



Secundum Artem

Current & Practical Compounding
Information for the Pharmacist.

COMPOUNDING GELS

INTRODUCTION

Gels are semirigid systems in which the movement of the dispersing medium is restricted by an interlacing three-dimensional network of particles or solvated macromolecules of the dispersed phase. A high degree of physical or chemical cross-linking may be involved. The increased viscosity caused by the interlacing and consequential internal friction is responsible for the semisolid state. A gel may consist of twisted, matted strands often wound together by stronger types of van der Waals forces to form crystalline and amorphous regions throughout the system, e.g. tragacanth and carboxymethylcellulose.

Some gel systems are as clear as water in appearance and others are turbid, since the ingredients may not be completely molecularly dispersed or they may form aggregates, which disperse light. The concentration of the gelling agents is mostly less than 10%, usually in 0.5 to 2.0% range.

According to the USP, gels or jellies are semisolid systems consisting of suspensions made up of small inorganic particles or of large organic molecules interpenetrated by a liquid. Where the gel mass consists of a network of small discrete particles, the gel is classified as a two-phase system. In these two-phase systems, if the particle size of the dispersed phase is large, the product is referred to as a magma. Single-phase gels consist of organic macromolecules uniformly distributed throughout a liquid in such manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase gels may be made from synthetic macromolecules or from natural gums (mucilages). The continuous phase usually is aqueous but it also can be alcoholic or oleaginous.

For best consumer appeal, gels should have clarity and sparkle. Most gels are water washable, water soluble, water absorbing, greaseless, and act as absorption bases. The gel should also maintain its viscosity and character over a wide temperature range.

TERMINOLOGY RELATED TO GELS

Imbibition is the taking up of a certain amount of liquid without measurable increase in volume.

Swelling is the taking up of a liquid by a gel with an increase in volume. Only those liquids that solvate

a gel can cause swelling. The swelling of protein gels is influenced by pH and the presence of electrolytes.

Syneresis occurs when the interaction between particles of the dispersed phase becomes so great that on standing, the dispersing medium is squeezed out in droplets and the gel shrinks. Syneresis is a form of instability in aqueous and nonaqueous gels. Separation of a solvent phase is thought to occur because of the elastic contraction of the polymeric molecules: in the swelling process during gel formation the macromolecules involved become stretched and the elastic forces increase as swelling proceeds. At equilibrium, the restoring force of the macromolecules is balanced by the swelling forces, determined by the osmotic pressure. If the osmotic pressure decreases, e.g. on cooling, water may be squeezed out of the gel. The syneresis of an acidic gel from *Plantago albicans* seed gum may be decreased by the addition of electrolyte, glucose and sucrose, and by increasing the gum concentration. pH has a marked effect on the separation of water. At low pH marked syneresis occurs in carboxypolymethylene gels, possibly due to suppression of ionization of the carboxylic acid groups, loss of hydrating water, and the formation of intramolecular hydrogen bonds. This would reduce the attraction of the solvent for the macromolecule.

Thixotropy is a reversible gel-sol formation with no change in volume or temperature—a type of non-Newtonian flow.

A **xerogel** is formed when the liquid is removed from a gel and only the framework remains. Examples would include gelatin sheets, tragacanth ribbons and acacia tears.

APPLICATION OF GELS

Gels have a variety of applications in the administration of medications orally, topically, intranasally, vaginally and rectally. Gels can serve as ointment bases. Examples are Plastibase™ and mineral oil gels made with aluminum monostearate.

Nasal absorption of drugs from gels has been investigated extensively. Some reports of drugs administered by nasal methylcellulose gels, e.g. propranolol, show the drug is better absorbed than when administered orally.

CLASSIFICATIONS AND TYPES OF GELS

Table 1 is a general classification of gels, listing two classification schemes. The first scheme divides gels into "inorganic" and "organic".

Gels have a variety of applications in the administration of medications orally, topically, intranasally, vaginally and rectally.

Gels containing penetration enhancers are especially popular for administering anti-inflammatory and antinauseant medications.

