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Influence of cryogenic grinding on properties of a self-emulsifying formulation

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Abstract

Recently, self-emulsifying drug delivery systems (SEDDS) have been developed as a method to deliver lipophilic drugs. Gelucire® 44/14 is an excipient, from the lauroyl macrogolglycerides family, producing a fine oil-in-water emulsion when introduced into an aqueous phase under gentle agitation as SEDDS, improving thereby solubility of poorly water-soluble drugs and their bioavailability. The aims of this study were to process Gelucire® 44/14 into a powder by cryogenic grinding to produce solid oral dosage forms and to investigate influence of this process on different properties of a formulation made of Gelucire® 44/14 and ketoprofen (90/10). Cryogenic grinding produced Gelucire® 44/14 in a powder form and this process did not change its physical properties, emulsification capacities and dissolution performances of the formulation tested. However, interactions took place between ketoprofen and Gelucire® 44/14 with a decrease of the melting peak and a reduction of the droplet size of the formed emulsion. The influence of drug–Gelucire® 44/14 interactions must be investigated case by case in any formulations.

Keywords: Lipid formulations; Self-emulsifying systems; Gelucire® 44/14; Ketoprofen; Bioavailability; Cryogenic grinding

1. Introduction

Many new drug candidates exhibit low oral bioavailability due to their poor aqueous solubility. To overcome this problem, various formulation strategies are reported, including salt formation, complexation with cyclodextrins, micronization, solid dispersions and lipid-based formulations (Humberstone and Charman, 1997; Kim and Ku, 2000).

Recently, self-emulsifying drug delivery systems (SEDDS) have been developed as a method to deliver lipophilic drugs. SEDDS are described as mixtures of oil, surfactant, cosurfactant and drug. They form fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation (Pouton, 2000). Such mixtures are expected to self-emulsify quickly in the aqueous media of stomach, the digestive motility providing the agitation required for emulsification. Several mixtures of oils (long- and medium-chain triglycerides), non-ionic surfactants with relatively high hydrophilic–lipophilic balance (HLB) and suitable solubilizing agents have been used

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to produce self-emulsifying systems (Constantinides, 1995). However, only specific combinations led to efficient self-emulsifying systems and each case is an intricate problem (Halbaut et al., 1996; Pouton, 1997).

An alternative to this complex formulation could be the development of self-emulsifying excipient, ready for use—i.e. an all-in-one formulation—as lauroyl macrogolglycerides (e.g.: Gelucire® 44/14 from Gattefossé, St Priest, France).

Gelucire® 44/14 has been already been used to improve the solubility of poorly water-soluble drugs, thereby enhancing their bioavailability (Pillay and Fassihi, 1999; Hülsmann et al., 2000).

Therefore, taking into account its low melting point (44 °C) and complex composition, Gelucire® 44/14 must be melted before using, then mixed with drug under a sufficient temperature and capsules filled with the molten mixture (Hülsmann et al., 2000). Only semi-solid oral dosage forms could be obtained.

An interesting approach to improve handling of this excipient is to process Gelucire® 44/14 into a powder to produce solid dosage forms as pellets, tablets and hard capsules (Newton et al., 2001).

Grinding is regularly used in the pharmaceutical industry to reduce particle size but it generates heat, sound and vibrational energy (Crowley and Zografi, 2002). It must be performed at a temperature below the melting temperature. Cryogenic grinding is chosen because it is a process carried out at low temperature with frozen samples, used for different biological materials (plants, animal tissues) and unstable compounds (vitamins, volatile substances, etc.) (Kamogawa et al., 2001). However, grinding induces disorder: mechanical activation and generation of energy can lead to physical and chemical changes in crystalline solid which can affect its efficacy (Crowley and Zografi, 2002).

The aims of this study are to investigate the influence of cryogenic grinding process on different properties of a self-emulsifying formulation made of Gelucire® 44/14 and ketoprofen as model drug. This work is specially focused on physical characterizations of formulations manufactured without or with cryogenic grinding and on emulsification properties with their effects on dissolution enhancement.

2. Materials and methods

2.1. Materials

Gelucire® 44/14 conforms to the European Pharmacopoeia 4th Edition, "Lauroyl Macrogolglycerides" monograph (Gattefossé, batch number = 26362). It consists of mono-, di- and triglycerides (20%), mono- and di-fatty acid esters of polyethylene glycol (72%) and of free polyethylene glycol 1500 (8%). The fatty acid distribution of this excipient is shown in Table 1.

Gelucire® 44/14, with a drop point of 44 °C and an HLB value of 14, is an inert semi-solid waxy material with amphiphilic properties. It is a Generally Recognized As Safe (GRAS) compound.

Ketoprofen (Nordic Synthesis, Sochibo Francochim, batch number = 18112167) was chosen as drug model due to its poor water solubility (1 g in more than 10 L, at 20 °C). It is a weak acid with a $pK_a = 4.55$ and a melting point of 94.5 °C (Vergote et al., 2001).

