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Nano-emulsion formulation using spontaneous emulsification: solvent, oil and surfactant optimisation

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Abstract

Nano-emulsions consist of fine oil-in-water dispersions, having droplets covering the size range of 100–600 nm. In the present work, nano-emulsions were prepared using the spontaneous emulsification mechanism which occurs when an organic phase and an aqueous phase are mixed. The organic phase is an homogeneous solution of oil, lipophilic surfactant and water–miscible solvent, the aqueous phase consists on hydrophilic surfactant and water. An experimental study of nano-emulsion process optimisation based on the required size distribution was performed in relation with the type of oil, surfactant and the water–miscible solvent. The results showed that the composition of the initial organic phase was of great importance for the spontaneous emulsification process, and so, for the physico-chemical properties of the obtained emulsions. First, oil viscosity and HLB surfactants were changed, α-tocopherol, the most viscous oil, gave the smallest droplets size (171 ± 2 nm), HLB required for the resulting oil-in-water emulsion was superior to 8. Second, the effect of water–solvent miscibility on the emulsification process was studied by decreasing acetone proportion in the organic phase. The solvent–acetone proportion leading to a fine nano-emulsion was fixed at 15/85% (v/v) with EtAc–acetone and 30/70% (v/v) with MEK–acetone mixture. To strength the choice of solvents, physical characteristics were compared, in particular, the auto-inflammation temperature and the flash point. This phase of emulsion optimisation represents an important step in the process of polymeric nanocapsules preparation using nanoprecipitation or interfacial polycondensation combined with spontaneous emulsification technique.

Keywords: Spontaneous emulsification; Emulsions; Formulation and optimisation

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1. Introduction

Nano-emulsions are fine oil-in-water dispersions, having droplet covering the size range of 100–600 nm (Nakajima et al., 1993; Nakajima, 1997). Nano-emulsions are also referred to as mini-emulsions (Ugelstadt et al., 1973; El-Aasser et al., 1988). Unlike microemulsions (which are also transparent or translu-

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cent and thermodynamically stable) nano-emulsions are only kinetically stable. However, the long-term physical stability of nano-emulsions (with no apparent flocculation or coalescence) makes them unique and they are sometimes referred to as "approaching thermodynamic stability" (Tadros et al., 2004; Girard et al., 1997).

The attraction of nano-emulsions for application in personal care and cosmetics as well as in health care is due to the following advantages:

(1) Unlike microemulsions (which require a high surfactant concentration, usually about 20% and higher), nano-emulsions can be prepared using lower surfactant concentration, a surfactant concentration comprised between 3–10% may be enough.
(2) The small size of the droplets for cutaneous use allows them to deposit uniformly on skin.
(3) Nano-emulsions are suitable for efficient delivery of active ingredients through the skin (Sonneville-Aubrun et al., 2004). The large surface area of the emulsion system, the low surface tension of the whole system and the low interfacial tension of the O/W droplets allow enhancing penetration of actives agents.
(4) Due to their small size, nano-emulsions can penetrate through the "rough" skin surface and this enhances penetration of actives.
(5) The fluidity nature of the system (at low oil concentrations) as well as the absence of any thickeners may give them a pleasant aesthetic character and skin feel.
(6) Nano-emulsions can be applied for delivery of fragrants, which may be incorporated in many personal care products. This could also be applied in perfumes, which are desirable to be formulated alcohol free.
(7) Nano-emulsions may be applied as a substitute for liposomes and vesicles (which are much less stable) and it is possible in some cases to build lamellar liquid crystalline phases around the nano-emulsion droplets.
(8) Nano-emulsions constitutes the primary step in nanocapsules and nanospheres synthesis using nanoprecipitation (Fessi et al., 1986, 1989, 1992) and the interfacial polycondensation combined with spontaneous emulsification (Bouchemal et al., 2004; Montasser et al., 2001). These two techniques require the spontaneous emulsification step in the same optimised conditions.

The droplets size and size distribution are depending on the spontaneity of emulsification (Gopal, 1968; Becher, 1983; Shahizdadeh et al., 1999). The spontaneity of the emulsification is poorly defined, since it should account not only for the rate of the emulsification process, but also for the volume and the particle size distribution of the produced emulsion. The spontaneity of the emulsification process depends mainly on the following variables: interfacial tension, interfacial and bulk viscosity, phase transition region and surfactant structure and concentration (Lopes-Montilla et al., 2002; Davies and Rideal, 1961; Aveyard et al., 1986; Miller, 1988; Miller and Raney, 1993; Miller, 1996; Hackett and Miller, 1988; Davies and Haydon, 1957).

