

# The phase diagram of cetomacrogol 1000–water–benzaldehyde in the presence of gallate antioxidants

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The phase equilibria of the system cetomacrogol 1000–water–benzaldehyde have been examined in the presence of a homologous series of gallates. Differential scanning calorimetry indicates that a bonded complex is formed in solution between the cetomacrogol and the gallate. The surface-active agent has, therefore, been considered as being the total amount of cetomacrogol and gallate in the system and different ratios have been used to prepare the phase diagrams. As the proportion of gallate increases, the liquid crystal phases become smaller and eventually disappear. It is suggested that this is because the bulky cetomacrogol 1000–gallate complex is unable to form the highly orientated liquid crystal micelles.

Equilibria in systems containing surface-active agents are often complex and may best be described by ternary diagrams in which water and the surface-active agent are two of the components and the solubilizate the third (Mulley, 1964). There is a general similarity in the pattern and nature of the phases found, but the concentration and temperature at which analogous regions occur vary with the chemical nature of the solubilizate and surface-active agent. Information about non-ionic surface-active agents is sparse but it has been suggested (Hyde, Langbridge & Lawrence, 1954) that the same regions will be present as in anionic and cationic surface-active agents. In most cases, however, the chain lengths of the surface-active agents studied have been low because of difficulties in preparation and determining the phases present. The effect of a fourth component on the system has received little attention. The fourth component has either been at a fixed concentration for the determination of the whole solubility diagram or present in a fixed ratio to one of the other components.

The present work describes the phase diagrams of a cetomacrogol 1000–water–benzaldehyde system in the presence of a series of gallate antioxidants. This was of interest as a precursor to a study of gallates as antioxidants for solubilized systems. Because of their phenolic nature, these materials are likely to form bonded complexes with the non-ionic surface-active agent and as a consequence the surface-active agent has been considered to be a cetomacrogol 1000–gallate mixture throughout this text.

## MATERIALS AND METHODS

*Cetomacrogol 1000.* The commercial product Texofor AIP (Glovers Chemicals Ltd.) was used. M.p. 45–46°. Acetyl value 41.1. C:H:O ratio 59.3:10.1:30.3.

*Surface-active agent* was prepared by melting a mixture of cetomacrogol 1000 with different proportions of gallate esters. Ratios are expressed as w/w.

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*Benzaldehyde* was obtained from British Drug Houses Ltd. Refractive index 1.545; weight per ml 1.045 at 20°. Assay 99.5%.

*Gallates.* Propyl gallate (British Drug Houses Ltd.) had m.p. of 147°. Ethyl, octyl and dodecyl gallates (NIPA Laboratories) had m.p. 150–151°, 92–93° and 96–98° respectively, after crystallization.

*Water* was triple distilled from an all glass still.

*Preparation of phase diagrams.* A mixture of surface-active agent with either water or benzaldehyde was prepared, depending on the position in the diagram being examined. To the cetomacrogol:gallate mixtures, in ungreased glass stoppered flasks, the third component was gradually added and allowed to equilibrate at the appropriate temperature  $\pm 0.1^\circ$ . Equilibrium was rapidly established and was unchanged for up to three days at the chosen temperature. The phase changes, if any, were noted between each addition of the third component. As far as possible, initial cetomacrogol:gallate mixtures were chosen so that on the addition of the third component the phase boundary was crossed as near as possible at 90°. Phase changes involving liquid crystal were observed with plane polarized light. The liquid crystal phases were all birefringent and, depending on their position within the phase diagram, varied from rather fluid jelly like liquids to solid gels. Where the position of the boundaries could not be determined more accurately than within 1% they are shown as dotted lines.

*Differential scanning calorimetry.* Cetomacrogol 1000 and propyl gallate were warmed together to give homogeneous mixtures. An accurately weighed quantity was placed in the standard sample pans of the differential scanning calorimeter (Perkin-Elmer DSC-1), the covering hood flushed with liquid nitrogen and a scan made between 240–450° K. With a uniform rate of scan the height of the peak was found to give a similar proportionality to the area under the curve.

