

Section 14

Avicel® RC/CL, Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF, BP

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Table of Contents

Avicel RC/CL, Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF, BP.....	1
Table of Contents.....	1
Introduction.....	3
Disperse Systems.....	3
Guidelines for Suspension Formulation.....	3
Particle Size.....	4
Wetting.....	4
Viscosity.....	4
Flocculation and Deflocculation.....	5
Characteristics of Commonly Used Suspending Agents.....	6
Avicel RC and CL, Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF, BP.....	6
Carrageenan, NF.....	7
Algins and Alginate.....	7
Other Commonly Used Suspending Agents.....	8
Other Suspension Excipients.....	9
Avicel RC and Microcrystalline Cellulose, NF.....	11
Introduction.....	11
Structure and Properties.....	11
Chemical and Physical Specifications.....	12
Microbiological Specifications.....	13
Effect of pH and Temperature on the Viscosity of Colloidal Avicel.....	13
Effect of Other Hydrocolloids on Viscosity.....	13
Advantages of Formulating Disperse Systems with Colloidal Avicel.....	14
Preparation of Colloidal Avicel.....	15
Dry Mix Dispersion.....	15
Liquid Mix Dispersion.....	15
Rheology of Avicel Dispersions.....	15
Viscoelastic Properties.....	15
Pharmaceutical Applications.....	21
Example of Use of Colloidal Avicel as a Suspending Agent.....	21
Example of an Analgesic Oral Suspension Using Colloidal Avicel RC-591.....	21
Example of an Antacid Suspension Using Colloidal Avicel RC-591.....	22

Example of Use of Colloidal Avicel® as an Oil/Water Emulsifier.....	22
Example of Use of Colloidal Avicel as a Thickener, Emulsion Stabilizer and Opacifier for Pharmaceutical Creams and Gels	23
Example of Use of Colloidal Avicel as an Oil/Water Emulsifier for Cosmetic Lotions.....	23
Example of Use of Colloidal Avicel as a Suspending Agent for Reconstitutable Suspensions	24
Suspension Powder for Reconstitution	24
Example of a Drug (Active) Powder Formualtion for Reconstitution.....	24
Equipment and Suppliers.....	25
Mixers.....	25
Mills	25
Deaerator-Defoamer.....	26
Micronizer-Pulverizer.....	26
Viscometers.....	26
Rheometers.....	26
Special Equipment.....	26
Particle Size Analyzer.....	26
References	27
Acknowledgement	27

Introduction

Disperse Systems

The science of suspensions and dispersions is fundamental in the field of food, drugs and cosmetics where the drug or actives are neither soluble nor precipitated. Disperse systems are classified broadly as systems in which one substance, the dispersed phase, is distributed throughout another substance, the continuous phase. Examples of disperse systems are suspensions, emulsions, creams, ointments, aerosols, pastes, etc. These dosage forms can be administered by oral, ophthalmic, intranasal, dermatological or by parental routes of administration.

One of the most important challenges of a disperse system is to have the dispersed phase remain dispersed in the dispersion medium. Thus, the control of sedimentation is of primary importance in maintaining the integrity of a disperse system. The most practical method of controlling sedimentation is by the use of viscosity building agents. Various substances, such as sugars and polyols, have been used over the years to build viscosity in aqueous drug systems. However, they needed to be used in large amounts to achieve the required viscosity and these solutions are usually Newtonian in nature. Polymers, on the other hand, are needed in small amounts to meet the viscosity requirements and have the added advantage of being non-Newtonian in nature, i.e., they have a yield point or are thixotropic. These properties are advantageous in overcoming sedimentation and are easier to process. Thus, polymers are used in suspensions, emulsions and other dispersions mainly to control or minimize sedimentation. Various substances such as natural, synthetic and semi-synthetic polymers, have been used over the years to build viscosity in aqueous drug systems.

The objective of this chapter is to highlight the features of colloidal Avicel®, a polymer that is a combination of microcrystalline cellulose and

sodium carboxymethylcellulose as a suspending agent/thickener, etc. in oral suspensions, creams and lotions. The bulk of the information presented is from reviews of FMC literature, brochures technical reports, Kennon and Storz (1), Nash (2), Boylan (3), Macek (4) and Haines and Martin (5).

Guidelines for Formulation of a Suspension

Oral aqueous suspensions constitute the largest portion of suspensions marketed in the pharmaceutical industry. Drugs are dispensed as suspensions for various reasons, the primary one being poor aqueous solubility. Suspensions also improve the taste since less of the drug is in solution. In addition, greater chemical stability is achieved since the drug is not in solution and, in some cases, bioavailability is enhanced. This is of particular importance to children and geriatric patients. Suspensions also offer advantages for those patients who have difficulty swallowing tablets or capsules.

A suspension can be defined as a two-phase system consisting of a finely divided solid dispersed in a solid, liquid or gas. Oral suspensions usually have the active drug, which is insoluble or poorly water soluble, dispersed in water (liquid), which is the continuous phase.

The main objective in suspension formulation is to ensure that the dispersed particles do not settle on standing, or if the particles do settle, the particles should be easily dispersed on shaking and should produce a uniform dose on administration. The suspension should also be pleasant tasting, and be stable physically and chemically. Since the specific properties of various suspended drugs differ, no single procedure will always produce a successful suspension product. However, certain principles are affirmed to be fundamental in all successful formulations.

They are:

1. Particle size of the suspended drug
2. Wetting/surfactants
3. Viscosity
4. Flocculation/deflocculation

Particle Size

A major goal of a suspension formulation is to slow or prevent sedimentation of the drug particle to avoid a non-uniform distribution of the drug. The particle size of the drug plays a significant part in determining formulation elegance, rate of settling, absence of caking, rate of drug release and final stability of the product.

Particle size of the suspended drug is a critical parameter in a suspension formulation. According to Stokes' Law, the rate of settling of the insoluble drug is directly proportional to the square of the particle diameter.

$$V = d^2 \frac{(\rho_1 - \rho_2)g}{18\eta}$$

where V = sedimentation rate of a particle
 d = mean particle diameter
 ρ_1 = particle density
 ρ_2 = density of the dispersion medium
 g = acceleration due to gravity
 η = viscosity of the dispersion medium

Therefore, smaller particles will settle more slowly than larger particles. The majority of pharmaceutical suspensions have drug particles in the range of 1-50 microns in diameter. If particles are less than about 3 microns and their density does not differ by more than 20% from that of the dispersion vehicle, the particles will remain suspended due to Brownian motion. Therefore, reduction of particle size has a beneficial effect upon the physical stability of the suspension. In practice, however, there is a limit to particle size reduction because, after reaching a certain particle size, further reduction can be expensive due to the time and equipment involved. Moreover, movement of small particles due to Brownian motion often produces particle

aggregation, followed by settling of the aggregates and frequently caking. Redispersion of the drug after caking is often impossible.

Wetting

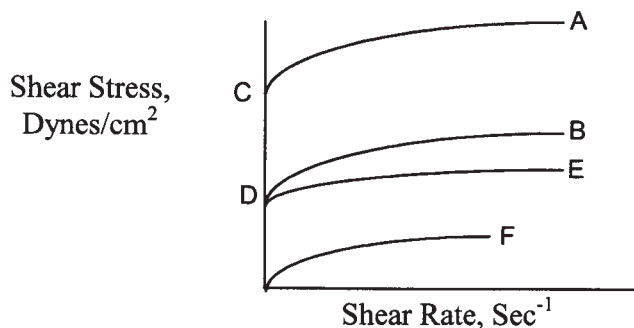
Since most drugs in a suspension are hydrophobic, they float on the surface of the dispersion medium due to poor wetting. A wetting agent helps disperse the poorly soluble drug in the dispersion medium. Wetting of the solid phase by the suspended liquid is necessary to produce a good suspension. Low concentrations of surfactants are commonly used as wetting agents to aid dispersion of the particles in the suspension vehicle. However, excess amounts of surfactants may impart foaming or an unpleasant taste.

Viscosity

Stokes' Law describes the inverse relationship between viscosity of the dispersion medium and rate of particle settling. An increase in viscosity produces a slower sedimentation rate and increases physical stability. The most common method of increasing viscosity is by adding a suspending agent. Suspending agents with high viscosity do not always prevent sedimentation. Meyer and Cohen in 1959 (6) suggested that yield value is an important mechanism to keep a particle suspended. The yield value for a suspension must balance or exceed the force of gravity on the settling particles. This mechanism is gaining recognition and was reviewed by Hem and White. (7) The yield value of a dispersion medium can be determined experimentally by using a rotational viscometer and plotting shear stress (dyne/cm²) as a function of shear rate (sec⁻¹). The curve as shown in the Figure 1 does not pass through the origin, but intersects the axis of shear stress as in curves A and B. The intersection at C or D is the yield value. The slope of the curve is the apparent viscosity, which varies with shear rate, and therefore, the entire curve is required to describe the viscosity of these systems. Additional information on the

rheological properties of suspending agents and suspensions will be covered in this chapter.

