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Application Note

High Shear Mixing Technology for the Pharmaceutical Industry

INTRODUCTION

For years, the Pharmaceutical industry has been required to have a validated process. Meaning each step of the batch process must be clearly defined, followed, recorded and verified. Therefore, the Pharmaceutical industry leads all other industries with regards to defining the processing procedure to ensuring repeatable quality and consistency through validation.

Unfortunately, most of this work was completed without the availability of application specific equipment. Utilizing existing batch tank mixing technology, the key operations of powder incorporation, dispersion, de-agglomeration and mixing are achieved by the random chance of the ingredients passing through or near the higher shear influence of the mixing head or impeller.

This resulted in a normal distribution whereby a small percent of the incoming powders sees maximum impeller shear, a small percent sees almost no shear, and much of the powder will see only the bulk tank or average shear. To compensate for this in-tank mixing reality, the mixing intensity and duration is often increased to obtain an adequate result.

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High Shear Mixing Technology for Manufacturing Pharmaceuticals

Conventional Industry Practice

Typically, the production of any in tank batch is a “hit and miss” approach, whereby the

variation in the quality of a batch is directly proportional to the number of operators.In response, common industry practices for a validated process include several unnecessary steps based on uncertain equipment performance and the utilization of excess shear, excess time and testing to guarantee results. The importance of ensuring the ingredients - including actives! - are evenly dispersed and homogeneously mixed throughout the batch is obvious, therefore so is the procedure “sprinkle to surface, slowly mix at 750 rpm for two hours, re-circulate through a shear pump for 30 minutes, let stand to de-aerate for 1 hour, etc.” This leaves a lot to be desired with its inherent problem of operator interpretation of qualitative instructions such as “Sprinkle to surface, slowly....”.

Pharma Process Requirements

- Dispersion of cellulose derivatives and pigments for clear, lump free solutions for consistency in film formation and color of the tablet coatings
- Dispersion of viscosity building stabilizers without lumps to produce a proper suspension of ingredients.
- Dispersion of the active ingredient to ensure each particle is separated from another to allow it to be homogeneously mixed throughout the batch.
- The homogeneous top to bottom mixing of active ingredients throughout the vessel regardless of viscosity characteristic to ensure equal dose in every gram.
- Minimized heating and cooling to reduce vapor loss and product degradation.
- Minimize over shearing, which can affect viscosity and stability over time.
- Minimize over shearing, which can result in an ever-widening particle size distribution effecting dosage.
- Minimize over processing which can affect consistency from batch to batch.
- Verification of process and the parameters in which it was processed.

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Quadro Approach

ZC Technology

Ytron utilizes single pass technology which is equivalent to the introduction of PLC's and electronics to the validation process. Viscosity building thickeners added to the batch tank through the ZC guarantees perfect dispersion, instant

hydration and consistent viscosity much like a PLC guarantees the correct valve opening or load scale reading. This single step eliminates the variability introduced by operator powder addition, extensive mix time, high shear in-tank dispersers, heating and cooling or recirculation. The use of Ytron® equipment establishes a well-defined and repeatable process step, exactly what was required in the first place with the introduction of the validated process.

Each piece of equipment in the Ytron® line will perform an exact process step instantly,

replacing the art of in tank process batching with the science of in-line single pass processing.

Benefits

- Results are completely free of lumps and "fish eyes," and batch-to-batch product consistency is improved.
- Product yield is maximized, and wastage is reduced or eliminated.
- High speed dispersion and hydration performance result in batch time reductions of up to 90%.
- Dramatically reduces product de-aeration time.
- Scalable solutions — from pilot to production capacities
- Meets 3-A® Sanitary Standards

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Quadro Approach

The Quadro HV

High shear rotor-stator mixer Quadro HV are used extensively in the Pharmaceutical industry for high shear processing.

Quadro HV significantly improves the milling efficiency of downstream milling equipment which is why rotor/stator HV mills are also employed as "wet mills" for particle size reduction of API slurries.

As API slurry flows through the tooling, it is rapidly accelerated and broken tangentially and radially through the tooling, resulting in particle fracturing. The desired particle size range for an API material is achieved by adjusting the parameters of rotor and stator slot width, number of shear slots, number of tooling stages, tip speed, flow rate, and back pressure. These parameters “dial in” the appropriate shear rate, shear frequency, and hold-up time which can then be used for predictable and reliable scale-up, ensuring product consistency from laboratory to full production.

Benefits

- Improves particle size reduction
- Improves Product yield (less degradation for certain APIs)
- Reduce milling time
- Scalable from lab to production with the capability to handle customer specific requirements
- Option of Variety of tooling available