## RESULTS

Figs 1 and 2 show the effect on the solubility phase diagram of gradually increasing the proportion of propyl gallate in the cetomacrogol:gallate mixture which has been considered as one component for the purposes of constructing the solubility diagram.

Fig. 1 shows the basic solubility diagram for cetomacrogol 1000–water–benzaldehyde. A large region of unstable emulsions of the two conjugate liquids ( $L_1$  and  $L_2$ ) exists over the lower part of the curve. Within this region compositions towards the left-hand portion are the more stable.

In the lower left-hand corner an isotropic liquid phase,  $L_1$ , exists containing hydrophilic spherical micelles. The reverse type of micellar system,  $L_2$ , in which benzaldehyde is the continuous phase and the water the solubilizate, occurs at high concentrations of benzaldehyde in the lower right side of the diagram. These two isotropic phases merge above the two phase region and have been designated, L, as it was impossible to determine the proportionate composition of the two micellar types.

Anisotropic liquid crystal phases, LC, exist both in a central position and associated with high concentrations of surface-active agent on the left-hand side of the diagram. Surrounding the central liquid crystal is a heterogeneous mixture of LC + isotropic phase. This is a relatively narrow band where the liquid crystal faces onto the single isotropic liquid phases, but is more extensive on its lower boundary where it is

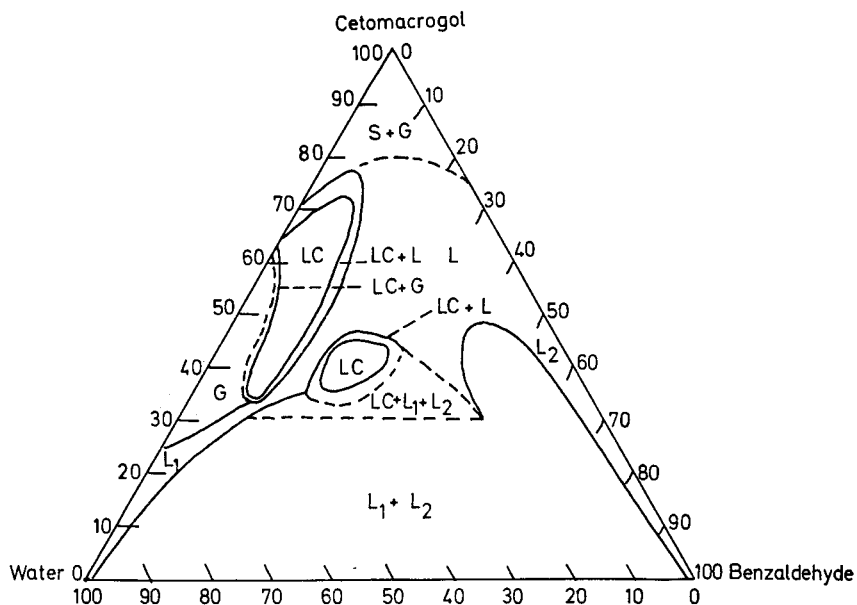


FIG. 1. Phase equilibria in the system cetomacrogol–benzaldehyde–water at 25°.  $L_1$  and  $L_2$  isotropic spherical micelles, LC liquid crystal, G isotropic gel phase, S solid.

associated with the two phase  $L_1 + L_2$  systems. The boundary of this mixed region is difficult to determine exactly, because it is temperature sensitive; it has been shown by a dotted line in the diagrams.

