INVESTIGATION OF THE STABILITY OF DRUG–CONTAINING

(MULPLE–PHASE) EMULSIONS

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THE AUTORS HAVE STRIVEN TO PREVENT THE DECREASE OF MULTIPLE–PHASE CHARACTER IN W/O/W EMULSIONS BY DIFFERENT TECHNOLOGICAL METHODS. PARTLY THE INTERNAL WATER PHASE OF MULTIPLE–PHASE EMULSIONS WAS GELLED BY GELATINE AND PARTLY THE VISCOSITY OF OIL PHASE WAS INCREASED BY SOLID EMULSIFIERS OF LOW HLB VALUE. THE GELATINE CONCENTRATION REQUIRED FOR STABILIZATION AND THE OPTIMAL CONCENTRATION OF SOLID EMULSIFIERS HAVE BEEN DETERMINED.

Introduction

Multiple–phase emulsions belong to the controlled drug delivery systems. The active ingredient dissolved or suspended in the internal water phase releases with an appropriate rate determined by the technologist. The following factors can be used for regulation of this rate:

— modification of drop size and surface of the internal water

— structure and compactness of emulsor film surrounding the internal wateer phase

— permeability of oil layer separating the enternal and external water phases [1].

Publications about the application of antigenic substances [2], antitumour medicines [3] and insulin [4] in w/o/w emulsions report on animal and clinical tests of promising results and good therapeutical benefit, too.

More widespreading practical use is prevented by the fact that the multiple—phase emulsions, among these w/o/w systems, are not stable. By splitting of the oil layer the external and internal water unite, hereby the multiple—phase character decreases and the multiple—phase emulsions is transformed gradually into a simple o/w emulsion. Many attempts [5—8] have been made to stabilize the multiple—phase character but this problem can't be considered as a completely solved one yet.

In our previous investigations [9] we have explained that the formation of the multiple—phase emulsion is facilitated by optimal concentration of emulsifier 1, optimal volume ratio of w/o emulsion in w/o/w emulsion, increase of viscosity of the oil and that of the external water phase and the relatively short mixing time in the second step of preparation as well.

Our further aim was to increase the stability of multiple—phase emulsions by means of:

1. Gelling the internal water phase in order to prevent the uniting of external and internal water phases.

2. Increasing the resistance and elasticity of oil layer separating the two water phases. For realizing the first step of emulsification such solid emulsifiers of relatively low HLB value were chosen which considerably increase the viscosity of oil and gel the oil as well.

Materials and methods

The oil phase of w/o/w emulsions was liquid petrolatum (Paraffinum liquidum of quality of Ph.Hg.VII).

For the preparation of w/o/w emulsions the following emulsifiers were used in the first step of emulsification: Span 20, 40, 60, 80 (Atlas GmbH, GFR), Imwitor 780 K

(Dynamit Nobel AG, GFR), Tegin (Goldschmidt AG, GFR), cetyl stearil alcohol, gly—cerol monostrearate, lanalcol (Ph.Hg.VII).

The concentration of emulsifiers was changed in the range of 10–12 g/100 w/o emulsion. Aqueous solution of 1% of Tween 20 was used in the second step of emul—sification to form w/o/w emulsion.

The preparation of w/o emulsion, — the first step of emulsification — was perfor—med as follows: Solid emulsifiers together with the oil phase were heated over the melting point in water bath. The water phase of the same temperature was emulsified in the melt under constant conditions. The w/o emulsion was stirred mechanically until cooling down. The second step of emulsification was performed at room tempe—rature. Emulsions stabilized by gelatine were prepared in the above—mentioned manner.

As indicator substance ephedrine hydrochloride of 1 % wt was dissolved in the water phase of w/o emulsion for controlling the efficiency of formation and stability. The amount of chloride ion appearing in the external water phase was measured by a OP—CI—0711 P chloride selective membrane electrode, using a calibration curve. From the amount of chloride ion measured immediately after preparation the amount of formed w/o/w emulsion was determined. From the values measured after given storage time the decrease of the amount of multiple—phase emulsions and their stability we estimated.

