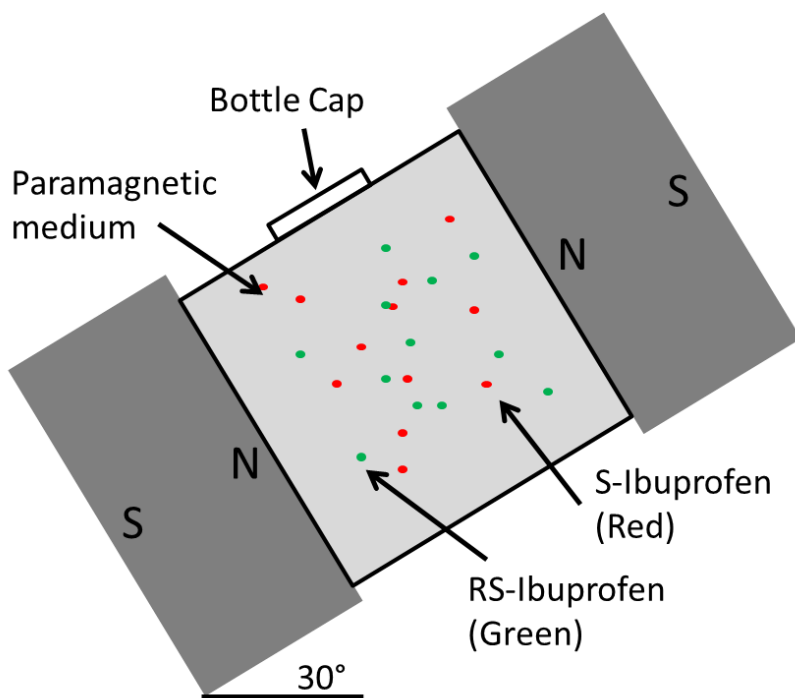


Figure 1. Schematic illustration of MagLev device. A cubic glass bottle (filled with the crystals and paramagnetic solution) is placed between two magnets with like poles facing each other. The bottle cap can be opened and the two populations of crystals can be withdrawn by pipettes.

Levitation Heights:

When an object is placed in the MagLev device, the “levitation height” is defined as the distance from the center of the object to the center of the bottom magnet (aligned along the perpendicular distance between two magnets).

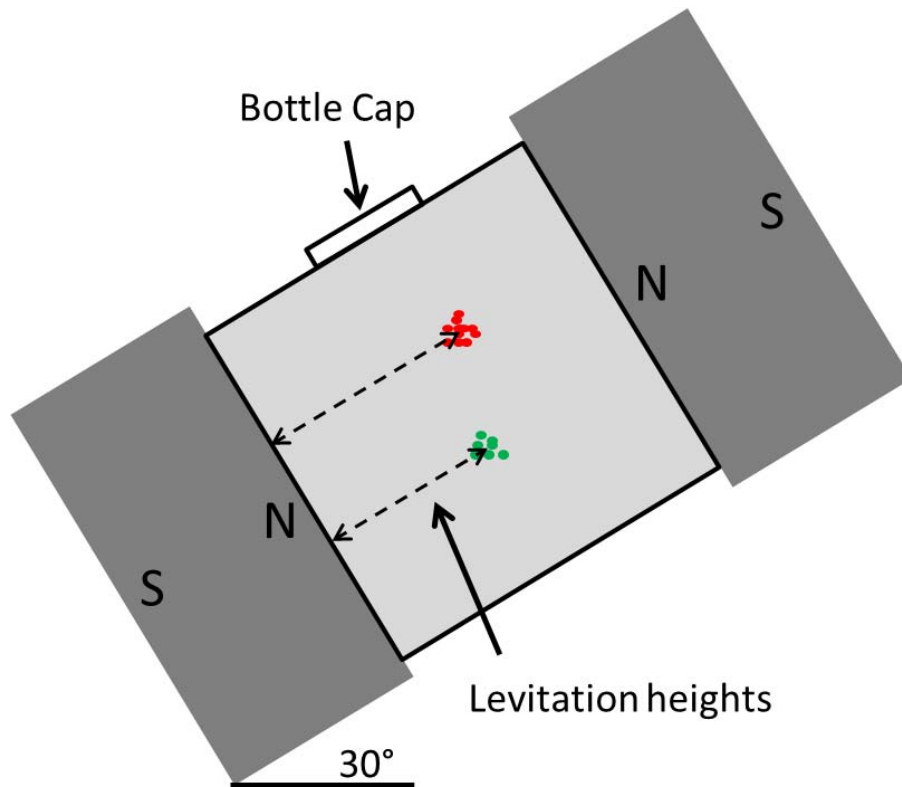
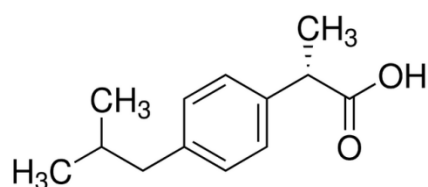


