

**Mixing Technologies in the
Pharmaceutical and Medical Industries**

A White Paper Prepared By
Charles Ross & Son Company



Mixing Technologies in the Pharmaceutical and Medical Industries

Abstract

This white paper presents an overview of mixing technologies implemented across many of today's highly competitive pharmaceutical and medical industries, as well as new equipment designs that are increasingly being recognized as potential solutions to prevailing mixing challenges. Mixing applications falling within the broad spectrum of mass produced pharmaceutical goods and medical devices are too many and complex to discuss in detail hence this paper will touch on a few general classifications as well as a few examples within that mixing category. Phase and viscosity are used as bases for classification.

Introduction

Process equipment used in the healthcare industry follow rigid specifications for accuracy, consistency and cleanliness. These regulations ensure that end products are safe, pure, and effective. In particular, mixing equipment employed in the production of pharmaceuticals and medical devices deal with a higher level of complexity because their use is more specialized. Not one design fits all.

Mixing fulfills many objectives beyond simple combination of raw ingredients. These include preparing fine emulsions, reducing particle size, carrying out chemical reactions, manipulating rheology, dissolving components, facilitating heat transfer, etc. So even within a single pharmaceutical product line, it is not uncommon to employ a number of different style mixers to process raw ingredients, handle intermediates and prepare the finished product.

Moreover, most pharmaceuticals are highly process-dependent. Next to the chemistry of the formulation itself, the mixing operation has a decided influence on whether a drug will deliver the accurate dosage, have an acceptable appearance and texture, or be stable for the appropriate length of time. The importance of proper mixer selection and optimal operation can hardly be over-estimated.

Dry Blending

In the manufacture of many vitamins, dietary supplements and drugs in tablet form, at least one dry blending operation is performed to combine the active ingredient, binder, fillers and additives (lubricant, glidant, anti-adherent, disintegrant, preservative, etc.). Relatively small amounts of liquid may be added to the solids in order to coat or absorb coloring, flavoring, oils or other solutions.

Several types of blenders accomplish this task. Three of the most common ones are as follows:

1. The **Ribbon Blender** consists of a U-shaped horizontal trough and an agitator made up of inner and outer helical ribbons that are pitched to move material axially in opposite directions, as well as radially. The ribbons rotate with tip speeds of approximately 300 fpm. For blends that require a gentler mixing action, the same trough can be utilized but the ribbon assembly is replaced with a paddle agitator. A horizontal paddle blender has less surface area at the periphery of the agitator, providing lower shear and less heat development compared to the ribbon design.

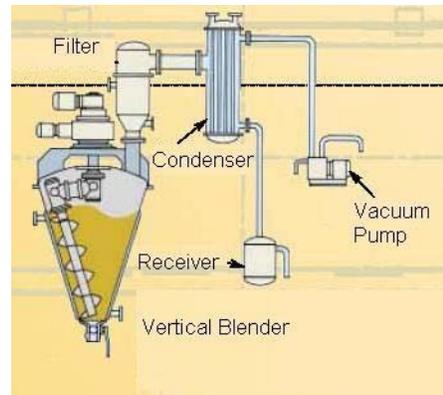
Liquid addition is best accomplished through the use of spray nozzles installed in a spray bar located just above the ribbon or paddle agitator.

This blender design is very efficient and cost-effective for dry mixing. Its attractive price makes it appealing and widely used for relatively low margin-high volume lines such as nutraceutical beverages, and whey supplements.

2. In comparison, the blending action of a **Vertical Blender**'s slow turning auger is far gentler than that of a horizontal blender making it more suitable for delicate applications. The auger screw orbits a conical vessel wall while it turns and gently lifts material upward. As materials reach the upper most level of the batch, they cascade slowly back down in regions opposite the moving auger screw. Spray nozzles may also be installed in the vertical blender for liquid addition purposes.

Vacuum Drying

A common use for vertical blenders is vacuum drying where the starting material is in the form of wet granules or even a slurry, and the end product is typically a free-flowing powder. Requiring only low heat to drive off moisture or solvents, vacuum drying is an excellent method for drying heat-sensitive pharmaceutical products without fear of thermal degradation. The gentle and thorough agitation of the vertical blender promotes better heat transfer than simple oven drying operations wherein the product is stationary.



3. The **Tumble Blender** is characterized by a rotating vessel that usually comes in a double-cone or V-shaped configuration. Asymmetric vessels designed to reduce blend times and improve uniformity are also available. Generally, tumble blenders operate at a speed of 5 to 25 revolutions per minute. Materials cascade and intermix as the vessel rotates. Mixing is very low-impact.

The intensifier bar is a feature commonly seen on tumble blenders. Because the blending action is very gentle, this type of blender benefits from having a high speed intensifier bar with one or more chopper blades. The intensifier bar breaks up agglomerates and also provides a means for liquid addition.

Comparative Advantages

Aside from level of shear, other factors such as space requirements, completeness of discharge, and batch size flexibility help determine which type of blender will work most efficiently in a certain application.

