THE USE OF SURFACE ACTIVE AGENTS IN PHARMACEUTICAL PREPARATIONS:

THE EVALUATION OF EMULSIFYING POWER

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Received May 29, 1952

DURING the past twenty years economic and other circumstances have led to an increasing use of synthetic surface active agents in pharmaceutical products. At present their use is primarily as alternatives to excipients of natural origin, such as gums and waxes, but there are indications that certain of their properties may be used advantageously to modify drug action by increasing the solubility of sparingly soluble substances, aiding skin penetration and so on. It has also been shown that some surface active agents have bactericidal power and hence may be used as independent therapeutic agents. Several factors have tended to limit the use of these synthetic materials to specialised pharmaceutical manufacture and to delay their introduction into normal dispensing practice. In the first place, relatively few surface active agents have been made specifically for use in pharmacy, with the result that no accepted quality standards exist for many otherwise satisfactory products. Secondly, much remains to be done in investigating the pharmacology of the new materials to ascertain their particular suitability to the various routes of administration. Thirdly, the efficiency of surface active agents in various formulations has not yet been fully established, chiefly due to the absence of satisfactory methods of evaluation; hence, their advantages and disadvantages relative to one another and to corresponding natural products are not clearly understood. This latter situation is particularly true of emulsifying power and as an initial attack on the general problem of assessing the pharmaceutical potentialities of surface active agents it was decided, in the work described here, to seek a method of measuring the efficiency of these substances as emulgents. Since it was already known that their emulsifying power was approximately of the same order as that of soaps, it seemed clear that the method of evaluation should be capable of detecting relatively small differences.

The term "efficiency," when applied to emulgents, may be interpreted in various ways. One of the most useful of these links the "efficiency" of an emulgent with the stability of the emulsions which it will produce under standard conditions. For this reason, the method selected for the present work was based essentially on:—(i) preparation of standard oil/water emulsions; (ii) homogenisation; (iii) globule counts at time intervals during storage.

Standard Emulsions. It is recognised that the relative efficiencies of two emulgents may depend on the concentration and chemical nature of the disperse phase. Two oils of different type commonly encountered

in pharmaceutical practice were selected and emulsions were prepared at an arbitrary concentration of 15 per cent.

Homogenisation. As part of the standardisation of an emulsifying process, it is necessary to fix the amount of mechanical work. This is best done by controlled homogenisation which can be set at a fixed quantity, in comparison with which the amount of work done in preliminary mixing becomes negligibly small. It might be argued that this simplifies unduly the rôle of the emulgent but it should be borne in mind that homogenisation is now common manufacturing practice.

Globule Count. It is generally accepted that the most accurate representation of the state of an emulsion at any given time is provided by a size frequency analysis, i.e., an examination of globule size based on the counting and measuring of a large number of globules. Moreover, it has been shown by King *et al.*[1] that when interfacial areas (calculated from size frequency analysis) are plotted against storage life a linear relationship is obtained. Similarly, Jellinek and Anson[2] have derived various other functions from size frequency analyses and have shown that certain of these are also linearly related with time. Size frequency analyses, however, are inherently tedious, some methods necessitating the counting and measuring of approximately 2000 globules in order to obtain statistically reliable results. A simpler method proposed by Smith and Grinling,[3] requiring a direct count of a substantially smaller number of globules and eliminating the necessity for measurement, appeared to provide a suitably accurate alternative. In preliminary tests, the method, with slight modifications in technique, was found to give reproducible results, and was therefore chosen for the present purpose.

Storage. The inherent stability of homogenised emulsions prepared with surface active agents is such that significant changes can only be detected after long storage. It was therefore necessary to apply a standard artificial breakdown stress, and centrifugal force was chosen for this purpose, although it is not suggested that any simple relationship exists between the behaviour of an emulsion in a centrifuge and under normal storage conditions. It was found that spinning at 20,000 r.p.m. in a Sharples Supercentrifuge for periods of 5, 10, 15, 20 and 25 minutes produced a suitable degree of progressive deterioration.