2.2. Preparation of self-emulsifying formulations

Gelucire® 44/14 was melted in a microwave oven (200 W, 1 min). After stirring, it could be used in a liquid state.

Drug (ketoprofen) was added (10%) and dissolved in the molten excipient under stirring. Then, the formulation solidified by cooling at room temperature.

Formulation could be investigated just as it was or after cryogenic grinding.

Cryogenic grinding was performed using a cryogenic impact mill (Model 6750, SPEX CertiPrep). Sample (1 g) was inserted in a polycarbonate cylinder, immersed in liquid nitrogen in which a stainless steel rod was vibrated by means of a magnetic coil (10 Hz

Table 1
Fatty acid distribution of Gelucire® 44/14

Fatty acid distribution	Gelucire® 44/14 (%)
Caprylic acid (C8)	4–10
Capric acid (C10)	3–9
Lauric acid (C12)	40–50
Myristic acid (C14)	14–24
Palmitic acid (C16)	4–14
Stearic acid (C18)	5–15

for 2-min periods separated by 2-min cool down periods) (Crowley and Zografi, 2002). The powder obtained was stored at low temperature (−20 ± 2 °C) before using.

Thus, each method was applied on four formulations called: molten Gelucire® 44/14, cryogenic grinded Gelucire® 44/14, molten Gelucire® 44/14/ketoprofen mixture and cryogenic grinded Gelucire® 44/14/ketoprofen mixture.

2.3. Methods of physical characterization

Before evaluating self-emulsifying properties, it is clearly essential to have some considerations of the physical characteristics of these systems. These properties are correlated with the quality of produced product and have an effect upon stability and dissolution performance of solid dosage forms (Brittain, 1995).

2.3.1. Scanning electron microscopy (SEM)

Scanning electron micrographs were taken with a Jeol JSM-6400 F electron microscope to determine morphological parameters (size, shape and roughness) after nickel coating (5 kV, magnification 250× and 3000×). These parameters influence powder flow and compaction, processes always involved in the production of solid dosage forms.

2.3.2. Differential scanning calorimetry (DSC)

DSC is the most widely used method of thermal analysis to monitor endothermic processes (melting, solid–solid phase transitions and chemical degradation) as well as exothermic processes (crystallization and oxidative decomposition). It can be extremely useful in preformulation studies since it can indicate the existence of possible drug–excipient interactions in a formulation. In the DSC method, the sample and reference are kept at the same temperature and the heat flow required to maintain the equality in temperature is measured. 4–8 mg of the molten mixture or of cryogenic grinded powder was sealed in aluminum pan and analyzed using a differential scanning calorimeter (DSC 7, Perkin-Elmer) calibrated with azobenzol ($T_m = 68\,^\circ C$) and indium ($T_m = 156.6\,^\circ C$, $\Delta H_m = 26.6\,J\,g^{-1}$).

Thermal analysis was carried out, in triplicate ($n = 3$), between 0 and 100 °C at a heating rate of $10\,^\circ C\,min^{-1}$.

2.3.3. X-ray diffraction

This technique reveals the crystalline structure of sample. The powder pattern consists of a series of peak detected at various scattering angles providing a full crystallographic characterization of the product. Samples were exposed to Cu Kα radiation ($\lambda = 1.540596$ Å) in an X-ray diffractometer (CPS 120 INEL). The X-ray diffraction patterns were recorded automatically with increments of 0.05° 2θ up to 2 h.

2.4. Methods to evaluate self-emulsifying performances

As a final goal, self-emulsifying performances were investigated using different methods.

2.4.1. Visual observations

To assess the self-emulsification properties, formulation (1 g) containing 1% of hydrophilic (quinoline yellow) or lipophilic (butter yellow) dye instead of drug was introduced into 1000 mL of 37 °C water under a gentle agitation of 50 rpm in a rotating paddle dissolution apparatus (Erweka DT6).

Visual observations were noted in triplicate, such as dye dispersability of the formulation.

2.4.2. Emulsion droplet size analysis

Formulation (1 g) was diluted with purified water filtered through a 0.22 μm filter at 37 °C with a stirring rate of 50 rpm using a rotating paddle dissolution apparatus (Erweka DT6).

Emulsions were observed with an optical microscope under polarized light (Nikon Eclipse E600).

The droplet size distribution of the resultant emulsions after 30 min was determined by photon correlation spectroscopy using a PSS Nicomp 380 ZLS (PSS Nicomp, Santa Barbara, USA), able to measure sizes between 10 and 5000 nm. Photon correlation spectroscopy analyses the fluctuations in light scattering due to Brownian motion of particles. Light scattering was monitored at 37 °C, at a 90° angle and $\lambda = 632.8$ nm. Particle size distribution was expressed in volume.

