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Evaluation of the digestibility of solid lipid nanoparticles of glyceryl dibehenate produced by two techniques: Ultrasonication and spray-flash evaporation

Vincent Jannin[a,*], Lucia Blas[b], Stéphanie Chevrier[a], Cédric Miolane[a], Frédéric Demarne[a], Denis Spitzer[b]

[a] Gattefossé SAS, 36 chemin de Genas, 69804 Saint-Priest cedex, France
[b] Laboratoire NS3E, UMR 3208 ISL-CNRS-UNISTRA, 5 rue du Général Cassagnou, 68301 Saint-Louis, France

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ABSTRACT

Objective: To evaluate the digestibility of Solid Lipid Nanoparticles (SLN) of glyceryl dibehenate prepared either with surfactants by ultrasonication or without surfactant by spray-flash evaporation.

Methods: SLN of glyceryl dibehenate (Compritol® 888 ATO) were produced by two processes: (i) high-shear homogenization with a solution of water-soluble surfactants followed by ultrasonication (ii) and Spray-Flash Evaporation (SFE) of the pure lipid. The digestibility of these nanoparticles was then tested by *in vitro* lipolysis using a pH-stat apparatus and the assay of glycerides by gel phase chromatography.

Results: SLN of glyceryl dibehenate prepared by ultrasonication exhibited a mean particle size of 180 nm and showed a limited digestion of the lipid excipient. SLN comprising only glyceryl dibehenate produced by SFE have a mean particle size between 235 and 411 nm depending on process parameters. These nanoparticles were not digested by lipases. The presence of surfactant at the lipid/water interface of the SLN seems to be mandatory to allow the adsorption of the lipase and degradation of glyceryl behenate.

Conclusions: Glyceryl dibehenate as a solid particle – even as a SLN – is not digested by pancreatin during *in vitro* lipolysis test.

1. Introduction

Solid lipid excipients composed of long chain fatty acids are classically used for sustained-release and solid lipid nanoparticles (SLN) formulations. These lipids are considered as non-erodible and non-digestible (Rosiaux et al., 2014). Drug sustained-release or drug vectorization can only be effective if the lipid matrix/nanoparticle retains its shape during its transit through the gastrointestinal tract. However, lipid-based excipients can be digested by a large variety of lipases secreted either by the stomach or by the pancreas (N'Goma et al., 2012). The digestibility of long-chain lipids depends on the degree of unsaturation. For example, dietary lipids are often composed of unsaturated long chain fatty acids (*e.g.* oleic acids) that are liquid at 37 °C. Hence, these lipids can easily be emulsified by the bile components and the subsequent interfacial tension decrease at the lipid-water interface allows the adsorption of lipases. In the case of sustained-release matrix tablets or SLN, the lipid-based excipients used are mainly composed of saturated long chain fatty acids and are solid at 37 °C. For example, two such lipid excipients are glyceryl distearate (Precirol® ATO 5) (Jannin et al., 2006; Patel et al., 2015) and glyceryl dibehenate (Compritol® 888 ATO) (Keen et al., 2015; Parejiya et al., 2013; Patere et al., 2013) used to produce solid oral dosage forms by various techniques (direct compression, capsule molding, hot-melt extrusion, …). Apart from the lowering of the interfacial tension, another factor could favor the digestibility of lipids: the reduction of their particle size leading to an increased surface area. In that regard we evaluated in a previous study the digestibility of Precirol® ATO 5 when formulated as (SLN). We found that this lipid is readily digested with the degradation of glycerides in a few minutes using the *in vitro* pH-stat method (Jannin et al., 2015a, 2015b).

In this study, we want to evaluate the digestibility of Compritol® formulated as SLN to check the impact of the fatty acid chain length - increase from 18 to 22 carbons - on the degradation of the solid lipid nanocarrier. It has been shown that the digestibility of SLN decreases with the increase of the fatty acid chain length from 14 to 18 (Christophersen et al., 2013). No comparison has been done so far

* Corresponding author.
E-mail address: vjannin@gattefosse.com (V. Jannin).

