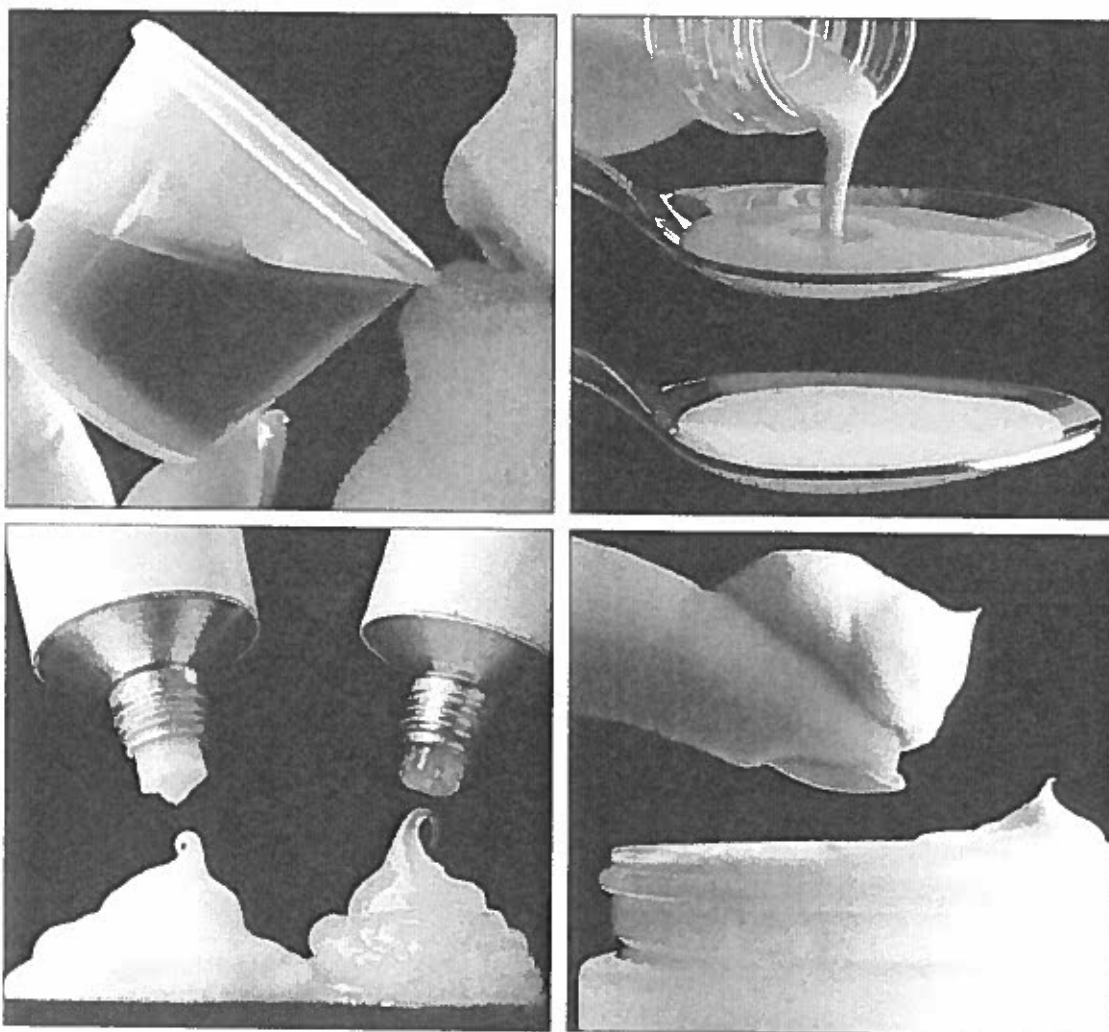


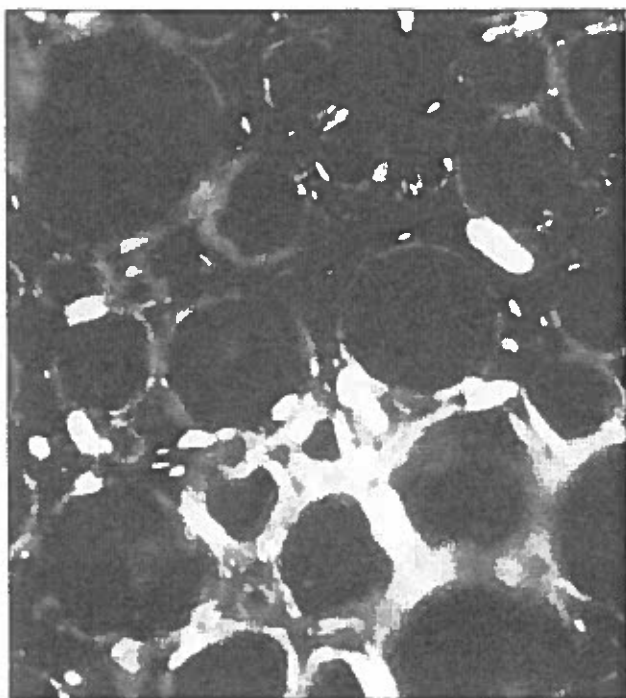
Avicel® RC-591
Microcrystalline Cellulose and
Carboxymethylcellulose Sodium, NF, BP

**Pharmaceutical Emulsions
and Suspensions**
Stabilization Technology For Liquid
And Semi-Solid Dosage Forms

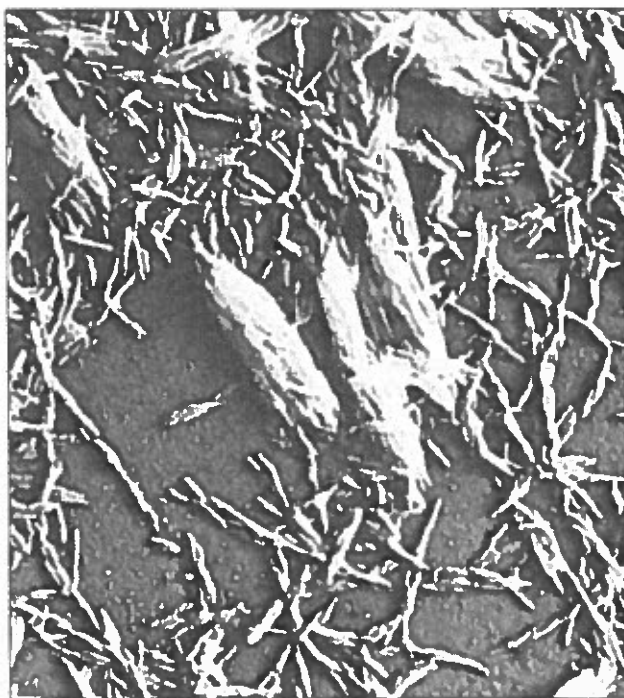


Avicel® RC-591

Microcrystalline Cellulose, NF, BP



Avicel RC-591 emulsion



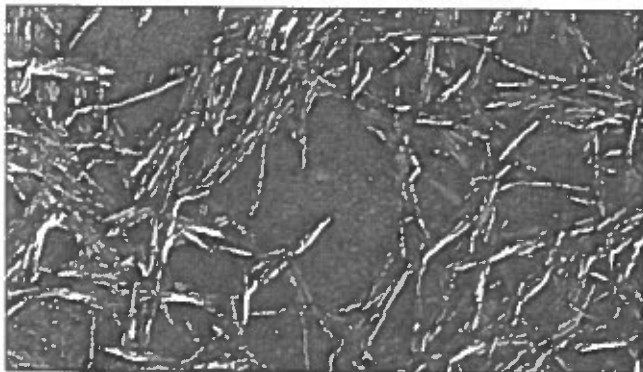
Cellulose microcrystals and crystallite aggregates

