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Polymer Handling and Storage

More details regarding the properties of mucilages are found in Pharmaceutical Bulletin 6: "Thickening Properties"

Handling and Storage of the Dry Polymer

Shelf Life

Lubrizol will guarantee that Carbopol®* polymers stored in sealed, standard Lubrizol containers will continue to meet the specification ranges for two years after the production date. Based on published literature and the stability test programs conducted at Lubrizol, it can be concluded that Carbopol® polymers in the dry powder state are chemically very stable under normal storage conditions. Studies showed that none of the chemical parameters were subject to significant changes during 5 years. The detected impurities also did not increase during storage, indicating a chemical shelf time of the powder of minimum 5 years.

Moisture

Carbopol®, Pemulen™* and Noveon®* polymers are very hygroscopic. As shipped, they contain a maximum of 2% moisture. When exposed to open air at room temperature and 50% relative humidity, the product's equilibrium moisture pickup is 8%. Moisture pickup does not affect efficiency of the polymers, but polymer containing high levels of moisture is more difficult to disperse and weigh accurately. Therefore, containers of Carbopol®, Pemulen™ and Noveon® polymers must be tightly closed and stored out of contact with water.

Effect of Heat

Heating at temperatures below 104°C (220°F) and for up to two hours, will not affect the efficiency of dry Carbopol®, Pemulen™ and Noveon® polymers. When the polymer is exposed to excessive temperatures, it can become sintered. Sintered polymer changes the drug release rate from tablets and is difficult to disperse and slower to gel in liquid formulations. The product will become discolored depending on the temperature and exposure time. Decomposition is complete, for all practical purposes, in 30 minutes at 260°C (500°F).

Re-Test Recommendations

Carbopol® polymers, Pemulen™ polymeric emulsifiers and Noveon® polycarbophil should be tested for moisture content every six to twelve months after the initial testing. The frequency of retesting should be determined based on the humidity of the storage conditions.

In very dry conditions, testing should be done every 12 months, while in very humid environments, retesting should be done every six months.

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Dust Precautions

Because Carbopol® polymers are light, fluffy powders, normal precautions should be observed to prevent loss or hazard from dusting. Any material that has a fine particle size is potentially hazardous if it can be readily detonated. Some other important explosion-hazard variables are the magnitude of detonation and the rate of pressure increase. These criteria for evaluating the risk of explosion, as well as others, were determined with Carbopol® polymers by the Explosion Safety Department of TNO in Delft, Holland. Results indicate that a very high concentration of dust of Carbopol® polymers in air (100 gm/m^3) is needed to reach the lower explosion limit. At such a concentration, one could not see through the cloud of dust.

Routine safety precautions should be observed for handling fine-particle-size powders. Such precautions may include equipment grounding and bonding, adequate ventilation, good housekeeping, etc.

NIOSH-approved dust masks such as MSA Dustfoe® 88 (Mine Safety Appliance Company) and 3M #8233 or 8293 (3M Company) should be worn when large quantities of Carbopol® polymer are being handled.

Handling and Storage of Dispersions or Mucilages

Storing Dispersions

Aqueous dispersions of unneutralized Carbopol® polymers can be stored as stock solutions at concentrations up to 5% with Carbopol® 934, 980 and Ultrez 10 NF polymers; 4% with Carbopol® 981 polymer; and 3% with Carbopol® 940 and 941 polymers, when prepared following the instructions in *Bulletin 4: "Dispersing Procedures – Small Quantity Batch Dispersions"*, and as high as 12% when prepared with an eductor or mechanical disperser. The dispersion should be prepared and stored in corrosion-resistant equipment. Glass-lined or Type 316 stainless steel vessels are recommended. Carbopol® polymers will not support mold or bacterial growth, but will not suppress it either. For prolonged storage, preserve the stock solution with materials such as a 1:1 blend of methyl p-hydroxybenzoate/propyl p-hydroxybenzoate at a 0.1% concentration to prevent mold or bacteria growth in the water. See Microbial Activity, below, for more details.