2.4.3. Dissolution studies

In vitro dissolution studies were performed (in triplicate—$n = 3$) using the rotating paddle method

(Erweka DT6 apparatus) at 37.0 ± 0.5 °C and 50 rpm up to 90 min. Topfena Ge® 50 mg capsules (Ethypharm) were used as reference product (batch number = 00684).

Capsules were filled with self-emulsifying formulations (molten or cryogenic grinded formulations) (500 ± 50 mg) corresponding to 50 mg of ketoprofen.

The dissolution medium (1000 mL) was simulated gastric buffered solution (pH 1.2). Samples (3 ml) were withdrawn from the dissolution vessels at predetermined time intervals and assayed for ketoprofen with a spectrophotometer at 262 nm (Uvikon K930, Kontron Instruments).

Cumulated released amounts were plotted as a function of time. Time corresponding to 20, 50 and 90% ketoprofen release (T20, T50 and T90) were also calculated as dissolution specifications.

3. Results and discussion

3.1. Physical characterizations

3.1.1. Scanning electron microscopy pictures

Fig. 1 shows different electron micrographs of molten Gelucire® 44/14 (panel a) or cryogenic grinded

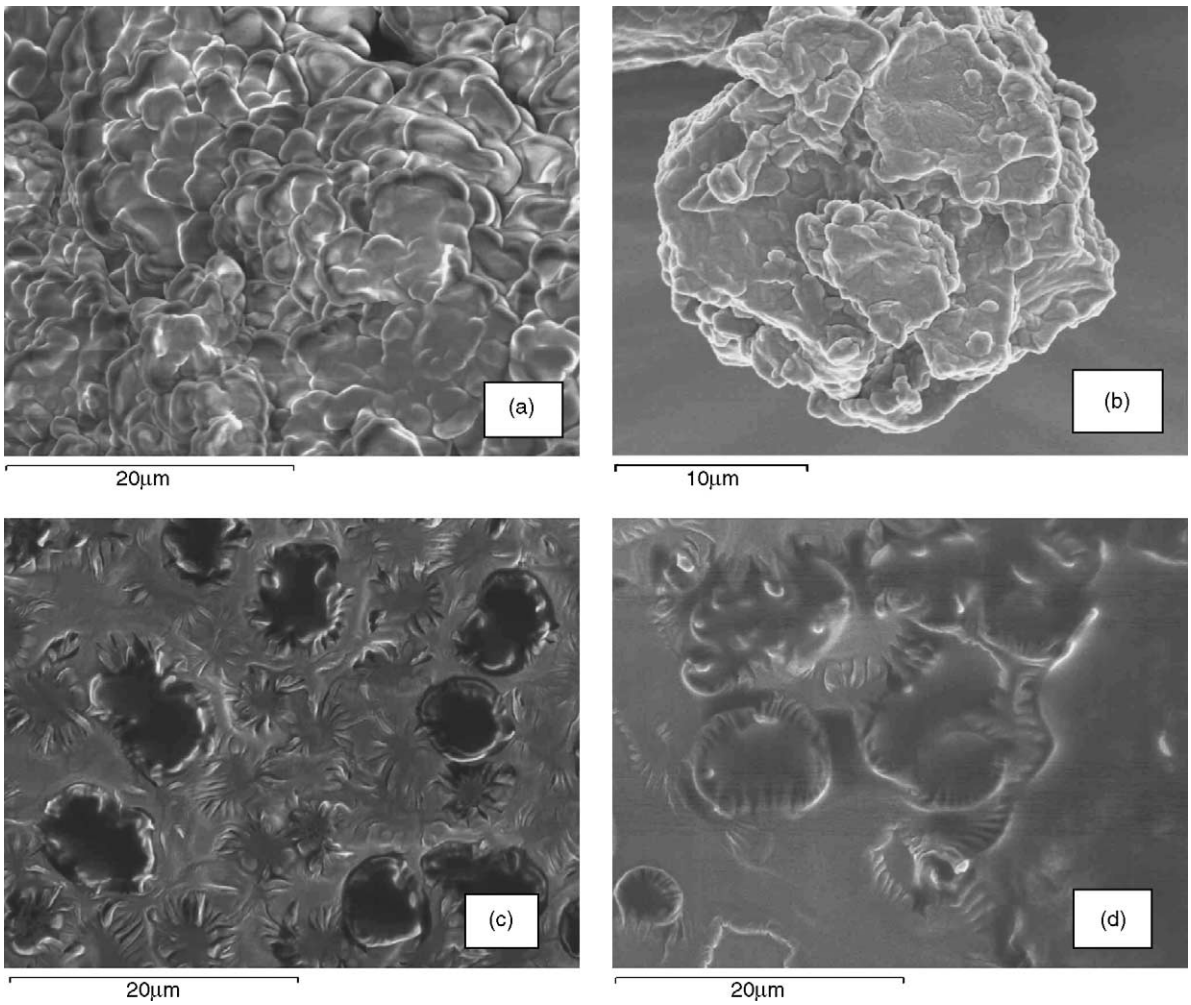

Fig. 1. Scanning electron micrographs (3000×) of molten Gelucire® 44/14 (a), cryogenic grinded Gelucire® 44/14 (b), molten Gelucire® 44/14/ketoprofen mixture (c) and cryogenic grinded Gelucire® 44/14/ketoprofen mixture (d).

