

THE EMULSIFYING PROPERTIES OF POLYETHYLENEGLYCOL ETHERS OF CETOSTEARYL ALCOHOL

By J. W. HADGRAFT

From The Pharmaceutical Department, The Royal Free Hospital, London

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IN recent years, emulsified ointment bases have come increasingly into use, due mainly to the introduction of emulsifying agents of the sulphated alcohol type. Official recognition of this type of preparation came in 1948 when the British Pharmacopœia included emulsifying wax, consisting of a mixture of sodium laurylsulphate and cetostearyl alcohol. In the formulation of a number of pharmaceutical preparations, emulsifying wax has proved to be very satisfactory, but it is not without disadvantages.

From a pharmaceutical standpoint, the main disadvantage of emulsifying wax is its incompatibility with nitrogenous bases such as proflavine. Although, by the inclusion of sufficient wax or fatty substances, apparently stable emulsions may be obtained, the antiseptic activity of proflavine and similar dyestuffs is seriously impaired in the presence of sodium laurylsulphate. Not only is emulsifying wax unsuitable for antiseptic creams of this type, but it is also incompatible with many new medicaments, such as the antihistamines, which include a positively charged nitrogen atom in their constitution.

Non-ionic emulsifying agents provide an alternative to sodium laurylsulphate for the formulation of emulsified ointment bases and creams containing nitrogenous organic compounds. They may be combined with cetostearyl alcohol to give added stability. Although cases of skin sensitivity to sodium laurylsulphate are rare, they have been reported and in such cases, the non-ionic emulsifying agents provide a useful alternative.

Non-ionic emulsifiers of various types have become available in this country during the past few years. They consist for the most part, of derivatives of polyethyleneglycol and the most commonly used types have been the stearate esters of polyethyleneglycol and the polyethyleneglycol ethers of sorbitan esters of fatty alcohols. Polyethyleneglycol monostearate can be combined with cetostearyl alcohol to form a non-ionic emulsifying wax, but has been found to have two disadvantages in such a preparation. In the first place, emulsifying properties may vary from one sample to another owing to the difficulty of manufacturing the monostearate free from contamination with the distearate. Secondly, in preparations of an acid or alkaline reaction, hydrolysis of the ester may occur on storage with consequent breakdown of the emulsion.

Ethers of polythyleneglycol and cetostearyl alcohol have received less attention than the esters, but since they are more resistant to hydrolysis and have been stated to be more consistent in their behaviour as emulsifying agents, they merit attention as possible alternatives. These compounds have the general chemical formula, $\text{CH}_3 \cdot (\text{CH}_2)_{16} \cdot \text{CH}_2 \cdot \text{O} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot (\text{OC}_2\text{H}_4)_n \cdot \text{OH}$, in which "n" can be varied over a considerable range. Cetomacrogol 1000,

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which has been included in the British Veterinary Codex, is a compound in this series in which the average value of "n" is between 19 and 23.

A series of ethers of this type has been the subject of the present investigation in order to determine their possible pharmaceutical uses and any limitations to their employment. An attempt has also been made to determine the variation in emulsifying properties with variation in the length of the ether chain. Table I records the compounds investigated,

TABLE I
SOLUBILITY OF CETOSTEARYL POLYETHYLENEGLYCOL ETHERS

Ether value of "n"	Appearance	Solubility in water	5 per cent. in liquid paraffin	5 per cent. in arachis oil
2	Plastic waxy solid	Dispersible	Soluble	Soluble
4	Semi-liquid, unctuous mass	Dispersible	Soluble	Soluble
6	Plastic waxy solid	Dispersible	Dispersible (solid gel)	Dispersible (liquid)
10	Plastic waxy solid	Soluble	Dispersible (solid gel)	Dispersible (liquid)
14	Plastic waxy solid	Soluble	Dispersible (solid gel)	Dispersible (liquid)
18	Solid wax	Soluble	Dispersible (liquid)	Dispersible (liquid)
24	Solid wax	Soluble	Insoluble	Dispersible (solid gel)
30	Solid wax	Soluble	Insoluble	Dispersible (solid gel)

together with their solubility in water, liquid paraffin and arachis oil. It should be emphasised that the value for "n" given in the table is only an average, empirical figure, the compounds not being pure single entities. The information given, however, is of value since it applies to materials which are commercially available and indicates the general trend of change in the properties with increasing length in the polyethyleneglycol ether chain.

