Pharmaceutical Emulsions. I A Study of the Continental Method*,†

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INTRODUCTION

The theory and practice of emulsification have been widely studied in various fields. However, the time-honored emulsification techniques of pharmacy have perhaps not received as much scientific study as might have been desirable.

The present investigation was undertaken with a view of making a detailed study of the importance of various factors in the technique used in the English and Continental methods, employing various oils. These older methods were also compared in effiency with newer methods, *i. e.*, the use of the electric mixer and hand homogenizer. The quality of the emulsions was determined by making measurements of the size of the dispersed globules, using a filar micrometer, as well as by observing the appearance and rate of creaming. Likewise, in some instances, photomicrographs were taken to show the quality of the emulsion.

The present paper gives the results of a study of the Continental method of emulsification.

EXPERIMENTAL

Materials Used.—The fixed oils selected for study were cod liver oil, castor oil, heavy mineral oil and linseed oil; the oils were of U. S. P. quality. U. S. P. powdered acacia was employed. One-tenth per cent sodium benzoate was added to the distilled water to prevent mold growth in the emulsions while standing for observation.

General Methods.—The quality of the emulsions was determined by making microscopic measurements of the size of the dispersed globules, as well as by taking photomicrographs in some instances and by observing the appearance of the emulsions and the rate of creaming. In determining the average diameter of the oil globules a filar micrometer was employed. A slide was made from each emulsion by placing a drop of the emulsion on a slide and then placing a cover glass over it. In some cases it was necessary to dilute the emulsion slightly with water in order to obtain a field suitable for observation. A representative field was chosen for observation, using the 4-mm. objective, and the diameters of all the oil globules touching the lines on the scale were recorded. In this manner, the diameters of about 50 oil globules were taken and the average globule size was determined. The average size of the oil globules was determined immediately after the completion of each emulsion.

Throughout the work, the rate of trituration was maintained at approximately 150 revolutions per minute. In all cases the parts of oil and water were measured in cc., and the parts of acacia were measured in Gm.

For observation the emulsions were kept in ordinary 2-oz. wide-mouth bottles at room temperature.

By the term "primary emulsion" is meant the emulsion which resulted when the oil and the acacia were triturated together and a portion of the water was added all at once. The primary emulsion was considered successful if it gave a clicking sound when triturated, was creamy, opaque and showed no oil separation. In some cases, especially where more than 2 parts of acacia or more than 3 parts of water per 4 parts of oil were used no primary emulsion was formed, but on gradual addition of the remainder of the water a homogeneous preparation resulted having the appearance of a temporary emulsion. The average size of the oil globules was determined in such cases.

In the tables "Oil Sep." is used to indicate oil separation. The following abbreviations are used to indicate the average size of the oil globules.

A—Average diameter less than 2.5 microns.
B—Average diameter from 2.5 to 4 microns.
C—Average diameter from 4 to 6 microns.
D—Average diameter more than 6 microns.

Variation in Proportion of Acacia.—In studying the effect of variation in proportion of acacia, the proportions of oil and water were kept constant. Sixty cc. of a 12½% oil emulsion was prepared in each case. The 4 parts of oil and the acacia were first triturated well for about a half minute, and then the 2 parts of water was added all at once. The primary emulsion was triturated for about 2 to 3 minutes and the remainder of the water was added gradually with constant trituration. A No. 1 wedgwood pestle, 17.5 cm. in length and 3.5 cm. in diameter at the base, and a No. 1 wedgwood mortar were used; in some instances a porcelain pestle, 15.0 cm. in length and 4.5 cm. in diameter at the base, was employed. The results of the effect of variation in proportion of acacia are given in Table I.

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Table I.—Variation in Proportion of Acacia