TABLE 1
General Classification and Description of Gels

| Class | Description | Examples |
|-------------------|---|--|
| Inorganic Organic | Usually are two-phase systems Usually are single-phase systems | Aluminum hydroxide gel; Bentonite Magma <i>Carbopol</i> ; Tragacanth |
| Hydrogels | Contain water | Silica, bentonite, pectin, sodium alginate, methyl cellulose, alumina |
| Organogels | Hydrocarbon type | Petrolatum, Mineral Oil/Polyethylene gel <i>Plastibase</i> |
| | Animal/Vegetable fats | Lard, Cocoa butter |
| | Soap base greases | Aluminum stearate with heavy mineral oil gel |
| | Hydrophilic Organogels | <i>Carbowax</i> bases (PEG Ointment) |
| | Polar | |
| | Nonionic | |
| Hydrogels | Organic Hydrogels | Pectin paste, ragacanth jelly |
| | Natural & synthetic gums | Methylcellulose, Sodium CMC; <i>Pluronic F-127</i> —nonionic polyoxypropylene-polyoxyethylene surface active polymer (ave mw 11,500) |
| | Inorganic Hydrogels | Bentonite gel (10-25%), <i>Veegum</i> |

Inorganic Hydrogels are usually two-phase systems such as Aluminum Hydroxide Gel and Bentonite Magma. Bentonite also has been used as an ointment base in about 10-25% concentrations.

Organic Gels are usually single-phase systems and may include such gelling agents as carbomer and tragacanth and those that contain an organic liquid, such as *Plastibase*TM.

The second classification scheme divides gels into hydrogels and organogels with some additional subcategories.

Hydrogels include ingredients that are dispersible as colloids or are soluble in water and include organic hydrogels, natural and synthetic gums, and inorganic hydrogels. Examples are hydrophilic colloids such as silica, bentonite, tragacanth, pectin, sodium alginate, methylcellulose, sodium carboxymethylcellulose and alumina, which in high concentration, form semisolid gels. Sodium alginate has been used to produce gels that can be employed as ointment bases. In concentrations greater than 2.5% and in the presence of soluble calcium salts, a firm gel, stable between pH 5 and 10, is formed. Methylcellulose, hydroxyethylcellulose and sodium carboxymethylcellulose are among the commercially available cellulose products that may be used in ointments. They are available in various viscosity types, usually high, medium and low.

Organogels include the hydrocarbons, animal/vegetable fats, soap base greases and the hydrophilic organogels. Included in the hydrocarbon type is *Jelene*, or *Plastibase*, a combination of mineral oils and heavy hydrocarbon waxes with a molecular weight of about 1300. Petrolatum is a semisolid gel consisting of a liquid component together with a "protosubstance" and a crystalline waxy fraction. The crystalline fraction provides rigidity to the structure, while the protosubstance or gel former stabilizes the system and thickens the gel. The hydrophilic organogels, or polar organogels, include the polyethylene glycols of higher molecular weight, the *Carbowaxes*. They are soluble to about 75% in water and are completely washable. They gels look and feel like petrolatum. They are nonionic and stable.

Jellies are gels in which the structural coherent matrix contains a high proportion of liquid, usually water. They usually are formed by adding a thickening agent such as tragacanth or carboxymethyl cellulose to an aqueous solution of a drug substance. The resultant product is usually clear and of a uniform semisolid consistency. Jellies are subject to bacterial contamination and growth and thus most are preserved with antimicrobials. Jellies should be stored with tight closures since water may evaporate, drying out the product.

Some substances, such as acacia, are termed natural colloids because they are self-dispersing in a medium. Other materials that require special treatment for prompt dispersion are called artificial colloids. The special treatment may involve fine pulverization to colloidal size with a colloidal mill or a micropulverizer.

GELLING AGENTS

Examples of gelling agents include acacia, alginic acid, bentonite, carbomer, carboxymethylcellulose sodium, cetostearyl alcohol, colloidal silicon dioxide, ethylcellulose, gelatin, guar gum, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl

methylcellulose, magnesium aluminum silicate, maltodextrin, methylcellulose, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch, tragacanth and xanthan gum. A few of the more common ones will be discussed here.

Alginic acid is obtained from seaweed throughout the world and the prepared product is a tasteless, practically odorless, white to yellowish-white, fibrous powder. It is used in concentrations between 1 and 5% as a thickening agent in gels. It swells in water to about 200-300 times its own weight without dissolving. Crosslinking with increased viscosity occurs upon the addition of calcium salt, such as calcium citrate. Alginic acid can be dispersed in water vigorously stirred for approximately 30 minutes. Premixing with another powder or with a water-miscible liquid aids in the dispersion process.

