

WATER-SOLUBLE CELLULOSE DERIVATIVES

FACTORS AFFECTING THE VISCOSITY OF AQUEOUS DISPERSIONS. PART I

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The effects of temperature and of the presence of acid and alkali on the viscosity of aqueous dispersions of methyl-, methylethyl- and sodium carboxymethylcellulose have been studied. Irreversible viscosity decreases may occur on heating dispersions of all three. The magnitude of the decrease varied with the temperature and time of heating, and with the viscosity grade and type of derivative. The efflux time reductions caused by heat in the presence of acid were greater than in neutral or alkaline dispersions. Viscosity changes may also occur in unheated dispersions in the presence of acid and alkali. The magnitude of the changes was related to the pH value of the dispersion, the time of storage and the nature of the derivative. There were no significant pH changes in the dispersions either on heating or after storage.

By substituting alkoxy for a certain proportion of the hydroxyl groups in the anhydroglucose unit of the cellulose molecule, derivatives can be prepared which disperse in water to give viscous colloidal solutions. This property of water-solubility in cellulose ethers has been attributed to the ability of the substituent groups to prise apart adjacent cellulose chains, thereby rendering the remaining unsubstituted hydroxyl groups accessible to hydration^{1,2}. Water solubility depends partly on the chain length of the molecule, but to a greater extent on the nature of the substituent radicals, their evenness of distribution throughout the chain and their numerical ratio to the unsubstituted hydroxyl groups^{2,3}. Some derivatives, such as methyl- and methylethylcellulose, are soluble in cold water only; others, for example, sodium carboxymethylcellulose, are soluble both in cold and hot water, and this forms a convenient basis of classification. An important property of these ethers is the viscous nature of their aqueous dispersions. Although this viscosity is to some extent dependent on the degree of substitution, in the absence of certain complicating factors, it is essentially a function of the chain length of the molecule. Consequently, processes involving controlled degradation can be applied during manufacture to produce several viscosity grades of the same derivative⁴.

Monographs on methyl- and sodium carboxymethylcellulose were included for the first time in the United States Pharmacopeia in the fifteenth revision and their possible uses as gelling, suspending and emulsifying agents are now being recognised in Britain. Their suitability as such largely depends on the stability of the viscosity of their dispersions. From the literature it is apparent not only that gross variations in viscosity can occur, but that the various ethers behave differently. However, no published comparison which provides a basis for a selective and informed approach to formulation has been found. Further, although

viscosity variations might be expected to occur in the absence of visible reaction products, much of the work on the incompatibilities of these materials has been based on observations of precipitate-formation. These considerations led us to study the conditions under which viscosity changes occur in aqueous dispersions of the three most commonly used cellulose derivatives. The effects of concentration, temperature and the presence of acid and alkali are discussed in the present paper.

MATERIALS AND APPARATUS

Three viscosity grades of methylcellulose* and of sodium carboxymethylcellulose† (hereinafter referred to as low, medium and high) and one grade of methylethylcellulose‡ were studied in detail. All tests were made on single production batches of these materials. The batches were well mixed and their uniformity confirmed by viscosity determinations on several random samples.

The dispersions were made with Purified Water B.P. The chemicals, with stated exceptions, were of A.R. quality. Viscosities of dispersions containing added acid and alkali were measured with a U-tube viscometer (Ostwald No. 3). Others were measured with a Redwood No. 1 viscometer. All measurements were made at 25° except those on the effects of temperature variation.

pH measurements were made with a glass electrode on a Cambridge meter.

PREPARATION OF DISPERSIONS

Dispersions of all three ethers were prepared as follows: Half the required amount of distilled water containing 0.002 per cent phenylmercuric nitrate B.P. was added at 80° to 90° to weighed quantities of the cellulose derivative in a beaker. The mixture was stirred at intervals for 30 minutes and then made up to volume with distilled water at room temperature. The dispersion was then left to stand with occasional stirring for 24 hours.

