

Research Papers

Viscosity and stability relations of the system ascorbic acid: water: polysorbate 20

J. R. NIXON AND B. P. S. CHAWLA

The viscosity of dispersions of ascorbic acid in solutions of polysorbate 20 has been determined and found to be Newtonian at all concentrations studied. The course of the oxidation in polysorbate 20 appeared to be by the normal chain reaction, but the rate at which it occurred was modified by a number of factors. Incorporation within the micelle appeared to be responsible for an increase in oxidation rate, but the high viscosity of concentrated polysorbate 20 solutions, which would affect the diffusion of oxygen to the reaction site caused a much larger reduction in oxidation rate.

MANY pharmaceuticals have been prepared in recent years in which the medicament has been solubilised by non-ionic surface-active agents. Aqueous preparations of oil-soluble vitamins have been particularly popular and increased stability to oxidation has been claimed.

Previously this department has reported the oxidation of model relatively water insoluble substances in surface-active agents (Nixon, 1958; Mitchell, 1960; Swarbrick, 1963). It is possible to include the water-soluble vitamin ascorbic acid in this type of preparation and we now describe its oxidative behaviour in the model system ascorbic acid: water: polysorbate 20.

Experimental

Ascorbic acid. Assay (iodometric) 99%. M.p. 190-192°. $[\alpha]_D^{20}$ 2% in water + 22°. pH of 2% in water 2.5.

Polysorbate 20 (Tween, Honeywill-Atlas Ltd). This material complied with the manufacturer's specification dated October, 1956.

Copper sulphate. Analar. Used at $1 \times 10^{-4}M$ $CuSO_4 \cdot 5H_2O$ as a catalyst.

Buffer solution, pH 3.4. Na_2HPO_4 /citric acid (McIlvaine, 1921).

Determination of solubility. The solubility of the ascorbic acid was determined by equilibration in glass-stoppered flasks immersed in a water-bath at $25^\circ \pm 0.1^\circ$. The end-point was taken as the average between an under- and over-saturated dispersion. Because of the viscosity of high concentrations of polysorbate 20 it was necessary to warm the flask to 60° to speed the equilibration period. This did not affect the quantity solubilised. In all instances the excess ascorbic acid separated out as crystalline material.

Determination of viscosity. This was measured using a Ferranti-Shirley cone and plate viscometer fitted with an automatic flow curve recorder. The viscosity was measured at 25° using either a 4 cm (angle

From the School of Pharmacy, Chelsea College of Science and Technology, Manresa Road, London, S.W.3

20'. 26'') or 7 cm (angle 20'. 25'') cone. Flow curves were determined as the shear rate was continuously increased from zero up to 1800 sec⁻¹ and then decreased to zero again. The samples were also subjected to recycling.

Measurement of oxygen uptake. The oxidation of the systems was followed by means of a Warburg constant volume respirometer at 25° as previously described (Carless & Nixon, 1957). The oxygen uptake of polysorbate 20 in water was also measured and subtracted from the total uptake as a correction.

Chromatography of oxidised ascorbic acid solutions. The lower layer of a butanol:glacial acetic acid:water system (40:10:50) was used to develop the chromatogram. The Whatman No. 1 filter paper was equilibrated for 24 hr with the upper layer of the mixture before development. The spots were made visible with ammoniacal silver nitrate and the chromatograms were also examined under ultraviolet light.

Results

The presence of polysorbate 20 did not cause any large increase in the solubility of ascorbic acid (line AB, Fig. 1) and at high surface-active agent concentrations the solubility fell until in the polysorbate 20 itself only 5% w/w of ascorbic acid was soluble. None of the dispersions