Bentonite, a naturally occurring hydrated aluminum silicate, can be used to prepare gels by sprinkling the bentonite on the surface of hot water and allowing to stand 24 hours, stirring occasionally after the bentonite has become wetted. Glycerin or a similar liquid can be used to pre-wet the bentonite prior to mixing with water. Aqueous bentonite suspensions retain their viscosity above pH 6 but are precipitated by acids. Alkaline materials, such as magnesium oxide, increase gel formation. Alcohol in significant amounts can precipitate bentonite and, since bentonite is anionic, the antimicrobial efficacy of cationic preservatives may be reduced. Bentonite exhibits thixotropy: it may form a semirigid gel which reverts to a sol when agitated. The sol will re-form to a gel upon standing.

Carbomer (*Carbopol*[®]) resins were first described in the literature in 1955 and are currently ingredients in a variety of pharmaceutical dosage systems, including controlled release tablets, oral suspensions and topical gels. The USP-NF, British Pharmacopoeia, United States Adopted Names Council (USAN) and Cosmetic, Toilettries and Fragrance Association (CTFA) have adopted the generic name "carbomer" for the *Carbopol* family of resins. Carbomer resins are high molecular weight, allylpentaerythritol-crosslinked, acrylic acid-based polymers, modified with C10-C30 alkyl acrylates. They are fluffy, white, dry powders with large bulk densities, 2% maximum moisture, pK_a of 6.0 ± 0.5 . The pH of 0.5% and 1.0% aqueous dispersions are 2.7-3.5 and 2.5-3.0, respectively. There are many carbomer resins, with viscosity ranges from 0 to 80,000 cps. The resins commonly used in pharmacy are listed in Table 2.

Carbomers 910, 934, 934P, 940 and 1342 are official in USP 23/NF 18. Carbomer 910 is effective at very low concentrations when low viscosity is desired and is frequently used for producing stable suspensions. It is the least ion sensitive of these resins. Carbomer 934 is highly effective in thick formulations such as viscous gels. The two alternative resins, numbers 2984 and 5984, are polymerized in ethyl acetate/cyclohexane in place of benzene. Carbomer 934P is similar to 934 but is intended for oral and mucosal contact applications and is the most widely used in the pharmaceutical industry. In addition to thickening, suspending and emulsifying in both oral and topical formulations, the 934 polymer is also used to provide sustained-release properties in both the stomach and intestinal tract for commercial products. Carbomer 940, or 980, its cosolvent alternative, forms sparkling clear aqueous or hydroalcoholic gels. These are the most efficient of all the *Carbopol* resins and have very good non-drip properties. Carbomer 1342 and its cosolvent analogue, 1382, provide pseudoplastic rheology which is very effective in preparing pourable suspensions and stable emulsions and makes them especially good for preparations containing dissolved salts.

Carbopol 974P NF differs from *Carbopol* 934P NF in that ethylacetate is used instead of benzene in its preparation. *Carbopols* 980 NF and ETD 2001 differ from *Carbopol* 940 NF in that cosolvents are used in place of benzene for their preparation. Such is also the case with *Carbopols* 981 NF and ETD 2050 vs *Carbopol* 941 NF.

The addition of alcohol to prepared carbomer gels may decrease their viscosity and clarity. To overcome the loss of viscosity, an increase in the concentration of carbomer may be required; the amount may vary depending upon the pH of the product. When working with a preparation at pH 5.5 and going from 0% to 50% alcohol, an increase of 0.5% carbomer is required; similarly, an increase of 0.35% carbomer is required at pH 8.2 when going from 20% to 40% alcohol. Also, gel viscosity is dependent upon the presence of electrolytes and the pH. Generally, a maximum of 3% electrolytes can be added before a rubbery mass forms. Overneutralization also will result in decreased viscosity that cannot be reversed by the addition of acid. Maximum

viscosity and clarity occur at pH 7, but acceptable viscosity and clarity begins at pH 4.5 to 5.0 and extends to a pH of 11.