Figure 1: Yield Value



Reducing the difference in density between the particles and the dispersion medium can also lower the rate of sedimentation. However, water is usually the dispersion medium, and since added ingredients do not change its density to a great extent, i.e., this has not been a particularly successful method. Therefore, particle size and viscosity have been the properties that most formulators focus on to obtaining an optimum suspension formulation.

Flocculation and Deflocculation

The basic concern in developing a suitable suspension is to control adequately the rate of settling and ease of redispersion, as well as to prevent caking of the particles as a dense mass at the bottom of the container. Particle size reduction produces slower, more uniform rates of settling. Frequently, caking cannot be prevented by adding a suspending agent or reducing the particle size; in fact, these measures sometimes aggravate the problem of caking. The best approach to this problem is to achieve a controlled flocculation of the particles, where they appear as floccules or like tufts of wool with a loose fibrous structure. When such a system settles, two distinct layers form, a clear particle-free supernatant and a sediment. The particles are held together by weak van der Waals forces. Maintaining a drug in suspension with little or no separation results in a more elegant and permanent suspension.

One such process is flocculation. Flocculation is a process in which particles are allowed to come together and form loose agglomerates. The chief advantage of a flocculated suspension is in its redispersibility. The goal of controlled flocculation is to maintain reasonably sized aggregates or flocs. In this way, redispersibility and sedimentation rate are kept in balance.

Flocculation can be achieved by various means. One of the methods is based on electric charge. Charged particles of the same charge will repel each other and thus resist forming flocs. Reduction of particle repulsion permits the particles to get close enough to allow the attractive forces to dominate.

The use of polymers is another method to achieve flocculation. Polymers containing chemical groups that interact with the suspended particles can be added to the continuous phase. Polymer segments can then attach to individual particles to form a polymer-particle complex. As the polymer connects across two or more particles a floc is formed. Other ingredients such as protective colloids (e.g., carboxymethylcellulose), wetting agents such as polysorbates, and electrolytes such as sodium chloride can also act as flocculating agents.

The final suspension product should be evaluated for its stability in the final package after manufacture, at various temperature conditions for a given period of time to ensure physical and chemical stability. Several physical tests are employed to determine the stability of a suspension. The list below shows the various tests a formulator would conduct to determine the stability of a suspension, Ofner, Schnaare and Schwartz (8).

Summary of Physical Tests for Suspension Stability; The Stability of Actives is Assumed

1. Appearance
2. Sedimentation rate
3. Sedimentation volume
4. Redispersibility
5. Zeta potential measurement
6. Dissolution
7. Rheological measurements
8. Stress tests-Vibration-Transportation
9. pH
10. Specific gravity
11. Odor
12. Taste
13. Color-Light
14. Microbiological examination
15. Freeze-thaw cycles
16. Compatibility with container
17. Compatibility with cap liner
18. Torque
19. Microscopic-Photomicrographs
20. Crystal size
21. Uniform drug distribution
22. Toxicity
23. Use tests

Characteristics of Commonly Used Suspending Agents

One of the most important factors in formulating a suspension is selection of the proper suspending agent. It is the suspending agent that is used primarily to control or minimize sedimentation. The formulator must select the suspending agent best suited to support the drug in either a flocculated or deflocculated state.

The following listing of suspending agents and protective hydrocolloids most commonly used in the pharmaceutical industry provides pertinent functional, rheological and incompatibility characteristics, and is designed to give the formulator a quick overview. The many grades available for some particular hydrocolloids are not dealt with in this overview, and the formulator is referred to company literature, Idson and Scheer (9).

Avicel® RC and CL Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF; Dispersible Cellulose, BP

FMC BioPolymer
1735 Market Street
Philadelphia, PA 19103

Derivation

Colloidal Avicel is a modified microcrystalline cellulose product. It has a composition, on a dry basis, of 82-89% microcrystalline cellulose and 11-18% sodium carboxymethylcellulose, medium viscosity.

Water Dispersibility

Colloidal Avicel is a water-dispersible anionic hydrocolloid.

pH Stability

Colloidal Avicel is stable over a pH range of 3.5-11.

Rheology

1. Colloidal Avicel systems form thixotropic gels which have a finite yield value at low concentrations.
2. These gels are shear thinning and upon resting the yield value increases to re-establish the equilibrium value. Colloidal Avicel is a stable product. Its viscosity is unaffected by temperature.

Incompatibilities

Colloidal Avicel being anionic by nature flocculates when small amounts of electrolyte, cationic polymers or surfactants are added.

Advantages

The advantages and uses of Avicel RC and CL will be discussed in detail in the following sections of this chapter.

Carrageenan, NF

FMC BioPolymer
1735 Market Street
Philadelphia, PA 19103

Derivation

Carrageenan is an anaerobic polysaccharide derived from seaweed. Different types of Carrageenan have been identified such as kappa, iota and lambda Carrageenan. (See Chapter on carrageenan in Problem Solver).

Water Dispersibility

All forms of carrageenan are soluble in hot water, but only the sodium salts of iota carrageenan and lambda carrageenan are soluble in cold water. In the presence of certain ions such as calcium or potassium, gels of great strength are formed with definite melting temperatures.

pH Stability

Carrageenans are stable over a pH range of 4-10. They are least stable under either strongly acidic or alkaline solutions. Carrageenan solutions generally have a pH of 6-10.

Rheology

1. Carrageenans, especially the iota and kappa types, form thixotropic gels with a yield point at low concentrations.
2. A reversible loss in viscosity is seen at higher temperatures.

Incompatibilities

Carrageenans are anionic in nature and therefore are incompatible with cationics. Mono- and divalent ions such as potassium and calcium will crosslink the polymer to form gels. They hydrolyze and degrade in the presence of strong acids.

Advantages

1. Carrageenans are thickeners, film formers and suspending agents.

Algins and Alginate

FMC BioPolymer
1735 Market Street
Philadelphia, PA 19103

Derivation

Alginates are purified hydrocolloids obtained from brown seaweed (Kelp extract). (See chapter on Algins/Alginate in Problem Solver).

Water Dispersibility

Alginate is readily water dispersible and can be either pre-blended with other drug excipients like sucrose or wetted with glycols prior to water addition. High speed stirring is indicated.

pH Stability

Alginate is stable over a pH range of 4-10.

Rheology

1. Alginate systems exhibit pseudoplastic behavior.
2. Long term accelerated temperature conditions produce some viscosity losses (depolymerization).

Incompatibilities

Alginate is anionic in nature and therefore are incompatible with cationics. Calcium salts precipitate algin. Polyvalent ions will crosslink the polymer to form gels.

Algins are incompatible with heavy metal ions. They are sensitive to strong acids.

Advantages

1. Alginates are colloidal electrolytes.
2. Alginates are stabilizers, film formers and reasonable suspending agents.

Note: The formulator must strictly monitor rheological properties of alginate suspensions.

Other Commonly Used Suspending Agents

The pH stability, rheology, incompatibilities and uses of other common suspending agents are listed in alphabetical order.

Suspending Agent	pH Stability (Range)	Rheology	Incompatibilities	Uses
Carbomer, NF	5.0 - 11	Systems exhibit plastic flow	Sensitive to soluble salts; mono-, di- and polyvalent and to cationic polymers.	Good suspending agent at a pH value of 5.0
Methylcellulose, USP	3.0 - 11	Dispersions are pseudoplastic	High levels of electrolytes and surfacants affect MC dispersions.	Effective stabilizer and protective colloid. Usually used in conjunction with other suspending agents, not as a primary suspending agent.
Sodium Carboxymethylcellulose, NF (Cellulose gum) (NaCMC)	4.0 - 10.0	CMC systems exhibit pseudoplastic behavior. Viscosity of CMC systems is dependent upon temperature.	Incompatible with di- and trivalent salts.	Effective stabilizer and protective colloid especially for Avicel® RC-591 MCC.
Acacia, NF (Gum Arabic)	Viscosity is affected by pH	Newtonian flow exhibited at concentrations below 40%. High concentrations are pseudoplastic.	Acacia is anionic. It flocculates with small amounts of electrolytes, cationic polymers and surfacants.	—
Guar Gum, NF	4 - 10 Maximum viscosity is obtained at pH 6	Pseudoplastic behavior with no yield point.	May degrade irreversibly with time at elevated temperatures.	—
Xanthan Gum, NF	3.0 - 11.0	Dispersions are extremely pseudoplastic with significant yield value.	Incompatible with cationic dyes and polyvalent ions at high pH.	Effective suspending agent especially when used in conjunction with Avicel CL-611 MCC.

Should the formulator decide to use a natural gum either as a sole or adjunct suspending agent, strict attention must be given to the natural source derivation and rigid specifications regarding lot-to-lot uniformity must be implemented.

Other Suspension Excipients

- Functions
- Use levels
- Problems

The function, percent use level and problems that could surface relative to commonly used suspension excipients are listed in alphabetical order.

Percent levels used are approximate and represent general use levels.