In a typical experiment, therefore, a standard emulsion was prepared and a preliminary dilution made in order to ascertain the final dilution necessary for a satisfactory globule count. This count was then made on separate dilutions, after which the original emulsion was centrifuged for a series of time intervals and further counts made after each centrifuging. By suitable mathematical treatment, the results were interpreted so as to provide an expression of the stability of the emulsion.

EXPERIMENTAL

(1) *Materials*

(*a*) *Surface Active Agents.* The surface active agents were selected so as to provide examples of different chemical types (anionic, cationic

and non-ionic). The following were used, each at concentrations of 0·1, 0·5 and 1 per cent. w/v.

(1) Cetyltrimethylammonium bromide (Cetrimide B.P.).
(2) Polyoxyethylene sorbitan mono-oleate (Polysorbate 80 U.S.P.).
(3) Stearyl alcohol/ethylene oxide condensate.
(4) Alkyl phenol/ethylene oxide condensate ("Lissapol" NX).
(5) Cetyl alcohol/ethylene oxide condensate ("Lubrol" W).
(6) Sodium oleate.

The selection was made chiefly from non-ionic substances (2), (3), (4), (5) since these appear to offer the most promise as excipients, due to absence of chemical incompatibility. Sodium oleate was selected partly as a convenient anionic agent and partly as a control since the satisfactory properties of emulsions prepared with it are already well known in pharmacy. Lubrol W and lissapol NX are not commercially available as pharmaceutical excipients but were, nevertheless, included since they provide useful examples of certain types of ethylene oxide condensates.

(*b*) *Disperse Phase.* Separate emulsions were made of arachis oil B.P. and of liquid paraffin B.P., using the same samples throughout. The concentration of the disperse phase was arbitrarily fixed at 15 per cent. v/v for all experiments.

(2) *Preparation of Emulsions* (*Quantities of* 600 *ml.*)

(*a*) *Equipment.*

(i) *Moritz Turbo-Emulsifier:* This comprises a rotating impeller surrounded by an emulsifying crown. The latter has a large number of pins which finely divide the liquid veins centrifugally thrown by the impeller. The speed of rotation is controlled by means of a variable resistance.

(ii) *Weir Junior Homogeniser:* This consists of a motor driven, single cylinder pump designed to operate at pressures up to 3500 lb./sq. in. The pump forces the premixed emulsion through a fine orifice in the discharge valve. To permit recirculation of the emulsion through the homogeniser the outlet was connected to the inlet *via* a reservoir of approximately 1 l. capacity.

(*b*) *Method:* In all cases except stearyl alcohol/ethylene oxide condensate and sodium oleate, the required weight of surface active agent was dissolved in the calculated volume of water and added to the oil. In the case of stearyl alcohol/ethylene oxide condensate, the required weight was dissolved in the oil with the aid of gentle heat and added to the calculated volume of water heated to the same temperature. The sodium oleate was made *in situ* by dissolving the calculated quantities of sodium hydroxide and oleic acid in the water and oil respectively. The liquids were premixed by the turbo-emulsifier at approximately 3000 r.p.m. for 5 minutes, and the emulsion so formed was then re-circulated through the homogeniser at maximum pressure for 5 minutes. All emulsions were introduced into the homogeniser at 20° to 23° C.,

the rise in temperature during homogenisation being approximately 5° C. for all emulsions.

(3) *Accelerated Breakdown of Emulsions*

(*a*) *Equipment. Sharples Centrifuge:* This consists essentially of an accurately balanced hollow rotor or "bowl" capable of being rotated about a vertical axis at speeds up to 28,000 r.p.m. The centrifuge was used in conjunction with a sensitive tachometer driven directly from the spindle, and a Variac resistance.