Viscosity or emulsions were measured by Rheotest—2 rotary viscosimeter at 298 ± 1 K. Besides observation and measurement of spontaneous separation, the stability of the emulsion was determined by centrifuging for 10 minutes at a rate of 3000 rpm in centrfuge of Janetzki K—23 type.

Results and discussion

1.) The effect of geling by geletine on the properties and stability of w/o/w emulsions.

Our concept related to gelling of the internal water phase was to avoid the decrease and transformation of the multiple — phase character by preventing the uniting of the internal and external waters.
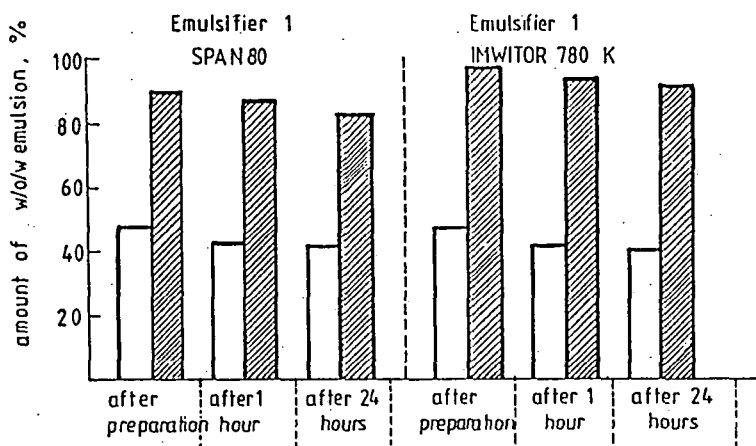

Figure 1: Stability of w/o/w emulsion without gelatine ☐ and with gelatine ▨ of 3 %.

Our hypothesis has been proved correct by Fig.1. Gelatine considerably increased the efficiency of formation of the multiple—phase emulsion and stabilized suitably the formed emulsion.

Many emulsifier of low HLB value were tested in our previous experiments to work out the first step of emulsification. The effect of the best two emulsifiers (Span 80 and Imwitor 780 K) are compared in Fig.1. Emulsifying features of Span 80 have been already known from the literature [5,6]. The excellent emulsifying capabvility of Imwitor 780 K (partial glyceride of isostearic acid, with a HLB value of 3,7) and its stabilizing effect exceeding that of Span 80 have been testified by our investigations.

Gelatine solutions of 1, 3, 4, 5 and 6 % wt were used as water phase in w/o/w emulsion to determine the optimal concentration of 1 % wt was a viscous sol, while the other systems became gelatinous ones after cooling. (it was found that gelatine concentration of 3 % wt was sufficient to stabilize effectively the multiple—phase character. In the case of systems with 4, 5 and 6 % wt gelatine concentration neither the efficiency of emulsification nor the stability of emulsions were greater (Fig.2).

Viscosity of emulsions was increased by gelatine to such an extent that the nearly ideal—viscous systems of low viscosity were transformed into structure—viscous ones (Table I).

Only data of emulsions of 24 hours are shown in Figs. 1 and 2. Investigation of multiple—phase character by means of ion—selective membrane was performed for a longer period (48 hours, 1 and 2 weeks and 1 month). Data relating to these experiments have not been published because of the instability of systems after 48 hours or 1 week. This instability became visible as separation and creaming of emulsions, respectively. This phenomenon was scarcely distinguishable but it became significant after 1 month. The multiple—phase emulsion separated into a concentrated multiple—phase emulsion (in which the multiple—phase character slightly decreased compared to the value after preparation) and water. Our investigations on the stability of distribution and the rate of separation have already been published

Table I

Rheological character and equilibrium viscosity of multiple–phase
emulsion stabilized by gelatine