Contents

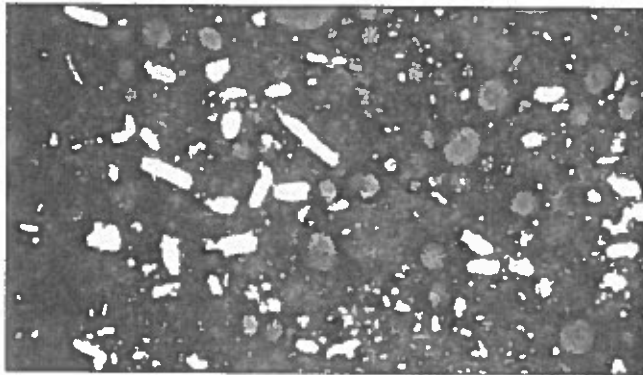
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Advantages of formulating suspensions and emulsions with Avicel® RC-591

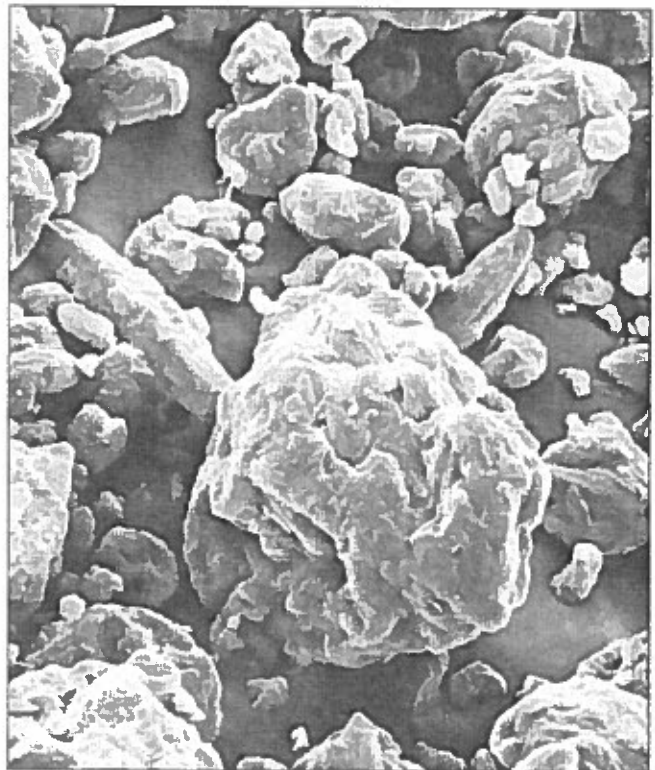
- Viscosity regulator and modifier
- Thixotropic characteristics
- Heat and freeze-thaw stable
- Long shelf-life stability
- Lengthy hydration times eliminated
- Stable at pH range 4-11
- Odorless, tasteless



Avicel Colloidal MCC



Undispersed Avicel RC-591 suspension



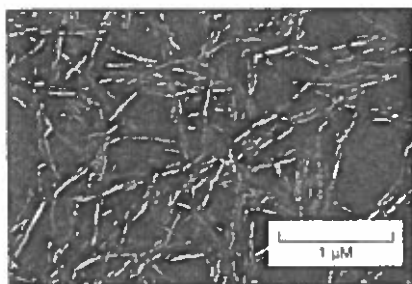
Spray dried Avicel RC-591

600X

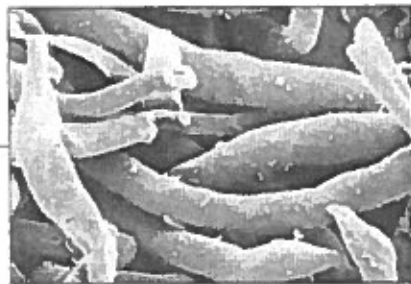
Avicel® RC-591

- A water dispersible organic hydrocolloid used in the preparation of pharmaceutical suspensions and emulsions.
- A spray-dried blend of microcrystalline cellulose (MCC) and sodium carboxymethylcellulose (CMC).

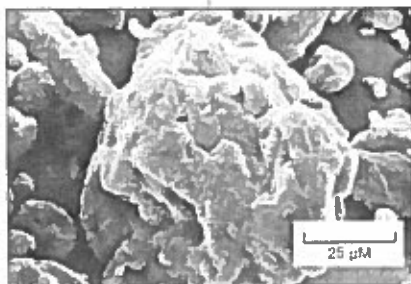
The colloidal MCC provides a structured dispersion vehicle while the CMC facilitates dispersion and serves as a protective colloid.



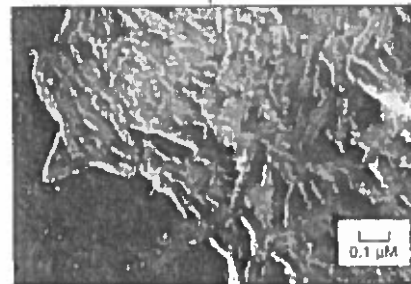
*Avicel Colloidal MCC
(Insoluble component)*



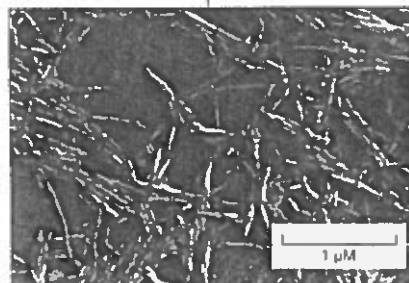
*Sodium carboxymethylcellulose
(Soluble component)*



*Powder particle of
Avicel RC-591*



*Cut powder particle shows tightly
packed microcrystals*



*Aqueous dispersion
of Avicel RC-591*

Structure and Function

Microcrystals of Avicel[®] microcrystalline cellulose are leashed together with chains of soluble CMC to form a mesh-like powder particle (Fig. 1).

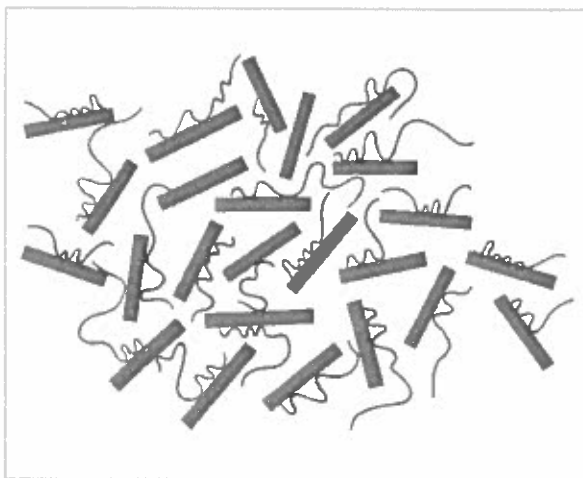


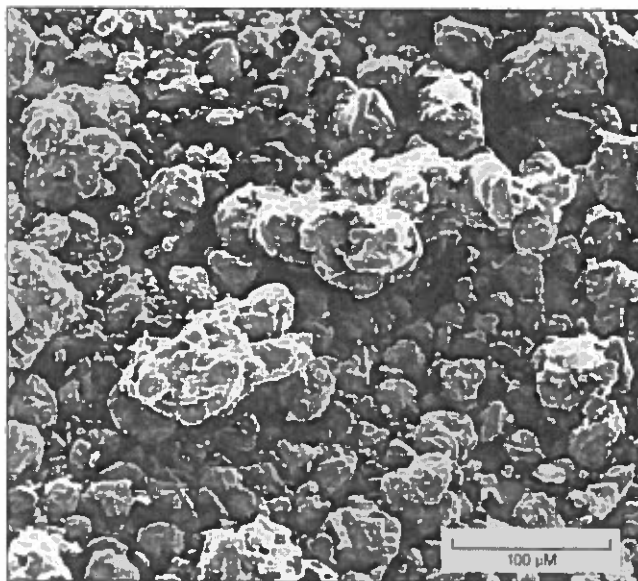
Figure 1.—Powder particle Avicel RC-591

Due to the small size of the microcrystals (approximately 60% of the crystallites in dispersion are $<0.2 \mu\text{M}$), there are a large number of microcrystals packed in each powder particle. (Fig. 2).