Spontaneous emulsification is produced by different mechanisms which seem to be affected by the systems compositions and their physicochemical characteristics (Lopes-Montilla et al., 2002). In this paper, the influence of the physical properties of oils and of the surfactant nature on the emulsion size distribution was first studied. Once the oil and the surfactant optimised, the effect of water–solvent miscibility on the emulsification process was studied by changing acetone proportion in the organic phase.

2. Methods and materials

2.1. Materials

Solvents such as ethanol, acetone, tetrahydrofuran (THF), methyl ethyl ketone (MEK), methyl acetate (MeAc) and ethyl acetate (EtAc) were obtained from Sigma–Aldrich chemicals.

Oils such as caprylic/capric triglycerides (Miglyol® 812, Myritol® 318) were supplied by CONDEA-France, α-tocopherol and hexyl laurate were obtained from COLETICA (France).

Surfactants (Span® 80, Span® 85, Tween® 20, Tween® 80, Pluronic® F68) were supplied by SEPPIC (France). Lipoid® S75 was obtained from Lipoid GmbH Ludwigshafen-Germany.

Table 1
Nano-emulsion constituents proportions % (w/w) using the spontaneous emulsification process before and after solvent evaporation

Compound	Before evaporation (% (w/w))	After solvent evaporation (% (w/w))
Lipophilic surfactant	0.06	0.18
Hydrophilic surfactant	0.113	0.33
Oil	0.33	1
Water	66.50	98.49
Water–miscible solvent	33.00	ppm

2.2. *Preparation of nano-emulsions*

The methodology for obtaining emulsions by spontaneous emulsification presents three steps.

- Preparation of the homogeneous organic solution (S_1) composed of oil (400 mg of Miglyol® 812, Myritol® 318, hexyl laurate or α-tocopherol) and a lipophilic surfactant (86 mg of Span® 80, Span® 85, or Lipoid® S75) in water–miscible solvent (40 ml) (Table 1). The homogeneous aqueous phase (S_2) was formed by water (80 ml), and hydrophilic surfactant (136 mg of Tween® 20, Tween® 80 or Pluronic® F68).
- The organic phase was injected in the aqueous phase under magnetic stirring: the o/w emulsion was formed instantaneously by diffusion of the organic solvent in the external aqueous phase leading to the formation of nanodroplets. The magnetic stirring was maintained during 30 min to let the system reach equilibrium.
- The totality of the water–miscible solvent was removed by evaporation during 45 min under reduced pressure. Nanodroplets of oil were dispersed in an aqueous solution of water and hydrophilic surfactant.

2.3. *Optimisation of the oil, surfactant and water–miscible solvents*

All experiments concerning the optimisation of the emulsion formation were performed at 25 °C.

2.3.1. *Oil optimisation*

The influence of the oil nature on the emulsion size was studied using different kinds of oil in the organic phase (Miglyol® 812, Myritol® 318, hexyl laurate or α-tocopherol). Other components were fixed: (Span® 85/Tween® 20) as surfactants and acetone as water–miscible solvent.

2.3.2. *Surfactant optimisation*

In order to determine the required HLB of the emulsion, the organic phase containing Miglyol(r) 812, acetone and lipophilic surfactant was injected in the homogeneous solution of water and hydrophilic surfactant. The couples of surfactant used were (Lipoid® S75/Pluronic® F68), (Span® 80/Tween® 80) and (Span® 85/Tween® 20) at proportions indicated in Section 2.2.

2.3.3. *Solvent optimisation*

Once the oil and the surfactant optimised, the size distribution of the emulsion obtained using various solvents mixtures were studied. The list of solvents which are totally or partially miscible with water was selected on the European Pharmacopoeia (4th edition, 2002). There is a wide variety of solvents used in pharmaceutical processing. These solvents have been classified according to their toxicity on three classes:

- Class I: Solvents to be avoided.
- Class II: Solvents to be limited.
- Class III: Solvents with low toxic potential.

For safety reasons, solvents of the Class III were chosen in the process of spontaneous emulsification. Table 2 gives the list of Class III solvents listed in the European Pharmacopoeia (4th ed., 2002) which are totally or partially miscible with water.