(*b*) *Method:* A 100-ml. sample was placed in the centrifuge and the speed adjusted by means of the Variac resistance. The time of centrifuging was taken from the moment of attaining a speed of 20,000 r.p.m. until the centrifuge was switched off. The contents of the bowl were thoroughly mixed before a sample was withdrawn.

(4) *Examination of Emulsions*

(*a*) *Equipment. Helber Counting Chamber:* This consists of a microscope slide having a central portion sunk 0·02 mm. below the surface of the slide and ruled into 16 blocks of 16 small squares, each of area 0·0025 sq. mm. The sunken portion is surrounded by an annular well into which the superfluous liquid can overflow. A Helber counting chamber was preferred to a hæmocytometer since its shallower chamber permits thorough searching of the ruled area with minimum focussing.

(*b*) *Method:* The emulsion was first diluted to such an extent that when a drop was placed on the central portion of the slide, and covered with a specially thick and optically plane cover-glass, a countable number of globules (10 to 40) was contained in each small square, when observed through a microscope fitted with a 1/6th in. objective and a × 10 eyepiece. In practice, the degree of dilution varied between 1 in 100 and 1 in 400. The dilution was made by thoroughly mixing a pipetted volume of the emulsion with a sufficient quantity of 80 per cent. aqueous glycerin to produce half the final volume of the dilution, after which a 10 per cent. aqueous solution of nigrosin was added with constant stirring to produce the final volume. In order to ensure that the globules remain evenly dispersed in the dilution, Smith and Grinling employed a 25 per cent. acacia mucilage as the diluting fluid. In the method described here, the aqueous glycerin adequately fulfils the function, and in the present authors' opinion is preferable to acacia mucilage. In addition to possessing the advantages of chemical stability and a standard viscosity, aqueous glycerin has no intrinsic emulsifying action and thus eliminates risk of additional emulsification of the oil. It was also shown experimentally that the converse risk, i.e., of break-down of emulsion on dilution, was absent. The inclusion of nigrosin makes the globules more conspicuous since by suitable adjustment of substage illumination they can be made to appear as bright circles against a blue background. The initial dilution of the emulsion with aqueous glycerin was found to yield a more uniform dispersion of the globules than was obtained by adding the emulsion to a premixed glycerin/water/nigrosin solution. When

the counting chamber containing the dilution of appropriate strength had been prepared, the ruled area was examined to ensure that the distribution of the globules was uniform: if not, the chamber was cleaned and refilled. When the distribution was satisfactory, the globules contained in 20 small squares selected at random were counted, the entire depth of each square being well searched for small globules. In order to avoid counting the same globule twice, the count for each square included all those globules which lay on or touched the top and left hand side, and excluded all those which lay on or touched the bottom right hand side. After each complete count the chamber slide and cover slip were thoroughly washed with soapy water, rinsed with warm water and distilled water, and dried with a clean cloth. A final polish was given with a lens tissue and before re-use it was examined under the microscope to ensure absence of débris.

Results

(1) *Methods of Calculation.* From the total number of globules counted in 20 squares the following values can be calculated.

(*a*) "H," which expresses the number of millions of globules into which 1 cu. mm. of oil has been subdivided.

Volume under 20 small squares in the Helber chamber = (20 × 1/50 × 1/20 × 1/20) = 1/1000 cu. mm.

If N is the number of globules counted in this volume of a 1 in Z dilution of an emulsion containing 15 per cent. v/v. of oil then,

$$\text{"H"} = N \times 1000 \times Z \times \frac{100}{15} \times \frac{1}{10^6}$$
$$= N \times 1000 \times Z \times 6{\cdot}67 \times 10^{-6}$$

(*b*) "D," the "root mean cube diameter," which is derived from "H" and represents the diameter (in microns) the globules would have if they were uniform in volume and the same in number as in the emulsion examined.

$$\text{Volume of a globule (assumed spherical)} = 4/3\ \pi r^3 = \frac{\pi d^3}{6} = \frac{1}{H \times 10^6}$$

$$\text{therefore d (in mm.)} = \sqrt[3]{\frac{6}{H \times 10^6 \times \pi}}$$

$$\text{and "D" (in microns)} = 10 \times \sqrt[3]{\frac{6}{\pi H}}$$

It is emphasised that "D" is not the arithmetic mean diameter because it is derived from the mean volume. It is probably a more useful measure of the average globule size than the former quantity. From the rate of change of either "H" or "D" separate but equivalent expressions of stability can be derived.

