

WATER-SOLUBLE CELLULOSE DERIVATIVES

FACTORS AFFECTING THE VISCOSITY OF AQUEOUS DISPERSIONS. PART II

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A study has been made of the effects of salts, alcohol and surface-active agents, of contamination by micro-organisms, and of storage at various temperatures on the viscosities of aqueous dispersions of methyl-, methylethyl-, and sodium carboxymethylcellulose. Small concentrations of salts decreased the viscosity of sodium carboxymethylcellulose sols but had no effect on methyl- and methylethylcellulose sols. Larger amounts caused the viscosities of methyl- and methylethylcellulose sols to increase. Industrial methylated spirit, propylene glycol and glycerol increased the viscosities of all dispersions. The effect of sodium lauryl sulphate on sodium carboxymethylcellulose sols was similar to that of salts, and cetrimide precipitated the derivative. Methyl- and methylethylcellulose dispersions increased and then decreased in viscosity with increasing concentrations of sodium lauryl sulphate; cetrimide increased the viscosity. All derivatives were degraded by micro-organisms. The viscosity of preserved dispersions of methyl- and methylethylcellulose altered little over a year. The greatest decreases occurred in the highest viscosity grade samples stored at the highest temperature (30°). All dispersions of sodium carboxymethylcellulose decreased in viscosity over the storage period; storage in light producing the most unstable sols. The pH change of any dispersion on storage was negligible.

In an earlier paper¹ we reported the viscosity variations in aqueous dispersions of three cellulose derivatives under the influence of heat and in the presence of acid and alkali. Considerable changes were observed under those conditions and there were distinct differences in the behaviour of methyl- and methylethylcellulose sols and sodium carboxymethylcellulose sols. The effects on these systems of various added substances, of contamination by micro-organisms and of storage have now been examined.

MATERIALS AND APPARATUS

The cellulose derivatives used and the method of preparing the dispersions were those previously described.¹ Reagents were of A.R. quality unless otherwise described. Purified water B.P. was used. The viscometer was the Redwood No. 1 and viscosity measurements were made at 25°. pH determinations were made with a Cambridge bench pH meter.

EXPERIMENTAL AND RESULTS

Effect of Added Substances

Dispersions of methyl- (medium), methylethyl-, and sodium carboxymethylcellulose (medium) were prepared in suitable concentrations and the additive, dissolved or mixed with the calculated volume of water, incorporated.

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Salts. With methylcellulose the presence of sodium chloride in concentrations below 6 per cent w/v was without effect. As the salt concentration was increased, however, the dispersion thickened, becoming turbid and thixotropic, eventually forming a gel. Similar results were obtained with methylethylcellulose (Table I). In contrast, the addition

TABLE I
EFFECT OF ADDED SODIUM CHLORIDE ON THE EFFLUX TIMES OF METHYL- AND METHYLETHYLCELLULOSE SOLS AT 25°

NaCl content per cent w/v	Methylcellulose (medium, approx. 0.8 per cent w/v)		Methylethylcellulose (approx. 3 per cent w/v)	
	Efflux time (sec.)	Appearance	Efflux time (sec.)	Appearance
0	180	Opalescent mucilage	147	Turbid mucilage
4.5	—	—	157	As above
5.25	—	—	177	As above
6.0	181	As above	265	As above
7.5	190	Turbid, tending to separate into two layers—upper thicker than lower. Dispersible on shaking	765	Semi-solid mucilage
9.0	330, 277, 208	Turbid and thixotropic. (See decreases in consecutive efflux times)	—	Soft gel. Syneresis on standing
12.0	—	Gelation. Considerable syneresis on standing	—	Soft gel with syneresis. Milky appearance
15.0	—	As above	—	Gel with considerable syneresis

of small quantities of sodium chloride to sodium carboxymethylcellulose dispersions produced decreases in viscosity, and, as the salt concentration was further increased, the viscosity fell to a minimum (Table II). An