Oxidative Degradation of Carbopol® Polymers

In liquid formulations, carbomers are subject to reaction with oxygen, which causes a permanent reduction or loss of viscosity. This process, which has been studied scientifically, is catalyzed by sunlight, UV light, and certain metals present in the water.[2] Trace levels of iron and other transition metals can catalytically degrade Carbopol® polymers. Heat may accelerate this reaction. In one case where viscosity loss was experienced upon sterilization at 121°C, the problem was stopped by deaerating the formulation under vacuum and breaking the vacuum with inert gas.[3] This degradation is most often seen in clear gel systems, where ultraviolet (UV) light accelerates breakdown. The degradation reduces the viscosity of clear gel mucilages and may cause separation and creaming in some emulsions. Adjust the pH or use additives to help prevent degradation. At pH 10 or greater, gels of Carbopol® polymers are insensitive to UV light. Also, inorganic salts of Carbopol® polymer are slightly more resistant than organic salts to such degradation.

Water-soluble UV absorbers such as benzophenone-2 and benzophenone-4 (CTFA) are effective. In many gel formulations, these absorbers are used in combination with disodium or tetrasodium salts of ethylene diamine tetra-acetic acid (EDTA). There is a synergistic effect when these two components are used. Typical usage levels of each component are 0.05 - 0.10% in the finished formulation.

Electrolyte Sensitivity

Electrolytes tend to reduce the viscosity of Carbopol® polymer or Noveon® AA-1 polycarbophil based gels, and may destabilize emulsions formed with Pemulen™ polymeric emulsifiers. Therefore, a topical gel may serve as a base for ionizable medicaments only if a higher concentration of the polymer is used, or if a less ion sensitive polymer is used. Due to their anionic character, Carbopol® polymers form precipitates with polyvalent and some large monovalent cations.

Temperature Stability

Carbopol® polymers, Pemulen™ polymeric emulsifiers and Noveon® AA-1 polycarbophil are not subject to hydrolysis or oxidation under normal conditions. Furthermore, mucilages and emulsions containing these polymers which are freeze/thaw stable can be prepared. Mucilages of Carbopol® polymers, Pemulen™ polymeric emulsifiers and Noveon® polycarbophil drop in viscosity slightly upon exposure to high temperatures. This effect is reversible when returned to the original temperature.

Sterilization and Irradiation

Literature data suggest that there is little to no change in the viscosity or pH upon repeatedly subjecting a Carbopol® polymer gel to autoclaving (at 121°C for 30 minutes).[1]

Gamma irradiation may sometimes result in an increase in the viscosity of the formulation, but S.G. Deshpande[2] has described gamma irradiation (2.5 Mrad) of ophthalmic sustained release formulations of pilocarpine. In general, 2.5 Mrad may be used for sterilization of Carbopol® polymer gels without significant impact. Special care should be taken regarding the relative stability of drugs under sterilization conditions. I. Adams et al[1,3] have shown that a gamma irradiated sterilizable lubricant gel of lidocaine base (2%) of optimal consistency can be formulated in which 5-10% ethanol protected the Carbopol® polymer gel structure against degradation. European patent 396394 describes a radiation sterilizable surgical gel comprising 1% of Carbopol® 934 NF or 940 NF polymer and 5% glycerol.

Microbial Bioburden

Several tests were conducted to determine the bioburden of both a benzene polymerized and an ethyl acetate polymerized Carbopol® polymer. Carbopol® 940 NF and 974P NF polymers were chosen as models. Specifically, the test was to determine whether Lubrizol Advanced Materials, Inc. could meet or exceed a target of <100 gram positive organisms and <10 gram negative organisms per gram of Carbopol® polymer.

