Influence of the emulsification processes on the size of the droplets and on the stability of the emulsified systems

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Abstract

The aims of this study were to compare two different processes to manufacture pharmaceutical emulsions (HLB Method and PIT Technique) on their stability and on the size of dispersed phase. The stability of the manufactured emulsions was determinated by measuring the evolution of the sizes of the internal emulsified phases. Optimal conditions (stirring rates, HLB values, temperatures, frequencies of the adding of the amounts of the aqueous phase) to manufacture the emulsification processes were also studied. The results provide evidence of the emulsification process to improve our understanding of the different parameters to influence the stability and size of the dispersed phase.

Introduction

Due to an increasing demand for the production of stable and cheap emulsion systems, the technological processes involved in the emulsification are being continuously enhanced. In order to obtain the ultimate drop size in an emulsion it is necessary to choose the right emulsification process and conditions. Stability is also very important for employment of emulsions for the novel drug delivery system. The stability of an emulsion depends on its composition and the size of the emulsion droplets. Typically the droplet size of conventional emulsions is larger than 1 μm. Depending on the preparation method different droplet size distribution might be achieved, explaining why the route of preparation can have an influence on the emulsion stability.
Direct emulsification requires large energy. The use of phase inversion can be considered as a possible mean getting cheaper emulsions. Phase inversion is the process whereby an oil-in water O/W emulsion inverts into water-in-oil W/O. There are two type of phase inversion. A "catastrophic" [1-4] inversion occurs when the inversion takes place because of a change of the volume fraction of the dispersed phase. A "transitional" [1-3] inversion occurs when there is a change in the surfactant affinity- by changing the salinity of the water phase, the hydrophilic-lipophilic balance (HLB) of the surfactant or the temperature. We use here two approaches: an empirical as in Griffin's HLB method [4] and an experimental measurement as in Shinoda's PIT method [5]. These are essentially physicochemical models that give a more or less appropriate description of the interface tendency to bend in one way or the other. A method based of changing the temperature of the system, forcing a transition from O/W emulsion at low temperature to W/O at higher temperature is referred to as PIT method [5]. Increasing of the temperature of O/W emulsions with polyoxyethylenated nonionics surfactant, makes the emulsions more hydrophobic and the emulsion may invert to W/O. The drops get to become the continuous phase, and what was the continuous phase becomes dispersed as drops. During cooling the system crosses and this promoting the formation of finely dispersed oil droplets.
In the present work, the preparation of O/W emulsions stabilized by one or a mixture of surfactants was studied. The influence of the preparation route, the effects of surfactant type, concentration, HLB, stirring rate, temperature on the stability and the size of dispersed phase were investigated.

Materials and methods

Materials

Montanox® 20, 40, 80 and Montane® 20, 40, 80 were obtained from Seppic (France). Vitamin E-TPGS was bought from Unipex (France). Miglyol 810®, Miglyol 812® (medium-chain triglyceride oil) and Miglyol 840® (medium chain digesters of propylene glycols) were a generous gift from Sasol Corp (Werk Witten, Germany).

Methods

1. The aqueous phase
The aqueous phase was composed of distilled water containing 0,5 % (w/w) of NaCl. NaCl was added into the aqueous phase in order to enhance the electrical conductivity.

2. The oily phase
Different oily phases (Miglyol 810, Miglyol 812 and Miglyol 840) having various hydrophilic/ lipophilic balances have been used.

3. The surfactants
The surfactant used singly was: Vitamin E-TPGS with a HLB value of 13 and Montanox 80 with a HLB value of 15. Three pairs of nonionics surfactants were used to prepare mixture with a range of HLB values. The first pair used was Montane 20/Montanox 20 which has respectively HLB values of 10, 14 or 16. The second pair was constituted of a mixture of Montane 40/Montanox 40 having a HLB value of 11 and the last was constituted of Montane 80 /Montanox 80 having respectively HLB values of 12 and 13.
Knowing the desirable HLB value of the surfactant mixture and HLB of the surfactants, the weight fractions of the corresponding surfactants were calculated by using the below formula:
$\mathbf{HLB_{Mixture} = f_A \cdot HLB_A + (1- f_{A)} \cdot HLB_B}$
where $\mathbf{f_A}$ - the weight fraction of surfactant A and $\mathbf{(1- f_A)}$ -the weight fraction of surfactant B
The concentration of surfactant/surfactant mixture in the emulsions was respectively 1, 5, 10, 15 and 20 % [w/w].