TABLE II
EFFECT OF ADDED SODIUM CHLORIDE ON THE EFFLUX TIME OF SODIUM CARBOXYMETHYLCELLULOSE SOLS AT 25°

NaCl content per cent. w/v	Sodium carboxymethylcellulose (medium, approx. 0.9 per cent w/v)	
	Efflux time (sec.)	Appearance
0	176	Clear mucilage
0.01875	169	As above
0.0375	155	As above
0.075	137	As above
0.15	118	As above
0.3	103	As above
0.75	83	As above
1.5	73	Slight opalescence
7.5	62	Opalescent mucilage
15.0	63	As above

extension of this study to other salts indicated that the efflux time reductions caused by cations of the same valency were approximately equal and that the magnitude of the reduction varied with the valency (Table III).

Alcohol (I.M.S. 74 o.p.). Dispersions of all three derivatives behaved similarly on the addition of alcohol, their efflux times increasing with increased alcohol content (Table IV). Further, there was a linear relation between efflux times and alcohol content. Excess of alcohol precipitated the ether without gel formation.

Alcohol and Salts. Of two 20-ml. quantities of a methylcellulose dispersion, one was diluted with an equal volume of water and the other with industrial methylated spirit. A saturated solution of sodium chloride was added slowly from a burette, stirring continuously. Neither sample precipitated after 20 ml. of salt solution had been added. When the experiment was repeated with a sodium carboxymethylcellulose

TABLE III
EFFECTS OF ADDED SALTS ON THE EFFLUX TIME OF SODIUM
CARBOXYMETHYLCELLULOSE SOLS AT 25°

Salts in 0.2 M concentration	Sodium carboxymethylcellulose (medium, approx. 1 per cent w/v)	
	Efflux time (sec.)	Appearance
—	222	Clear mucilage
Potassium iodide	114	Very faint opalescence
Potassium chloride	117	Very faint opalescence
Potassium thiocyanate	115	Clear mucilage
Potassium nitrate	111	Clear mucilage
Potassium acetate	120	Clear mucilage
Potassium bromide	115	Very faint opalescence
Sodium chloride	119	Clear mucilage
Ammonium chloride	111	Very faint opalescence
Magnesium chloride	89	Very faint opalescence
Calcium chloride	85	Slight turbidity
Ferric chloride	—	Gel—insoluble salt

TABLE IV
EFFECT OF ADDED INDUSTRIAL METHYLATED SPIRIT ON THE EFFLUX TIMES
OF METHYL-, METHYLETHYL- AND SODIUM CARBOXYMETHYLCELLULOSE
SOLS AT 25°

Constitution of sample (ml.)			Efflux times (sec.)		
Dispersion	Water	I.M.S. (74 o.p.)	Methyl- (medium, approx. 0.8 per cent w/v)	Methylethyl- (approx. 3.25 per cent w/v)	Sodium carboxymethyl- (medium, approx. 0.9 per cent w/v)
100	100	—	179	201	184
100	90	10	216	—	212
100	80	20	257	261	—
100	75	25	—	—	266*
100	60	40	334	328	310*
100	50	50	—	—	353*
100	40	60	411	392	—
100	25	75	—	—	420*
100	20	80	472	435	—
100	—	100	548*	528	487†

* Slight initial turbidity, clearing almost immediately.

† The ether at first partly precipitates with milky floccules and gelatinous threads. On shaking and allowing to stand for a few minutes, the dispersion clears.

dispersion, the sample diluted with water remained no more than faintly opalescent when 20 ml. of salt solution had been added, whereas that containing alcohol gave a copious precipitate with less than one ml. of the salt solution.

Propylene glycol and Glycerol. The inclusion of increasing concentrations of propylene glycol (Laboratory Reagent grade) or glycerol caused a progressive thickening of dispersions of all three derivatives.