If floor space is tight, a vertical blender is ideal as it requires a much smaller footprint. If overhead space is limited, a horizontal ribbon blender allows the use of a low-profile loading system; a multi-level operation is usually not necessary. A tumble blender of a similar blend capacity will occupy the most space.

The vertical blender and tumble blender give virtually 100% discharge, but not a ribbon blender.

Ribbon blenders must be filled to at least 40% of the maximum working capacity while vertical blenders can efficiently handle as little as 10%. Tumble blenders are more sensitive to fill method – generally, it is more beneficial to add raw materials in layers rather than side by side and fill level is critical (minimum of around 70%) for applications that require maximum contact with the intensifier bar.

High Shear Mixing and Emulsification

Throughout the pharmaceutical industry, rotor/stator **High Shear Mixers (HSM)** are widely used in the preparation of emulsions such as medicated lotions, balms, ointments, creams and eye drops.

Available in batch (vertical) or inline (horizontal) configurations, high shear mixers are comprised of a rotor that turns at high speed within a stationary stator. As the blades rotate, materials are continuously drawn into one end of the mixing head and expelled at high velocity through the openings of the stator. The hydraulic shear generated promotes fast mixing, breaks down agglomerates and reduces the size of droplets. Rotor tip speeds between 3,000 to 4,000 ft/min are typical.

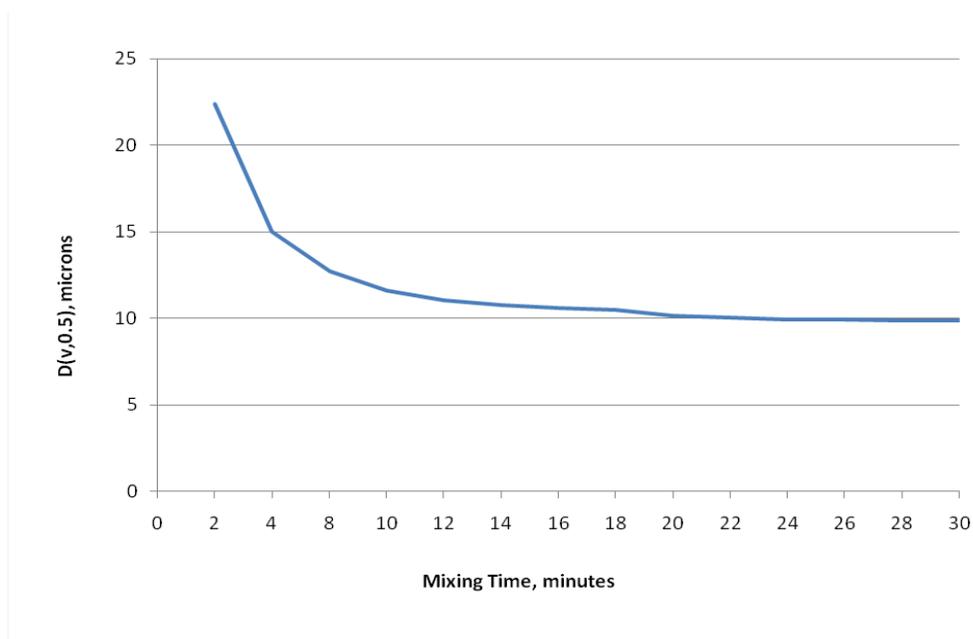
In a stable emulsion, the dispersed phase is suspended uniformly as droplets throughout the continuous phase, the two phases immiscible with each other. Big and small drops coexist in the emulsion and their size distribution gives the best description of the emulsion, affecting both stability and viscosity. The length of time in which a considered stable emulsion does not change its aspect is relative. In the case of pharmaceuticals, a storage stability period of a few years is reasonable to expect.

For emulsification to take place and remain in equilibrium, sufficient mixing energy is required. A common generalization is that the higher the shear put into creating the emulsion, the finer the droplets produced, and the more stable the emulsion. However, some emulsions are shear-sensitive such that droplets start to coalesce past a certain level of mixing. Of course, many other factors apart from shear input affect emulsion stability including individual properties of the

dispersed phase and the continuous phase, temperature, presence and type of surfactant, etc. In other words, the “ideal” average drop size varies from one formulation to another. Accordingly, one cannot generalize what drop size a particular mixer can achieve. Droplet size is a parameter unique to a specific formulation; hence, mixer comparison experiments, to be truly meaningful, must be carried out using the same raw materials and their relative percentages.

In an inline high shear rotor/stator mixer, the greatest extent of droplet size reduction occurs within the first few passes. This phenomenon is true for almost any emulsion. Past this phase of sharp decrease in droplet size, the emulsion hovers at an equilibrium size despite subsequent recirculation. The same trend applies to batch rotor/stator mixing systems although the actual number of product turnovers is not as easy to define. Identifying the number of passes that it takes to achieve the desired or equilibrium droplet size is very useful to avoid over-processing. Over-processing not only unnecessarily consumes time and power, but may also heat up the emulsion to the point of causing droplets to recombine or induce an irreversible change in viscosity.

To illustrate, an intermediate for an emulsion-based drug delivery system processed in a batch high shear mixer exhibits the below profile:



The batch starts with heating mineral oil to 70°C followed by adding a surfactant in pellet form which dissolves easily through the high shear mixer. In a separate vessel, the water phase is prepared and also heated to 70°C.