With the low viscosity grade of methylcellulose and the sample of methylethylcellulose anomalous viscosity readings were observed; these were traced to undispersed fibre. The difficulty was finally overcome by passing the dispersions through a hand-operated homogeniser. The viscosities of the mucilages were not altered by this treatment.

One other variation was observed. This was a progressive decrease in viscosity for the first few viscosity readings. The following are typical: 457, 454, 452, 447, 446, 446 seconds. There was no evidence that the effect was due to the shearing of gelatinous aggregates, and Heymann's⁵ work on methylcellulose sols does not suggest that thixotropic phenomena are encountered at temperatures much below gel point. Other investigators⁶, however, considering that the colloiddally dispersed particles exist

* Low: Celacol M20 (British Celanese Ltd.).
Medium: Celacol M2500 (British Celanese Ltd.).
High: Methocel 4000 (Dow Chemical Co.).

† Cellofas B, low, medium and high (Imperial Chemical Industries Ltd.).

‡ Edifas A (Imperial Chemical Industries Ltd.).

as flexible coils, have advanced the hypothesis that such coils would be deformed in passing through a streaming field and require a definite relaxation time to return to their original shapes. The pattern of results is similar to that observed by Middleton⁷ in the course of viscosity determinations on tragacanth mucilage using a falling sphere viscometer, although his explanation of "stream orientation" would not seem to be applicable in the present instance.

Percentage solutions of the derivatives were made on the basis of the dry weight, calculated by drying at 105° for 3 hours. Methyl- and methylethylcellulose samples contained from 5 to 8 per cent moisture and sodium carboxymethylcellulose from 12 to 15 per cent.

The mean efflux time is from two samples. The average efflux time is from three estimations. Variation between samples falls within ± 3 per cent.

EXPERIMENTAL AND RESULTS

Effect of Concentration

Within the range of concentrations examined, a sensibly linear relation was shown to exist between the concentrations of dispersions and the logarithms of the differences between their efflux times and the efflux time of water. Samples prepared by dilution of more concentrated dispersions gave efflux times similar to those of extemporaneously-prepared dispersions of the same concentration.

Effect of Temperature

On heating dispersions of methylcellulose the viscosity gradually decreases until a temperature is reached (about 50°) at which the ether separates. At this point, depending on the concentration of the dispersion, either discrete gel particles or an opaque continuous gel is formed, and, in the latter case, further small increases in temperature produce large increases in viscosity. On cooling, the gel reverts to a sol. This inverse sol-gel transformation of methylcellulose has been extensively studied by Heymann⁵. We obtained typical heating-cooling curves. The gelation temperature varies inversely with the concentration of the dispersion and the viscosity grade of the derivative. Similar results were obtained with methylethylcellulose, except that the gel differed physically from that produced by methylcellulose, being softer and more easily disrupted. With sodium carboxymethylcellulose, efflux times decreased progressively with rise of temperature, no gel being formed since the derivative is soluble in hot water. With the exception of gelled methylcellulose samples, in which pronounced hysteresis phenomena were observed, heating and cooling curves with dispersions of all three derivatives were nearly coincident.

Effect of Time and Temperature of Heating

Dispersions of methyl- (medium), methylethyl-, and sodium carboxymethylcellulose (medium) of approximately equal efflux times were stored at 50°, 98° and 115° for periods of 15, 30, 45, 60, 120 and 240 minutes. The

dispersions stored at 50° and 80° were rapidly pre-heated to temperature in a water bath before being transferred to an electric hot-air oven. The dispersions at 98° were heated in a free-steaming autoclave, and those at 115° in an autoclave under pressure. Heating at 115° was subsequently extended to a range of concentrations of methylethylcellulose and of the high and low viscosity grades of the two other derivatives. Also studied were the effects of autoclaving dispersions prepared with powdered and fibrous batches of methylcellulose, and dispersions of all three derivatives which had been made acid or alkaline. The influence of heat on the dry materials was also investigated. Efflux times and pH values were measured before and 24 hours after heating the dispersions. The results may be summarised as follows:

Heating dispersions of the three derivatives at 50° (a temperature at which methyl- and methylethylcellulose samples begin to gel) for periods of up to 4 hours had no effect on their efflux times.