2.4. *Droplets size distribution measurements*

The droplets size distribution, one of the most important physical characteristics of a nano-emulsion, was measured by a diffusion method using a light-scattering particle size analyzer Coulter LS 230 (Beckman Coulter, Coultronics France). The LS 230 measures the size distribution using the diffusion of laser light by particles.

Information about droplets smaller than 600 nm is limited in diffraction pattern, so another technique is used. Thus, the LS 230 includes another measurement assembly, called polarization intensity differential scattering (PIDS). The PIDS assembly consists of an incandescent light source and polarizing filters, a PIDS

Table 2
Water miscibility of Class III solvents according to the European Pharmacopoeia (fourth ed., 2002) and to the Handbook of Chemistry and Physics (74th ed., 1993–1994)

Solvents	Water miscibility
Acetone	Miscible
Ethanol	Miscible
Tetrahydrofuran	Very soluble
Methyl ethyl ketone	Very soluble
Methyl acetate	Very soluble
Ethyl acetate	Partially miscible
Isopropyl acetate	Partially miscible

sample cell and an additional seven photodiode detectors (six to measure scattered light plus one to monitor the beam strength). To measure the droplets size distribution, 0.5 ml emulsion was introduced in the measure compartment (125 ml of water). The results were presented as the volume distribution ($n = 3$).

2.5. Microscopic observations

Morphology and structure of the emulsions were studied using the transmission electron microscopy (TEM) TOPCON 002B operating at 200 kV and of a 0.18 nm capable point-to-point resolution. Combination of bright field (BF) imaging at increasing magnification and of diffraction modes was used to reveal the form and size of the emulsions and to determine the amorphous or crystalline character of their components.

In order to perform the TEM observations, the concentrated emulsion was first diluted in water (1/10), a drop of the diluted emulsion was then directly deposited on the holey film grid and observed after drying. The emulsion appears dark and the surroundings are bright, a "positive" image is seen. The direct observation also enabled us to perform selected area electron diffraction (SAED) to check the crystallinity of the emulsion core components (Guinebretière et al., 2002; Louchet et al., 1988).

3. Results and discussion

3.1. Oil optimisation

3.1.1. α-Tocopherol

The mean size of nano-emulsion obtained from [α-tocopherol/acetone/(Span® 85/Tween® 20)] system before and after evaporation was determined. The mean size of the nano-emulsions was (163 ± 2 nm) before acetone evaporation, this size increased slightly after acetone evaporation (171 ± 2 nm), this increase can not be considered as significant in view of the system accuracy. Microscopic observations showed the presence of spherical drops (Figs. 1 and 2). The mean size calculated from 94 drops measurement was estimated at 180 nm, in agreement with granulometric analysis.

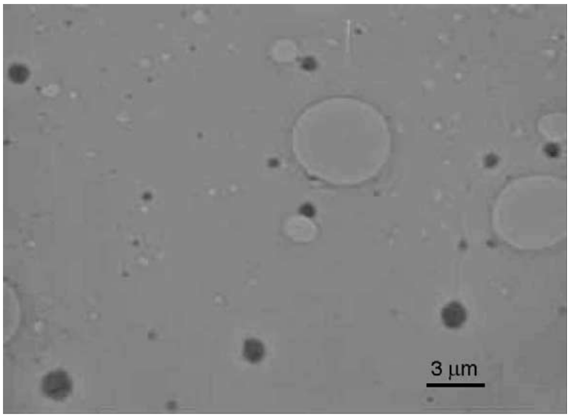

Fig. 1. TEM picture characteristic of emulsion drops obtained using α-tocopherol after acetone evaporation.

These pictures show clearly the existence of solid phase in the core of the emulsion drop (Fig. 2A and B). This could be explained by the fact that the oil-in-nano-emulsion core may crystallise during samples preparation before microscopic observations (high vacuum).

3.1.2. Caprylic/capric triglycerides (Myritol® 318, Miglyol® 812) and hexyl laurate

The nano-emulsion was examined by the naked eye and the presence of aggregates or impurities was not detected even after several weeks of storage. The granulometric analysis of the emulsions based on Myritol® 318 and Miglyol® 812, showed two populations of drops; a population of nano-drops with a mean size of 320 ± 26, 310 ± 14 nm, and a population of micro-drops with a mean size of 1986 ± 70, 1986 ± 7 nm, respectively.