(*c*) *Rate of increase of "D":* In preliminary work it was found that the relationship between log. "D" and time of centrifuging was sensibly linear. Figure 1 shows this relationship for the system arachis oil/lubrol

W 0·5 per cent. The slope of a line chosen to fit the points obtained was considered a satisfactory measure of the stability of the emulsion tested. This slope was calculated by the method of least squares.[4] If Figure 2 represents a typical result, then the slope, i.e., the increase in log. "D" per 5 minute interval, is given by the following expression, which is applicable to six results at equal 5 minute intervals:—

$$\frac{-5D_1 - 3D_2 - D_3 + D_4 + 3D_5 + 5D_6}{35}$$

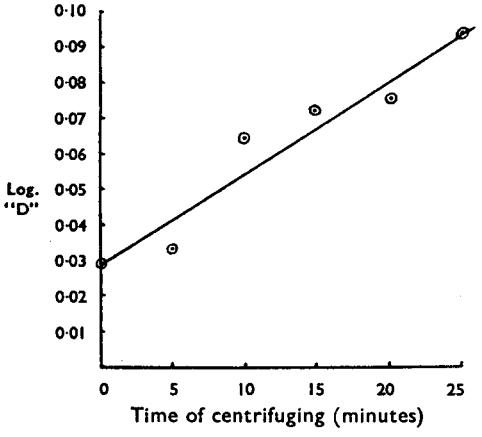

FIG. 1. Relationship of log. "D" with time of centrifuging (arachis oil emulsion prepared with 0·5 per cent. lubrol W).

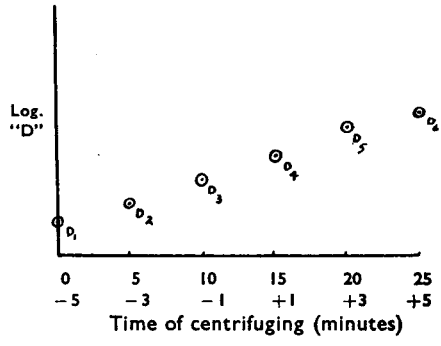

FIG. 2. Application of formula to calculate slope.

For convenience of expression the numerical value obtained was multiplied by 10,000. This value is, of course, not a constant but relates to the particular experimental conditions adopted here. The higher the value, the less stable the emulsion and *vice versa.*

(*d*) *Rate of decrease of* "H"*:* The decrease in "H" per 5 minute interval ($H_1 - H_2$) may also be used as an index of stability and is most conveniently expressed as a percentage, i.e., $\left(1 - \frac{H_2}{H_1}\right) 100$. The actual values may be obtained either by first calculating the slope of log. "H" (by the method of least squares) or by derivation from the slope of log. "D." In the case of arachis oil/0·1 per cent. polysorbate 80, for example, the latter method may be applied as follows:—

Slope of log. "D"/5 minute interval = 0·0395

therefore $\log. \frac{H_2}{H_1} = -3 \times 0{\cdot}0395 = -{\cdot}1184$ or $\bar{1}{\cdot}8816$

therefore $\frac{H_2}{H_1}$ = antilog. $\bar{1}{\cdot}8816$ = 0·7614

and $\left(1 - \frac{H_2}{H_1}\right) 100 = 23{\cdot}8$ per cent.

Clearly an increased percentage indicates lower stability.