Crosslinked carbomer resins may swell in water up to 1000 times their original volume to form gels, when exposed to a pH environment above 4.0-6.0. Since the pK_a of these polymers is about 6.0, the carboxylate groups on the molecules ionize, resulting in repulsion between the negative particles of the polymer backbone which contributes to the swelling of the polymer. It is difficult to determine the molecular weight of the carbomers and while the average molecular weights of the polymerized resins are in the order of about 500,000, the actual molecular weight of the crosslinked resin is in the billions.

Carbomer resins are very hygroscopic and should be stored in tight containers, away from moisture and extreme temperatures. Moisture does not affect the efficiency of the resins, but high levels make them more difficult to disperse and weigh accurately. Autoclaving appears to have no effect on the viscosity or pH of the prepared gels. Aqueous dispersions of carbomer that have not been neutralized can be stored as stock solutions at concentrations up to 5%.

Carbomer resin powders do not support bacteria, mold or fungus while in powder form. When present in aqueous systems, however, mold and some bacteria can grow. Table 3 lists commonly used preservatives and their compatibility with carbomer resins. The addition of 0.1% methylparaben or propylparaben as preservatives is acceptable and does not affect the resins' efficiency. Carbomer resins are anionic and may decrease the efficiency of some of the cationic preservative agents.

Glass, plastic or resin-lined containers are recommended for storage of carbomer products. Aluminum tubes should be used only when a product as a pH of less than about 6.5. With other metallic materials, a pH of about 7.7 or greater is preferred. Cleaning up equipment after preparing carbomer products is easier using warm water containing salt, a commercial detergent and sufficient sodium hydroxide or ammonium hydroxide to a pH of 11 or higher. If the material has dried, soak in water before using this cleaning solution.

Preparation of aqueous dispersions of carbomer resins: Carbomer preparations are primarily used in aqueous systems, although other liquids can be used. In water, a single particle of carbomer will wet very rapidly but, like many other powders, carbomer polymers tend to form clumps of particles when haphazardly dispersed in polar solvents. As the surfaces of these clumps solvate, a layer is formed which prevents rapid wetting of the interior of the clumps. When this occurs, the slow diffusion of solvent through this solvated layer determines the mixing or hydration time. To achieve fastest dispersion of the carbomer, it is wise to take advantage of the very small particle size of the carbomer powder by adding it very slowly into the vortex of the liquid as it is stirred very rapidly. Almost any device, like a simple sieve, that can sprinkle the powder on the

TABLE 2
Typical Properties of Selected Carbopol Pharmaceutical Resins

| Product | Viscosity* | Properties and Uses |
|-------------------|---------------|---|
| Carbopol 907 | 0-3,000 | Very water soluble. Good lubricity at low viscosity. A "linear" polymer that is not cross-linked. |
| Carbopol 910NF | 3,000-7,000 | Effective in low concentrations. Good ion tolerance. |
| Carbopol 934 NF | 30,500-39,400 | Good stability at high viscosity. Good for thick formulations, such as medium to high viscosity gels, emulsions and suspensions. |
| Carbopol 2984 | 45,000-80,000 | |
| Carbopol 5984 | 25,000-45,000 | |
| Carbopol 934P NF | 29,400-39,400 | Good for zero-order release of products, such as oral and mucoadhesive applications. Excellent for transdermals and topicals. |
| Carbopol 974P NF | 29,400-39,400 | |
| Carbopol 940 NF | 40,000-60,000 | Excellent thickening efficiency at high viscosities and very good clarity. Produces sparkling clear aqueous or hydroalcoholic topical gels. |
| Carbopol 980 NF | 40,000-60,000 | |
| Carbopol ETD 2001 | 45,000-65,000 | |
| Carbopol 941 NF | 4,000-11,000 | Produces low viscosity sparkling clear gels. Good stabilizer for emulsions. Effective in moderately ionic systems. More efficient than 934 and 940 at low to moderate concentrations. |
| Carbopol 981 NF | 4,000-11,000 | |
| Carbopol ETD 2050 | 3,000-15,000 | |

*Typical viscosities of a 0.5% solutions, pH 7.5, except for Carbopol 907 which was a 4.0% solution.

rapidly stirred liquid is useful. A metallic screen will help by reducing the particle size and diffusing static charge buildup. Generally, the higher the agitation rate of the liquid, the better, but extremely high shear mixers should not be used as they can break down the polymers and reduce gel viscosity. Propeller or turbine type mixers running about 800-1200 rpm work very well for this purpose. Variable speed mixers are especially desirable to reduce vortexing when the mixture begins to thicken and will help minimize the incorporation of air into the gel. The propeller should be located very close to the bottom of the mixing vessel. The goal is to prevent clumping by slowly sprinkling the very small particle size powder over the rapidly agitated water. Once the powder is incorporated, continued stirring for 10-15 minutes at reduced speed is recommended to avoid excess air entrapment.