Fig. 3 shows that the mean size emulsions prepared with various oils increased considerably after solvent evaporation (acetone) except for α-tocopherol based

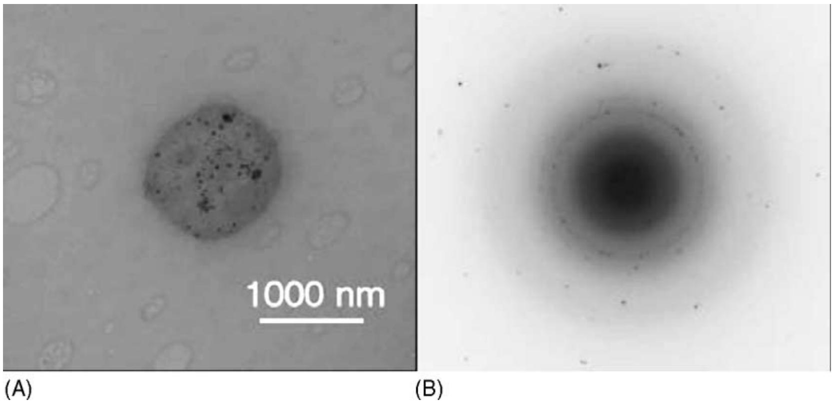

Fig. 2. TEM and selected area electron diffraction (SAED) pictures of spherical drop of α-tocopherol with a beginning of crystallization.

nano-emulsion. This increase of emulsion drops mean size after evaporation is probably due to the agglomeration of the small droplets, caused by the evaporation of acetone present in the external phase.

There is a wide difference in the average size of the emulsion drops according to the nature of the oil used. It is clear that α-tocopherol (171 ± 2 nm) and hexyl laurate (335 ± 37 nm) gave better results than Myritol® 318 and Miglyol® 812 according to the objectives of a mean size smaller than 600 nm. Pal researches (1998) reveal that drops size emulsion decreased when emulsion viscosity increased, these observations are in agreement with our results; α-tocopherol, the most viscous oil, gave the smaller drops size (171 ± 2 nm). Myritol® 312 and Miglyol® 812 have the same viscosity (27–33 mPa s at 20 °C) (Table 3); the size distributions were closely similar.

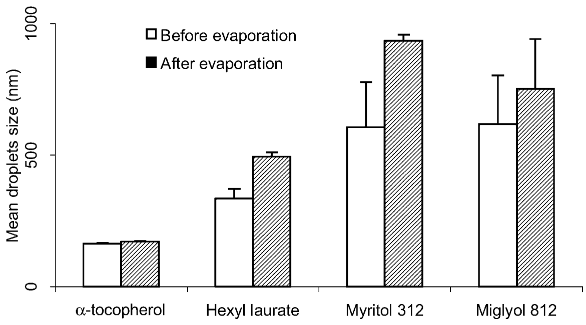

Fig. 3. Comparative study between the average sizes of the emulsions using different oils before and after solvent evaporation (acetone).

Nevertheless the high viscosity of oil is not a sufficient condition to obtain emulsions with small drops size, since hexyl laurate presents the lower viscosity (4.5–7.5 mPa s at 20 °C) and allowed to obtain nano-emulsion with a small mean size (310 ± 14 nm).

3.2. *Choice of surfactants*

As described above, nano-emulsions were stabilized by a combination of two surfactants. Table 4 shows the hydrophilic–lipophilic balance (HLB) of the system calculated according to Eq. (1). All surfactants cited in the literature have theoretical values of HLB from 1 to approximately 50 (Griffin, 1954). The more hydrophilic emulsifiers have HLB values greater than 10, while the more lipophilic emulsifiers have HLB values from 1 to 10.

$$\mathrm{HLB} = \frac{(X_{\mathrm{a}}\mathrm{HLB_a}) + (X_{\mathrm{b}}\mathrm{HLB_b})}{X_{\mathrm{a}} + X_{\mathrm{b}}} X_{\mathrm{a}} = \frac{m_{\mathrm{a}}}{m_{\mathrm{a}} + m_{\mathrm{b}}} X_{\mathrm{b}} = \frac{m_{\mathrm{b}}}{m_{\mathrm{a}} + m_{\mathrm{b}}} \qquad (1)$$