(2) *Limits of Error:* The reproducibility of the method is clearly dependent on (*a*) the accuracy of preparation and homogenisation of the emulsion, and (*b*) the accuracy of sampling, diluting and counting. In the case of cetrimide and lubrol W, two batches of each test emulsion were prepared and two samples from each batch diluted and counted. The results obtained showed that the experimental error was almost exclusively associated with (*a*) above. It was therefore decided that, in the case of polysorbate 80, stearyl alcohol ethylene oxide condensate, lissapol NX and sodium oleate, it was sufficient to prepare the emulsions in duplicate and to examine single samples from each batch. From the results obtained using the latter technique, a 95 per cent. limit of error, having a numerical value of ± 0·0034, has been calculated for the slope of log. "D" per 5 minute interval. Thus, the value of 395 reported for the emulsion prepared using 0·1 per cent. of polysorbate 80 with arachis oil would lie within the range 361 to 429 in 95 per cent. of determinations. This limit of error is only applicable to emulsions which withstood 25 minutes in the centrifuge without separation of oil, thus enabling

TABLE I

EMULSION OF ARACHIS OIL WITH 0·5 PER CENT. OF LUBROL W. GLOBULE COUNTS ON A 1 : 400 DILUTION

Sq. No.	Sample A						Sample B					
	Time in Minutes						Time in Minutes					
	0	5	10	15	20	25	0	5	10	15	20	25
1	35	28	23	23	19	18	29	27	25	20	22	19
2	30	27	24	20	19	20	30	26	20	19	20	17
3	30	32	24	22	25	19	32	26	22	26	21	18
4	28	24	22	23	22	24	34	26	22	20	18	17
5	26	27	23	20	20	19	36	31	23	21	18	16
6	32	25	22	19	22	18	29	29	24	18	18	17
7	26	30	20	21	21	21	28	27	26	22	20	22
8	25	28	25	18	19	18	30	24	21	24	22	19
9	24	28	23	24	19	19	26	30	19	18	24	19
10	32	29	21	22	26	17	26	28	27	20	19	15
11	31	30	24	23	22	22	28	28	26	22	19	20
12	31	28	25	19	22	20	28	27	25	24	20	16
13	29	26	23	20	25	16	29	26	24	22	21	19
14	28	26	25	26	20	18	30	28	23	19	17	16
15	26	26	23	24	18	19	28	21	20	24	21	17
16	28	27	25	26	19	18	27	25	22	24	20	18
17	29	28	26	20	23	16	28	22	25	18	25	17
18	30	28	22	19	20	17	30	28	26	22	20	18
19	31	27	23	21	24	18	28	27	26	25	22	16
20	30	26	26	25	22	17	28	28	21	25	20	18
TOTAL ..	581	550	469	435	427	374	584	534	467	433	407	354