Excipient	Purpose	% W/V Range Used	Problem
Alcohol 95%, USP	Solvent for preservatives, flavors, or other insolubles.	3-10	Could solubilize small percentage of drug. Incompatibility with suspending agent.
Benzoic Acid	Preservative.	0.05-0.25	pH of the system should be below 4.5 for the preservative to be effective. Solubility, precipitation not uncommon.
Buffer Acids	pH adjustment buffer system.	Depends on pH of system	Incompatibility with drug or suspending agent.
Colorants	Provides color-system.	q.s.	Excessive levels may cause staining of teeth, skin, or clothing. Quaternary ammonium compounds interact with FD&C Blue #1 and FD&C Yellow #10
Disodium Edetate (Na ₂ EDTA)	Sequesterant.	0.001-0.005	—
Flavors	Taste improvement.	q.s.	Reactions with drug and/or other flavors. Excessive levels impart bitterness, burning sensation.
Glycerin	Solvent for preservatives. Bodifying agent. Drug dispersing vehicle. Used with Sorbitol in combination to produce cap lock resistant blends.	5-15	Could impart hot acrid taste at high levels.
Methyl Paraben	Preservative.	0.1-0.2	Can impart an objectionable taste and a feeling of numbness at high levels.
Propyl Paraben	Preservative.	0.01-0.1	Poor water solubility.
Propylene Glycol	Solvent for preservative or flavors. Drug dispersing vehicle.	5-10	Unpleasant taste.
Sodium Benzoate	Preservative.	0.05-0.25	See Benzoic Acid

Other Suspension Excipients Continued.....

Excipient	Purpose	% W/V Range Used	Problem
Sodium Chloride	Modification of bitterness. Taste modifier.	0.1-0.3	Incompatibility with drug, suspending agent, or protective colloid.
Sorbitol Solution, 70%	Improves flavor. Imparts sweet cool taste. Bodifying agent. Helps retard cap locking tendency.	10-40	—
Sucrose	Natural sweetener.	10-60	Cap locking. Incompatibility with suspending agent. Drug incompatibility possible but rare.
Pluronic Polyol – F68 (HLB = 5.8)	Wetting agent. Defoamer.	0.1-1.0	—
Polyoxyethylene (8) Stearate (HLB = 11.1)	Wetting agent. Increases hydrophilic properties of clay suspending agents.	0.1-0.5	—
Polyoxyethylene (20) Sorbitan Monostearate (HLB = 14.9)	Wetting agent.	0.05-0.1	—
Polyoxyethylene (20) Sorbitan Monooleate (HLB = 15.0)	Wetting agent. Solubilizer for flavors. Viscosity control.	0.1-0.5	Can solubilize small percentage of drug. Taste is soapy and bitter.
Sodium Lauryl Sulfate (HLB = 40)	Wetting agent.	0.001-0.05	Powerful solubilizer. Can solubilize some drugs.
Sorbitan Monolaurate (HLB = 8.6)	Wetting agent.	0.001-0.05	—

Avicel® RC and CL Microcrystalline Cellulose, NF

Introduction

Colloidal Avicel is not a water-soluble cellulose derivative, but a water-dispersible organic hydrocolloid. It is prepared by chemical depolymerization of highly purified wood pulp. The original crystalline areas of the fiber are combined with sodium carboxymethylcellulose (NaCMC) to produce the colloidal Avicel product. NaCMC serves as a protective colloid and also aids in dispersion of the product. Soluble hydrocolloids (e.g., NaCMC) are produced by chemical substitution of functional groups in cellulose. Other types of cellulose products (e.g., flocs) are made by mechanical grinding of pulp fibers to a finer particle size. Thus, with the microcrystalline celluloses, we have a different class of products with different properties and different functions.

RC and CL types of Avicel microcrystalline cellulose (MCC) are water-dispersible products for use in pharmaceutical and cosmetic preparations. They contain sodium carboxymethylcellulose (NaCMC) to aid dispersion and to serve as a protective colloid.

Structure and Properties

There are four types of Avicel RC/CL: RC-501, RC-581, RC-591, and CL-611. All types are white, odorless, and tasteless hygroscopic powders. They are insoluble in organic solvents and dilute acids, and partially soluble in both dilute alkali and water (CMC fraction). Due to the small size of the microcrystals (about 60% of the crystallites in the dispersion are $< 0.2\mu\text{m}$), there are a large number of microcrystals packed in each powder particle. The large number of small microcrystals foster product elegance by slowing the rate of sedimentation, increasing the stability of a dispersion, and eliminating hard packing of settled particles. The highly compact nature of the powder particle is evident in the scanning electron micrograph as shown in Figure 2.

To achieve maximum dispersion, RC-501 and RC-581 require high shear mixing while RC-591 and CL-611 require low to moderate shear mixing. With RC-501, RC-581, RC-591, and CL-611, approximately 60% of the particles in the dispersion are less than $0.2\mu\text{m}$ when properly dispersed. Concentrations of less than 1% solids produce fluid dispersions, while concentrations of more than 1.2% solids produce thixotropic gels. CL-611 needs a concentration slightly higher than 1.2% for thixotropy.

When stirred in water, Colloidal Avicel powder disperses to form either a colloidal sol or a white opaque gel, depending on the Avicel concentration. When properly dispersed in water, the individual RC-591 powder particles disintegrate and form a dispersion of cellulose microcrystal aggregates. These aggregates are elongated solid particles that range in size from a few microns to a few tenths of a micron. At concentrations of less than 1% solids, Avicel RC-591 forms colloidal pseudoplastic dispersions; but at concentrations greater than 1%, thixotropic gels are formed.

Even though Avicel RC-591 and RC-581 are equivalent in colloid content and gel strength when fully peptized, high shear equipment such as colloid mills and homogenizers are required for dispersion of Avicel RC-581. In this case, the point of complete or maximum RC-581 peptization must be predetermined, and an "in process" viscosity control has to be established in order to equate time versus number of passes through a colloid mill (or homogenizer) versus viscosity. A consistent maximum hydration value must be obtained.

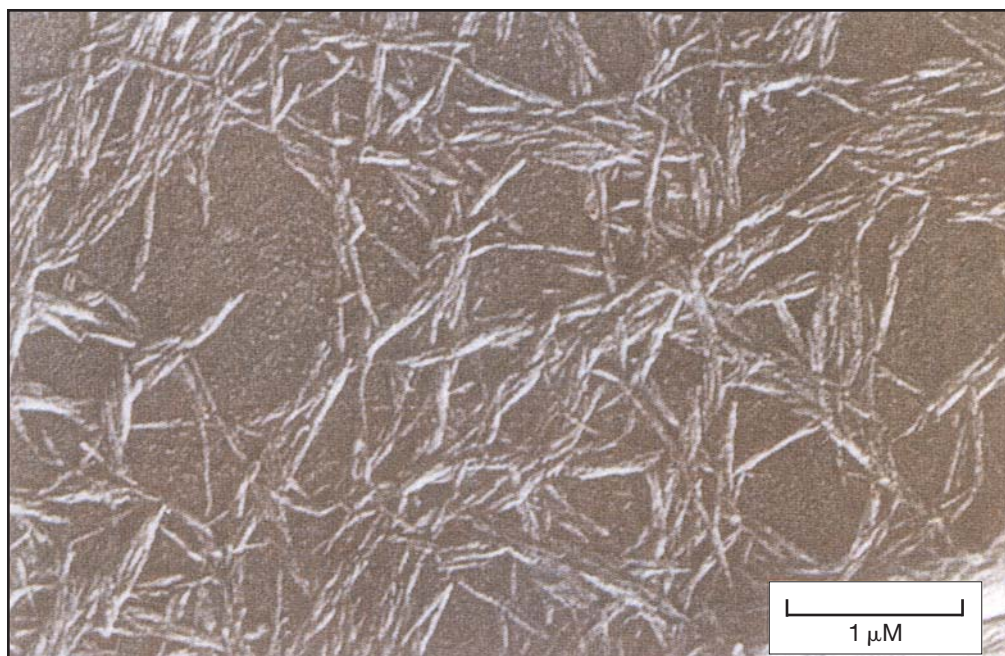
On a practical basis, a colloid mill or Manton Gaulin-1000 psi homogenizer is representative of the most efficient equipment for processing Avicel RC-581 MCC dispersions. The most efficient mixer, a Waring blender, is not considered standard production equipment in the pharma-

ceutical industry. Care should be exercised not to lose sight of this fact when formulating (on a laboratory scale) a product geared for production. Avicel® RC-591 or Avicel CL-611, when used alone or with other hydrocolloids, is the microcrystalline cellulose of choice for

the preparation of suspensions.

Avicel RC-501, RC-581, RC-591, and CL-611 are listed as Microcrystalline Cellulose and Carboxymethylcellulose Sodium in the *U.S. Pharmacopoeia/National Formulary*.