Solubility in water increases with increasing length of the ethyleneglycol chain and complete solubility in water at 20° C. occurs when "n" is 10 or more. With smaller ethyleneglycol chains, the ethers are not soluble but will disperse in water. In common with other ethyleneglycol derivatives, the ethers have negative solubility coefficients with temperature and the solutions become cloudy on heating. According to Doscher¹ dehydration occurs above 60° C., the temperature depending upon the length of the ethyleneglycol chain, and the solutions become turbid due to the association of the molecules into larger colloidal aggregates.

Solubility in liquid paraffin follows a reverse course, the lower members being soluble whilst the higher members are insoluble. Solubility in arachis oil is much the same, but the two higher members are more readily dispersed in arachis oil, forming solid gels. The compounds having 10, 14 and 18 ethyleneglycol units in the ether chain are the most evenly balanced between lyophilic and lyophobic properties since they combine solubility in water with dispersibility in liquid paraffin and arachis oil.

EMULSIFYING PROPERTIES OF THE ETHERS

In order to determine the comparative emulsifying properties a series of emulsions, each containing 50 per cent. of liquid paraffin, was prepared containing 1, 2 and 3 per cent. of each of the ethers. The emulsions were prepared by dissolving the appropriate ether in the phase in which it was soluble and vigorously shaking with the other phase. The emulsions containing 3 per cent. of the ethers were duplicated by a series passed through a Q.P. hand homogeniser to determine whether such treatment would extend the range of complete emulsification.

The emulsions were stored at room temperature and observed after one month. The observations were based solely on visual examination for cracking and creaming and no attempt was made to determine emulsion stability other than to determine whether emulsification was complete or not under the conditions of the experiment. It is hoped to extend this investigation to include a consideration of globule counts and globule size distribution but, in these preliminary experiments, visual examination was sufficient to indicate gross variation in emulsifying properties in the series. The following are the criteria on which the observations were made:—

- Emulsification complete .. No visual evidence of cracking or creaming.
- Creaming Formation of a separate layer of aqueous phase.
- Cracking Visual evidence of separation of oil.

It will be seen from Tables II and III that the lower members of the series were more effective in obtaining complete emulsification. There was no significant difference in the behaviour of the ethers towards liquid paraffin and arachis oil. Whilst passage through an homogeniser prevented cracking of some of the emulsions of the higher members of the ether series, it did not effect complete emulsification where this was not achieved by hand preparation. Both series of emulsions were again observed after a

TABLE II
EMULSIONS OF LIQUID PARAFFIN (50 PER CENT.)

Concentration of ether, per cent.	Ether (value of "n")						
	2	4	6	10	18	24	30
1	Creaming	Creaming	Creaming	Creaming. Slight separation of oil	Cracked	Cracked	Cracked
2	Creaming	Creaming	Creaming	Creaming. Slight separation of oil	Cracked	Cracked	Cracked
3	Emulsification complete	Emulsification complete	Creaming	Creaming	Cracked	Cracked	Cracked
3 (Homogenised)	Emulsification complete	Emulsification complete	Creaming	Creaming	Creaming	Creaming	Creaming

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TABLE III
EMULSIONS OF ARACHIS OIL (50 PER CENT.)