The water phase is poured into the oil phase and, keeping mixer speed constant, a sample is drawn at every time interval using a pipette.

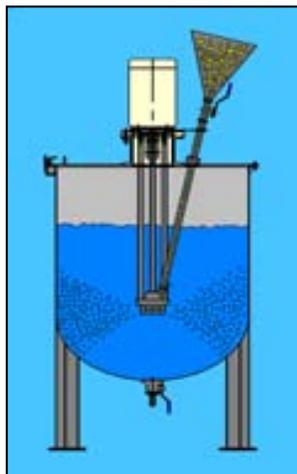
The target droplet size for this intermediate is <12 microns. Particle size analysis revealed that this was achieved in 8-10 minutes of processing under a batch high shear mixer with slotted stator and four-blade rotor.

High Shear Mixing and Powder Dispersion into Liquid

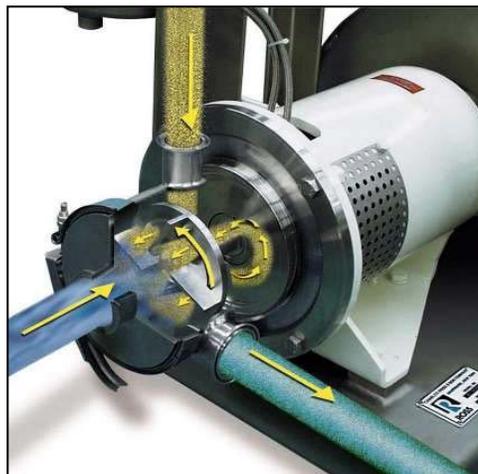
Different powders behave differently when added into liquid, and some require more coaxing in order to dissolve, hydrate or disperse completely than others. The ‘easier’ ones need only gentle agitation as provided by low speed propeller, turbine or paddle agitators. More challenging powders benefit from higher speed devices such as open disc type blades which generate a powerful vortex into which the powders are added for faster wet-out. When dealing with solids that tend to form tough agglomerates which do not easily break apart, a high shear mixer is often installed to replace or supplement the existing propeller or disc type disperser in the vessel. For this reason, many solutions and dispersions are made in high shear mixers, from tablet coatings and vaccines to pharmaceutical inks and disinfectants.

Adding hard-to-disperse powders slowly into a small batch of vigorously agitated liquid is not an issue in lab-scale batches. However, in a full-scale production setting, this method of addition is very costly and time-consuming. In addition, if powders are added too slowly, an uncontrolled viscosity build-up can occur mid-processing thus preventing the rest of the solids to be fully dissolved. On the other hand, charging too fast can cause some powders to clump up. These agglomerates can solvate to form a tough outer layer which prevents complete wetting of the interior particles. These “fish eyes” lead to solution defects such as grainy texture and reduced viscosity. The high shear conditions usually needed to break up these agglomerates may overshear the already hydrated or dispersed particles leading to a permanent loss in viscosity. In an effort to correct below-target viscosity, many will actually resort to adding more solids than is really needed and subsequently filtering agglomerates out of the mixture, which not only drives up raw material costs but also wastes power, lowers productivity and constrains over-all production.

A key development in HSM design is the SLIM (Solids/Liquid Injection Manifold) Technology, a high speed powder induction system available on Ross High Shear Mixers. The modified rotor/stator assembly is specially designed to create negative pressure (vacuum) behind the rotor, which can be used as the motive force to inject powdered (or liquid) ingredients directly into the high shear zone.



Batch SLIM



In-line (Continuous) SLIM

The SLIM is particularly useful in inducting hard-to-disperse powders such as fumed silica, carboxymethyl cellulose (CMC), hydroxyethyl cellulose (HEC) starch, pectin, talc, carbomers, xanthan gum, Agar, guar gum, carrageenan, tragacanth, etc. into a liquid phase. These powders are notorious for driving up processing costs in the form of labor and reduced production. Even with a strong vortex in an open vessel, they resist wetting out and often float on the surface for hours. In the SLIM system, solids are added not to the top of the liquid but right in the mix chamber where they are instantly subjected to intense shear. As solids and liquids are combined and mixed simultaneously, agglomerates are prevented from forming because dispersion is virtually instantaneous.

The inline configuration of the SLIM is a superior design compared to earlier venturi or eductor systems. In eductor systems, the process liquid is pumped at high velocity into a venturi chamber and passes into a downstream inline mixer. The combination of the pump, venturi and the pumping action of the mixer creates a vacuum in the venturi chamber. Powder fed through an overhead hopper is drawn by this vacuum into the eductor where it joins the liquid flow. A rotor/stator then mixes the powder and liquid, and propels the flow downstream.

While this set-up eliminates the dusting and floating issues of batch systems, it also presents serious limitations. With three separate devices in series, maintenance is intensive. Balancing the performance of the pump, eductor and mixer is often difficult, and in many applications, downtime is quite high.

