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DRUG-CONTAINING MULTIPLE-PHASE EMULSIONS

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We studied the effectiveness of the formation of w/o/w emulsions as a function of composition and mixing time. We found that concentration of emulsifier 1, the concentration and HLB of emulsifier 2, the viscosity of the oil phase and the external water phase as well as the mixing time in step two of making the emulsion characteristically influence the effectiveness of emulsification and the stability of the emulsions.

Introduction

The "complex" emulsions (multiple phase emulsions, doppelte Emulsionssysteme) are disperse systems in which the disperse phase contains droplets of the external (coherent) phase. Two types are known: "water-in-oil-in-water" (w/o/w) and "oil-in-water-in oil" (o/w/o) [1].

As concerns the structure of w/o/w emulsions, water droplets in an oil coating are present in a coherent water phase (w_2 phase, "external" water phase) [2,3] (Fig. 1).

The prospective uses of these systems justify investigations of their formation, properties and stability. Hungarian research in this field began only recently [4,5].

So far, the chemical industry, the food industry and the drug industry apply complex emulsions [1]. Their use as drug delivery systems seems especially important and promising.

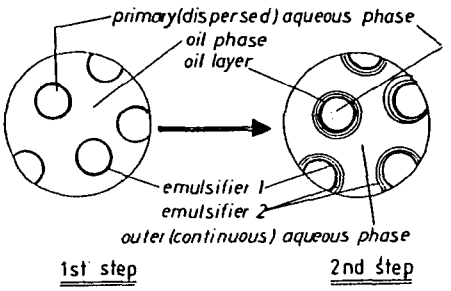

Figure 1.: Two-step procedure for emulsification and structure of w/o/w emulsions [3].

Their application in pharmaceutics is based on their following favourable properties [6-8]:

- protection of an agent dissolved in an internal water (or oil) phase is ensured,
- a prolonged effect can be achieved,
- in cases of overdosing, they have a detoxicating effect.

w/o/w and o/w/o emulsions have so far been used with more or less success in the formulation of vaccines, analgetics and antiphlogistics, hormone preparations, antitumour

agents, antibiotics and morphine antagonists [6-12].

For the production of stable w/o/w emulsions, the following are necessary:

- a non-ionic emulsifier with a low HLB value in a relatively high concentration (in order to form a w/o emulsion),
- an emulsifier with a high HLB value in a relatively low concentration (ensuring dispersion of the w/o emulsion in the coherent water phase),
- a suitable volume of the w/o emulsion withing the complex emulsion [2, 3, 12].

The aim of our investigations was to develop a stable w/o/w emulsion. Our primary task was to elucidate the relationship between the composition, and especially the concentrations of the two emulsifiers, and the result of emulsification. We set out to improve the stability (at the optimum composition) by increasing the viscosity of the external water phase and by thickening the oil phase. A further aim was to learn whether a stable w/o/w emulsion is suitable as a drug delivery system. At what rate and in what quantities is the active substance liberated from the complex emulsions?

The present paper reports on studies concerning the effectiveness of production of w/o/w emulsions.

Materials and methods

w/o/w emulsions were made from liquid petrolatum (Paraffinum liquidum, satisfying Ph.Hg.VI), Span 80, Span 20 and Tween 80 (Atlas GmbH, FRG). The viscosity of the external water phase was improved with hydroxyethyl-cellulose (Cellosize QP, Union

Carbide, USA). The oil phase was thickened with ceresine. Emulsions were prepared in a two-step procedure [2,3]. In the first step, Span 80 (lipophilic emulsifier) was dissolved in liquid paraffin, after which water was emulsified in it by mechanical stirring at an even rate. The internal water phase of the model emulsions was a 10^{-1} mol dm^{-3} potassium chloride solution; the drug-containing emulsions contained 1 mass per cent of ephedrinium chloride solution. In the second step, the w/o emulsion obtained in this way was emulsified in an aqueous solution of Tween 80 (hydrophilic emulsifier) or a Tween 80-Span 20 mixture.

