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Interest of Multifunctional Lipid Excipients: Case of Gelucire® 44/14

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ABSTRACT This paper focuses on the interest of a multifunctional lipid excipient from the lauroyl macrogolglycerides, i.e., Gelucire® 44/14. This compound, characterized by a drop point of 44°C and a HLB (Hydrophilic Lipophilic Balance) of 14, is made of a specific mixture, leading to particular properties. Gelucire® 44/14 forms a fine emulsion in contact with aqueous fluids, inducing a pseudo-solubilization of poorly water-soluble active substances and thus increasing their bioavailability. It could be used either as a binder for immediate release pellets by melt granulation or as a self-emulsifying drug delivery system by capsule molding or as a powder obtained by cryogenic grinding. These different methods and their interests are then discussed.

KEYWORDS Excipient, Lipids, Functionality, Gelucire® 44/14, Self-emulsifying drug delivery system, Melt granulation

INTRODUCTION

In the last decades, new excipients called multifunctional excipients or high functionality excipients have been put on the market. They impart high levels of performance to drug formulations without complex processing.

This paper focuses on the interest of Gelucire® 44/14, a multifunctional lipid excipient from the lauroyl macrogolglycerides.

GELUCIRE® 44/14: COMPOSITION AND REGULATION

Gelucire® 44/14 is an inert semisolid waxy material, amphiphilic and characterized by a drop point of 44°C and a HLB of 14 (Gattefossé, France). Gelucire® 44/14 conforms to the *European Pharmacopoeia* 5th edition (2005), "Lauroyl Macrogolglycerides" monograph and the pending *United States Pharmacopoeia* "Lauroyl Polyoxylglycerides" monograph (draft published in the Pharmacopoeial Forum). Gelucire® 44/14 is GRAS (generally recognized as safe).

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TABLE 1 Fatty Acid Distribution of Gelucire® 44/14

Caprylic acid C8	Capric acid C10	Lauric acid C12	Myristic acid C14	Palmitic acid C16	Stearic acid C18
4–10%	3–9%	40–50%	14–24%	4–14%	5–15%

Gelucire® 44/14 is obtained by polyglycolysis of hydrogenated palm kernel oil with PolyEthylene Glycol 1500. Its composition is a mixture of the following:

· Mono-, di-, and triglycerides—20%
· Mono- and di-fatty acid esters of PEG 1500—72%
· Free PEG 1500—8%

The fatty acid distribution of Gelucire® 44/14 is given in Table 1.

Because of its unique composition with surfactants (mono- and diesters of PEG), cosurfactants (monoglycerides), and oily phase (di- and triglycerides), Gelucire® 44/14 presents interesting properties.

In contact with aqueous fluids, it forms a fine emulsion at body temperature. This induces a pseudo-solubilization of poorly water-soluble drugs and, subsequently, increases their bioavailability (Pillay & Fassihi, 1999).

The main physicochemical characteristics of Gelucire® 44/14 are its thermal behavior recorded by differential scanning calorimetry (DSC) and its physical state following x-ray diffraction. A thermogram of Gelucire® 44/14 showed a large endothermic event (15–44°C) with an asymmetric rise. The melting peak onset is at 38.2°C, and the melting peak is at 43.2°C with $\Delta H = 115.3$ J/g. The x-ray diffraction patterns of Gelucire® 44/14 revealed the crystalline structure of the sample and no change in this structure upon aging, indicating good stability (Roussin & Laforet, 1997).

SOLID FORMULATIONS: BINDER FOR IMMEDIATE RELEASE PELLETS BY MELT GRANULATION

Melt granulation or pelletization is a process allowing the densification of a powder mix and the spheronization of the granules obtained (pellets).

The energy produced by the impeller frictions and the double-heated jacket of the high-shear mixer melts the binder, or a fraction of the binder, hence, leading to melt granulation or thermoplastic pelletizing.

Three main steps comprise that process: nucleation, densification, and breakage.

During the nucleation step, the melted binder comes into contact with the powder bed and some liquid bridges are formed, leading to the formation of small agglomerates. The size, the viscosity of the binder, and the speed of the impeller influence the mechanism of nucleation.