Although Carbopol® polymer has no history of contamination problems for Lubrizol Advanced Materials, Inc., many customers have requested documentation or testing of microbial bioburden for their raw materials.

The following tests were performed: Total Aerobic Bacterial Plate Count (TABPC), Total Gram Negative Bacterial Plate Count (TGNBPC), Total Yeast and Mold Count (TYMC) and Total Accelerated Mold Plate Count (TAMPC).

Results indicated that the Carbopol® polymers tested easily meet or exceed the targets using the testing protocols described below.

Materials

Letheen Broth (LB) and Tween® 80 (TW-80) were furnished by Difco Laboratories. Nutrient Agar (NA), Sabouraud Dextrose Agar (SDA), Nutrient Broth (NB), Potato Dextrose Agar (PDA), H-C Agar (HCA) and Triphenyltetrazolium Cholide (TTC) solution were furnished by Microbiology Systems. Falcon (1029) Optilux petri plates and sterile disposable pipettes were furnished by Fisher Scientific.

Methods

The general method for these procedures is to suspend or dissolve the test materials in a nutrient broth medium which contains an ingredient to neutralize preservatives (Letheen broth). Aliquots of the solution are then mixed with molten agar (45°C) in petri dishes and allowed to solidify. After appropriate incubation periods, the colonies are counted and the bioburden estimated per gram of test material.

All media, containers and other supplies were sterilized (usually by autoclaving) and aseptic techniques were used throughout the study.

Preparation of Carbopol® Polymer Dispersions

The highest optimum concentration for adequate mixing and pipetting was found to be 1.1 grams of Carbopol® polymer in 99 ml of letheen broth.

Aliquots of the Carbopol® polymer samples were added to sterile 8-ounce wide-mouth jars containing 99 ml of letheen broth. Mixing was achieved by shaking (at least 25 times) until the solution appeared to be uniformly dissolved.

Preparation of Media

Since the purpose of this study was to find all microbes, NA+TTC was used. TTC is useful in detecting the growth of many types of organisms, particularly in opaque media. TTC was added to nutrient agar immediately before use to achieve a final concentration of 0.01%.

Media were prepared according to the manufacturer's instructions with the addition of 2% Tween® 80 where noted.

Growth of Common Organisms in the Presence or Absence of Carbopol® Polymer

Four common organisms were chosen to serve as positive controls for the system. NA and SDA plates were prepared with and without Carbopol® as described under the section Microbial Test Limits Procedures. The agar surfaces were then streaked with 1 µl of a broth culture or spore suspension using a sterile inoculating loop. The plates were incubated 48 hours at 35°C and examined for growth.

Preparation of Bacterial Innocula

Lyophilized cultures of bacteria obtained from Difco were used to inoculate nutrient broth. The broth was incubated overnight at 36°C. The strains utilized were Staphylococcus epidermis ATCC 12228, Pseudomonas aeruginosa ATCC 28753 and Klebsiella pneumonia ATCC 13883.

Preparation of Fungus Spore Suspension

A five day culture of Aspergillus niger ATCC 16404 grown on Sabouraud dextrose agar was washed with 10 ml of 0.1% solution of Tween® 80 in 0.9% NaCl. The solution was centrifuged, the pellet washed with saline, the solution recentrifuged and the pellet resuspended in 5 ml saline solution.

Microbial Limits Test Procedures

Ten-milliliter aliquots of each of the four Carbopol® polymer-letheen broth solutions as well as a broth without Carbopol® polymers were pipetted into a series of coded sterile petri dishes. Twenty milliliters of appropriate molten agar (45°C) was added to each dish and gently swirled to mix. The plates were allowed to solidify and then incubated. All conditions were plated in triplicate. Agars used and incubation temperatures and times are shown in Table 1.