But the most serious limitation relates to the inherent operating limitations of the venturi or eductor. Clogging is routine. The system is temperamental and requires a lot of operator experience and attention to operate successfully. Since the feed rate of the eductor relies on the vacuum created by a fast-moving stream, it is also extremely viscosity-dependent. As the viscosity of the stream rises, velocity falls and the efficiency of the eductor drops off steadily until it finally stops.

The Ross SLIM design is a breakthrough based on one simple idea — eliminate the eductor. In the older powder induction designs, solids are combined with the moving liquid stream in the eductor, and then mixed farther down the line. That distance between the eductor and the mixer is critical. Material that had been combined but not yet mixed intimately could clog the pathway before reaching the rotor/stator mixer where agglomerates could be disintegrated and small particles are forced into a dispersion that could flow quickly without problems. In addition, clumps produced in the venturi chamber would form that tough outer layer which will prevent interior particles from being wetted out.

Sample Applications

During a pilot manufacturing program, a pharmaceutical company was processing its glucosamine product using a batch rotor/stator mixer. Powdered glucosamine and chondroitin were simply added to filtered water in a 400-gal tank, along with minor ingredients such as MSM, collagen, vitamins, and natural flavor. Since the product delivers a highly concentrated dose, the dispersion was heavily loaded. Even with a batch-type rotor/stator mixer, a long period of agitation was required to complete the process.

When the company pushed through with full scale production, the pilot 400-gal vessel was replaced with a new line equipped with two 1500-gal vessels. A single inline high-shear mixer with SLIM was selected to serve both vessels. Powdered glucosamine and chondroitin are now pre-dispersed into a moving stream of filtered water (within the SLIM rotor/stator assembly) before it enters the mix vessel. Injected under vacuum and intense hydraulic shear, the powders are instantly reduced to extremely small particle sizes and dispersed in the stream. When they enter the primary mix vessel, the chief cause of delay in the original process has already been eliminated. Inside the vessel, only a simple turbine mixer is required to keep the batch agitated while it is discharged to downstream bottling equipment.

The present system completes a 1500-gal batch in the same time that the original batch system required to process 400 gallons. This represents an increase in throughput of 275%. The SLIM mixer has also given the company processing flexibility. While one 1500-gal vessel is mixing, the other can be discharging to the bottling line, making the process virtually continuous. Changeover is fast, too. Since the mixer and piping are cleaned easily, the production crew can shift gears with minimal effort and respond quickly to demand for other products. For instance, the same system is used to make liquid calcium supplement wherein the SLIM unit inducts powders such as calcium citrate, tricalcium phosphate, vitamins, maltodextrin, citric acid, xanthan gum, cellulose gum, flavor and sweeteners.

Another SLIM installation in the pharmaceutical industry is dedicated to the preparation of sterile solutions of sodium chloride. An operator used to pre-weigh salt powder and climb up a mezzanine to manually dump the solids into one of six 500-gallon tanks. The plant manager sought to improve this procedure to create a safer and more efficient working environment.

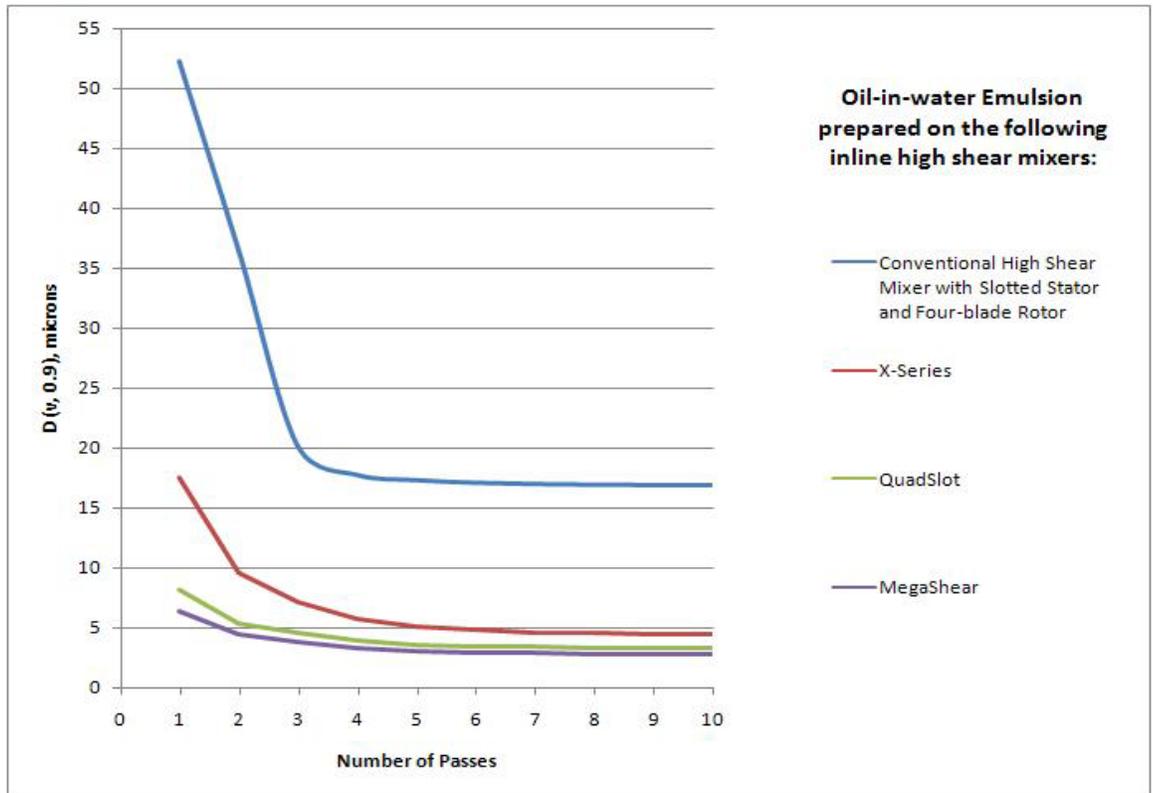
An inline SLIM system was installed in the weighing section where the operator now weighs the solids right in the hopper and simply opens the induction valve to introduce powders into the batch. The mixer is piped to all six 500-gallon tanks; selecting a specific vessel for recirculation is accomplished by mere manipulation of piping valves.