A neutralizer is added to thicken the gel after the carbomer is dispersed. Sodium hydroxide or potassium hydroxide can be used in carbomer dispersions containing less than 20% alcohol. Triethanolamine will neutralize carbomer resins containing up to 50% ethanol. Other neutralizer agents include sodium carbonate, ammonia and borax.

Air bubbles incorporated into the gel should be removed prior to adding the neutralizing agent, otherwise the air will remain entrapped in the product. Air bubbles can be removed using an ultrasonic unit or by allowing the product to stand. It may be necessary to acidify the gel, remove the air and neutralize it again. For this, hydrochloric and phosphoric acid should be used in an amount equal to 0.5% based on the weight of the carbomer, NOT the total weight of the product. These acids will not produce significant salt levels upon neutralization that might occur with other acids, e.g. citric or lactic.

Carboxymethylcellulose in concentrations of 4 to 6% of the medium viscosity grades can be used to produce gels; glycerin may be added to prevent drying. Precipitation can occur at pH values less than 2; it is most stable at pH levels between 2 and 10, with maximum stability at pH 7 to 9. It is incompatible with ethanol.

Carboxymethylcellulose Sodium (CMC Sodium): Sodium carboxymethylcellulose is soluble in water at all temperatures. The sodi-

um salt of CMC can be dispersed with high shear in cold water before the particles can hydrate and swell to sticky gel grains that agglomerate into lumps. Once the powder is well dispersed, the solution is heated with moderate shear to about 60°C for fastest dissolution. These dispersions are sensitive to pH changes because of the carboxylate group. The viscosity of the product is decreased markedly below pH 5 or above pH 10.

Colloidal silicon dioxide can be used to prepare transparent gels when used with other ingredients of similar refractive index. Colloidal silicon adsorbs large quantities of water without liquefying. The viscosity is largely dependent of temperature. Changes in pH may affect the viscosity: it is most effective at pH values up to about 7.5. At higher levels, the viscosity-increasing properties are reduced at pH greater than 10.7 and the silicon dioxide dissolves to form silicates with no viscosity-increasing properties. Colloidal silicon dioxide (fumed silica) will form gels when combined with 1-dodecanol and n-dodecane. These are prepared by adding the silica to the vehicle, sonicating for about one minute to obtain a uniform dispersion, sealing and storing at about 40°C overnight to complete gelation. This gel is more hydrophobic in nature than the others.

Gelatin: Gels are prepared from gelatin by dispersing the gelatin in hot water followed by cooling. As an alternative, moisten the gelatin with about 3 to 5 parts of an organic liquid that will not swell the polymer, such as ethyl alcohol or propylene glycol, add the hot water and cool.

Magnesium aluminum silicate, Veegum, in concentrations of about 10%, forms firm, thixotropic gels. The material is inert and has few incompatibilities but is best used above pH 3.5. It may bind to some drugs and limit their availability.

Methylcellulose is a long-chain substituted cellulose that can be used to form gels in concentrations up to about 5%. Since methylcellulose hydrates slowly in hot water, the powder is dispersed with high shear in about 1/3 of the required amount of water at 80-90°C. Once the powder is finely dispersed, the rest of the water is added cold or as ice with moderate stirring to cause prompt dissolution. Anhydrous alcohol or propylene glycol may be used to help pre-wet the powders. Maximum

TABLE 3
Compatibility of Selected Preservatives with Carbomer Gels

| Preservative | Conc. | Appearance | Compatible |
|-----------------------|-------|------------|------------|
| Benzalkonium Chloride | 0.01% | Clear | Yes |
| | 0.1% | Cloudy | No |
| Sodium Benzoate | 0.01% | Clear | Yes |
| | 0.1% | Cloudy | No |
| Methylparaben | 0.18% | Clear | Yes |
| Propylparaben | 0.05% | | |
| Thiomersal | 0.01% | Clear | Yes |
| | 0.1% | Clear | Yes |

clarity, fullest hydration and highest viscosity will be obtained if the gel is cooled to 0-10°C for about an hour. A preservative should be added. A 2% solution of methylcellulose 4000 has a gel point about 50°C. High concentrations of electrolytes will salt out the macromolecules and increase their viscosity, ultimately precipitating the polymer.