Table 1
SUMMARY OF TEST CONDITIONS

Test	Medium	Incubation (days)	Temperature
TABPC	NA +2.0% TW-80	3	35°C
TGNPC	NA + 0.01% TTC	3	35°C
TY&MC	PDA + 2.0% TW-80	21	28°C
TAMC	HCA	3	28°C
TABPC	NA	7	28°C
TY&MC	SDA	21	Ambient

KEY: TABPC = Total Aerobic Bacterial Plate Count
TGNPC = Total Gram Negative Plate Count
TY&MC = Total Yeast & Mold Count
TAMC = Total Accelerated Mold Count

Results

Positive and negative control data to validate the system are shown in Table 2. Absence of growth on uninoculated plates shows the media to be free from contamination. Growth of all organisms on NA shows that the challenge organisms are visible and that NA supports growth. The three strains of bacteria grew on neutral media (NA), but not on acidic media (SDA, NA+C and SDA +C) while the fungus grew on all media. This demonstrates the ability of a common fungus to thrive in a low pH environment where common bacteria are inhibited.

No bacterial growth occurred on any of the plates in the study. This is not unexpected since the presence of Carbopol® polymers significantly lowers the pH of agar. One fungus colony was observed on one plate in the study (Table 3). The colony occurred on a PDA + 2% TW-80 plate which contained Carbopol® 940 polymer. That colony represents <1 organism per gram of that particular sample. All media throughout the study would be expected to support the growth of fungi. Thus, if all the data are pooled, the result equals <0.1 organism per gram of Carbopol® polymer.

Using the methods described and assuming that the sample lots are representative of all Carbopol® 940 NF and 974P NF polymer lots, these products meet or exceed the target of <100 gram positive organisms and <10 gram negative organisms per gram of product with a wide margin for safety.

Table 2
EFFECT OF CARBOPOL® POLYMERS ON ORGANISM GROWTH IN AGARS

	Agar			
Culture	NA	SDA	NA+C	SDA+C
Dlebsiella pneumonia	+	-	-	-
Pseudomonas aeruginosa	+	-	-	-
Staphylococcus epidermis	+	-	-	-
Aspergillus niger	+	+	+	+
Blank	-	-	-	-

KEY: + = Growth
– = No Growth
NA = Nutrient Agar
SDA = Sabouraud Dextrose Agar
NA+C = Nutrient Agar + Carbopol® Polymer
SDA+C = Sabouraud Dextrose Agar + Carbopol® Polymer

Table 3
BIOBURDEN OF CARBOPOL® POLYMER TEST LOTS

	Blank			Carbopol® 940 NF Lot 1			Carbopol® 940 NF Lot 2			Carbopol® 974P NF Lot 1			Carbopol® 974P NF Lot 2		
Plate Number	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Medium	**Colonies Per Plate**														
NA – 2.0% TW-80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NA = 0.01% TTC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
HCA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PDA + 2.0% TW-80	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
SDA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

KEY:
NA = Nutrient Agar
TW-80 = Tween 80
TTC = Triphenyltetrazolium Chloride
HCA = Chloramphenical Agar
PDA = Potato Dextrose Agar
SDA = Sabouraud Dextrose Agar

Microbial Activity

Carbopol® polymers, Pemulen™ polymeric emulsifiers and Noveon® polycarbophil do not support bacteria, mold or fungus growth in powder form. The polymers also do not prevent bacterial or fungal growth on nutrients found in normal water systems. In mucilages of Carbopol®, Pemulen™ or Noveon® polymers, mold and some bacteria can develop. Although the gel properties are not affected by such growth, this phenomenon is usually unacceptable. The addition of appropriate preservatives prevents mold and bacterial growth in mucilages of these polymers.

The polymers are compatible with many biocides used for prevention of bacteria and fungus growth. The addition of DMDM Hydantoin, methyl paraben, propylparaben, Dowicil® 200 or other suitable preservative prevents bacteria growth in mucilages and should not affect the polymers' efficiency. Table 4 illustrates the successful use of several preservatives at low concentrations.

