Mixing simulation tools in process development

KEYWORDS: Mixing simulations, process development, scale-up, scale-down, reactor performance.

Abstract
Pharmaceutical manufacturers are facing ever-growing needs of quality by design practices for the development of robust and predictable chemical processes. In this context, the use of modern simulation techniques has emerged as a valuable tool to cope with these demands. To illustrate the potential of this approach we will cover some of the challenges faced during process development and scale-up regarding sensitive crystallizations, gas-liquid reactions, liquid-liquid extractions and equipment design emphasizing on the mixing phenomena. The use of mixing simulation tools increases the understanding on the chemical processes during Active Pharmaceutical Ingredient (API) manufacturing. This allows chemists and process engineers to mitigate risk, achieve better performances and long lasting results.

INTRODUCTION
Over the past decades, pharmaceutical industries lost millions of dollars in commercial scale manufacturing due to mixing problems that went undetected in laboratory experiments [1]. However, this situation is changing since a more competitive global business market, coupled with growing client demands, has stimulated researcher’s attention towards simulation tools [2]. To meet today’s quality by design standards, the industry has been gaining new allies in process development and troubleshooting. The use of state-of-the-art modelling tools, namely mixing simulation technology [3], is allowing chemists and process engineers to gain comprehensive insights on vessel mixing performance as part of a “right first time” strategy.

EXACTLY WHAT LEVEL OF MIXING IS ADEQUATE FOR A GIVEN APPLICATION?

The answer to this question depends on a deep understanding of the mixing impact in the process stage being manufactured (Figure 1). Good experimental work on the evaluation of the mixing mechanisms is critical to obtain useful data, robust solutions and long-lasting results. Ignoring these fundamentals can ultimately expose scale-up and technology transfer operations to failure. Mixing related parameters can be analysed to select suitable process conditions for each development stage, such as batch size, stirring speed, addition point, among others. Based on quantitative data, decisions on choosing the right vessels and adequate equipment modifications for manufacturing scale-up are made more efficiently.

By using mixing studies it is possible to maintain similar mass-transfer properties, which are scale-dependent and can have a crucial impact in the process outcome in different equipment [1]. Laboratory data can also be used to predict the outcome of different scenarios at manufacturing by searching for correlations between batch performance and mixing parameters. Moreover, process troubleshooting and optimization has been made easier through the use of simple scale-down strategies for laboratory research. This approach results in more cost-efficient manufacturing processes since it allows to anticipate most scale-related problems in laboratory experiments. Furthermore, process engineers can determine the best equipment design for a specific purpose, for instance, reagent addition points, impeller designs and baffle types. All these and other adjustments can be tested for their performance simply by using a standard computer.
The growing world market competition and the need for fast arrival to market have placed contract manufacturer organizations (CMO’s) under increased pressure. Therefore innovative R&D solutions are required to promote the fast development for large scale commercialization. Particularly in process scale-up, mixing conditions play an important role that can jeopardize months of work. If these fail to produce the required product attributes, the launch of the product may be delayed or even cancelled. Bearing this in mind, this article briefly highlights advances in the understanding of the mixing phenomena and how this knowledge can be used to improve API manufacturing.

**CRYS TALIZATION**

Controlling particle characteristics, such as crystal shape and population size, has an overwhelming importance in the pharmaceutical industry due to its ability to generate distinct physical properties. Besides the influence on the drug performance, different crystal shapes, sizes and morphologies can have a tremendous impact in the timelines and logistics of downstream filtration and drying operations (4). Regarding batch crystallizations, mixing conditions regulate the initial nucleation rate and the subsequent crystal growth profile that, together, define the crystal’s final specifications (5). During solvent/anti-solvent crystallizations scale-up, disregarding the energy of dissipation at the solvent addition point, could lead to local supersaturations and excessive nucleation or agglomeration. Mixing simulation tools coupled with process analytical tools (PAT) for laboratory data analysis, provide an opportunity to uncover the mixing impact in the process thus mitigating the risk of batch failure. For instance, when using the Lasentec FBRM® probe to monitor at laboratory scale a crystallization very sensitive to mixing, it was possible to observe the impact of mixing parameters such as energy dissipation at different addition points (Plot 1).

Using mixing simulations we found a zone inside the reactor with low energy of dissipation. When the product is added in that zone, the nucleation rate detected by Lasentec FBRM® is lower leading to bigger crystals. This observation supported the selection of the adequate mixing conditions for this crystallization batch size when it was increased at manufacturing. This successful operation resulted in 50% savings in manufacturing costs.

