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Sarkar

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[54] **PHARMACEUTICAL CAPSULES FROM IMPROVED THERMOGELLING METHYL CELLULOSE ETHERS**

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 528,830, Dec. 2, 1974, abandoned.

[52] **U.S. Cl.** ..... **536/84;** 106/170; 106/197 R; 264/25; 264/301; 264/DIG. 37; 424/35

[51] **Int. Cl.²** **B29C 13/00;** C08B 11/08; C08B 11/193

[58] **Field of Search** ..... 260/231 A, 231 R; 264/25, 301, DIG. 37; 424/35; 106/170, 197 R

[56] **References Cited**

UNITED STATES PATENTS

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3,453,261	7/1969	Scherff	260/231 A
3,493,407	2/1970	Greminger et al.	264/301
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3,712,886	1/1973	Koyanagi et al.	260/231 R
3,852,421	12/1974	Koyanagi et al.	260/231 R
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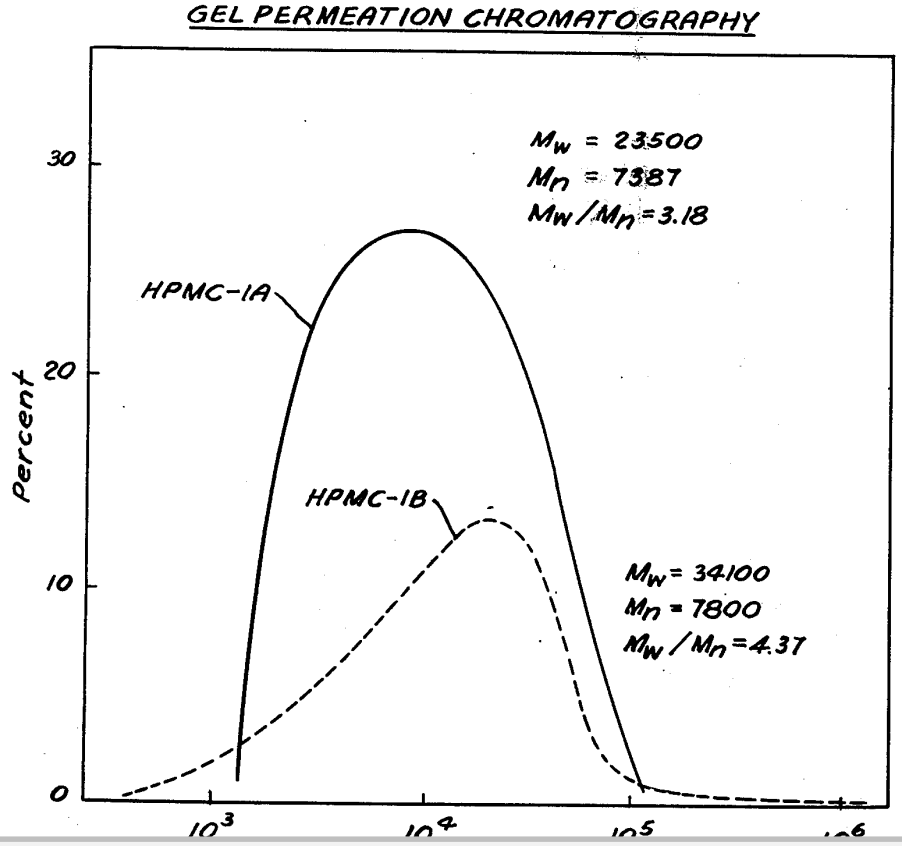
Primary Examiner—Ronald W. Griffin
Attorney, Agent, or Firm—David B. Kellom

[57] **ABSTRACT**

Improved thermogelling methyl cellulose ether compositions for use in preparing pharmaceutical capsules by the pin dip coating process are prepared by blending the properties of water soluble methyl and C_2-C_3 hydroxyalkyl cellulose ethers to achieve an essentially Newtonian dip coating solution and a rapid high thermal gel yield strength. These properties require a cellulose ether with a relatively narrow molecular weight distribution. Blends of low viscosity methyl cellulose and hydroxypropylmethyl cellulose provide particularly suitable dip solution properties, gel yield strength, and capsule dissolution rates.