4. Emulsification-Emulsions O/W
Several O/W emulsions have been formulated and had the following compositions: 0, 5 % (by weight) of NaCl; 1, 5, 10, 15 or 20 % [w/w] of surfactant/ surfactant mixture and the water to oil ratio was kept constant at 50:50 [w/w]. Each sample was prepared with a total mass of 200 g. The surfactants were mixed into the oil phase at 80 °C. The water (also at 80 °C) and oil phases were mixed with a homogenizer Heidolph IKA with a stirring rate of 100-500 rpm. Every 5 minutes, the amounts of the aqueous phase (in the quantity of 1, 5, 10 or 20 ml) were added to the oily phase. The samples were cooled by decreasing the water bath temperature with ice under moderate stirring at 150 rpm.

5. The determination of the phase inversion
The phase inversion was determined by measuring the conductivity. The conductivity measurements were carried out using a Knick Conductimeter (Model). The measurements were made at different temperatures rates between 25-80 °C.

6. The determination of the stability of the emulsions
The studies of stability of the O/W emulsions were realized at room temperature.

7. The determination of the size of the internal phase of the emulsions
The sizes of the internal phases of the O/W emulsion were determined by using an optical microscope (Zeiss, France).

Results and discussion

The emulsification was carried out directly in a glass beaker with a nominal volume of 300 ml. The temperature was first maintained at 20°C during 10 minutes and then was made to increase monotonically up to 80°C at a heating rate of 1°C/s. Upon increasing the temperature the system morphology changed distinctly. The rigour stirring was maintained. Optical microscope was used to determine the sizes of the dispersed drops. In most cases the drops do not have the same size.

1. The oily phase
The most stable emulsions were prepared by using Miglyol 840. The emulsions manufactured with Miglyol 810 and 812 had the worst stability.

2. The surfactants-stability and size of the dispersed phase of the emulsions

For the emulsions manufactured with oily phase consisted of Miglyol 840 the obtained results were the following:

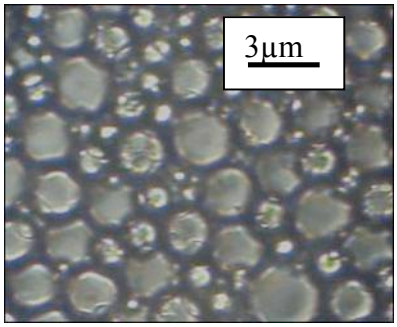

Fig.1: Emulsion manufactured with 15 % [w/w] of a surfactant mixture containing Montane 80/Montanox 80(HLB=12).

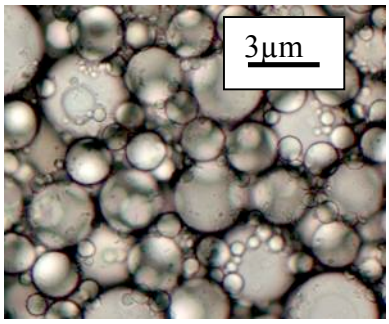

Fig.2: Emulsion manufactured with 20 % [w/w] of a surfactant mixture containing Montane 80/Montanox 80(HLB=12).

