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COMMUNICATIONS

Peroxide removal from non-ionic surfactants

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It was recently reported that peroxides formed by polyoxyethylene-derived surfactants during storage accelerate the decomposition of benzocaine HCl (Azaz et al 1973a), corticosteroids (McGinity et al 1975) and vitamin A acetate (Azaz & Segal 1977). Since most commercial samples of such surfactants contain significant quantities of peroxides, a method for eliminating these seemed necessary. Various methods have been developed for the removal of polyoxyethylene glycols, which often contaminate polyoxyethylene ethers. We wondered whether the method devised by Weibull (1960), which is uncomplicated and highly effective, could be adapted to the removal of peroxides from surfactants.

A 10% solution of Polysorbate 40 in ethyl acetate (AR) was twice extracted with saturated aqueous NaCl, dried over $MgSO_4$ and the solvent evaporated at reduced pressure under N_2 at 30 °C. Although initially the peroxide concentration was slightly reduced, it regained and even surpassed its original concentration after 5 days storage at room temperature (20°), (Table 1, I). All the peroxides were eliminated by extracting

Table 1. Peroxide number* of polysorbate-40 under different purification conditions.

Sample	Solvent	Purification method†	Yield %	PN initial	PN after 5 days storage‡
	—	Control§	100	2·5	3·0
I	Ethyl acetate	Sat. NaCl (2 extracts)	82	1·5	4·0
II	,, ,,	(a) 1% $Na_2S_2O_5$ in sat. NaCl (2 extracts) (b) Sat. NaCl (2 extracts)	80	0	4·2
III	Dichloro-methane	Sat. NaCl (2 extracts)	99	2·0	3·0
IV	,,	(a) 1% $Na_2S_2O_5$ in sat. NaCl (2 extracts) (b) Sat. NaCl (2 extracts)	97	0	0·3

* Peroxide number (PN) in = mequiv kg^{-1} was determined according to Azaz, Donbrow & Hamburger (1973b), on 1% solutions.
† Polysorbate-40 solutions (10%), extracted with solutions stated, dried over $MgSO_4$ and evaporated (vacuum, 30 °C, N_2), then dissolved in bidistilled water to give 3% solutions.
‡ Aqueous solutions (3%) were stored at room temperature (~20 °C) in clear glass vessels provided with air condensers.
§ Detergent without solvent treated exactly as described for extracted sample i.e. heated for 20 min to 30 °C under reduced pressure and N_2, then dissolved to give a 3% solution.

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Table 2. Peroxide number and pH* of cetomacrogol-1000 samples with and without ethyl acetage treatment after various periods of storage†.

Sample treatment	Yield %	PN Time of storage 0 days	PN Time of storage 3 days	PN Time of storage 4 days	pH Time of storage 0 days	pH Time of storage 3 days	pH Time of storage 4 days
Control	100	0·2	0·4	0·6	9·4	8·4	6·8
	100	0·2	0·45	1·4	9·8	7·8	7·5
Soln extracted with sat. NaCl (2 extracts)	89	0·6	18	>50	5·4	5·0	3·8
	88	1·0	20	>50	5·6	4·8	3·7
	89	1·0			7·3		
	90	0·3			5·5		
Soln without extraction ‡.	100	2·5	20	>50	5·5	6·5	5·1
					7·6		
Soln in freshly distilled ethyl acetate	100	0·2	15	>50	9·4	8·4	4·2

* pH was determined on a 2% solution in double-distilled water.
† Aqueous solution (3%) of the cetomacrogol samples were stored in clear glass vessels at 50 °C; loss of water, determined by weighing the samples before and after storage was negligible.
‡ Cetomacrogol-1000 solution in ethyl acetate (10%), evaporated in the final stage at reduced pressure and under N_2.

Table 3. Peroxide number, acidity and cloud point of cetomacrogol purified* using CH_2Cl_2 as solvent.

Storage† time days	PN		Acidity‡ (mequiv g^{-1})		pH		Cloud point	
	Cont.	Pur.	Cont.	Pur.	Cont.	Pur.	Cont.	Pur.
0	0·2	0			9·7	5·4	89	89
1	0·8	0·4			9·0	4·5		
5	45	10			3·8	4·1		
6	60	25						
7			0·066	0·026			87·1	88·1
9	100	70	0·13	0·06	3·2	3·4	85·7	87·2
19	150	140	0·98	0·78	2·8	2·8	62·7	71·4

* Purification was achieved by extracting a 10% solution of cetomacrogol-1000 in distilled CH_2Cl_2, first with 1% $Na_2S_2O_5$ solution in sat. NaCl (two extractions), then with sat. NaCl (two extractions), drying and evaporating as described.

† The conditions and methods used were as described in the footnotes to Table 2. The storage temperature was 50 °C.

‡ Acidity was determined by titrating 5 ml of a 2% solution of detergent in NaCl (1 M) with NaOH (0·01 M) using phenolphthalein as indicator (Hamburger & others, 1975).

Cont. = control Pur. = purified

the ethyl acetate solution twice with 1% sodium metabisulphite in saturated NaCl, then twice with saturated NaCl. However, after a lapse of 5 days the peroxides had reappeared and had attained the same concentration as in the sample extracted with NaCl only (see Table 1, II).

This finding implies that a factor catalysing peroxide formation is introduced in the purification process. In the experiments aimed at determining this factor, cetomacrogol 1000 (Glover) was preferred as a model surfactant because the solid commercial sample is generally devoid of peroxides. The results, summarized in Table 2, show that the ethyl acetate used as solvent accelerates peroxide formation and decrease in pH, since peroxides occurred in a solution of cetomacrogol in the freshly distilled solvent. These findings are not surprising as ethyl acetate readily decomposes to acetic acid, which would catalyse peroxide formation (Hamburger et al 1975).

Dichloromethane, a stable compound with a low boiling point and excellent solution capacity for these surfactants was therefore used instead of the ethyl acetate. The same double extraction method with 1% $Na_2S_2O_5$ in saturated NaCl, followed by saturated NaCl was used and the effect on the peroxide number and pH of storage of the solution at 50 °C exposed to air and light was followed. The results summarized in Table 3 show that with this solvent, peroxides were not only eliminated in the initial stage, but were kept, at a much reduced concentration compared with the control for some time. Acidity measured either by pH determination or by titration was also below control values. However, the pH does not reflect the full picture of acidity changes during storage, since the purification process removed basic compounds in the cetomacrogol. Change in the cloud point, an indicator of the stability of the detergent (Donbrow et al 1975), was less pronounced in the purified sample than in the control.

In previous work it was estimated that decrease in temperature increases the induction period of 3% aqueous cetomacrogol from days to months (Hamburger et al 1975). From the results in Table 3, which were obtained at 50°, it can be deduced that the stability would be increased at room temperature to several months.

Preliminary results obtained with Polysorbate-40 indicate that this detergent may be similarly purified (Table 1, Samples III and IV).

With polysorbate as well as with cetomacrogol, t.l.c. examination according to the method of Thakkar et al (1967) showed that free polyoxyethylene glycols, which always accompany the commercial surfactants, could be removed only when ethyl acetate was used as solvent. This fact is also reflected in the overall yield obtained when dichloromethane was used as solvent (Table 1). However, since polyoxyethylene glycols have no adverse effect on drug stability, extraction of the detergent solution in dichloromethane with 1% $Na_2S_2O_5$ in saturated NaCl solution followed by extraction with saturated NaCl solution, may be recommended for the removal of peroxides from polyoxyethylene derived surfactants.

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