The large number of small, microcrystal particles help promote

- Slower more uniform settling rate
- Suspension stability
- Formulation elegance
- Absence of hard packing

The highly compact nature of the powder particle is evident in this scanning electromicrograph (Fig. 3).



Avicel RC 591 powder particles

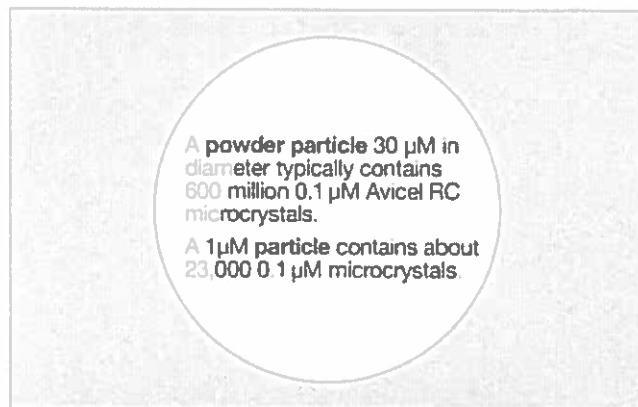


Figure 2.—Colloidal powder particle

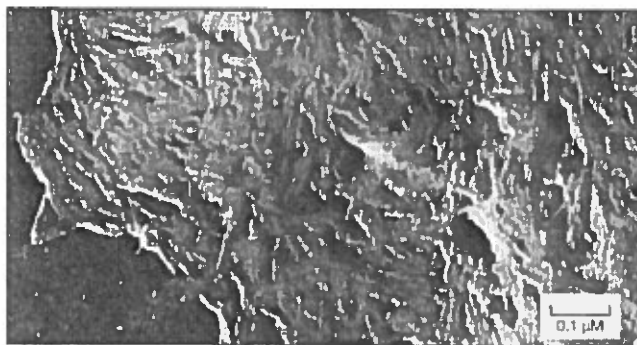


Figure 3.—Cut powder particle

Structure and Function (continued)

In the presence of water and mild shear, the Avicel® RC-591 powder particles swell and are then peptized, forming a dispersion of cellulose microcrystals. These microcrystals create a stable lattice structure for use in the formulation of suspensions and emulsions. (Fig. 4).

- Concentrations <1% solids form colloid dispersions.
- Concentrations >1% solids form thixotropic gels.

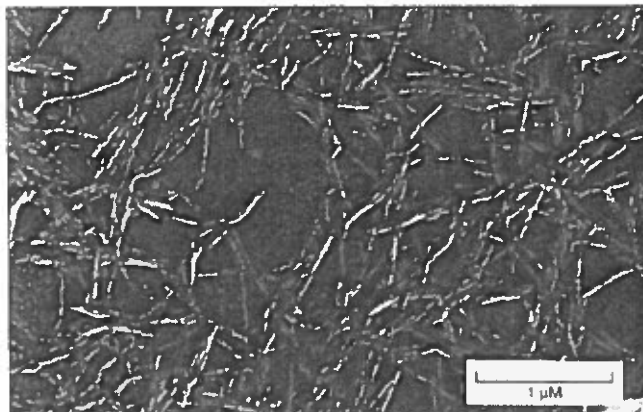


Figure 4.—Fully peptized (activated) Avicel colloidal microcrystalline cellulose

Rheological Properties

Thixotropy

Avicel RC-591 gels are highly thixotropic and have a finite yield value which begins approximately at a 1% solids concentration. (Fig. 5).

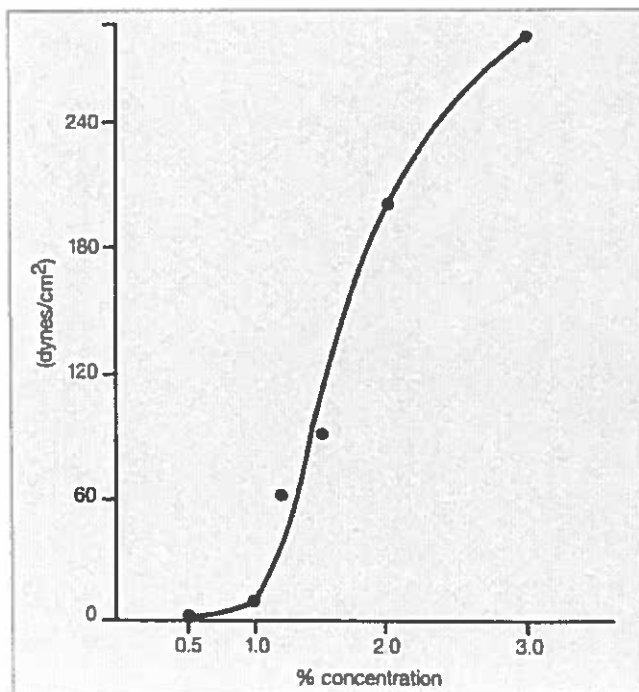


Figure 5.—Yield stress vs. concentration of RC-591, T=25°C

Process

The thixotropy and yield value of RC-591 gels are due to the lattice structure formed by the microcrystals. When a shearing force is applied to the gel, the particles separate and align with a corresponding reduction in resistance to flow (shear thinning). Then, as the dispersion is allowed to rest, a yield value is re-established and the solid particles reform the mesh-like network (Fig. 6).

Effects of Hydrocolloids

Figure 7 illustrates how the thixotropic nature of Avicel® RC-591 decreases 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.

Effect of Temperature

Changes in temperature have little effect on the viscosity of Avicel RC-591 dispersions. This is beneficial in maintaining long-term stability (Fig. 8).

Effect of pH

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

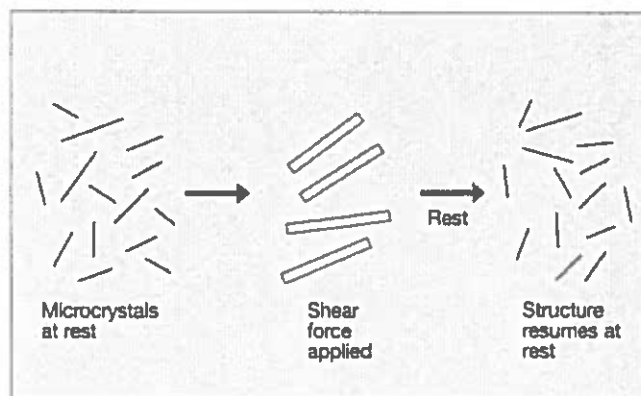


Figure 6.—Thixotropic process

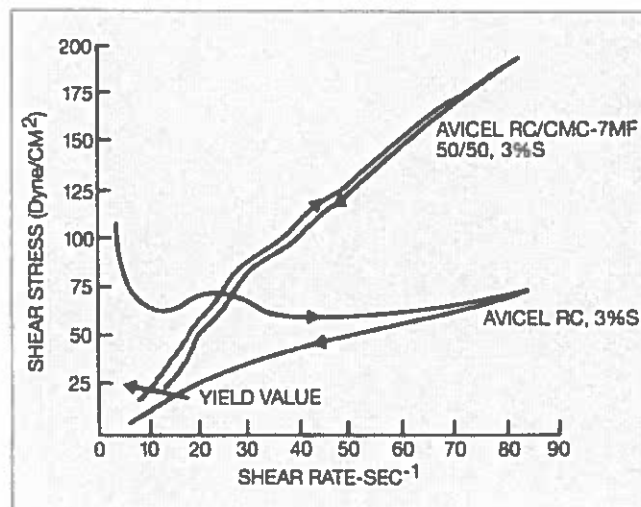


Figure 7.—Flow properties of an Avicel RC dispersion and a 50:50 blend of Avicel RC/CMC-7MF

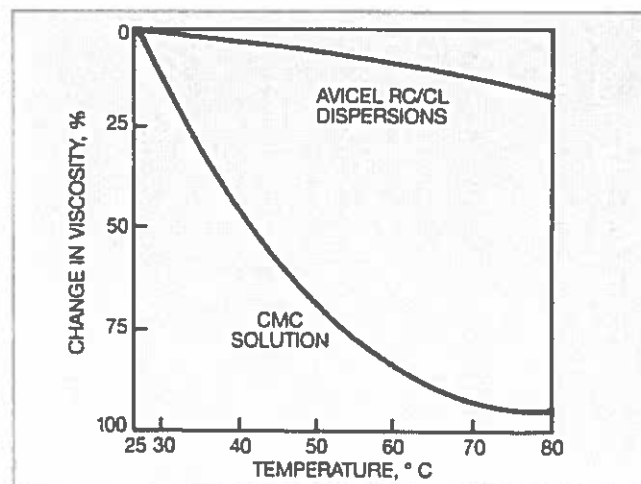


Figure 8.—Effect of temperature on viscosity

RC-591 as a Suspending Agent

Avicel® RC-591 microcrystalline cellulose, either alone or in combination with other hydrocolloids, is an excellent suspending agent. Formulations containing 1.2% RC-591 are well structured suspension vehicles, thixotropic, and have a finite yield value.