Figure 2: Fully peptized (activated) Avicel colloidal microcrystalline cellulose



Chemical and Physical Specifications

Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF, BP

Product	Avicel RC-501	Avicel RC-581	Avicel RC-591	Avicel CL-611
<i>Specifications</i>				
Loss on drying, %	*NMT 6.0	*NMT 6.0	*NMT 6.0	*NMT 6.0
Heavy metals, %	NMT 0.001	NMT 0.001	NMT 0.001	NMT 0.001
NaCMC, %	7.1-11.9	8.3-13.8	8.3-13.8	11.3-18.8
Sieve fraction, wt. %	+60 mesh NMT 0.1 +200 mesh NMT 40	+60 mesh NMT 0.1 +200 mesh NMT 35	+60 mesh NMT 0.1 +325 mesh NMT 45	+60 mesh NMT 0.1 +325 mesh NMT 50
pH	6.0-8.0	6.0-8.0	6.0-8.0	6.0-8.0
Viscosity, cps	72-168 (2.1 % solids)	72-168 (1.2% solids)	39-91 (1.2% solids)	50-118 (2.6% solids)
Residue on ignition, %	NMT 5.0	NMT 5.0	NMT 5.0	NMT 5.0
*Not More Than				

Microbiological Specifications

Total aerobic microbial count/g.....	NMT 100
Total yeast and mold count/g.....	NMT 20
<i>Escherichia coli</i>	None present in a 10g sample
<i>Staphylococcus aureus</i>	None present in a 10g sample
<i>Salmonella species</i>	None present in a 10g sample
<i>Pseudomonas aeruginosa</i>	None present in a 10g sample

Effect of pH and Temperature on the Viscosity of Colloidal Avicel®

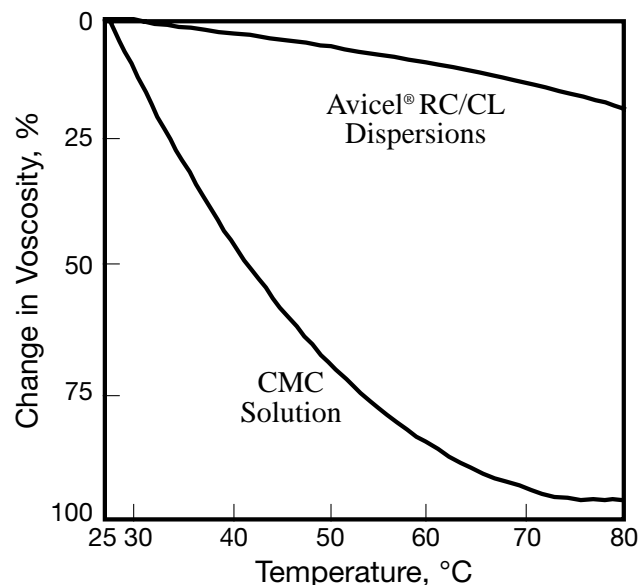
Effect of pH

Viscosity is stable over a pH range from 4.0-11.0.

Effect of Temperature

Changes in temperature have little effect on the viscosity of Avicel RC-591 and CL-611 dispersions. This is beneficial in maintaining long-term stability. Figure 3 shows the reversible change of viscosity for an Avicel gel dispersion and a CMC solution over a temperature range from 25°C to 80°C.

Figure 3: Effect of Temperature on Viscosity



Additional data has indicated that sterilization in a sealed container at 120°C for 75 minutes will not alter the physical properties of the Avicel gels. However, there is a minimal change in the viscoelastic properties of the gel.

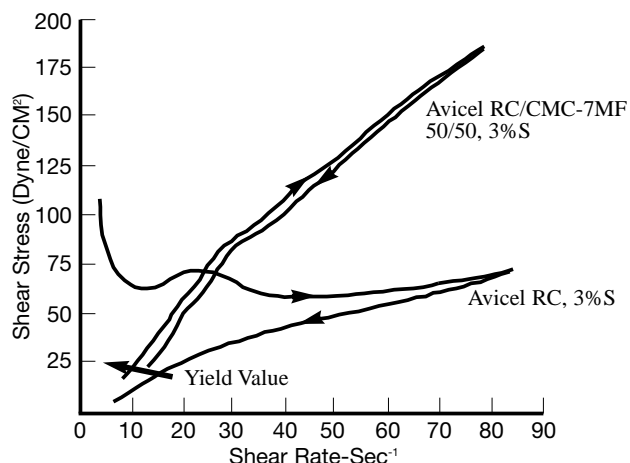
Suspensions prepared with Colloidal Avicel show little to no viscosity changes after exposure to accelerated temperatures, prolonged (5+ years) storage at room at 5°C (refrigeration), or after freeze-thaw shock and stress testing.

Effects of Other Hydrocolloids on Viscosity

Figure 4 illustrates the thixotropic nature of Avicel RC-591 decrease with the addition of CMC. This same phenomenon occurs with mixtures of RC-591 and methyl cellulose. RC-591 has a synergistic effect on the viscosity of Keltrol®, magnesium aluminum silicate, and various other gums.

Colloidal Avicel is compatible with many other hydrocolloids such as alginate, carrageenans, carbomer, guar gum, pectin and the cellulose ether polymers.

Figure 4: Flow properties of an Avicel® RC dispersion and a 50:50 blend of Avicel RC/CMC-7MF



Advantages of Formulating Disperse Systems with Colloidal Avicel

1. Colloidal Avicel can be dispersed quickly in water in any pharmaceutical plant using standard low or high shear mixing equipment.
2. When stirred in water, Colloidal Avicel disperses to form a smooth, uniform colloidal sol or white opaque gel depending on the type and concentration of Colloidal Avicel.
3. Colloidal Avicel can be hydrated and used the same day. Lengthy hydration is not required as equilibrium viscosity is rapidly attained.
4. Colloidal Avicel can help mask many unpleasant drug, surfactant, or oily tastes.
5. Colloidal Avicel gels are highly thixotropic with finite yield values, are shear thinning, and upon resting, yield values return to an equilibrium value (isothermal gel-sol-gel transformation). Consideration of this phenomenon and formulating with an optimum colloidal Avicel level will result in a well structured suspension vehicle that will not exhibit any phase separation for the shelf-life of the product. Thixotropy is evident with an Avicel RC-591 level as low as 1%.
6. Suspensions prepared with Colloidal Avicel can tolerate large quantities of glycol and alcohol excipient liquids commonly used in suspension compounding .
7. Colloidal Avicel is odorless and tasteless.
8. Colloidal Avicel suspensions do not leave a residual chalky, drying effect after oral administration.
9. Colloidal Avicel suspensions are not stringy on pouring.
10. Dispersions of Colloidal Avicel are readily flocculated by small amounts of electrolytes, cationic polymers, and surfactants. This flocculated colloidal dispersion settles but prevents hard packing of suspended materials.
11. When colloidal Avicel is used with protective colloids, the mixed system combines the stability of the polymer solution with yield value and dispersion of the microcrystals to form a long lasting suspension.

The best protective colloids for use with Colloidal Avicel are:

- Xanthan gum
- CMC (carboxymethylcellulose)
- Guar gum

Preparation of Colloidal Avicel®

1. To achieve maximum functionality, Avicel RC-591 should be fully dispersed and hydrated. Effective dispersion can be achieved by selecting the proper dispersion medium, order of adding the drug and excipients, and proper selection of shear and process equipment. Dispersibility is severely affected in the presence of electrolytes, sucrose, polyols, and alcohols. One exception is that preservatives, such as methyl and propyl paraben, will not affect Avicel RC-591 hydration. The main objective is to avoid competition for available water.
2. Water is the medium of choice to disperse Avicel RC-591 using low shear or high shear mixing. High shear can be obtained using a stator-rotor mixer (e.g., Silverson, Ultraturrax, etc.). Low shear mixing can be obtained with a Scott Turbon mixer or conventional propeller. Low shear mixing rates provide high viscosity and thixotropy values, which are process sensitive and subject to change with mixing time and shear. On the contrary, high shear rates give less viscosity and thixotropy; hence, they are less process sensitive and easier to scale-up and validate. For a faster and more efficient dispersion a high shear stator-rotor is preferred, Carlin (10).
3. In suspensions, which are formulated with sucrose or polyols, such as sorbitol in granular form, Avicel RC-591 should be premixed with the granular sucrose or sorbitol and then added to water. Avicel RC-591 should also be dispersed in sucrose solution or sorbitol solution.
4. Heating of the Avicel RC-591 dispersions is contraindicated. Avicel RC-591 has a yield value and heating of the dispersion is more difficult, because convection currents cannot distribute heat as they normally do in a Newtonian fluid. Thus, significant energy and time would be expended.

5. Add all other formula excipients before lowering the pH or adding salts.

6. Avicel RC-591 will not form colloidal dispersions in alcohols or glycols.

*Note: *For Avicel RC-581 and Avicel CL-611 dispersion, follow the same guidelines listed for Avicel RC-591 with the following exception: Suspensions made with Avicel RC-581 require additional shearing such as homogenization. Avicel CL-611 will be effectively dispersed with low or medium shear.*

Rheology of Avicel Dispersions

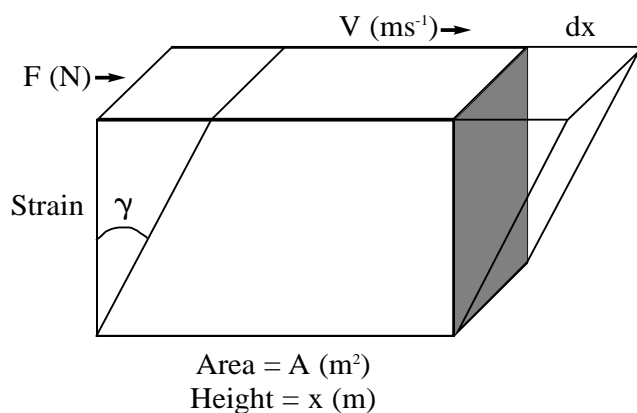
Aqueous Avicel dispersions provide a unique rheological combination of thixotropy with low viscosity and viscoelasticity, giving unrivaled suspension functionality. With excellent long-term physical stability, the shelf life of these structured non-sedimenting pourable vehicles can be in the order of several years. Although not essential for the practical use of Avicel dispersions, some understanding of rheology is desirable, if only to address the common misconception that viscosity alone can be used to design functional suspensions (10).

