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Engineering of phosphatidylcholine-based solid lipid nanocarriers for flavonoids delivery

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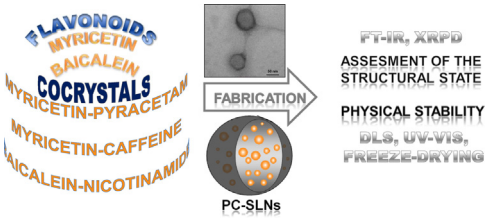
HIGHLIGHTS

- Phosphatidylcholine-SLNs loaded with flavonoids and their cocrystals were prepared.
- The most monodisperse SLNs were formed for the surfactant:lipid ratio equal to 3:2.
- The crystalline structures of the active cargoes were confirmed by FT-IR and XRPD.
- Storage for nine months and freeze drying had no effect on the (PC)-SLNs stability.

GRAPHICAL ABSTRACT



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ABSTRACT

The present study has been focused on determination and evaluation of three different preparation techniques, i.e., solvent-diffusion, hot homogenization-ultrasonification and microemulsification, applied in fabrication of biocompatible phosphatidylcholine solid lipid nanoparticles ((PC)-SLNs), containing Polawax National Formulary (NF) in the internal lipid phase. The fabricated lipid nanoparticles were loaded with the newly synthesized flavonoid cocrystals, i.e., baicalein–nicotinamide (1:1) (BaiNam), myricetin–piracetam (1:1) (MyrPac) and myricetin–caffeine (1:1) (MyrCaf) cocrystals in relation to the starting flavonoids, differing in solubility and physical state. The assessment of all studied drugs entrapment and availability in aqueous SLN dispersions has been carried out; the size along with size distribution of lipid nanoparticles loaded with the studied flavonoids cocrystals and flavonoids was determined by the DLS technique, while the structural changes—by FT-IR spectroscopy and X-ray powder diffraction (XRPD) of the lipid nanomatrices. XRPD and FT-IR analyses confirmed that parent flavonoids as well as their cocrystals are present in the nanoparticles fabricated with solvent-diffusion method as physical mixtures with the lipid and their crystalline structures at least partially conserved. Summarizing, we designed and fabricated the biocompatible SLN-type nanocarriers of enhanced physical stability and availability for the flavonoids delivery—a vast group of naturally occurring polyphenolic compounds, considered as active pharmaceutical ingredients.

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1. Introduction

Solid lipid nanoparticles (SLNs) – successfully developed in the early 1990s – provide currently one of the most convenient colloidal carrier systems as alternative materials to polymeric nanoparticles, fat emulsions, nanoemulsions and liposomes which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion being replaced by a solid or a semi solid lipid. They have many advantages such as good stability, biocompatibility, application versatility, possible targeting by suitable chemical modification, good protection of encapsulated bioactive molecules and sustained drug release, ease of scale-up procedures and low cost [1–5]. Several techniques for SLN fabrication have been developed in the last decade, including both high-pressure homogenization and solvent emulsification–evaporation, but also numerous dispersion techniques such as high speed stirring and ultrasonication, as well as microemulsion-based methods, spray drying or a variety of precipitation techniques [2,3,6–9]. It has to be emphasized that the fabrication of such lipid nanoparticles for targeted applications by means of any of the above mentioned methods often requires close monitoring of the particle size along with its distribution, charge, shape, physical state and other interfacial properties such as, e.g., rheology, density, biological responsiveness. Commonly, SLNs are produced using techniques based on high pressure homogenization, microemulsion and solvent emulsification–evaporation under different processing parameters to study the effect of a number of variables on their particle size [10–12]. The added value of the above methods resides mainly in the current industry established know-how regarding dispersion and homogenization techniques, making the preparation process flexible and compatible with a full scalability [13].

Generally, the preparation efficacy of solid lipid nanoparticle dispersions and their structural state is strictly related to the selected surfactants, stabilizing the system by means of structure design principles [14]. A variety of different emulsifiers have already been used for the SLNs fabrication such as phospholipids, bile salts, poloxamers, and other ionic and non-ionic surfactants. In parenteral formulations the stabilizing agent is responsible for the SLNs physical stability during storage and upon administration, and then it has to prevent any aggregation phenomena that could lead to serious side effects. In the case of per-oral or dermal routes the surfactants selection is less critical, but its presence may have influence upon the physiological interactions within the formulation components, also on the chemical nature of surfactants, lipids, and active compounds [8,15]. In bulk triglycerides, for instance, admixture of different types of surfactants can cause significant effects upon the kinetics of polymorphic transitions after crystallization [16]. Additionally, high surfactant concentrations might reduce the surface tension and facilitate the particle partition during fabrication and, thus, may affect the SLNs quality and efficiency as the decrease in particle size leads to a tremendous increase in surface area [17,18].