10 Claims, 2 Drawing Figures



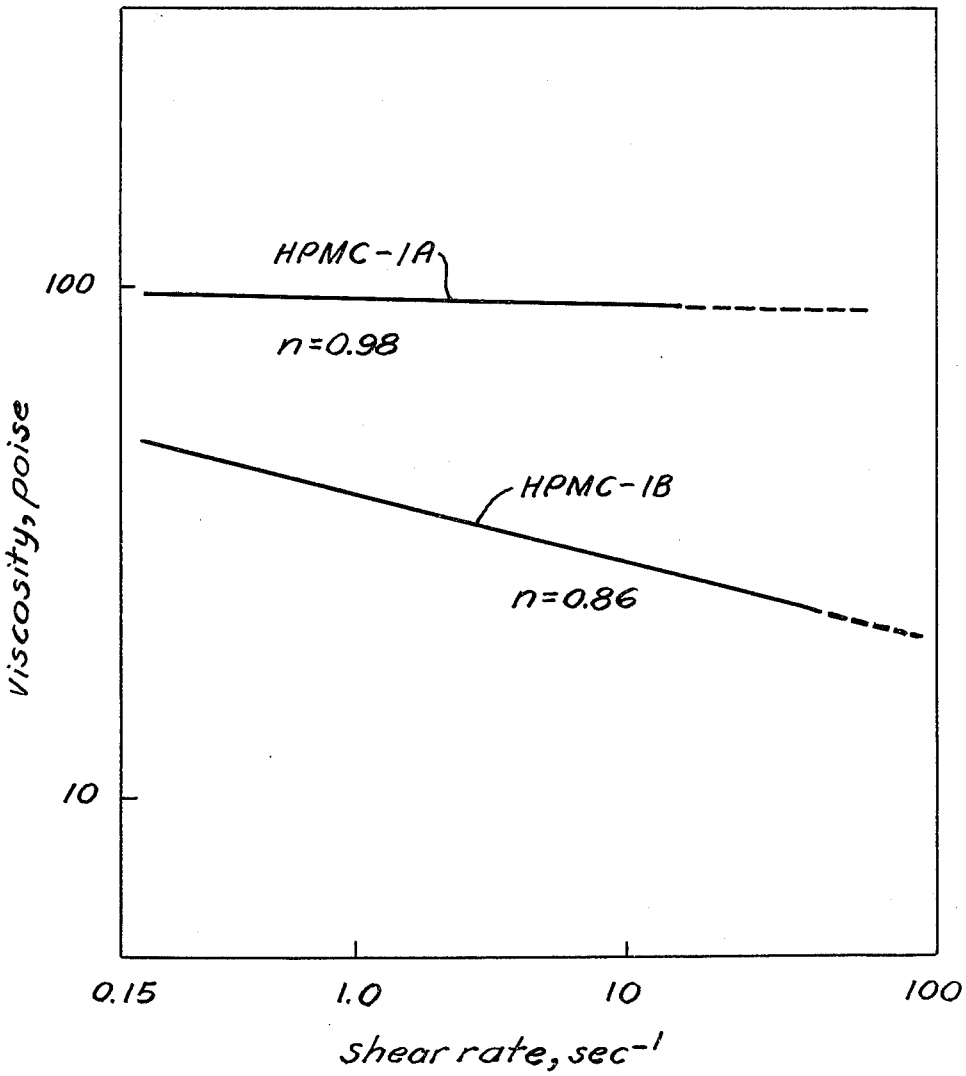


Fig. 1

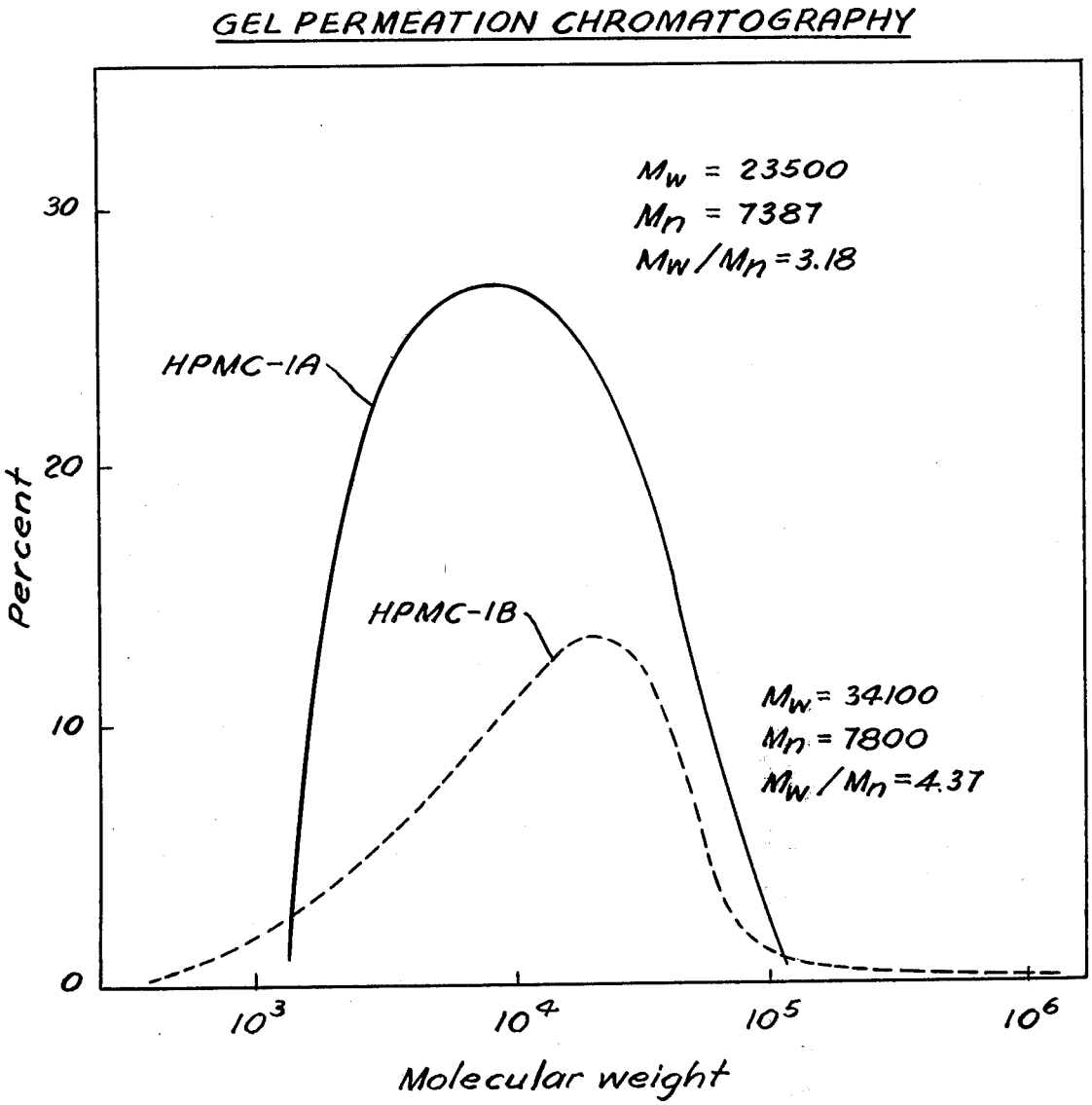


Fig. 2

PHARMACEUTICAL CAPSULES FROM IMPROVED THERMOGELLING METHYL CELLULOSE ETHERS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 528,830 filed Dec. 2, 1974, now abandoned.

BACKGROUND OF THE INVENTION

In 1950 Murphy U.S. Pat. No. 2,526,683 first described a process for preparing methyl cellulose medicinal capsules by a dip coating process using the apparatus described in U.S. Pat. No. 1,787,777 or similar dip coating apparatus. The process consists of dipping a capsule forming pin pre-heated to 40°–85° C into a cellulose ether solution kept at a temperature below the incipient gelation temperature (10°–30° C), withdrawing the pins at a predetermined withdrawal speed and then placing the pins in ovens kept at temperatures above the gelation temperature (45°–85° C), exposing the pins to a lower temperature first and then gradually to higher temperature until the film is dry. The dry capsule is then stripped, cut to size and the body and caps are fitted together.

The resulting methyl cellulose capsules had several advantages over conventional gelatin capsules including resistance to microorganisms and greater stability under extreme humidity conditions. However, these capsules failed to dissolve in the gastrointestinal fluid at body temperature in an acceptable time. Furthermore, the different rheological properties of the thermally gelling methyl cellulose made handling on the Colton machines designed for gelatin extremely difficult.

To overcome some of these problems, Greminger and Davis, U.S. Pat. No. 3,493,407, proposed the use of non-thermal gelling dip coating solutions of certain hydroxyalkylmethyl cellulose ethers in aqueous solvents. Langman, U.S. Pat. No. 3,617,588, describes the use of an induction heater to thermally gel cellulose ether dip coated pins after removal from the coating bath. However, these advances have not yet met the rigid requirements of commercial production.

STATEMENT OF THE INVENTION

The invention relates to medicinal capsules, particularly to capsules of thermal gelling cellulose ethers such as methyl cellulose and hydroxypropylmethyl cellulose. These cellulose ethers are soluble in cold water and insoluble in hot water. The viscosity of aqueous solutions decreases with the rise in temperature and then rapidly increases through a relatively narrow range of temperature with gel formation a few degrees above the temperature at which minimum viscosity is observed.