Surface-active Agents. The effect of adding sodium lauryl sulphate B.P. to sodium carboxymethylcellulose sols was comparable with that of salt addition. With methyl- and methylethylcellulose dispersions, the

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reaction was more complex. At first, with increasing quantities of sodium lauryl sulphate, the viscosity rose, as on the addition of sodium chloride. As the concentration of sodium lauryl sulphate was further increased, however, the system began to decrease in viscosity. In the extreme case, the efflux time of a methylcellulose sol was reduced to little more than that of water. The ether appeared to have settled out as minute fibres to give a perfectly clear supernatant layer which, since it showed no turbidity on heating, contained no hydrated methylcellulose. With intermediate concentrations of sodium lauryl sulphate, sols which had undergone a diminution in viscosity tended to thicken again on standing. (Table V.)

TABLE V
EFFECT OF ADDING SODIUM LAURYL SULPHATE TO METHYLCELLULOSE SOLS

Constitution of sample (ml.)			Efflux time (sec.)*	Appearance	Behaviour on heating
Methylcellulose sol (medium, approx. 1.6 per cent w/v)	Water	Sodium lauryl sulphate soln. (10 per cent w/v)			
100	180	—	180	Opalescent mucilage	Gel. Slight syneresis
100	99.5	0.5	230	Turbid mucilage	As above
100	97.5	2.5	315	As above	As above
100	90	10	865	As above	Gel. Considerable syneresis
100	75	25	Initial: 573 After 5 mins.: 685	Less turbid	No gel, but tendency to coagulate
100	50	50	After 8 hrs.: 762 Initial: 54, 60, 66, 74, 79, 85, 90 After 15 mins.: 101, 105, 107 After 16 hrs.: 162 After 24 hrs.: 162	Less turbid	Slight increase in turbidity
100	25	75	46	Almost clear	No change
100	—	100	47	Clear; fibrous sediment	No change

* Single samples.

When an equal volume of a 10 per cent solution of the cationic substance cetrinide B.P. was added to the anionic sodium carboxymethylcellulose sols there was an immediate precipitate. With methyl- and methylethylcellulose dispersions, the addition of increasing concentrations (maximum 5 per cent) of cetrinide led to progressive increases in viscosity.

Effect of Contamination by Micro-organisms

A suspension of micro-organisms isolated from laboratory dust was used to inoculate 6 samples each of methyl-, methylethyl- and sodium carboxymethylcellulose dispersions. One pair of samples consisted of the derivatives in water; another pair contained in addition 0.001 per cent phenylmercuric nitrate; the third pair consisted of the derivatives in water to which 0.012 per cent of thiourea had been added—it having been noted that dispersions containing thiourea were particularly prone

to what was assumed to be bacterial degradation. The efflux times were determined initially and at intervals after incubation at 37°.

Of the six samples of methylcellulose, only two—those containing thiourea—underwent gross viscosity decreases. In these dispersions the percentage decreases in efflux time after two months were 63 and 86 per cent respectively. The most rapid decrease occurred during the first two weeks. All other dispersions retained from 85 to 93 per cent of their original efflux times after storage for two months. Apart from mycelia in one of the thiourea-containing samples, there was no change in the appearance of the dispersions.

Of the six samples of methylethylcellulose, only one showed a gross decrease in efflux time (38 per cent) after storage for two months; this sample consisted of the derivative in water alone. The viscosity dropped most rapidly during the third week after inoculation. The remaining dispersions retained between 83 and 96 per cent of their original efflux times after two months. There was no change in the appearance of any of the dispersions at the end of this period.

All the dispersions of sodium carboxymethylcellulose decreased in efflux time on storage. The two samples containing phenylmercuric nitrate retained 60 and 65 per cent respectively, of their original efflux times after eight weeks, compared with 15 to 27 per cent in the non-preserved dispersions. The appearance of the preserved dispersions was unchanged. Of the remainder, two contained traces of mycelia, and one, a bulky diffusible sediment. In the non-preserved samples the most rapid decrease in efflux time occurred during the first two weeks of storage.