Parts of Acacia[a]	Linseed Oil: Appearance of Emulsion, 1 Hour	Linseed Oil: Average Size of Oil Globules	Cod Liver Oil: Appearance of Emulsion, 1 Hour	Cod Liver Oil: Average Size of Oil Globules	Castor Oil: Appearance of Emulsion, 1 Hour	Castor Oil: Average Size of Oil Globules	Mineral Oil: Appearance of Emulsion, 1 Hour	Mineral Oil: Average Size of Oil Globules
			(Wedgood Mortar and Wedgwood Pestle)					
4.0	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*C*
3.0	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*C*
2.4	Oil Sep.	*C*	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*D*
2.0	Creaming	*B*	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*D*
1.6	Creaming	*B*	Creaming	*B*	Oil Sep.	*D*	Oil Sep.	*D*
1.0	Creaming	*D*	Creaming	*B*	Stable	*C*	Oil Sep.	*D*
0.8	Oil Sep.	*D*	Creaming	*D*	Stable	*C*	Oil Sep.	*D*
0.6	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*D*
0.4	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*D*
			(Wedgood Mortar and Porcelain Pestle)					
4.0	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*D*	Creaming	*B*
3.0	Oil Sep.	*C*	Oil Sep.	*D*	Stable	*A*	Creaming	*A*
2.4	Oil Sep.	*C*	Oil Sep.	*D*	Stable	*A*	Stable	*A*
2.0	Creaming	*B*	Oil Sep.	*C*	Stable	*A*	Stable	*A*
1.6	Creaming	*B*	Stable	*B*	Stable	*A*	Stable	*B*
1.0	Creaming	*C*	Stable	*B*	Stable	*B*	Stable	*C*
0.8	Oil Sep.	*D*	Stable	*D*	Stable	*C*	Creaming	*D*
0.6	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*D*
0.4	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*D*	Oil Sep.	*D*

[a] Number of parts of acacia used for 4 parts of oil and 2 parts of water.

Results of Table I show that emulsions prepared according to the 4:2:1 rule are not always best. When using smaller proportions of acacia a decrease in the amount of acacia caused an increase in the size of oil globules. Langevin (1), working with linseed, castor and cod liver oils, found similar results.

The use of a porcelain pestle of 4.5-cm. diameter showed a distinct advantage over a wedgwood pestle of 3.5-cm. diameter in that it caused a further reduction in the size of the oil globules and produced more stable emulsions. When using a wedgwood pestle, emulsions could not be formed when mineral oil was employed and with castor oil, emulsions were formed only when 0.8 and 1 part of acacia were used.

Variation in Time of Trituration of Primary Emulsion.—Making 60 cc. portions of 12½% oil emulsions, primary emulsions were triturated for various lengths of time using the 4:2:1 proportion and following the same procedure of preparation as in the previous experiment. A No. 1 wedgwood mortar and a No. 1 wedgwood pestle were employed in each case except the mineral oil emulsions which were prepared with the use of a porcelain pestle, 15.0 cm. in length and 4.5 cm. in diameter at the base, and a No. 1 wedgwood mortar. The results of variation in time of trituration of the primary emulsion are given in Table II.

Data of Table II show that when making 60 cc. of a 12½% cod liver oil emulsion, at least 4 minutes of trituration of the primary emulsion was necessary to produce an optimum finished product. Since further trituration of the primary emulsion seemed to be of no value, it was felt that 5 minutes of trituration should be ample to insure the best finished product. The results show that 5 minutes of trituration of the primary emulsion gave *A* products in the case of cod liver and castor oil with reference to the size of the globules. Linseed oil showed a grade *C* and mineral oil showed a grade *B* with 5 minutes of trituration.

Using the 4:2:1 proportion and a No. 3 wedgwood mortar and a No. 3 wedgwood pestle, eight ounces of cod liver oil emulsion was prepared to see if 5 minutes of trituration of a greater quantity of primary emulsion would also reduce the size of the oil globules in the finished product. It was found that the average size of the oil globules was grade *B* as compared to the 2 ounces of cod liver oil emulsion in which the average size of the globules was grade *A*. When making larger quantities of oil emulsions, it appears that more than 5 minutes of trituration of

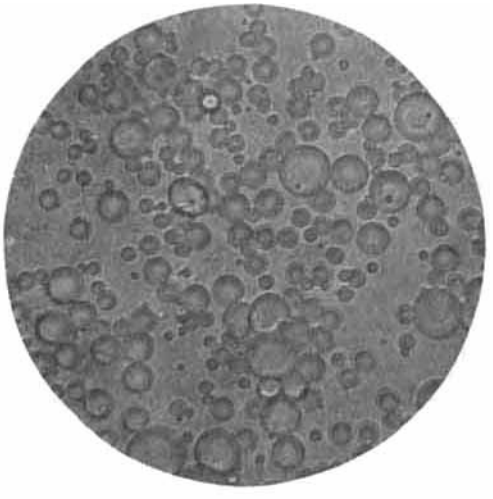

Fig. 1.—Linseed Oil (430×).

