Chemistry and Physics of Lipids 165 (2012) 438–453

Contents lists available at SciVerse ScienceDirect

Chemistry and Physics of Lipids

journal homepage: www.elsevier.com/locate/chemphyslip

Lipospheres and pro-nano lipospheres for delivery of poorly water soluble compounds

Anna Elgart, Irina Cherniakov, Yanir Aldouby, Abraham J. Domb, Amnon Hoffman*

Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

ARTICLE INFO

Article history:
Available online 9 February 2012

Keywords:
Lipospheres
Pro-nano lipospheres
Solid lipid nano-particles
Drug delivery
Oral drug delivery
Ocular drug delivery
Parenteral drug delivery

ABSTRACT

Lipospheres are a drug encapsulation system composed of water dispersible solid microparticles of particle size between 0.01 and 100 μm in diameter with a solid hydrophobic lipid core stabilized by a layer of phospholipid molecules embedded in their surface. The bioactive compound is dissolved or dispersed in the solid lipid matrix of the internal core. Since lipospheres were introduced in the beginning of the 1990s, they have been used for the delivery of multiple types of drugs by various routes of administration. Later, a self-assembling pro-nano lipospheres (PNL) encapsulation system was developed for oral drug delivery. Lipospheres have several advantages over other delivery systems, such as better physical stability, low cost of ingredients, ease of preparation and scale-up, high dispersibility in an aqueous medium, high entrapment of hydrophobic drugs, controlled particle size, and extended release of entrapped drug after administration, from a few hours to several days.

This review article focuses on updated information on several aspects of lipospheres and PNL, including preparation techniques, physicochemical properties and *in vitro* evaluation methods. Additionally, it covers lipospheres and PNL utilization for oral, ocular, and parenteral delivery, with special attention to unique considerations and aspects for each route of administration.

1. Introduction

The introduction of combinatorial chemistry accompanied by advances in *in vitro* high throughput screening methods has resulted in the rapid identification of many highly potent but poorly water soluble drug candidates. In fact, to date, more than 40% of new chemical entities are lipophilic and exhibit poor water solubility (Lipinski et al., 2001). Development of such poorly water soluble compounds towards clinically available drugs presents a great challenge facing the pharmaceutical scientists. Consequently, the understanding that the development of new active compounds alone is not enough to guarantee adequate pharmacotherapy of various disease states became widely accepted. Promising results obtained in *in vitro* studies very often are not corroborated by successful *in vivo* data. Multiple reasons stand behind these *in vivo* results. Some drugs do not reach sufficient plasma concentrations due to limited solubility, poor absorption and extensive first pass metabolism. Some are characterized by unpredictable fluctuations in plasma drug levels and thus lack effective dose–response correlation. Poor water solubility might exclude the possibility for IV administration as well. Other drugs are distributed to additional tissues besides the site of action and cause harsh adverse effects or toxicity. Toxicity and lack of therapeutic effect might also result from a drug's decomposition during its voyage from the intestinal lumen to the systemic blood circulation.

A promising strategy to overcome these obstacles is the development of suitable drug delivery systems (DDS). The understanding that the *in vivo* fate of the drug is dictated not only by the drug itself, but also by the mode of administration and the carrier system which should enable an optimal drug release profile according to the therapy requirements is crucial for such development (Mehnert and Mader, 2001). One of the most popular pharmaceutical approaches to overcome these obstacles is the use of various nano-dispersion systems as carriers of drug substances.

Though the concept of the essential scientific field of modern times – nanotechnology – was introduced in 1959 by Feynman in his famous lecture "There's plenty room at the bottom", the primary development of nanotechnology occurred only in the

Abbreviations: AFM, atomic force microscopy; AUC, area under the curve; BCS, biopharmaceutical classification system; BS, bile salt; CNS, central nervous system; CsA, cyclosporine A; DDS, drug delivery system; DG, diglyceride; DSC, differential scanning calorimetry; EE, entrapment efficiency; FA, fatty acid; GI, gastro-intestinal; HLB, hydrophilic lipophilic balance; LC, loading capacity; LD, laser diffraction; MG, monoglyceride; NMR, nuclear magnetic resonance; PCS, photon correlation spectroscopy; PE, phosphatidylethanolamine; PNL, pro-nano lipospheres; RES, reticuloendothelial system; SEM, scanning electron microscopy; SLN, solid lipid-based nanoparticle; TEM, transmission electron microscopy; TG, triglyceride; TNBS, trinitrobenzenesulfonic acid; XRD, X-ray diffractometry.

* Corresponding author at: Department of Pharmaceutics, School of Pharmacy, The Hebrew University of Jerusalem, P.O. Box 12065, Jerusalem 91120, Israel. Tel.: +972 2 6757014; fax: +972 2 6757246.
E-mail address: amnonh@ekmd.huji.ac.il (A. Hoffman).

0009-3084/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.chemphyslip.2012.01.007

nineteen eighties and the early nineties. The invention of the scanning tunneling microscope (STM) by Binnig and Rohrer is considered by some to be the actual beginning in the development of nanotechnologies. There are many variations of the definition of the term "nanotechnology" according to the field in which nanotechnology is applied. The US National Science Foundation defined nanotechnology as science, engineering, and technology conducted at the nano-scale of approximately 1–100 nm.

The application of nanotechnology in drug delivery systems is a very popular approach in the pharmaceutical industry to improve the bioavailability of drugs. There are a number of areas in which nanotechnology is being applied in drug delivery, *e.g.* improving the bioavailability of poorly water soluble drugs (Hu et al., 2004; Li et al., 2009; Zhang et al., 2011; Manjunath and Venkateswarlu, 2006), drug targeting *i.e.* transporting therapeutic agents to a specific cell or tissue (Wong et al., 2007) and controlled release delivery systems (Yang et al., 1999; zur Muhlen et al., 1998).