Table 3
Density and viscosity of α-tocopherol, hexyl laurate, Myritol® 312 and Miglyol® 812

	Density at 20 °C (g m^3)	Viscosity at 20 °C (mPa s)
α-Tocopherol	0.940–0.960	3000–4500
Hexyl laurate	0.840–0.850	4.5–7.5
Myritol® 312	0.945–0.949	27–33
Miglyol® 812	0.950	27–33

Table 4
Results from studies of surfactant influence on the average size of Miglyol® 812 based emulsions after evaporation of acetone

Formulation	Liposoluble surfactant	HLB_a at 25 °C	Hydrosoluble surfactant	HLB_b at 25 °C	HLB system at 25 °C	Droplets size (nm)
1	Lipoïd® S75	7	Pluronic® F68	29	21.23	124 ± 46
2	Span® 80	4.3	Tween® 80	15	11.03	516 ± 71
3	Span® 85	1.8	Tween® 20	16	10.98	725 ± 198

$m_a = 80$ mg for 40 ml of organic phase; $m_b = 136$ mg for 80 ml of aqueous phase; X_a and X_b represent the weight proportions of lipophilic and hydrophilic surfactant, respectively. m_a and m_b representing the weight of lipophilic and hydrophilic surfactant, respectively, were determined according to a previous study (Montasser, 1999).

It is clear that nano-emulsion size varied widely according to the surfactant system (124 ± 46 nm) with (lipoïd® S75/pluronic® F68), (516 ± 71 nm) with (span® 80/Tween® 80) and (725 ± 198 nm) obtained using (span® 85/Tween® 20). The mean particle size decreased when the HLB value of the system increased as expected with an o/w emulsion (Table 4).

Our results are in agreement with Bru (1998) and Seijo (1990) which observed a particle size decrease using Pluronic® F68 and Tween® 80 as hydrophilic surfactants. Pluronic® F68 contributes to reduce the particle size: Frisbee and McGinity (1994) demonstrated that the use of Pluronic® F68 as the emulsifying agent produced the smallest size of nano-emulsion (Frisbee and McGinity, 1994). Furthermore, Seijo et al. (1990) concluded that the concentration of Pluronic® F68 is able to influence greatly the size distribution profile of the obtained submicronic dispersions (nano-emulsions or nanoparticles) (Guinebretière, 2001; Bru et al., 1998; Seijo et al., 1990).

3.3. Solvent optimisation

The purpose of this part of the study was to determine a solvent or a mixture of solvents allowing the formation of a nano-emulsion with particle size less than 600 nm. Solvent optimisation is a very interesting step applicable to emulsion preparation by spontaneous emulsification for pharmaceutics and cosmetics uses.

3.4. Ethanol and acetone

The nano-emulsions obtained using acetone or ethanol presented homogeneous aspect without aggregates or phase separation. The mean size diameter was around 171 ± 2 and 195 ± 5 nm, respectively (Figs. 4 and 5).

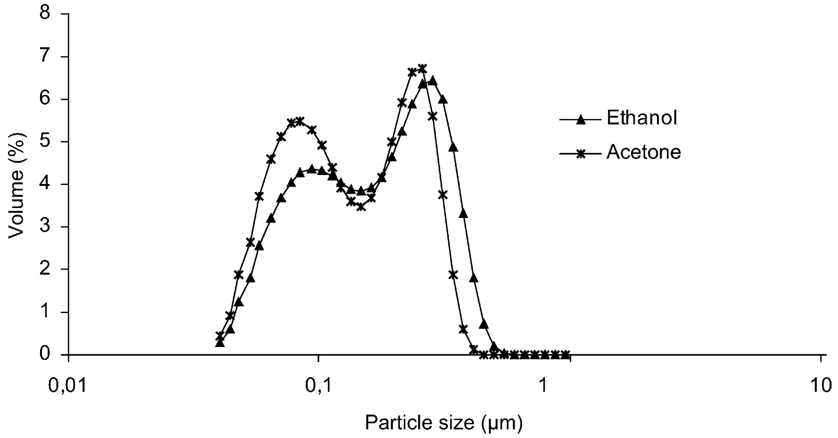

Fig. 4. Particle size distribution of emulsion obtained using acetone and ethanol as solvent.