Fine or atomized binders with low viscosity and high impeller speed favor a homogenous distribution of the binder onto the surface of the powder, whereas large particles of binder with a high viscosity and low impeller speed preferably induce the immersion of the powder into the binder (Schaefer & Mathiesen, 1996). The mechanism of nucleation depends on the binder viscosity at high impeller speed and the binder particle size at low speed (Seo & Schaefer, 2001).

The mechanism of densification depends on the liquid saturation of granules and their ability to deform themselves during collisions. These collisions can lead to the coalescence of two granules or the layering of fine particles onto the surface of preexisting granules.

There is an equilibrium between densification and breakage of granules. Granules that cannot withstand the shear of the impeller and chopper will break, and their fragments will participate in the densification by layering (Eliasen et al., 1998, 1999). In a high-shear mixer, that phenomenon of breakage insures the control of the granule size distribution.

Polyethylene-glycols (PEGs) of various molecular weights have commonly been used as meltable binders in melt agglomeration of immediate release granules or carriers for solid dispersions (Damian et al., 2000; Dordunoo et al., 1991; Eliasen et al., 1998; Seo et al., 2003). Gelucire® have also been used as meltable binders, because they present broad melting ranges that are particularly adapted for this kind of process. The progressive melting of the binder allows the control of the process and the selection of the granule's size. For example, Gelucire® 50/13 (stearoyl macrogolglycerides) was used with that technique in

order to increase the bioavailability of a poorly water-soluble active substance such as diazepam (Seo et al., 2003). In that study, Seo et al. demonstrated the superiority of Gelucire® 50/13 over PEG 3000 in term of dissolution rate. The surface active and self-emulsifying properties of Gelucire® help to increase the dissolution rate of poorly water-soluble drugs (Damian et al., 2000; Dordunoo et al., 1991).

In this study, Gelucire® 44/14 acts as a meltable binder with a quantity ranging from 15 to 17% wt/wt, fat blue dye (LCW, France) as a lipophilic tracer (quantity fixed at 1% wt/wt) with an aqueous solubility of 1 μg/mL and α-monohydrate lactose (Lactochem 200 Mesh, Borculo Domo Ingredients, Netherlands) as a diluent (up to 100% wt).

Gelucire® 44/14 is a semisolid excipient and must be melted at 60–65°C under stirring before weighting the quantity needed for the process. Then it should stay at room temperature for at least 24 h to insure the crystallization in its most stable form.

Granules are produced in a 25 L high-shear mixer (VG25, Glatt, Germany) in a three-step process:

1. The mix of the three solid components with a low impeller speed (200 rpm) in order to soften the Gelucire® 44/14 (the temperature of the mix slowly increases)—the double-heated jacket temperature is fixed at a temperature close to the melting point of the binder, and the chopper speed is 400 rpm
2. The densification of the powder and the spheronization of the granules with a higher impeller speed (600 rpm)
3. The discharge of the granules on a tray in order to allow the complete crystallization of the binder

The three factors studied were the double-heated jacket temperature (40–48°C), the percentage of binder (15–17% wt/wt), and the mixing time (10–20 min).

The responses selected for this study were the particle size distribution, the shape, and the size of the dispersion in water.

In order to investigate the influence of these three parameters on the quality of granules, a full factorial design of experiments (two levels) was used (Modde 5.0, Umetrics, USA). Thus, 11 batches of pellets were produced: eight batches with parameters either at minimum or maximum level and three batches with parameters fixed at the center of the domain studied (center points).

Figure 1 shows the influence of the mixing time and the percentage of binder on the geometric mean diameter of pellets (response surface modeling). The increase of both of these parameters produces bigger