TABLE II

EVALUATION OF LUBROL W

Strength of agent per cent.	Time of centrifuging (minutes)	Arachis Oil								Liquid Paraffin							
		"H"				"D"				"H"				"D"			
		Emulsion 1		Emulsion 2		Emulsion 1		Emulsion 2		Emulsion 1		Emulsion 2		Emulsion 1		Emulsion 2	
		Sample A	Sample B	Sample A	Sample B	Sample A	Sample B	Sample A	Sample B	Sample A	Sample B	Sample A	Sample B	Sample A	Sample B	Sample A	Sample B
0·1	0	369	351	368	372	1·73	1·76	1·73	1·73	564	564	540	523	1·50	1·50	1·52	1·54
	5	336	332	328	332	1·78	1·79	1·80	1·79	483	478	463	455	1·58	1·59	1·60	1·61
	10	306	296	306	317	1·84	1·86	1·84	1·82	313	314	311	289	1·83	1·82	1·83	1·88
	15	280	284	294	294	1·90	1·89	1·87	1·87	Oil separated after centrifuging							
	20	281	278	262	259	1·90	1·90	1·94	1·95								
	25	245	243	241	239	1·98	1·99	1·99	2·00								
0·5	0	1550	1558	1622	1630	1·07	1·07	1·06	1·05	855	851	851	841	1·31	1·31	1·31	1·31
	5	1468	1424	1558	1516	1·09	1·10	1·07	1·08	766	767	767	734	1·36	1·36	1·36	1·38
	10	1251	1246	1414	1409	1·15	1·15	1·11	1·11	723	724	710	715	1·38	1·38	1·39	1·39
	15	1161	1155	1169	1280	1·18	1·18	1·18	1·14	599	606	615	603	1·47	1·47	1·46	1·47
	20	1139	1086	1056	1070	1·19	1·21	1·22	1·21	564	560	562	534	1·50	1·51	1·50	1·53
	25	998	944	977	966	1·24	1·27	1·25	1·26	478	475	464	479	1·59	1·59	1·60	1·59
1·0	0	1702	1686	1516	1470	1·04	1·04	1·08	1·09	1280	1319	1276	1286	1·14	1·13	1·14	1·14
	5	1443	1491	1464	1505	1·10	1·09	1·09	1·08	987	1010	1002	997	1·25	1·24	1·24	1·24
	10	1446	1462	1468	1369	1·10	1·09	1·09	1·12	923	934	916	930	1·28	1·27	1·28	1·27
	15	1478	1464	1403	1428	1·09	1·09	1·11	1·10	694	682	678	700	1·40	1·41	1·41	1·40
	20	1310	1331	1348	1304	1·13	1·13	1·12	1·14	706	676	692	710	1·39	1·41	1·40	1·40
	25	1169	1150	1139	1206	1·18	1·18	1·19	1·17	520	586	540	531	1·54	1·48	1·52	1·53

the slope to be derived from 6 values. In those cases where separation of oil was observed after 10 or 15 minutes centrifuging, thus permitting only 2 or 3 examinations respectively, the emulsions were considered too unstable to be evaluated under the experimental conditions described.

(3) *Tabulated Data:* A typical series of globule counts is given in Table I, using emulsions prepared from arachis oil and lubrol W as the example. The full examination of a single surface active agent is illustrated

TABLE III

SUMMARISED RESULTS FOR ALL SURFACE ACTIVE AGENTS

Agent	Concentration per cent.	Initial "H" value		Slope of log. "D" per 5 minute interval × 10^4		Percentage decrease in number of globules per 5 minute interval	
		Arachis oil	Liquid paraffin	Arachis oil	Liquid paraffin	Arachis oil	Liquid paraffin
Cetrimide*	0·1	342	255	[5]	[5]	[5]	[5]
	0·5	440	400	247	253	15·7	16·0
	1·0	1079	446	103	220	6·9	14·1
Lubrol W*	0·1	365	548	113	[15]	7·5	[15]
	0·5	1590	850	147	167	9·7	11·0
	1·0	1593	1290	78	227	5·2	14·5
Lissapol NX† ..	0·1	429	266	550	[10]	31·6	[10]
	0·5	1094	532	107	577	7·1	32·8
	1·0	1763	548	71	164	4·8	10·7
Polysorbate 80† ..	0·1	624	472	395	402	23·8	24·2
	0·5	1584	750	163	380	10·6	23·1
	1·0	1861	804	85	202	5·7	13·0
Stearyl alcohol/ethylene oxide condensate†	0·1	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
	0·5	412	346	218	270	14·0	17·0
	1·0	657	416	89	237	5·9	15·1
Sodium oleate† ..	0·1	532	339	223	[10]	14·3	[10]
	0·5	875	241	126	280	8·3	17·6
	1·0	1633	467	90	110	6·0	7·3

[ ] Oil incompletely emulsified using this concentration.
[5] Separation of oil after 5 minutes centrifuging.
[10] Separation of oil after 10 minutes centrifuging.
[15] Separation of oil after 15 minutes centrifuging.

* Average of four results. † Average of two results.

in Table II, where the results are expressed as "H" and "D" values. Similar data were obtained for the remaining 5 surface active agents and these are summarised in Table III, results being expressed as initial "H" values together with rates of change of both "H" and "D."