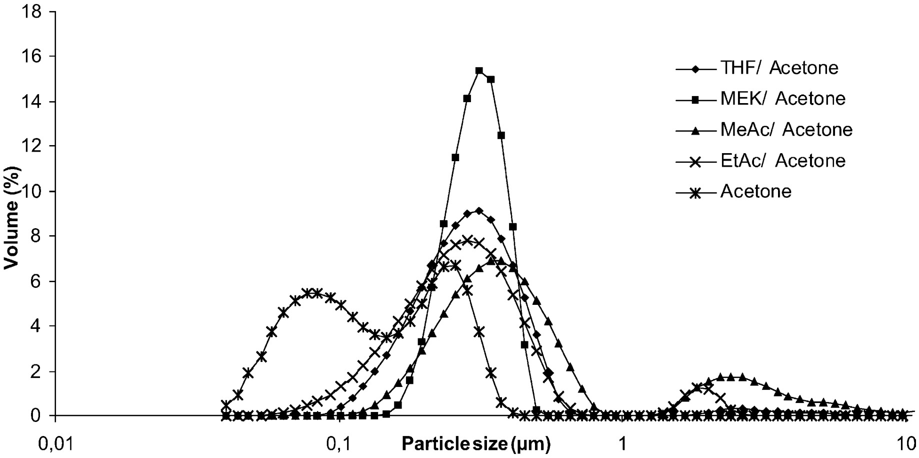

Fig. 5. Results from nano-emulsion size distribution using solvent–acetone mixture at 15/85%.

In spite of the fine droplets size, size distribution and stability of nano-emulsions obtained using ethanol, this solvent is not acceptable because it creates a secondary reaction between alcohol compounds (–OH) and different monomers (acid dichloride –CO–Cl or diisocyanates –N=C=O) used for nanocapsules synthesis during interfacial polycondensation (Montasser et al., 2001; Bouchemal et al., 2004). The solvent used must be inert and applicable to all techniques; for this reason, we selected other solvents.

The principal property required for the solvent used in spontaneous emulsification, is the quasi-total miscibility with of the continuous phase (water). Considering only this point, acetone is the most appropriate solvent; however, the high inflammability could limit its industrial use. For this reason we studied the effect of the acetone substitution with other solvents or mixture of solvents.

3.4.1. Mixtures of solvents at 15/85% (v/v): THF–acetone, ethyl acetate–acetone, MEK–acetone and methyl acetate–acetone

Five formulations were prepared using acetone: THF–acetone, ethyl acetate–acetone, MEK–acetone and methyl acetate–acetone at 15/85% (v/v).

Particle size distributions were evaluated by granulometric analysis. Emulsions obtained using MEK–acetone and ethyl acetate–acetone appeared through necked eye examination as the most stable without phase separation compared with those obtained from other solvent mixtures. So, we tried to decrease the acetone volume in these two mixtures of solvents in order to determine the minimum volume possible to obtain droplets with mean diameter <600 nm.

3.4.2. ethyl acetate–acetone mixture with different proportions: 20/80, 15/85 and 10/90% (v/v)

Nano-emulsions size distributions after solvent evaporation are presented on Fig. 6. Nano-emulsions obtained using ethyl acetate–acetone mixtures at three different proportions of each solvent presented two populations of drops, a population of nano-drops and a population of micro-drops, the proportion of the last one increasing with ethyl acetate amount increase, 15% (v/v) represents the highest proportion of ethyl acetate acceptable in the organic solvent mixture. The measured mean size was 505 ± 82 nm, this relatively high value is due to the existence of the second population of micrometric drops 1908 ± 21 nm. Nevertheless, the two populations of drops could eventually be separated using filtration.

As represented in Fig. 7, the solvent evaporation did not have any influence on the mean size of emulsion made with (Ethyl acetate/ acetone) mixtures.

3.4.3. MEK–acetone at 50/50, 40/60 and 30/70% (v/v)

Three MEK–acetone mixtures were prepared with varying MEK–acetone proportions: 30/70, 40/60 and 50/50% (v/v).