Effect of Prolonged Storage

Dispersions of low, medium and high viscosity grades of methyl- and sodium carboxymethylcellulose and of one grade of methylethylcellulose were prepared in 0.001 per cent phenylmercuric nitrate solution. The concentrations were chosen so as to give an efflux time of about 200 seconds. The containers were clear-glass 8-oz. jars with cardboard-lined screw caps. These were made air-tight by dipping in paraffin wax. Duplicate samples were stored at room temperature, in a refrigerator (4°) and in an oven (30°). Of the two samples stored at room temperature, one was kept on a shelf exposed to daylight and the other in a cupboard in the dark. Efflux times and pH values were determined initially and, thereafter, at periods of 2 weeks, 1, 2, 3, 4, 8 and 12 months. The results may be summarised as follows:

Methylcellulose. The efflux times of dispersions of the low viscosity grade remained constant over a year's storage. The efflux times of the medium viscosity grade increased slightly, mainly during the first two weeks of storage. Only very small increases occurred thereafter, the efflux times at the end of the year being from 10 to 15 per cent above the initial value. With the high viscosity grade, efflux times declined in all samples during the storage period; the efflux times of dispersions stored at room temperature and at 4° were 79 per cent of the original at the end

of the year. Those of dispersions stored at 30° were lower, at 66 per cent of the original. The pH values of the dispersions remained substantially unchanged.

Methylethylcellulose. The efflux times of dispersions remained constant for a year. The pH values of the dispersions remained substantially unchanged.

Sodium carboxymethylcellulose. Except for a darkening in colour in low viscosity grade dispersions, there was no difference between the behaviour of the three grades. All dispersions decreased in efflux time over the storage period. The most stable samples were those stored at 4° which retained 69 to 79 per cent of their original efflux times after a year. The most unstable samples were those stored at room temperature in the light, having final efflux times equivalent to only 39 to 45 per cent of the original, compared with 62 to 74 per cent for similar dispersions stored in the dark. With the exception of the highest viscosity grade, samples stored at 30° showed greater decreases in efflux time than samples stored at room temperature in the dark, the final values being 48 to 52 per cent of the original. The pH values of the dispersions remained substantially unchanged.

A subsequent experiment showed that dispersions of sodium carboxymethylcellulose could decrease in efflux time by over 50 per cent in one month when stored in positions in which they received the maximum amount of direct daylight. The maximum decrease in control samples stored in the dark for the same period was 10 per cent. These losses were augmented rather than diminished by the inclusion of 0.1 per cent sodium metabisulphite, presumably as a result of the lowered pH. It did, however, prevent the darkening of low viscosity grade dispersions on storage.

DISCUSSION AND CONCLUSIONS

Effect of Added Substances

The viscosity of dispersions of hydrophilic colloids has been variously attributed to the film of solvent which envelopes each particle, to the existence of ramifying micellar aggregates which hinder the flow of the sol, and to the electric charge on the particle (electro-viscous effect). Similarly, the stability of such sols is ascribed both to the electric charge which makes the particles mutually repellent, and to the surrounding hydration sheaths which prevent them approaching each other closely. Since these two mechanisms can operate independently, there are three possible types of disperse system, stabilised by (a) an electrical double layer only, (b) an hydrated sheath and (c) both mechanisms, the last of these three being in general the most stable.² Further, it is well known that in order to flocculate systems of the last-mentioned kind both discharge and dehydration are necessary. Thus, the addition of small quantities of electrolyte generally tend to decrease the viscosity of a hydrophilic sol considerably, the particle losing all or part of its charge. The addition of further electrolyte causes no appreciable difference until it is present in a concentration sufficient to exert a dehydrating action,

which leads eventually to coagulation. Alternatively, a sol discharged by a small quantity of electrolyte may be dehydrated and coagulated by adding alcohol, and vice versa.