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between 18 (Precirol® ATO 5) and 22 (Compritol®). The digestibility of SLN is evaluated by assaying the glyceride composition of the lipid excipient and not by the volume of NaOH added during the lipolysis experiment. This technique is more accurate in order to precisely evaluate the digestibility of glycerides than the classic pH-stat technique relying on the volume of NaOH added to neutralize the released fatty acids. In fact, it was recently demonstrated that the direct titration method underestimates the real digestibility of SLN when the back-titration method tends to overestimate the digestibility of SLN (Heider et al., 2016).

We also want to check the impact of surfactants in the composition of SLN on the digestibility of Compritol® because we know that lipases are able to adsorb at the interface when the interfacial tension is sufficiently lowered. To do so we plan to produce SLN of Compritol® with surfactants by the ultrasonication technique and without surfactants by a newly developed process: Spray Flash Evaporation (Risse et al., 2013). The flash evaporation is the physical phenomenon occurring when the boiling point of a liquid is lower than its actual temperature, due to a sudden drop of pressure and/or a quick increase of temperature. The excess of heat is instantly converted into latent heat of vaporization, cooling both liquid and vapor down to the saturation temperature. In practice, the compound that needs to be nanosized is dissolved in a volatile solvent and that solution is heated just before being sprayed into vacuum, where the crystallization is triggered by the sudden temperature depression and the solvent evaporation (Pessina, 2016).

2. Materials and Methods

2.1. Materials

For the preparation of SLN, the following excipients were used: Compritol® 888 ATO (Glyceryl dibehenate, Gattefossé, Saint-Priest, France), Tween® 80 (Polysorbate 80, Sigma-Aldrich, Saint-Quentin Fallavier, France) and Pluronic® F127 (Poloxamer, Sigma-Aldrich).

For digestion experiments, $CaCl_2$ and Tris (hydroxymethylaminomethane) were purchased from Chimie Plus Laboratoire (Décines, France). NaCl, HCl 37%, and NaOH pellets were bought from Merck KGaA (VWR, Bourges, France). Sodium taurodeoxycholate (NaTDC), tributyrine, pancreatin (from porcine pancreas), and L-α-phosphatidylcholine were purchased from Sigma-Aldrich. All solvents used were HPLC grade.

2.2. Methods

2.2.1. Preparation and Characterization of Solid Lipid Nanoparticles (SLN) by Ultrasonication

2.2.1.1. Preparation of Lipolysis Buffer. The lipolysis buffer is prepared by adding Tris (0.474 g/L), $CaCl_2$ (0.208 g/L) and NaCl (8.810 g/L) in Milli-Q water. The pH is adjusted at 6.5 with NaOH 0.6 M.

2.2.1.2. Preparation of SLN by Ultrasonication. In order to compare the digestibility of the lipid matrix (Compritol® - C22 based-glycerides) with results from our previous study with another lipid matrix (Precirol® ATO 5 – C18 based-glycerides), the same mixture of surfactants will be used to emulsify the lipidic phase and the same protocol of preparation by homogenization and ultrasonication will be used (Jannin et al., 2015a, 2015b). SLN were prepared directly in the lipolysis buffer to avoid a subsequent dilution of the preparation during the lipolysis test. Briefly, the aqueous phase was prepared dissolving 960 mg of Tween® 80 and 960 mg of Pluronic® F127 in 120 mL of lipolysis buffer, heated at 80 °C (above the melting temperature of the lipidic phase). On the other hand, the lipidic phase was composed by 1920 mg of Compritol® 888 ATO. The lipidic phase was melted at 80 °C and, after the addition of the aqueous phase, the mixture was homogenized at 24000 rpm for 5 min (Ultraturrax S25N18G-0.01-1.5L, IKA, Germany). After homogenization, the nanodispersion was rapidly cooled down by storage at − 20 °C for 10 min, to obtain the solidification of the lipidic droplets produced in the emulsification step. Finally, SLN were sonicated for 15 min to reduce nanoparticle aggregation and then stored at + 4 °C until use.

