Colloids and Surfaces A 537 (2018) 20–27

Contents lists available at ScienceDirect

Colloids and Surfaces A

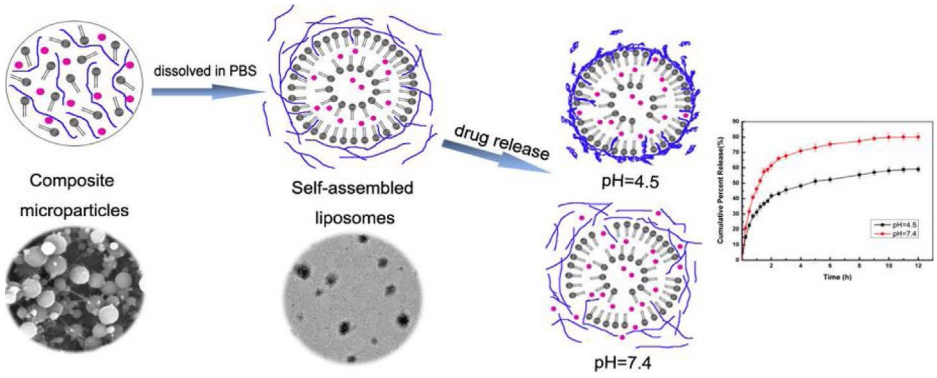
journal homepage: www.elsevier.com/locate/colsurfa

pH-responsive liposomes self-assembled from electrosprayed microparticles, and their drug release properties

Kailin Liu[a], Heyu Li[a], Gareth R. Williams[b,*], Junzi Wu[a], Li-Min Zhu[a,c,**]

[a] College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai, 201620, China
[b] UCL School of Pharmacy, University College London, 29-39 Brunswick Square, London, WC1N 1AX, UK
[c] Key Lab of Science & Technology of Eco-Textiles, Ministry of Education, Donghua University, China

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
pH-dependent liposome
Electrosprayed microparticle
Self-assembly
Oral drug delivery

ABSTRACT

In this work, composite Eudragit L100/phosphatidyl choline microparticles were fabricated through electrospraying. pH-responsive liposomes were found to self-assemble from these when the microparticles were added into aqueous media. The microparticles and the liposomes were both approximately spherical in shape according to electron microscopy, but the liposomes have much smaller diameters (200–300 nm) than the electrosprayed particles (1.6–1.7 μm). The zeta potential of the liposomes is approximately −30 mV, which suggests the formation of stable suspensions. Varying the pH conditions used for self-assembly causes the liposomes to change their shape and structure, due to the influence of the Eudragit molecules. Microparticles comprising Eudragit, phosphatidyl choline and the model drug ketoprofen were also prepared. Upon their addition to water, ketoprofen was found to be loaded into the liposomes self-assembled from the particles with an entrapment efficiency of 75%. pH-dependent release was observed from the drug-loaded liposomes. At pH 4.5, only 58% of the drug loaded was released after 12 h, while 80% was released at pH 7.4. Overall, these results demonstrate that the pH-dependent liposomes developed have great potential for application as stimuli-responsive drug delivery systems.

* Corresponding author at: UCL School of Pharmacy, University College London, 29-39 Brunswick Squre, London, WC1N 1AX, UK.
** Corresponding author at: College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai, 201620, China.
E-mail addresses: g.williams@ucl.ac.uk (G.R. Williams), lzhu@dhu.edu.cn (L.-M. Zhu).

http://dx.doi.org/10.1016/j.colsurfa.2017.09.046
Received 12 July 2017; Received in revised form 24 September 2017; Accepted 25 September 2017
Available online 27 September 2017
0927-7757/

1. Introduction

In recent years, a range of pH-sensitive liposomes, which can control the release of a loaded drug in response to the pH of the surrounding medium, have been reported [1–3]. These liposomes can serve as carriers of many different active ingredients, for instance small organics, peptides, RNA, DNA, and diagnostic agents [4–7]. They also generally have good biocompatibility [8]. There are two key types of pH-dependent liposomes, which are bounded either by natural lipid bilayers or polymer functionalized lipid bilayers. A pH-driven phase transition of the lipid bilayers or of the polymer attached to them permits their contents to be freed into solution in a responsive manner [9]. However, natural phospholipid-based liposomes usually have low stability at low pH values [10]. It is therefore desirable to prepare polymer-functionalized systems to improve stability.

Many studies have reported that liposomes decorated with pH-sensitive polymers are capable of pH-responsive release [11–13]. Eudragit L100, which is synthesized from methacrylic acid and methacrylic acid methyl ester, is one such pH-sensitive polymer. It is widely used in the pharmaceutical industry, for instance as enteric coatings for tablets. It can also be employed for preparing microspheres and nanoparticles for use as targeted gastro-intestinal drug delivery systems [14,15]. Eudragit L100 dissolves only at pH values higher than 6.0, and is insoluble in aqueous media below this pH. Thus, it can be specifically applied to release an incorporated drug only in the lower parts of the gastro-intestinal tract [16].