Inline Ultra-High Shear Mixing

Running a rotor/stator at a particular tip speed yields a corresponding mixing equilibrium, which can be represented through the particle size distribution of a dispersion or emulsion. Operating below this tip speed will likely produce a different distribution profile. The maximum speed setting of a mixer, therefore, provides the optimal mixing results in terms of particle or droplet size reduction. Under-processing is a common mixing mistake. Many are reluctant to run their mixer at the maximum speed setting for fear of overworking the machine. As long as the power draw (amperage) is within the machine's range, running at the maximum speed is desirable, as you benefit from the highest tip speed that the mixer can deliver. Well-designed mixers work just as optimally running at maximum speed as at lower speeds.

For applications that still fall short of the desired particle size distribution even at the maximum speed setting of the rotor/stator mixer, a move to a higher energy HSM design is recommended. Charles Ross & Son Company offers the **X-Series**, **QuadSlot** and **MegaShear** for applications that conventional rotor/stators cannot process adequately.

On the right is a graph comparing the equilibrium droplet size distributions of an oil-in-water emulsion prepared on a regular rotor/stator and on the X-Series, QuadSlot and MegaShear ultra-high shear mixers (UHSM's).



X-Series



QuadSlot



MegaShear

The X-Series head (US Patent No. 5,632,596) consists of concentric rows of intermeshing teeth. The product enters at the center of the stator and moves outward through radial channels in the rotor/stator teeth. Tolerances are extremely close and the rotor runs at very high tip speeds typically up to 11,300 fpm. This combination subjects the product to intense shear in every pass. The gap between adjacent surfaces of the rotor and stator can be set as close as 0.003” and is adjustable for fine-tuning shear levels and flow rates.

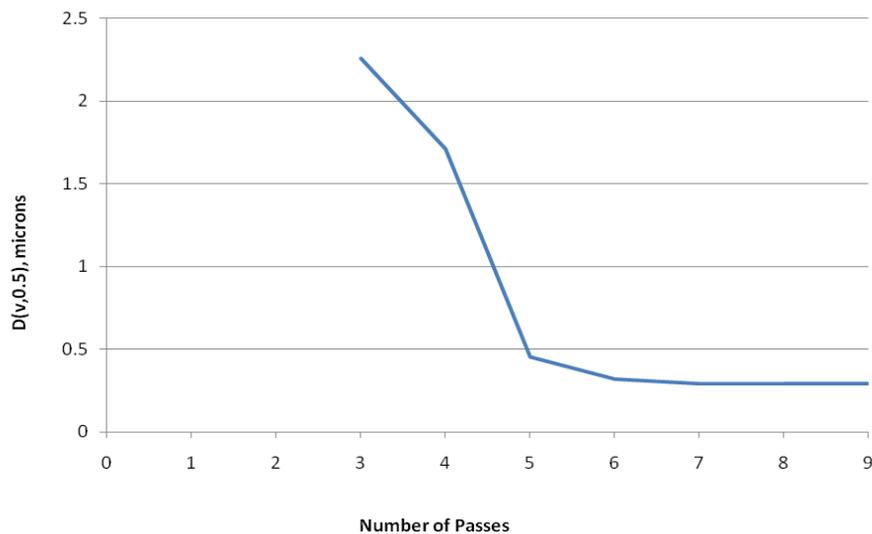
The QuadSlot mixing head is a multi-stage rotor/stator with a fixed clearance. This generator produces higher pumping rates and requires higher horsepower compared to an X-Series rotor/stator set running at similar speeds.

The MegaShear head (US Patent No. 6,241,472) operates at the same tip speed as the X-Series and QuadSlot heads, but is even more aggressive in terms of shear and throughput levels. It consists of parallel semi-cylindrical grooves in the rotor and stator towards which product is forced by high velocity pumping vanes. Different streams are induced within the grooves and collide at high frequency before exiting the mix chamber.