Concentration of ether, per cent.	Ether (value of "n")						
	2	4	6	10	18	24	30
1	Creaming. Supernatant emulsion coarse	Creaming	Creaming	Creaming. Supernatant emulsion coarse	Creaming. Supernatant emulsion coarse	Creaming. Supernatant emulsion coarse	Creaming. Supernatant emulsion coarse
2	Slight creaming	Emulsification complete	Creaming	Creaming. Supernatant emulsion coarse	Creaming. Supernatant emulsion coarse	Creaming. Supernatant emulsion coarse	Creaming. Supernatant emulsion coarse
3	Emulsification complete	Emulsification complete	Creaming	Creaming	Creaming. Supernatant emulsion coarse	Creaming. Supernatant emulsion coarse	Creaming. Supernatant emulsion coarse
3 (Homogenised)	Emulsification complete	Emulsification complete	Slight creaming	Slight creaming	Creaming	Creaming	Creaming

period of 8 months and, although some of the emulsions had cracked to a greater extent, the general trend of emulsifying properties running through the series remained the same.

EMULSIFYING PROPERTIES OF NON-IONIC EMULSIFYING WAXES

It is well known that combination with cetostearyl alcohol stabilises emulsions containing surface active agents. The emulsifying properties of a series of non-ionic emulsifying waxes prepared from the ethers were investigated.

The non-ionic emulsifying waxes were prepared according to the following general formula:—

Cetostearyl-polyethyleneglycol ether .. 20 g.
Cetostearyl alcohol 80 g.

The mixture was prepared by melting together the two substances over a water bath.

A. *Concentration of Emulsifying Agent (Liquid Paraffin Series).* In order to determine the optimal concentration of non-ionic emulsifying wax, a series of emulsions were prepared containing 50 per cent. of liquid paraffin, distilled water and 2, 3, 4 and 5 per cent. of each of the waxes. The liquid paraffin was heated over a water bath to a temperature of about 50° C. and the non-ionic emulsifying wax was added. The distilled water was heated to about 50° C. and added to the mixture. The preparation was stirred by hand until cool.

The series was duplicated by a similar series which was ultimately passed through a Q.P. hand homogeniser. Observations were made at the time of preparation and after storage at room temperature for 2 months. The results are recorded in Table IV.

It is interesting to note the effect of combination with cetostearyl alcohol on the emulsifying properties of the ethers. A concentration of

3 per cent. of the non-ionic emulsifying wax represented a concentration of only 0.6 per cent. of the corresponding ether. This concentration was sufficient, in combination with cetostearyl alcohol, to effect complete emulsification whereas as much as 3 per cent. of the higher ethers alone was insufficient. The variation in the emulsifying properties between the higher and lower members of the series was almost completely masked by combination with cetostearyl alcohol.

TABLE IV
EMULSIONS OF LIQUID PARAFFIN (50 PER CENT.)
(containing non-ionic emulsifying waxes)

Ether value of "n"	Concentration of non-ionic emulsifying wax (per cent.)				
	1	2	3	4	5
<i>Prepared by hand</i>					
2	Cracked	Slight creaming Emulsion coarse	Coarse emulsion	Coarse emulsion	Emulsification complete
4	Creaming	Emulsification complete	Emulsification complete	Emulsification complete	"
6	"	Slight creaming	Slight creaming	"	"
10	"	Emulsification complete	Emulsification complete	"	"
18	"	Slight creaming	"	"	"
24	"	"	"	"	"
30	"	Emulsification complete	"	"	"
<i>Homogenised preparations</i>					
2	Creaming	Emulsification complete	Emulsification complete	Emulsification complete	Emulsification complete
4	"	"	"	"	"
6	"	"	"	"	"
10	"	"	"	"	"
18	"	"	"	"	"
24	"	"	"	"	"
30	"	"	"	"	"

The preparations were re-examined after a storage period of 10 months and showed little material change; the hand-prepared emulsions containing the lower percentages of the non-ionic waxes tended to show cracking in a few cases, but the homogenised preparations showed little change from the observations recorded after two months' storage. Emulsions containing the higher concentrations of the non-ionic emulsifying waxes (4 or 5 per cent.), on prolonged storage, tended to develop a surface skin. This was thought to be due possibly to surface concentration of the ether with the lyophilic polyethyleneglycol portion directed inwards to the continuous aqueous phase of the emulsion and the cetostearyl portion directed outwards to the air, thus forming a surface pellicle.

