Colloids and Surfaces A: Physicochem. Eng. Aspects 354 (2010) 308–313

Contents lists available at ScienceDirect

Colloids and Surfaces A: Physicochemical and Engineering Aspects

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

Induced surface activity of supramolecular cyclodextrin–statin complexes: Relevance in drug delivery

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ARTICLE INFO

Article history:
Received 22 June 2009
Received in revised form 2 September 2009
Accepted 3 September 2009
Available online 9 September 2009

Dedicated to Professor Dieter Vollhardt.

Keywords:
Cyclodextrins
Statins
Inclusion complexes
Surface activity
Drug delivery
Supramolecular associates

ABSTRACT

Complexation of active therapeutic agents with cyclodextrins (CDs) offers potential uses in pharmaceutical and biomedical applications for controlling drug delivery and targeting. This paper reports on possible enhancement of the aqueous solubility and bioavailability of sparingly soluble statins (simvastatin and lovastatin) by inclusion complexation with native β-cyclodextrin and a chemically modified β-cyclodextrin, respectively. Complexation-induced surface activity of the supramolecular associates and the effect of the pure CDs and the amphiphilic CD–statin complexes on the physical stability of colloidal liposomes of dipalmitoyl phosphatidyl choline (DPPC) are discussed.

It was shown that complexation with either cyclodextrin may lead to considerable improvement of the aqueous solubilities of both statins. Randomly methylated β-cyclodextrin (RAMEB) showed particularly outstanding solubilizing effects.

The cyclodextrin molecules dissolved in the medium of liposome dispersions strongly reduced the physical stability of the phospholipid membranes. Complexation of the hydrophobic DPPC chains with cyclodextrins may ultimately lead to disintegration of the vesicles. In ternary systems, where due to the complexation of the pharmacon with the cyclodextrin amphiphilic CD–statin associates could develop, an enhanced and prolonged physical stability of the vesicles could be ensured.

1. Introduction

Improvement of the efficacy and safety of existing medicaments is a fundamental point in pharmaceutical sciences and the related fields. For this reason, considerable efforts have been made, for example, to develop suitable systems for controlled drug delivery, release and targeting, to enhance the solubility and bioavailability of pharmacons and also, to reduce their side effects [1–6].

Over the last decades growing attention has been paid to colloidal and supramolecular drug delivery systems [7–14]. Nanoscale carriers represent novel classes and unique models for delivery of various active materials and as nanoreactors. They may offer potential in improvement the physico-chemical and pharmacological behaviour of drugs bounded to or incorporated into vehicles. Appropriate chemical stability of pharmacons that is required for their applications can also be ensured. Nevertheless, the literature involving nanoscale drug carriers is limited with regard to complex delivery systems [15–21]. Much less is known about how the functional properties can be controlled in combined systems of supramolecular and liposomal drug carriers.

Statins are key pharmacons in coronary heart disease therapy. They can inhibit the rate-limiting steps in cholesterol synthesis and therefore, provide crucial benefits when used in lipid lowering treatments. Chemically different statins differ mostly in their plasma protein binding and solubility, therefore they may exhibit varied efficacy in reducing the low-density lipoprotein (LDL) as well. A hard obstacle in statin therapy is the very low aqueous solubility of the pharmacons. Their bioavailability is, therefore, also low and may exhibit high variability in individuals [22–24].

Cyclodextrins (CDs) are widely used as complexing agents for lipophilic and amphiphilic substances. CD molecules are peculiar cyclic oligomers of α-D-glucose, their shapes resemble truncated cones with primary and secondary hydroxyl groups located around their narrower and wider rim, respectively [25,26]. The mostly used native cyclodextrins consist of 6, 7, and 8 glucose units and according to the number of monomers in the macrocycle, they are named as α-, β-, and γ-cyclodextrin. These molecules have a hydrophobic inner cavity, while the large number of hydroxyl groups on the outer surface makes them water-soluble. Due to this special molecular structure, cyclodextrins are capable of forming inclusion complexes with many drugs and other compounds by taking up a lipophilic guest molecule (or its hydrophobic part) of the appropri-

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doi:10.1016/j.colsurfa.2009.09.008

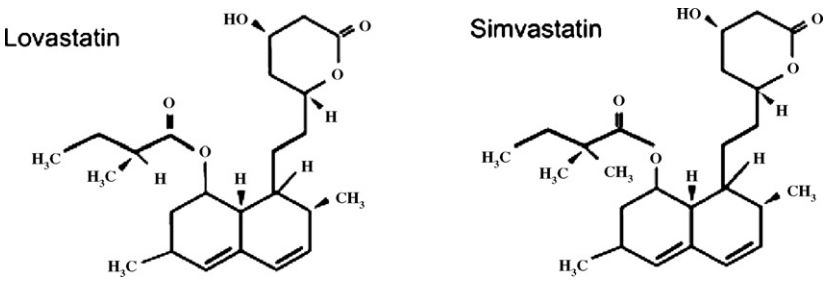

Fig. 1. Chemical structure of lovastatin and simvastatin.

ate size into the cavity [3,16,26]. The chemical structure of CDs can be expediently modified by esterification of the 2-, 3-, and 6-hydroxyl groups and also, other functional groups can be introduced at these sites. For instance, these structural changes perturb the internal hydrogen-bond network of β-CDs, resulting in an elevated water-solubility [10,17,21].