Plastibase/Jelene is a 5% low-molecular-weight polyethylene/95% mineral oil mixture. The polymer is soluble in mineral oil above 90°C, close to its melting point. When cooled below 90°C, the polymer precipitates and causes gelation. The mineral oil is immobilized in the network of entangled and adhering insoluble polyethylene chains which probably even associate into small crystalline regions. This gel can be heated to about 60°C without substantial loss of consistency.

Poloxamer, or Pluronic, gels are made from selected forms of polyoxyethylene-polyoxypropylene copolymers in concentrations ranging from 15 to 50%. Poloxamers generally are white, waxy, free-flowing granules that are practically odorless and tasteless. Aqueous solutions of poloxamers are stable in the presence of acids, alkalis and metal ions. However, they do support mold growth and should be preserved. Commonly used poloxamers include the 124 (L-44 grade), 188 (F-68 grade), 237 (F-87 grade), 338 (F-108 grade) and 407 (F-127 grade) types, which are freely soluble in water. The "F" designation refers to the flake form of the product. The trade name "Pluronic" is used in the US by BASF Corp for pharmaceutical and industrial grade poloxamers. Pluronic F-127 has good solubilizing capacity and optical properties, low toxicity and is a good medium for topical drug delivery systems.

Polyvinyl alcohol (PVA) is used at concentrations of about 2.5% in the preparation of various jellies which dry rapidly when applied to the skin. Borax is a good agent that will gel PVA solutions. For best results, disperse PVA in cold water, then add hot water. It is less soluble in the cold water.

Povidone, in the higher molecular weight forms, can be used to prepare gels in concentrations up to about 10%. It has the advantage of being compatible in solution with a wide range of inorganic salts, natural and synthetic resins and other chemicals. It has also been used to increase the solubility of a number of poorly soluble drugs.

Propylene glycol alginate is used as a gelling agent in concentrations of 1 to 5%, depending upon the specific application. The preparations are most stable at a pH of 3-6 and should contain a preservative.

Sodium alginate can be used to produce gels in concentrations up to 10%. Aqueous preparations are most stable between pH 4-10; below pH 3, alginic acid is precipitated. Sodium alginate gels for external use should be preserved with, for example, 0.1% chloroxylenol or the parabens. If the preparation is acidic, benzoic acid may be used. High concentrations will result in increased viscosity up to a point where the sodium alginate is salted out; it occurs at about 4% with sodium chloride.

Tragacanth gum has been used to prepare gels that are most stable for pH 4-8. These gels must be preserved with either 0.1% benzoic acid or sodium benzoate or a combination of 0.17% methylparaben and 0.03% propylparaben. These gels may be sterilized by autoclaving. Since powdered tragacanth gum tends to form lumps when added to water, aqueous dispersions are pre-

pared by adding the powder to vigorously stirred water. Also, the use of ethanol, glycerin or propylene glycol to pre-wet the tragacanth is very effective. If other powders are to be incorporated into the gel, they can be mixed with the tragacanth in the dry state.

EXAMPLE GEL FORMATIONS

Starch Glycerite

| | |
|----------------|-------|
| Starch | 100 g |
| Benzoic Acid | 2 g |
| Purified Water | 200 g |
| Glycerin | 700 g |

The starch and benzoic acid are rubbed in the water to a smooth mixture. The glycerin is added and mixed. The mixture is heated to 140°C with constant, gentle agitation until a translucent mass forms. The heat ruptures the starch grains and permits the water to reach and hydrate the linear and branched starch molecules which trap the dispersion medium in the interstices to form a gel.

Bentonite Magma

| | |
|-------------------|--------|
| Bentonite | 50 g |
| Purified Water qs | 100 mL |

Bentonite is sprinkled on 800 mL of hot purified water and allowed to hydrate for 24 hours, with occasional stirring. Additional Purified Water is added to make 1000 mL. If a mechanical blender is used, approximately one-half of the water is placed in the blender, and the bentonite is added while the blender is in operation. Purified water is then added to make the volume of 1000 mL and the blender is operated for 10 minutes.