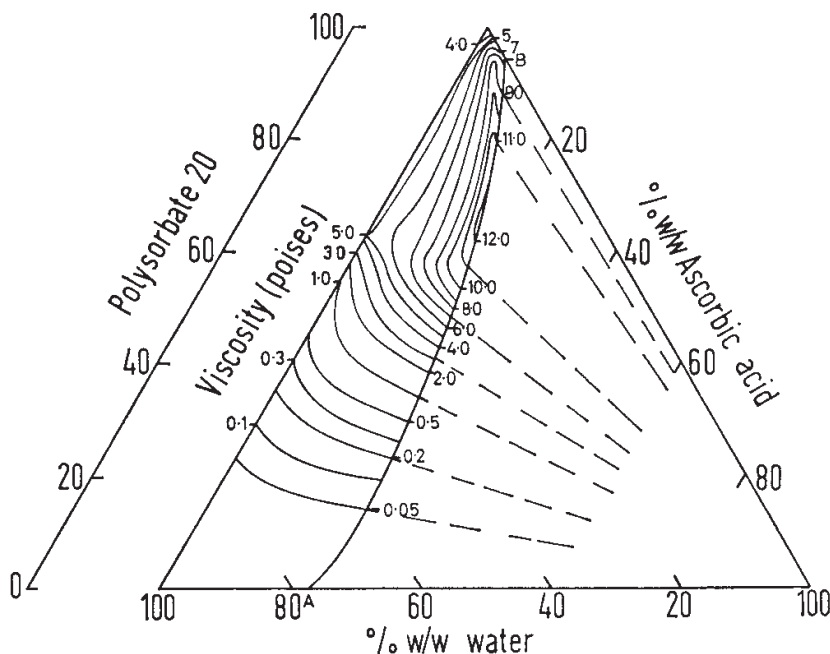


FIG. 1. Viscosity and solubility relationships in the system polysorbate 20/ascorbic acid/water. Line A-B is the solubility curve of ascorbic acid. — Viscosity contours of one phase system. - - - Viscosity contours of equilibrium liquid in contact with excess ascorbic acid.

showed birefringence when examined under polarised light, indicating the absence of liquid crystals.

The viscosity of all the dispersions was Newtonian and did not vary on recycling

The rather complicated viscosity map, produced by connecting similar viscosities within both the solubilised and solubilised plus excess solid regions, is shown superimposed on the solubility curve in Fig. 1.

In the binary system polysorbate 20:water there was a very slow increase in viscosity to 30% w/w polysorbate 20 after which the increase was extremely rapid and reached a maximum of 5.2 poises at 62.8% w/w polysorbate 20. The viscosity then fell gradually and polysorbate 20 itself had a viscosity of 3.81 poises.

The initial addition of ascorbic acid to any polysorbate 20:water system caused an increase in viscosity. The subsequent behaviour on further addition of ascorbic acid depended on the starting concentration of polysorbate 20. At concentrations up to about 60% w/w polysorbate 20 a point was reached where further addition of ascorbic acid caused little or no change in the viscosity. This occurred after the addition of 10-12% w/w of ascorbic acid. From 60-90% w/w polysorbate 20 the viscosity of the dispersions continued to increase with addition of ascorbic acid until the solubility limit was reached. In the heterogeneous region of Fig. 1, the viscosity of solutions on the same tie line was, as expected, found to be constant. This proved a useful check on solubility data which would otherwise have been difficult to determine. For initial concentrations of polysorbate 20 in excess of 90% w/w a third behaviour pattern was observed. Here the initial increase of ascorbic acid caused a rapid increase in viscosity but on further addition the contours turned back upon themselves and the result was a slight fall of viscosity.

The viscosity of saturated solutions of ascorbic acid in polysorbate 20:water exhibited a similar form to the binary polysorbate 20:water. The peak viscosity was 12.3 poises at 68% w/w polysorbate 20.

The catalysed oxidation of ascorbic acid in water at pH 3.4 and 6.0 was a first order reaction. The rate was approximately twice as fast at the higher pH but both showed a rapid increase in oxidation rate at ascorbic acid concentrations of less than 8% w/w (Table 1).

TABLE 1. OXIDATION OF AQUEOUS ASCORBIC ACID

Concentration of ascorbic acid % w/w	Oxidation rate (ml/kg/hr)	
	pH 3.4	pH 6.0
2.7	7,500	13,600
5.95	3,300	5,900
8.1	1,950	3,400
11.9	1,650	2,900
16.2	1,500	2,800

Catalyst: $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$

The induction period of ascorbic acid in polysorbate 20 was much more extended than in water alone, and after the induction period a rise to an approximately steady oxidation rate occurred. The period of declining oxidation rate was also extended.

