J. Pharm. Pharmac., 1968, **20**, 249–254 Received September 14, 1967

The stability of sucrose monolaurate: rate of formation of lauric acid

R. A. ANDERSON AND A. E. POLACK*

At concentrations below the critical micelle concentration, sucrose monolaurate hydrolyses to give lauric acid at first-order rates. At concentrations above the critical micelle concentration first-order kinetics are not obeyed. In systems buffered to pH values sufficiently high for the liberated lauric acid to ionize, the laurate ions appear to form mixed micelles with the ester and these carry negative charges. Coulombic repulsion of hydroxyl ions by these negative charges protects neighbouring ester molecules from attack and so reduces hydrolysis rates.

THE sucrose fatty acid esters are non-ionic surface-active agents which differ from many non-ionic water-soluble surfactants in that they do not possess polyoxyethylene chains. They appear to be useful pharmaceutical adjuncts, but little information is available about their stability.

Osipow, Snell & others (1956) heated a solution containing 0·5% sucrose stearate and 1% sodium tripolyphosphate (pH 9·5) at 60° and found 8·9% hydrolysis after 1 hr and 14·9% after 4 hr. Stability to acid was determined using 0·1% ester in 0·1N hydrochloric acid. After 2 hr at 37°, stearic acid equivalent to 2·5% of the ester had been formed, and 30 min at 100° showed 6·9% hydrolysis. Kakemi, Arita & others (1962) have examined the decomposition of sucrose monostearate in some ethanol–water media.

Sucrose monolaurate is the most water-soluble of the common sugar esters and has been chosen for further study.

Experimental

MATERIALS

Sucrose monolaurate, "purified", 27-2037 (Colonial Sugars Co.) was further purified by the method of Mima & Kitamori (1964). The product was checked by thin-layer chromatography for absence of free sucrose, sucrose dilaurate and higher esters, and was shown by complete hydrolysis and quantitative gas chromatography to be free of residual solvents and esters of other fatty acids.

Lauric, myristic and palmitic acids were "specially pure" laboratory reagent grade, B.D.H.

The following buffer solutions were used to prepare the sucrose monolaurate solutions: hydrochloric acid–potassium chloride (pH 2·10; 2·51); chloroacetic acid–sodium hydroxide (pH 3·00); acetic acid–sodium acetate (pH 4·06; 5·08); potassium dihydrogen phosphate–dipotassium hydrogen phosphate (pH 5·80; 6·80; 7·20); boric acid–sodium hydroxide (pH 9·30). With the exception of one of the phosphate buffers (specifically noted in Fig. 6), the ionic strength of all buffer solutions

From the Pharmacy Department, University of Sydney, Australia.
* Present Address: Pharmacy Department, South Australian Institute of Technology, Adelaide, South Australia.

was 0·2. The pH measurements were made at 25° using a "Radiometer" 23 pH meter.

METHODS

Degradation of ester. Solutions of sucrose monolaurate were made in the selected buffer and accurately measured volumes were pipetted into thin-glass ampoules. In a few cases palmitic acid was included by adding an appropriate volume of an ethanolic solution of the acid just before adjustment to volume. A fine suspension was formed and the suspension was measured into ampoules as before.

The ampouled solutions were heated at 100°, 71°, 46° or 25° ± 0·1°. At selected intervals, ampoules were withdrawn and cooled in an ice bath.

Estimation of free lauric acid. The contents of an ampoule of sucrose laurate solution was quantitatively transferred to a separating funnel along with diethyl ether and an accurately measured volume of a standard ethanolic myristic acid solution. The pH of the aqueous phase was lowered (if necessary) to about 5 by addition of 0·1N hydrochloric acid and the funnel shaken. The aqueous layer was removed and the ethereal layer washed twice with ether-saturated water. The procedure was shown to completely extract the free fatty acids and reject sucrose monolaurate (Polack, 1967).

The fatty acids in the ethereal solution were converted to the methyl esters by diazomethane (Schlenk & Gellerman, 1960), and the ethereal solution was analyzed by gas chromatography using a "Panchromatograph" (Pye) fitted with a Speedomax G recorder. A 5 ft column of 10% Silicone Elastomer 30 on Chromosorb W (HDMS) 60–80 mesh was used under isothermal conditions at 175°. Using nitrogen as the carrier gas at a flow rate of 80 ml/min, the retention times for lauric, myristic and palmitic acids (as methyl esters) are 2, 4 and 8 min respectively.