Sodium carboxymethylcellulose dispersions, although having a high resistance to dehydration by electrolytes (no precipitation occurring even in the presence of an equal volume of a saturated solution of sodium chloride), conform in other respects to the general pattern of behaviour of sols stabilised by both charge and hydration sheath. With methyl- and methylethylcellulose sols, however, the charge (which must be ascribed to the preferential adsorption of hydroxyl ions, as opposed to ionisation of the colloid as in the case of sodium carboxymethylcellulose) does not appear to be of first importance as a stabilising factor. Indeed, it has been suggested that methylcellulose in dispersion is substantially uncharged.³ This view receives not a little support from the present finding that methyl- and methylethylcellulose sols, unlike those of sodium carboxymethylcellulose, are not "sensitised" to dehydrating agents by the addition of electrolyte in very low concentration.

The addition of alcohol to a hydrophilic sol will partially or completely dehydrate the particles, depending on the quantity added. From one point of view it might be expected that dehydration of sols of the cellulose derivatives would be accompanied by decreases in viscosity, since the effective size of the particles is reduced by removal of their hydration layers. The results show, however, that addition of alcohol leads to an increase in viscosity with all three derivatives. Indeed, with methyl- and methylethylcellulose sols, this increase in viscosity is a feature of dehydration whether it be accomplished by adding salts or alcohol, or (when the concentration is high enough) by heating.¹ But although the effects of alcohol may be interpreted solely in terms of dehydration as far as these two derivatives are concerned, with sodium carboxymethylcellulose sols account has also to be taken of the stabilising effect of the charge. Thus the addition of alcohol must tend not only to dehydrate the particle, but also, probably by adsorption on to its surface, lower the ζ -potential⁴.

Whereas sodium carboxymethylcellulose sols behave in a predictable manner towards wetting agents, the reactions of methyl- and methylethylcellulose dispersions are more complex. It seems reasonable to postulate that the increase in viscosity which occurs with these two derivatives in the presence of cetrimide and, at first, with sodium lauryl sulphate, results from a progressive removal of some of the bound water. But the reason for the subsequent decrease in viscosity when the proportion of sodium lauryl sulphate is further raised is not immediately apparent. However, it is well known that soaps are readily adsorbed at interfaces, that compounds containing hydroxyl groups adsorb them very strongly⁴, and that adsorption can occur with orientation in the reverse sense (the hydrophilic groups being bound to the surface of the particle and the hydrophobic groups being orientated towards the aqueous phase)². The assumption of such an interaction occurring in the present instance would satisfy all the observed results; the cellulose ether particles would be

completely dehydrated, the incipient gel structure destroyed, and the viscosity of the system would become minimal.

Effect of Contamination with Micro-organisms

A survey of the literature reveals several contradictory statements regarding the stability of dispersions of the cellulose derivatives to bacterial attack. One manufacturer of methylcellulose has stated that if contamination occurs some loss of viscosity will result⁵. Osborn and DeKay⁶ reported that mucilages of methylcellulose "are stable over a long period of time and require no preservative." The effect of bacterial contamination on the viscosity of dispersions of sodium carboxymethylcellulose and methylethylcellulose has been investigated by Freeman and colleagues⁷. They found that both derivatives suffered degradation through the growth of bacteria widespread in soil and normally present in manufactured soluble cellulose derivatives. Pollok⁸ studied the stability of sodium carboxymethylcellulose in detergent solutions and concluded that, in combination with anionic commercial detergents, the derivative was "not likely to cause trouble from bacterial decomposition". Two manufacturers^{9,10} of sodium carboxymethylcellulose advise the addition of a preservative when contamination is possible or when dispersions are to be stored for any length of time, but a third states that "only rarely is it desirable to add some form of antiseptic"¹¹. The present results show that all three derivatives are susceptible to microbiological attack, while the frequency and extent of the viscosity decreases in sodium carboxymethylcellulose dispersions suggest that they support growth much more readily than do those of the two other ethers. The viscosity losses in preserved samples are evidently the result of an ageing process and have been ascribed to an irreversible chemical breakdown of the derivative⁷. It may be of interest to record that whereas Freeman and colleagues observed that viscosity decreases in contaminated dispersions were most marked between 32 and 61 days after inoculation, in the present work the most rapid decreases generally occurred within 21 days.

