AMX AGITATORS IN PHARMACEUTICAL

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introduction

The delicate dynamics and manufacturing tolerances utilised in the fine chemical/pharmaceutical processes, coupled with the vast variation of products, indicates the possible variations of agitator designs required to suit the specific application processes within this industry.

Most of the mixing in this industry supports a chemical reaction process, and the solution stays resident in the same mixing vessel for batch or semi-batch processing.

This type of mixing is used to support:

- Homogeneous and heterogeneous mixing until complete chemical conversion has occurred.
- The accurate adding of reagents to the vessel including gases.
- Productivity and flexibility by implementing impellers that have a wide scope of operational characteristics that are coupled to variable speed drives.

Some challenges exist in the mixing of fine chemicals which include the following:

- Uniformity of the mixture, based on a time constraint that has an impact on by-product production.
- Stopping the reaction at the optimum point to avoid chemical wastage.
- Efficient mixing speeds that assist with heat transfer.
- Thermal hazards related to volume production in exothermic reactions.
- The settling of fine chemicals below baffles or inconsistent suspension of solids. Entrained vapours cause foaming and cavitation of the mixing process which has led to the development of specialised solutions that scale within a given set of performance parameters.

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specialised finishes & coatings

This industry has a wide variety of coatings that are used to protect the wetted parts and vessel from the chemicals, thereby affording chemical and wear protection. AFX has specialised knowledge of the industry standard glass-lined coatings and includes the tolerances related to these coatings into the designs.

specialised impeller blades

The following types of blades are the standard blade types used in this industry:

- Retreat blades
- Anchor impellers
- Turbine impellers
- Curved blades
- Pitch blades
- In-line static mixers

support for scaling applications

Some laboratory-based production designs cannot be scaled efficiently into production quality and quantity solutions, especially in multiphase processes. The industry has developed many methods to handle this nuance successfully by incorporating design alternates.

Continuous reactors

Continuous reactors are used when thermal heat transfer affects the production values. It is more desirable to avoid large quantities of the mixing products being together, as this has an exponential heating effect on the batch. Various solutions are used to achieve this type of reaction. Small batch mixing based on a packed bed, fluid bed or trickle bed allow for fine control of the production output.
Static in-line mixers or tubular mixers form part of the solution. These mixers are highly efficient and offer good control over reaction temperatures and better control over constant mixing intensities, and their reactions occurring.

Reaction calorimetry

Calorimetry is the heat by-product of a reaction that is used to determine the state of a reaction, which ultimately determines whether the reaction has completed and a successful product created.
In-line mixers with invasive temperature probes have an advantage over moving impellers for high sample rate requirements. Moving impellers normally require external non-invasive measurements normally achieved with Infra-Red light. AFX can incorporate the positioning of these temperature collection probes into the design of the static mixer.

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homogenous reactions

Slow acting reactions are normally fairly scalable. Reactions that are fast are normally more sensitive to the mixing variables with heat transfer being directly related to production volume. These mixing parameters are:

Mixing Sensitive Reactions
When a significant conversion occurs rapidly, the concentration of by-products and the distribution need to be controlled to ensure product purity. This process directly affects the product certification or registration if impurities cannot be effectively removed downstream in the process.

Prediction of Mixing Sensitivity
Laboratory-based testing incorporates predicting the mixing sensitivity of a product with the focus on expanding the process to full-scale production volumes. Certain steps are incorporated into this stage to determine if a potential problem exists: For consecutive reactions, an excess reagent is added to induce a test for the buffers and an overreaction. If no overreaction occurs, it can be determined that no pathway exists for consecutive reactions and hence scaling should not be a problem.

For parallel or consecutive reactions, a difference in mixing result, between different runs, should be noted for further investigation. Poor lab mixing is an indication of an inefficient process.

The test reaction vessel should be a cylindrical shape, with a standard turbine impeller, alloy or glass coatings and the mechanical agitator system fitted with baffles, to avoid swirl or cavitation.

Scale-up of Pilot to Production
Scale-up in the pharmaceutical industry in considered simple in homogenous reactions in which kinetics play the dominant role of the reaction and the heat is controlled by conventional methods. Special attention is given to the distribution of products in the vessel as small deviations can lead to product separation and subsequent purity issues.

Many of these applications use static mixers or multi-stage impellers. The selection of the agitator depends on the required mixing action, the process data and the process engineer's instruction on what the agitator is to aid in eliminating.

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final stage product development

The final stages of product development involve purification and product isolation. Many processes involve simultaneous extraction or crystallisation during the reaction phase. The following reactions are used to promote extraction in the process:

GAS-LIQUID & GAS-LIQUID-SOLID REACTIONS

Gas as a reagent

The design of a hydrogenation system normally requires an excess hydrogen supply to ensure there is no limiting reaction on the catalyst. This is normally achieved with the addition of a sparge ring in the mixing vessel and on occasion assisted by pressurising the vessel to slow the process and force reabsorption in the pressurised space.

Gas as a by-product

Special design consideration is given when a reaction creates a gas by-product that is part of the reaction process. This gas needs to be kept in contact with the reaction in the appropriate concentration so as to ensure the principal product and expected yields are met. The gas is then distilled off the process once the reaction completes. Some issues arise with foaming, which normal is attributed to impurities, fine solids or a second liquid phase. AFX uses its standard F3 impeller or a specially designed rake, to remove these impurities along with Food Grade Teflon scrapers on the anchor.