Discussion

The problem of evaluating emulsifying power can be approached in various ways. An approximate assessment, meeting many of the requirements of the dispensing counter, can be obtained rapidly and simply by

shaking or trituration of the materials under test followed by visual (macroscopic) examination of the emulsion produced. Such a procedure is obviously subject to severe limitations, since it provides no information on the internal state of the emulsion and is only capable of detecting relatively large differences in behaviour. There are many circumstances which demand a more scientific approach yielding accurate quantitative data. For example, during the testing of new potential emulgents prepared synthetically, it is necessary to record relatively small differences in efficiency so as to decide on what are the most promising compounds.

The work described here in no sense approaches a full assessment of even a limited number of surface active agents. It is simply an attempt to provide a technique of evaluating emulsifying power with a sufficient degree of accuracy to make it possible to assess materials of this type. It is hoped that this technique, or modifications of it, will prove of value to other workers in this field. We have found the method to be reliable and reproducible, and, in contrast to methods involving size-frequency analysis followed by "shelf" storage, it is reasonably straightforward and more rapid in application. There is, of course, no necessity to employ the particular homogeniser and centrifuge described. The basic requirement is that the homogenising procedure should be adequate to produce an emulsion capable of being suitably degraded by a convenient time of centrifuging. The technique with appropriate modifications could probably be extended to water/oil emulsions and to emulsions of organic liquids, other than oils.

The following appear to be the most significant facts which can be deduced from the experimental results.

(1) The technique is capable of detecting small differences in emulsions, both in regard to their initial physical state and to their storage life. It should, therefore, provide a useful method of assessing emulgents, particularly from the viewpoint of their use in pharmaceutical manufacture. Subsequent "shelf" storage tests have so far confirmed the results obtained.

(2) The relationship between either log. "D" or log. "H" and the time of centrifuging is sensibly linear for all the emulsions examined. The existence of a linear relationship has not previously been shown for an artificial breakdown stress.

(3) Although it might have been expected that an initial small globule size would be indicative of emulsion stability (and *vice versa*), the results do not confirm this.

(4) Under the conditions of the test, all the surface active agents examined were approximately of the same order of efficiency as sodium oleate.

(5) In all cases, an increase in the concentration of surface active agent produced a larger initial "H" value and, in most cases, an increased stability. At the lowest concentration studied (0·1 per cent.) there was a marked difference in the behaviour of the various emulgents. At 1·0 per cent. this difference was almost insignificant, particularly in emulsions of arachis oil. It is possible, of course, that a change in the

conditions of homogenisation and centrifuging would reveal differences in behaviour, even at higher concentrations.

(6) It was not possible to arrange the surface active agents in any single order of efficiency applicable to all concentrations, although certain trends could be observed, e.g., cetrimide was the least satisfactory emulgent for arachis oil at all concentrations.

(7) In accordance with the normal behaviour of emulgents, the materials under test were less effective for liquid paraffin than for arachis oil.

SUMMARY

A method is described for the evaluation of emulsifying power of surface active agents, based on the measurement of stability of the emulsions they yield.

We are indebted to Dr. O. L. Davies for the mathematical treatment of the results and to Mr. A. G. Fishburn for help in the preparation of the paper.

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DISCUSSION

The paper was presented by Mr. J. R. Cockton.

The CHAIRMAN pointed out that it was sometimes desirable clinically that an emulsion should not be too stable.

MR. H. LEVIUS (Dagenham) said that the authors referred to size frequency analyses, and claimed that the method of globule counts was quicker. That method was also more accurate in order to determine "H" and "D." Artificial ageing would give a better picture of emulsion stability than centrifuging; it more closely approximated storage tests and, although not exactly analogous, it gave useful information. King, in the paper quoted by the authors, tried to show a linear relationship between storage time and decrease in specific interface. Was there any reason why the present authors had determined "D" in preference to area? It appeared that the authors had assumed a direct relation between the efficiency of an emulsifying agent and the stability of the emulsion produced.