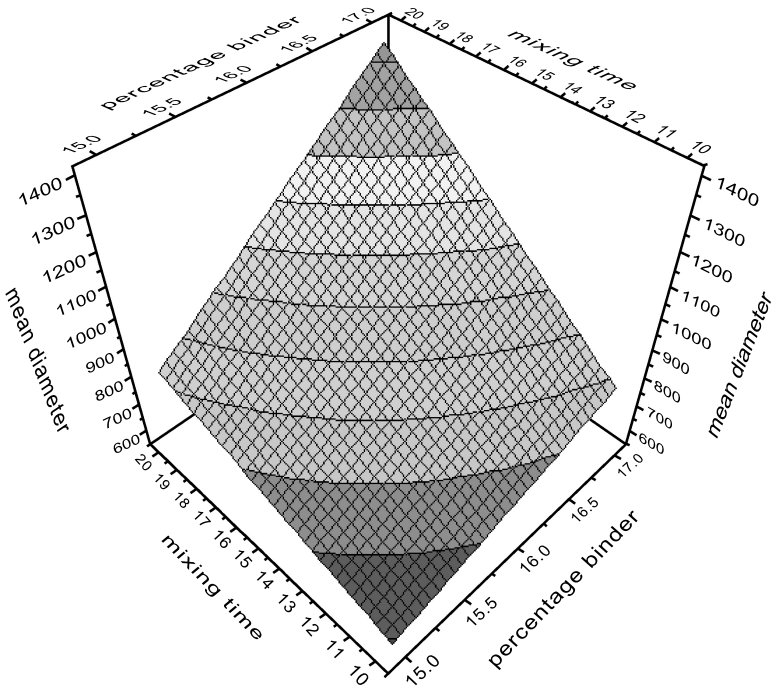

FIGURE 1 **Response Surface Modeling: Influence of Mixing Time and Percentage of Binder on the Geometric Mean Diameter.**

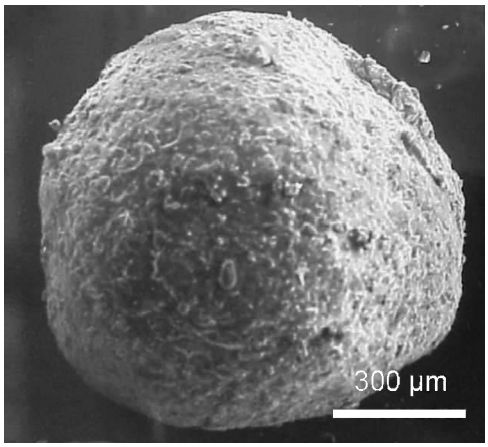

FIGURE 2 **Gelucire® 44/14 Pellets. (Pellets Produced with a Double-Heated Jacket Temperature of 44°C, 16% wt/wt of Binder, and a Mixing Time Fixed at 15 min.)**

granules. In fact, as the mixing time increases, the impeller generates more frictions, resulting in a product temperature increase and a higher liquid fraction of the binder. Again, if the percentage of binder increases, the liquid fraction rises, allowing for a better densification of the powder. The double-heated jacket temperature possesses a less prone effect on the granule size, as the product temperature inside the mixer is sufficiently high to allow for the complete melting of the binder, even with the lowest temperature tested (due to the impeller frictions).

Granules obtained are spherical, as shown on the scanning electron micrograph in Fig. 2. The rough surface is due to the lactose particle size that is rather large for this kind of process (lactose 200 mesh= 74 µm). Finer lactose with a mean diameter of about 20–25 µm gives smoother pellets.

These granules present a narrow particle size distribution (LS200, Coulter, USA) with a geometric mean diameter ranging from 550 to 1400 µm depending on the process parameters. A linear correlation was found between the mean diameter predicted by the model and mean diameter measured (R^2=0.989). The three center points (produced with a double-heated jacket temperature of 44°C, 16% wt/wt of binder, and a mixing time fixed at 15 min) present monomodal size distributions with mean diameters ranging from 831 to 922 µm showing the reproducibility of the process.

The self-emulsifying properties of pellets were assessed by dispersing 1 g of pellets into 900 mL of purified water at 37°C. The medium was stirred with a paddle (USP apparatus II) for 30 min before sampling and size measurement by photon correlation spectroscopy (PSS Nicomp 380 ZLS, USA, Fig. 3). These granules containing Gelucire® 44/14 disperse instantaneously in water and form a fine blue oil-in-water emulsion with a mean particle size of 300 nm.