Investigation of "efficiency" of formation of emulsions

The efficiency of formation of the complex emulsion was determined as the proportion of chloride ions added to the internal water phase which penetrated into the external water phase:

$$\text{efficiency } (\%) = \frac{c_{KCl} - \text{measured } c_{KCL}}{c_{KCl}} 100 \qquad (1)$$

Chloride ion concentration was measured with a Radelkis OP-CI-0711 P membrane electrode and a Radelkis OR-205/1 precision pH and voltage-meter immediately after emulsification and after different periods of waiting.

Investigation of drug release

The liberation of ephedrinium chloride dissolved in the internal water phase was studied by the membrane dialysis method (leading to equilibrium). A synthetic membrane was attached to one end of the dialysing tube, and a constant volume of emulsion was measured on it. The tube was placed in a flask containing 20.0 ml distilled water at body temperature. The membrane just touched the surface of the water. This apparatus was placed in a thermostat at 305 K. The amount of ephedrinium chloride that passed through the membrane was measured with a Spektromom 195 spectrophotometer at 290 nm. Examination of the liberation of the agent was also found to be suitable for numerical characterization of the efficiency of emulsification. In agreement with the literature, a linear correlation was obtained between the amount of ephedrinium chloride measured in the dialysis liquid (Q) and the square root of the time of dialysis (t) [14]:

$$Q = a\sqrt{t}. \qquad (2)$$

a is the rate of liberation of the agent. We determined the rates of liberation of the drug from the w/o emulsion and from a w/o/w emulsion that contained ephedrinium chloride in the external water phase. If the two steps of emulsification were perfect, then the rate of dialysis would be rate of liberation of drug from the w/o emulsion. If no w/o/w emulsion was formed in step 2, but all of the agent passed into the external water phase, then the rate of drug release would be that of a w/o/w emulsion in which the agent was already dissolved in the external water. Therefore, if we consider the first 100 and the latter 0 % emulsifications, with

a known rate constant of dialysis, we can determine the efficiency of the emulsion formation by means of a nomogram (calibration line, Fig. 2):

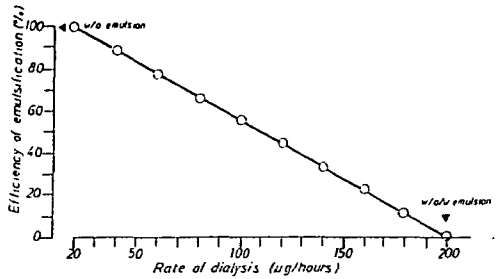

Figure 2.: Efficiency of emulsification determined via rate of dialysis

Rheological examinations

Rheological measurement (leading to flow and viscosity curves) were made with a Rheotest-2 and a Höppler rheoviscosimeter at 298 K.

Results and discussion

1. *Effect of composition on effectiveness of emulsification*

The effectiveness of formation of w/o/w emulsions is mainly influenced by the amount of lipophilic emulsifier [1-3]. In the studies on the production of stable emulsions,

the amount of lipophilic emulsifier was varied at constant amount of hydrophilic emulsifier and volume ratio. It can be seen from Fig. 3 that the effectiveness of emulsification increased with the concentration of emulsifier 1, but even in the presence of 20 % lipophilic emulsifier only 70 % complex emulsion was formed. Figure 3 shows the correlation between the volume ratio and effectiveness. The effectiveness of emulsification increased with increase of the volume of the o/w emulsion.