The oxidation of ascorbic acid in polysorbate 20 is slightly complicated due to the slow uptake of oxygen by the polysorbate 20 itself. This occurs more rapidly at acid pH and at high polysorbate 20 concentrations

ASCORBIC ACID : WATER : POLYSORBATE 20

could form a significant proportion of the total oxygen uptake. Fig. 2 shows the uptake of oxygen by polysorbate 20 and it can be seen that although increasing viscosity did initially cause a fall in oxidation rate, at high polysorbate 20 concentrations this had increased again and was now in excess of dispersions with low viscosity. The method of increasing gas:liquid transfer by increasing the shaking rate did not cause any noticeable increase in this oxygen uptake.

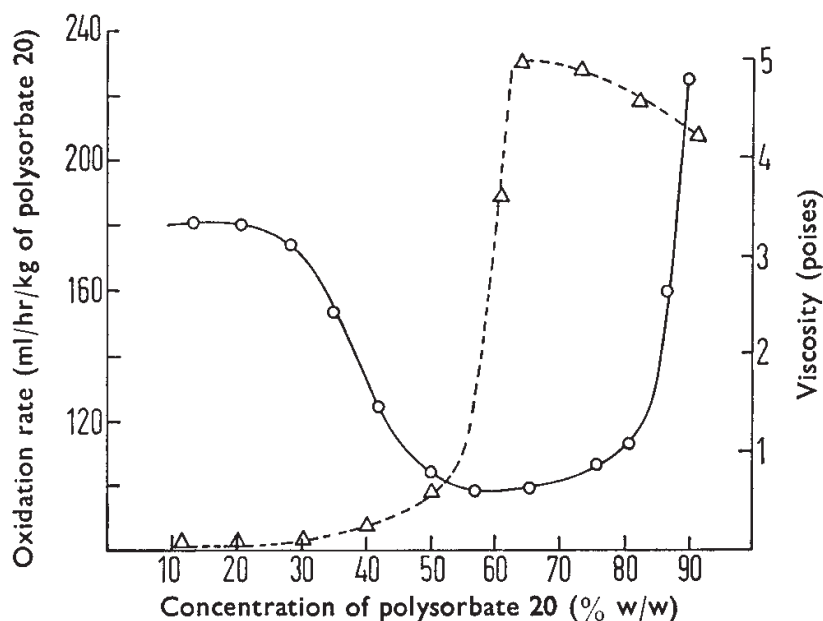


FIG. 2. The oxidation of polysorbate 20. Temperature 25°. Catalyst $1 \times 10^{-4}M$ $CuSO_4 \cdot 5H_2O$. pH 3.4. — Oxidation rate. - - - Viscosity.

Before studying the oxidation in relation to the viscosity solubilisation diagram (Fig. 1) the effect of catalyst and pH was determined. Saturated solutions in 15 and 30% w/w polysorbate 20 were used. With both polysorbate concentrations the rate of oxidation increased rapidly with

TABLE 2. EFFECT OF COPPER CATALYST ON THE RATE OF OXIDATION OF SATURATED SOLUTIONS OF ASCORBIC ACID

Polysorbate concentration % w/w	Copper sulphate M	Steady oxidation rate ml/kg/hr
15	0	15
	1×10^{-5}	130
	5×10^{-5}	480
	1×10^{-4}	670
	5×10^{-4}	1,100
30	0	15
	1×10^{-5}	220
	5×10^{-5}	580
	1×10^{-4}	750
	5×10^{-4}	1,240

increasing catalyst concentration, although no linearity was found (Table 2). An increase in pH also caused an increased oxidation rate except in the region pH 5.6 to 7.2 where a plateau existed (Fig. 3).