In certain cases, an ultra-high shear mixer will effectively replace a high pressure homogenizer or a colloid mill. Manufacturers that find this to be true for their particular formulations welcome the change because high pressure homogenizers and colloid mills are high maintenance machines; during crossovers of different batches, the clean-up procedure is labor-intensive. Also, throughput rates of a similarly-powered ultra-high shear mixer are far greater compared to that of a high pressure homogenizer or colloid mill. Lastly, ultra-high shear mixers cost less upfront.

Sample Application

An ophthalmic emulsion consisting of an aqueous continuous phase and castor oil has a target median droplet size of <0.5 microns. The desired distribution is achieved within 5 passes through the X-Series mixing head.



Aside from emulsions, high quality dispersions are also processed in ultra-high shear mixers. These include slurries containing micron- and nano-sized particles.

Inline Static Mixing

Static mixing is another technology employed in the preparation of pharmaceutical products and intermediates. It is used for continuous blending of fluid streams, emulsification, dispersion of gas(es) into liquid, pH control, dilution and heat exchange. A static mixer is unique in that there are no moving parts in this device and it relies on external pumps to move the fluids through it.

An array of static mixer elements or a central shaft with baffle plates is placed inside a pipe and the mixing operation is based on splitting and diverting input streams. Various designs are available for selection based on flow regime (laminar or turbulent), viscosity, allowable pressure drop, solubility and other factors.

Batch Mixing of Viscous Formulations

Dual-Shaft and Triple Shaft Mixers are used in the pharmaceutical industry for batching moderate to relatively high viscosity applications such as syrups, suspensions, pastes, creams, ointments and gels.

This type of mixing system is comprised of two or more independently-driven agitators working in tandem. A low speed anchor complements one or two stationary high shear devices, such as an open disc style disperser blade or a high shear mixer rotor/stator assembly. On its own, a disperser blade will produce acceptable flow patterns in batches up to around 50,000 cP; the rotor/stator up to around 10,000-20,000 cP. Hence, for higher viscosities, there is a need for a supplemental agitator to improve bulk flow, deliver material to the high speed devices and constantly remove product from the vessel walls for better heat transfer.

The most common low speed agitator designs are the two-wing and three-wing anchor. For added efficiency, especially in terms of axial flow, a three-wing anchor can be modified to feature helical flights in between wings. In combination, stationary high shear devices and an anchor will process formulations that are several hundred thousand centipoise.

Another mixer design widely used in the pharmaceutical industry is the **Counter-Rotating Agitator** with bottom homogenizer (rotor/stator). In some of these machines, the agitation system is a fully top-supported coaxial shaft arrangement driving three simultaneous mixers, namely: (1) the outer anchor agitator with blades and wall scrapers; (2) the inner blades positioned inside the anchor, rotating in opposite direction to the anchor to create a contrasting series of flow patterns; and (3) the homogenizing head with rotor and stator, centrally positioned at the lowest end of the agitation system. In other configurations, the rotor/stator

assembly is bottom-entering and/or installed as an external inline unit designed for product recirculation.

The following table discusses various design advantages between the multi-shaft mixer and counter-rotating agitator design.

COMPARISON OF DESIGN ADVANTAGES		
	Multi-Shaft Mixer	Counter-Rotating Agitator with Bottom Homogenizer
Clean design	Having no bearings or agitator seals submerged in the product zone helps reduce contamination risks.	
Flexibility	Change can design enables for semi-continuous mixer operation when multiple vessels are used.	Smaller batch volumes are possible in this mixer because the rotor/stator is positioned lower in the vessel.
Powder induction	The SLIM technology can be adapted into the rotor/stator component of a Multi-Shaft Mixer.	Powders may be added from the vessel bottom through a vacuum port (but note that this technique requires careful manipulation by the operator to avoid the tendency to blow powders straight through the liquid surface).
Ease of discharge	Vessel may be designed for use with a Ross Discharge System for efficient and thorough discharge of high-viscosity mixtures. (See below <i>Ease of Discharge</i> section on Double Planetary Mixing for more details.)	Tiltable vessel is common.

Sample Application

Ross Triple-Shaft Mixers are used in the production of transdermal drug delivery systems. At the heart of a transdermal patch manufacturing process are two important mixing steps: preparation of the pressure sensitive adhesive (PSA), and preparation of the drug-adhesive solution consisting of the active pharmaceutical ingredient, the adhesive, enhancers/excipients and solvent.

Medical adhesives used are commonly acrylic (polyacrylate), PIB (polyisobutylene) or silicone (polydimethylsiloxane). Tackifiers and plasticizers are added to provide tack, soften the adhesive mass and modify viscosity (i.e. hydrocarbon resins, rosin esters, mineral oil, etc.).

The Triple-Shaft Mixer delivers the following key parameters required in the manufacture of biocompatible PSA's and drug-adhesive solutions:

1. Homogeneity – Samples are taken from the top, middle and bottom of the mixing vessel to establish batch homogeneity.
2. Predictable Viscosity – A well-mixed solution will yield consistent viscosity readings at defined temperatures.
3. Consistent Drug Content – Samples are analyzed for drug content on a weight percentage basis.
4. Variable Agitator Speeds - Mechanical variable speed drives or variable frequency inverters enable the operator to independently control the speed of each agitator to fine tune flow patterns and optimize the vortex for ingredient charging purposes. This feature is likewise very important for shear control because excessive shear can irreversibly alter viscosity.

