Electronic Supplementary Information (ESI)

Mixture preparation.

Carbamazepine (CBZ, cod. C4024, M.W. 236.27 g/mol) for III and saccharin (SAC, cod. 240931, M.W. 183.18 g/mol), from Sigma-Aldrich, were used as received. Ethanol (reagent grade) was from Carlo Erba. SAC was dissolved in bi-distilled water at 50 °C and then left to equilibrate at 25 °C overnight. The saturated solution was then filtered by 0.2 μ m PES membrane to remove the solid deposit. An aliquot of the saccharin saturated solution was dried in an oven at 70 °C for 24 h and the solid residue was weighted to estimate the effective amount of SAC dissolved in the aqueous solution. A fixed amount of CBZ (around to 60 mg) and the appropriate amount of SAC were dissolved in ethanol to achieve the right initial molar ratios, as reported in Table 1. The overall crystallizing solutions were prepared by mixing the required amounts of the aqueous and the alcoholic fractions (see Table 1) to have a final mass of 100 g. From saccharin solubility, determined gravimetrically, and the amount of aqueous solution used for each tests, the overall CBZ/SAC molar ratio in the water/ethanol mixture have been calculated and reported in Table 1. Crystallizing solution was then fed to a membrane crystallization apparatus (Figure S1).^{1,2}

Crystallization tests.

In membrane crystallization process, several experimental parameters have a direct influence on transmembrane flux and hence on the degree and the rate of generation of supersaturation.¹ These parameters are: feed and transmembrane temperature, solutions circulation flow rate, membrane properties (material, pore size, porosity, etc.). Experiments were performed by using homemade glass membrane modules with overall available membrane area of $5.0 \times 10^{-3} \text{ m}^2$. Hydrophobic polypropylene hollow fibers membranes (Accurel PP S6/2, nominal pore size 0.2 µm, inner diameter 1800 µm, wall thickness 450 µm, 73% porosity, from Membrana GmbH) were used for all the tests.

Process activation was performed through generating a vapor pressure gradient between the two sides of the membranes by a temperature difference: 25 °C on the feed (crystallizing) side and 10 °C on the distillate side. Feed and distillate solution flow rate were 20 mL/min. During each test, water/ethanol composition in the crystallizing solution was quantified by ex-situ refractive index measurements on fixed aliquots of the distillate solution, after calibration. The transmembrane flux was measured as the reduction of the volume of the crystallizing solutions as a function of the time. Experiments were performed at fixed transmembrane flux by fixing the operative conditions: same membranes and membrane module configuration, feed and transmembrane temperature, solutions circulation flow rate. The membrane module was kept at higher temperature than the crystallizing solution in order to avoid crystallization inside the module/above the membrane surface.

Crystal's characterization.

Crystals obtained from experiments were harvested from the crystallizing solution by filtration with filter paper and stored in a desiccators at 5 °C before analysis. Crystal morphology was assessed by an optical microscope (DM 2500M from Leica Microsystems GmbH) equipped with a video camera. Figure S2 displays crystals obtained in test 3 and 8 (Table 1). Infrared analyses were performed by using a Fourier transformed infrared (FT-IR) spectrophotometer, Spectrum One from Perkin Elmer, in transmission mode by KBr pellets. Averages of 50 scans at 4 cm⁻¹ resolution were taken for each sample. Table S1 reports the main signals associated to each spectra.

Powder X-ray diffraction (PXRD) analysis was performed by using a Bragg-Brentano powder diffractometer from Rigaku, model ROTAFLEX CN4148C3 RU-H2R (12kW), series RINT2000, equipped with a rotating anode generator and an INEL linear detector, and the program Quanto³ for quantitative analysis. The wavelength is 1.54056 (Cu K_{α 1}) and the temperature of data collection is

298°K. The PXRD spectra obtained from the different tests are shown in Figure S3, where it can be noted that the features of the pattern corresponding to test 8 are clearly different from those of the preceding tests. A full-pattern fit was executed on the measured spectra by means of the Rietved method, with the aim of deriving the weight fraction of each crystalline phase present in the polycrystalline mixtures. The crystal structure of the four known anhydrous polymorphic forms of CBZ,^{4,5,6,7}, of its dihydrate form⁸, of SAC⁹ and of the two known polymorphic forms of cocrystal CBZ-SAC^{10,11} were considered in the fitting procedure. As a first step, samples from pure forms of the different compounds were processed, in order to set the experimental and analysis protocols. In this context, the commercial form of CBZ was best fitted by the phase corresponding to the polymorphic form III, with the resulting fit reported in Figure S4. Afterwards, the powders obtained by the crystallization tests were considered. The graphic output of the Quanto program shows the experimental diffraction pattern (blue curve) superimposed to the calculated profile (in grey). They are plotted versus 20 values, together with the positions of the reflections from the crystalline phases included in the fit. As results of the fitting procedure, a curve representing the background modeled by a polynomial function is summed up to the calculated profile (green curve) and the difference between the measured and the total calculated profiles is reported in red. The weight fraction of the phase content was determined with a fitting error of less than 1% for all the considered samples.