A liquid blend of methyl or propylparaben and phenoxyethanol or diazolidinyl urea can also be used. Germaben® II, from Sutton Laboratories (a division of ISP), is a liquid blend of Germall® II (diazolidinyl urea), methylparaben, propylparaben and propylene glycol. This system is soluble at levels of 1.0% in both aqueous solutions and emulsions.

The advantage to using Germaben® II is that it is a liquid system solubilized in propylene glycol, will have a long shelf life stability and is completely compatible with the polymers. Germaben® II can be used without additional co-preservatives and is compatible with a wide variety of ingredients.

Certain preservatives have been shown to decrease the viscosity of 0.5% neutralized Carbopol® 934P NF polymer at high concentrations. For example, benzalkonium chloride at a concentration of 0.1% reduces the viscosity to nearly one-fourth of the original viscosity. Benzoic acid and sodium benzoate will reduce the original viscosity to approximately one-third of the original when used at too high a concentration. This data will generally apply to the other polymers.

Table 4
CARBOPOL® POLYMER PRESERVATIVE COMPATIBILITY

Preservative	Concentration (%)	Appearance	Compatibility
Benzalkonium Chloride	0.01	Cloudy	No
Sodium Benzoate	0.01	Clear	Yes
Sodium Benzoate	0.10	Cloudy	No
Methyl Paraben	0.18	Clear	Yes
Propyl Paraben	0.02		
Thiomersal	0.01	Clear	Yes
Thiomersal	0.10	Clear	Yes

NOTE: High concentrations of the preservative were used in order to obtain a clearly identifiable precipitate.

Reference: DRUG STANDARDS, Vol. 25, No. 5, p. 156

Packaging

Glass, plastic or polymer-lined containers are recommended for products which contain Carbopol® polymers, Pemulen™ polymeric emulsifiers or Noveon® polycarbophil. In general, use only aluminum tubes when a product formulation has a pH of approximately 6.5 or less. With other metallic materials, a pH of approximately 7.7 or greater is preferred.

General Housekeeping and Equipment Cleaning

Housekeeping

If dry polymers are spilled, sweep or vacuum up the majority of the product. We recommend that you flush away the remaining polymer with saline solution. Water is not recommended, as this will cause a slippery film to form on floors and equipment.

Equipment Cleaning

For equipment used in making mucilages, clean with warm water containing salt, any commercial detergent, and sufficient sodium hydroxide or ammonium hydroxide to achieve a pH of 11 or higher. (This should be a very small amount.) This solution should generally be sufficient to reduce the polymer to its thinnest, most soluble form to facilitate removal.

CAUTION: We suggest the use of goggles and rubber gloves due to the possibility of splattering. When preparing solutions using dry sodium hydroxide pellets, slowly add small amounts to avoid localized, violent boiling and splattering. Dry sodium hydroxide should not be added to hot water.

If the dispersion or mucilage has dried on the equipment, flush with water to reswell the polymer. The equipment may then be cleaned with water containing salt or detergent and the strong base.

A high pressure water lance may be required to remove the last traces in some cases.

IMPORTANT PRECAUTION: Avoid manufacturing in reactors where steam or hot water enters the reactor jacket just above the liquid level. This can cause deposits that are especially difficult to remove.

References:

1 Adams, Isobel and Davis, Stanley S., “Formulation and Sterilization of an Original Lubricant Gel Base in Carboxypolymethylene,” J. Pharm. Pharmacol., 25(8), 640-6, 1973.

2 Deshpande, S.G. and Shirolkar, Satish, “Sustained-Release Ophthalmic Formulations of Pilocarpine,” J. Pharm Pharmacol., 41 (3) 197-200, 1989.

3 Adams, Isobel, Davis, Stanley S. and Kershaw, R., “Formulation of a Sterile Surgical Lubricant,” J. Pharm Pharmacol., 24 (Supp.) 178P, 1972.