Peak heights were measured and the ratio of the concentrations of lauric acid to myristic acid was calculated from the relationship shown in Fig. 1. At least four chromatograms were run for each ethereal solution and the results averaged.

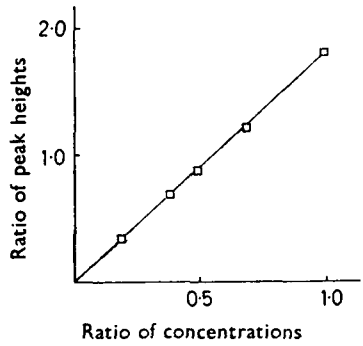

FIG. 1. The relation between the ratio of peak heights (lauric acid : myristic acid) and the ratio of concentrations.

Results and discussion

The degradation of sucrose monolaurate could possibly proceed in two ways. The molecule might split at the bond joining the dextrose and fructose units giving a hexose laurate, or hydrolysis might take place at the ester link liberating lauric acid.

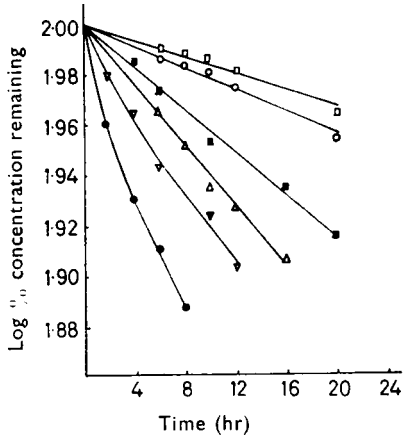

FIG. 2. Hydrolysis of sucrose monolaurate at 100° at various pH values. ● pH 2·10 Initial concentration 0·0096 M. ▽ pH 2·51 Initial concentration 0·0097 M. △ pH 3·00 Initial concentration 0·0099 M. □ pH 4·06 Initial concentration 0·100 M. ○ pH 5·08 Initial concentration 0·0102 M. ■ pH 5·80 Initial concentration 0·0099 M.

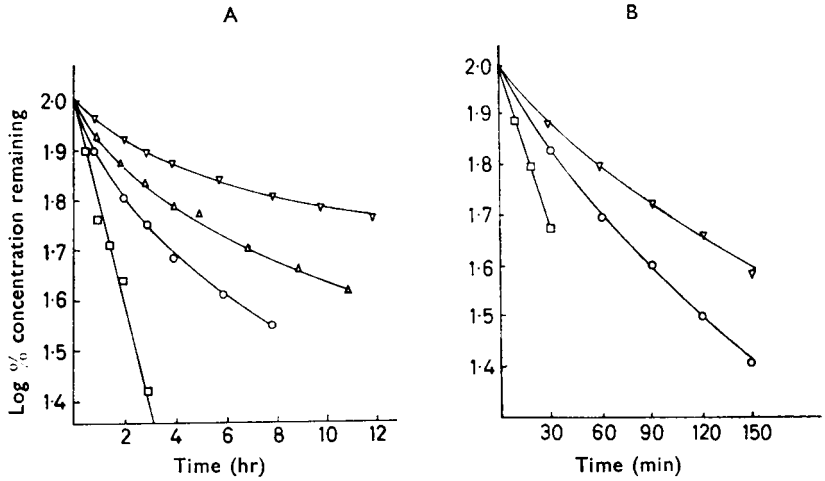

FIG. 3. A. Hydrolysis of sucrose monolaurate at 100° at pH 7·20 at various initial concentrations. ▽ Initial concentration 0·0200 M. △ Initial concentration 0·0100 M. ○ Initial concentration 0·0040 M. □ Initial concentration 0·0004 M.
B. Hydrolysis of sucrose monolaurate at 71° at pH 9·30 at various initial concentrations. ▽ Initial concentration 0·0200 M. ○ Initial concentration 0·0100 M. □ Initial concentration 0·0002 M.

Using thin-layer chromatography a faint spot at an Rf value similar to that of sucrose dilaurate was detected from some acid solutions (pH <4) but not from neutral or alkaline solutions, and this seems to indicate that hydrolysis of the sucrose part of the molecule is unimportant in neutral and alkaline solutions.