	Surfactant(s)	HLB	Results
1 trial	Montanox 80	15	
	1%		Stable 10 min
	5%		Stable 30 min
	10%		Stable 24 hours
	15%		Stable 48 hours
	20%		Stable 48 hours
2 trial	Vitamin E-TPGS	13	
	1%		Stable 15 min
	5%		Stable 5 hours
	10%		Stable 48 hours
	15%		Stable 48 hours
	20%		Jellified
3 trial	Montane/Montanox 20	10	
	1%		Stable 5 min
	5%		Stable 30 min
	10%		Stable 12 hours
	15%		Stable 12 hours
	20%		Stable 24 hours
4 trial	Montane/Montanox 20	14	
	1%		Stable 15 min
	5%		Stable 5 hours
	10%		Stable 8 hours
	15%		Stable 12 hours
	20%		Stable 18 hours
5 trial	Montane/Montanox 20	16	
	1%		Stable 5 min
	5%		Stable 2 hours
	10%		Stable 10 hours
	15%		Stable 12 hours
	20%		Stable 25 hours
6 trial	Montane/Montanox 40	11	
	1%		Stable 10 min
	5%		Stable 30 min
	10%		Stable 24 hours
	15%		Stable 48 hours
	20%		Stable 72 hours
7 trial	Montane/Montanox 80	12	
	1%		Stable 30 min
	5%		Stable 78 hours
	10%		Stable 4 days
	15%		Stable 6 days
	20%		Stable 12 days
8 trial	Montane/Montanox 80	13	
	1%		Stable 30 min
	5%		Stable 78 hours
	10%		Stable 24 hours
	15%		Stable 3 days
	20%		Stable 3 days

From these trials, it was concluded that the ideal surfactants to manufacture an emulsion for which the oily phase is Miglyol 840, must have a hydrophilic/lipophilic balance comprised between 11 and 13 and its concentration comprised between 15 and 20 % [w/w] in order to obtain an optimal stability.

3. Frequencies of the adding of the amounts of the aqueous phase

Every 5 minutes, the amounts of the aqueous phase (in the quantity of 1, 5, 10 or 20 ml) were added to the oily phase. The drop sizes were found to decrease when the rate of addition of component decreased. The best frequencies were: 1 and 5 ml/5 min.

4. Stirring rate

The stirring rate used for the manufacture of the emulsion was comprised between 100 and 2000 rpm. The most stable emulsions were obtained with a stirring rate of 1500 rpm. The influence of the stirring rate on the size of the droplets of the dispersed phase was important until 500 rpm. At this stirring rate, the sizes of droplets were the smallest (about 1µm). Above this stirring rate, no change was observed and the sizes stay similar.

5. The determination of the phase inversion

The inversion of the dispersed systems was monitored by electrical conductivity measurements. The initial O/W emulsion exhibits a high conductivity from 20°C up to 70°C. Just after 70°C the conductivity decreases into 100-200 µS/cm and at about 80°C this one was to ~ 0 µS/cm. The initial O/W emulsion was inverted in W/O emulsion. We can consider that phase inversion occurred at 70°C. By decreasing the temperature of this "inverted W/O emulsion", initial O/W emulsion was again obtained.

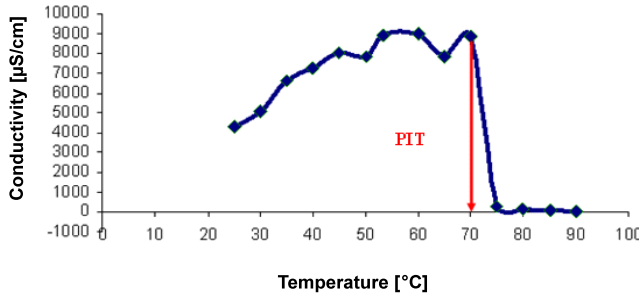

Fig.3: Conductivity variations as the temperature increases for one of emulsions O/W: 5 % [w/w] of surfactant mixture Montane80/Montanox 80 with HLB value of 12

Conclusion

The results demonstrated the importance of the way of emulsification on the droplet sizes distribution and on the emulsion stabilities. The frequencies of the adding of the amounts of the aqueous phase and the stirring rate influence the size of the droplets of the dispersed phase.
The amount of surfactant is very important too. The higher the surfactant concentration, the smaller the droplets that can be obtained. HLB of surfactant or surfactants mixtures influence the stability of the system. It must be accordant with the HLB of the oily phase in order to guarantee the best stability of the dispersed system.

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