SEMISOLID FORMULATIONS: ALL-IN-ONE EXCIPIENT FOR CAPSULE MOLDING

Recently, self-emulsifying drug delivery systems (SEDDSs; SMEDDS = self-micro emulsifying drug delivery system) have been developed to deliver lipophilic drugs (Pouton, 2000). They are described as mixtures of oils, surfactants, cosurfactants, and drug (Gershanik & Benita, 2000). However, only specific combinations lead to efficient self-emulsifying systems, and each case is an intricate problem (Constantinides, 1995). An alternative to this complex formulation is the development of a self-emulsifying excipient ready for use, i.e., an all-in-one formulation, such as lauroyl macrogolglycerides (e.g., Gelucire® 44/14 from Gattefossé, St Priest, France). In the aqueous media of the stomach, with digestive motility, Gelucire® 44/14 self-emulsifies quickly and forms a fine oil-in-water emulsion (droplet sizes from a few nanometers to 300 nm).

To produce formulation in capsules, Gelucire® 44/14 must be melted at 60–65°C under stirring. Then, drug is added in the molten excipient, and the capsules

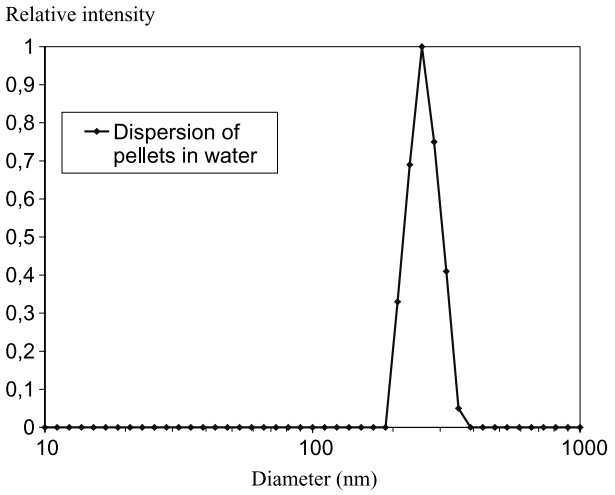

FIGURE 3 **Droplet Sizes Distribution of the Dispersion in Water by Photon Correlation Spectroscopy. (Pellets Produced with a Double-Heated Jacket Temperature of 44°C, 16% wt/wt of Binder and a Mixing Time Fixed at 15 min.)**

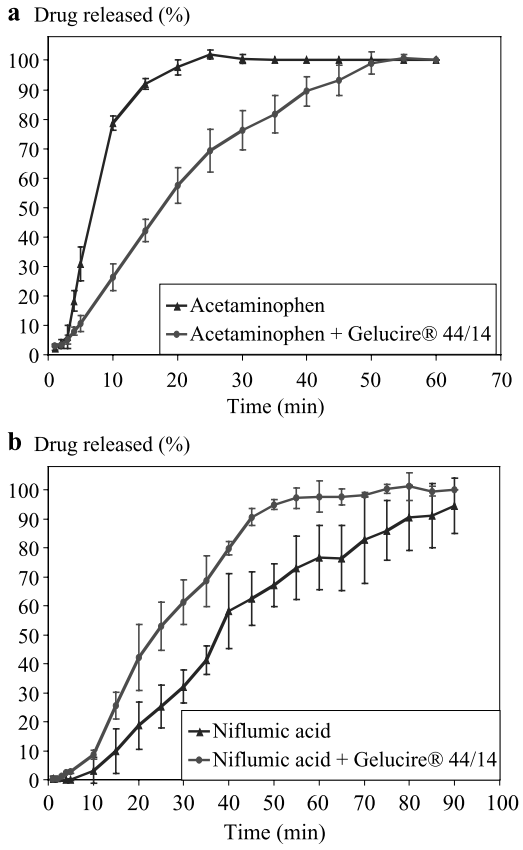

FIGURE 4 **In Vitro Dissolution Profiles Obtained with Acetaminophen and Niflumic Acid after Capsule Molding.**

are filled with the molten mixture in volume. The formulation solidifies when cooling at room temperature.

In vitro dissolution studies were performed using the rotating paddle method (Erweka DT 6 apparatus) at 37.0±0.5°C and 50 rpm up to 90 min. The dissolution medium (1000 mL) was simulated gastric-buffered solution (pH 1.2). Two model drugs were studied: acetaminophen (molecular weight = 151.2 g/mol; melting point = 169±1°C; sparingly soluble in water and soluble in hot water) and niflumic acid (molecular weight = 282.2 g/mol; melting point = 294±2°C; very slightly soluble in water). For each drug, capsules tested were produced after mixing drug (10% wt/wt) in the molten Gelucire® 44/14 in comparison with capsules containing the same amount (60 mg) of native drug powder (in triplicate). Drug release was assayed over 60 or 90 min (100% drug released) by ultraviolet (UV) spectrophotometry at λ=255 nm or λ=287 nm for, respectively, acetaminophen and niflumic acid (Fig. 4).