Heat at 80° for periods of up to 4 hours had little effect on the efflux times of methyl- and methylethylcellulose dispersions. The efflux times of sodium carboxymethylcellulose dispersions, however, began to decrease after as little as 15 minutes' heating (by 14 per cent), and, after 4 hours' heating, the efflux time had decreased by 33 per cent (Fig. 1).

Heating at 98° for periods of up to 4 hours had little effect on the efflux times of methyl- and methylethylcellulose dispersions. Samples of the former exhibited considerable syneresis at the end of the heating period. With sodium carboxymethylcellulose, 15 minutes heating reduced the efflux time by 27 per cent and 4 hours heating reduced it by 46 per cent (Fig. 1).

The efflux times of dispersions of all three derivatives were lowered by heating at 115°. For methylcellulose the decreases after 15 minutes and 4 hours were 6 and 43 per cent respectively. The corresponding decreases with methylethylcellulose were 11 and 38 per cent and for sodium carboxymethylcellulose 53 and 72 per cent (Fig. 2).

When a range of concentrations of the various viscosity grades of the three derivatives was heated at 115° for 30 minutes the greatest decrease in efflux time among the methylcellulose samples was exhibited by the high viscosity grade, the reduction being 16 to 33 per cent, compared with 10 and 11 per cent for the low and medium grades. Under the same

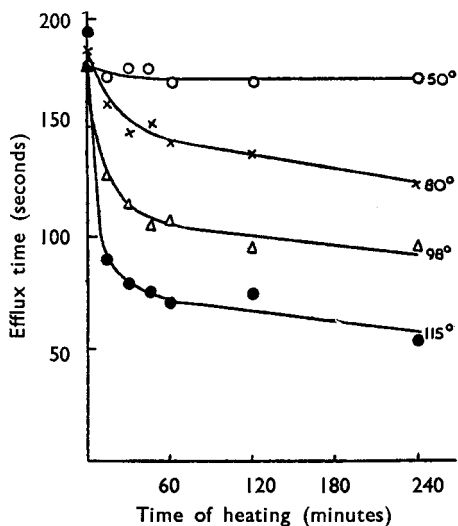


FIG. 1. Variation of efflux time of a sodium carboxymethylcellulose sol (medium) with temperature and time of heating.

conditions, dispersions of sodium carboxymethylcellulose (low) decreased in efflux time by up to about 50 per cent and darkened in colour. With the medium grade the decreases were greater (up to 65 per cent) and in the high grade were lower (maximum 39 per cent).

There was little difference between the efflux time decreases brought about by heating dispersions made with powdered and fibrous samples of four viscosity grades of methylcellulose for 2 hours at 115°.

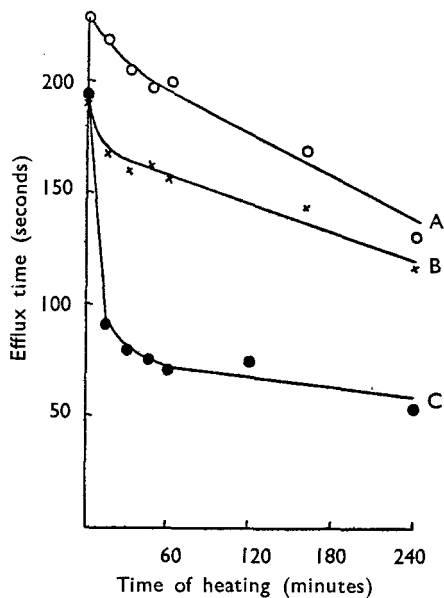


FIG. 2. Variation of efflux time with time of heating at 115°. A, Methylcellulose (medium); B, Methylethylcellulose; C, Sodium carboxymethylcellulose (medium).