Liquid-solid Emulsion Gel

| | |
|---------------------------|-------|
| Gelatin Solution: | |
| Gelatin, 200 bloom | 8 g |
| Phosphate Buffer, pH 7 qs | 40 mL |
| Gel Product: | |
| Gelatin Solution | 40 mL |
| Long chain alcohol | 10 g |

Liquid-solid emulsion gels can be prepared from gelatin and a selection of an alcohol from a homologous series, e.g., octanol, nonanol, decanol, undecanol or dodecanol. The initial step involves the formulation of an aqueous gelatin base such as 20% (w/w) 200 bloom gelatin in phosphate buffer (pH 7.0) prepared by melting (at 60°C) the gelatin/water mixture which has previously matured for about one hour at room temperature. The molten gel is left at 60°C for a further two hours to allow escape of air bubbles. Next, 10 g of the long-chain alcohol, preheated to 60°C, is added to 40 g of the heated molten aqueous gel and stirred at high speed for about two minutes. The drug can be previously added to the appropriate phase. The molten mixture is poured onto a plate or between two plates to set or "cast". Circular or other shaped portions of the gel can be cut out and applied to the skin area to release the enclosed drug.

Liqua-Gel™ (Paddock) is a non-greasy, water soluble liquid lubricating gel that can be used to dissolve or suspend a variety of topically-applied dermatological agents. It contains purified water, propylene glycol, glycerin, hydroxypropyl methylcellulose, and potassium sorbate. Sodium phosphate and boric acid are used to buffer the gel to a pH of about 5.0. Diazolidinyl urea, methylparaben and propylparaben are included as preservatives. It is a clear, colorless gel with a faint characteristic odor which is very viscous at 25°C.

Lubricating Jelly Formula:

| | |
|---------------------------|--------|
| Methylcellulose, 4000 cps | 0.8% |
| Carbopol 934 | 0.24% |
| Propylene glycol | 16.7% |
| Methylparaben | 0.015% |
| Sodium hydroxide, qsad | pH 7 |
| Purified water, qs ad | 100% |

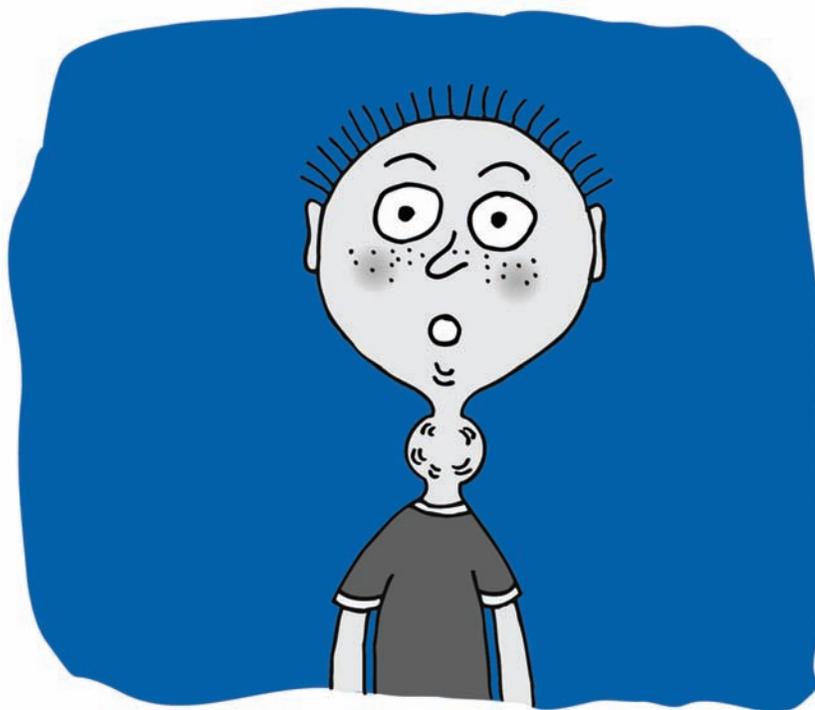
Disperse the methylcellulose in 40 mL of hot (80-90°C) water. Chill overnight in a refrigerator to effect solution. Disperse the Carbopol 934 in 20 mL water. Adjust the pH of the dispersion to 7.0 by adding sufficient 1% sodium hydroxide solution (about 12

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mL is required) and bring the volume to 40 mL with purified water. Dissolve the methylparaben in the propylene glycol. Mix the methylcellulose, Carbopol 934 and propylene glycol fractions, using caution to avoid incorporating air.