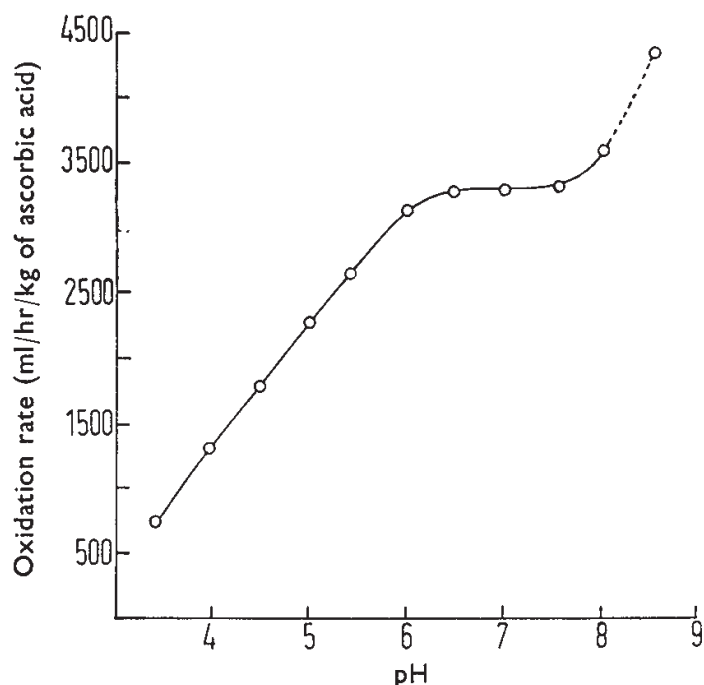


FIG. 3. The effect of pH on the oxidation of ascorbic acid in polysorbate 20. Polysorbate concentration 30% w/w Temperature 25°. Catalyst $1 \times 10^{-4}M$ $CuSO_4 \cdot 5H_2O$.

The oxidation of ascorbic acid-saturated dispersions, both catalysed and uncatalysed, was studied at pH 3.4. This pH was adopted to prevent the catalysed oxygen uptake rate becoming too fast to measure. The large increase in the viscosity of concentrated polysorbate 20 dispersions had a negligible effect on the oxidation rate of the uncatalysed reaction. As the concentration of polysorbate increased, the oxidation rate rose slightly, although there was a sharp fall in rate at polysorbate 20 concentrations greater than 90% w/w (Fig. 4).

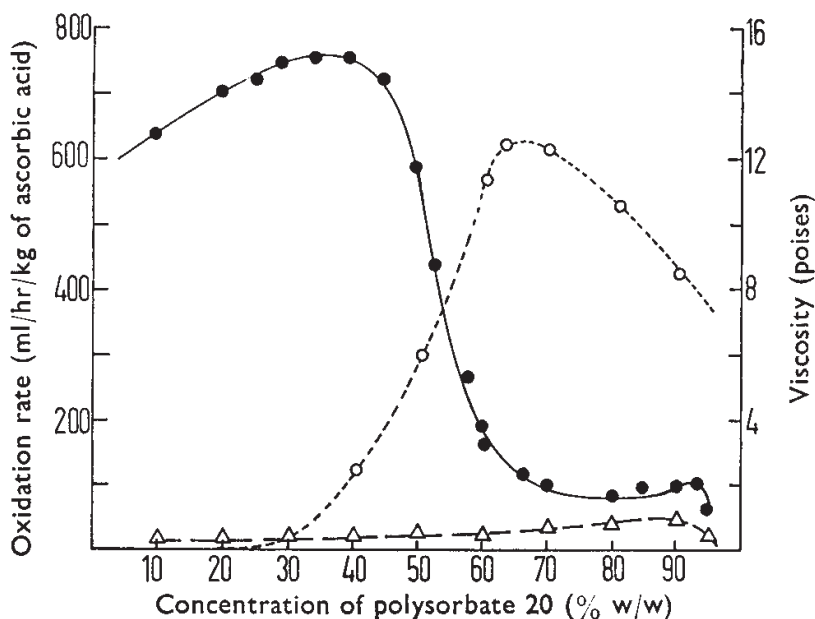


FIG. 4. The oxidation of saturated solutions of ascorbic acid in polysorbate 20. Temperature 25°. pH 3.4. — Catalyst $1 \times 10^{-4}M$ $CuSO_4 \cdot 5H_2O$. - - - Uncatalysed. --- Viscosity.

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