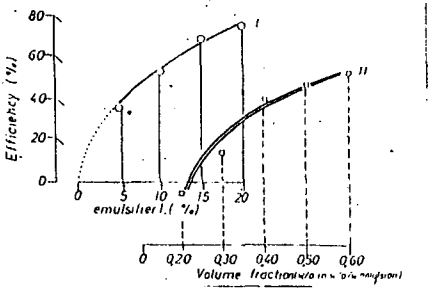

Figure 3.: Effects of concentration of lipophilic emulsifier (I) and volume fraction (II) on formation of w/o/w emulsions

In the next phase, the concentration of the second emulsifier (Tween 80) was also changed. Figure 4 shows an interesting phenomenon. In the presence of 0.1 % hydrophilic emulsifier, emulsification was complete, but then not a liquid emulsion, but a cream-like substance with a specific structure was formed. An increase of the amount of the hydrophilic emulsifier sharply reduced the effectiveness of emulsification until a minimum was reached. Further increase of the concentration led to a maximum in the graph of the function. On increase of the concentration of the lipophilic

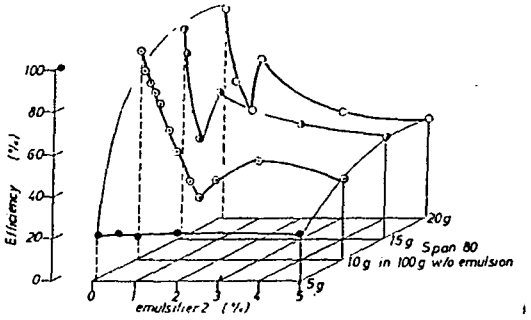

Figure 4.: Effect of emulsifier 2 concentration on formation of w/o/w emulsions

emulsifier, the maximum is situated at lower and lower concentrations of emulsifier 2.

The HLB value of the hydrophilic emulsifier also influences the effectiveness of emulsification: the correlation between HLB and effectiveness exhibited a maximum. With increase of the concentration of emulsifier 1, the optimum HLB shifted towards higher values.

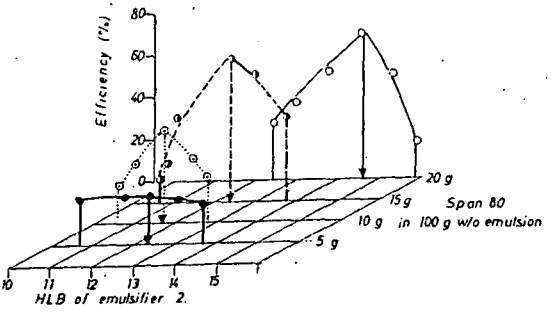

Figure 5.: Effect of HLB on formation of w/o/w emulsions

2. *Drug release from w/o/w emulsions. Evaluation of effectiveness of emulsification via rate of dialysis*

The emulsion deemed most suitable on the basis of its effectiveness was used to prepare a drug-containing emulsion. One mass per cent of ephedrinium chloride was dissolved in either the internal or the external water phase. The process of liberation of the agent was studied (Fig. 6).

In this series of experiments the stability of the emulsions and the effectiveness of emulsification were closely connected: the rate constant of the 8-hour dialysis was determined and used to calculate the effectiveness of emulsification via Fig. 2. The effectiveness determined in this was characterized the stability. If the rate of dialysis was low (i.e. not higher than the rate of the w/o emulsion), then emulsification was successful and the emulsion remained stable for 8 hours.

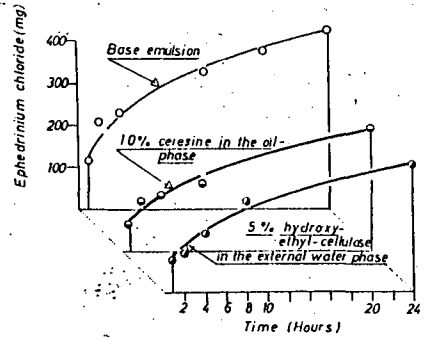

Figure 6.: Drug release from w/o/w emulsions

The effectiveness of emulsification was found to be increased considerably by an increase of the viscosity of the oil phase (addition of ceresine). Increase of the viscosity of the continuous water phase with hydroxyethyl-cellulose had less effect on the stability. The duration of emulsification was of vital importance: mixing for a longer time than optimum or just necessary destroyed the w/o/w emulsion (Table I).

Investigation of the relationship between the stability values calculated on the basis of dialysis and the results of ion-selective membrane electrode examinations is continuing.