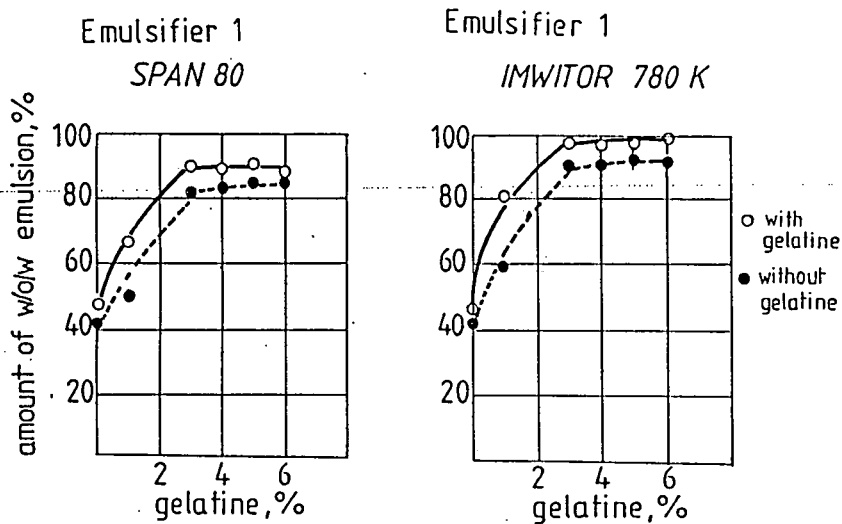| Emulsifying agent	Gelatine %	Rheological Character	Equilibrium viscosity (mPa.s)
Span 80	0	idealviscous	4,3
	3	structurviscous	11,5
	4	structurviscous	18,5
	5	structurviscous	34,9
	6	structurviscous	40,8
Imwitor 780 K	0	idealviscous	5,7
	3	structurviscous	19,5
	4	structurviscous	16,4
	5	structurviscous	12,5
	6	structurviscous	13,5

Figure 2: Effect of gelatine on the formation and stability of multiple–phase emulsion

elsewhere [10].

It can be concluded that the gelling of water phase ensures the stability of the multiple—phase character but not that of the distribution.

2.) The increase of viscosity of the oil phase by solid emulsifiers of low HLB value.

Our other effort for stabilization was the use of solid, gel forming emulsifiers in the first step of emulsification. In the basis of our previous experiments of centri—fuging, cetyl stearil alcohol, glycerol monostearate, Span 40 and 60 were chosen (Table II).

Table II

Macroscopic changes after centrifuging

Solid emulsifier g/100g emulsion	10	12	14	16	18	20
Cetyl stearyl alcohol	Oo	Oo	Oo	Oo	●	●
Cetyl stearyl alcohol + Span 20	Ooo	Oo	Oo	Oo	Oo	●
Glycerol monostearate	Ooo	Oo	Oo	Oo	●	●
Glycerol monostearate + Span 20	Ooo	Oo	Oo	●	●	●
Lanalcol	Ooo	Ooo	Ooo	Oo	Oo	Oo
Lanalcol + Span 20	Oo	Oo	Oo	Oo	Oo	Oo
Span 40 + Span 20	Oo	Oo	Oo	Oo	Oo	●
Span 60	Oo	Oo	Oo	Oo	●	●
Span 60 + Span 20	Oo	Oo	Oo	Oo	●	●
TEGIN	Ooo	Ooo	Oo	Oo	Oo	●

Ooo — three layers   Oo — two layers   ● — it remained stable

From the point of view of rheology these systems were thixotrope ones with yield point. Their equilibrium viscosity increases considerably with the amount of gel forming emulsifier (Fig. 3).
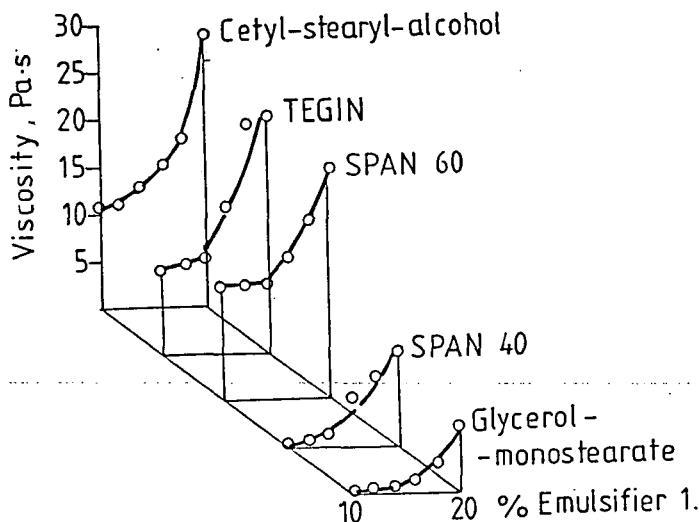