In Rheology one studies the deformation and flow of matter, Barnes (11). Rheology has its roots in the ancient Greece of about 2500 years ago when Heraclitus said “everything flows” (Πάντα ρεῖ) (12). One perhaps would not care to know what makes toothpaste retain its shape after it is squeezed onto the toothbrush or what governs the pouring of ketchup from the bottle, but many biological processes depend on the rheology or viscosity of body fluids without which blinking of the eye (tears), swallowing (saliva) or joint movement (synovial fluid) would not be possible.

So what is viscosity? Viscosity is the measurement of a material's resistance to flow. This becomes more apparent (Figure 5) when a layer of fluid is forced to move relative to a parallel stationary layer in response to a **shear stress (σ)**, defined as the force per unit area

($\sigma = F/A$) acting in the plane of fluid moving with velocity $V \text{ ms}^{-1}$. In real life one experiences shearing when the fluid is physically disturbed as in shaking, pouring, mixing, spreading and so on. The units of shear stress are Pascals (Newtons per square meter or dynes per square centimeter). A **velocity gradient** ($\dot{\gamma}$) can be calculated (by dividing the velocity of the moving layer by the gap between it and the stationary layer) known as the **shear rate**. The unit of shear rate is the reciprocal second ($\text{ms}^{-1}/\text{m} = \text{s}^{-1}$). **Viscosity** (η) can then be defined as the ratio of **shear stress/shear rate** ($\sigma/\dot{\gamma}$) with units of Pascal seconds ($\text{Pa}\cdot\text{s}$) (Newton seconds per square meter) or Poise (dyne second/centimeter²). **One milli-Pa•s = one centipoise.**

Figure 5: Viscosity, Terms and Units



Viscosity can be regarded as reciprocal fluidity so that the higher the viscosity the smaller the induced velocity or flow in response to a shearing force, or, conversely, more force is required to induce a given velocity (i.e.: harder to stir!).

Fluids may be classified as Newtonian if their viscosity remains constant at all rates of shear for a given temperature and pressure (e.g., water). However, many fluids (especially suspensions) exhibit non-Newtonian behavior, where the viscosity depends on the rate of shear. Factors leading to non-Newtonian behavior could be suspended particle size, shape and size distribution, high volume fractions, electrostatic interactions and any polymer chain interactions. Where there is a decrease in viscosity with

increasing shear rate the fluid is said to be **shear thinning or pseudoplastic**. Shear thinning could be due to alignment of anisotropic (different shape) particles with flow streamlines, break-up of aggregates, and random coil polymer elongation. Materials, which have shear thinning properties, are Avicel® dispersions (Figure 6), paints, hand creams, ketchup and salad dressings. Also, one can have an increase in viscosity with increasing shear rate, **rheopexy**, where the material is said to be **shear thickening or dilatant**. Shear thickening is usually caused by aggregation of suspended particles or polymer entanglement. Examples of shear thickening materials are pure cornstarch dispersed in water, clay slurry, and sand/water mix. Figure 7 shows Newtonian behavior and properties of shear thinning and shear thickening. Because the viscosity of non-Newtonian systems varies with the shear rate, the term **apparent viscosity** is used for a measurement at a given shear rate (especially where the rate of shear is not known).

Figure 6: Colloidal Avicel

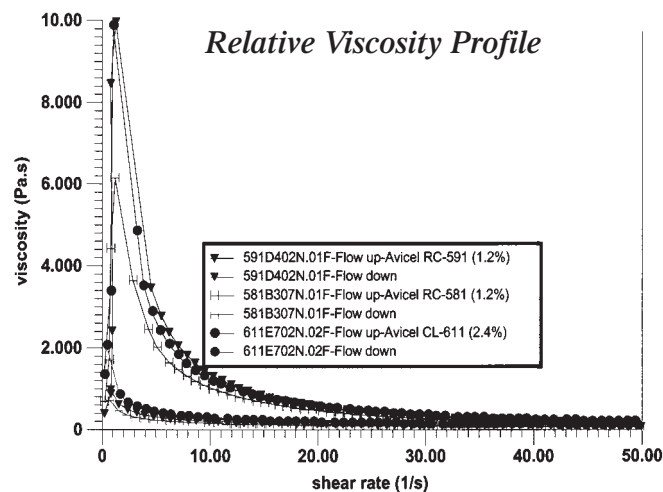
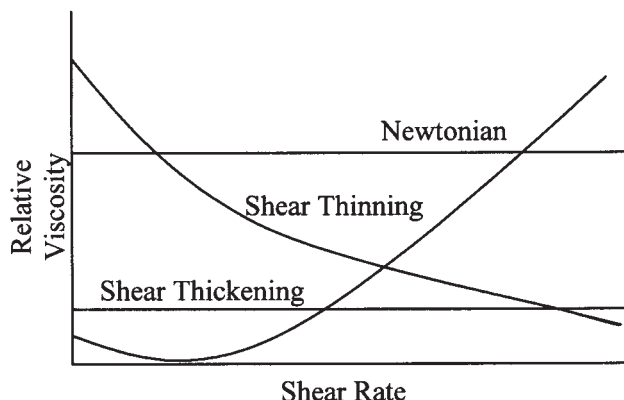


Figure 7: Flow Behavior



Newtonian systems with a single viscosity are unsuitable for suspension purposes as a viscosity low enough to allow pouring will not resist sedimentation, and a viscosity high enough to slow sedimentation to negligible levels will not be pourable.

On most rotational rheometers, stress is plotted against the shear rate and, on such rheograms, the viscosity is the gradient of the curve at a given shear. As shown in Figure 8, only the Newtonian system gives a straight line. Pseudoplastic systems are asymptotic to the stress axis, but eventually tend to a straight line at higher rates of shear, corresponding to an upper Newtonian viscosity, which is the residual viscosity of the vehicle after all structure has been wiped out at high shear. Most pseudoplastic rheograms show an apparent intercept on the stress axis (Figure 8), although this often has more to do with curve fitting or lack of rheometer sensitivity. Such **Apparent Yield Stresses** are usually specific to the equipment used to measure them. The **Yield Stress** is defined as the minimum stress that must be exceeded before any flow begins (Figure 9). In practice, if the time scale of observation or rheometer sensitivity is increased, flow can be measured at ever decreasing stress levels.

Figure 8: Flow Behavior

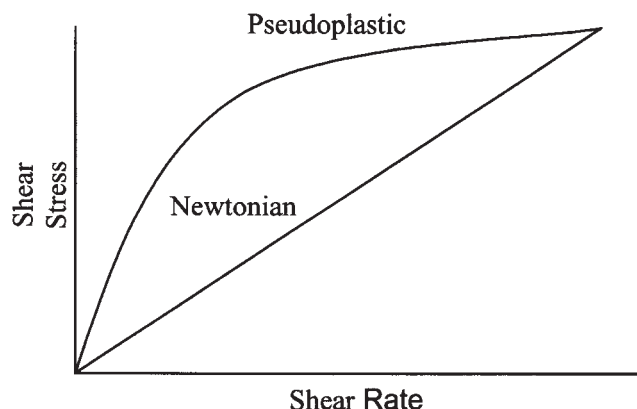
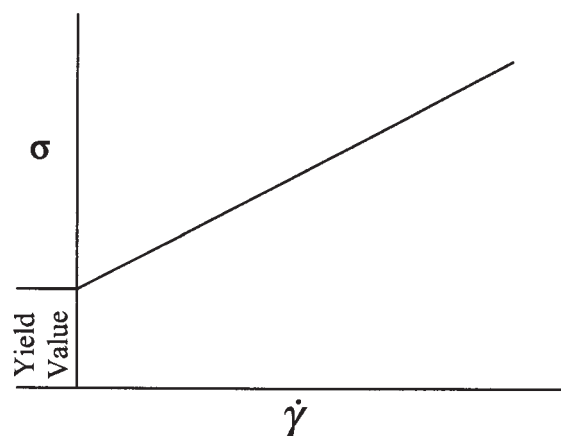


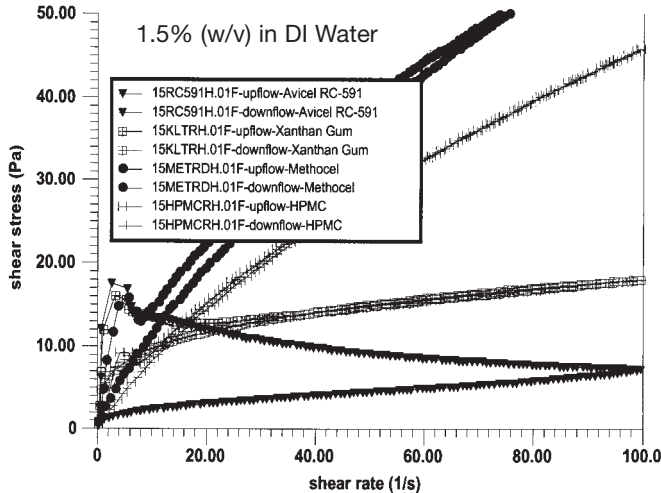
Figure 9: Apparent Yield Stress



Hydrocolloid dispersions have yield stress. Yield values are useful in processing and production of Avicel suspensions. They can correlate with other properties of suspensions and emulsions such as physical stability (separation/sedimentation) and pourability. Figure 10 displays the apparent yield stress of colloidal Avicel® RC-591NF dispersions in deionized (DI) water at 1.5% (w/v) compared to other hydrocolloids such as xanthan gum, Methocel, and HPMC (hydroxypropylmethylcellulose) at the same concentration.