Gelucire® 44/14 (panel b) and Gelucire® 44/14/ketoprofen mixtures without (panel c) or after cryogenic grinding (panel d).

Cryogenic grinding is a process which produces pulverulent material from Gelucire® 44/14. However, particles were sticky and not well differentiated as soon as they came back to room temperature (magnification 250× not shown). Gelucire® 44/14 structure appeared to be undamaged by grinding process. At magnification 3000×, it seemed to be made of different sheets intimately joined.

When drug was added, points were noticed on all sample surfaces (magnification 250× not shown). At magnification 3000×, droplets were identified with crinkled structure and this appearance was identical whatever the manufacturing process.

3.1.2. DSC studies

Thermograms of Gelucire® 44/14 alone or mixed with 10% ketoprofen are provided in Fig. 2 (panel a: molten formulations, panel b: cryogenic grinded formulations) and thermograms analysis are presented in Table 2. Gelucire® 44/14 (A, B) produced a large endotherm (12–44 °C) with an asymmetric rise, characteristic of the various chemical entities shown in Table 1. Gelucire® 44/14 had a melting peak at 41.5 °C while ketoprofen (E) demonstrated a melting point at 93 °C. When drug was included into Gelucire® 44/14

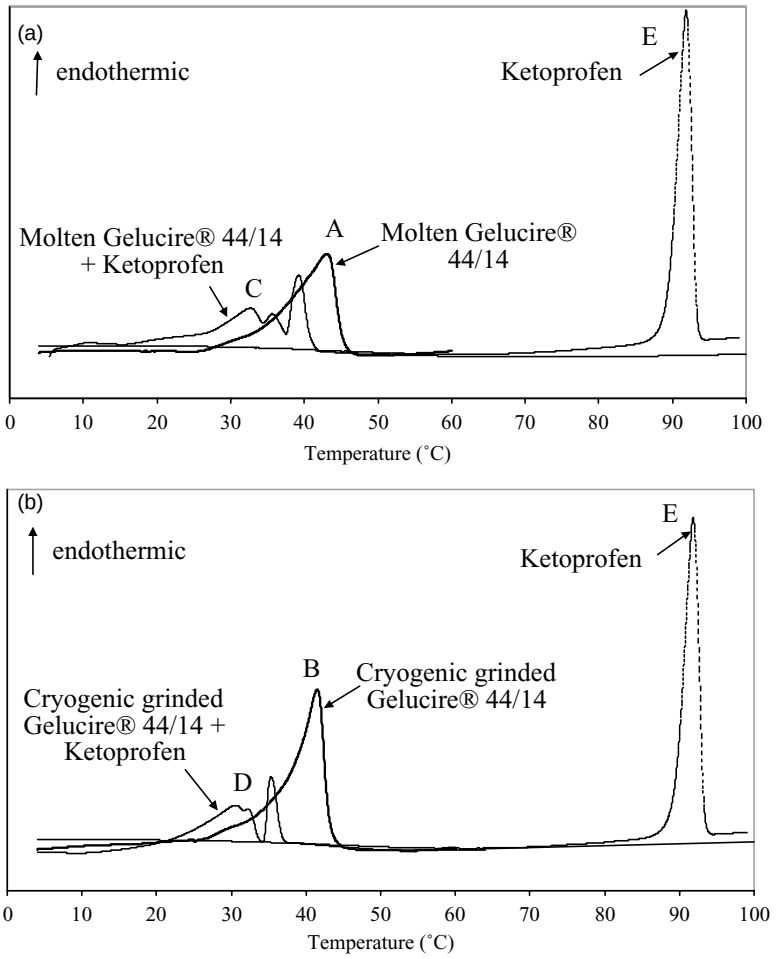

Fig. 2. Thermograms of molten Gelucire® 44/14 (a) and cryogenic grinded Gelucire® 44/14 (b).

Table 2
Thermograms analysis after DSC studies ($n = 3$)

Formulations	Maximun melting peak (°C)
Molten Gelucire® 44/14	41.5 ± 1.4
Cryogenic grinded Gelucire® 44/14	41.7 ± 1
Molten Gelucire® 44/14 + ketoprofen	38.6 ± 2.6
Cryogenic grinded Gelucire® 44/14 + ketoprofen	36.9 ± 0.8
Ketoprofen	92.9 ± 1.9

(C, D), the maximum melting peak of Gelucire® 44/14 was lowered to 36 °C, the large endotherm was separated in three parts and no endotherm corresponding to the melting of ketoprofen was noticed. Those changes were due to the solubilization of ketoprofen into a fraction of the molten Gelucire® 44/14. It was also confirmed by the change of consistency of the material. This phenomenon was also obtained with nifedipin (Pillay and Fassihi, 1999) and they concluded that their formulation was a solid dispersion. The physical nature of solid dispersions remains unanswered in many cases (Craig, 2002). Different possibilities are reported including eutectic systems, solid solutions and monotectic systems. Here, the DSC results were more in agreement with a solid solution since the melting point of drug disappeared in mixture with Gelucire® 44/14. In a solid solution, drug is present as a molecular dispersion in the carrier. Again, questions still remain as to whether the drug is dispersed on a molecular basis and what is the stability of such structure. Nevertheless, no significant difference was found between formulations obtained without or with cryogenic grinding.