Figure S1. (a) Scheme of the membrane crystallization system, operating in solvent/antisolvent demixing configuration, used in this work. T1-T4: temperature probes; PG1-PG2: pressure gouges; P1-P2: peristaltic pumps; (b) Picture of the experimental plant with the different components.



membrane modules



Figure S2. Optical micrographs of crystals obtained in test 3 (up) and test 8 (down) – unit bars 100 µm.



Table S1. Main signals associated to FTIR spectra of CBZ III (commercial), SAC, CBZ I, and CBZ-SAC I.

| CBZ III (comm.) | | SAC | | CBZ I | | CBZ-SAC I | |
|------------------------------------|------|------|------|-------|------|-----------|------|
| v _{max} /cm ⁻¹ | | | | | | | |
| 3465 | 1306 | 3848 | 1013 | 3484 | 1114 | 3498 | 1177 |
| 3340 | 1269 | 3791 | 1007 | 3342 | 1039 | 3433 | 1158 |
| 3282 | 1244 | 3401 | 972 | 3284 | 1021 | 3316 | 1134 |
| 3158 | 1203 | 3093 | 900 | 3196 | 998 | 3257 | 1112 |
| 3069 | 1161 | 2973 | 856 | 3152 | 983 | 3183 | 1083 |
| 3020 | 1151 | 2694 | 795 | 3051 | 968 | 3111 | 1056 |
| 2965 | 1127 | 2599 | 774 | 3023 | 954 | 3077 | 1040 |
| 2850 | 1111 | 2510 | 758 | 2796 | 876 | 3048 | 1027 |
| 2758 | 1039 | 2391 | 703 | 2617 | 853 | 3028 | 1018 |
| 2614 | 1019 | 2233 | 630 | 1984 | 804 | 2926 | 989 |
| 2548 | 987 | 2011 | 592 | 1962 | 792 | 2664 | 956 |
| 2408 | 980 | 1976 | 529 | 1944 | 774 | 1976 | 902 |
| 2285 | 943 | 1941 | 517 | 1934 | 753 | 1942 | 978 |
| 2225 | 870 | 1901 | | 1870 | 719 | 1837 | 859 |
| 2044 | 851 | 1865 | | 1839 | 705 | 1802 | 807 |
| 1959 | 801 | 1719 | | 1782 | 698 | 1731 | 793 |
| 1919 | 790 | 1655 | | 1758 | 648 | 1645 | 787 |
| 1889 | 763 | 1593 | | 1688 | 624 | 1597 | 777 |
| 1849 | 724 | 1551 | | 1603 | 583 | 1574 | 769 |
| 1831 | 704 | 1504 | | 1593 | 554 | 1565 | 758 |
| 1814 | 647 | 1463 | | 1563 | 545 | 1516 | 747 |
| 1792 | 623 | 1458 | | 1489 | 537 | 1490 | 720 |
| 1677 | 579 | 1418 | | 1460 | 507 | 1462 | 703 |
| 1605 | 536 | 1336 | | 1440 | 500 | 1448 | 670 |
| 1594 | 486 | 1320 | | 1397 | 483 | 1424 | 648 |
| 1564 | 465 | 1297 | | 1305 | 472 | 1354 | 625 |
| 1526 | | 1257 | | 1271 | 457 | 1329 | 609 |
| 1515 | | 1177 | | 1251 | | 1310 | 592 |
| 1489 | | 1162 | | 1218 | | 1291 | 534 |
| 1462 | | 1139 | | 1206 | | 1275 | 520 |
| 1436 | | 1120 | | 1156 | | 1249 | 485 |
| 1384 | | 1054 | | 1129 | | 1205 | 467 |

Figure S3. Powder diffraction spectra as a function of the 2θ variable (in degrees) acquired for the crystalline material obtained in all the crystallization tests. The test number follows that reported in Table 1. The data have been offset for clarity.



Figure S4. Graphic output of the Quanto program for the commercial CBZ form. Violet bars: positions of the reflections from CBZ form III; red curve: difference between observed and calculated profiles; green curve: fitted background function.



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