Scale-up

One of the key designs in operating with gas as a reagent, solids and catalysts is the power requirement to achieve equivalent mass transfer for scale-up. AFX has designed a unique impeller, the P4 impeller, which produces high mass transfer rates while maintaining blending and solids suspension efficiency. If the mixer energy is too low, the entire effect of the flow pattern is destroyed by the gas-flow. Scale-up requires appropriate design to balance the mixing variables.

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LIQUID-LIQUID DISPERSED PHASE REACTIONS

Reactivity

Slow reacting reactants can have improved solubility with the addition of a third solvent, used to improve the mutual solubility between the reactants. This process is often avoided due to the requirement to separate the impurities in a downstream process. A more recognised method of attaining the required products to mix is to create a large interfacial area of intense mixing, followed by the removal of one of the phases via distillation of the more volatile solvent and thereby combining the reactants in the remaining phase. AFX uses the F3 hydrofoil impellers throughout these various mixing processes to achieve its process guarantees.

Selectivity in Liquid-Liquid dispersed phase reactions

A key process design criteria is to protect reactants and products from consecutive competitive reactions, which cause the manufacturing of undesired by-products. Conventional mixing in a vessel is not feasible because of rapid decomposition of the main products, and hence, a static in-line mixer is preferred.

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SOLID-LIQUID PROCESSES

Solids as dissolving reagents

Dissimilar particle sizes in both organic and inorganic reagents cause an insoluble solution under standard conditions. The process engineering normal tackles the chemical kinetics and then addresses the dissolution limitations and then decides on the mixing required.

SOLIDS AS PRECIPITATING PRODUCTS

This is normally the effect of crystallisation in the vessel and impeller speed is crucial in creating the appropriate size particles. The particle size is affected by supersaturation, reaction rate, mixing and other factors that affect crystallisation. Mixing plays a key role in this process whereby a balance between circulation and shear has to occur to ensure micro-mixing and meso-mixing while avoiding shredding or crystal fracture. Having carefully combined the technology of the hydrofoil impellers with the delicate process of crystallisation, AFX has become the sought after mechanical solution provider for these difficult applications.

Scale-up

Scale-up in this reaction is often characterised with power levels that are above the normal mixing in a homogenous suspension. These systems often create agglomerate and therefore an increased power is required to ensure adequate dispersion. A further critical design parameter is the layering and the creation of the films of precipitated products becoming covered by one of the solids in the vessel or second of complex three-phase liquids. This affects the mass transfer rate and could cause the reaction to prematurely end, affecting the yields. Surfactants are sometimes used to modify surface properties or prevent the creation of these separating films. AFX uses a combination of shear impellers, namely the FS4 or shear disk, with the F3 axial flow hydrofoil impellers. The turbine combination can also include a P3 or P4 impellers for viscous or high mass transfer applications.

Mixing & Crystallisation

The interaction during mixing and crystallisation needs to be planned for in the design process. Crystallisation is affected by the process of nucleation, crystal growth and the maintenance of the crystal slurry. A careful optimisation is required to achieve the required mixing as one aspect of the process and the preservation of formed products as the other. This aspect creates a scale-up operation that is challenging, and careful design criteria must be met to be successful.

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Mixing & Crystallisation

The workhorse of this process is the AFX F3 axial flow hydrofoil turbine, which creates effective pumping but has a low shear value, giving good circulation, while avoiding the destruction of formed crystals. These vessels are almost always baffled to avoid cavitation or swirl. Two alternative crystallisation processes are available, mainly fluidising beds and impinging jets. Fluidising beds limit nucleation, and impinging jets promotes nucleation.

The aspects of crystallisation affected by mixing are:

Nucleation

Primary and secondary nucleation are the derived processes with secondary nucleation being of interest and the major part of the crystallisation process. The following interactions apply during nucleation:

- Crystal-crystal impact is defined by local micro-mixing (at shear impact between particles), and the overall macro-mixing (at tank mixing).
- Crystal-impeller and crystal-wall impact is a function of tip speed and impact against the vessel wall.
- The absorbed layer thickness of the solution decreases with an increase in mixing.

These factors affect the rate of crystallisation which determines the number of nuclei formed and their size. The number of nuclei formed is exponential, but on scale-up, a smaller particle size may result as local power dissipates. Critical factors remain as impeller speed, type of impeller and their influence in local turbulence and overall circulation in the tank. Nucleation rate is affected by concentration and variances in the tank, and this makes it difficult to maintain scale-up performance in the process. Scale-up can be achieved initially by the calculated power per unit required to achieve nucleation in a calculation known as equal power per unit.

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Growth of crystals

Mixing affects crystal growth as follows:

- Mass transfer rate
- Bulk turnover rate
- Heat transfer rate
- Shear on crystal breakage
- Dispersion of the reagent or anti-solvent
- Growth rate dispersion
- Minimising impurity concentration at the crystal surface

If the process relies on nucleation, AFX recommends that information is obtained, for the purpose of design, on the impeller speed, the width of the metastable region (overall tank movement) and the impeller speed compared to the rate of nucleation.

The process of scale-up has been discussed above, but there may be a requirement to have homogeneous dispersion, while not breaking the crystals, but at the same time avoiding settling on the bottom of the vessel, which results in encrustation.

AFX has specialised knowledge in mixing for crystallisation processes. Although the industry solutions have, in the past, not upscaled well, AFX's team of application engineers have the tools and experience to design mechanical solutions.

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