ABSTRACT

The use of two-phase crystallization media, based on mixed reverse micelles and w/o microemulsions, in the design of crystallization processes used for the purification of crude active pharmaceutical ingredient (API) orlistat was studied. An *n*-heptane solvent was used for the continuous, organic phase. Sodium dioctyl sulfosuccinate (AOT) and sodium diamyl sulfosuccinate (DAS) were applied as surface-active agents, and water was added for the formation of the dispersed phase.

The physical properties of the prepared two-phase crystallization media were studied in dependence of water concentration, the surface-active agents concentration and the molar ratio DAS/AOT. The transport properties were determined by measuring electrical conductivity and viscosity. The microstructural properties of the prepared liquid systems were analyzed using differential scanning calorimetry (DSC) and small-angle x-ray scattering (SAXS). Crude orlistat and the obtained products were characterized with high-pressure liquid chromatography and mass spectrometry for identification and quantization of structurally related impurities.

The prepared liquid systems, mixed reverse micelles and w/o microemulsions, were used as crystallization media for purification of the crude API orlistat. By changing the composition of two-phase crystallization media we could influence batch crystallizations, the characteristics of which we then compared to the characteristics of the reference crystallization samples of crude orlistat obtained from *n*-heptane. The defined crystallization processes, performed in two-phase crystallization media, result in an enhanced yield and improved separation of structurally related impurities.

We defined the composition of the two-phase crystallization medium water-AOT-DAS-*n*-heptane and the crystallization process parameters that enable purification of crude orlistat (chromatographic purity 90.2 area%) in two consecutive crystallization steps and preparation of a product with a chromatographic purity of >99.5 area%, content of structurally related impurities of <0.10 area%, and an overall yield of approximately 80 molar%.