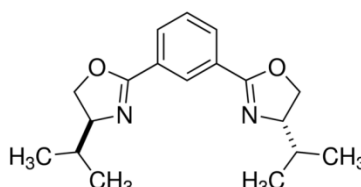
Figure 2. Schematic illustration of definition of levitation heights.

Materials:

S-Ibuprofen (>98%, Catalog number I4883) and RS-Ibuprofen (>99%, Catalog number 375160) were purchased from Sigma-Aldrich and used as received. Densities of S-ibuprofen and RS-ibuprofen were reported to be 1.093 g/cm³ and 1.110 g/cm³, respectively, in the literature. These samples were characterized by X-ray powder diffraction (XRPD) and differential scanning calorimeter (DSC), and the results showed that both forms of ibuprofen are pure crystalline materials while no impurity peaks were detected. S-Phebox (Catalog number RNI00022) and RS-Phebox (Catalog number RNI00024) were obtained from Sigma-Aldrich and used as received. Phebox is normally used as an efficient auxiliary for asymmetric catalysis. Manganese(II) chloride tetrahydrate (>99%, Catalog number M3634), sucrose (>99.5% Catalog number S9378) and Tween 20 (Catalog number P1379) were also obtained from Sigma Aldrich.



S-ibuprofen



S-Phebox

Experimental Setup:

We placed a mixture of S- and RS- ibuprofen in a 35 mm*35 mm*62 mm glass bottle containing the paramagnetic solutions (0.55M MnCl₂, 0.36M Sucrose and 0.5% v/v Tween 20). The mixture was initially dispersed with gentle shaking followed by a 3-min of sonication. From the experiment, we noted that good dispersion is crucial for MagLev separation; however, magnetic stir bar, normally used for strong mixing, may break the crystals into smaller pieces. We applied a 3-minute water bath sonication treatment. Some bubbles emerged due to the presence of the surfactant, and therefore we degassed the solution to remove all bubbles. After the dispersion, the sample bottle was placed at the center between the magnets of the MagLev device and left overnight (~ 12 hours) for crystals to separate (it takes less than 5 minutes for ~ 80% (volume percentage by visual inspection) crystals to achieve equilibrium position, but it takes overnight for the remaining small crystals to equilibrate).

The selection of the paramagnetic solution for separations of enantiopure from racemic crystals is important, if the products are to be used as drugs. First, all components in the solution should be approved by the FDA as excipients non-toxic to humans. Second, the resulting product should meet the United States Pharmacopeia standard after the separations. Considering these restrictions, we used an aqueous solution of 0.55 M MnCl₂ as paramagnetic medium (containing Tween 20 surfactant, 0.5% v/v and 0.36 M sucrose to increase its density). We chose MnCl₂ salt because it is relatively cheap (< 0.2 cent/g in industry), and produces a transparent aqueous salt solution, allowing direct visual observation of levitating crystals at their levitation heights. Although it is possible that trace amount of the paramagnetic salt may stick to the crystal surfaces (after separation in MagLev), one or several washing steps with water after the separation should be sufficient for the residual salt to a safe level (based on our experience with

handling impurity during crystallization). We used water with Tween 20 (0.5% (v/v)) as the solvent system because ibuprofen is fairly insoluble in water; however, to prevent sample loss during MagLev separation, we pre-saturated the paramagnetic solution with the same solid compositions as the ibuprofen testing mixture.