3.1.3. X-ray diffraction analysis

The X-ray patterns (Fig. 3) reveals a specific crystalline structure either for Gelucire® 44/14 samples (A, B) or for ketoprofen (E). For Gelucire® 44/14/ketoprofen mixtures (C, D), the pattern recorded could be superposed upon the Gelucire® 44/14 pattern and the characteristic rays of ketoprofen disappeared. Again, no difference was observed when self-emulsifying formulation was prepared by cryogenic grinding. The drug lost its crystalline structure during the mixing step. A change in physical state of ketoprofen during manufacturing process was already shown with floating microparticles (El-Kamel et al., 2001) and drug exhibited crystalline characteristics alone and amorphous pattern in microparticles. Also, a disappearance of drug melting peak was observed in DSC studies: X-ray diffraction could strengthen the structure interpretation of these self-emulsifying formulations. It has also been reported that the formation of solid dispersions often led to the conversion of a crystalline drug into a higher energy state, i.e. the amorphous state. Thermodynamically, this high-energy state is metastable and can, in time, be reconverted into the stable crystalline state and the biopharmaceutical performance could be, as a consequence, affected (Damian et al., 2002).

3.2. Self-emulsifying performances

3.2.1. Visual observations

Whatever dye polarity, self-emulsifying formulation formed spontaneously a transparent yellow emulsion with a homogeneous distribution of dye even with lipophilic dye. This emulsion appeared to be stable and no coalescence was noted up to 48 h. Clearly, this test is qualitative (Gershanik and Benita, 1996) and gives a measure of the spontaneity of emulsification but not of the quality of emulsion (Kommuru et al., 2001; Nazzal et al., 2002). However, visual observations may provide important information about the self-emulsifying properties of the mixture and about the resulting dispersion system. In general, there was a good correlation between visual observations and particle size measurements: good emulsification properties were reflected by low droplet size. Self-emulsifying formulation could form microemulsion where particle sizes were less than 100 μm (Pouton, 2000).

The mechanism by which self-emulsification takes place is not yet well understood (Gershanik and Benita, 2000). However, in these systems emulsification requires very low energy, positive or negative (i.e. the emulsification process occurs spontaneously). One mechanism suggested is that a liquid crystalline phase forms between the oil–surfactant and water phase which effectively swells, thereby allowing spontaneous formation of an interface between the oil droplets and the water (Craig et al., 1995). The ease of emulsification could be associated with the ease by which water penetrates into the liquid crystals formed on the surface of the droplet. Then, penetration of water aided by gentle agitation causes interface dis-

