Continuous Hydrolysis and Liquid–Liquid Phase Separation of an Active Pharmaceutical Ingredient Intermediate Using a Miniscale Hydrophobic Membrane Separator

Continuous hydrolysis of an active pharmaceutical ingredient intermediate, and subsequent liquid–liquid (L-L) separation of the resulting organic and aqueous phases, have been achieved using a simple PTFE tube reactor connected to a miniscale hydrophobic membrane separator. An alkoxide product, obtained in continuous mode by a Grignard reaction in THF, reacted with acidic water to produce partially miscible organic and aqueous phases containing Mg salts. Despite the partial THF–water miscibility, the two phases could be separated at total flow rates up to 40 mL/min at different flow ratios, using a PTFE membrane with 28 cm² of active area. A less challenging separation of water and toluene was achieved at total flow rates as high as 80 mL/min, with potential to achieve even higher flow rates. The operability and flexibility of the membrane separator and a plate coalescer were compared experimentally as well as from a physical viewpoint. Surface tension-driven L-L separation was analyzed in general terms, critically evaluating different designs. It was shown that microporous membrane L-L separation can offer very large operating windows compared to other separation devices thanks to a high capillary pressure (Laplace pressure) combined with a large number of pores per unit area offering low pressure drop. The separation device can easily be operated by means of a back-pressure regulator ensuring flow-independent separation efficiency. Simple monitoring and control strategies as well as scaling-up/out approaches are proposed, concluding that membrane-based L-L separation may become a standard unit operation for continuous pharmaceutical manufacturing.

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