Effect of Prolonged Storage

The variations in viscosity of dispersions of the cellulose derivatives on storage is usually discussed in relation to the effects of contamination by micro-organisms. It has been stated, however, that high-viscosity types degrade more rapidly than low-viscosity types, that the changes are irreversible, that at high temperatures the reduction in viscosity continues indefinitely, but at room temperature appears to cease after a time, and that the rate of degradation in a given solvent is independent of concentration. It has further been suggested that all these factors can be explained by assuming that the drop in viscosity is due to a shortening of the average chain-length¹²—the chance of a chain breaking becoming greater as the chain becomes longer, and the effect of a given reduction in molecular weight on viscosity being much greater if the original chain is very long. The literature, generally, however, gives the impression that in the absence of contamination, the viscosity of dispersions of these ethers alters little on

storage, although Freeman and colleagues noted that the viscosity of dispersions, even when preserved, tended to decrease over a period of 61 days. The results now obtained show that the viscosities of dispersions of methyl- and methylethylcellulose remain, in general, remarkably constant over the period of a year. Some loss of viscosity occurred with the high-viscosity grade methylcellulose and illustrates the greater susceptibility to degradation of the longer molecular chain. The increase in viscosity of medium-grade samples, which is considered to be a delayed-hydration effect, was unexpected, since preliminary studies¹ had indicated that hydration was usually complete 24 hours after the dispersion had been prepared. The results with sodium carboxymethylcellulose illustrate once more its relatively high instability and recalling the effect of heat on this derivative¹ the viscosity decreases in the samples stored at 30° are not surprising. It has been reported¹² that cellulose ether dispersions are sensitive to oxygen under the influence of light. The present results show that sodium carboxymethylcellulose sols are particularly susceptible, and that gross decreases in viscosity occur under these conditions. According to Ott the action may be practically eliminated by the addition of oxygen inhibitors, although it is evident that the inhibitors must be carefully chosen to avoid creating conditions which will themselves bring about a decrease in viscosity.

GENERAL OBSERVATIONS

It is well known that several substances yield precipitates with cellulose ether dispersions and very many reactions of the kind have been recorded¹³⁻¹⁸. What has seemed an undue preoccupation with precipitates has tended to imply however that in the absence of a visible reaction product the stability and properties of these systems remain unaffected by anything that may be added to them. The present work amply demonstrates the fallacy of such an assumption. For while such purely chemical reactions as the liberation of free carboxymethylcellulose or the formation of insoluble salts can be detected visually, the cellulose derivatives, like other hydrophilic colloids, are subject to changes of a physico-chemical nature which although they might not cause the slightest alteration in the appearance of a sol can radically change its properties. The electro-viscous effect of very small concentrations of salts on sodium carboxymethylcellulose dispersions is a striking example. Because many of the pharmaceutical applications of the cellulose derivatives are directly linked to the viscosity of their aqueous dispersions, these reactions—whether they result in a thinning or thickening of the mucilage—are of first importance to the formulator. To what extent such changes influence the efficiency of these ethers as suspending and emulsifying agents remains to be determined, and work is proceeding to that end.

From the results obtained on contaminated dispersions it would seem prudent to include a preservative in all dispersions of sodium carboxymethylcellulose and all dispersions of methyl- and methylethylcellulose which are to be stored for much longer than two weeks. Further, in the absence of a suitable oxygen inhibitor, sodium carboxymethylcellulose

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dispersions should be protected from light as well as from elevated temperature if gross viscosity losses on storage are to be avoided.

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