Mould growth was observed in a number of the emulsions and a preservative would be needed in preparations containing these emulsifying agents.

B. *Concentration of Emulsifying Agent (Arachis Oil Series).* A similar series of emulsions containing 50 per cent. of arachis oil was prepared and observed under the same conditions.

There was little difference in the behaviour of the non-ionic emulsifying waxes towards arachis oil, but the arachis oil emulsions containing the

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higher members of the ether series were less stable than the corresponding paraffin emulsions, on storage over a period of 10 months. The formation of a surface pellicle was less marked in the case of arachis oil emulsions. Mould growth was again observed in a number of the emulsions.

TABLE V
EMULSIONS OF ARACHIS OIL (50 PER CENT.)
(containing non-ionic emulsifying waxes)

Ether value of "n"	Concentration of non-ionic emulsifying wax (per cent.)			
	2	3	4	5
<i>Prepared by hand</i>				
2	Cracking	Emulsification complete	Emulsification complete	Emulsification complete
4	Creaming	" "	" "	" "
6	" "	" "	" "	" "
10	" "	Slight creaming	" "	" "
18	" "	" "	" "	" "
24	Cracking	Cracking	" "	" "
30	Creaming	Slight creaming	" "	" "
<i>Homogenised preparations</i>				
2	Cracking	Emulsification complete	Emulsification complete	Emulsification complete
4	Creaming	" "	" "	" "
6	" "	Creaming	" "	" "
10	" "	Emulsification complete	" "	" "
18	" "	Slight creaming	" "	" "
24	" "	Emulsification complete	" "	" "
30	" "	Slight creaming	" "	" "

C. *Variation in Concentration of Disperse Phase (Liquid Paraffin).* To determine the effect of varying the concentration of the disperse phase, a further series of emulsions containing 20, 30, 40, 60 and 70 per cent. of liquid paraffin was prepared, using 4 per cent. of each of the non-ionic emulsifying waxes. The emulsions were prepared as before, stored at room temperature and examined after an interval of 2 months.

From Table VI, it will be seen that the intermediate members of the ether series ("n" = 4, 6 or 10) were more effective in emulsifying higher concentrations of liquid paraffin (70 per cent.). With the non-ionic emulsifying waxes prepared from the higher members of the series "n" = 18, 24 or 30), the maximal concentration of liquid paraffin to be completely emulsified was 60 per cent.

The emulsions were again examined after storage at room temperature for 10 months and showed little change from the observations recorded after 2 months' storage.

D. *Variation in Concentration of Disperse Phase (Arachis Oil).* The experiments described above were repeated using varying concentrations of arachis oil as the disperse phase emulsified with 4 per cent. of each of the non-ionic emulsifying waxes.

In the case of emulsions of arachis oil, it was again the waxes prepared from the intermediate members of the ether series which were most effective in securing complete emulsification of 70 per cent. of the oil, but there was a slight shift in favour of the higher members ("n" = 6, 10 or 18). Emulsions containing the 2 lower members ("n" = 2 or 4) and the 2

TABLE VI
EMULSIONS OF LIQUID PARAFFIN OF VARYING CONCENTRATION
(containing non-ionic emulsifying waxes)

Ether value of "n"	Concentration of liquid paraffin (per cent.)				
	20	30	40	60	70
<i>Prepared by hand</i>					
2	Coarse emulsion creaming	Coarse emulsion. Slight creaming	Coarse emulsion	Coarse emulsion	Cracking
4	Emulsification complete	Emulsification complete	Emulsification complete	Emulsification complete	Emulsification complete
6	"	"	"	"	"
10	"	"	"	"	"
18	"	"	"	"	Cracking
24	"	"	"	"	"
30	"	"	"	"	"
<i>Homogenised preparations</i>					
2	Emulsification complete	Emulsification complete	Emulsification complete	Emulsification complete	Cracking
4	"	"	"	"	Emulsification complete
6	"	"	"	"	Slight separation of oil
10	"	"	"	"	"
18	"	"	"	"	Cracking
24	"	"	"	"	"
30	"	"	"	"	"

higher members ("n" = 24 or 30) showed cracking above a concentration of 60 per cent. of arachis oil. The two members in which "n" was 6 or 10 were equally effective in securing complete emulsification of 70 per cent. of both liquid paraffin and arachis oil.