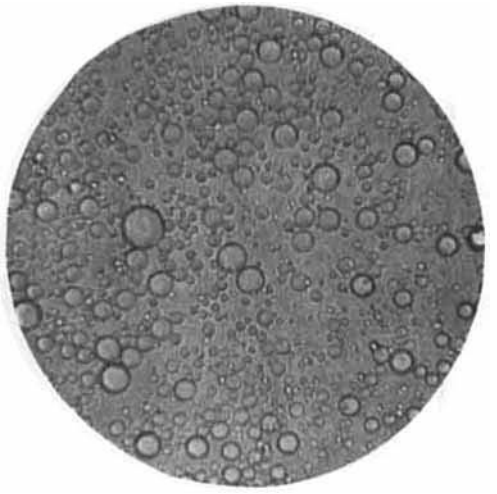

Fig. 2.—Mineral Oil (430×).

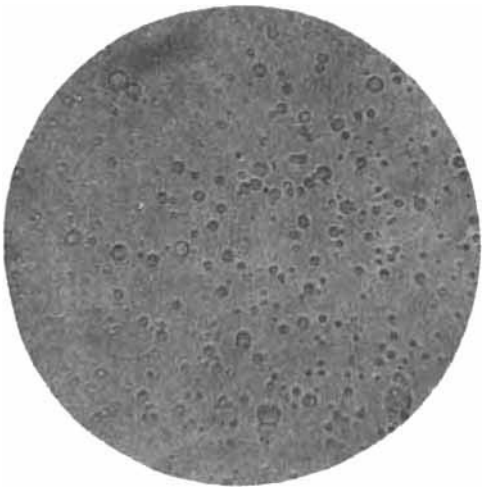

Fig. 3.—Cod Liver Oil (430×).

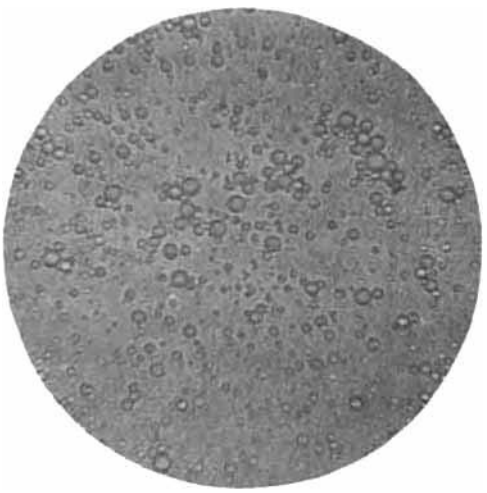

Fig. 4.—Castor Oil (430×).

the primary emulsion is necessary in order to produce an optimum dispersion.

Table II.—Variation in Time of Trituration of Primary Emulsion

	Time of Trituration in Minutes	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules
Cod liver oil	1	Creaming	*C*
	3	Creaming	*B*
	4	Stable	*A*
	6	Stable	*A*
Castor oil	3	Stable	*B*
	5	Stable	*A*
Linseed oil	5	Creaming	*C*
	7	Creaming	*C*
Mineral oil	3	Stable	*C*
	5	Stable	*B*

Variation in Time of Trituration of Acacia and Oil in Making Primary Emulsion.—Most textbooks on pharmacy advise against excessive trituration of the acacia and oil before adding the 2 parts of water in the making of an emulsion by the dry gum method. It is generally thought that excessive trituration tends to make acacia colloidally soluble in the oil, thus favoring a water-in-oil rather than an oil-in-water emulsion. Sixty cc. portions of 12½% cod liver oil emulsions were prepared using the 4:2:1 proportion and using a No. 1 wedgwood mortar and a No. 1 wedgwood pestle. The acacia and oil were triturated for various lengths of time and the time of trituration of the primary emulsion was also varied in some instances. The remainder of the water was added gradually with constant trituration.

Table III.—Variation in Time of Trituration of Acacia and Oil in Making Primary Emulsion

(Cod Liver Oil)

Time of Trituration of Acacia and Oil	Time of Trituration of Primary Emulsion	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules
1 minute	2 minutes	Creaming	*B*
3 minutes	2 minutes	Creaming	*B*
5 minutes	2 minutes	Creaming	*B*
5 minutes	5 minutes	Stable	*A*

The results show that as much as 5 minutes of trituration of the acacia with the oil did not seem to affect the finished emulsion; a grade *A* preparation, with respect to the size of the oil globules, was obtained when triturating the primary emulsion for 5 minutes.