Flocculating/Electrolytes

Dispersions of Avicel RC-591 are readily flocculated by small amounts of electrolytes, cationic polymers, and surfactants. This flocculated colloidal dispersion settles but prevents hard packing of suspended materials.

Protective Colloids

Because Avicel RC-591 colloidal dispersions contain a high concentration of particles smaller than 0.2 μM and have a finite yield value, a stable, elegant suspension may be formulated.

When RC-591 is used with protective colloids, the mixed system combines the stability of the polymer solution with the yield value and dispersion of the microcrystals to form a long lasting suspension.

The best protective colloids for use in RC-591 dispersions are:

- Xanthan gum
- CMC (carboxymethylcellulose)
- Methocel® 90 HG
hydroxypropylmethylcellulose

Suspended materials are either

- Allowed to settle and can be redispersed, or
- Kept in suspension with very little phase separation.

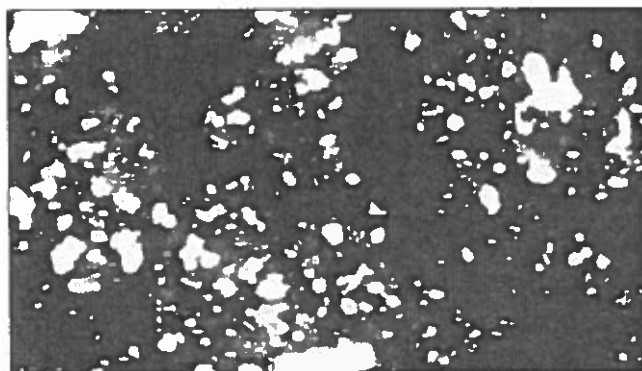


Figure 9. — Flocculated system

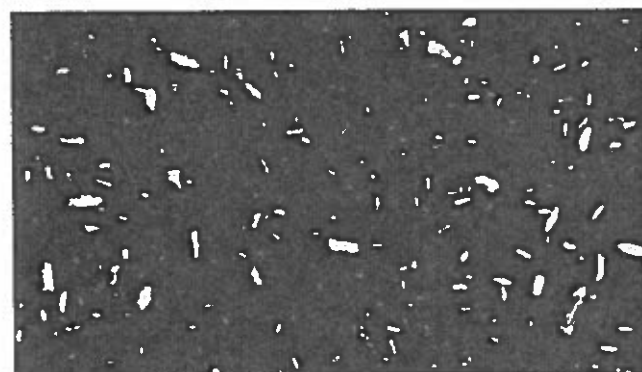


Figure 10. — Fully dispersed system

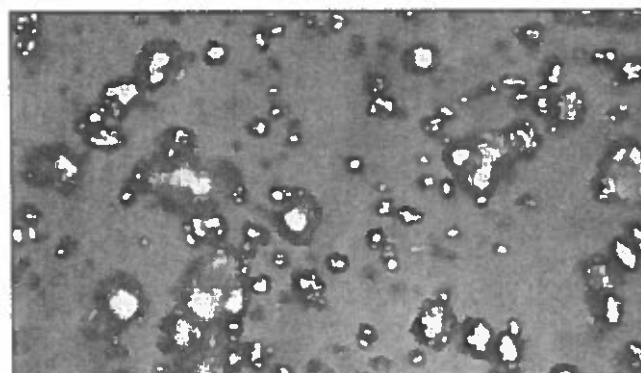


Figure 11. — Undispersed system

Dispersion Factors

When stirred in water, Avicel® RC-591 powder disperses to form either a colloidal sol or white opaque gel, depending upon the Avicel RC concentration.

Water Addition

Avicel RC-591 can be added to water very easily. Two important things should be noted:

- Sufficient water should be available for easy dispersion.
- RC-591 should be dispersed in water prior to the addition of other formulation ingredients. The few exceptions are seen with preservatives such as methyl and/or propylparaben, and sodium benzoate. (Fig. 12).

Preparation

To prepare a product containing a 1.5% concentration of Avicel RC-591, the dispersion ratio shown in Fig. 13 is recommended.

This ratio results in a lump-free dispersion which can be easily handled in processing.

The functionality of Avicel RC-591 may be severely affected when other ingredients are added to water first. Neither a thixotropic system nor a structured vehicle may be obtained.

Equipment

Standard laboratory and production equipment can be used to prepare dispersions of Avicel RC-591 MCC in monovalent salt solutions. Fig. 14 illustrates that a high-speed propeller mixer will provide adequate shear for proper dispersion at the most common concentration levels of these salts.

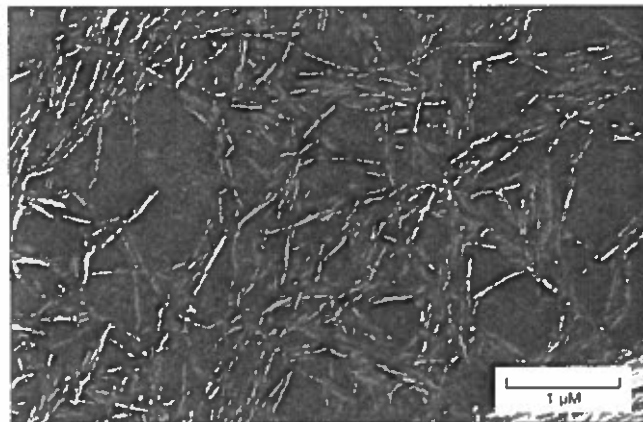


Figure 12.—Fully peptized (activated) Avicel colloidal microcrystalline cellulose

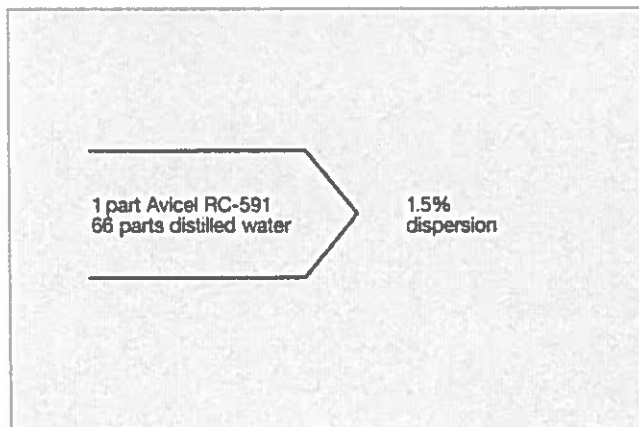


Figure 13.—Suggested dispersion ratio

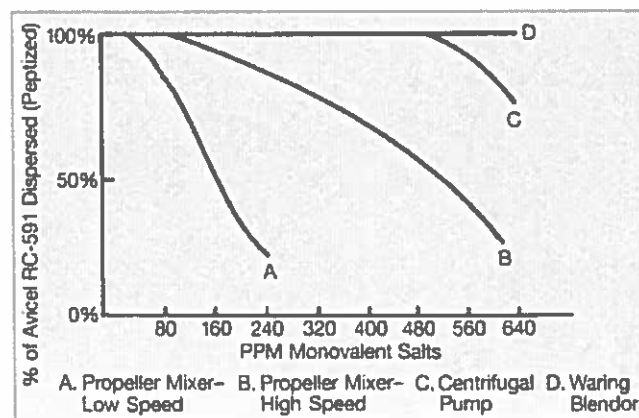


Figure 14.—Equipment types required for various PPM monovalent salts

Dispersion Factors (continued)

Temperature

Avicel® RC-591 microcrystalline cellulose can be dispersed in either hot or cold water. A lower viscosity is obtained when hot water (>60°C) is used. Thixotropy is also reduced but remains a characteristic flow property.

