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CORRELATION BETWEEN NATURE OF EMULSIFIER AND MULTIPLE EMULSION STABILITY

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ABSTRACT

The effect of emulsifier type on the preparation and stability of multiple emulsions was studied. The influence on the yield of preparation and stability with regard to the HLB of emulsifier II was found to be different for each emulsifier. The best stabilities of the multiple emulsions were obtained when there is a similarity between the hydrophobic part of the emulsifier and the oil phase.

INTRODUCTION

The concept of multiple emulsions is very promising for prolonged drug release and there are already some reports on *in vivo* experiments (1,2). The complicated nature of the multiple emulsions causes various problems of instability due to release of the drug from the inner droplets of the emulsion via some possible mechanisms (3).. Some of the drug is already released while preparing the multiple emulsion, causing low yields of preparation (y_1 , defined as precentage of the solute remained in the inner droplets). It was recently found that there is an optimal HLB and emulsifier concentration for

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obtaining high yields of preparations. The fact that the optimal HLB(at high concentrations of the second step emulsifier)is close to the required HLB of the oil phase, leads to the idea that there snould be an optimal emulsifier giving high stability and yield of preparation of the multiple emulsion.

The purpose of this work is to study the differences between multiple emulsions prepared by various emulsifiers, and to point out some conclusions which are important for obtaining stable multiple emulsions.

Experimental

Light mineral oil, Pazdina 15, was obtained from Paz – Israel. All the emulsifiers used were commercial products of Atlas Europol S.P.A. Those noniomic emulsifiers were sorbitan fatty acid esters (Spans*), and ethoxylated sorbitan fatty and esters (Tweens**).

The W/O emulsion was prepared by a dropwise addition of the water phase to the oil followed by twenty minutes of homogenization (Silyerson Homogenizer), at a constant speed. The internal phase contains NaCl, serving as a marker for the determination of the yield of preparation of the emulsion. The primary emulsion was composed of:

10 wt %	Span-Tween 80, HLB=6	(Emulsifier I)
60 wt %	light mineral oil	
30 wt %	NaCl solution (1% W/W)	

All multiple emulsions were prepared by two steps procedure (4). The primary W/O emulsion is added dropwise into the water phase, containing the second emulsifier, at a constant stirring rate (magnetic stirring). The addition is completed within 10 minutes.

The composition of the multiple emulsion is:

20 wt %	primary W/O emulsion
5 wt %	emulsifier II
75 wt %	deionized water

The yield of preparation is determined by titration of the chloride ions present at the external phase of the multiple emulsion.

Duplicates of 2.5 g samples of multiple emulsions were titrated for chloride determination, by the mercuration method (5), using lower concentrations of $Hg(NO_3)_2$ (1.2 g in 1 liter) and HNO_3 (0.75 ml conc. nitric acid in 1 liter). The reproducibility of the titrations was in the range of ±8%.

A systematic deviation from the real end point was observed for each emulsion, since the white color of the emulsion has a masking effect on purple end point color. A correction factor of 0.86 for each result was therefore used (6).

* Sp 20	Sorbitan	mono	Laurate
Sp 40	''	''	Palmitate
Sp 60	''	''	Stearate
Sp 80	''	''	Oleate
Sp 85	''	tri	Oleate

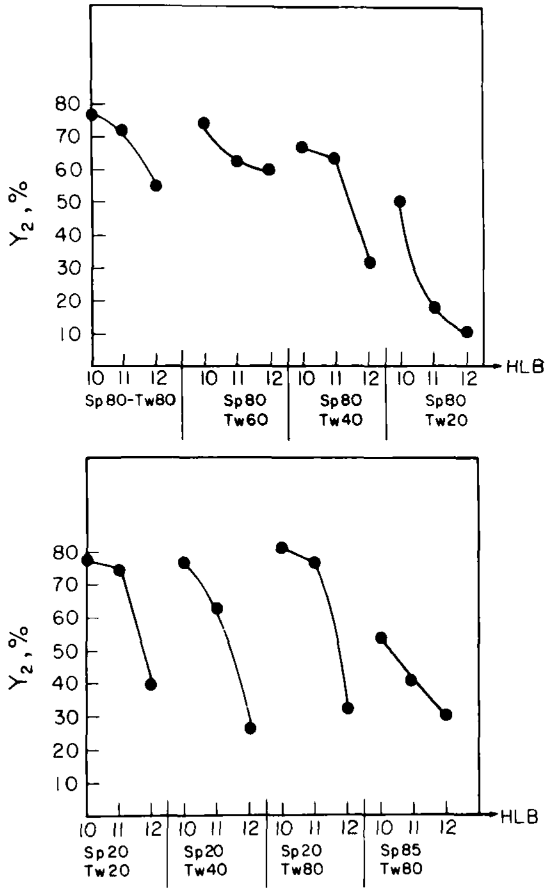
** Tw 20	ethoxylated	Sp 20
Tw 40	''	Sp 40
Tw 60	''	Sp 60
Tw 80	''	Sp 80