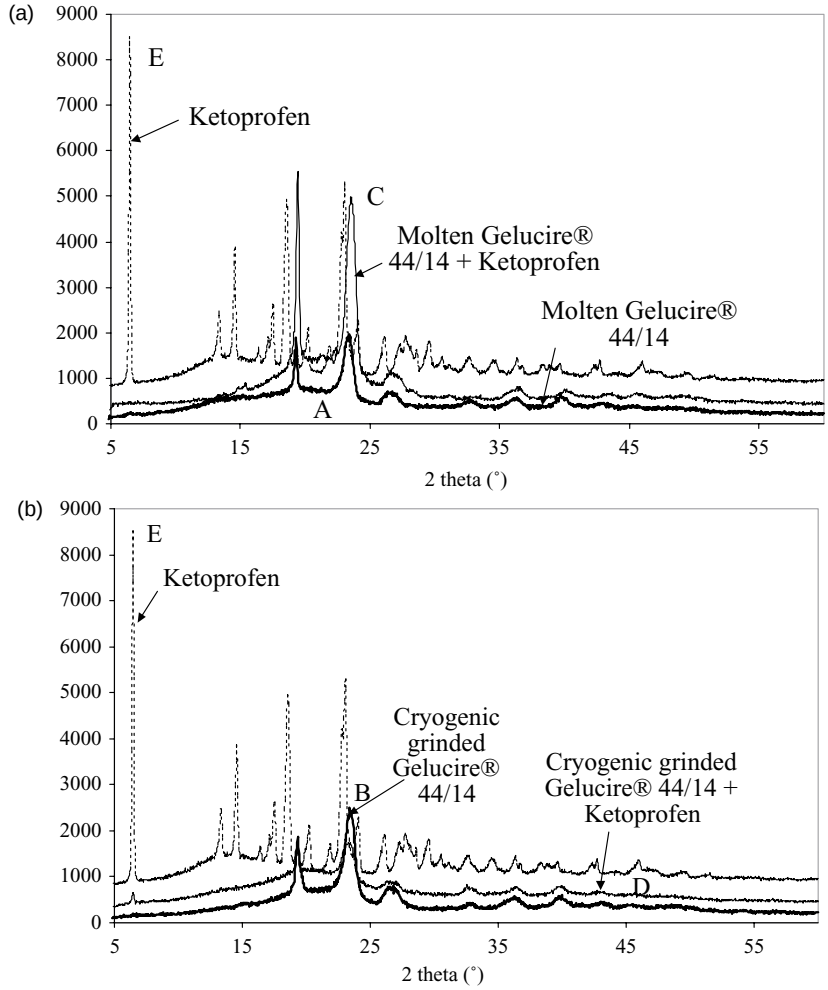

Fig. 3. X-ray patterns of molten Gelucire® 44/14 (a) and cryogenic grinded Gelucire® 44/14 (b).

ruption and droplet formation (Gershanik and Benita, 2000). Dielectric studies provided evidence that the formation of the emulsions may be associated with liquid crystal formation (Craig et al., 1995).

3.2.2. Emulsion droplet sizes analysis

The emulsion droplets were first observed under polarizing microscope. Fig. 4 reveals droplets with lamellar liquid crystals domains (birefringent texture). These liquid crystalline textures were already reported (Nazzal et al., 2002) but the type of liquid crystal seemed not well defined (probably lamellar type).

The droplet size analysis showed the quality of emulsion formed. However, the measure of emulsion droplet size must be carefully monitored because microemulsions or fine emulsions are not always stable (Itoh et al., 2002). The modification of electrostatic forces between droplets or/and temperature could dramatically change the droplet size. Also, droplet size measurement was performed immediately after sampling at 37 °C.

Droplet sizes distribution of Gelucire® 44/14 is shown in Fig. 5a. Size range was narrow and droplet size was small (less than 150 nm). The formulation of self-emulsifying systems influences the droplet size of emulsion obtained. A small droplet size may be the result of more surfactant being available to stabilize the oil–water interface (Kommuru et al., 2001). Short,

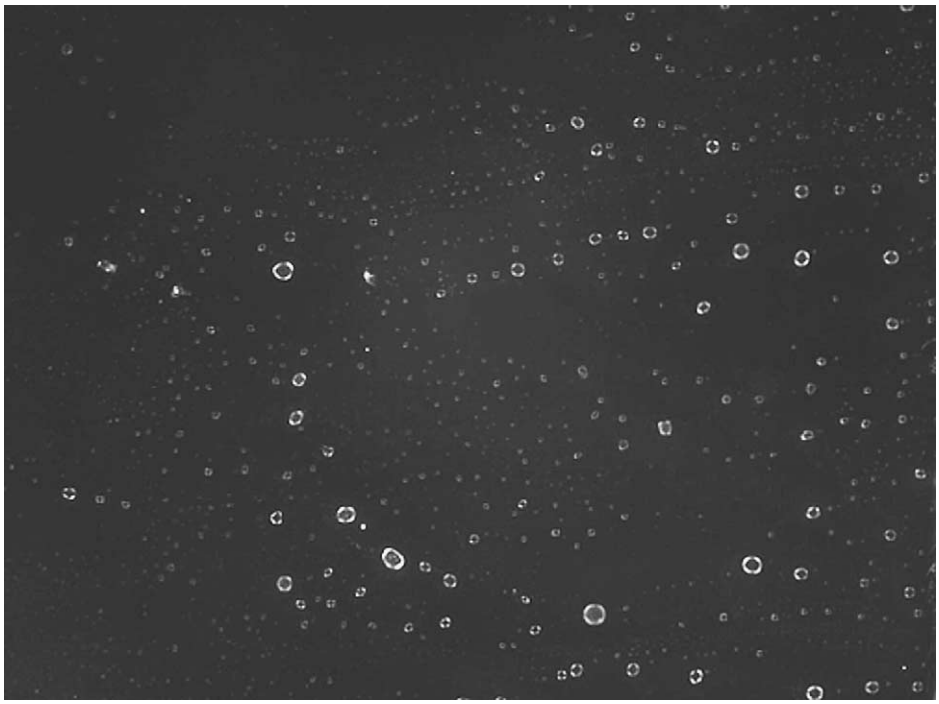

Fig. 4. Emulsion droplets under polarizing microscope.

medium and long chains of fatty acids contained in Gelucire® 44/14 had also an effect upon the curvature of the interfacial film, thereby on the stability of oil droplets. No difference was noticed whatever the manufacturing process. Average droplets diameter (in volume) was 125.9 ± 23.3 nm and 124.2 ± 24.3 nm for molten Gelucire® 44/14 and cryogenic grinded Gelucire® 44/14, respectively.