Other important mixer features include vacuum processing capability (to allow the removal of air during mixing, resulting in a smoother air-free product and eliminating additional downstream deaeration steps), pressure capability (the empty space inside the mixer may be blanketed with an inert gas during or after mixing to prevent contamination, reduce oxidation and ensure longer product life), thermocouples and jacketed mix vessel (to control batch temperature), Teflon scrapers staggered on the arms and wings of the anchor (to scrape materials from the sides and bottom of the mix can, promote batch homogeneity and improve heat transfer between the product and the jacket, especially during the cooling stage), sight ports and charging ports (to allow the operator to view the batch and to add raw materials without raising the agitators), and double mechanical seals for the agitator shafts.

Double Planetary Mixing

As product viscosity continues to build up, a multi-agitator mixing system will eventually fail to produce adequate flow as can be characterized by an anchor carving a path through the batch (instead of pushing product away from the walls and into the center) or by high-temperature zones near the disperser and rotor/stator assemblies. At this point, stationary shaft agitators no longer suffice and a move to a **Double Planetary Mixer (DPM)** is recommended. The agitators of a planetary mixer rotate on their own axis while being revolved around a central axis in the vessel. This motion allows the blades to pass through every point within the batch, not just along the periphery.



Ross Double Planetary Mixer with High Viscosity “HV” Blades

The DPM can be equipped with rectangular stirrer blades, finger blades or High Viscosity “HV” blades (US Patent No. 6,652,137). The HV blade design generates a vertical mixing action owing to its precisely angled helical contour. This sweeping curve firmly pushes the batch material forward *and downward*, a unique mixing action that solves the ‘climbing’ problem commonly experienced when processing highly filled materials. In addition, the HV blades do not have a lower crossbar so they can be cleanly lifted out of a very viscous batch and can pierce right through it just as easily.

It is worth mentioning that not all viscous applications can be successfully made in a double planetary mixer.* For these, there are **Kneader Extruders (Sigma Blade Mixers)**, high torque machines that can muscle through blocks of rubbery or hard semi-solids. They remain to be the most powerful tools for manufacturing extremely viscous formulations. That said, there are several considerations which make planetary mixers a better choice for certain applications.

One of those considerations is that sigma blade mixers rely on the product being highly viscous at all times in order to mix properly – liquid components must be added very slowly, portion by portion, or else they can act like a lubricant and reduce shearing efficiency. While this issue is also present in a vertical double planetary mixer, its blades run at higher tip speeds than sigma blades making it less sensitive to liquid additions or shifts in viscosity.

Other advantages of the double planetary mixer design include:

**See table on last page for typical viscosity ranges of the mixer designs discussed in this white paper.*

- *Ease of cleaning*

A vertical mixer design has no shaft seals, bearings, packing glands or stuffing boxes submerged in the product zone. In addition, the agitators are raised and lowered in/out of the mix vessel by a hydraulic lift. This allows easy access for cleaning between batches. Mix vessels are interchangeable and can be dedicated to a particular formulation and/or color. There is less concern for cross contamination from batch to batch.

- *Ease of discharge*

The ability to use a Discharge System is a big advantage to the DPM design. The platen-style hydraulic discharge system improves speed, efficiency and cleanliness of the discharge operation. With the mix can positioned beneath the discharge system, a platen is lowered hydraulically into the vessel. A specially-fitted O-ring rides against the vessel wall, literally wiping it clean. Product is forced out through a valve in the bottom of the vessel, or through the top of the platen. A Discharge System eliminates wasted hours of scraping heavy or sticky materials from a tilt-style sigma mixer.

- *Semi-continuous operation*

With the use of extra mix vessels, the double planetary mixer can produce material in a semi-continuous basis: one vessel is being charged while other vessels in the loop are under the mixer, being discharged, and/or cleaned.

- *Floor space requirement*

Footprint of the double planetary mixer is considerably less than that of a double arm / sigma blade mixer.

- *Capital cost*

Depending on specifications, a double planetary mixer is generally 1/2 – 1/3 the cost of a comparably sized new sigma blade mixer.

- *Energy savings*

Since the double planetary mixer uses less motor horsepower to operate, everyday energy/operating costs will be less. This can be significant over time.

A lesser known fact is that double planetary mixers are not limited to processing viscous end products, but are also capable of gentle and thorough blending of low viscosity materials or even powders. This versatility makes them suitable for wet granulation and drying operations.

Below are application snapshots within each of these mixing functions.