The emulsions were again examined after a storage period of 10 months. In the case of arachis oil, the hand-prepared emulsions were rather less stable than the corresponding emulsions of liquid paraffin, but the homogenised preparations showed little material change from the observations made after two months' storage.

FORMULATION OF NON-IONIC EMULSIFYING OINTMENT

The cetostearyl-polyethyleneglycol ether was chosen for further study because it has been included in the British Veterinary Codex as cetomacrogol 1000 and also because it is a constituent of the commercially available non-ionic emulsifying wax, Collone N.I. The B. Vet. C. allows a tolerance of 19 to 23* for values of "n" in cetomacrogol 1000, whereas the material used had an average value of 24, but complied with the requirements of the B. Vet. C. in other respects.

The following ointment was prepared according to the formula of emulsifying ointment, B.P. with the substitution of non-ionic emulsifying wax in place of emulsifying wax, B.P. :—

Non-Ionic Emulsifying Ointment (24)

Cetomacrogol 1000	18 g.
Cetostearyl Alcohol	72 g.
White Soft Paraffin	150 g.
Liquid Paraffin	60 g.

* I am advised by Glover's Chemicals Ltd., who supplied this material, that the correct tolerance is 20 to 24.

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The ointment was prepared by melting together the ingredients over a water bath and the effects of incorporating varying proportions of water were observed. The creams thus obtained were stored at room temperature and examined after an interval of 8 months. The ointment gave stable creams when incorporated with water ranging from 30 to 80 per cent. and was capable of infinite dilution with water,

TABLE VII
EMULSIONS OF ARACHIS OIL OF VARYING CONCENTRATIONS
(containing non-ionic emulsifying waxes)

Ether value of "n"	Concentration of arachis oil (per cent.)				
	20	30	40	60	70
<i>Prepared by hand</i>					
2	Coarse emulsion	Emulsification complete	Emulsification complete	Emulsification complete	Cracking
4	Emulsification complete	"	"	"	"
6	"	"	"	"	Slight separation of oil
10	"	"	"	"	Emulsification complete
18	"	"	"	"	"
24	"	"	"	"	Cracking
30	Coarse emulsion	"	"	"	"
<i>Homogenised preparations</i>					
2	Emulsification complete	Emulsification complete	Emulsification complete	Emulsification complete	Cracking
4	"	"	"	"	"
6	"	"	"	"	Emulsification complete
10	"	"	"	"	"
18	"	"	"	"	"
24	"	"	"	"	Cracking
30	"	"	"	"	"

COMPATIBILITY WITH DERMATOLOGICAL MEDICAMENTS

The compatibility of non-ionic emulsifying ointment (24) with a range of substances commonly used in dermatology was determined by preparing creams according to the following general formula:—

Medicament	q.s.
Non-ionic Emulsifying Ointment	30 g.
Chlorocresol	0.1 g.
Distilled Water	to 100 g.

The creams were stored at room temperature and observed after 2 months.

The incompatibility of phenol was further investigated by examining the effect of incorporating 2 per cent. of phenol into emulsions containing 50 per cent. of liquid paraffin and varying proportions (4, 5, 6, 7 and 8 per cent.) of non-ionic emulsifying wax (24). Complete separation of all emulsions occurred after standing for 24 hours and after standing for 3 days, a third phase separated in the form of a large globule at the bottom of the aqueous phase. An emulsion containing 50 per cent. of liquid paraffin and 4 per cent. of non-ionic emulsifying wax (24) was found to

