Low-temperature concentration of solutions using supercritical carbon dioxide to support the flow chemistry developments of the pharma industry

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Continuous production of active pharmaceutical ingredients(APIs) and even pharmaceutical formulations is getting increasingly interesting for the global players of the pharmaceutical industry. Flow chemistry offers enhanced heat transfer and controllability than batch synthesis in several cases thus increased selectivity and environmentally favorable API production. [1] However, typically, the flow chemistry synthesis has to be followed by several purification steps to remove all contaminants e.g. residual reagents, products of side reactions. [2] Although there are numerous options for the continuous formation of solid formulations e.g. crystallization, precipitation, freeze-drying of even electrospinning techniques [3] any of these may become a realistic alternative of the traditional batch methods if the concentration of the API in the solution is above a particular, technique depending threshold. In most of the cases, the solution of the API does not have a concentration high enough for any of these precipitation techniques right after the purification steps. While continuous distillation like distillation columns, short pass distillation or molecular distillation might be a viable option, they require elevated temperatures being not preferable in the case of heat-sensitive APIs. We present a novel technique using supercritical carbon dioxide to overcome these issues. Our novel method allows a steady-state removal of the excess solvent.

Concentration enhancement was defined as the ratio of the final API concentration and initial API concentration in the feed and product solutions, respectively. Starting from a 0.5 m/m% solution of ibuprofen in ethyl acetate, the steady-state operation was possible at mixing temperature of 40 °C with any desired concentration enhancement values between 1.1 and 18, where the saturation of the solution was achieved. The main process parameter controlling the concentration enhancement is the mass flow ratio of the feed and the carbon dioxide, which was confirmed by flash simulations using Peng-Robinson equation of state.

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