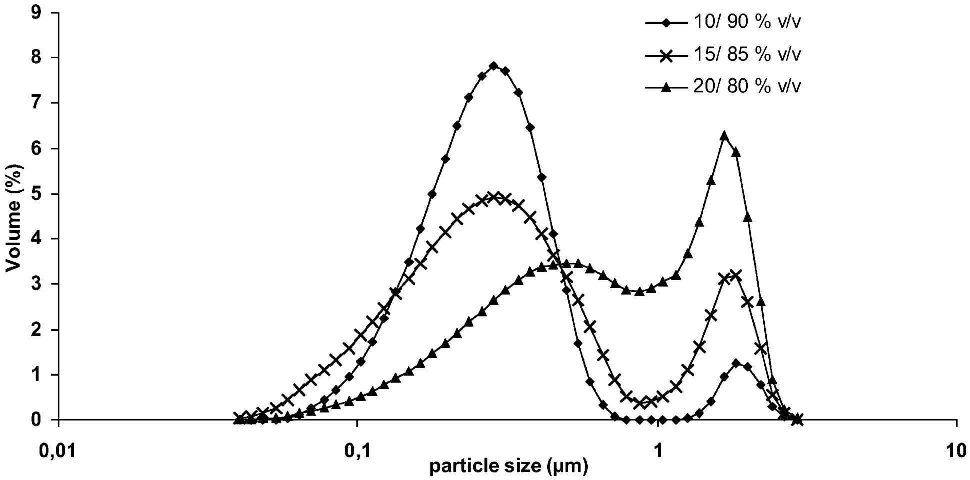

Fig. 6. Comparative study of nano-emulsions particle size distribution after evaporation of ethyl acetate–acetone mixture at different proportions: 10/90, 15/85 and 20/80% (v/v).

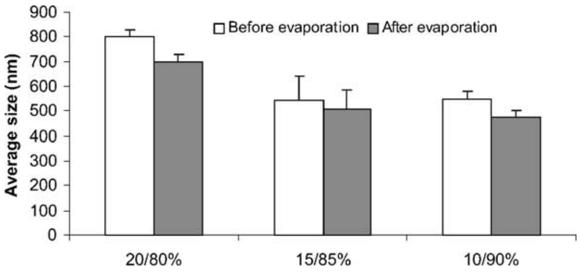

Fig. 7. Effect of the solvent evaporation on the mean size of emulsion obtained with different ethyl acetate–acetone mixtures: 20/80, 15/85 and 10/90% (v/v).

Using MEK–acetone at 50/50% (v/v) and 40/60% (v/v), unstable nano-emulsions (phase separation) were obtained even few minutes after their preparation. MEK–acetone at 30/70% (v/v) represented the limit to obtain nano-emulsions with particle size <600 nm. Methyl ethyl ketone allowed to decrease the acetone volume from 100 to 70% (v/v), and led to nano-emulsion with monomodal distribution (Fig. 8). Again, the solvent evaporation had no influence on the size distribution.

The droplets size and size distribution are dependent on the emulsification process kinetic which

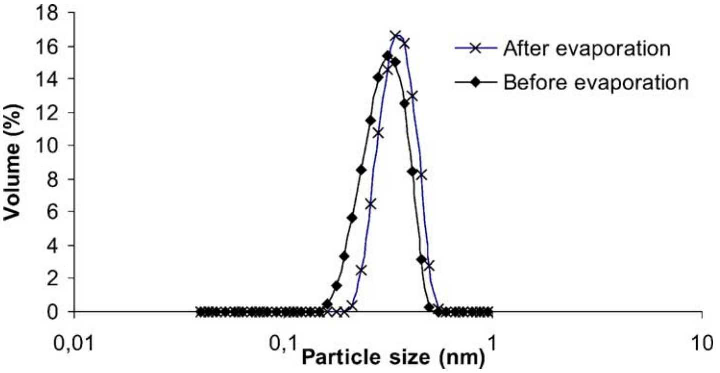

Fig. 8. Nano-emulsion granulometric analysis before and after evaporation of the solvent mixture (MEK–acetone) at 30/70% (v/v).

