Mixing analysis for scale-up of batch processing for critical controlling step in pharmaceutical process

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Abstract

Agitation is a key operation involved in transformation processes and more particularly in manufacturing of active pharmaceutical ingredients (API). It is necessary at many stages and it can have varying degrees of complexity depending on the substances used, on the operating conditions run and on the purpose of the agitation. If agitation is not carried out properly, for example with poorly sized vessels or non-optimal operating conditions, it can lead to significant losses in terms of productivity (inadequate product quality, reduced yield, impurities generation, etc.).
When a company needs to increase the production volume to meet demand or reach industrial-scale production, it is often necessary to increase the capacity of the manufacturing unit. Extrapolation of process conditions from lab or pilot scale to larger manufacturing scale is then critical when designing a new production line.
Firstly, it is necessary to identify the appropriate plant geometry and, secondly, to determine the operating conditions required to maintain product quality in large-scale production. It is therefore important to define the phenomena in the tank and the characteristics of the mixing operation that will be limiting or critical. They will have to be kept constant throughout the various production stages.
Working at a small scale (laboratory scale - few milliliters to 10 liters vessels) allows to build up knowledge of phenomena (mixing, kinetics, etc) in the tank, and to generate data required for designing the industrial tank and determining associated operating conditions. The sizing of the industrial tank can then be estimated based on correlations and modeled using numerical tools based on scale-up criteria identified at laboratory or pilot scales.

In this work, the mixing conditions in two unit operations were assessed: a reaction step characterized by an instantaneous reaction occurring in a single organic phase, on one hand, followed by the quenching of the reaction mixture in an aqueous-based solution, on the other hand. The latter forms a biphasic system, to remove any remaining reactive species and preserve the reaction mixture its desired composition.
These two unit operations are part of a multiple chemical steps synthesis of an API at UCB. They were identified as potentially affected by scale-up. Specific mixing conditions encountered during operation at different scales were assessed and compared to identify scale-up criteria to be used for large-scale manufactory operations.
The assessment was carried out using simulation on DYNOCHEM and VISIMIX mixing simulation softwares. In addition, a series of lab tests was performed to put the numerical simulations in perspective with experimental data.

Visimix was preferred to perform the simulations as it takes into account more parameters, such as the fill level of the vessels, for the calculations (at least for the power number). From the simulations, it appears that the mixing time obtain in the current lab and pre-manufacturing scale vessels for the single-phase unit would be quite difficult to reproduce on the hypothetical industrial scale (ten-time volume scale-up). On the other hand, concerning the biphasic system, it appears that the dispersion could be achieved if the maximum impeller speed is used and in that case, the conditions will be better than those currently observed in the lab and pre-manufacturing scale. However, Visimix may overestimate the impeller speed required to achieve dispersion, whereas it seems to realistically estimate mixing times in a single-phase system.