

Dispersion Techniques for Lubrizol Pharmaceutical Polymers

Carbopol[®]* polymers, Pemulen[™]* polymers and Noveon[®]* polycarbophil are highly efficient thickeners, suspending aids, emulsion stabilizers and bioadhesives when dispersed in water or other polar solvents. Much of the exceptional utility of the polymers results from their hydrophilic nature.

Like many fine powders, traditional Carbopol[®] polymers, as well as Pemulen[™] polymers and Noveon[®] polycarbophil, tend to agglomerate when improperly added to the solvent. Therefore, proper dispersion techniques must be followed to prevent excessively long mixing cycles and dispersion defects such as a grainy texture, reduced viscosity and the formation of insoluble particles resembling “fish eyes.” If improper dispersion techniques are utilized, the surface of the agglomerated particles solvates to form a tough outer layer which prevents complete wetting of the interior polymer particles. As a result, total mixing time is governed by the slow diffusion of solvent through this solvated layer to the dry interior. This issue has been addressed by introduction of the Carbopol[®] interpolymers such as Carbopol[®] Ultrez 10 NF polymer and Carbopol[®] ETD 2020 NF polymers which disperse easily in water.

Dispensing Procedures

Two dispersion methods can be used to prepare aqueous dispersions of Carbopol[®] polymers, the direct method and the indirect method.

Direct Method (Carbopol[®] polymer is added directly to water or other polar solvent)

The proper method to use when adding Carbopol[®] polymer directly to water depends on the quantity and concentration of the dispersion to be prepared.

A. Batch Dispersions

Batch dispersions up to several hundred gallons with concentrations of up to 2.0 weight percent Carbopol[®] polymer, Pemulen[™] polymer or Noveon[®] polycarbophil can be prepared by slowly sifting the polymer into the vortex of the moderately agitating liquid. The sifting method allows the slow, controlled addition of the dry polymer, enabling each particle to wet out separately in the water vortex. The sieve or screen permits the breakup of any loose agglomerates formed due to the static charge on the particles.

For small quantity batches, the impeller should be submerged very close to the bottom of the vessel and be angled to generate a vortex which is one to one-and-one-half its diameter. The mixing speed should be approximately 800-1500 rpm. A coarse sieve or a stainless steel 20 mesh screen can be used for sieving the polymer.

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Once all of the dry polymer has been introduced, the agitation rate should be reduced to 300-800 rpm and the impeller should be re-angled to a vertical position to avoid the entrapment of excess air and foaming. Mixing is continued for approximately 15 minutes or until a uniform dispersion is attained.

If persistent foam is generated, it can be broken by partially collapsing the polymer with the addition of a very low level of acid before neutralization with a suitable base. Hydrochloric acid or phosphoric acid are effective at 0.5% of the weight of the polymer used. This level of acid does not result in a significant contribution of salt when neutralizing the polymer and does not significantly affect the viscosity of the end product.

In order to prepare an emulsion with Pemulen™ polymer, the polymer dispersion should be prepared in the same manner that is used to prepare a Carbopol® polymer dispersion. The oil phase can be added to the polymer dispersion by rapid mixing (800-1500 rpm) followed by neutralization with a suitable base. Use rapid mixing to reduce the oil droplet size and obtain a shiny product.

Details on the neutralization procedure for dispersions and emulsions can be found in Bulletin 5. Active pharmaceutical ingredients can be incorporated in the water or solvent used to prepare the polymer dispersion or they can be added after the dispersion is made.

Agitation Guidelines

Moderate agitation is recommended. Agitation enhances the rate of solvation of Carbopol® polymers, Pemulen™ polymers and Noveon® polycarbophil. Best dispersion and solvation results are achieved with moderate agitation at approximately 800-1500 rpm.