Before performing the lipolysis test, the SLN suspension was supplemented with L-α-phosphatidylcholine (0.576 g/L) and NaTDC (1.565 g/L) as in the lipolysis medium preparation.

2.2.1.3. Dimensional Characterization of SLN. The dimensional characterization of SLN was performed by Dynamic Light Scattering (PSS-NICOMP Particle Size Systems, Santa Barbara, CA, USA). One milliliter of SLN was diluted either in 10 mL of lipolysis buffer or medium and filtered through a 0.45 μm-syringe filter (Acrodisc® 25 mm syringe filter, 0.45 μm glass fiber membrane, Pall Life Science, VWR). The refractive index and viscosity of the dispersing medium at 37 °C is measured and used to calculate the average size derived from the intensity-average diffusion coefficient obtained after 2 runs of 5 min (Chamieh et al., 2015). All particle size measurements are performed in triplicate and expressed in Gaussian intensity (mean ± standard deviation, n = 3).

2.2.2. Preparation and Characterization of SLN of Compritol® by Spray Flash Evaporation

2.2.2.1. Preparation of Solid Nanoparticles of Compritol® by Spray Flash Evaporation. SLN of pure Compritol® were produced using the Spray-Flash Evaporation process developed by the NS3E laboratory (Risse et al., 2013). SFE is a new technique to continuously prepare nanocrystals or nano-cocrystals of organic materials (Risse et al., 2012; Spitzer et al., 2014). The process consists in a continuous nanocrystallization by superheating a solvent sprayed into vacuum thus flashing. The solution of Compritol® in dichloromethane is maintained under pressure at 40 bar and heated at 160 °C and then sprayed by a hollow cone nozzle (60 μm diameter) in a tank under vacuum (5–10 mbar). The pressure difference and the sudden temperature decrease result in the dichloromethane evaporation and crystallization of Compritol® in SLN. The concentration of lipid in dichloromethane tested in this study was 1, 2, 4 and 10% *w*/w. After the SFE process, the SLN of pure Compritol® possess the same chemical composition and physical state as Compritol® 888 ATO as demonstrated by Differential Scanning Calorimetry, X-ray Diffractometry, Infrared and Raman spectroscopies (Figs. SI 1–4).

2.2.2.2. Dimensional Characterization of SLN Obtained by SFE. The dimensional characterization of SLN obtained by SFE was performed by scanning electron microscopy - field emission guns (SEM-FEG, NanoSEM 450, FEI-Thermo Fisher, Merignac, France) at 15 kV. The magnification used is × 20,000. Before analysis samples were metallized with a thin gold layer (8–10 nm).

The particle size distribution was calculated from the analysis of about 500 particles from SEM images with the software Gwyddion 2.40. All particle size measurements are performed in quadriplicate and expressed in number (mean ± standard deviation, n = 4).

2.2.3. In vitro Lipolysis of SLN

2.2.3.1. Preparation of Media and Enzyme Suspension. The lipolysis medium and pancreatin solution were prepared according to the recommendations of the Lipid Formulation Classification System (LFCS) Consortium as described in (Williams et al., 2012).

The lipolysis medium is prepared by adding L-α-phosphatidylcholine (0.576 g/L) and NaTDC (1.565 g/L) in the lipolysis buffer. The medium is stirred overnight to allow the complete solubilization of L-α-phosphatidylcholine.

The pancreatin solution is prepared by adding 1 g of pancreatin powder in 5 mL of lipolysis buffer. After 10 min of magnetic stirring the suspension is centrifuged (Universal centrifuge 320R, Hettich, Germany) at 2800*g* and 5 °C for 10 min. The supernatant is sampled to

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