DR. W. MITCHELL (London) asked whether the authors had found much variation in the emulsifying power of different batches of proprietary emulsifying agents. In practice he found such a gross variation that it was often necessary to reformulate either the quantities of material or the method of making an emulsion for each batch of emulsifying agent received. He also asked whether their method, and in particular the mathematical treatment of the results, applied equally well when the emulsifying agent was dissolved in either phase or present as solid.

MR. E. ADAMS (Plymouth) said that the authors assumed that the reduction in the number of globules of oil was proportional to the reduction in total area of the interface. If the globules of an oil dispersed in water were uniform in diameter that would seem logical, but in practice the diameter varied quite considerably.

MR. D. E. SEYMOUR (Welwyn) asked whether the authors had considered interfacial tension measurement as a means of assessing emulsifying power. He agreed that size frequency analysis was a tedious method, and in his experience did not correlate so directly with stability as the paper implied. A good way of assessing the stability of an emulsion was to store it at about 40° C., rather than at room temperature; most emulsions broke down in a short time. With water-in-oil emulsions oxidation of the emulgent could be a serious factor in breakdown, for there was a high degree of surface distribution. Metallic ions tended to increase the degree of oxidation. He confirmed that initial globule size was not connected with ultimate stability.

MR. T. D. WHITTET (London) said that little was known about the pharmacology of the large number of emulgents coming into use. Intravenously-fed emulsions were beginning to be used, and it would be useful to know the toxicity or otherwise of many of the substances referred to. The stability of an emulsion was not necessarily related to its clinical efficiency. The work of Fraser on the absorption of fats had shown that if an emulsion of liquid paraffin had a small enough particle size, the paraffin was absorbed. Emulgents were not necessarily inert pharmacologically. Polysorbate 80 and sodium cetyl sulphate were given orally in capsules, the former to aid the emulsification of fats, the latter to inactivate gastric lipase.

MR. D. N. GORE (Dorking) thought that unless there was some over-riding therapeutic reason for presenting a drug in the form of an emulsion it should never be done.

MR. A. G. FISHBURN (Manchester) suggested that the answer to the unsatisfactory position with regard to emulsifying agents might be found in synthetic materials.

MR. A. E. DAVIS (Nottingham) pointed out that the statement was made that all surface active agents examined were approximately of the same order of efficiency as sodium oleate, and asked whether that did not show a serious defficiency in the methods used to determine the various results. The non-ionic agents would be more stable over a wider range of *p*H. He asked whether it was possible to relate centrifuging time to shelf storage time, and why they had used concentrations of 0·1, 0·5 and 1 per cent. for their comparisons. They showed a big difference in stabilising properties of the emulsifiers, but the concentrations were not the strengths used in practice.

MR. A. F. CALDWELL (Singapore) said that there was always the possibility of bacterial or fungal infection causing decomposition in emulsions and it was important to know that there were no bacteria or fungi present in the emulsifying agents.

MR. J. R. COCKTON, in reply, said that the calculation of interfacial

area was considered, but it was felt that accuracy would be in doubt owing to the admittedly approximate nature of the calculation. There was a batch-to-batch variation in surface-active agents, but they had had the advantage of working with a specially purified set. The effect of electrolytes was not known. In reply to Mr. Adams, homogenisation was employed, as it tended to make the globule size more homogeneous. Visual observation methods had been tried. The emulsions were very similar in appearance when prepared, and even after standing for 6 months there was very little visible deterioration. Storage had been carried out at high temperature and at room temperature, approximately 20° to 25° C. Oxidation had to be considered, but the main purpose of the work had been to investigate the differences between the surface-active agents. It was hoped that toxicity tests on the emulsifying agents would be carried out shortly. The concentrations of surface-active agents were purposely selected in order to emphasise the differences.