Tomato ketchup is a classic example of a pseudoplastic and, even though it thins on shaking, it usually rethickens immediately and will not pour out of the bottle until its apparent yield stress is exceeded by a well-aimed slap on the bottom of the bottle!

Figure 10: Apparent Yield Stress



Regardless of whether or not the pseudoplastic vehicle has a true yield stress, the combination of high apparent viscosities at low shear (corresponding to gravitational velocities imparted to suspended particles according to Stokes' Law) and low apparent viscosities at higher shear (corresponding to shaking the bottle) appears more relevant to suspensions than Newtonian rheology. Pseudoplastic suspensions are stable, but can be problematic for bottled suspensions if the pouring viscosity is significantly higher than the shaking viscosity, as rethickening on cessation of shaking the bottle is instantaneous. In these suspensions, thixotropy becomes of paramount importance.

Thixotropy is a time dependent behavior. If the viscosity of a material decreases with time (seconds or fractions of seconds) at constant shearing and its structure increases at rest, the material is said to be thixotropic. If the viscosity of a material increases under shear, it is said to be anti-thixotropic or rheopectic (Figure 11). Thixotropy is an important rheological property of colloidal Avicel® RC-591NF, Avicel RC-581N, and Avicel CL-611NF. Suspensions made with colloidal Avicels display excellent yield values and thixotropy. As such, they make physically stable pharmaceutical suspensions with good aesthetic qualities such as pourability, low viscosity, taste, and mouthfeel. However, as shown in Figures 12 and 13, not all hydrocolloids exhibit thixotropy.

For instance, xanthan gum, Methocel, and HPMC dispersed in DI water have little or no thixotropy compared to Avicel RC-591NF and Avicel CL-611NF.

Figure 11: Time dependent Behavior

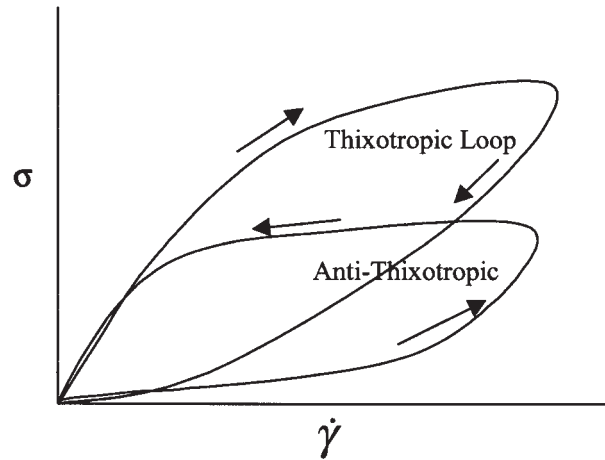


Figure 12: Thixotropy Profile

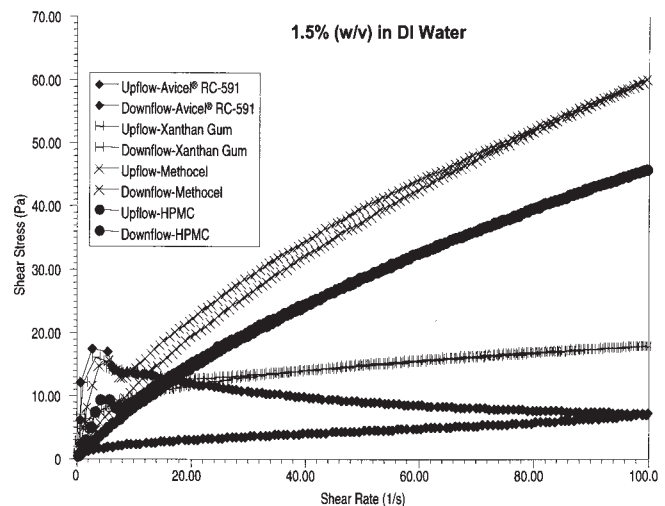
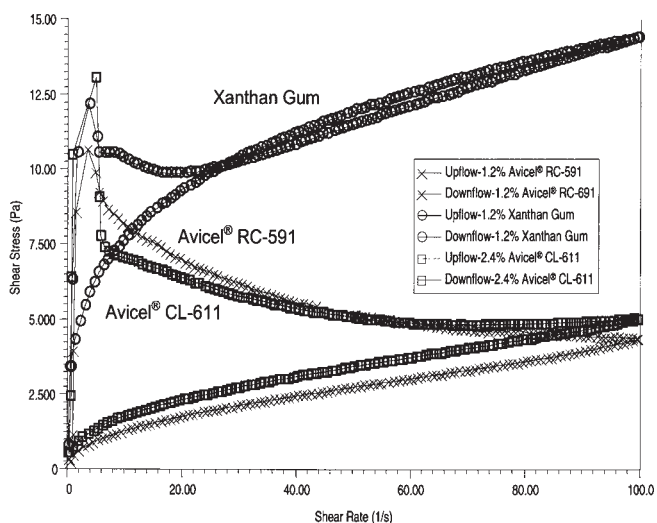


Figure 13: Thixotropy Profile



Viscoelastic Properties

In general, materials which are 100% elastic (solid) obey Hook's law (a material will not continuously change its shape when subjected to a given stress) Barnes (11), and materials which display Newtonian behavior are 100% viscous (liquid). However, many materials possess both solid-like and liquid-like properties. These materials are said to be viscoelastic. Many hydrocolloids, including colloidal Avicel dispersions, are known to be viscoelastic. Suspensions made with colloidal Avicel have strong elasticity (solid-like properties) that enables them to suspend insoluble particles and increase shelf life despite their liquid behavior.

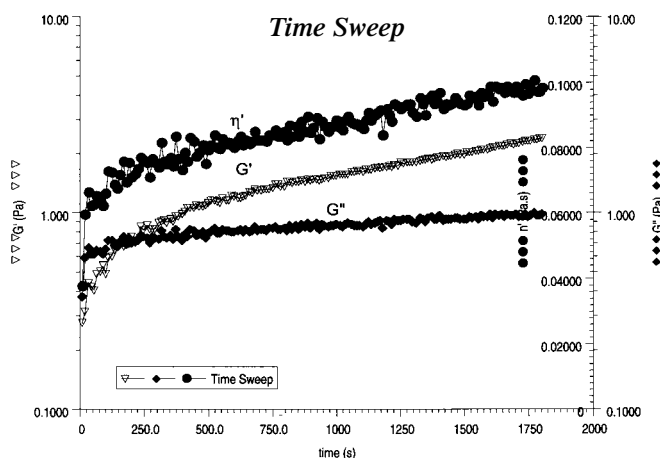
One can measure the viscoelastic properties of materials by measuring their G' and G'' . G' is the elastic (solid-like), storage energy modulus indicating elasticity related to the structure (gelling) of the material. G'' is the viscous (liquid-like), loss of energy modulus. Dynamic viscosity (η'), phase angle δ , and $\tan \delta$ are additional viscoelastic parameters one can measure to explain the viscoelastic properties of a suspension. Dynamic viscosity is not shear viscosity. It is a direct measure of the viscous component G'' ($\eta' = G''/\omega$ where ω = angular frequency). Angle phase δ is the phase difference between the input and output (stress and strain). For

perfectly viscous materials such as water or oil the delta value is 90° . For perfectly elastic (solid) materials the delta value is 0° . Therefore, $90^\circ > \delta > 0^\circ$, and $\tan \delta = G''/G'$. Hence, a system with small delta value or tan value has strong elasticity (solid like properties) and vice versa.

One can measure viscoelastic parameters using a stress or strain rheometer in which the test material is subjected to a minimum deformation (stress or strain). A constant shear viscometer measures only relative viscosity; it cannot differentiate between the elastic (solid-like) and viscous (liquid-like) components. For instance, it is possible for two materials to have the same relative viscosity, but they differ in viscoelastic properties such as elasticity. One can do various oscillatory tests (dynamic mechanical) to measure the viscoelastic properties of a material such as Time Sweep with and without pre-shearing, Strain Sweep, Frequency Sweep, Temperature Sweep, and Creep.