Clear Aqueous Gel with Dimethicone

| | |
|----------------------|-------|
| Water | 59.8% |
| Carbomer 934 | 0.5% |
| Triethanolamine | 1.2 |
| Glycerin | 34.2 |
| Propylene Glycol | 2.0 |
| Dimethicone copolyol | 2.3 |

Prepare the carbomer gel, add the other ingredients, and mix well. Dimethicone copolyol is included to reduce the sticky feel associated with glycerin.

Poloxamer Gel Base

| | |
|--------------------------|-----------|
| Pluronic F-127, NF | 20 g-50 g |
| Purified Water/Buffer qs | 100 mL |

PRESERVATION OF GELS

Many gels will not promote bacterial or mold growth nor will they prevent it. Consequently, they need to be autoclaved or contain preservatives. Table 3 lists a number of preservatives and concentrations that have been used in the preparation of gels.

GENERAL DISCUSSION

In gel preparation, the powdered polymers, when added to water, may form temporary gels that slow the process of dissolution. As water diffuses into these loose clumps of powder, their exteriors frequently turn into clumps of solvated particles encasing dry powder. The blobs of gel dissolve very slowly because of their high viscosity and low diffusion coefficient of the macromolecules.

As a hot, colloidal dispersion of gelatin cools, the gelatin macromolecules lose kinetic energy. With reduced kinetic energy, or thermal agitation, the gelatin macromolecules are

associated through dipole-dipole interaction into elongated or threadlike aggregates. The size of these association chains increases to the extent that the dispersing medium is held in the interstices among the interlacing network of gelatin macromolecules, and the viscosity increases to that of a semisolid. Gums, such as agar, Irish moss, algin, pectin and tragacanth, form gels by the same mechanism as gelatin.

Polymer solutions tend to cast gels because the solute consists of long, flexible chains of molecular thickness that tend to become entangled, attract each other by secondary valency forces, and even crystallize. Crosslinking of dissolved polymer molecules also causes the solutions to gel. The reactions produce permanent gels, held together by primary valence forces. Secondary valence forces are responsible for reversible gel formation. For example, gelatin will form a gel when lowered to about 30°C, the gel melting point, but aqueous methylcellulose solutions will gel when heated above about 50°C because the polymer is less soluble in hot water and precipitates. Lower temperatures, higher concentrations and higher molecular weights promote gelation and produce stronger gels. The reversible gelation of gelatin will occur at about 25°C for 10% solutions, 30°C for 20% solutions and about 32°C for 30% solutions. Gelation is rarely observed for gelatin above 34°C and, regardless of concentration, gelatin solutions do not gel at 37°C. The gelation temperature or gel point of gelatin is highest at the isoelectric point. Water soluble polymers have the property of thermal gelation, i.e., they gel on heating, whereas natural gums gel on cooling. Thermal gelation is reversed on cooling.

Inorganic salts will compete with the water present in a gel and cause gelation to occur at lower concentrations. This is usually a reversible process and, upon the addition of water, the gels will re-form. Alcohol may cause precipitation or gelation because alcohol is a

nonsolvent or precipitant, lowering the dielectric constant of the medium and tending to dehydrate the hydrophilic solute. Alcohol lowers the concentrations at which electrolytes salt out hydrophilic colloids. Phase separation by adding alcohol may cause coacervation.

Aqueous polymer solutions, especially of cellulose derivatives, are stored for approximately 48 hours after dissolution to promote full hydration, maximum viscosity and clarity. If salts are to be added, they are incorporated at this point rather than by dissolving in the water prior to adding the polymer; otherwise the solutions may not reach their full viscosity and clarity.

SUMMARY

Gels provide the pharmacist with an excellent drug delivery system for different routes of administration and are compatible with many different substances. Gels containing penetration enhancers are especially popular for administering anti-inflammatory and antinauseant medications. They are relatively easy to prepare and are very efficacious.



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