Table I

Effectiveness of formation of w/o/w emulsions

	COMPOSITION	*EFFICIENCY (%)*
Base emulsion	*10 g Span 80 in 100 g w/o emulsion* *1 g Tween 80 in 100 g w/o/w emulsion* *0,4 volume fraction (w/o in w/o/w)*	*67,9*
Increase of viscosity of oil phase	*0 % ceresine*	*67,9*
	5 % ceresine	*78,0*
	10 % ceresine	*79,9*
Increase of viscosity of continuous w phase	*3 % HEC*	*75,9*
	4 % HEC	*74,3*
	5 % HEC	*75,4*
Time of 2nd step (mixing time)	*1 minute*	*80,9*
	3 minutes	*63,3*
	5 minutes	*40,4*

3. *Rheological investigation of w/o/w emulsions*

The development of w/o/w emulsions from w/o emulsions involves important rheological changes. From the structurally viscous w/o emulsion with high viscosity, ideally viscous systems with much lower viscosity are formed (Fig. 7).

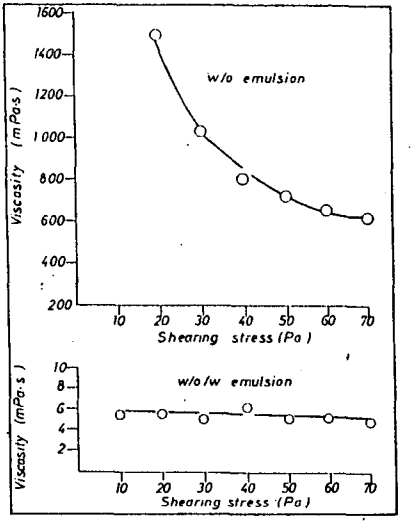

Figure 7.: Viscosity curves of w/o and w/o/w emulsions

Dissolution of the polymer in the external water phase increases the viscosity of w/o/w emulsions (Fig. 8).

Comparison of the viscosity curves of the emulsions made with different mixing times (Fig. 9) proved our assumption that, during a long mixing time, w/o/w emulsions undergo transformation into simple o/w emulsions. The viscosity

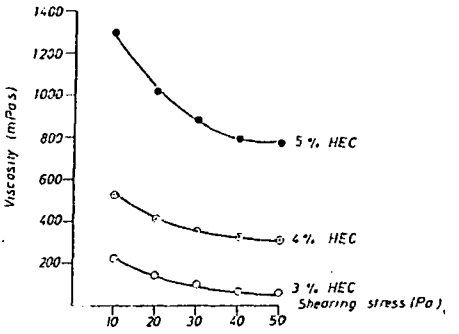

Figure 8.: Effect of hydroxyethyl-cellulose (HEC) content on viscosity of w/o/w emulsions

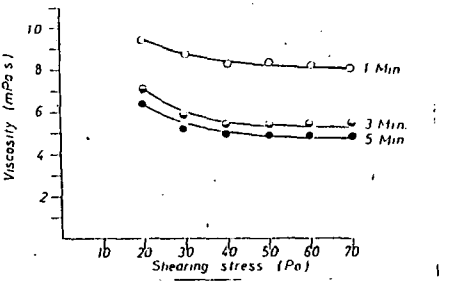

Figure 9.: Effect of mixing time (2nd step) on viscosity of w/o/w emulsions

of a w/o/w emulsion made by mixing for 5 minutes is about half that of an emulsion made by mixing for 1 minute.

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ДРОГ-СОДЕРЖАЩИЕ МНОГОКРАТНЫЕ ЭМУЛЬСИИ

Я. Балаж, И. Эреш, М. Тачи и И. Петер

Изучена эффективность образования эмульсий в/м/в в зависимости от состава и времени перемешивания. Показано, что на эффективность образования многократных эмульсий и на их стабильность оказывают определяющее влияние концентрация эмульгатора 1, концентрация и ГЛБ эмульгатора 2, вязкость масляной и водной фаз, а также время перемешивания во второй ступени приготовления эмульсии.