Avoid high shear mixing. Extremely high shear mixers such as Waring blenders or rotor-stator homogenizers should be avoided or carefully employed because such mixing can shear the opened polymer and result in permanent functionality loss. **For best results**, use a motorized mixer such as the Eppenbach, Caframo, Arde Barinco, Janke and Kunkel, or Lightnin' Mixer with a conventional open-blade impeller (pitched marine or saw tooth propeller). These types of impellers do not impart excessively high shear rates, and can be used to mix dispersions for extended periods with virtually no decrease in polymer efficiency.

Care must be taken when using in-line mixers, such as colloid mills or homogenizers. The polymer should be initially wetted-out with rapid (800-1500 rpm) agitation to minimize the mixing time required using the high shear mixers. The lowest shear rate and shortest mixing time should be used to achieve a homogeneous mixture. A one pass configuration is preferred to a multiple pass configuration.

Air entrapment can be minimized using a variable drive motor whenever possible. Once the Carbopol® polymer has been dispersed, air entrapment can be minimized by repositioning the impeller and reducing the mixing speed.

B. Large Batch Dispersions Using an Eductor

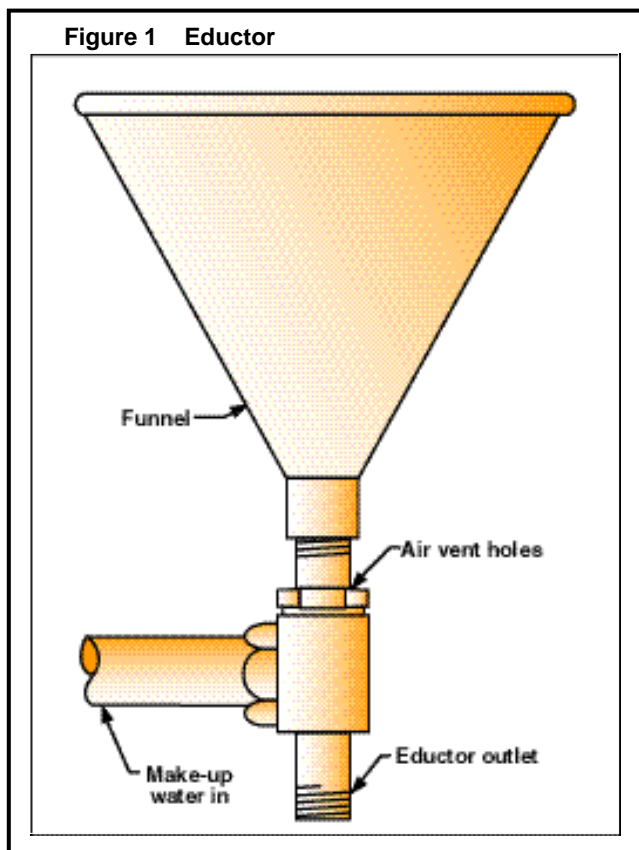
Dispersions with polymer concentrations of up to three weight percent, may be prepared with an eductor or flocculent disperser. This technique is a fast, inexpensive way of dispersing Carbopol® polymers, Pemulen™ polymers and Noveon® polycarbophil with reduced dusting.

Figure 1 shows the basic design of the eductor. It is a small, metal or plastic valve which exerts a partial vacuum on the powder inlet via the Bernoulli effect. The polymer is pulled from the eductor funnel into the eductor valve throat. The partial vacuum is created by the flow of incoming makeup water through the

venturi of the eductor throat. The turbulence of the water within the valve rapidly wets out the polymer to aid in forming quality dispersions and minimize agglomeration.