Quantifying Enantiomeric Composition by DSC:

DSC analysis was carried out on a TA Q2000 Differential Scanning Calorimeter. Samples were placed in Tzero[®] pans and sealed airtight by pressing the lids on the pans. A heating rate of 5°C/min was used.

A typical DSC curve is shown below. The calculation of the sample compositions follows:

$$\frac{S_A}{S_B} = \eta \frac{x_A}{x_B}$$

Where S_A/S_B is the melting peak area for species A/B (enthalpy change during melting, H(S-ibuprofen)/H(RS-ibuprofen) in our case), x_A/x_B is the weight percentage of species A/B, and η is a constant. The DSC calibration curve of S/RS-ibuprofen presented a linear relationship $y = 0.77x$ ($R^2 = 0.99$). This relationship works perfectly to calculate the composition for the bottom population of mainly RS-ibuprofen. For the top population of mainly S-ibuprofen, we subtracted the results of the lower population (mainly RS-ibuprofen) from the initial masses of S-ibuprofen and RS-ibuprofen (Mass Balance) and calculated the percentage.

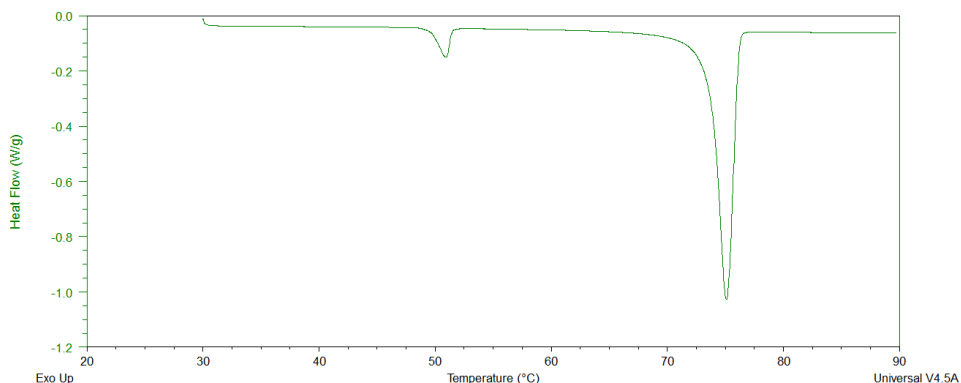


Figure 3a. A typical DSC curve of a mixture of S- (1st peak) and RS-ibuprofen (2nd peak).