When ketoprofen was added, the droplet size decreased to 8.7 ± 1.0 nm and 11.5 ± 1.5 nm for molten and cryogenic grinded formulation, respectively (Fig. 5b). Again, no significant difference was shown between molten and cryogenic grinded formulation. The drug was solubilized into oil droplets and interfered on self-emulsifying performance probably by interaction with the liquid crystalline phase or by penetration into the surfactant interfacial film (Gershanik and Benita, 2000) leading to a change in the droplet size distribution.

Moreover, emulsion droplet size is a decisive factor in self-emulsifying formulation performance since it determines the rate and the extent of drug release. A smaller droplet size improves drug release and provides larger interfacial area across which drug can diffuse into the gastrointestinal fluids and thus increases drug absorption (Constantinides, 1995).

3.2.3. *In vitro dissolution studies*

Fig. 6 shows the dissolution profiles obtained with Topfena® reference capsules and capsules filled with Gelucire® 44/14/ketoprofen mixtures after melting or cryogenic grinding process. T20, T50 and T90 corresponding to these curves are stated in Table 3. When Gelucire® 44/14 was added into capsules, dissolution rate and amount of ketoprofen released were increased. This point was more marked after 15 min.

Table 3
Time (min) corresponding to 20, 50 and 90% ketoprofen released

Formulations	T20	T50	T90
Ketoprofen	6.8 ± 1.3	10.5 ± 1.5	52.2 ± 8
Molten Gelucire® 44/14 + ketoprofen	4.6 ± 0.7	10.4 ± 1.8	22.8 ± 2.8
Cryogenic grinded Gelucire® 44/14 + ketoprofen	4.9 ± 0.4	8.1 ± 0.9	18.9 ± 3.7

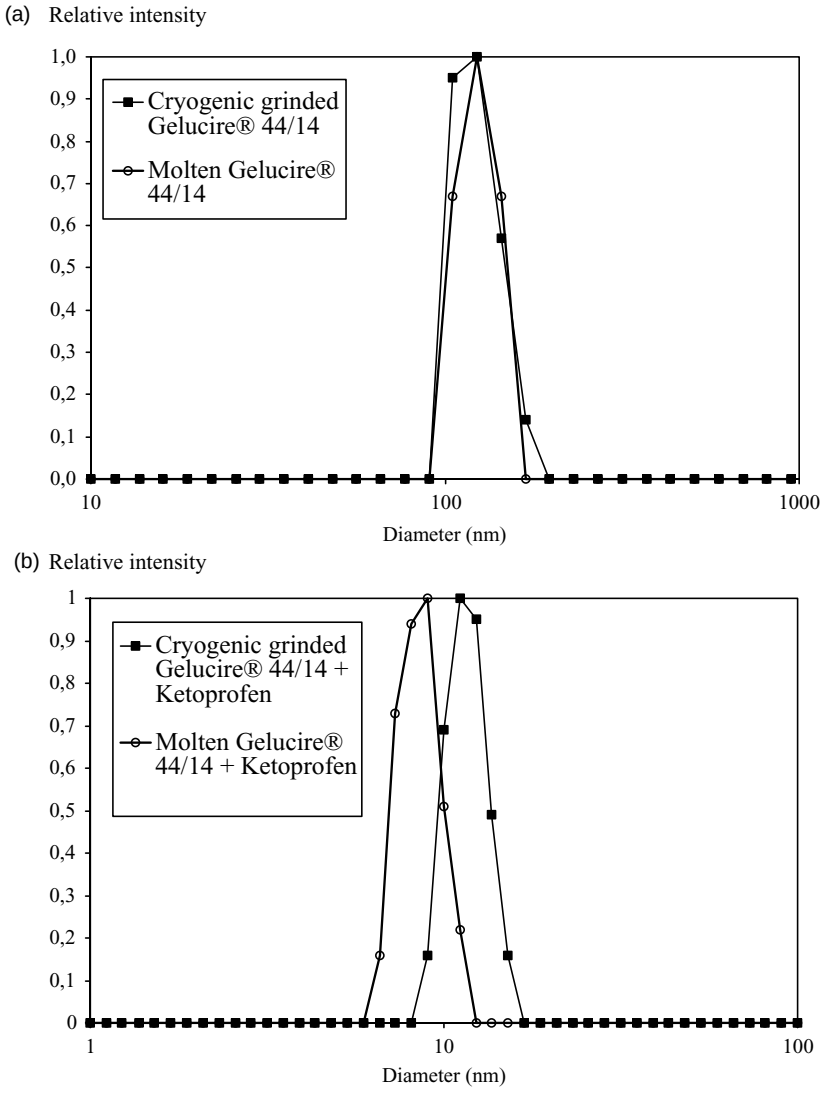

Fig. 5. Droplet size distribution of molten or cryogenic grinded Gelucire® 44/14 alone (a) and with ketoprofen (b).