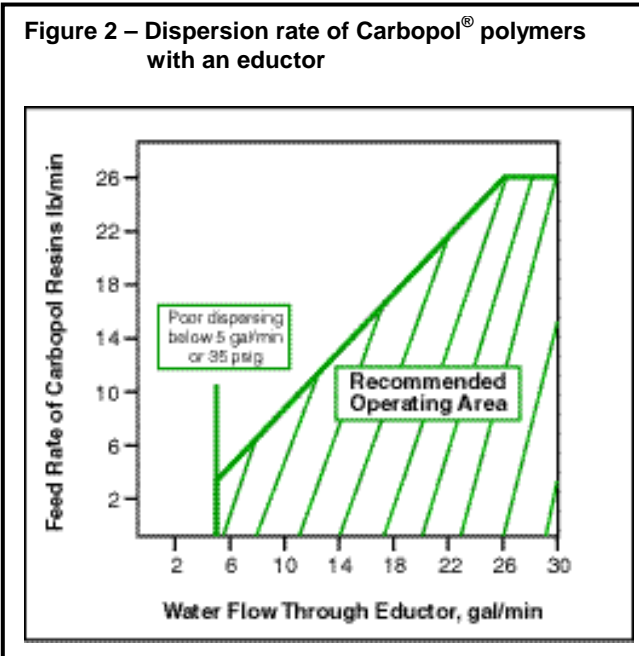
The eductor outlet should have enough piping (4 to 5 ft) to build up enough back pressure to direct the polymer/water slurry into an agitated mix tank filled with water to complete hydration.

Figure 2 shows how the rate of dispersion increases with an increase in water pressure.



Tips for Using an Eductor

- Select a solid particle dispersion eductor.** Do not use a liquid eductor model.
- Avoid using hot water,** as the water vapors will prematurely swell the polymer and clog the eductor.
- At least a ¾ inch pipe and 35 psig water pressure** are required for an eductor. Constant pressure must be maintained. If necessary, include a pump for inlet water.
- Prevent plugging** by attaching an air-driven or electric vibrator, or simply tapping on the side of the funnel. Start the water flow before adding the polymer to the eductor funnel. If the eductor plugs with dry polymer, care should be taken when inserting any object for cleaning so that the eductor orifice size is not altered.
- Thoroughly clean after use.** The eductor should be installed with easily removable plumbing fitting to facilitate cleaning.
- Cover the funnel** with a polyethylene bag to keep out moisture when idle.



Further information regarding eductors can be obtained from these manufacturers:

FOX VALVE DEVELOPMENT CORPORATION
Hamilton Business Park, Unit 7A
Dover, NJ 07801
Phone: (973) 328-1011

TYCO VALVES
320 Locust Street
Prophetstown, IL 61277
Phone: (815) 537-2311

SCHUTTE AND KOERTING
2233 State Road
Bensalem, PA 19020
Phone: (215) 639-0900

C. Large Quantity Continuous Production Dispersions

The continuous production of good quality, high-solid dispersions of Lubrizol pharmaceutical polymers is possible with mechanical in-line powder dispersers. Mechanical dispersers use a high velocity eductor coupled with an in-line homogenizer to rapidly disperse and wet each individual polymer particle instantaneously. This highly turbulent, high-shear mixer operates at such a rapid rate that the particles are wetted and expelled prior to polymer swelling. Agglomerate formation and polymer degradation from mechanical shearing are eliminated.

The valved powder hopper feed of mechanical dispersers can significantly reduce the level of air entrapment or foaming. Dispersed particles are expelled from the dispersers directly into a tank with low/moderate agitation. Table 1 provides a comparative outline of mechanical dispersers and their features.

Table 1				
Mechanical Dispersers for Carbopol® Polymers				
Model	Manufacturer/ Distributor	Carbopol® Polymer Capacity (lbs./hr.)	Maximum Carbopol® Polymer Solids (wt. %)	Water Flow Rate (lbs./hr.)
ZC	YTRON QUADRO	1,200	15*	15,000
Silverson Flashblend	Silverson Machines Ltd., UK	7,500	15-20*	50,000
Arde Vacuum Dilumelt	Arde Barinco, Inc.	1,000	4	30,000
*Dispersions of greater than 5 weight percent Carbopol® polymer become dense, solid-like, and impractical to pump or handle.				