Liposomes are now essential drug delivery vehicles of therapeutics. Phospholipid vesicles with alternating hydrophilic and hydrophobic domains provide opportunities for the formulation of controlled release and site-specific delivery systems. Due to the biphasic nature of vesicles, in principle both lipophilic and hydrophilic ingredients can be accommodated; consequently, almost any type of drug can be encapsulated [1,3,15]. A common disadvantage in using liposomal carriers is, however, that the vesicles usually exhibit a relatively low kinetic stability. For an effectual utilization of the favourable carrier properties of liposomes, an adequate control of their stability is, therefore, a key issue in many practical applications. To ensure prolonged therapeutic activity of active ingredients either bounded or incorporated, keeping long-term vesicle stability is also required [2,3,9,15].

This paper reports on complexation-induced surface activity of supramolecular associates and its possible utilization in drug delivery. To this end, inclusion complexation of two sparingly soluble pharmacons (simvastatin and lovastatin) with cyclodextrins in aqueous media, as well as the interfacial behaviour of statin–cyclodextrin complexes and of their constituents was studied. In addition, the physical stability of colloidal vesicles of dipalmitoyl phosphatidyl choline in combined delivery systems with cyclodextrins and CD-pharmacon inclusion complexes respectively was investigated.

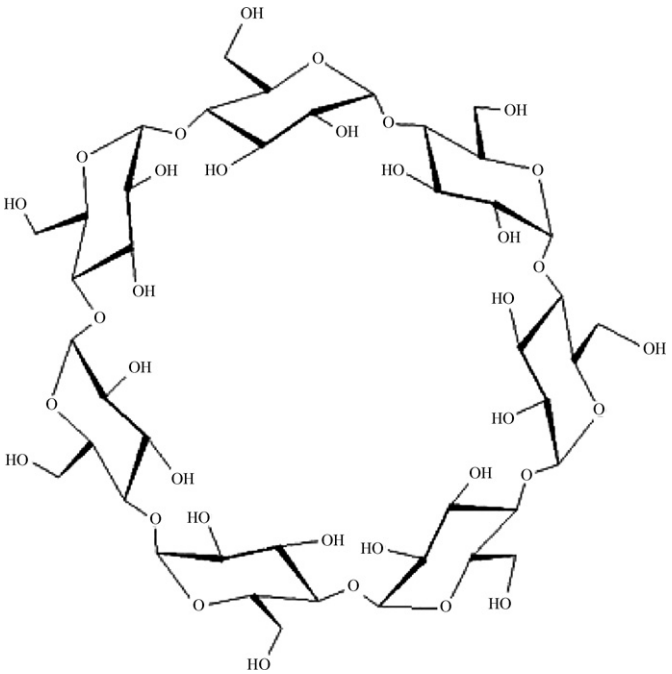

Fig. 2. Simulated model of β-cyclodextrin.

2. Experimental

2.1. Materials

Lovastatin and simvastatin of USP23-grade (Chiesi Farmaceutici SpA, Parma, Italy), as well as native β-cyclodextrin and randomly methylated β-cyclodextrin [RAMEB, *average degree of methylation: 1.8 methyl groups/glucose monomers*] were used in these experiments. Schematic molecular structure of lovastatin and simvastatin is illustrated in Fig. 1.

The cyclodextrins were of analytical grade and manufactured by Cyclolab R&D Ltd. (Budapest, Hungary). A simulated model of β-cyclodextrin is shown in Fig. 2.

L-α-Dipalmitoyl phosphatidyl choline (DPPC) was used for the preparations of liposomes in aqueous dispersions. The phospholipids purchased from Sigma Chemical Co. (St. Louis, MO) were of analytical grade.

2.2. Methods

2.2.1. Solubility measurements

Phase-solubility studies of the statins in aqueous solutions of the cyclodextrins were carried out according to the Higuchi–Connors procedure, as described elsewhere in detail [27,28]. Various amounts of CD were generally dissolved in distilled water and lovastatin or simvastatin was added to the solutions in vast excess. Twenty-four hours of temperature-programmed incubation period in a refrigerated bath (HAAKE PhoenixII C35P instrument) was usually ensured for the dissolution of the pharmacon.

The statin content of the solutions was determined with a UV-spectrophotometric assay based on the Ph Eur directives [30]. The absorbance of lovastatin and simvastatin was measured at 236 and 240 nm, respectively. For these measurements a computer-controlled spectrophotometer (PerkinElmer Lambda Series 2S instrument) was used and the raw spectra were evaluated by OriginLab Origin 7.0 software suite. The solubility isotherms were calculated by using calibration curves determined with ethanolic statin solutions of known concentrations.

2.2.2. Surface tension determinations

Surface tension of the aqueous solutions of pure cyclodextrins and CD–statin solutions of equilibrium state, respectively was measured at 25 °C by computer-controlled Wilhelmy-plate method, using a KSV Sigma 70 instrument.

The concentration of the statin in each solution used for the surface tension measurements corresponded to its saturation concentration, i.e. no unsoluble statin was present in the solution. The