Gelucire® 44/14 improves the solubility of poorly water-soluble drugs (i.e., niflumic acid) and thereby enhances their in vivo bioavailability. Numerous studies describe this phenomenon with various drugs: nifedipine (Pillay & Fassihi, 1999), 17 β-estradiol (Hülsmann et al., 2000), and α-tocopherol (Barker et al., 2003) mixed with Gelucire® 44/14 and also in other SEDDS with progesterone, halofantrine (Khoo et al., 1998), indomethacin, ubiquinone (Nazzal et al., 2002), and so forth. This improvement of the dissolution was already assigned to a solid dispersion structure (Craig, 2002). A solid dispersion is defined as "the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method enhancing drug in vitro release in comparison with conventional dosage forms" (Craig, 2002, p. 131). Carriers used have been water-soluble or water-miscible polymers, such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP), or water-insoluble carriers, such as Gelucire® and Eudragits®. Some authors (Damian et al., 2000; Dordunoo et al., 1991) compared the use of PEG and Gelucire® and focused on the possible mechanisms of increased dissolution rates. Many parameters were involved, especially a solubilization effect of the carrier and an improved drug wettability. The choice of the carrier is an important point, but it depends mainly on the drug and on the release profiles required without forgetting the stability of the systems (Craig, 2002).

On the other hand, Gelucire® 44/14 can create a lipid matrix with some water-soluble drugs (i.e., acetaminophen). This sustained release effect was already studied with different mixtures of Gelucire® and drug, for example, salbutamol sulfate (San Vicente et al., 2000) is a good candidate for the development

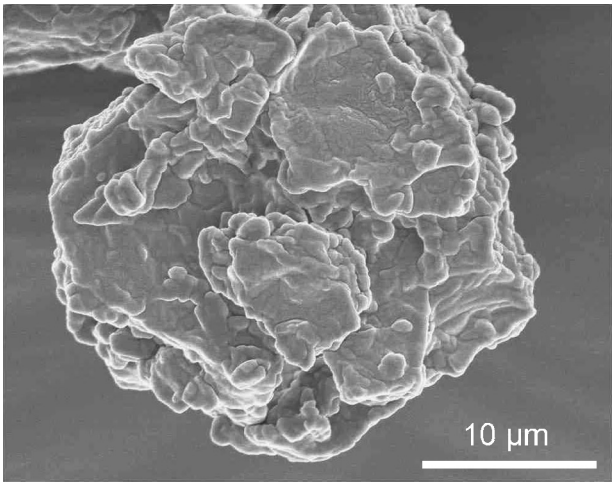

FIGURE 5 **Scanning Electron Micrographs of Cryogenic Grinded Gelucire® 44/14.**

of a controlled release formulation due to its short half-life (about 5 h). Some authors (Sutananta et al., 1995) investigated the mechanisms of theophylline release from lipid matrices made of Gelucire®, estimating the part of diffusion and erosion process.

However, during capsule molding processing, the major problem encountered is the melting step, which is time consuming and needs, at least, a temperature of 60–65°C.

A solution to overcome this disadvantage can be to process Gelucire® 44/14 into a powder to produce solid dosage forms such as pellets, tablets, and hard capsules with the classical manufacturing process.

NEW FORMULATIONS: POWDER OBTAINED BY CRYOGENIC GRINDING

Gelucire® 44/14 can be changed into a powder by cryogenic grinding. Grinding is commonly used in the pharmaceutical industry to reduce particle size. Cryogenic grinding was chosen because it is a process carried out at low temperature and is often used for biological materials and unstable compounds. Cryogenic grinding was performed using a cryogenic impact mill (model 6750, SPEX CertiPrep). Gelucire® 44/14 sample (1 g) was inserted into a polycarbonate cylinder and immersed in liquid nitrogen, in which a stainless steel rod was vibrated by means of a magnetic coil (10 Hz). The powder obtained was stored at a low temperature (−20±2°C).