**MONITORING EMULSIFICATION**

Agitation plays an important role in liquid-liquid extractions (LLE) as it controls drop breakup, the combining of drops (drop coalescence) and the distribution of drops throughout the system. Although there are extensive literature reports underlying the mechanisms on liquid-liquid contacts (mostly related with surface tension agents applications), this remains one of the least known mixing problems (6). During LLE, vigorous mixing is required to generate efficient two-phase contact, but too much turbulence may cause an emulsion. This is a major concern at manufacturing since it can lead to several days of phase separation efforts with inherent costs and equipment unavailability. Moreover, it can decrease the process overall yield. In fact, part of the API may be lost if the emulsion is discarded or it can compromise the final product purity and specifications.

By using mixing simulations to scale-down the manufacturing reactor, it is possible to evaluate at lab scale if the reaction mixture is prone to emulsion formation. A wide range of laboratory apparatus (reactor, impeller, baffles…) are simulated in the software until a manufacturing-like mixing intensity is detected. Afterwards, several batches are made in laboratory reactors in order to select the adequate mixing conditions that can minimize emulsion formation probability at manufacturing (Plot 2), while maintaining the LLE purpose unharmed (Plot 3).

Plot 1. Lasentec FBRM® total counts vs addition time. Addition of the product in a zone of low energy dissipation (Low E.D.) leads to a slower nucleation rate which ultimately resulted in larger particle size distribution.

Plot 2. Mixing simulations can be used to plan laboratory experiments in order to find relationships between LLE outcomes (in this specific case emulsion formation) and mixing intensity. The optimized conditions resulted in very low amounts of emulsion.

Plot 3. The purpose of this LLE was to remove an impurity. The optimized mixing conditions found at the laboratory scale (Plot 2), maintained the product inside specification as did the initial mixing conditions.
An efficient strategy is to use mixing simulations in the early stages of process development where, besides emulsification, other LLE relationships can be detected such as product degradation, by-product formation or even extraction efficiency.

**GAS-LIQUID REACTIONS**

The perfect gas-liquid mixing conditions are those where the gas dispersion in a reaction mixture leads to the highest mass-transfer surface area. In batch reactors, good mass-transfer properties depend on small gas bubbles sizes, high gas fractions and long gas residence times in the liquid phase. However, excessive gas fractions can be undesirable since the batch reactor productivity comes from the amount of liquid it can hold. Furthermore, it can also lead to unwanted secondary reactions. Once the unreacted gas escapes to the reactor headspace it can be reincorporated in the reaction mixture, usually through the vortex, surface turbulence or using specialized impeller designs (1). In most cases, the chemical reaction rate is determined by the mass-transfer coefficient that strongly depends on the vessel geometry and impeller design (7-8). Considering all these observations, the reactor mixing properties have a crucial impact during scale-up or technology transfer operations of gas-liquid reactions.

Mixing simulation tools can be an advantage to support decisions during technology transfer operations. For instance, it is possible to simulate a reactor where a successful gas-liquid reaction (e.g. hydrogenation) was made and quantitatively measure its mixing intensity. The adequate mixing conditions to be used in a different reactor are then selected by reproducing the previously measured values. These tools can also support the rationale for unexpected results by estimating reactors gas-liquid parameters, such as gas hold-up, gas surface reincorporation and mas-transfer coefficients. Upon evaluating data from laboratory process development, gas-liquid parameters can frequently exhibit correlations with faster reaction times or by-product formation, as the one depicted in Plot 4.

**EQUIPMENT DESIGN**

By gaining comprehensive insights on the process performance, multidisciplinary teams can cross information to select equipment going beyond mechanical and financial considerations. Mixing simulations tools can be used to estimate parameters such as critical frequencies, shaft integrity and heat-transfer ability, to select the best mixing devices within the available options, to prepare data for equipment design and ordering, to analyse and compare efficacy of different equipment alternatives. Mixing simulations can also be used to find optimized reagent inlet positions that ultimately lead to the desired mixing profile (Figure 2). In this process, an efficient mixing was required upon reagent addition. By using mixing simulations we were able to pin point the zone inside the reactor with the highest turbulence and in that basis to design the optimal addition point. Inexpensive ways to modify equipment can be found from mixing calculations – sometimes a simpler process-guided impeller modification can be a far better investment when compared to a new batch reactor purchase.

**REFERENCES**

3. Visimix software. “Visimix uses mathematical models and methods of calculations which are based on fundamental equations of turbulent transport of energy, momentum and mass. The equations were formulated and simplified using experimental data of flow pattern and other characteristics of an agitated flow.”

![Figure 2. Specific reagent inlet position radius (r) and height (h) were selected accordingly with the highest turbulence zone, thus promoting this process mixing demands.](image)
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