Available online at www.sciencedirect.com
ScienceDirect
Journal of Colloid and Interface Science 317 (2008) 611–619
JOURNAL OF Colloid and Interface Science
www.elsevier.com/locate/jcis

The effect of added liposomes on the rheological properties of a hydrogel: A systematic study

Spyridon Mourtas [a], Maria Haikou [a], Maria Theodoropoulou [a], Christos Tsakiroglou [b], Sophia G. Antimisiaris [a,b,*]

[a] *Laboratory of Pharmaceutical Technology, Department of Pharmacy, School of Health Sciences, University of Patras, 26510 Rio, Greece*
[b] *Foundation for Research and Technology Hellas, Institute of Chemical Engineering and High Temperature Chemical Processes, 26504 Rio, Greece*

Received 19 June 2007; accepted 25 September 2007

Available online 29 September 2007

Abstract

Rheological characteristics of liposome-containing-hydrogels were studied. Sonicated unilamellar vesicles (SUV), prepared by probe sonication and multilamellar vesicles (MLV) prepared by thin film hydration were loaded in a hydrogel containing carbopol 974 NF and hydroxyethylcellulose (Natrosol 250 HX). Phosphatidylcholine (PC) or hydrogenated-PC (HPC) liposomes, plain or mixed with cholesterol (chol) were used. Static (steady-stress sweep-tests) and dynamic (frequency sweep-tests) rheological measurements were carried out. All gels had a shear thinning behaviour (fitted well by Cross model). Zero-rate shear viscosity and power law index values, revealed that PC liposome addition in the hydrogel had minimum effect on its rheological properties even at the highest lipid concentration used (20 mg/ml). Oppositely, HPC (or HPC/chol) liposome addition resulted in significant modulations of the same rheological characteristics (which increased with increasing lipid concentration). HPC liposomes also caused a significant increase in gel relaxation time, which indicates that the elastic character of the gel strengthens as HPC liposome concentration increases. Concluding, liposome composition (membrane rigidity) and lipid concentration, but not liposome size, seem to be very important factors that determine the rheological modulations caused by liposome addition in gels.
© 2007 Elsevier Inc. All rights reserved.

Keywords: Rheological properties; Hydrogels; Gels; Liposomes; Lipid composition; Topical administration; Vaginal

1. Introduction

When mucosal or topical (especially vaginal) delivery of liposome formulations is considered [1,2], the rheological and/or mucoadhesive properties of the liposome dispersions should be adjusted accordingly, depending on the intended route of administration. This can be achieved by adding gelling agents in liposome dispersions [3,4], resulting in drug-in-liposome-in gel, complex formulations.

Such complex gel formulations have been recently studied in our lab in terms of vesicle integrity and drug release kinetics [5,6]. In those studies it was demonstrated [5], that the integrity of liposomal vesicles when dispersed in gels is determined by the rigidity of their lipid membrane. Furthermore, it was observed that liposomal vesicles are protected from the disruptive effects of specific excipients when dispersed in gels, compared to aqueous media [6]. However, the release of drugs from such complex gels is determined by different factors according to the properties of the drug molecule [5]; for hydrophilic drugs (calcein was used as a model) release from complex gels is retarded when rigid-membrane liposomes are used (faster release from PC-compared to DSPC/chol-[liposome-containing] complex gels) while the release rate is not affected by the amount of lipid loaded in the gels. Oppositely, for amphiphilic/lipophilic drugs, as griseofulvin (that was used as a model drug), the release from complex gels is determined by the amount of lipid loaded (or better drug loaded, in the form of liposomes); at high drug loading levels (compared to the aqueous solubility of the drug), complex gels release the drug with constant rate irrespective of the liposome type (PC or DSPC/chol) they contain. In other words, in cases of amphiphilic or lipophilic drugs the lipid concentration added in the gels has a significant impact on

* Corresponding author. Fax: +30 2610 996302.
E-mail address: santimis@upatras.gr (S.G. Antimisiaris).

0021-9797/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.jcis.2007.09.070

the drug release kinetics, while liposome membrane rigidity is not important.

Depending on the specific therapeutic need, lower or higher lipid concentrations may be needed when formulating complex gels, in order to load the required amount of drug in the formulation. In such cases, depending on the drug physicochemical properties, the release kinetics of the drug can be adjusted according to the conclusions of our previous study [5], as discussed above. However, since it is well known that rheological properties of pharmaceutical gels that are intended for topical and especially vaginal administration are very important determinants of their therapeutic outcome [7,8], it is also very important to know if, and to what extent, the presence of liposomes in gels influence their rheological properties. This is the purpose of the present study.