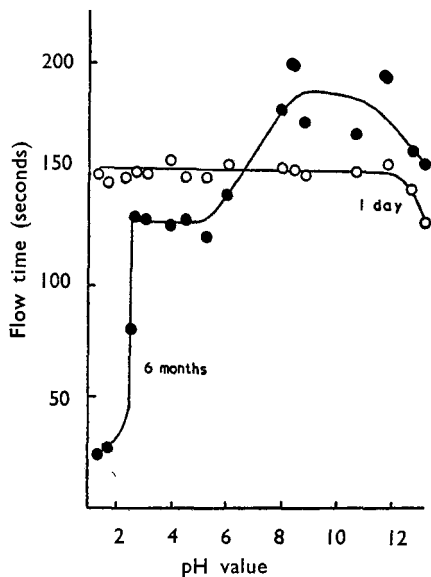


FIG. 3. Variation in flow time of a methylcellulose sol (medium) with pH.

When dispersions which had been made acid with hydrochloric acid (methyl- and methylethylcellulose, pH 3, sodium carboxymethylcellulose, pH 5) or alkaline with sodium hydroxide (pH 10) were heated for $\frac{1}{2}$ hour at 115° together with control samples (methylcellulose, pH 6-7.6; methylethylcellulose, pH 4.7; sodium carboxymethylcellulose, pH 6.5-7.2), the results were as follows:

Methylcellulose (low): Acid, alkaline and control samples remained unaffected; (medium)—acid dispersions showed a flow time decrease of 56 per cent, compared with 4 and 5 per cent, respectively, in the control and alkaline samples; (high)—acid dispersions decreased in flow time by 56 per cent, compared with 19 per cent (control) and 17 per cent (alkaline).
Methylethylcellulose: The flow time decrease in the acid dispersion (16 per cent) was twice as great as in the control and alkaline samples.
Sodium carboxymethylcellulose: The flow time decreases with all three grades were greatest in the acid samples (about 60 per cent). In the control and alkaline samples the decreases were about 50 per cent.

When dispersions were prepared with samples of the derivatives which had been heated at 105° for 4 hours, their efflux times were, in all cases, lower than those of dispersions of the same concentration prepared with non-heated material. For methylcellulose the percentage decreases were 20, 25, and 18, respectively, for the low, medium and high grades; for methylethylcellulose, 20; for sodium carboxymethylcellulose, 30, 34, and 18, for the low, medium and high grades, respectively.

There was no significant variation in the pH values of any of the above dispersions on heating.

Effect of Acid and Alkali

One hundred ml. quantities of dispersions of the medium grades of methyl- and sodium carboxymethylcellulose and of methylethylcellulose were prepared in such concentration that, when diluted with an equal volume of water, the dispersions would have a flow time of between 100 and 200 seconds. Each of these "double-strength" dispersions was then diluted with an equal volume of distilled water to which had been added varying quantities of 0.1N hydrochloric acid or 0.1N sodium hydroxide solution. The pH values of the dispersions were measured initially and at intervals during storage. Flow times were determined initially and after 1 week, 2 months, 4 months and 6 months. All the dispersions were stored in clear glass jars, with screw caps, in daylight, on a shelf. Airtight seals were obtained by dipping the necks of the jars in molten paraffin wax. The results were as follows:

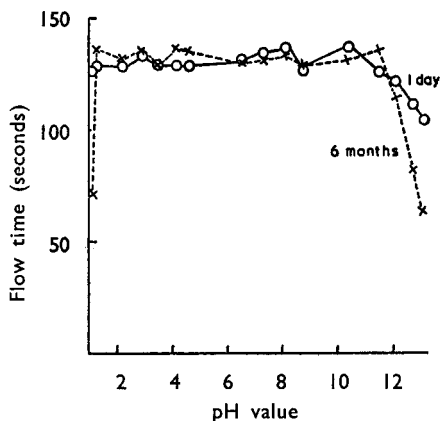


FIG. 4. Variation of flow time of a methylethylcellulose sol with pH.