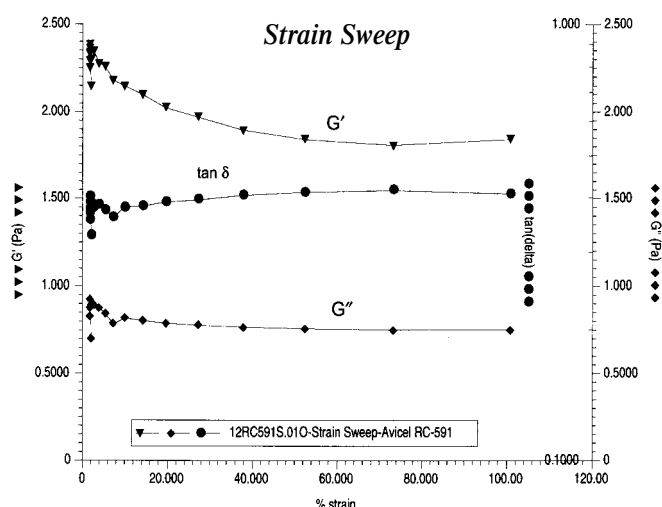
In **Time Sweep**, the frequency and stress are fixed and the G' (elasticity, gelling) is investigated as a function of time (Figure 14). Avicel RC-591NF dispersion in DI water shows G' crossing over G'' indicating fast transit time to gel after pre-shearing (13,14). After crossing, G' is predominant over G'' for the duration of the test, indicating strong elasticity (gelling) that would effectively suspend insoluble particles. The dynamic viscosity η' remains constant with respect to G'' (Figure 14).

Figure 14: Time Sweep



In **Strain Sweep** the frequency is fixed and the strain is changed. This test monitors the structural property of the sample subjected to increased deformation (strain). Points of interest are the position and magnitude of the G' and G'' , as well as the shape of G' and G'' with respect to strain (Figure 15). If G' and G'' remain constant, the structure is strong and this system will support long term stability, as shown for Avicel® RC-591NF dispersion. The strong elasticity of Avicel RC-591NF is also supported by the low tan delta value.

Figure 15: Avicel RC-591NF 1.2% (w/v)



stress and relaxation curve after the stress is removed (Figure 17). The creep test can simulate real life processes and situations such as prediction of shelf life for a suspension, if compared to a sample with known stability. The retardation and relaxation curves of Ibuprofen suspension (20 mg/mL) made with 1.3% (w/v) Avicel RC-591NF are shown in Figure 18. This Ibuprofen suspension displays excellent structure recovery after the stress is removed.

Figure 16: Avicel CL-611NF 2.4% (w/v)

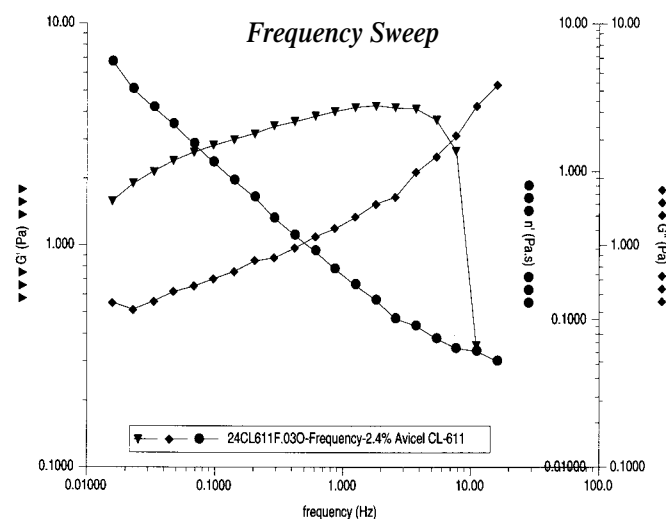
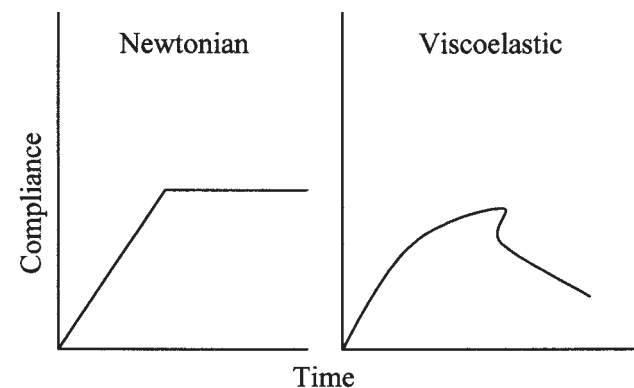


Figure 17: Creep Evaluation

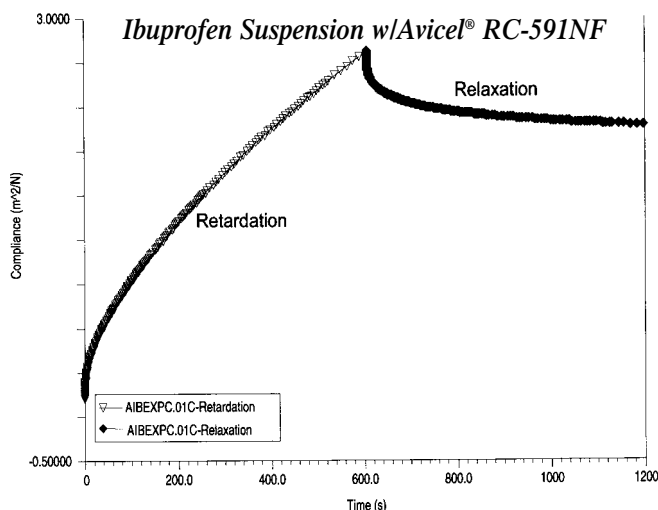


In **Frequency Sweep**, the oscillatory stress or strain is fixed and frequency is the variable. The structure of a material is well defined by investigating the position, magnitude, and shape of G' and G'' as a function of frequency. Figure 16 shows the elasticity of Avicel CL-611NF dispersion (2.4%w/v) with varying frequency.

In **Temperature Sweep**, one can measure at one frequency the phase transitions, gel temperature, and gel time with respect to changes in temperature.

In **Creep Test**, the material is subjected to a constant stress for a finite period of time and then the stress is removed. One can investigate a material for viscoelastic behavior by studying the retardation curve during the application of the

Figure 18: Creep Test



Pharmaceutical Applications

Colloidal Avicel® is a versatile dispersion vehicle with a range of pharmaceutical applications. The broad scope of applications for colloidal microcrystalline cellulose is demonstrated by the following list:

- As a suspending agent for pharmaceutical and cosmetic suspensions, and for readily constitutable suspensions.
- As an emulsion stabilizer for pharmaceutical and cosmetic creams.
- As a foam stabilizer for aerosol foams
- As a thickener and opacifier for pharmaceutical and cosmetic creams and gels.
- And as an oil/water emulsifier for pharmaceutical and cosmetic lotions and creams.

Examples of various formulations described below illustrate systems of suspensions, creams and lotions using either colloidal Avicel as a suspending agent or a combination of suspending agents. The objective of the suspending agent varies in each formulation to achieve good flow properties and ease of redispersal. Absence of sedimentation has also been the goal in some of these formulations.

Example of Use of Colloidal Avicel as a Suspending Agent

A typical suspension formula—usually geared to deliver the drug dosage per teaspoonful (5 ml)—normally contains the following basic excipients:

- Drug
- Dispersant
- Protective colloid
- Suspending agent
- Sweetener
- Bodying agent
- Preservatives
- Buffer system
- Sequestering agent
- Flavor
- Colorant
- Water, distilled

Example of an Analgesic Oral Suspension Using Colloidal Avicel RC-591

Ingredients	(% w/v)
Purified Water	45.0
Acetaminophen, USP	3.20
Tween® 80	0.10
Glycerin 99% USP	5.0
Sucrose, NF	40.0
Avicel RC 591, NF	1.30
Sodium Benzoate, NF	0.25
Citric Acid, USP	0.20
Coloring Agent, q.s.	—
Flavors, q.s.	—
Purified Water, q.s.	100.0

Procedure:

1. Weigh the required amount of water in an appropriate container. Disperse and hydrate the Avicel RC-591 using a low to moderate shear mixer, e.g., Scott Turbon mixer.
2. Add the sucrose, glycerin, coloring agent and Tween 80 and mix until dissolved.
3. Add the Acetaminophen and mix until well dispersed. Add the sodium benzoate and mix well until dissolved. Add the citric acid and

- flavors and mix well until dissolved.
4. Make up to the required volume with deionized water.

Example of an Antacid Suspension Using Colloidal Avicel® RC-591

Ingredients	(% w/v)
Calcium Carbonate, USP	5.0
Sorbitol Solution, 70% USP	10.0
(Saccharin) Sodium, USP	0.16
Deionized Water, USP	40.0
Propylene Glycol, NF	5.0
Methyl Paraben, NF	0.1
Propyl Paraben, NF	0.01
Avicel RC-591, NF	1.6
Deionized Water, USP (q.s.)	100.0

Procedure:

1. Weigh the required amount of water in an appropriate container. Disperse and hydrate the colloidal Avicel using a moderate shear mixer .
2. In a separate container weigh the propylene glycol and dissolve the Parabens using a low shear propeller mixer.
3. Add this mixture from step 2 to the mixture in step 1.
4. Add the Saccharin Sodium, and Sorbitol and mix until dissolved.
5. Add the calcium carbonate and mix until dispersed.
6. Make up to the required volume with deionized water.