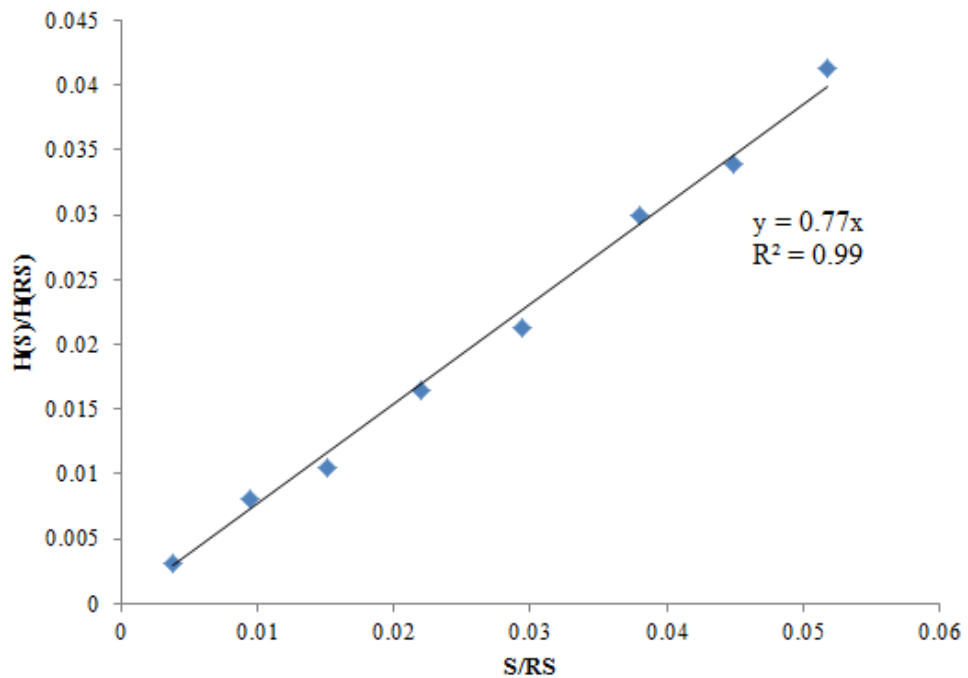


Figure 3b. Calibration curve of melting peak area for species A/B (enthalpy change during melting, $H(S\text{-ibuprofen})/H(RS\text{-ibuprofen})$ in our case) vs. the weight percentage of species A/B.

Separation of Phebox crystals (A mixture of S-phebox and RS-phebox crystals):