However, grinding induces disorders (mechanical activation, generation of energy) (Crowley & Zografi, 2002) that can affect the crystalline solid. So, the influence of cryogenic grinding on different properties of Gelucire® 44/14 must be investigated in different fields: physicochemical characterization (microscopy, differential scanning calorimetry, x-ray diffraction), emulsification properties, and dissolution performance.

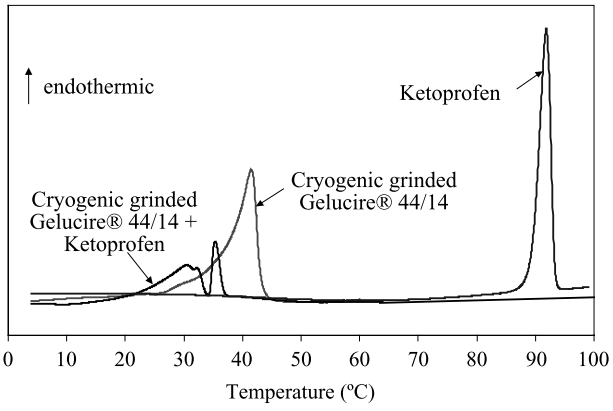

FIGURE 6 **Thermograms of Cryogenic Grinded Gelucire® 44/14.**

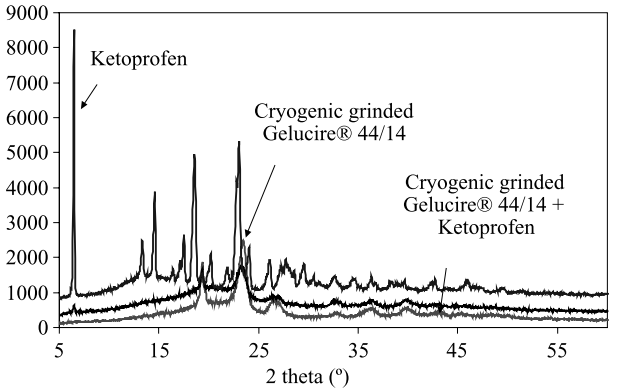

FIGURE 7 **X-ray Diffraction Patterns of Cryogenic Grinded Gelucire® 44/14.**

By scanning electron microscopy (SEM; Jeol JSM-6400 F, nickel coating, 5 kV, magnification 250× and 3000×), Gelucire® 44/14 particles can be observed (Fig. 5), but they are sticky and not well differentiated as soon as they return to room temperature. Thermograms (DSC 7, Perkin-Elmer, n=3, temperature range=0–100°C, heating rate=10°C·min^{-1}) of cryogenic grinded Gelucire® 44/14 (Fig. 6) are similar to those of molten Gelucire® 44/14, with a melting peak at 42.5±1.2°C (Roussin & Laforet, 1997). Again, x-ray diffraction patterns (CPS 120 INEL) exhibit similar profiles with a specific crystalline structure (Fig. 7). No change is noticed after cryogenic grinding (Chambin et al., 2004). However, interactions occur between drug and Gelucire® 44/14, with consequences upon the different properties of the self-emulsifying formulation, particularly upon thermal behavior. This

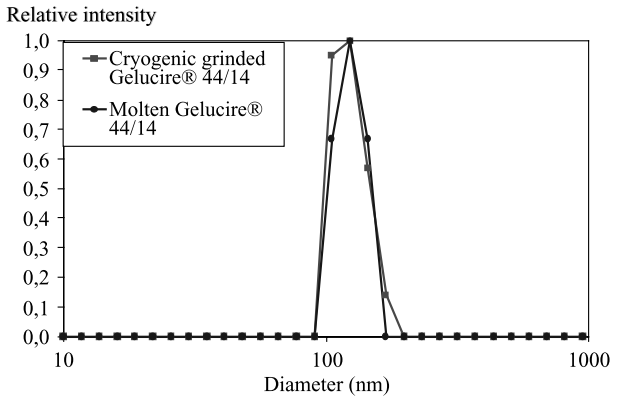

FIGURE 8 **Droplet Size Distribution of Molten or Cryogenic Grinded Gelucire® 44/14 by Photon Correlation Spectroscopy.**