The physical techniques which are used for the study of polymer gel properties, are divided into three general categories [9]: (1) techniques that examine the details of cross-linking at the molecular level (e.g., spectroscopic methods-NMR, UV, IR, etc., with length scale of resolution between 0.1–10 nm); (2) techniques that probe over intermediate distances (e.g., rheo-optical methods, with length scale of resolution between 10 and 10^3 nm); and (3) techniques that probe over long distances (e.g., steady and oscillatory rheological tests, with length scale of resolution between 10^4 and 10^6 nm). The viscoelastic behavior of gels, detected by classical rheology (category 3), depends on various factors like the composition and concentration of the dispersed materials and the lag time between preparation and measurement [10–12]. Like polymer blends [13] the rheological properties of gels are expected to change drastically with the addition of liposomes into them. However, although some studies have been performed for specific formulations, no systematic study has been carried out to examine if and how rheological properties of gels are affected by addition of liposomes, and which liposome characteristics determine the magnitude of such modifications.

Herein we investigated the effect of adding increasing amounts of liposomes in hydrogels on the rheological properties of the hydrogel. Two different types of vesicles (small (sonicated) unilamellar (SUV) and multilamellar (MLV) (which are large vesicles)) consisting of three different lipid compositions (phosphatidylcholine PC, hydrogenated PC (HPC), and HPC/chol (cholesterol)) were added in the gel at different concentrations, in order to study the effects of liposome size, lipid membrane rigidity and lipid concentration on the rheological characteristics of the gel. PC and HPC lipids were selected as two lipids that form membranes with substantially different rigidity (PC forms liquid-state and HPC gel-state membranes). Additionally, since as natural lipids they would be preferable for construction of gels intended for vaginal delivery.

Carbopol 974, an acrylic acid-based polymer, as well as cellulose based hydroxyethyl-cellulose (HEC), are main components of many semisolid formulations (either commercially available or under preclinical evaluation) some of which are intended for vaginal drug delivery. It was recently proposed that mixtures of the above two polymer types have improved rheological properties for vaginal administration of drugs [14]. Indeed such mixture gels were found to be more stable toward temperature and pH changes, compared to the two gels when used individually [15]. For the above stated reasons we chose to use this specific type of mixture gel, in our study.

2. Materials and methods

Phosphatidyl-choline (PC, egg lecithin) and hydrogenated-PC (egg) (HPC) were purchased from Lipoid Gmbh (Ludwigshafen, Germany). The chemical purity of the phospholipids was verified by thin layer chromatography, as described before [16]. Cholesterol (99%) (chol), was purchased from Sigma–Aldrich Hellas (Athens, Greece). Hydroxyethylcellulose (HEC), as Natrosol 250 HX (Hercules Inc.) was kindly provided by Unipharma (Athens, Greece). Carbopol 974 P NF (CRB) was kindly provided by Chemix S.A (Athens, Greece).

All solvents used had analytical or HPLC grade and were purchased from Merck (Germany). All other materials (as salts used for buffer preparation, reagents for lipid concentration determination and surfactants for liposome disruption) had analytical grade and were purchased from Sigma–Aldrich Hellas (Athens, Greece).

A Shimadzu UV-1205 spectrophotometer was utilized for measurement of liposomal lipid concentration.

2.1. Preparation of liposomes

Multilamellar vesicles (MLV) were prepared by the thin film hydration method [17]. In brief, the appropriate weight of lipid (or lipids) was dissolved in a chloroform/methanol (2:1 v/v) mixture, and subsequently evaporated under vacuum until the formation of a thin lipid film. The lipid film was hydrated with the appropriate volume of citrate buffer (pH 5.0), at a temperature above the transition temperature of the lipid used in each case; room temperature in the case of PC liposomes and at 60 °C in the case of HPC. After complete lipid hydration and formation of liposomes, the vesicle dispersion was placed in a bath sonicator (Branson, USA) for 30 min, for vesicle size reduction.

Sonicated unilamellar (SUV) liposomes were prepared by subjecting part of the MLV dispersions prepared (as described above) to probe sonication (Sonics, Vibra Cell, UK) for one or two 10 min cycles, until the dispersions were completely clear. After this, the SUV dispersions were centrifuged at 10.000 rpm (Heraeus Biofuge 28RS, Germany) for 10 min, in order to precipitate any titanium fragments released from the probe as a result of the high intensity of sonication.

Finally all the liposome dispersions prepared, were incubated at a temperature above the lipid transition temperature (in each case) for 1–2 h, in order to anneal structural defects.

2.2. Characterization of liposome preparations

Lipid concentration of liposomes was measured by the Stewart colorimetric assay. In this assay, phospholipids form a colored complex with ammonium ferrothiocyanate (OD 485 nm) that is extracted with chloroform [18]. After measurement, the

Download English Version:

https://daneshyari.com/en/article/611764

Download Persian Version:

https://daneshyari.com/article/611764

Daneshyari.com