If hot water must be used in dispersing RC-591 when a high viscosity is also required, then approximately 0.5% additional Avicel RC-591 will compensate for the temperature difference.

Glycols/Polyols

Avicel RC-591 will not disperse in glycols or alcohols alone. However, once an aqueous dispersion is formed, water miscible liquids can be added (Fig. 15).

A formulation requiring a large quantity of glycols may have a limited amount of water available for an RC-591 dispersion. In this case, a portion of the water may be replaced with glycerin or sorbitol 70%. Figure 16 shows examples of "replacement" quantities and the resulting viscosities. However, substituting even a portion of the water used to disperse Avicel RC-591 is not recommended. (Fig. 16).

Compatibility of Avicel RC-591 with Miscible Liquids

Parts of 1% Avicel RC-591 Dispersion/Parts of Water Miscible Liquid:

40/60 Ethanol 40/60 Propylene Glycol
40/60 Glycerine 40/60 Sorbitol Solution (70%)

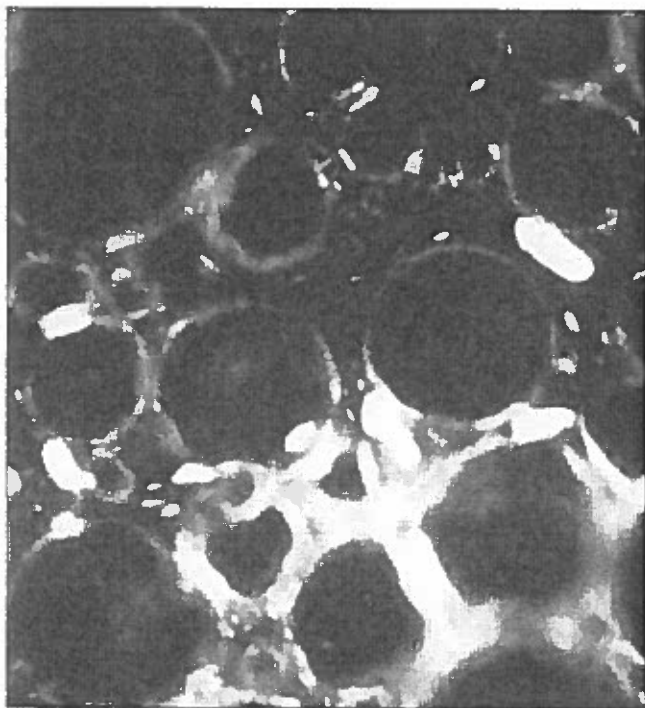
Figure 15.

Viscosity Comparisons of 3.75% Avicel RC-591 Dispersions With Glycols/Polyols

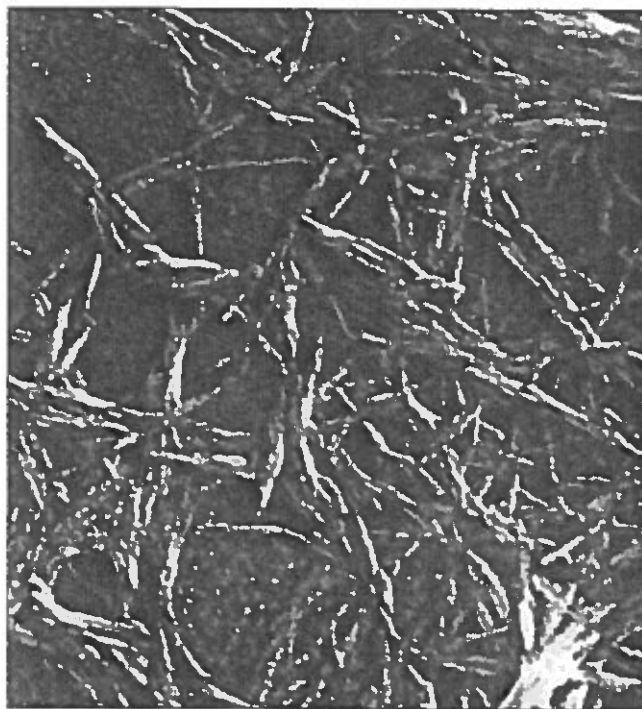
Water (ml)	Glycerin (ml)	Sorbitol 70% (ml)	Alcohol (ml)	Viscosity (cps)
300	100			16,000
300		100		28,000
300			100	2,000
400				22,000

Figure 16.

Avicel® RC-591 Microscopic Features

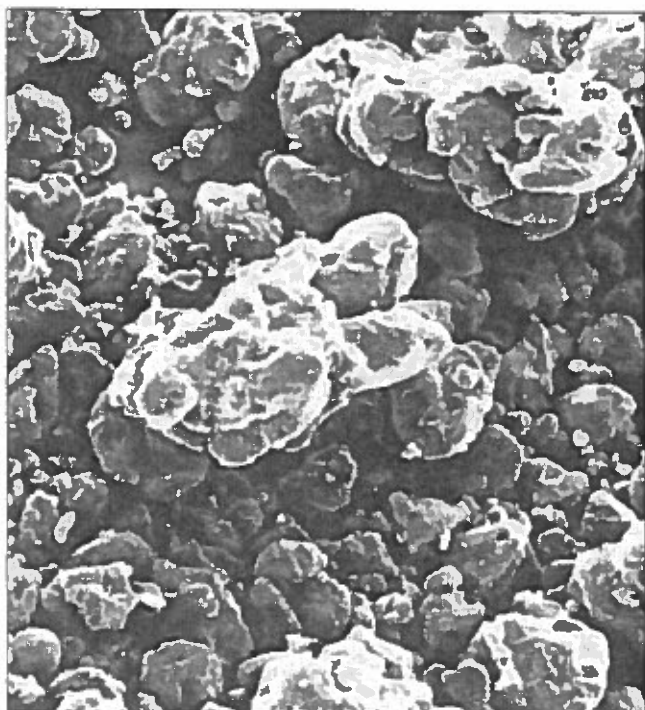


Avicel® RC-591 oil and water emulsion



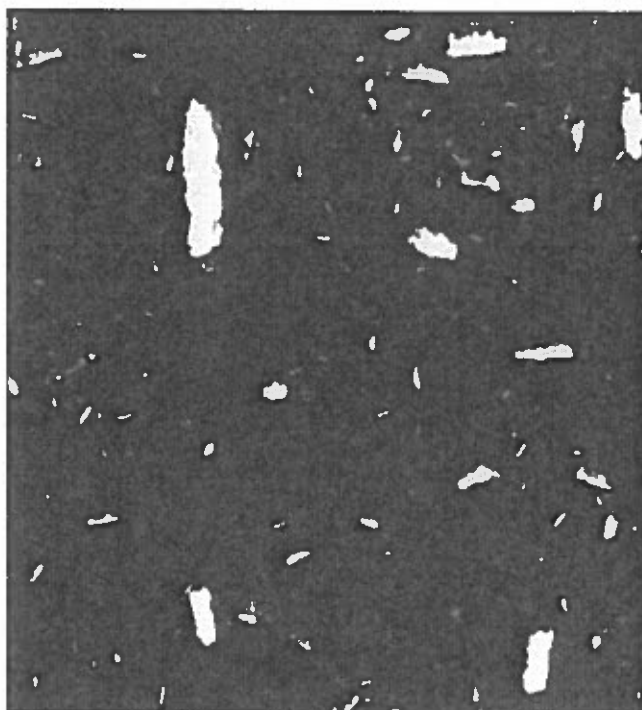
Avicel colloidal before drying with hydrophilic dispersant

200X



Avicel RC-591 powder particles

300X



Fully dispersed Avicel RC suspension

Avicel® RC-591 as an Emulsion Stabilizer

Avicel RC-591 particles make excellent emulsifying agents or emulsion stabilizers for oil-in-water systems. This is due to the unique crystalline structure of cellulose from which RC-591 is derived. (Fig. 17).