Example of Use of Colloidal Avicel as an Oil/Water Emulsifier

Example of a Topical Anti-Acne Skin Lotion Using Colloidal Avicel CL-611

Ingredients	(% w/v)
Purified Water, USP	50.0
Avicel CL-611, NF	2.0
Benzoyl Peroxide @ 70%	7.3
Disodium Edetate, USP	0.05
Dioctyl Sodium Sulfosuccinate, USP	0.70
Glycerin, 99% USP	10.0
Propylene Glycol, NF	5.0
Methyl Paraben, NF	0.10
Propyl Paraben, NF	0.02
Purified Water q.s.	100.0

Procedure:

1. Add the appropriate amount of deionized water to a suitable container.
2. Weigh and add the required amount of viscosifier (Avicel CL-611) to the water and stir using either a Scott Turbon mixer or a Silverson mixer.
3. Once the viscosifier is either completely dispersed or hydrated, add the glycerin to the same container.
4. Add the dioctyl sodium sulfosuccinate to the above container and mix until well dispersed.
5. Add the Benzoyl peroxide and mix until well dispersed.
6. In a separate container dissolve the methyl and propyl paraben in propylene glycol using a propeller mixer.
7. Add the contents from step 6 to the dispersion in the main container
8. Add the Disodium Edetate and mix well until dissolved.
9. Qs to volume with sufficient deionized water.

Example of Use of Colloidal Avicel® as a Thickener, Emulsion Stabilizer and Opacifier for Pharmaceutical Creams and Gels

Formulation of an Antifungal (Micanozole) Cream

Ingredients	(% w/v)
Deionized water (w)	4.0
Avicel CL-611 (3% dispersion) (w)	40.0
Viscarin® GP-209 (2% solution) (w)	10.0
Micanozole	1.0
Propylene Glycol (w)	1.0
Cerasynt SD (Glyceryl Stearate) (O)	2.5
Cyclomethicone (O)	8.0
Arlacel® 165 (Glyceryl Stearate and PEG 100 Stearate) (O)	2.5
Promulgen® D (Ceteryl Alcohol and Cetareth-20) (O)	3.0
Methyl Paraben (w)	0.10
Propyl Paraben (w)	0.02
Deionized water q.s.	100.0

Procedure:

1. Heat the oil phase to 80°C and mix until homogeneous.
2. Heat the water to 85°C and dissolve the parabens in the hot water. Add Viscarin GP-209 solutions and the Avicel CL-611 dispersion to the hot water and mix until homogeneous.
3. Add this water phase to the oil phase and mix gently until well dispersed using a Silverson mixer. Cool the resultant solution to 50°C and add the Micanozole and mill to a uniform texture. Fill warm into containers.

Example of Use of Colloidal Avicel as an Oil/Water Emulsifier for Cosmetic Lotions

Example of a Topical Sun Screen Lotion Using Colloidal Avicel CL-611

Ingredient	(% w/v)
Water, DI	33.69
Gelcarin® GP-379 (2% solution)	10.0
Avicel CL-611 (3% dispersion)	40.0
Propylene Glycol	1.0
Phenoxyethanol	0.5
Methyl Paraben	0.25
Propyl Paraben	0.06
Arlacel 165	2.0
Cyclomethicone	3.0
Promulgen D	1.5
Ganex® WP660	1.0
Z-Cote®	1.0
Titanium Dioxide TA100	6.0

Procedure:

1. Prepare a 3% stock suspension of Avicel CL-611 in DI water.
2. Prepare a 2% stock solution of Viscarin GP-209 in DI water.
 - Place 900 ml of DI water in a stainless steel beaker
 - Heat water to 85°C with agitation.
 - Carefully disperse 20g of carrageenan.
 - Heat and agitate until carrageenan is fully dissolved and activated.
3. Add the appropriate amount of water to a stainless steel beaker (#1), and place the beaker in a water bath and heat to 80°C.
4. Agitate the water, and add the methyl and propyl parabens to the water.
5. Cover the beaker and allow the parabens to dissolve.
6. Add the appropriate quantities of Avicel CL-611 and Viscarin GP-209 to a stainless steel beaker (#2).
7. To the beaker #2, add the contents of beaker #1, the phenoxyethanol, and the propylene glycol.
8. Heat beaker #2 with agitation to 75°C while agitating with a Scott Turbon mixer.

9. Combine all the ingredients in the oil phase in a stainless steel beaker and heat to 90°C with agitation at a setting of 10-20 (≈3800-5000 rpm).
10. Add the oil phase to the water phase and cool to room temperature with agitation at a setting of 10-20 (≈3800-5000 rpm).
11. Package the resulting product.

Example of the Use of Colloidal Avicel® as a Suspending Agent for Reconstitutable Suspensions

Suspension-Powder for Reconstitution

In cases where drug stability in the presence of water is poor, the product may be prepared as a powder blend designed to be reconstituted with water by the pharmacist.

Two approaches can be taken in dealing with reconstitutable powders. The blends can contain either drug per se or drug which has been admixed with a portion of another excipient like sugar, granulated with isopropyl alcohol, milled, dried, and passed through a granulator. The granulated material is then mixed and blended with the remaining excipients. The granulating procedure is preferred when formulating with microfine drugs which would be difficult to disperse owing to entrained air and static charge.

The end result of dry blending of reconstituted powders is to attain an optimum level of physical uniformity. The blend must be uniform as to assure no variations in potency during processing, bulk storage, and the filling/packaging procedure.

Example of a Drug (Active) Powder Formulation for Reconstitution

Ingredients	(% w/v)
Drug (Active)	13.04
Sucrose	79.20
Potassium Sorbate	0.23
Sodium Citrate, dihydrate	2.05
Citric Acid, anhydrous	0.20
Xanthan, Keltrol F	0.20
Colloidal Avicel CL-611	5.08
QS with Sucrose	100.0

Procedure:

1. Screen active ingredients through a 25 US standard mesh screen.
2. Weigh out active and excipients into properly labeled containers.
3. In a V-blender transfer half the amount of total sucrose and combine Potassium Sorbate, Sodium Citrate and Citric Acid and Active to the Sucrose and mix for 3 minutes.
4. Weigh the remaining amount of sucrose. To this add the weighed amounts of Xanthan gum and Colloidal Avicel. Add this mixture to the ingredients in the V-blender and mix for an additional eight minutes.
5. Transfer blend into an appropriate container that is properly labeled.

Equipment and Suppliers

Mixers

Silverson Machines Inc.
P.O.BOX 589
East Longmeadow, MA 01028

High Shear L4RT

Charles Ross and Son Co.
710 Old Willets Path
Hauppauge, NY 11787

Mixer, Emulsifier

Arde Barinco
19 Industrial Avenue
Mahwah, NJ 07430

Mixer, Blender,
Disperser, Emulsifier

Greerco Corporation
Executive Drive
Hudson, NH 03051

Homogenizer, Mixer

Lightnin' Mixing Equipment Co., Inc.
195 Mt. Read Blvd.
Rochester, NY 14603

Blender, Mixer, Aerator,
Lightnin' Mixer, Portable
Air Mixer, Impellers

Jayco Inc.
199 Seventh Ave.
Hawthorne, NJ 07506

Mixer, Blender,
Disperser, Emulsifier

Scott Turbon Mixer
Van Nuys, CA 91409

XML

Mills

Greerco Corporation
Executive Drive
Hudson, NH 03051

Colloid Mill

Deaerator-Defoamer

The Cornell Machine Co.
45 Brown Avenue
Springfield, NJ 07081

Versator

Jayco Inc.
199 Seventh Avenue
Hawthorne, NJ 07506

Romaco Mixer

Micronizer-Pulverizer

Fluid Energy Processing and Equipment
153 Penn Avenue
Hatfield, PA 199440

Jetomizer

Pulverizing Machinery
Division of U.S. Filter
Corporation
10 Chatham Road
Summit, NJ 07901

Mikropulverizer

Viscometers

Brookfield Engineering
Laboratories, Inc.
Stoughton, MA 02072

Brookfield Synchro-
Lectric Viscometer

Rheometers

TA Instruments, Inc.
109 Lukens Drive
New Castle, DE 19720,USA

AR 1000N, Carri-Med CSL2100

Haake, Inc.
244 Saddle River Road
Saddle Brook, NJ 07662

Rotovisco

Special Equipment

Zeta-Meter, Inc.
1720 First Avenue
New York, NY 10028

Electrophoretic
Mobility Determinator

Coulter (Counter)
Electronics, Inc.
Hialeah, FL 33011

Particle Size
(Counter)

Particle Size Analyzer

HORIBA INSTRUMENTS, INC.
17671 Armstrong Ave
Particle Size Analyzer
Irvine, CA 92714

HORIBA LA 910, Laser Light Scattering, Particle

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2. Nash, R.A., Drug and Cosm. Ind. 97, 843 (1965); 98, 40 (1966).
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