Methylcellulose: On the first day there were no marked differences in the flow times of dispersions with pH values between 1 and 12. In more alkaline samples the flow time was slightly below the average level. At the end of 7 days there was a marked drop in the flow times of dispersions with pH values below about 2.5. In the remaining samples there was a small diminution in flow times. At the end of 2 months the dispersions below pH 2.5 showed further large decreases in viscosity. There was little difference in the remainder of the samples. At the end of 4 months the viscosities of the most acid dispersions were found to have continued to decrease. The remainder of the acid-containing dispersions remained the same but alkaline samples became more viscous. After 6 months' storage, the two most acid samples had diminished in flow time by over 80 per cent. Between pH 2.5 and pH 6 the losses averaged about 20 per

cent. The increase in viscosity of the alkaline dispersions was marked, all having exceeded their original flow times—two by one third (Fig. 3).

Methylethylcellulose. Dispersions of pH 1.25 to 11.5 retained their original viscosities for 6 months, and flow times of acid, neutral or alkaline samples were the same. The viscosity of a dispersion of pH 1.08 decreased slowly on storage, and, after 6 months, the flow time was reduced by one-half. Dispersions with a pH above 11.5 had, originally, a flow time that was lower than the average for the series. This difference became more marked on storage and the flow time of the most alkaline sample after 6 months was about half that of the dispersions between pH 1.25 and 11.5 (Fig. 4).

Sodium carboxymethylcellulose. On preparation, the most viscous dispersions were those with pH values between 5 and 7. There was a sharp fall in the viscosity of dispersions below pH 5 and above pH 10. In the two most acid samples (pH 1.05 and pH 1.42), carboxymethylcellulose was immediately precipitated and the viscosity was reduced to a

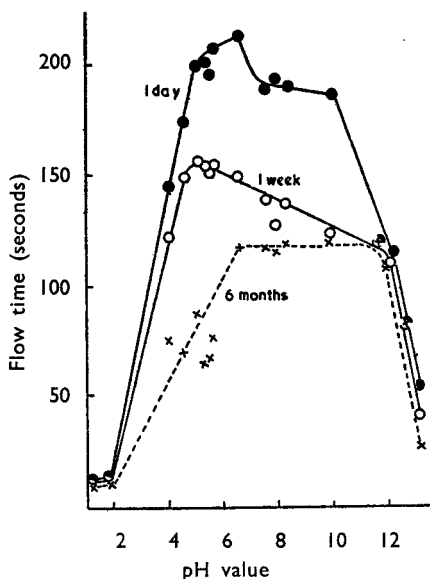


FIG. 5. Variation in flow time of a sodium carboxymethylcellulose sol (medium) with pH.

minimum. At the end of a week there was a general reduction in the viscosity of the samples. Dispersions with a pH below 7 continued to decrease in viscosity on further storage, and, at 6 months, those samples that had not precipitated had decreased in flow time by about two-thirds. The flow time, of the alkaline dispersions, however, did not alter appreciably after the first week of storage, and, at the end of six months, those with pH values between 7 and 12 had the highest flow times of the series (about 60 per cent of the original) (Fig. 5).

There was no significant variation in the pH values of any of the above dispersions on storage.

DISCUSSION AND CONCLUSIONS

Effect of temperature. The gradual decrease in the viscosity of methylcellulose sols on raising the temperature has been attributed by Heymann⁵ to a decrease in the effective volume of the particle on dehydration. The hydrated particle cannot be quantitatively defined, but is built up of water molecules adsorbed with decreasing bonding energy as the thickness of the hydration layer increases. At low temperatures there is no marked limit to the hydration layer but a more or less smooth transition to free

water. On heating, water molecules are shed from the outer layer, decreasing the size of the hydrated particles while increasing their freedom of motion, until a point is reached where the particles come within each other's sphere of influence and coagulate¹. Provided the temperature and duration of heating are kept within certain limits, the sol-gel transformation is strictly reversible and the dispersion on cooling regains its original viscosity. The diminution of viscosity which occurs on prolonged heating, however, is a separate and quite distinct process which, in the case of methylcellulose, was considered by Heymann to be due to depolymerisation. Brown and Houghton⁸ who investigated similar viscosity losses in heated sodium carboxymethylcellulose sols, compared the reaction with the denaturation of proteins. They suggested that the chemical changes involved are probably somewhat similar and might be due to the breaking of cross-linkages or hydroxyl bonds, or to the evolution of carbon dioxide. This latter, which assumes a change in the structure of the ether, has been contested by Caldwell and Watters⁹ who found that when sodium carboxymethylcellulose which had undergone this lowering of viscosity was precipitated, dried and redispersed, it regained its original viscosity.