This thermogelling characteristic is critical to the dip coating process. However, some rigid restrictions that the solution must follow from a rheological standpoint have now been identified by further research. These discoveries have led to improved methyl cellulose ether compositions for producing medicinal capsules. By controlling the non-Newtonian properties of cellulose ether solution, the gel strength at elevated temperature, and the solution rate of the capsules by proper adjustment of molecular weight distribution, degree and type of substitution, improved medicinal capsules are obtained.

More specifically, these improved cellulose ether compositions for use in preparing pharmaceutical capsules by the pin dip coating process are characterized by having:

A. A methoxyl degree of substitution (DS) of about 1.5–2.0 and a C_2-C_3 hydroxyalkoxyl molar substitution (MS) of about 0.1–0.4;

B. As a 2 wt % aqueous solution, a viscosity of about 2–10 cps at 20° C and a thermal gel point of about 50°–80° C;

C. As a 15–30 wt % aqueous solution at 20° C, a viscosity of about 1,000–10,000 cps with essentially Newtonian fluid properties as defined by a power law coefficient, n, of 0.9–1.0 at shear rates of between 0.1–10 sec^{-1}; and

D. As a 15–30 wt % aqueous solution, a 50 sec gel yield strength at 65° C of at least 150 dynes/cm^2.

In practice the capsules are prepared by dipping pins preheated to about 40°–85° C in an aqueous dip coating bath containing about 15–30 weight percent of the improved cellulose ether composition at a bath temperature below about 40° C. The dip coated pins are then withdrawn and dried at a temperature above the gel point of the cellulose ether to obtain the dry capsule shells.

General Description — Rheological Requirements

In spite of continued developments in the design of capsule dip baths, as shown for example by Whitecar, U.S. Pat. No. 3,592,445, the rheological requirements of the dip solution used with the Colton capsule machines have not been previously examined in detail.

When the hot pin is dipped into the solution in the dipping dish, the solution gels in the surface of the pin and as the pin is withdrawn, a film of gelled liquid of certain thickness is formed on the pin. The pin is then turned 180° to an upright position and placed in the oven to dry. To obtain the desired 4±0.5 mils dry film thickness, a wet gel thickness of about 20–60 mils is required. Furthermore it is essential that the wet gel film thickness as the pin is withdrawn be quite uniform and that the wet film have sufficient strength to prevent rundown or other distortion from gravitational pull on the film or rotational forces as the pin moves to the drying oven.

To achieve the essential uniform coating of the pins with a wet thermal gel of sufficient strength, requires that the cellulose ether dip coating solution and the thermal gel meet some rigid rheological requirements.

First the cellulose ether concentration of the solution in the dipping dish must be sufficiently high (15–30 percent) to ensure proper film formation and ease of drying. Then the complex flow patterns in the dipping dish and around the pins result in a shear rate on the moving pin that varies from point to point. To obtain uniform wet gel film thickness under these conditions requires that the dipping solution be essentially Newtonian.

Assuming a 12.5 percent variation of film thickness is acceptable (4.0±0.5 mils), the viscosity variation between the highest and lowest shear rates on the pin should not be more than 25 percent. Using the standard viscosity power-law equation (cf. Van Wazer ea "Viscosity and Flow Measurement", Interscience Publishers, New York, 1963, p. 15):

$\eta = K\sigma^{n-1}$

where η is the viscosity, σ the shear rate, K the consistency index constant, and n the power law coefficient, it has been found essential that the dip coating solution have a power law coefficient of 0.9–1.0 over a shear rate range of 0.1–10 sec^{-1} to achieve the requisite gel film uniformity.

Such an essentially Newtonian solution (n=0.9–1.0), can be obtained by appropriate control of the cellulose ether molecular weight and dip bath conditions. Thus as shown further in the examples it is important to keep:

1. The molecular weight fairly low, i.e., a 2 wt % aqueous solution viscosity of about 2–10 cps at 20° C;
2. The molecular weight distribution fairly low with minimum amount of very high MW fractions, i.e., less than about 0.1 wt % MW above 200,000;
3. The salt concentration in the bath less than 1 wt % and
4. The dip bath concentration and temperature as low as possible consistent with the necessary wet gel thickness.

The importance of the molecular weight distribution is shown in FIG. 1. The two hydroxypropylmethyl cellulose ether samples have essentially the same chemical composition and 2 percent aqueous solution viscosities. However Sample B, with a wide molecular weight distribution and more than 0.15 weight percent of a very high MW fraction, has a wholly unacceptable power law coefficient of 0.86. In general a M_w/M_n ratio less than about 3.5 is desired.