Likewise, a muller was tried. One part of acacia was mixed well for about 2 minutes with a portion of the 4 parts of cod liver oil on a ground glass ointment slab using a muller. The pasty mass was then scraped off the ointment slab and placed in a No. 1 wedgwood mortar. The remainder of the 4 parts of cod liver oil was added and the entire mixture was triturated with a No. 1 wedgwood pestle for about another half minute. After the 2 parts of water was added all at once, the resulting primary emulsion was triturated for 5 minutes; the remainder of the water was added slowly with constant trituration.

The average diameter of the oil globules was about 2 microns. Better mixing of the oil and gum by the use of a muller was of no advantage.

Variation in Proportion of Water in Making Primary Emulsion.—In studying the effect of variation in proportion of water in making the primary emulsion, the acacia (1 part) and the oil (4 parts) were kept constant throughout the experiment. In all cases 60 cc. portions of 12½% oil emulsions were prepared using a porcelain pestle 15.0 cm. in length and 4.5 cm. in diameter at the base and a No. 1 wedgwood mortar. The procedure of preparation of the emulsions was the same as for Table I except that the primary emulsion was triturated for 5 minutes. Results are given in Table IV.

twice as much water as the acacia; only castor oil gave an emulsion. In Table I it is seen that when using 0.8 part of acacia with 2 parts of water an emulsion was formed in several cases whereas in Table V only castor oil yielded an emulsion when using 0.8 part of acacia with 1.6 parts of water. The principle of using 2 parts of water for 4 parts of oil appears to be well founded.

Rate of Addition of Water in Making Primary Emulsion.—In making the primary emulsion, inferior results were obtained when the water was added slowly or in divided portions to the oil-acacia mixture. The principle of adding the water all at once in making the primary emulsion appears well founded.

Table IV.—Variation in Proportion of Water in Making Primary Emulsion

	Linseed Oil		Cod Liver Oil		Castor Oil		Mineral Oil	
Parts of Water[a]	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules
4.0	Creaming	*D*	Creaming	*D*	Creaming	*D*	Creaming	*D*
3.0	Creaming	*D*	Creaming	*B*	Creaming	*D*	Creaming	*D*
2.5	Creaming	*D*	Stable	*A*	Stable	*A*	Creaming	*C*
2.0	Creaming	*C*	Stable	*A*	Stable	*A*	Stable	*B*
1.5	None formed		None formed		Stable	*A*	None formed	
1.0	None formed		None formed		None formed		None formed	

[a] Number of parts of water used for 4 parts of oil and 1 part of acacia.

Only castor oil gave a primary emulsion when as little as 1½ parts of water was used; the other oils required at least 2 parts of water. When using more than 2 parts of water an increase in the amount of water caused an increase in the average size of the oil globules. When making emulsions using 4 parts of oil and 1 part of acacia, at least 2 parts of water and not more than 2½ parts of water should be used when making the primary emulsion to insure an optimum finished product.

Variation in Proportion of Acacia and Water.—Using the same size and type of mortar and pestle and the same method of preparation as in the preceding experiment, 60 cc. portions of 12½% oil emulsions were prepared. The proportion of oil (4 parts) was kept constant throughout. In all cases in the preparation of the primary emulsion twice as much water as acacia was used. Results of the effect of variation in proportion of acacia and water are given in Table V.

Rate of Dilution of Primary Emulsion.—Experiments showed that after the primary emulsion had been prepared, the rate of addition of the remainder of the water had no effect on the finished product.

Direction of Trituration.—There has been some question as to whether the direction of trituration in the preparation of emulsions should be clockwise or counterclockwise. Experiments showed that the direction of trituration had no effect on the quality of the emulsion.

Use of Dried Acacia.—It was found that the use of dried acacia had no advantage over undried acacia in the preparation of emulsions.

Use of Wet Mortar.—The usual directions to use a dry mortar and pestle appear to be well founded, since the use of a moist mortar prevented emulsification.

Fifty Per Cent Emulsions.—Experiments were carried out with 50% oil emulsions to see whether or not the results obtained with the 12½% oil emul-

Table V.—Variation in Proportion of Acacia and Water

		Linseed Oil		Cod Liver Oil		Castor Oil		Mineral Oil	
Parts of Acacia[a]	Parts of Water[a]	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules
1.0	2.0	Creaming	*C*	Stable	*A*	Stable	*A*	Stable	*B*
0.8	1.6	None formed		None formed		Stable	*A*	None formed	
0.6	1.2	None formed		None formed		Stable	*A*	None formed	
0.4	0.8	None formed		None formed		None formed		None formed	
0.2	0.4	None formed		None formed		None formed		None formed	

[a] Number of parts used for 4 parts of oil.