The second and larger liquid crystal phase occurs as a band between 35 and 72.5% cetomacrogol. Most of this region is associated with 6 to 10% benzaldehyde, but it tapers towards the binary cetomacrogol–water axis and liquid crystal exists on this axis between 64 and 65.5% cetomacrogol. This second liquid crystal phase is surrounded, as usual, by a region of isotropic liquid + liquid crystal particularly narrow on its lower side. Bordering this lower edge, the isotropic liquid phase,  $L_1$ , becomes very viscous and gel like, but shows none of the properties associated with liquid crystal. The gel-like isotropic phase reappears at the apex of the diagram, but in this region it is associated with the separation of solid cetomacrogol.

Fig. 2 shows the effect of gradually increasing proportions of propyl gallate. It is apparent that as the proportion of gallate in the surface-active agent increases, the number of phases which co-exist decreases, thus simplifying the solubilization diagram.

The size of the large  $L_1 + L_2$  region shows little variation up to a ratio of cetomacrogol:propyl gallate of 6:1 (Fig. 1). At cetomacrogol:propyl gallate ratios below this, the main  $L_1 + L_2$  boundary begins to move to higher surface-active agent concentrations and by the ratio of 2:1 has risen so far as to smooth out the curve of the  $L_1 + L_2$  area.

Until a cetomacrogol:propyl gallate ratio of 9:1 is reached, the width of the  $L_1$  phase increases at the expense of the  $L_1 + L_2$  region, whilst the onset of formation of the isotropic gel phase recedes gradually to higher surface-active agent concentrations. At a ratio of 4:1 this latter pseudo phase exists only as a narrow strip and disappears when the proportion of propyl gallate is increased to give a ratio of 2:1 cetomacrogol:gallate.