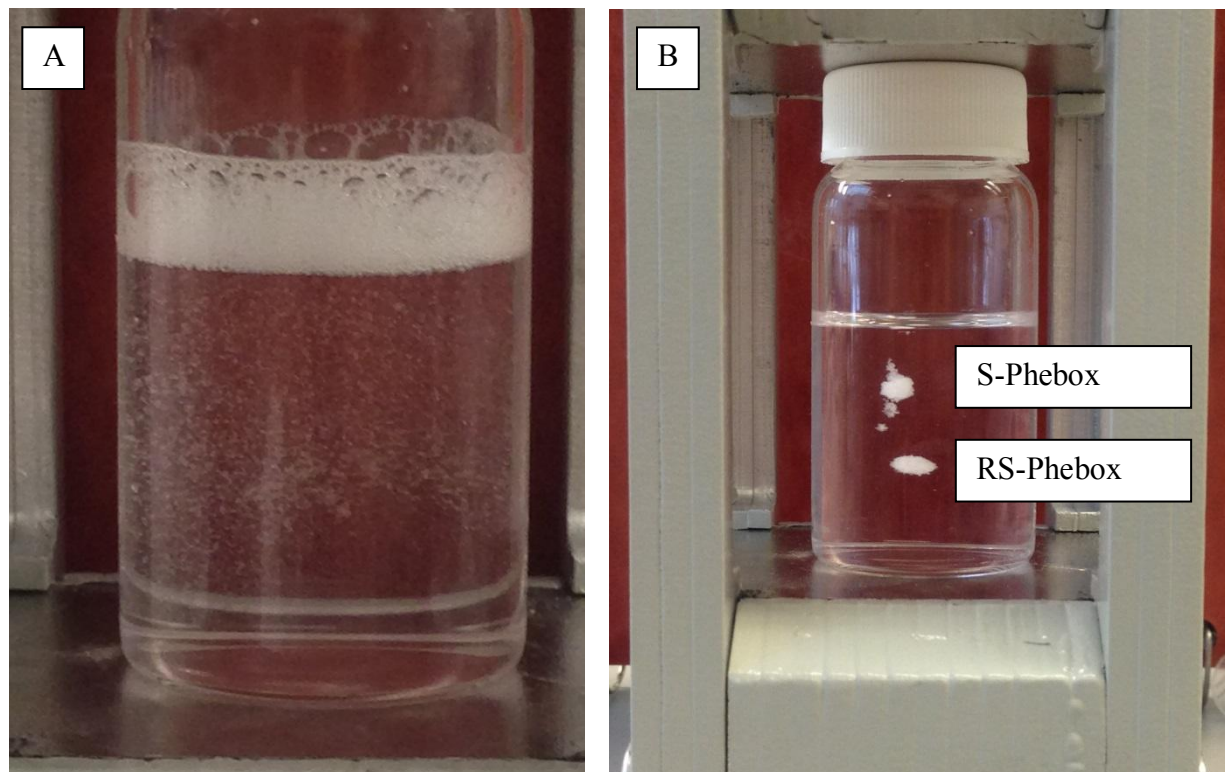


Figure 4. Picture showing S- and RS- phebox crystals dispersed in aqueous 1M MnCl_2 immediately when the bottle was placed between the magnets (A), and after allowing the crystals to separate overnight in the MagLev device (B). The MagLev device was set up in vertical position (no tilt).

Additional photographs on separation of S-ibuprofen and RS-ibuprofen crystals:

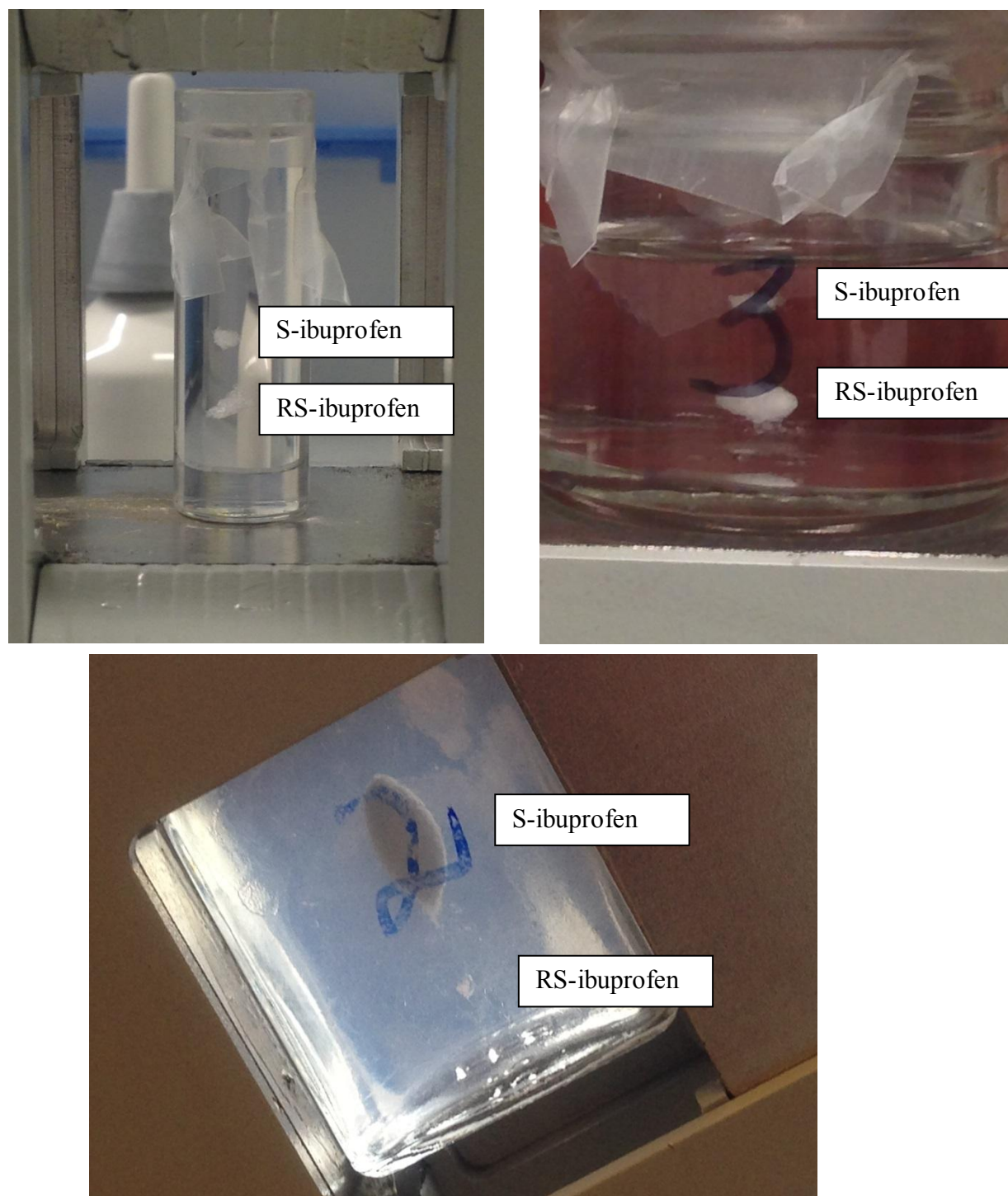


Figure 5. The top two photos were shot with the vertical setup (no tilt), and the bottom one was taken with the tilting setup.