The concentrations of sucrose laurate remaining undegraded, and which are seen in Figs 2 to 6, are calculated on the assumption that the only quantitatively important degradation is hydrolysis to give free lauric acid. Fig. 2 shows the rates of hydrolysis of about 0·01M solutions at 100° at various pH values (2·10 to 5·80) and indicates a maximum stability at pH 4 to 5.

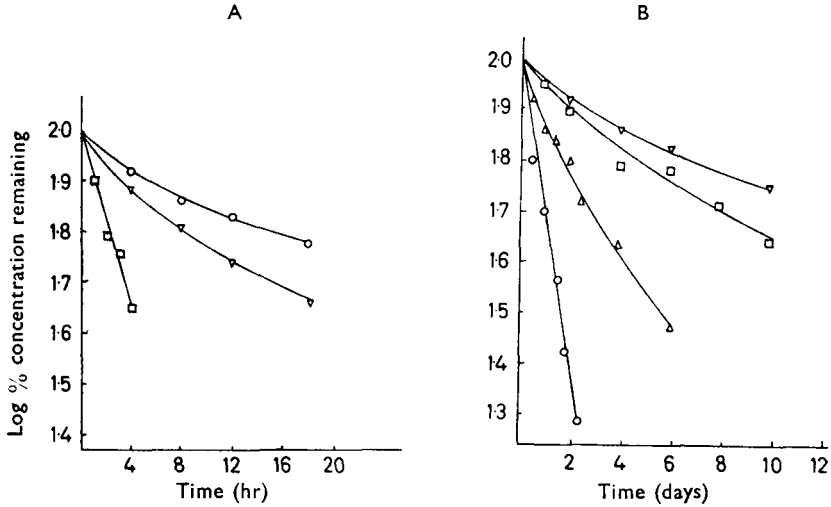

FIG. 4. A. Hydrolysis of sucrose monolaurate at 46° at pH 9·30 at various initial concentrations. ○ Initial concentration 0·0200 M. ▽ Initial concentration 0·0100 M. □ Initial concentration 0·0002 M.
B. Hydrolysis of sucrose monolaurate at 25° at pH 9·30 at various initial concentrations. ▽ Initial concentration 0·0200 M. □ Initial concentration 0·0100 M. △ Initial concentration 0·0010 M. ○ Initial concentration 0·00025 M.

Figs 3 and 4 show the effect of variation of initial concentration of sucrose laurate on hydrolysis rates. Above the critical micelle concentration (CMC), sucrose monolaurate is present both as individual molecules and associated as micelles, and differences would be expected for the rate constants for hydrolysis of free and micellar forms. The CMC for sucrose monolaurate was reported by Osipow, Snell & Hickson (1957) to be $3{\cdot}4 \times 10^{-4}$M at 27°. Using the same technique (surface tension measurements), Polack (1967) found a CMC of $2{\cdot}4 \times 10^{-4}$M at 25°, this value being essentially unaffected by the presence of 10^{-3}M lauric acid at pH 7·2.

At concentrations below the CMC the hydrolysis proceeds at first-order rates; at concentrations above the CMC the rate constant decreases with increase in initial concentration of ester but does not remain constant during the degradation. If, as seems reasonable, the rate constant for

hydrolysis of molecules in the micellar state is lower than that of unassociated molecules, plots of the logarithm of the percentage of ester remaining against time would be expected to show increased (negative) slope as the degradation proceeds; in the extreme case that micellar material does not undergo hydrolysis, the overall reaction would proceed at zero-order rates and plots of concentration against time would be linear. Clearly, some other factor is involved.

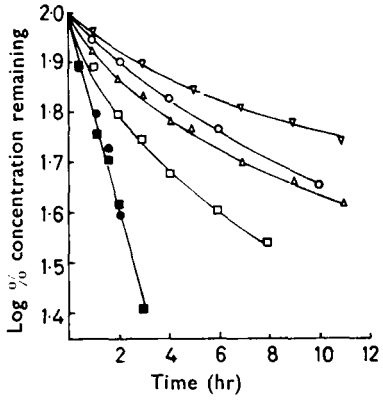

FIG. 5. Effect of palmitic acid on the hydrolysis of sucrose monolaurate at 100° at pH 7·20. □ Initial concentration 0·0040 M sucrose monolaurate. ○ Initial concentration 0·0033 M in presence of 0·0056M palmitic acid. △ Initial concentration 0·0100M sucrose monolaurate. ▽ Initial concentration 0·0102M in presence of 0·0140M palmitic acid. ■ Initial concentration 0·0004M sucrose monolaurate. ● Initial concentration 0·0004M in presence of 0·0006M palmitic acid.