A number of methods can be applied to obtain pH-sensitive liposomes. For instance, Straubinger et al. used oleic acid and phosphatidylethanolamine to fabricate pH-sensitive liposomes via the evaporation method [17]. In other work, Catalan-Latorre et al. fabricated multicompartment liposomes loaded with curcumin through combining Eudragit S100, hyaluronic acid and a phospholipid using the freeze-drying method [18]. However, these methods can be complex, and often there is solvent residue in the liposomes. As a result, researchers have sought alternative methods for producing liposomes [19–21].

Liposomes form as a result of molecular self-assembly, driven by noncovalent interactions. The spontaneous association of amphiphilic molecules, isolating lipophilic sections from an aqueous medium, for instance, leads to the creation of stable and well-defined supramolecular structures [22]. This approach is important for the fabrication of biomaterials [23–25], but it is challenging to control such a bottom-up process. Therefore, methods to direct the contacts between building blocks and drive the assembly process towards a desired conclusion are required [26–28].

One route that may be used to obtain control over self-assembly processes is electrospraying, a hydrodynamic atomization approach. This is a top-down process which exploits electrical energy to evaporate the solvent from a polymer solution, resulting in solid dispersions in the form of micron-sized particles. Electrospinning is a similar technique, and yields nanoscale fibers. Both electrosprayed particles and electrospun fibers can be exploited as templates to direct the self-assembly of nanoscale-objects from multiple components [29,30]. Self-assembly is achieved by a simple dissolution of the fiber or particle precursors, and the resulting aggregates can easily be loaded with an active ingredient during the assembly process. For instance, Yu et al. prepared core/shell nanofibers by electrospinning, and were able to use these to self-assemble drug-loaded nanoparticles with controllable sizes [31]. Jin and co-workers have also prepared thermosensitive ketoprofen-loaded liposomes via the dissolution of electrosprayed composite microparticles of poly(N-isopropylacrylamide) and phosphatidyl choline [19]. During dissolution, the polymer matrix (which is typically made of a hydrophilic fast dissolving polymer) is believed to help confine the assembling components in close proximity, facilitating their self-aggregation to minimize any interactions between the aqueous medium used for assembly and hydrophobic components in the composites. The liposomes fabricated in this way are generally found to have uniform diameters, and high drug entrapment efficiencies. The fact that they are produced on demand from stable solid dispersions means that the stability issues commonly arising with liposomal formulations can be effectively ameliorated.

The studies reported to date on stimuli-responsive liposomes have generally employed the evaporation method, and there is little work on using electrospinning or electrospraying to this end [19,32]. In this study, we sought to exploit electrospraying to generate microparticles of Eudragit L100 loaded with phosphatidyl choline (PC). When the microparticles were added to water, the PC was found to self-assemble into liposomes, and the physicochemical and biological properties of these were studied in detail. Ketoprofen-loaded systems were further prepared, and their drug release properties examined.

2. Experimental

2.1. Materials

Eudragit L100 (average molecular weight *ca.* 135,000) was provided by Rohm GmbH (Darmstadt, Germany). Phosphatidyl choline (PC, extracted from soybean) was procured from the Sinopharm Chemical Reagent Co. (Shanghai, China). Chloroform and N,N-dimethylacetamide were purchased from the Traditional Industries Co. (Shanghai, China). Ketoprofen (KET) was obtained from Shanghai Greentech Industries Co. (Shanghai, China). Water was double distilled prior to use.

2.2. Electrospraying

Solutions were prepared by adding Eudragit L100 and PC to a mixture of chloroform/N,N-Dimethylacetamide (4:1 v/v) at room temperature and stirring for at least 20 h. Details of the solution compositions are given in Table 1. The fully dissolved solutions were then loaded in 5 mL syringes, which were fitted with a stainless-steel flat-tipped needle (internal diameter 0.5 mm). The syringes were mounted on a syringe pump (KDS100, Cole-Parmer, Vernon Hills, IL, USA) and solution expelled at a rate of 1.0 mL/h. A voltage of 16 kV (ZGF- 2000 power supply, Shanghai Sute Electrical Co. Ltd., China) was supplied between the spinneret and a flat aluminium foil-covered collector (10 × 10 cm). The tip-to-collector distance was set at 25 cm, and experiments performed at 25 ± 2 °C and relative humidity of 50 ± 5%. Six formulations were prepared in total (see Table 1).

2.3. Preparation of liposomes

0.1 g of the electrosprayed particles were removed from the collector and added to 100 mL of phosphate buffered saline (PBS, pH = 7.4) at room temperature.

2.4. Characterization of microparticles

The surface morphology of the microparticles was observed using a JSM-5600LV scanning electron microscope (SEM; JEOL, Tokyo, Japan). The average particle diameter was calculated through measuring more than 100 different particles in SEM images, using the ImageJ software

Table 1
The compositions of the solutions used for electrospraying.

Concentration	F_1	F_2	F_3	F_4	F_5	F_6
$C_{Eudragit}$ (%w/v)	2	2	2	2	2	2
C_{PC} (%w/v)	0	0.5	1	1.5	2	1
C_{KET} (%w/v)	0	0	0	0	0	0.4

$C_{Eudragit}$ denotes the concentration of Eudragit, C_{PC} the concentration of PC, and C_{KET} the concentration of KET.