APPLICATIONS OF DOUBLE PLANETARY MIXERS

High Viscosity Mixing	Drying	Granulation
<ul style="list-style-type: none"> • Bone Graft Substitutes (in the form of injectable paste, gel or moldable putty) • Collagen-based Wound Care Products • Dental Composites and Pastes • Small Intestinal Submucosa (SIS) Tissue Repair Grafts • Medical and Pharmaceutical Gels • Platinum-cure Two-part Silicone Rubbers (elastomer component of various implantable products such as microcatheters, stents, defibrillators and pacemakers) 	<ul style="list-style-type: none"> • Drying of Wet Cakes <div style="border: 1px solid black; border-radius: 15px; padding: 10px; margin: 10px 0;"> <p style="text-align: center; margin: 0;">Sample Application</p> <p>A biphosphonate drug was previously dried in a vacuum oven wherein the starting wet cake (80% moisture) transforms into a free-flowing powder (10% moisture) after 26 hours of drying at 120°C. The new process employs a vacuum-capable Double Planetary Mixer which completes the drying operation in one hour.</p> </div>	<ul style="list-style-type: none"> • Wet Granulations <div style="border: 1px solid black; border-radius: 15px; padding: 10px; margin: 10px 0;"> <p style="text-align: center; margin: 0;">Sample Application</p> <p>A 150-gallon Double Planetary Mixer is being used for batching a wet granulation consisting of lithium carbonate, yellow iron oxide, corn starch, alginic acid and povidone solution. The powder ingredients are blended together and the povidone binder solution is metered into the mix vessel as the planetary stirrers continue to agitate the batch. In 45 minutes, the wet granulation reaches the desired consistency. The mixture is then dried and compressed to form extended-release tablets.</p> </div>

High Speed Planetary Mixing

Some highly filled and highly viscous formulations benefit from a hybrid planetary mixer which combines the traditional thorough mixing action of a planetary mixer with the added advantage of a high speed disperser. Both the planetary blade and the high speed disperser rotate on their own axes while revolving around a central axis. The planetary blade orbits through the mix can continuously sweeping the vessel walls, as well as the vessel bottom, and carrying material toward the high speed disperser. The close tolerance sweeping action of the planetary blade also

insures that the heat which can be created by the disperser blade is evenly distributed throughout the batch. Variable speed allows precise control of shear rates to minimize the degradation of any shear-sensitive components.

Sample Applications

One pharmaceutical application of the Ross PowerMix hybrid planetary mixer is a parenteral drug for cancer treatment. Production-size PowerMix units are used for dissolving phospholipids in an organic cocktail mix (dichloromethane, methanol and water). Another ingredient in aqueous phase is pumped into the vessel to form an emulsion. Nitrogen is then sparged through the suspension to blow off essentially all organic solvents. During this stage of the process, there is considerable foam formation; product viscosity shoots from water-thin to a pudding state and dives back to water-thin -- a typical event in liposome preparation. The rate of mixing and sparging is critical to the ultimate particle size of the liposomes which need to be on the order of 200-300nm. The jacketed vessel and self-adjusting orbiting sidewall scraper arm help to tightly control batch temperature between 50°C to 80°C.

Another PowerMix application is a non-animal soft gel capsule material. The batch begins with a starch-water slurry and a carrageenan solution in glycerol which are combined and heated in the PowerMix. This viscoelastic gel formulation could not be processed in a multi-shaft mixer because of poor flow characteristics. Its rheology is also the reason why a double planetary mixer is not quite able to achieve the same level of dispersion as the high speed disperser and planetary stirrer combination of the PowerMix.

Conclusion

There are two distinct approaches in the selection of mixing systems. One is to issue mechanical specifications (speed, blade diameter, power, etc.) based on previous in-house experience. The other is to supply the vendor with just the process specs including the engineering purpose for the mixer, as well as expectations of mixer performance. The ideal situation is somewhere in between these two approaches.

Cycle times, particle size distribution and other parameters are influenced not just by mixer design but also by product chemistry, operating temperature, pressure/vacuum conditions, quality of raw materials, presence of additives, etc. Process guarantees are really more misleading than helpful most especially in the absence of any empirical data gathered from mixer testing wherein your own formulation or a fairly similar one was actually utilized.

Ultimately, most of the mixer features will depend on the requirements of your specific process. Some aspects worth discussing in detail with your mixer manufacturer include construction and polish of wetted parts, sanitary connections and valves, CIP/SIP capability, batch size flexibility, sufficient horsepower(s), ease of discharge, level of maintenance, sealing arrangements and the degree of sophistication you expect to have in the mixer controls.

It is essential for R&D scientists and process engineers to be continually updated on new mixer systems and improved designs. In reality, many of today’s mixing technologies overlap in use and function such that certain applications can actually be successfully produced by two or more types of mixing systems. In these situations, economics rule out the more costly initial investments, but difference in efficiencies must also be taken into account. A trusted manufacturer that offers long-term experience, rental and testing resources will make for a very strategic partner whether you are selecting a mixer for a new product or simply updating an existing process.

Mixer Applicability	
MIXER DESIGN/CONFIGURATION	TYPICAL VISCOSITY RANGE
High Shear Mixer	Up to 20,000 cP
High Speed Dispenser	Up to 50,000 cP
Multi-Shaft Mixer	Up to 500,000 cP
PowerMix	Up to 2 million cP
Double Planetary Mixer with Rectangular Blades	Up to 3 million cP
Double Planetary Mixer with HV Blades	Up to 8 million cP
Kneader Extruder	10+ million cP