Avicel RC-591 colloidal particles help create a stable oil-in-water emulsion by:

- Congregating at the oil/water interface
- Reducing oil droplet movement and possible coalescence when sufficient RC-591 is used to produce a yield value in the aqueous phase

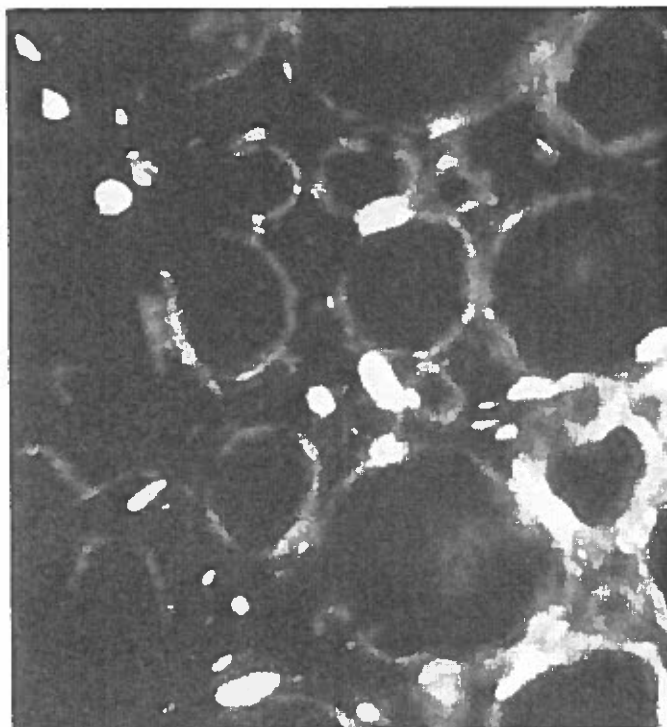


Figure 17.— Avicel RC-591 emulsion

Mechanism

Avicel particles are wetted by oil and water. The particles reside at the oil/water interface producing an interfacial film of considerable strength and stability. (Fig. 18).

The film formation is a result of the molecular character of cellulose as well as the Avicel RC-591 crystalline structure. It has been observed that hydroxyl groups available within the lattice of the cellulose molecules are aligned in one plane. The two hydroxyl dominant sides of the crystal have an affinity for water while the remaining two sides of the crystal are more readily wetted by oil. Therefore, the crystals line up at the oil/water interface to physically structure an emulsion.

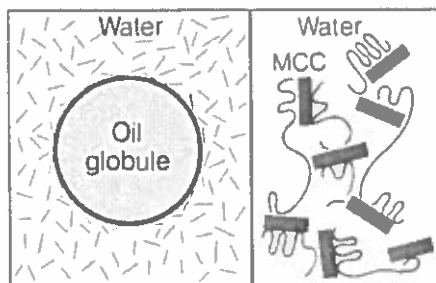
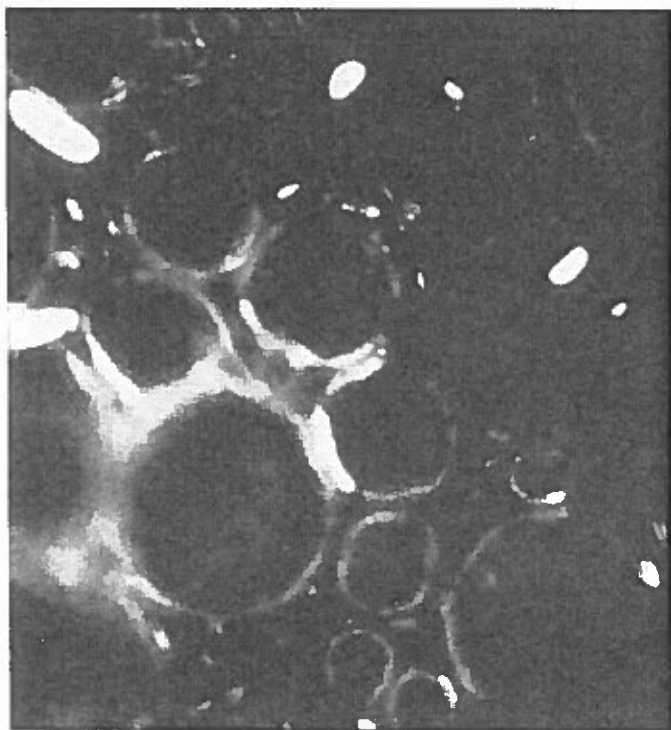
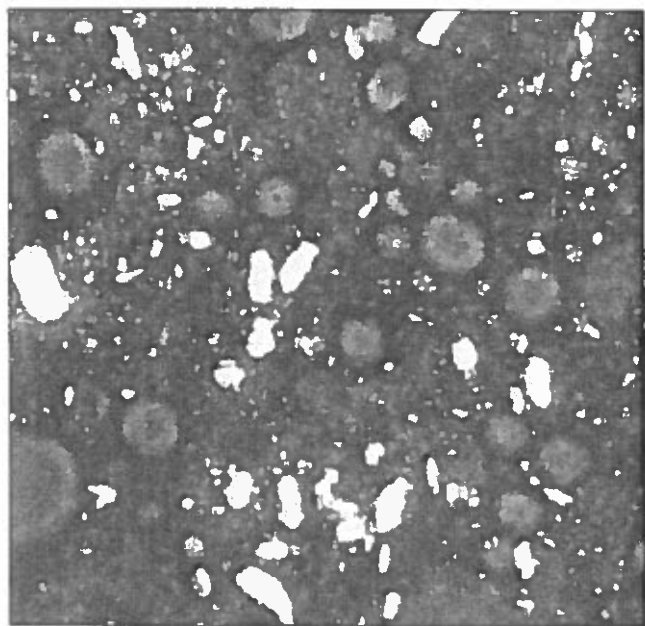


Fig. 18 MCC stabilizes emulsions



Manufacturing

- Because Avicel® RC-591 microcrystalline cellulose does not lower the interfacial tension of an oil/water system, high shear must be used to produce small oil droplets.
- Avicel RC-591 must be dispersed in water prior to the addition of other water soluble excipients. (Do not add RC-591 powder directly to the emulsion after the oil and water phases have been combined.)
- Small amounts of surface active materials should be added to a formulation to produce an emulsion of very small particle size.



Undispersed Avicel RC-591 emulsion system

Stability

Emulsions made with Avicel RC-591 are stable:

- Under sterilization conditions
- After prolonged storage
- Under freeze-thaw and stress testing conditions

Avicel® Colloidal Dispersion Procedures

Avicel colloidal (RC/CL grades) microcrystalline cellulose products are water-dispersible, water-insoluble hydrocolloid materials used in the preparation of pharmaceutical suspensions and emulsions. These products are co-processed mixtures of microcrystalline cellulose (MCC) and sodium carboxymethylcellulose (CMC). The MCC provides a structured dispersion vehicle while the CMC serves as a protective colloid, as well as facilitating dispersion. This section describes techniques and critical factors in dispersing Avicel colloidal and demonstrates performance attributes due to proper and improper dispersion.