Lipospheres are lipid-based water dispersible solid particles of particle size between 0.01 and 100 μm in diameter composed of a solid hydrophobic lipid core (triglycerides), stabilized by a layer of phospholipid molecules embedded in their surface. The lipospheres are suitable for oral, parenteral and topical drug delivery of bioactive compounds and are designed to overcome the drawbacks associated with traditional colloidal systems such as emulsions, liposomes and polymeric nanoparticles (Domb et al., 1996; Maniar et al., 1991).

The internal core contains the bioactive compound dissolved or dispersed in the solid fat matrix (Bekerman et al., 2004).Various lipospheres have been used for the controlled delivery of different types of drugs including anti-inflammatory compounds, local anesthetics, antibiotics, and anticancer agents, as well as carriers of vaccines and adjuvants (Domb, 2006; Amselem, 1996; Amselem et al., 1992b,a).

Similar systems based on solid fats and phospholipids have been described, as well as solid lipid nanospheres (SLN) which are essentially nano-size lipospheres. All of the above were extensively reviewed elsewhere (Domb, 2006; Muller et al., 2000).

Passive and active targeting of nano-lipospheres is also possible based on two different approaches. Firstly, nano-lipospheres would be able to deliver a concentrated dose of drug in the vicinity of the tumor *via* the enhanced permeability (passive targeting) and retention effect. Secondly, active targeting to various tissues may be achieved *via* utilization of ligands on the surface of nanoparticles. In addition, nano-lipospheres would reduce the drug's presence in healthy tissues by limiting drug distribution to the target organ (Irache et al., 2011). The broad subject of targeting, and especially active and carrier mediated targeting of nanoparticles is beyond the scope of this review and is extensively reviewed elsewhere (Peer et al., 2007; Chrastina et al., 2011; Shapira et al., in press).

Lipospheres have several advantages over other particulate delivery systems such as emulsions, liposomes and microspheres, including: improved drug stability, formulation stability, the ability to freeze dry and reconstitute, the possibility for controlled drug release, high drug payload, controlled particle size and the avoidance of carrier toxicity and the presence of organic solvents. Advantages of the use of lipospheres for oral administration include the possibility for drug protection from hydrolysis, as well as increased drug bioavailability and prolonged plasma levels (Souto and Muller, 2007). In addition, the matrix is composed of physiological components and/or excipients of accepted status (*e.g.* GRAS status), which reduces the risk for acute/chronic toxicity (Domb, 2006). On the other hand, the disadvantages of such delivery systems are associated mostly with their preparation techniques involving high pressure and rapid temperature changes, and include high pressure induced drug degradation, lipid crystallization, gelation phenomena and co-existence of several colloidal species (Mehnert and Mader, 2001). Today, several techniques are employed to produce lipospheres, such as high pressure homogenization, hot and cold homogenization, solvent emulsification evaporation, *etc.* (Souto and Muller, 2007). An alternative method is *in situ* preparation of lipospheres with a particle size below 100 nm. This method was developed by using a dispersible preconcentrate system (Bekerman et al., 2004). This delivery system, termed pro-nano liposphere (PNL), is based on a solution containing the drug, triglyceride, phospholipid and other additives in a mixture of common surfactants, and an organic solvent that is miscible with all components. This solution spontaneously forms nanoparticles when gently mixed in an aqueous media, such as the upper GI lumen content.

This review will focus on updated information on the preparation, physicochemical properties and *in vitro* evaluation of lipospheres and PNL as carrier systems for poor water-soluble drugs. These lipid dispersions can be used for different routes of administration. The peroral route is the most preferred mode of drug administration and the parenteral route is the most challenging one. Thus, the center of attention of this review will be nano-dispersion systems for parenteral and peroral administration of poor water-soluble compounds. Nevertheless, ocular and CNS-targeted administrations will be discussed as well.

2. Preparation of lipospheres and PNL

The internal hydrophobic core of lipospheres is composed of lipids, mainly solid triglycerides, while the surface activity of liposphere particles is provided by the surrounding phospholipid layer. The clear advantage of lipospheres is the fact that the lipid core consists of physiological naturally occurring biodegradable lipids, thus minimizing the danger of acute and chronic toxicity.

The lipid that constitutes the core component of the lipospheres and PNL is solid at room temperature, and might melt, or stay solid at body temperature, depending on the particle design. By utilizing solid lipid as a core, several setbacks associated with the usage of liquid or semi-liquid lipid core might be reduced or avoided, *i.e.* inherent instability and irreversible drug/excipient precipitation (Tang et al., 2008).

Usually, the oil, which has a maximum solubilizing potential for the drug under investigation, is initially selected with the intention of achieving the maximal drug loading in the lipospheres. Concurrently, the selected oil should be able to yield particles with nano-range size. Hence, the choice of the oily phase is often a compromise between its ability to solubilize the drug and its ability to facilitate formation of a nano-encapsulation system with desired characteristics (Date et al., 2010).

The neutral lipids that are usually utilized for the hydrophobic core of the liposphere formulations are tricaprin, trilaurin, tristearin, stearic acid, ethyl stearate, and hydrogenated vegetable oil. Modified or hydrolyzed vegetable oils have also been widely used since these excipients exhibit better drug solubility properties. They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion (Gursoy and Benita, 2004).

The choice of an appropriate surfactant for the liposphere formulations is often dictated by safety considerations. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants. Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen. The acceptability of the selected surfactant for the desired route of administration and its regulatory status (*e.g.*, generally regarded as safe [GRAS] status) must also be considered (Gursoy and Benita, 2004). It should be noted that the surfactants are not innocuous and they have