Secondly, in order to prevent rundown or other displacement of the wet thermal gel film prior to oven drying, the gel must have enough yield strength to counteract gravitational and rotational stresses while in wet form on the pin. For normal Size 000 to Size 5 pharmaceutical capsule body and cap pins (average diameters of 0.452–0.983 cm), yield values (S) calculated as a function of wet gel thickness required to eliminate rundown of wet gel range from about 60 to 160 dynes/cm^2 for wet film thicknesses of 20–50 mils. In practice a wet gel yield strength of at least 150 dynes/cm^2 measured after 30–50 sec at 65° C is desirable to cover the normal range of capsule sizes.

Factors found to influence the wet gel strength of aqueous cellulose ether solutions include:

1. The degree and type of alkyl substitution;
2. A high cellulose ether molecular weight;
3. High cellulose ether concentrations; and
4. High pin and oven temperatures.

Clearly a proper balance must be achieved of properties affecting the Newtonian character of the dip bath and the strength of the wet gel.

Methyl Cellulose Ethers

Critical to this invention are certain properties of the thermogelling methyl cellulose ether composition. That it has a 2 percent aqueous solution viscosity of about 3–10 cps and gel point of about 50°–80° C was recognized in the prior art. Also the degree and type of ether substituents is known to affect the rate of capsule dissolution in gastrointestinal fluid. However, the criticality of the molecular weight distribution, the wet gel yield strength, and the effect of the substituents on the gel strength have not been previously identified.

Required is a methyl cellulose ether composition hydroxylalkoxyl MS of about 0.1–0.4. The substituents can be combined in a single hydroxyalkylmethyl cellulose ether such as a hydroxypropylmethyl cellulose ether having a methoxyl DS of about 1.50–2.00 and a hydroxypropoxyl MS of about 0.1–0.3 and a 2 percent aqueous solution viscosity of about 2–10 cps at 20° C.

Alternately compositions with suitable substitution can be obtained by blending methyl cellulose with non-ionic hydroxyalkyl cellulose ethers. Particularly useful are blends of a methyl cellulose having a methoxyl DS of about 1.64–1.90 and a 2 percent aqueous solution viscosity at 20° C of about 5–4000 cps with hydroxypropylmethyl cellulose hydroxyethylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxyethylhydroxypropylmethyl cellulose, etc. Most useful are non-ionic hydroxyalkyl cellulose ethers having a 2 percent aqueous solution viscosity of about 2–10 cps at 20° C. and a thermal gel point below 100° C. Thus as shown in Example 2B blends of 20–50 weight percent methyl cellulose (methoxyl DS of 1.64–1.90) and 80–50 weight percent hydroxypropylmethyl cellulose (methoxyl DS of 1.68–1.80, hydroxypropoxyl MS of 0.17–0.30) provide a ready means for controlling rheological and other properties critical to this invention.

For example, a capsule prepared from 9 cps methyl cellulose (1.64–1.90 DS) required 20 minutes to dissolve under normal gastrointestinal conditions in contrast to the usual 3 minutes for gelatin capsules. But a 1:2.67 blend of this methyl cellulose with 2–10 cps hydroxypropylmethyl cellulose provides a capsule that dissolves in 4 minutes.

Suitable cellulose ethers are commercially available. However, their normal characterization by viscosity and type and degree of substitution is not alone adequate to define the improved cellulose ether compositions. As shown in Example 1, the rheological characteristics of the aqueous dip bath are extremely sensitive to other properties of the cellulose ether. To obtain an essentially Newtonian solution as defined by a power law coefficient (n) of 0.9–1.0 at shear rates of between 0.1–10 sec^{-1} requires a fairly narrow molecular weight range and elimination of any very high MW fractions. The presence of as little as 0.1 weight percent of a cellulose ether fraction having a molecular weight above about 200,000 will cause the solution to be non-Newtonian (n<0.9).

In practice, the power law coefficient determined at dip bath concentration (15–30 weight percent) and temperature (below about 40° C) at shear rates between 0.1–10 sec^{-1} is an accurate and functional measure of a suitable cellulose ether composition.

The gel strength of the cellulose ether solution is also greatly influenced by the ether substituents. Firmest gels are obtained with methyl substitution while hydroxyalkyl substituents provide softer gels with usually higher gel point temperatures. As noted above, a 50 sec yield value of at least 150 dynes/cm^2 and preferably about 150–300 dynes/cm^2 is required for effective operation with normal size capsule pins.

Again a direct measurement of the wet gel strength provides suitable process control. Also blends provide a ready means for adjustment to achieve the desired final properties.

Finally, note that the solution rate and gel strength both depend on hydroxypropyl substitution but in an opposite way. That is, solution rate of cellulose ether

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