Fig. 5 shows that the inclusion of palmitic acid slows the rate of hydrolysis when concentrations are appreciably above the CMC of the ester but not when the concentration of ester is in the region of the CMC. It seems likely that in systems containing micelles of sucrose laurate, free lauric acid or laurate ions will be taken up to form mixed micelles. The pKa value of lauric acid is about 5–6 (Rosano, Breindel & others, 1966), so that at pH 7·2 (and higher) most of the fatty acid will be in the form of laurate anions and the mixed micelles will carry a negative charge, the density of the charge increasing as the degradation proceeds. Coulombic repulsion of hydroxyl ions by these negative charges will serve to protect neighbouring ester molecules from attack. Similar effects have been reported for other systems. Riegelman (1960) has suggested that the anionic head groups of sodium lauryl sulphate provide a barrier to the approach of hydroxyl ions and protect solubilized benzocaine from hydrolysis; low (but not high) concentrations of cetyltrimethylammonium bromide increase the hydrolysis rate, probably by attracting hydroxyl ions to the benzocaine environment. Nogami, Awazu & others (1960) and Nogami & Awazu (1962) found that the hydrolysis of methantheline bromide in the presence of sodium lauryl sulphate was markedly dependent on pH; the base catalysis was suppressed by the surfactant whereas the

acid catalysis was promoted. Swarbrick (1965) has reported that this effect is probably due to the attraction and repulsion between the electrical charge on the micelle and the hydronium ion and hydroxyl ion respectively.

The effect of increasing ionic strength is shown in Fig. 6. The increased hydrolysis rate at the higher ionic strength reflects the reduced coulombic repulsion. The change of concentration of phosphate ions appears to have no effect, provided the ionic strength is held constant.

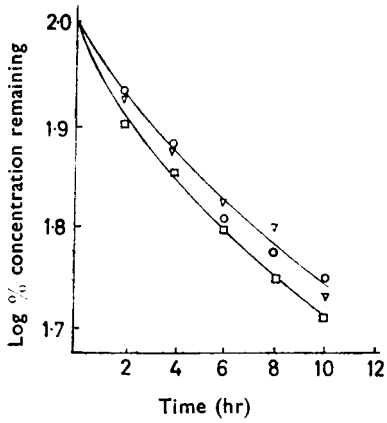

FIG. 6. Effect of buffer strength and ionic strength on hydrolysis of sucrose monolaurate at 100° at pH 6·80 in various phosphate buffer solutions. ▽ Initial concentration 0·0100M. Buffer strength 0·0917M. Ionic strength 0·2. ○ Initial concentration 0·0099M. Buffer strength 0·1834M. Ionic strength 0·2. □ Initial concentration 0·0102M. Buffer strength 0·0917M. Ionic strength 0·4.

References

Kakemi, K., Arita, T., Sazaki, H. & Katsura, Y. (1962). *Yakuzaigaku*, **22**, 163–167.
Mima, H. & Kitamori, N. (1964). *J. Am. Oil chem. Soc.*, **41**, 198–200.
Nogami, H., Awazu, S., Watanbe, K. & Sato, K. (1960). *Chem. pharm. Bull. Tokyo*, **8**, 1136–1141.
Nogami, H. & Awazu, S. (1962). *Ibid.*, **10**, 1158–1160.
Osipow, L., Snell, F. D. & Hickson, J. (1957). *Second International Congress of Surface Activity*, Vol. I, pp. 50–55. London: Butterworth.
Osipow, L., Snell, F. D., Marra, D. & York, W. C. (1956). *Ind. Engng Chem.*, **48**, 1462–1464.
Polack, A. E. (1967). M.Pharm. Thesis, University of Sydney.
Riegelman, S. (1960). *J. pharm. Sci.*, **49**, 339–343.
Rosano, H. L., Breindel, K., Schulman, J. H. & Eydt, A. J. (1966). *J. Coll. Inter. Sci.*, **22**, 58–67.
Schlenk, H. & Gellerman, J. L. (1960). *Analyt. Chem.*, **32**, 1412–1414.
Swarbrick, J. (1965). *J. pharm. Sci.*, **54**, 1229–1237.