The results of Table V show that in the case of linseed, cod liver and mineral oils no emulsion was formed when using less than 1 part of acacia and

sions would be applicable to emulsions containing higher proportions of oil. The results of experiments with 50% oil emulsions were in agreement

with the findings on the 12½% oil emulsions, except that when making 60 cc. of a 50% cod liver oil emulsion at least 7 minutes of trituration of the primary emulsion was necessary in order to produce a grade *A* product. With mineral, castor and linseed oils, 8 minutes of trituration of the primary emulsion gave finished products which were similar, with respect to the size of the oil globules, to the 12½% oil emulsions in which the primary emulsions were triturated for 5 minutes. It was found that the 50% oil emulsions were more stable than the 12½% oil emulsions when standing over a period of three hours.

DISCUSSION OF RESULTS

Ingredients.—The present study of emulsions of various fixed oils, using acacia as the emulsifying agent, showed that the various oils behave differently with respect to range of emulsification, stability and the average size of the oil globules. Serrallach and Jones (2), studying the strength of interfacial films of various oils with emulsifying agents, pointed out that the influence of the oil on the properties of the film was more definite than that of the emulsifier. These workers showed that cod liver oil formed strong films very readily with most of the emulsifiers studied; castor oil had a lesser tendency to form films, and mineral oil had the least of any of the oils studied. In the present work, it was found that cod liver oil and castor oil gave grade *A* products with reference to the average size of the oil globules, using the 4:2:1 proportion, whereas mineral oil gave a grade *B* product and linseed oil gave a grade *C* preparation.

Time of trituration of the primary emulsion does not seem to be stressed in any of the pharmaceutical textbooks, and yet this factor is very important in production of the best emulsion. It was found that 5 minutes of trituration of the primary emulsion was ample to insure an optimum finished product when making 60 cc. of a 12½% emulsion. A greater quantity of emulsion requires longer trituration.

Roon and Oesper (3), using cottonseed and mineral oils in the Continental method found that the proportions giving the best results were 4 parts of oil, 2 parts of acacia and 3 parts of water and that slight variations from the proper procedure or from the critical proportions yielded either less stable emulsions or none at all. In the present work, when using mineral oil, a No. 1 wedgwood mortar and a No. 1 wedgwood pestle, no emulsions could be formed no matter what proportion of acacia was used. However, when using the wedgwood mortar and a porcelain pestle good emulsions were formed with several proportions of acacia. Castor oil gave grade *A* emulsions with various proportions of acacia when using a No. 1 wedgwood mortar and a porcelain pestle, but when using a No. 1 wedgwood mortar and a No. 1 wedgwood pestle emulsions were formed only when 0.8 and 1 part of acacia were used for 4 parts of oil and 2 parts of water. Stocking (4) found that castor oil produced poor emulsions.

The use of acacia dried to constant weight at 105° C. or placed over calcium chloride for 72 hours and the use of tears of acacia, powdered to a No. 80 fineness, did not seem to have any advantage over the commercial powdered acacia.

SUMMARY

A detailed study was made of the importance of various factors in the technique used in the Continental method of preparing emulsions.

Time of trituration of the primary emulsion was found to be a very important factor in production of the best emulsion. Castor oil and cod liver oil gave grade *A* products when using the 4:2:1 proportion, but it was necessary to use more than 1 part of acacia for emulsifying linseed oil and mineral oil in order to produce satisfactory preparations.

The principle of using 2.0 parts of water for 4 parts of oil and 1 part of acacia when making the primary emulsion is well founded. The use of a dry mortar and dry pestle is likewise important.

The following factors in preparation of emulsions did not have any effect on the finished product: the use of dried acacia, rate of dilution of the primary emulsion, excessive trituration of the oil and acacia when making the primary emulsion and direction of trituration of the primary emulsion, *i. e.*, clockwise, counterclockwise or both directions of trituration.

REFERENCES

(1) Langevin, L. M., JOUR. A. PH. A., 22 (1933), 728.

(2) Serrallach, J. A., and Jones, G., *Ind. Eng. Chem.*, 23 (1931), 1016.

(3) Roon, L., and Oesper, R. E., *Ind. Eng. Chem.*, 9 (1917), 156.

(4) Stocking, C. H., JOUR. A. PH. A., 6 (1917), 954.

(*To be continued*)

Postage stamps have been issued by Italy in honor of the following: Leonardo da Vinci, painter, sculptor, architect and scientist; Alessandro Volta, electrophysicist; Luigi Galvani, physicist and anatomist.