TABLE VIII

COMPATIBILITY TESTS WITH NON-IONIC EMULSIFYING OINTMENT

Medicament	Observations
Phenol 2 per cent.	Slight separation
Benzoic acid 6 per cent. Salicylic acid 3 per cent.	" "
Salicylic acid 3 per cent. Sublimed sulphur 3 per cent.	" "
Proflavine hemisulphate 0.1 per cent.	No separation
Antazoline hydrochloride 2 per cent.	"
Calamine 10 per cent.	"
Zinc oxide 10 per cent.	"
Crystal violet 0.5 per cent.	"
Benzocaine 10 per cent.	"
Solution of coal tar 5 per cent.	Slight separation
Ammoniated mercury 2.5 per cent.	No separation
Methyl salicylate 25 per cent.	"
Resorcinol 10 per cent.	Complete separation
Tannic acid	" "
Sublimed sulphur 10 per cent.	No separation
Hydroquinone monobenzyl ether 5 per cent.	"
Benzalkonium chloride 1 per cent.	"
Copper sulphate 2 per cent.	"
Dibromopropamidine isethionate 0.15 per cent.	"
Hydrochloric acid 2 per cent.	"
Sodium phosphate 5 per cent.	"
Sodium acid phosphate 5 per cent.	"
Solution of lead subacetate 2.5 per cent.	"

show no separation under comparable conditions with 1 per cent. of phenol.

Phenol was added, in varying concentrations, to solutions of cetomacrogol 1000 of varying strengths. It was found that in certain concentrations a turbidity was formed between mixtures of phenol and the ether.

On standing, the turbid solutions separated into 2 immiscible liquid phases. On shaking the mixture, no frothing occurred, indicating that the surface activity of the ether had been considerably diminished.

A similar series of tests was performed to determine whether resorcinol would show a similar behaviour. On standing, the turbid solutions of resorcinol and cetomacrogol 1000 again separated into 2 immiscible liquids. The mixtures containing 4.5 per cent. of resorcinol with 8 per cent. of the ether and 7.5 per cent. of resorcinol with 20 per cent. of the ether were extraordinarily sensitive to temperature changes. At 20° C. they showed only a faint cloudiness, but became distinctly turbid when the temperature was raised to 22° C. On cooling below 20° C. they became

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clear solutions. The polyethyleneglycol ether, itself, has a negative coefficient of solubility with temperature and, on heating, solutions of the ether become turbid. It is therefore possible that the incompatibility of phenolic substances is due to a further lowering of the solubility coefficient, rendering the ether less soluble in the aqueous phase and thus interfering with its emulsifying properties. Another possibility is that co-ordination complexes are formed between phenols and the polyethyleneglycol ether and that these complexes have an even greater negative temperature coefficient of solubility.

The possibility of compound formation between resorcinol and cetomacrogol 1000 was investigated by examining the properties of a series of mixtures of the ether and resorcinol. Since cetomacrogol 1000 is an impure wax-like solid, the melting points of such mixtures were not easily determined. However, the results recorded in Table XI are adequate to show the general trend of the properties observed.

TABLE IX
SOLUTIONS OF PHENOL AND CETOMACROGOL 1000

Cetomacrogol 1000, per cent.	Phenol (per cent.)												
	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	
1	-	-	+										
2	-	-	-	+									
4	-	-	-	-	+								
6	-	-	-	-	+								
8	-	-	-	-	-	+							
10	-	-	-	-	-	-	+						
15	-	-	-	-	-	-	-	-	-	+			
20	-	-	-	-	-	-	-	-	-	-	-	-	+

- = Clear solution
+ = Turbidity
± = Haziness

At a concentration of 40 per cent. of resorcinol there is a sudden change in properties with a relatively clearly defined melting point of 57° to 60° C. Above this concentration, the mixtures soften at about the same temperature but do not become clear until higher temperatures. At lower concentrations of resorcinol, a minimum melting point is exhibited at 25 per cent., this mixture being liquid at room temperature. It therefore appears likely that compound formation occurs when the concentration of resorcinol is 40 per cent. Above this concentration the melting point remains constant but the mass does not clear until higher temperatures because excess of resorcinol is present. At lower concentrations, an eutectic point is exhibited at a concentration of 25 per cent. of resorcinol.