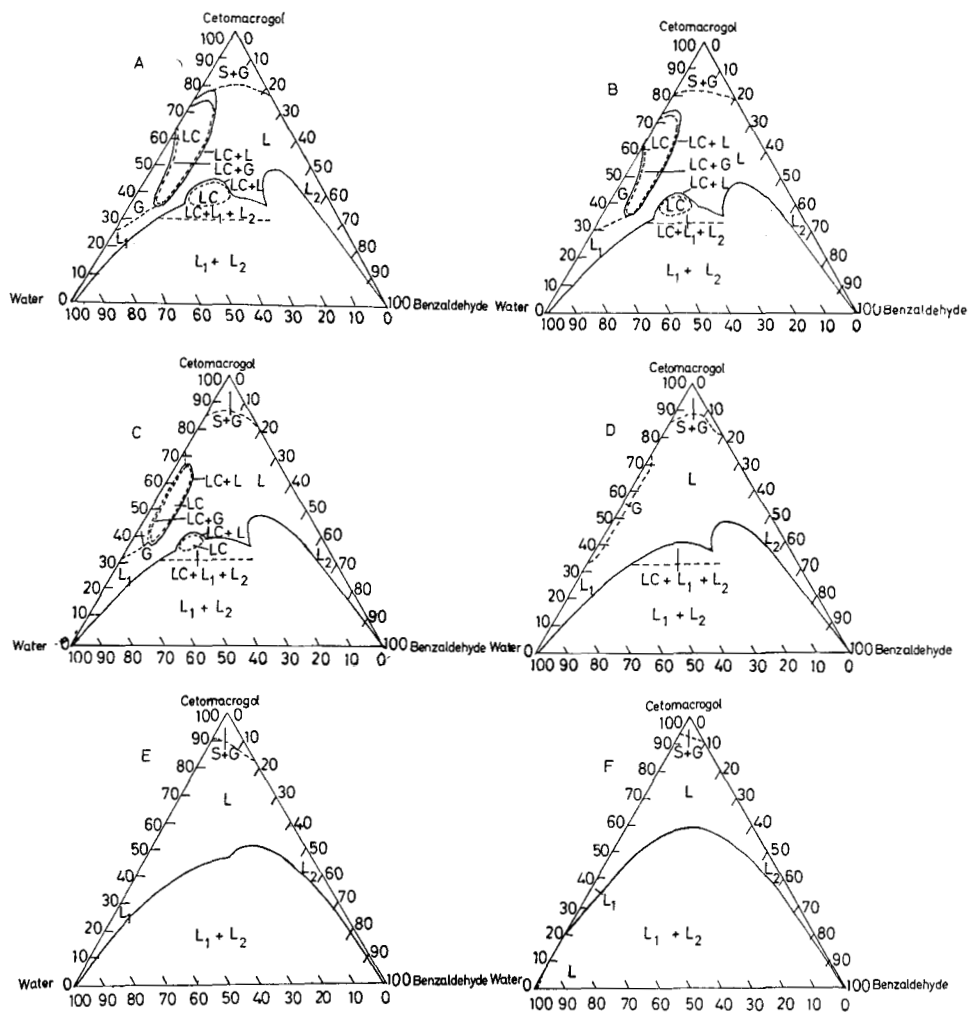


FIG. 2. Phase equilibria in systems containing cetomacrogol-propyl gallate-benzaldehyde-water at 25°. Ratio w/w cetomacrogol:propyl gallate; A 29:1, B 19:1, C 9:1, D 6:1, E 4:1, F 2:1.

The  $L_1$  phase increases with increasing proportion of propyl gallate in the surface-active complex to a maximum and then when the relative proportion of gallate increases above the cetomacrogol:gallate ratio of 6:1, the width of the isotropic  $L_1$  phase decreases swiftly until at a ratio of 2:1 no benzaldehyde solubilization occurs until the concentration of surface-active agent exceeds 23%. Corresponding changes in the width of the  $L_2$  region are small, although a decrease in the amount of this phase present occurs at a 2:1 ratio of cetomacrogol:gallate.

The most dramatic change that occurs relative to the proportion of propyl gallate present is the disappearance of the liquid crystal phases. The boundary between pure liquid crystal and the surrounding heterogeneous phases becomes difficult to determine accurately and at a ratio of 6:1 cetomacrogol:propyl gallate, a phase containing only liquid crystal is absent. All traces of liquid crystal disappears when the ratio was 4:1.

The liquid crystal associated with the binary axis increases in extent until a ratio of cetomacrogol to gallate of 29:1; thereafter it quickly decreases to disappear from the binary axis when the ratio is 9:1.

The isotropic gel present also initially increases as the proportion of propyl gallate increases. This appears to occur at the expense of the liquid crystal, but once again the gel phase is absent at higher propyl gallate concentrations. A small quantity of isotropic gel phase remains throughout all these changes associated with the separation of solid cetomacrogol 1000, but this recedes to the region of higher concentrations of surface-active mixture as the proportion of propyl gallate increases.

Temperatures up to 45° do not eliminate liquid crystal from the system if the ratio cetomacrogol:propyl gallate exceeds 29:1, but with higher proportions of propyl gallate the temperatures at which liquid crystal finally disappear were: 42° 29:1, 36° 19:1, 32° 9:1, 27° 6:1. In general, increasing temperature diminishes the liquid crystal regions and extends the L<sub>1</sub> region. The increase in the L<sub>1</sub> region is at the expense of the L<sub>1</sub> + L<sub>2</sub> phase and the isotropic gel phase associated with the surface-active agent-water axis.

The pattern of phases present, in position and extent is similar when gallates other than propyl gallate are used with cetomacrogol as the surface-active mixture.

A closer study of the boundaries of the L<sub>1</sub> and L<sub>2</sub> phases with the heterogeneous L<sub>1</sub> + L<sub>2</sub> phase shows that the gallates at low concentrations increase the solubility of benzaldehyde in the L<sub>1</sub> phase and of water in L<sub>2</sub>. An exception is that the presence of dodecyl gallate does not increase the size of the L<sub>2</sub> phase. At higher ratios of cetomacrogol:gallate the proportion of solubilizate within the micelle decreases except with L<sub>2</sub> systems with cetomacrogol:ethyl gallate as surface-active complex. The solubility of benzaldehyde in the cetomacrogol:gallate mixtures is in the reverse order of the gallate molecular weights (Table 1).