Dispersions with Carbopol® Ultrez 10 NF Polymer and Carbopol® ETD 2020 NF Polymer

Carbopol® Ultrez 10 NF and Carbopol® ETD 2020 NF polymers allow for greater versatility in formulating and processing because they can be directly added to water. The unique dispersion performance of these polymers allows them to wet quickly, yet hydrate slowly. This property helps minimize agglomeration, which can be problematic when turbulent mixing is not available during dispersion. Compared with traditional Carbopol® polymers, Carbopol® Ultrez 10 NF and Carbopol® ETD 2020 NF polymers provide dispersions in water that are much lower in viscosity prior to neutralization. The lower unneutralized dispersion viscosity enables easier handling in mixing tanks and process lines. Once the polymers are neutralized, they are highly efficient thickeners.

Indirect Addition of Pharmaceutical Polymers into Water

Indirect Method

The indirect method can be used for a formulation which contains liquids that do not solvate the polymer. Only anhydrous solvents should be used. This method avoids the rapid agglomeration of the polymer particles in water and leads to a uniform dispersion.

Carbopol® polymer, Pemulen™ polymer or Noveon® polycarbophil should be mixed into the oil or non-polar phase of the formulation so it is pre-dispersed when it contacts water. This dispersion is added under agitation (800-1500 rpm) to the water phase containing the neutralizer. Mixing should be continued for approximately 15 minutes, or until the polymer has swelled to produce a smooth product.

In the presence of some polar oils (aromatic or dicarboxylic acid esters) or molten oils above 65°C, Carbopol® polymers, Pemulen™ polymers or Noveon® polycarbophil will plasticize, hindering bioadhesion, thickening and stable emulsion formation. Dispersing the polymer directly into the water in these cases will result in smooth, stable products.

A. Oil-In-Water Emulsions

Traditional surfactant-based emulsions – Combine the ingredients of the oil phase and, if required, heat until all materials are liquid. (Temperatures must not exceed 65°C.) Add the Carbopol® polymer to the oil phase with moderate agitation (300-800 rpm) until the powder is wetted in the oil. Increase the rate of agitation to 800-1500 rpm and add the external phase (containing the surfactant). Continue mixing for 20 to 40 minutes, or until a smooth, non-grainy texture is apparent. Then add the appropriate base to neutralize and thicken the polymer.

Emulsions based on Pemulen™ polymers – Combine the ingredients of the oil phase and, if required, heat until all materials are liquid. (Temperatures must not exceed 65°C.) Disperse the Pemulen™ polymer in the oil phase with moderate agitation (300-800 rpm) until the powder is wetted in the oil. Under rapid agitation (800-1500 rpm), add the oil phase (containing the Pemulen™ polymer) to the water phase, containing the neutralizing alkali. Alternatively, the water phase can be added to the oil phase. Pemulen™ polymer will swell rapidly in the water phase causing a swift build of viscosity and the formation of a creamy emulsion. Continue with vigorous agitation for 15-20 minutes or until smooth.

Liquid nonionic surfactant (HLB 8-12) in a concentration of 0.1-0.4% may be added to the oil phase to reduce the size of the oil droplets, and improve the creamy appearance of the emulsion.

B. Aqueous Suspension from Insoluble Concentrates

High concentration dispersions of polymers in liquids that do not solvate the polymer (mineral oil or low HLB nonionic surfactants) can be prepared using moderate agitation. These dispersions should be incorporated immediately into the water phase to avoid polymer settling and plasticization. The pre-dispersion of the polymer delays the rate at which the Carbopol® polymer or Pemulen™ polymer swells or hydrates in the water, thus minimizing agglomeration or the formation of non uniform aqueous dispersions.

Incorporating Active Pharmaceutical Ingredients into Carbopol® Polymer Dispersions

Carbopol® polymers, Pemulen™ polymers and Noveon® polycarbophil dispersions can be used as the vehicle in liquid and semisolid dosage forms. Other pharmaceutical ingredients are incorporated into the formulation via two different methods depending on the physical/chemical properties.

Insoluble Ingredients

Insoluble ingredients can be incorporated into the polymeric dispersion either before or after it is neutralized.

Soluble Ingredients

Soluble ingredients can be dissolved in the water used to make the polymeric dispersion. Some soluble ingredients are added to the final formulation to avoid compatibility issues (example, electrolytes added at the end).