Doscher¹ has produced evidence to show that co-ordination complexes are formed between non-ionic surface-active agents and hydrated calcium ions. Trinchieri² has explained the water-solubility of the polyethyleneglycol surface-active compounds as due to the formation of either oxonium or polyoxonium derivatives by the attachment of water molecules

TABLE X
SOLUTIONS OF RESORCINOL AND CETOMACROGOL 1000

Cetomacrogol 1000, per cent.	(Resorcinol (per cent.))														
	1.0	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	
1	-	-	+												
2	-	-	-	+											
4	-	-	-	-	+										
6	-	-	-	-	-	+									
8	-	-	-	-	-	-	±	+							
10	-	-	-	-	-	-	-	+							
20	-	-	-	-	-	-	-	-	-	-	-	-	±	+	

- = Clear solution
+ = Turbidity
± = Haziness

TABLE XI
MIXTURES OF CETOMACROGOL 1000 AND RESORCINOL

Cetomacrogol 1000, per cent.	0	20	40	60	70	75	80	90	100
Resorcinol, per cent.	100	80	60	40	30	25	20	10	0
Appearance	Solid	Solid	Solid	Solid	Semi-solid	Liquid	Semi-solid	Solid	Solid
Approximate m.pt., ° C.	110	59	56	57	17	—	20	35	38

to the oxygen in the ether radical. It would therefore seem likely that phenols form similar complexes, thus displacing the water molecules and producing a turbidity.

It is interesting to note that a similar turbidity is produced by chlorocresol and cetomacrogol 1000 at low concentrations, but when the proportion of polyethyleneglycol ether to chlorocresol is 5 or more to 1, a solubilising effect is observed.

FORMULATION OF WATER-SOLUBLE OINTMENT BASE

In some skin conditions, it is desirable to apply a water-soluble base, free from fatty materials. Such bases have been formulated by combining propylene glycol with the simple polyethylene glycols. Cetomacrogol 1000 offers possibilities as an alternative in such combinations. The solidifying points of mixtures of propylene glycol and cetomacrogol 1000 are recorded in Table XII.

The mixture containing 60 per cent. of propylene glycol and 40 per cent. of cetomacrogol 1000 forms a smooth and unctuous combination, suitable for use as a water-soluble ointment base. It readily dissolves chloramphenicol, for which it provides a suitable base. An ointment containing 1 per cent. of chloramphenicol in this base was tested by a microbiological method and found to show no significant loss of potency after storage for 3 months at room temperature.

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TABLE XII
MIXTURES OF CETOMACROGOL 1000 AND PROPYLENE GLYCOL

Cetomacrogol 1000, per cent.	30	40	50	60
Propylene glycol	70	60	50	40
Approximate solidifying point, ° C.	28	29	30	31
Appearance	Soft unctuous wax-like semi-solid	Unctuous wax-like semi-solid	Fairly hard wax-like solid	Hard wax-like solid

SUMMARY

1. A preliminary survey of the pharmaceutical uses of a series of polyethyleneglycol ethers of cetostearyl alcohol has been made.
2. When used alone, the lower members of the series (2 or 4 ethylene oxide units) are more effective than the higher members in emulsifying both liquid paraffin and arachis oil.
3. In combination with cetostearyl alcohol, the ethers produce satisfactory non-ionic emulsifying waxes and the variation in emulsifying power is then less marked.
4. Non-ionic emulsifying waxes prepared from the members containing 6 or 10 ethylene oxide units were equally effective in emulsifying 70 per cent. of liquid paraffin or arachis oil.
5. The compatibility of a non-ionic emulsifying ointment containing cetomacrogol 1000 with a range of dermatological medicaments has been determined.
6. Evidence has been produced to suggest the formation of addition compounds between phenolic substances and the ethylene oxide derivatives.
7. A water-soluble ointment base suitable for chloramphenicol is suggested.

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DISCUSSION

The paper was presented by THE AUTHOR.

