

Neutralization Procedures

Introduction

The macromolecules of Carbopol^{®*} polymer, Pemulen^{™*} polymer or Noveon^{®*} polycarbophil in a presolvated state are tightly coiled. When dispersed in water, the molecules hydrate and uncoil to some extent. Even before neutralization, the dispersion of relatively low levels of traditional Carbopol[®] polymers, Pemulen[™] polymers or Noveon[®] polymers can result in significant viscosities. The Carbopol[®] ETD and Ultrez polymers have significantly lower dispersion viscosities at the same levels, enabling higher concentration dispersions to be made.

Polymer performance is maximized when the macromolecule is fully uncoiled and extended. This uncoiling can be accomplished in several ways (neutralization or hydrogen bonding).

Aqueous Systems Neutralization

In aqueous systems, the best way to achieve thickening, emulsification or suspending activity is by neutralizing the polymer with a base. The neutralization ionizes the polymer and generates negative charges along the backbone of the polymer. Repulsions of like charges then cause uncoiling of the molecule into an extended structure. This reaction is rapid and gives instantaneous thickening and emulsion formation/stabilization.

All of Lubrizol's pharmaceutical polymers operate with the same mechanism, but each polymer exhibits different rheological characteristics, suspending and emulsion forming capabilities. In addition, the performance characteristics of the various polymers are dependent upon the degree of neutralization (pH) and ionic strength of the aqueous solution.

Inorganic bases, such as sodium hydroxide or potassium hydroxide, or low molecular weight amines and alkanolamines will provide satisfactory neutralization. Some of the amine bases effective as neutralizing agents for aqueous formulations and o/w emulsions include: TEA (triethanolamine), AMP[®]-95 (aminomethyl propanol), Tris Amino[®] (tromethamine) and Neutrol[®] TE (tetrakis-2-hydroxypropyl ethylenediamine). Table 1 shows relative base strengths.

Amino acids such as β-alanine and lysine can also be used for neutralization and viscosity modification.

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General Tips for Neutralization

- **Prevent over-neutralization** by pre-weighing the neutralizing agent. Over-neutralization with strong bases such as sodium or potassium hydroxide results in severe viscosity loss. Amines lend better pH control. Small increases in amine levels at the equivalence point will not lead to large increases in pH.
- **Add strong inorganic bases as a 10-20% aqueous solution.**
- **For more precise neutralization**, use an equivalent weight of 76 for the Carbopol® polymer. The proper quantity of neutralizing base depends on its type and equivalent weight.
- **DO NOT use divalent inorganic bases** such as calcium hydroxide to neutralize the polymers. The soluble divalent cations ionically crosslink the polymers and cause precipitation.
- **Use slow agitation** to avoid entrapping air bubbles.
- **Wait for formulation to reach equilibrium** before further pH adjustment.

Procedure

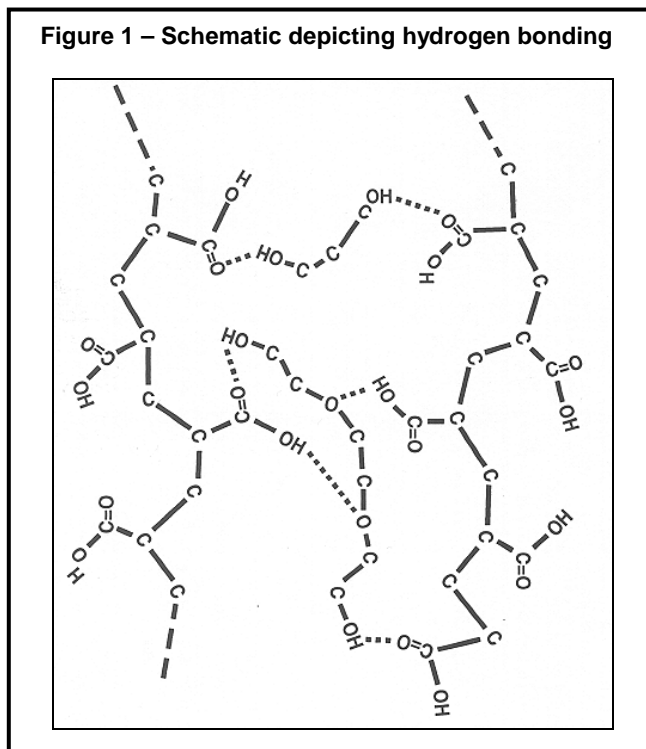
1. Let the acid dispersion stand to release entrapped air bubbles. If a concentrated stock dispersion has been prepared, dilute it to final desired concentration first, then let this diluted dispersion stand to release air bubbles.
2. Using moderate agitation (300 - 800 rpm) to avoid vortexing, add the neutralizing agent. Thickening will occur immediately.