Differential scanning calorimetry of cetomacrogol and propyl gallate gave peaks at 324–325° and 427° K respectively. Mixtures of the components in the same proportions as in the solubilization diagrams altered both the position and the height of the cetomacrogol peak. Calculated on the basis of total sample present, the height decreased as the proportion of propyl gallate increased (Fig. 3). If a molecular

Table 1. *The effect of ethyl, octyl and dodecyl gallates on the solubility of benzaldehyde in L<sub>1</sub> systems at 25°*

Gallate	Surface active mixture % w/w	Maximum solubility % w/w of benzaldehyde in L <sub>1</sub> type system with the given cetomacrogol 1000:gallate ratio					Maximum solubility % w/w of water in L <sub>2</sub> type system with the given cetomacrogol 1000:gallate w/w ratio				
		4:1	6:1	9:1	19:1	29:1	4:1	6:1	9:1	19:1	29:1
Ethyl gallate .. ..	5	1.6	2.0	1.9	2.0	1.5	2.0	2.0	2.0	2.0	1.8
	10	2.7	3.5	3.2	3.4	3.1	2.5	2.5	2.5	2.3	2.1
	15	4.0	5.1	5.0	5.0	4.6	2.9	2.8	2.7	2.6	2.3
	20	5.8	7.2	7.1	7.0	6.3	3.4	3.2	3.1	3.0	2.7
	25	7.9	10.0	9.9	9.4	8.6	4.0	3.8	3.7	3.5	3.0
Octyl gallate .. ..	30	10.6	13.4	12.8	12.5	12.0	4.7	4.6	4.5	4.0	3.8
	5	1.2	1.6	1.7	1.8	1.5	1.9	1.7	1.9	1.8	1.8
	10	2.1	2.7	2.9	3.1	2.9	2.0	2.0	2.2	2.1	2.0
	15	3.0	4.0	4.2	4.6	4.2	2.4	2.4	2.8	2.5	2.2
	20	4.0	5.2	5.8	6.1	6.1	2.8	2.8	3.3	2.8	2.7
Dodecyl gallate ..	25	5.2	6.8	7.5	8.5	8.0	3.1	3.3	4.0	3.1	3.2
	30	7.0	8.2	9.5	10.5	10.0	4.0	4.3	4.4	4.0	4.0
	5	1.4	1.6	1.7	2.2	1.6	1.5	1.9	1.9	1.8	2.0
	10	2.1	2.7	2.9	3.4	2.8	1.8	2.0	2.2	2.2	2.3
	15	2.9	3.6	4.2	5.0	4.2	2.0	2.5	2.4	2.4	2.8

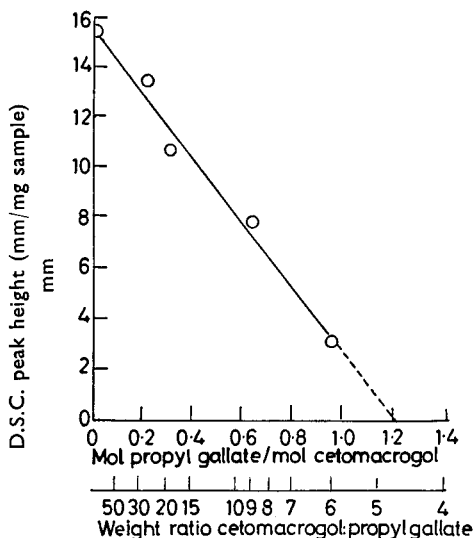


FIG. 3. The effect of propyl gallate on the height of the differential scanning calorimetry peak at 324–325° K.

weight of 1200 is assumed for cetomacrogol then the DSC peak reaches zero at a ratio of cetomacrogol propyl gallate of 1.2:1. In the presence of cetomacrogol, the propyl gallate peak ceased to exist at all concentrations.