DR. K. R. CAPPER (London) said that in a parallel series of experiments he had not found creams made with the esters were less stable on storage for six months than those made with the ethers. It was possible that longer storage, or more rigorous conditions, might show that creams made with the ethers were the more stable. One of the disadvantages of the esters, if made by esterification—as many commercial varieties

were—was that they were not pure monostearates but a mixture of distearates and monostearates. According to the composition of the mixtures, so the products would vary when they were used as emulsifying agents. Unless the proportion of distearate could be controlled, it seemed that the ethers were safer materials to use. One disadvantage was incompatibility with phenols.

PROFESSOR H. BRINDLE (Manchester) suggested that the author would have obtained more precise information had he used a method of examining the emulsions other than mere observation of creaming or separation. A method he had used some years ago for measuring globule sizes consisted of mounting the preparation on a slide, under a microscope, in 10 per cent. gel solution and projecting the image on to a screen. A figure was calculated called the specific interface value, being the relationship of the globule area to volume. By this means valuable and reproducible information could be obtained about the emulsifying powers of different emulgents.

MR. T. D. WHITTET (London) said he had used the new bases in the form of the proprietary wax mentioned in the paper, and in place of the official wax in emulsifying ointment. He had found the proprietary wax considerably superior; it was easier to manipulate and more versatile. He had used it in an aminacrine cream, an ointment base for local anæsthetics, and an undecylenate ointment.

DR. A. H. BECKETT (London) issued a warning about the use of non-ionic emulsifying agents. When chloramphenicol was formulated in this type of base, was there a reduction in antibacterial activity? The non-ionic agents were antagonised by phenols, and he felt that hydrogen bonding could be a causative factor. They would solubilise compounds which would hydrogen bond but were not as effective for solubilising hydrocarbons. In the formation of ointments, in particular, it was necessary to look closely at their antibacterial action.

MR. S. G. E. STEVENS (London) asked whether the author had had any experience of preparing these emulsions on a large scale. Using both ethers and esters, he had found it possible to adjust the hand-prepared creams to what seemed a satisfactory preparation, but when these were converted to an industrial scale the results left much to be desired. Undoubtedly a mere visual inspection of the cream did not give a true picture of what was happening. What was the change in particle size over the storage period? What effect was observed when stored at other than room temperatures?

MR. HADGRAFT, in reply, pointed out that if they were comparing the emulsifying power of similar percentage compositions they had to remember that the molecular concentration of the lower members of the series was higher than the molecular concentration of the higher members of the series because of the difference in molecular weights. In comparing molecular concentrations of these compounds they might find less variation in the emulsifying powers. He had compared 9 per

cent. of the ether containing 24 ethylene oxide units with 3 per cent. of the ether containing 2 units—the proportion of 3 to 1 being based approximately on the comparative molecular weights. Complete emulsification was achieved with 9 per cent. of the former, but the emulsion creamed fairly readily, showing that in the lower members of the series the property of forming viscous dispersions in the aqueous phase was an added factor. The viscosity factor was equally as important as the ability of the compound to form an interfacial film. Replying to Professor Brindle, he said that more exact methods of emulsion examination would be used in later work, but the paper was a pilot experiment to survey the whole field. He had no information on the relationship between hand-prepared preparations and those made on a large scale. The work done had been designed solely to determine the conditions of emulsification in circumstances which would approximate to extemporaneous preparation. He agreed with Mr. Whittet that the proprietary preparation was easier to use in producing small-scale hand-prepared emulsions. He agreed with Dr. Beckett on the need for caution in the use of these emulsifying agents in the presence of antiseptic substances. He had not been responsible for the microbiological assay of the chloramphenicol cream, but he understood that the activity obtained was of the order expected from the concentration present.

DR. R. E. STUCKEY (London) said Dr. Beckett had raised two separate issues—the results of a microbiological assay, which was strictly an *in vitro* method, and the activity of the ointment in use, which could be measured only by estimation of blood concentrations or observations over a period *in vivo*.