Table 5
Physico-chemical properties of organics solvents used

	Density (*D*20)	Boiling point (°C)	Water miscibility% (g/100 g of water at 20 °C)	Water miscibility% (V/100 V of water at 20°C)
Acetone	0.783	56.1	Total miscibility	Total miscibility
MEK	0.934	79.6	26.8	28.6
Ethyl acetate	0.902	77	8.7	9.6
Methyl acetate	0.805	56.9	24.5	30.4
THF	0.887	66	30	33.8

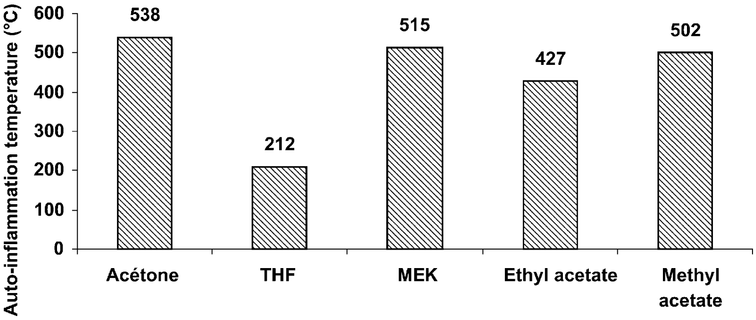

Fig. 9. Comparison of the auto-inflammation temperature of the different organic solvents.

depends mainly on the solubility of the organic solvent in water (Wehrle et al., 1995). As the concentration gradient between the aqueous and organic phase increases, the diffusion of solvent will be quicker and the drops formed smaller. The kinetics of spontaneous emulsification is most rapid when the miscibility between the organic phase and the aqueous phase is better. According to Table 5, ethyl acetate and MEK are miscible with water at 9.6 and 28.69% (v/v), respectively, experimental results shows that 15% of ethyl acetate and 30% of MEK represent the limits to obtain a water–miscible solvent mixture promoting the self-emulsification and leading to the formation of nano-emulsion with a low drop size.

To strength the choice of solvents, we compared their physical characteristics, and particularly the auto inflammation temperature (Fig. 9) and the flash point (Fig. 10).

The auto-inflammation temperature is the minimal temperature at which a compound ignites spontaneously without other provision of energy as flame or spark. The lower is this temperature; the most inflammable is the product. THF presents the highest risk of auto inflammation when heating.

Flash point is the lowest temperature at which a liquid can form an ignitable mixture in air near the surface of the liquid. The lower the flash point, the easier it is to ignite the material. The flash point is listed in °C in Fig. 10. MEK and ethyl acetate presents the lowest risk of ignition (−9 and −4.4 °C, respectively), unlike THF and acetone, which presents the most flammable solvents.

From all these considerations it should be concluded that MEK–acetone and ethyl acetate–acetone mixtures

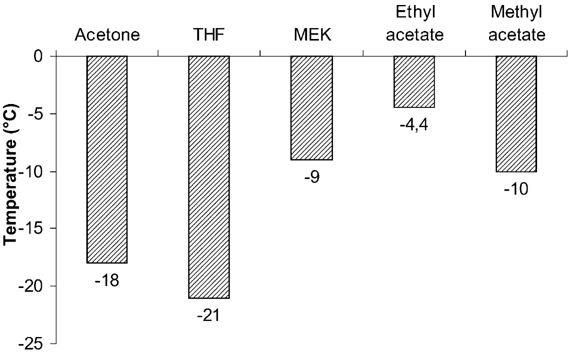

Fig. 10. Comparison of the flash point of the different organic solvents.

at 30/70 and 15/85% (v/v), respectively, present a good alternative to replace acetone in the preparation of nano-emulsions using spontaneous emulsification technique.

4. Conclusion

Owing to the potential of nano-emulsions in cosmetic products, an intensive study was performed in order to point out the role of physico-chemical properties of oils, surfactants and water–miscible solvent or mixture of solvents on nano-emulsion size distribution. The oil viscosity, the surfactant HLB and the solvent miscibility with water represent important parameters in determining the quality of the final nano-emulsions obtained by spontaneous emulsification process.

First, oil viscosity and HLB surfactants were changed, nano-emulsions smallest droplets size (171 ± 2 nm) were obtained using α-tocopherol, the most viscous oil, and the association of (Lipoïd® S75/Pluronic® F68) as surfactants. Second, acetone proportion in the organic phase was decreased using mixtures of solvents. Comparing the nano-emulsion size distributions and solvent physical properties (auto-inflammation temperature and the flash point), EtAc–acetone and MEK–acetone mixtures at 15/85 and 30/70% (v/v) were chosen as solvent mixtures to acetone replacement. This study of emulsion optimisation can be considered as an important step regarding the process of nanocapsules obtention using nanoprecipitation or interfacial polycondensation combined with spontaneous emulsification technique. Nanoparticles synthesis using one of these two techniques could be carried out in the same previous optimised conditions.

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