#### DISCUSSION

The addition of the gallate antioxidants to cetomacrogol–benzaldehyde–water systems may be regarded as the simple introduction of a fourth component into the system or the combination of cetomacrogol and gallate can be considered as a surface-active complex possibly arising from the occurrence in solution of a bonded complex between the –OH grouping of the gallate and the polyoxyethylene group of the surfactant. Evidence for this is obtained from the DSC results where the endothermic peak is due to the unbonded cetomacrogol. At ratios in excess of 1.2:1M, the cetomacrogol peak is absent and all cetomacrogol will have gallate associated with it. This may be present as a solid solution of the two components or as a complex. The shape and relative position of the phases in the solubilization diagram also support the suggestion that the cetomacrogol gallate mixture should be regarded as forming the surface-active agent. The gradually increasing amounts of gallate present produce a higher molecular weight molecule which behaves in much the same way as when solubility diagrams are prepared for a homologous series of surface-active agents. If the mixture of surfactant and gallate was not acting as a complex in solution then the relative position of the phases present would have been displaced.

In a liquid crystal phase the surface-active agent molecules are highly orientated. The decrease, and then disappearance, of the liquid crystal regions when the proportion of gallate present was increased suggests that the orderly arrangement of the liquid crystal was disturbed. This could be because the association of the gallate with the cetomacrogol produces a geometric arrangement of the molecules which cannot close-pack in the manner characteristic of the liquid crystal state.

Winsor's (1954) theories of micelle formation suggest that the surface-active agent functions as a cosolvent between the water and the water-immiscible compound, depending almost exclusively on the strength and balance of the interactions between the components of the system. The presence of gallates in the surface-active complex will decrease the hydrophilic character and, as the proportion of gallate is raised, the increasing lyophobic nature of the complex will allow the formation of  $L_1$  type micelles at a higher water and lower benzaldehyde concentration.

When the molar ratio cetomacrogol : gallate exceeds 1 : 1 (approximately 6 : 1 w/w) the liquid crystal is absent and only spherical micelles are formed.

With phases containing spherical micelles the increased bulk of the cetomacrogol gallate complex tends to reduce the amount of benzaldehyde solubilized although small amounts of gallate, by increasing the pallisade space between adjacent molecules of the micelle, at first allow a slight but significant increase in benzaldehyde solubilization. There are two possible reasons for this phenomenon; either the increased molecular bulk and increased lyophobic nature prevents the formation of micelles until higher surface-active concentrations are reached, or the competition for space within the pallisade layer of the micelles favours the gallate which can complex with the cetomacrogol at the expense of the benzaldehyde which cannot. Probably both factors play a part in the overall solubility picture. Table 1 shows that the maximum additive concentration of benzaldehyde in the  $L_1$  phase occurs at a cetomacrogol : gallate ratio of 6 : 1 for ethyl gallate, 9 : 1 for propyl gallate and 19 : 1 for octyl and dodecyl gallates. This appears to indicate that with increasing size of the gallate molecule less can be accommodated within the pallisade before competition with the benzaldehyde becomes a limiting factor in the solubilization of the latter.

With micelles of the  $L_2$  type, a similar situation should occur when water is the solubilize and benzaldehyde is the continuous phase. However, the distribution of the higher molecular weight gallates between benzaldehyde and cetomacrogol appears to be overwhelmingly in favour of the former. Because of this the size of the micelle remains approximately constant with respect to gallate concentration and hence there is little change in the amount of water solubilized. Any maximum additive concentration noted represents only a small increase over the amount solubilized in the absence of gallates. With ethyl gallate no maximum additive concentration was found.

#### *Acknowledgements*

R. S. Ul Haque would like to thank the British Council for financial aid during these studies.

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