Figure 3: Connection between emulsifier concentration and equilibrium viscosity in w/o/w emulsion

Fig. 4. proves that multiple—phase emulsions can be effectively stabilized by solid emulsifiers mentioned above. Their multiple—phase character didn't change considera—bly after 72 hours. Where as in emulsions containing Span 80 this character decreased significantly during 72 hours. macroscopically these systems were stable, water or oil separation couldn't be observed even after several months following the preparation.

Since solid emulsifier of 20 % gave the character of fairly viscous or even high consistency to the system in several cases, it was abvisable to use these emulsifiers together with Span 20 liquid emulsifier in a concentration of 10–10 %.
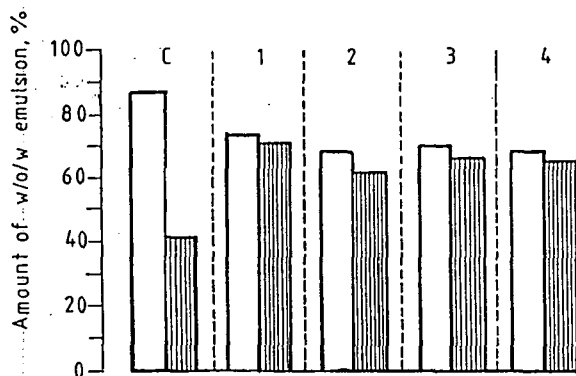
Figure 4:   Effect of gel forming emulsifier 1 on the stability of multiple phase emulsions (□ immediately after preparation, ▨ after 72 hours) C control (Span 80), 1 cetyl stearyl alcohol, 2 glycerol monostearate, 3 Span 40, 4 Span 60

Investigation of the formation of multiple—phase emulsions showed (Fig. 5) that almost each combination approached the efficiency of Span 20 — Span 80 combination. After 72 hours the multiple—phase character was unchanged in the case of cetyl stearyl alcohol — Span 20, Span 40 — Span 20 and glycerin monstearate — Span 20 systems, therefore these emulsifier mixtures have good proper stabiliziing effect. On the other hand, considerable decrease of multiple—phase character was observed in the case of Span 60 — Span 20 and Span 80 — Span 20 combinations. Explanation for this and for stabiliziing effect of different extent requires further investigations and
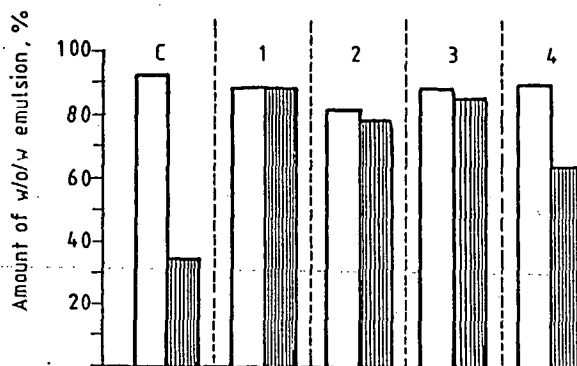
ditailed study of interfacial tenside film.

Figure 5: Conjugate effect of gel forming emulsifier and Span 20 on the stability of w/o/w emulsions (▢ immediately after preparation, ▥ after 72 hours) C control (Span 80), 1 cetyl stearyl alcohol, 2 glycerol monostearate, 3 Span 40, 4 Span 60

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