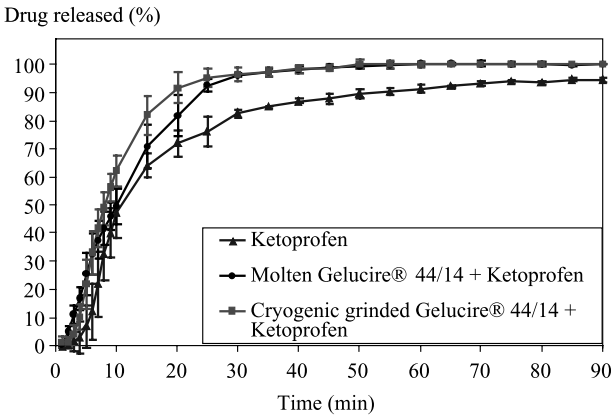

FIGURE 9 **In Vitro Dissolution Profiles Obtained with Ketoprofen, Molten Gelucire® 44/14, and Cryogenic Grinded Gelucire® 44/14 and Ketoprofen Mixtures.**

phenomenon was already described for nifedipine (Pillay & Fassihi, 1999) with a decrease of the melting peak that could be related to a physical structure such as a solid dispersion. Moreover, in water, cryogenic grinded Gelucire® 44/14 quickly forms a fine emulsion with droplet size similar to the droplet size obtained with molten Gelucire® 44/14 (mean diameter = 125 ± 20 nm) measured by photon correlation spectroscopy (Fig. 8) (PSS Nicomp 380 ZLS, Santa Barbara, CA, USA).

Finally, in vitro dissolution studies were performed, as described previously, with ketoprofen as the active drug (rotating paddle method, simulated gastric buffered solution pH = 1.2, 37.0 ± 0.5°C, 50 rpm, 90 min). Capsules made of cryogenic grinded Gelucire® 44/14 and ketoprofen (10% wt/wt) were tested in comparison with capsules made of molten Gelucire® 44/14 and ketoprofen and commercial capsules (Topfena®) as ketoprofen reference. Findings showed (Fig. 9) an improvement of the dissolution rate and extent when drug is mixed in Gelucire® 44/14, marked after 15–20 min. No significant difference was observed between the two manufacturing processes (molten or cryogenic grinded Gelucire® 44/14). The improvement in dissolution and bioavailability can be ascribed to different mechanisms (Craig, 2002): a particle size reduction and reduced agglomeration inducing an increase in the surface area of drug and dissolution medium, or an increased solubility and dissolution rate due to physical structure. In solid dispersion, drug dissolution arises out of the dissolution behavior of the carrier, with the drug being molecularly dispersed into it. Moreover, with self-emulsifying formulation, drug was quickly solubilized inside oil droplets, avoiding agglomerates formation and, thereby, enhancing bioavailability and also stomach tolerance (Newton et al., 2001). These characteristics are greatly searched for in this kind of drug, i.e., nonsteroidal anti-inflammatory drugs characterized by low water solubility and high permeability. These formulations could improve their performance, especially in painful conditions where an acute analgesic effect is desired (Yüksel et al., 2003).

Cryogenic grinding is a process producing a powder from Gelucire® 44/14 without significantly changing the physicochemical properties, self-emulsifying capacity, and dissolution performance, with the formulations tested (Chambin et al., 2004). However, interactions between drug and Gelucire® 44/14 and the effects upon the different properties of the formulation must be investigated on a case by case basis.

CONCLUSION

Gelucire® 44/14, a lauroyl macrogolglyceride, is a multifunctional lipid excipient that could be used as a binder for pellets by melt granulation or as a self-emulsifying base by capsule molding or by other classical processes for oral dosage forms when using the powder obtained after cryogenic grinding.

Nowadays, almost 40% of new drug compounds are hydrophobic in nature and need a specific drug delivery system in order to achieve efficiency (Gursoy & Benita, 2004). Gelucire® 44/14, because of its unique composition with surfactants, cosurfactants, and oily phase, presents interesting properties. Whatever the manufacturing process, this excipient is particularly advised to improve the bioavailability of the lipophilic drug, underlining the interest of such an excipient in drug delivery.

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