RESULTS AND DISCUSSION

1. Yield and HLB

Two main factors are involved at the second emulsification step of the w/o emulsion: the type of the oil phase and the emulsifier. Since this step can be considered as a preparation of an oil in water emulsion, it could be expected that by preparing the multiple emulsion with various emulsifiers, emulsions having different stabilities would be obtained. As was shown elsewhere(6), the optimal HLB of the multiple emulsion (at high concentrations of emulsifier II) is the required HLB of the oil. Since we are dealing with mineral oil, the required HLB is 10-11. Series of multiple emulsions were prepared at HLB 10-12 in order to study the effect of emulsifier type on the yield and stability of the multiple emulsions.

As shown in Fig. 1, for each emulsifier II combination, the yield of the multiple emulsion as measured one day after preparation (Y_2), decreases with the increase in the HLB, regardless of the emulsifier type. The type of emulsifier plays an important role in determining the dependence of the yield on the HLB change. For example, a change of HLB from 10 to 11, has almost no effect on the yield when Span 80 - Tween 80 are used, but when Span 80 - Tween 20 are used, a decrease from 50 to 17% is observed. It must be noted that



1. The yield of multiple emulsions after one day (Y_2), when prepared by various emulsifier II (5 wt %) and HLB's.

the Y_2 vs. HLB curves are quite similar for all combinations of Span 20 Tweens, but differ significantly for combinations of Span 80 - Tweens. Those differences can be explained by the compatability between the emulsifier and the oil phase, as will be discussed later.

2. Stability and Emulsifier Type

When the yield of preparation of the multiple emulsion is determined immediately after preparation (y_1), and one day later (y_2), it is possible to obtain information on the stability of the multiple emulsion towards release of the solute from the inner phase.

The stability index, R, is defined as: $R = \frac{y_1 - y_2}{y_1}$

This index indicates the relative change of the tracer concentration in the inner phase during one day. Therefore, a small R means a small amount of tracer released from the inner phase, and a more stable multiple emulsion, while a large R value means unstable emulsion with extensive amounts of tracer released from an inner phase.

The R values for multiple emulsions prepared by different emulsifiers are presented in Table 1. As it can be seen from this table, the value of R increases with the increase in the HLB from 10 to 12, indicating lower stabilities at higher HLBs. The explanation for this phenomenon is based on the particle size of the multiple emulsion and the nature of the interface around the multiple droplets. When the multiple emulsion droplets are very large the rupture of the inner droplets would take a long period of time, so the multiple emulsion would exhibit an improved stability. In addition, when a firm interface is formed around the droplets, it prevents the rupture of the inner droplets, yielding a high stability. Since the optimal HLB of those emulsions is 10-11, it is clear why the highest R values are obtained at HLB 12 for all the emulsifiers used.

The nature of the interface which is formed around the multiple droplets is determined by the compatability of the hydrophobic emulsifier with the hydrophilic one and the compatability of the emulsifiers pair with the oil phase. As can be seen (Table 1), when emulsions are prepared by combinations of Span 80 and various Tweens, R decreases (at all HLBs) while increasing the length of the hydrophobic part of the Tween emulsifier from C_{12} to C_{18}. This fact can be explained by the compatability of the emulsifier with the long carbon chains of the paraffinic oil. On the contrary, if there is incompatability between the two emulsifiers, as in the combination of Span 85 - Tween 80, due to steric hindrence, R values are higher, indicating a less stable emulsion. When the emulsions were prepared by combinations of Span 20 and various Tweens, the trend is not so clear probably because the formation of very big aggregates and oil separation in some of those emulsions.