No significant difference was observed between the two manufacturing processes. Gelucire® 44/14 enhanced ketoprofen release and allowed a complete discharge of drug into dissolution medium, contrary to classical capsules. This improvement in dissolution rate has subsequent implications for improving the drug bioavailability. Nowadays, the interest of SEDDS to improve the oral bioavailability of poorly water-soluble drugs is well known and documented with various drugs: progesterone (Gershanik and Benita, 1996), halofantrine (Khoo et al., 1998), indomethacin (Kim and Ku, 2000) and ubiquinone (coenzyme Q_{10}) (Kommuru et al., 2001; Nazzal et al., 2002).

The improvement in bioavailability occurs by different mechanisms (Craig, 2002):

- a particle size reduction and reduced agglomeration, inducing an increase in the surface area of drug and dissolution medium. In addition, many carriers used

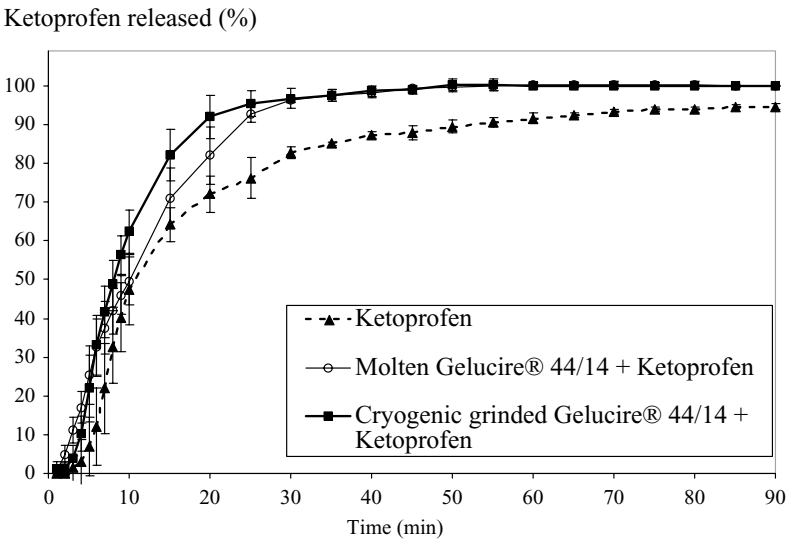

Fig. 6. Dissolution profiles obtained with ketoprofen (Topfena® capsules), molten Gelucire® 44/14/ketoprofen mixture and cryogenic grinded Gelucire® 44/14/ketoprofen mixture.

have good wetting properties giving very fine emulsions in water.

- an increased solubility and dissolution rate. In solid dispersions, when the drug is present as a minor component, drug dissolution will be dominated by the dissolution behavior of the carrier, drug being molecularly dispersed into it.

Solid dispersions induce also a transformation of drug physical state with creation of amorphous phases more reactive than crystalline state (Hülsmann et al., 2000).

During the first minutes of dissolution, ketoprofen release was controlled by the disintegration of the capsule shells (Halbaut et al., 1996) increasing the variability of ketoprofen titration. As a consequence, the results of drug dissolved amounts were not significantly different with the three formulations (Topfena® capsules, molten Gelucire® 44/14 or cryogenic grinded Gelucire® 44/14). After 15 min, the ketoprofen solubility became a rate-limiting factor in classical formulation in comparison with self-emulsifying formulations, especially as the dissolution medium was at pH = 1.2, below the pK_a value, decreasing drug solubility (El-Kamel et al., 2001; Vergote et al., 2001). The dissolution rate was slowed down with Topfena® capsules, ketoprofen forming aggregates inducing higher variability and drug retention in suspension with other ingredients. With both self-emulsifying formulations, drug was quickly solubilized inside oil droplets, preventing agglomerates formation and thereby, the effects of stomach irritation (Halbaut et al., 1996; Wu et al., 2002). Fine oil droplets should empty from the stomach and promote wide distribution of the drug throughout the gastrointestinal tract (Newton et al., 2001). This wide distribution provided a large interfacial area between drug and biological membrane, enhancing absorption and subsequent therapeutic efficacy.

4. Conclusions

Gelucire® 44/14, a compound from the lauroyl macrogolglycerides family, is a self-emulsifying excipient presented as an all-in-one formulation. It produces a fine oil-in-water emulsion when introduced into an aqueous phase under gentle agitation, improving solubility of a poorly water-soluble drug: ketoprofen.

By cryogenic grinding, it could be changed into a powder to produce solid oral dosage forms, such as pellets and tablets. This process did not modify either the physical properties, self-emulsifying capacity

or dissolution performance of the formulation tested made of Gelucire® 44/14 and ketoprofen (90/10).

However, when drug is added, interactions take place between drug and Gelucire® 44/14 and the effects upon the different properties of the formulation must be investigated case by case. With ketoprofen, thermal properties are modified with a decrease of melting peak and the droplet size of the formed emulsion is significantly reduced.

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