The present work shows that whereas dispersions of methyl- and methylethylcellulose are comparatively stable towards heat, the viscosity of sodium carboxymethylcellulose dispersions are irreversibly lowered by short periods of heating at relatively low temperatures. With the methyl- and methylethyl derivatives marked losses in viscosity occurred only in the samples heated at 115°, but, even at this temperature, the decrease generally is not large for heating periods appropriate to a sterilisation process. It is probable that the relatively large fall in efflux time which occurred in dispersions of the high viscosity grade of methylcellulose is simply a manifestation of the greater susceptibility of the larger molecule to degradative changes. The results of the experiments with sodium carboxymethylcellulose confirm those of Brown and Houghton. Not only is the temperature at which deterioration sets in lower with sodium carboxymethylcellulose than with the two other derivatives, but the viscosity decreases are much greater. The apparent stability of the highest viscosity grade of sodium carboxymethylcellulose, relative to the two lower grades of this derivative, is surprising.

With all three derivatives deterioration varies with both temperature and time. The decrease in efflux time was most rapid during the first 15 to 30 minutes of heating. Dispersions of methyl- and methylethylcellulose continued to decrease in efflux time beyond this point, whereas sodium carboxymethylcellulose dispersions became stabilised. This latter observation lends support to the suggestion⁸ that prolonged heating may reduce the viscosity of sodium carboxymethylcellulose dispersions to a limiting value.

Although acid or alkali in the quantities added had no immediate effect on the efflux times of dispersions of the three derivatives, the presence of acid in dispersions of the two higher grades of methylcellulose brought about a marked reduction in viscosity when the temperature was held at 115° for 30 minutes. These circumstances favour the degradation

of the polymer and treatment with acid at high temperatures is one method of bringing about depolymerisation⁴. Its effectiveness with the lowest viscosity grade of methylcellulose provides another illustration of the stability of a molecule of relatively short chain length. That the inclusion of acid did not bring about such a marked effect with sodium carboxymethylcellulose may be explained partly by the fact that the system acts as a buffer¹⁰; although the effect of heat alone on this derivative is so great that the limiting viscosity is nearly approached in the absence of acid.

It appears that sodium carboxymethylcellulose in the dry state is less readily degraded by heat than are its aqueous dispersions. The effect of heating the dry material for 4 hours at 105° is comparable with that of heating an aqueous dispersion for $\frac{1}{2}$ hour at 98°. With methyl- and methylethylcellulose, the result of heating the dry derivatives at 105° for 4 hours is roughly comparable with that of heating a dispersion at 115° for 2 hours.

Effect of acid and alkali. Provided the pH is not below 3, such viscosity losses as do occur in dispersions of methylcellulose in the presence of acid or alkali can, for most practical purposes, be ignored. The most interesting feature of this part of the study was the rise in viscosity which occurred in the presence of alkali after 4 months' storage. Campbell and others¹¹ have observed the viscosity of methylcellulose dispersions to increase as the pH increases, but do not state whether the rise was immediate, or delayed. Methylethylcellulose dispersions are seen to be even more stable, with the viscosities remaining unaffected over a wide pH range. The behaviour of sodium carboxymethylcellulose sols, in which the viscosity varied widely with pH and time of storage, provides a striking contrast. The results obtained with this derivative are in general agreement with those of Brown and Houghton⁸ who attributed the loss of viscosity on the alkaline side to the replacement of unsubstituted hydroxyl groups by -ONa. On the acid side, the lowering of viscosity is due to the precipitation of carboxymethylcellulose. However, even neutral dispersions containing no added material undergo a loss of viscosity on storage, probably as a result of some degree of depolymerisation. This "ageing" process does not appear to be accelerated by the presence of alkali, but on the acid side the more progressive decrease suggests that here the two effects potentiate each other.

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