TABLE 1: R index of mutliple emulsions prepared by various emulsifiers and percentage of oil separation from o/w emulsions prepared by the same emulsifiers.

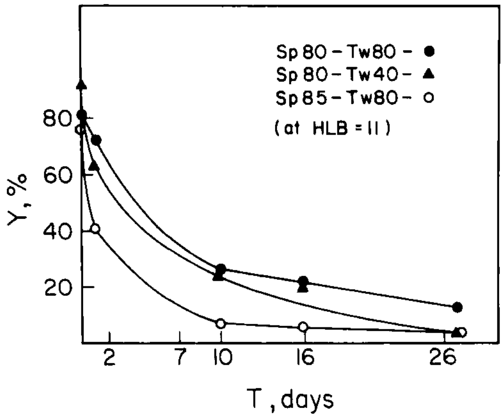
Emulsifiers	R, at various HLB's			% v/v oil separation (of o/w emulsion) at HLB 11
	10	11	12	
Sp 80 Tw 20	0.42	0.79	0.87	18
Sp 80 Tw 40	0.29	0.31	0.64	2
Sp 80 Tw 60	0.18	0.27	0.32	2.5
Sp 80 Tw 80	0.08	0.11	0.3	2.5
Sp 85 Tw 80	0.11	0.46	0.57	2.5
Sp 20 Tw 20	0.11	0.14	0.45	15.4
Sp 20 Tw 40	0.01	0.31	0.65	23
Sp 20 Tw 80	0.13	0.15	0.59	13.6

One would think that the stability of the multiple emulsion is directly derived from the stability of the similar o/w emulsion. In order to check this possibility, a series of o/w emulsions was prepared by the same emulsifier pairs which were used for the multiple emulsions (ϕ=20% w/w, 5% emulsifier at HLB 11). The separation of oil after one day at 55°C was measured and is shown in Table 1. From these results it is clear that there is no correlation between the stabilities of the o/w emulsions and w/o/w emulsions.

These findings indicate that the mechanism which leads to the coalesence of the multiple emulsion droplets is not necessarily combined with the mechanism of rupture of the inner multiple emulsion droplets. On the contrary, coalesence could increase the apparent stability of the multiple emulsion, due to the increase in the particle size.

In order to compare the R values with the stability of multiple emulsions for a long period of time, the yield of three emulsions was measured during one month (Fig. 2). These three emulsions were prepared at HLB 11, by different combinations of emulsifiers.

As can be seen, the process of emulsion rupture is very rapid during the first week after preparation of the multiple emulsion: when prepared using



2. The yield of multiple emulsions prepared by different emulsifier II combinations, as measured during one month.

Span 80 and Tween 40 or Tween 80, Y decreases from 81-91%, to 37-32%, respectively. After the first week, the decrease of Y is much slower, from 37-32% to 12-4% during 19 days. The same trend is observed when the multiple emulsion is prepared using Span 85 Tween 80: Y drops from 76% to 19% during one week, and then from 19% to 4% during 19 days.

When R values of those emulsions are compared it is expected that the combination of Span 80 - Tween 80 (R=0.11) would be better than Span 80 - Tween 40 (R=0.31), which is better than Span 85 - Tween 80 (R=0.46). The changes of Y during 10 days for these emulsions are 80 to 26% (Sp 80 - Tw 80), 92 to 24% (Sp 80 - Tw 40) and 76 to 8% (Sp 85 Tw 80), in accordance with the R values.

CONCLUSIONS

1. The yield of preparation and stability of multiple emulsion are dependent on emulsifier type and its HLB.

2. The most stable multiple emulsions are obtained when there is a chemical similarity between the oil phase and the hydrophobic part of the emulsifiers, as well as within the pair of emulsifiers.

3. The mechanism for rupture of multiple emulsion droplets is independent on the coalescence mechanism of the outer droplets.

4. The rupture of the multiple emulsion is very pronounced during the first days after preparation.

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