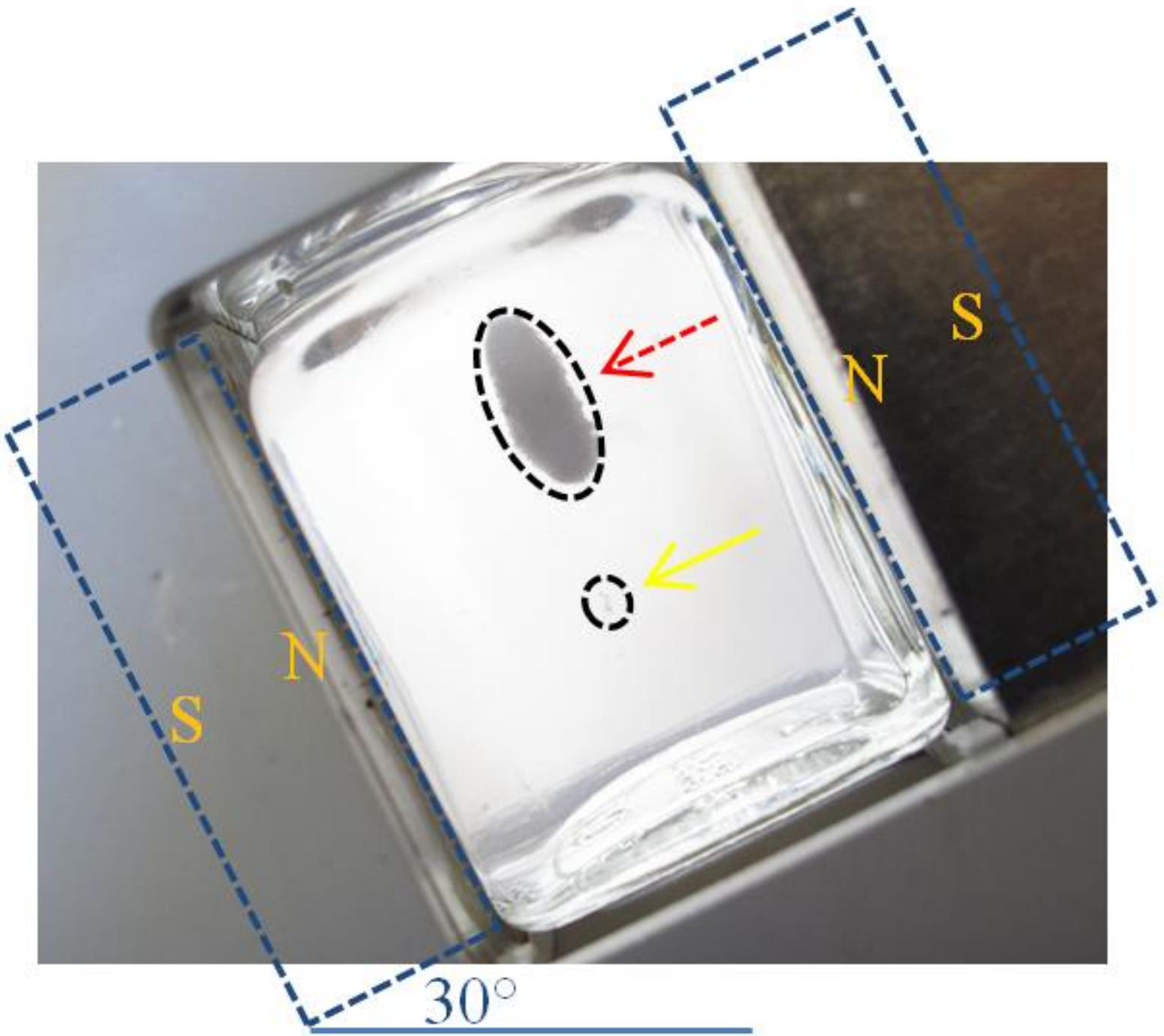


Figure 6. An enlarged version of Figure 4 in main text.

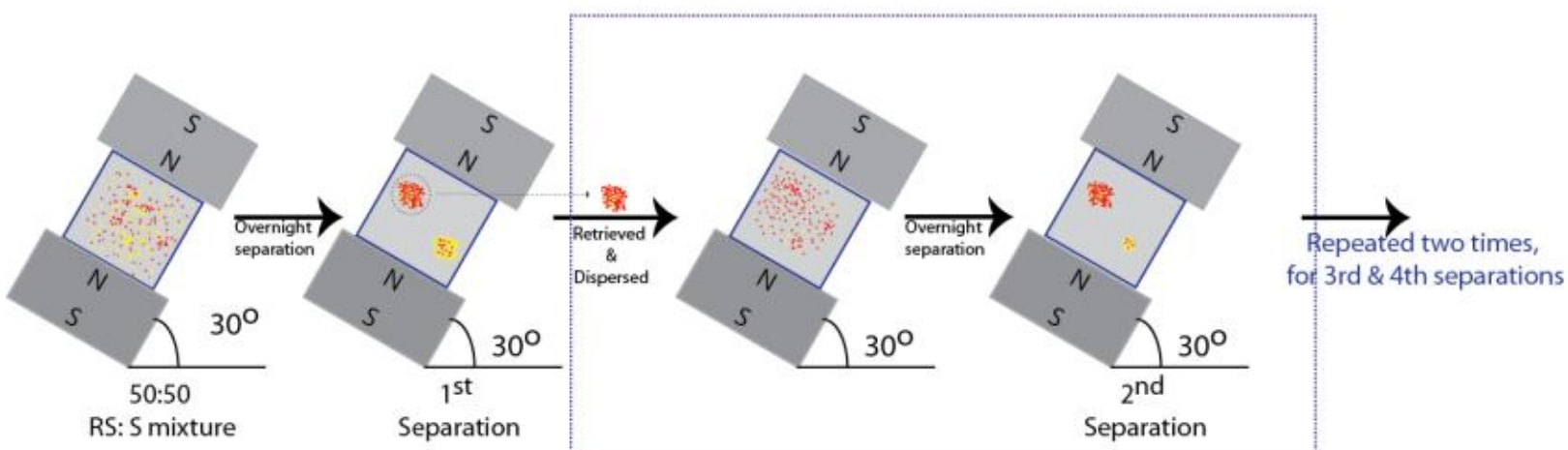


Figure 7. Iterative separation of the top population. Red dot: S-ibuprofen crystal; Yellow dot: RS-ibuprofen crystal. The numbers of red and yellow dots only represent relative amounts, and do not reflect a very accurate estimation of the experimental process. (1) At the beginning, known amounts of S- and RS-ibuprofen crystals are dispersed uniformly in the solution. (2) After overnight separation, two populations of crystals are clearly shown in the solution. The top one includes mostly S-ibuprofen and very few RS-ibuprofen crystals. The bottom one contains mostly RS-ibuprofen and very few S-ibuprofen crystals. (3) We retrieved the top population and dispersed it uniformly into another paramagnetic solution for the second separation. (4) After the second separation, the very few RS-ibuprofen crystals got separated out and formed the bottom population of crystals. Therefore, the purity of the top population in the 2nd separation is higher than the purity of the top population in the 1st separation.