When fully dispersed in water, these products possess unique functionality as structured, thixotropic gel systems. *Proper dispersion of Avicel colloidal is critical to obtaining this functionality.* If the Avicel is flocculated or not completely dispersed, the performance of the formulation will not be at its optimum level; inconsistent viscosity and performance results will be obtained.

Key factors to consider when dispersing Avicel RC/CL products are:

Order of addition — Avicel colloidal should be dispersed in water *before* other ingredients are added. Avicel does not bind water like other hydrocolloids and, therefore, will not interfere with the subsequent addition of other ingredients. However, water availability is important in the dispersion step to aid distribution of shearing energy to insure full dispersion.

Type of shear — The Avicel colloidal product used depends upon the amount of shear available in your process. The most readily dispersible products, Avicel® RC-591 and CL-611, can be fully dispersed with high speed mixing (e.g. Silverson®, Cherry-Burrell®). Less easily dispersed is Avicel RC-581, which requires homogenization (Fig. 19, Page 14). Homogenization of RC-591 and CL-611 dispersions can affect ultimate gel strength (Fig. 20, Page 15).

How to verify dispersion

- Visible clumps of powder are clearly indicative of undispersed material. Beyond that, however, the verification of proper dispersion requires an analytical approach.
- The most certain measure is to match your dispersion characteristics to a proper dispersion curve profile. Chart 1 demonstrates the dispersion profile of a typical RC-591 product. Initially, viscosity increases dramatically. This is a common effect when dispersing/dissolving gums and is caused by the apparent viscosity of undispersed lumps of material. As shear continues, the viscosity begins to drop and eventually becomes less apparent; it is at this point that Avicel can be said to be properly dispersed.
- This approach should be used in both product development and scaleup to verify dispersion.
- An optical method is a less precise, but sometimes adequate, means of checking dispersion. The photographs under polarized light show fully dispersed and undispersed Avicel.

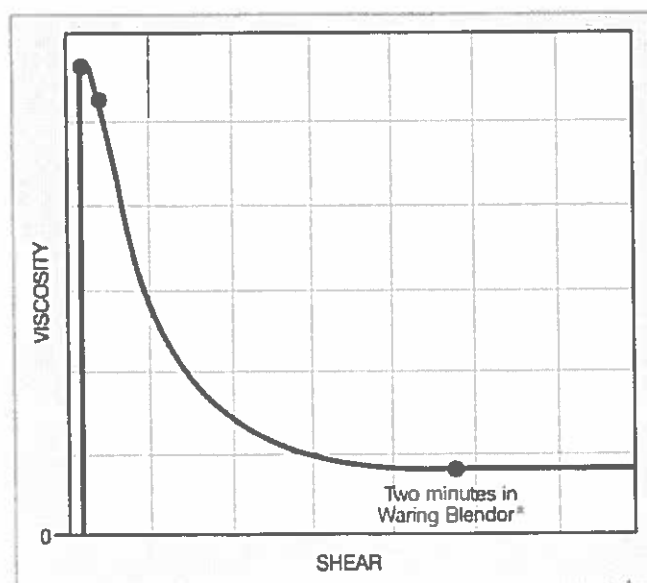
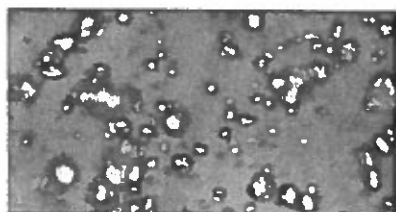


Chart 1. — DISPERSION PROFILE. Shear vs Viscosity

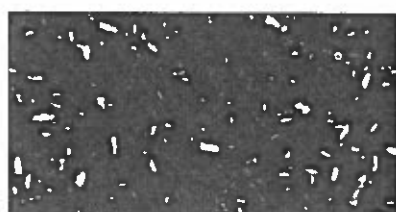
Checking Your Dispersion

- If Avicel® microcrystalline cellulose did not achieve dispersion, clumps of powder will be visible.
- If Avicel is properly dispersed, you will see a very even crystalline pattern under *polarized light*.
- If your dispersion is flocculated, you will see gaps where no microcrystals are present.
- To prevent flocculation, we recommend that a protective colloid be added immediately after dispersing Avicel. Carboxymethylcellulose and xanthan gum are the best protective colloids and should be added at 15-20% of the *weight of Avicel*. These colloids can also beneficially affect suspension properties.



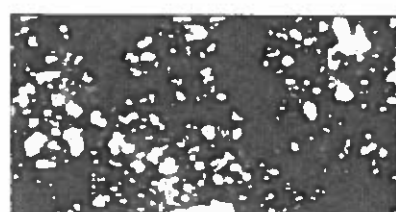
Undispersed

100x polarized light



Fully Dispersed

100x polarized light



Flocculated

100x polarized light

Factors that can interfere with obtaining a good dispersion

- Inadequate shear — refer to dispersion methods.
- Hard water/electrolytes — cations can cause flocculation.
- Improper order of addition — as noted above, Avicel® should be dispersed before addition of other ingredients.
- To prevent flocculation, protective colloids such as xanthan, methylcellulose, and carboxymethylcellulose can be added, generally at 15-20% w/w % of Avicel.

- Low pH — if the pH of the system is less than 4, a protective colloid may be needed.

Examples

While each mixing/dispersion system may be different, the following examples illustrate the requirements and relative dispersion performance of various dispersion mechanisms with varying batch sizes. Your own system should be evaluated to insure the proper dispersion times for the type of equipment and batch size. The following Figures (19, 20, 21) describe: Dispersion of Avicel RC-591; Comparison of Avicel RC-591 to Other Avicel Colloidal Types; and Effect of Concentration of Avicel RC-591.

Dispersion Equipment	Speed (rpm)	Batch size (liter)	Dispersion time (min.)
Silverson® L 2 R	7500	1	30 seconds
Silverson L 2 R	7500	5	3 - 5
Pressindustria TE3 VR 10	4000	10	2
Pressindustria TE3 VR 50	1500	50	5
Silverson BX	2800	50	4
Silverson BX	2800	150	7 - 8
Silverson GX 10 or FX 10	2950	500	3 - 5
Pressindustria BEMSX type 55	1000	3000	20 - 30

Figure 19. - Dispersion of Avicel RC-591

NOTE: Examples apply to maximum 2% concentration.

Comparing three types of Avicel® microcrystalline cellulose and the influence of concentration and homogenization. Batch size was 1 liter. Avicel was dispersed in demineralized water by stirring with a propeller at 500 rpm during 30 minutes.

Reference	Type	Concentration mg/ml	Homogenization time, minutes	Yield value Pa	Viscosity, mPas
A	RC-591	12	0	4.8	34
B	RC-591	12	1	8.7	27
C	CL-611	12	0	0.6	13
D	CL-611	12	1	0.25	12
E	CL-611	20	0	7.0	27
F	CL-611	20	1	5.6	25
G	CL-611	20	6	2.5	22
H	CL-611	25	0	12.9	40
I	CL-611	25	1	11.9	34
J	RC-581	12	0	0	18
K	RC-581	12	1	4.3	22
L	RC-581	14	1	4.5	28
M	RC-581	14	6	5.0	24
N	RC-581	16	1	6.3	33
O	RC-581	16	6	7.9	28

Conclusion: Avicel RC-581 has to be homogenized.
Avicel RC-591 has a much higher yield value when it is homogenized.
Avicel CL-611 has the highest yield value when it is not homogenized.

Comparable results: RC-591 at 12 mg/ml homogenized, RC-581 at 16 mg/ml homogenized, and CL-611 at 22 mg/ml not homogenized.

Figure 20. — Comparison of Avicel RC-591 to other Avicel colloidal types

Concentration, mg/ml	Yield value	Viscosity at 201 s ⁻¹ , mPas
2	0	3
4	0	6
5	0	8
6	0	11
7	0.2	14
8	0.5	16
9	1.1	19
10	2.4	22
11	4.3	25
12	6.5	27
13	8.8	30
14	10.9	33
16	15.5	42
18	20.0	51
20	26.3	78

Conclusion: 12-14 mg/ml is the right concentration for suspensions.