The work reported here extends our recent studies on new drug delivery nanocarriers, their fabrication and imaging, drug encapsulation, release profiles and biological impact [19–22] and has been mainly focused on determination and comparing of three different preparation techniques, i.e., solvent-diffusion (SD), hot homogenization-ultrasonification (HHU) and microemulsification (ME) of biocompatible phosphatidylcholine (PC)-SLNs, containing Polawax NF in the internal lipid phase. All these experiments were attempted to describe the physical state and stability, as well as enhanced availability in aqueous SLN dispersions of newly prepared flavonoid cocrystals, i.e., baicalein–nicotinamide (1:1) (BaiNam), myricetin–piracetam (1:1) (MyrPac) and myricetin–caffeine (1:1) (MyrCaf) cocrystals in relation to the starting flavonoids (for structures and abbreviations see Scheme 1). We applied the PC stabilizer, because stabilization of SLNs with phospholipids, e.g., lecithin, frequently yields those nanodispersions which are homogenous with lesser tendency to agglomerate [16,23]. The size distribution of lipid nanoparticles loaded with the studied flavonoids and their cocrystals was assessed by dynamic light scattering (DLS), shape and morphology—by transmission electron microscopy (TEM) and atomic force microscopy (AFM). The structural changes were monitored by Fourier transform infrared (FT-IR) spectroscopy and X-ray powder diffraction analysis (XRPD) of the lipid nanomatrices. The above mentioned cargo – flavonoid cocrystals and flavonoids themselves – are known to exhibit recognized health-prolonging effects, attributed mainly to their antioxidant, antitumor and anti-inflammatory properties. By virtue of low aqueous solubility and bioavailability, applications of hydrophobic flavonoids as therapeutic agents in treatment and prevention of civilizational diseases is limited and their derivatization has to come into focus [24–26]. Preparation of SLNs loaded with the studied flavonoid cocrystals can provide additional success to the cocrystallization approach [27,28], yielding further improvement of solubility of cocrystallized polyphenolic cargo. Whenever solubility is a limiting factor in the bioavailability of a compound, modulation of solubility can produce unexpected effects in the product bioavailability and its biological function [24] and that is why dissolution studies and entrapment potential are of prime importance in design and fabrication of promising drug delivery systems.

2. Experimental

2.1. Materials

Baicalein and myricetin (both >98% HPLC) were obtained from Sino-Future Bio-Tech Co. Ltd., piracetam (>98% TLC) was obtained from Sigma–Aldrich, whereas caffeine (98.5%) and nicotinamide (99%) were obtained from Acros Organics and all were used without further purification. L-α-Phosphatidylcholine from egg yolk (99% TLC) and polycaprolactone (PCL, M_w ~70,000–90,000) were delivered by Sigma–Aldrich. Emulsifying wax National Formulary (also called Polawax NF) was a kind gift from CRODA Inc. Other reagents and solvents were of commercial grade and were used as received. Water used for all experiments was doubly distilled and purified by means of a Millipore (Bedford, MA) Milli-Q purification system.

2.2. Cocrystallization via solvent-drop grinding

100 mg of flavonoid (baicalein, myricetin) and a 1:1 stoichiometric amount of coformer (nicotinamide, piracetam and caffeine) were combined along with ethyl acetate (one drop, ca. 25 μl) in a 5 ml stainless steel grinding jar with two 7 mm stainless steel grinding balls. Samples were ground in a Narva Vibrator Mill for 30 min (3 × 10 min with 5 min cooling periods) at a rate of 50 Hz. Resulting solids were dried overnight at ambient conditions. Molecular and crystal structures of the baicalein–nicotinamide (1:1) (BaiNam) and myricetin–piracetam (1:1) (MyrPac) cocrystals were previously reported [26,29]. Molecular and crystal structure of the myricetin–caffeine (1:1) (MyrCaf) cocrystal is described in patent application [30].

2.3. Preparation of solid lipid nanoparticles (SLNs) loaded with flavonoid-based cargo by solvent-diffusion and non-solvent techniques.

In the current research flavonoids and cocrystals-loaded SLNs were prepared by three different techniques, i.e., solvent-diffusion

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