Table 1
Relative Ratio of Base to One Part Polymer By Weight
(Neutralized to an approximate pH of 6.0-7.0)

Sodium hydroxide (18% solution)	2.30
Potassium hydroxide (18% solution)	3.30
Ammonium hydroxide (28% solution)	0.70
Triethanolamine (TEA)	1.50
Tromethamine (2-Amino 2-Hydroxymethyl-1, 3-propanediol)	1.30
Aminomethyl propanol (AMP)	0.95
Tetrahydroxypropyl ethylenediamine	2.30

Aqueous Systems – Thickening by Hydrogen Bonding

Thickening by hydrogen bonding is recommended in cases where it is not feasible to increase the pH of the final formulation. For example, hydrated molecules of Carbopol® polymers, Pemulen™ polymers and Noveon® polycarbophil can be uncoiled in water systems by adding 10-20% of a hydroxyl donor.



Some commonly used hydroxyl donors are: polyols (glycerine, propylene glycol and polyethylene glycol), sugar alcohols (mannitol, sorbitol), nonionic surfactants with five or more ethoxy groups, polyethylene oxide, and fully hydrolyzed polyvinyl alcohol, among others. These ingredients form hydrogen bonds with the polymer molecule causing it to uncoil. The hydrogen bonding is not instantaneous — maximum thickening may take from 5 minutes to three hours. Heating the dispersion hastens thickening, but temperatures above 60°C (140°F) should not be used.

Hydrogen Bonding in Aqueous Systems – Example

Ingredient	% by Weight
Hydroxyl donor	10.00
Water	89.00
Carbopol® polymer or Pemulen™ polymeric emulsifier	1.00
	100.00

Procedure:

1. Combine the hydroxyl donor and the water.
2. While agitating rapidly (800-1500 rpm), sift the Carbopol® polymer or Pemulen™ polymeric emulsifier into this blend slowly to avoid agglomeration.
3. Continue stirring until viscosity builds up. Heating to 60°C (140°F) usually hastens thickening.
4. Depending on their properties, additional ingredients, including the oil phase can be added to the thickened dispersion (under moderate to rapid agitation).

See also TDS-237: [“Neutralizing Carbopol® and Pemulen™ Polymers in Aqueous and Hydroalcoholic Systems”](#)

Solvent System

Anhydrous formulations can be designed using Carbopol[®] polymers. In these cases, the dispersions of Carbopol[®] polymer can be thickened by neutralization or hydrogen bonding.

Solvent System Neutralization

The tightly-coiled dry molecule of Carbopol[®] polymer or Pemulen[™] polymer uncoils slightly as the solvation process begins. Addition of an appropriate amine forms the solvent-swallowable salt of Carbopol[®] polymer. In this salt formation, the molecule of Carbopol[®] polymer uncoils into its extended structure.

Carbopol[®] polymers and Pemulen[™] polymers in the acid form are hydrophilic and tend to be more swallowable in water and polar organic solvents. However, dispersions in less polar solvents may be thickened by neutralizing the polymer with long-chain amines which are soluble in nonpolar solvents. The choice of neutralizing amine is very important. The amine salt of Carbopol[®] polymer or Pemulen[™] polymer must be swallowable in the solvent system. If it is not, it will precipitate and no thickening will occur.

The theory governing solvent thickening is complex and based on matching solubility parameters, hydrogen bonding and dipole moment properties of the solvent and the solute.

The recommended amines and usage levels for various solvents systems based on Lubrizol studies is shown in Table 2.

An alternate approach to using a nonpolar amine salt of the polymer is to modify the solvent system by adding 5 to 25% of a more polar, miscible solvent. This will enable use of more polar amines or, in some cases, inorganic bases.

Suggested Procedures for Neutralization in Solvent Systems

For a one-component system:

1. Add the neutralizing amine to the solvent and mix thoroughly.
2. After mixing, allow the air bubbles to escape.
3. With moderate agitation (300 - 800 rpm), disperse the Carbopol[®] polymer or Pemulen[™] polymeric emulsifier in the solvent/amine blend.
4. Thickening will occur within a few minutes.

NOTE: Generally, other ingredients should be dissolved prior to the addition of the amine.

For a blend of solvents:

1. Disperse the Carbopol[®] polymer or Pemulen[™] polymer in the least polar solvent. Thickening will not occur at this time.
2. Add the amine to the most polar solvent.
3. With moderate agitation (300 - 800 rpm), add the polymer dispersion to the solvent/amine blend.
4. Continue mixing until a uniform blend is achieved.

Table 2 Amine Required to Neutralize Carbopol® Polymer (Amine: Polymer)			
% Solvent A % Solvent B	Diisopropanolamine 2:1	Polyoxyethylene (15) coconut alkylamine 2.5:1	Triethanolamine 1.5:1
90 DMSO 10 Water		●	
Ethanol	●	●	
Glycerol	●		
90 Isopropanol 10 Water		●	
Propiolactone		●	
Propylene glycol	●	●	
90 Propylene glycol 10 Water		●	
Water		●	●

Solvent Systems – Hydrogen Bonding

Many polyhydroxy and polyethoxy solvents such as diols, triols, and polyols can be thickened with Carbopol® polymers without neutralization. Carbopol® polymers form strong hydrogen bonds with these solvents.

The hydrogen bonding mechanism is slow and can take one to four hours for maximum viscosity to be reached. Heating the dispersion will hasten swelling, but the temperature should not exceed 60°C (140°F).