Figure 21. — Effect of concentration of Avicel RC-591

Viscosity Measurement as Measure of Dispersion

One of the measures used to evaluate hydrocolloid dispersions is the measure of viscosity. Avicel® RC/CL products are thixotropic. A valuable property of thixotropic dispersions is that they establish a gel with a measurable yield point. Upon shear above the yield point the gels break to form a readily pourable liquid. The gel immediately begins to reform when shear is removed. Depending on the formulation, concentration of

Avicel, etc., the time to full gel reformation may vary. The viscosity measurement of gel-forming materials is very dependent on reproducibility in carrying out the analytical method. When comparing results to data obtained by other groups, it is very important to insure that methods, instruments, instrument settings and procedures are carried out exactly.

Methods of Dispersion

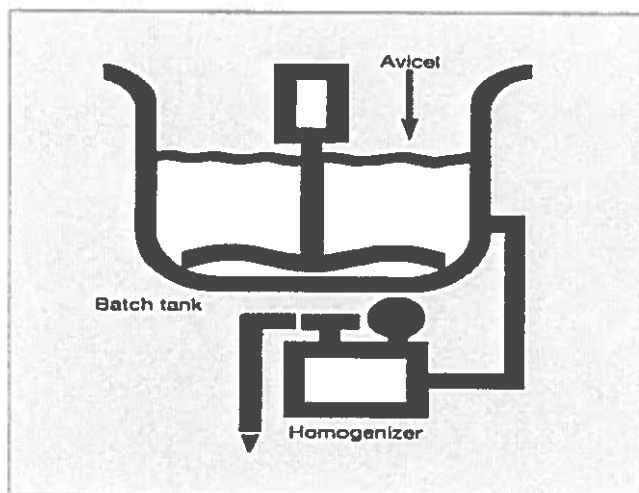
The steps necessary to properly disperse each grade of Avicel are described below.

Bulk-Dried Avicel Colloidal

This procedure pertains to Avicel RC-581 which requires homogenization for dispersion.

Procedure

- Add Avicel to water while agitating.
- Add protective colloids (if required).
- Agitate 10-15 minutes.
- Add other ingredients.
- Hold the salt and acids until last.
- Homogenize at 2000 psi.



Methods of Dispersion (continued)

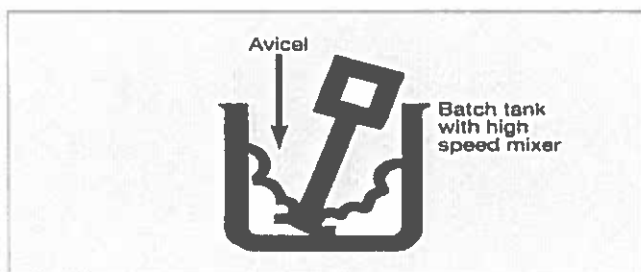
Spray-Dried Avicel® Colloidal

This procedure pertains to Avicel microcrystalline cellulose types RC-591 and CL-611 which require rapid agitation in water for dispersion.

Procedure

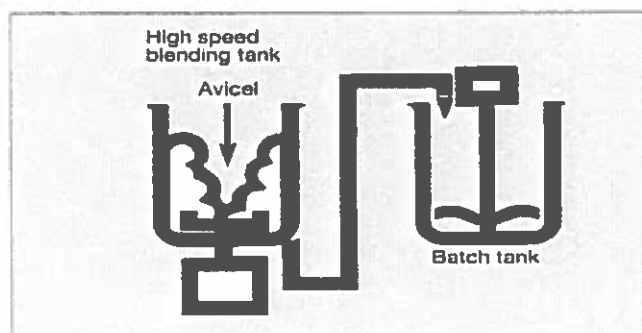
Option I: High-speed mixer

- Add Avicel to the water while agitating.
- Follow with a protective colloid if the pH of your system is less than 4.
- Agitate with high velocity agitator for 10-15 minutes.
- Add the other ingredients.
- Hold the salt and acids until last.



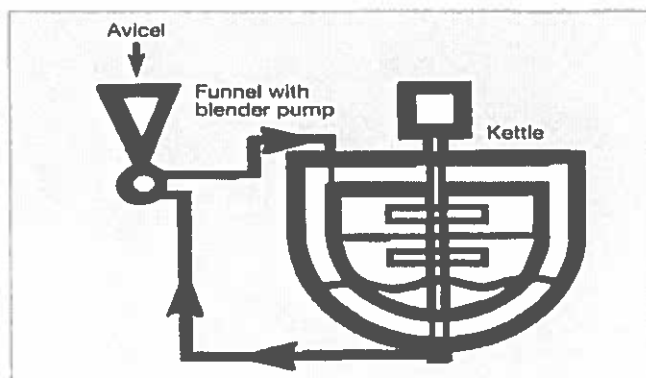
Option III: High-speed blending tank

- Using only the water portion of the batch, activate the Avicel product by utilizing a liquifier type dispersion tank.
- Mix for 3 minutes.



Option II: Funnel with blender pump

- Using only the water portion of the batch, activate Avicel using an ingredient funnel with a pump.
- Continue pumping for 10-15 minutes following the addition of Avicel.



Summarizing...

Avicel® RC-591 microcrystalline cellulose is a versatile, colloidal dispersion vehicle with broad pharmaceutical applications:

- Suspending agent
- Emulsion stabilizer
- Oil/water emulsifier

Formulation Benefits of Avicel RC-591

- Modifies viscosity
- Possesses thixotropic properties
- Stable under extreme temperatures
- Stable over wide pH range
- Long shelf-life stability

FMC Corporation

FMC BioPolymer

United States

Philadelphia, Pennsylvania

Sales/Technical Assistance:

Tel: 1 215 299 6534

Fax: 1 215 299 6669

Customer Service:

Tel: 1 800 526 3649

Fax: 1 215 299 6475

Europe

Brussels, Belgium

Sales/Technical Assistance:

Tel: +32 2 775 8311

Fax: +32 2 775 8300

Customer Service:

Tel: +353 21 4354 133

Fax: +353 21 4353 057

Asia-Pacific

Hong Kong

Tel: +852 2839 6600

Fax: +852 2576 3770

Tokyo, Japan

Tel: +81 3 3402 3739

Fax: +81 3 3402 3700

Latin America

Montevideo, Uruguay

Tel/Fax: +5982 6043030

Tel/Fax: +5982 6043104

Middle East

Amman, Jordan

Tel: +962 6 4618150

Fax: +962 6 4618156

www.fmcbiopolymer.com

pharm_info@fmc.com

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The products, processes and uses thereof described herein are covered by one or more patent applications or patents.

Warranty

Because of the numerous factors affecting results FMC ingredients are sold on the understanding that purchasers will make their own test to determine the suitability of these products for their particular purpose. The several uses suggested by FMC Corporation are presented only to assist our customers in exploring possible applications. All information and data presented are believed to be accurate and reliable, but are presented without the assumption of any liability by FMC Corporation.

Technical Service

The information contained in this bulletin is intended to be general in nature. Techniques and data pertaining to specific uses for FMC ingredients and new developments will be published periodically in the form of supplemental application bulletins.

Our technical staff is ready to offer assistance in the use of Avicel® RC-591.

Regulatory Status

Avicel RC-591, a colloid forming attrited mixture of microcrystalline cellulose and carboxymethylcellulose sodium, meet the standards set forth in the United States Pharmacopoeia/National Formulary for "microcrystalline cellulose and carboxymethylcellulose sodium" and in the British Pharmacopoeia for dispersible cellulose.

The colloid forming attrited mixtures of microcrystalline cellulose and sodium carboxymethylcellulose are generally recognized as safe (GRAS) by qualified experts. FMC maintains a Type IV Drug Master File (Excipients) to support the use of Avicel RC-591 in drug products.

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RC-591 (5/99)