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Gel formation in systems composed of drug containing catanionic vesicles and oppositely charged hydrophobically modified polymer

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ABSTRACT

The aim of this study was to explore if mixtures of drug containing catanionic vesicles and polymers give rise to gel formation, and if so, if drug release from these gels could be prolonged. Catanionic vesicles formed from the drug substances alprenolol or tetracaine, and the oppositely charged surfactant sodium dodecyl sulphate were mixed with polymers. Three polymers with different properties were employed: one bearing hydrophobic modifications, one positively charged and one positively charged polymer bearing hydrophobic modifications. The structure of the vesicles before and after addition of polymer was investigated by using cryo-TEM. Gel formation was confirmed by using rheological measurements. Drug release was studied using a modified USP paddle method. Gels were observed to form only in the case when catanionic vesicles, most likely with a net negative charge, were mixed with positively charged polymer bearing lipophilic modifications. The release of drug substance from these systems, where the vesicles are not trapped within the gel but constitute a founding part of it, could be significantly prolonged. The drug release rate was found to depend on vesicle concentration to a higher extent than on polymer concentration.

1. Introduction

Gels have a variety of pharmaceutical uses; ocular, cutaneous and nasal to name a few. Due to mucoadhesion [1] or because of their rheological properties [2], gels usually have a considerably longer contact time with mucosa than aqueous solutions. The prolonged contact time can only be advantageous if the drug substance is released from the gel throughout the contact time. As the gel typically contains at least 95% water, free drug molecules usually diffuse through the gel as quickly as through pure water. Therefore, to take advantage of a prolonged contact time the release rate of the drug substance from the gel needs to be prolonged. Prolonged release formulations may increase the bioavailability of the drug compound and/or reduce dosing frequency and thereby increase patient compliance. There has been many strategies to prolong the release from gel formulations; either by formulating the drug substance as a suspension in the gel [3], distributing the substance to micelles [4] or liposomes [5] in the gel, or letting the drug substance interact with the gel forming polymer [6]. A more recent way of prolonging the release of drug substances from gels is by incorporating so called catanionic aggregates, formed by drug substance and an oppositely charged surfactant in the gel [7–11].

Catanionic aggregates are formed spontaneously when solutions of a variety of oppositely charged surfactants are mixed [12,13]. The surfactant mixtures have a complex phase behavior and formation of vesicles and different types of micelles have been observed.

Polymers may stabilize vesicles and function as release rate controllers in drug delivery [14]. There are several possible ways of interaction between the vesicles and the polymers; hydrophobic parts of the polymer can interact with hydrophobic parts of the vesicle [15–17], in charged systems there can be electrostatic interactions [18,19], or there may be a combination of these types of interactions [18,19]. Cross-links formed as a consequence of the interactions may lead to gel formation.

Mixtures of polymers or polyelectrolytes and oppositely charged vesicles have been studied in the past. Interactions in these complex systems give rise to interesting phenomena that can be utilized in pharmaceutics, paint and the cosmetics industry. The polymers used may be of different origin, bear different charges, and have a large variety of modifications. Polymers investigated so far have been of both synthetic and biological origin [16,20]. Some of the latter systems have been suggested as models for living cells [21]. Previous studies have involved vesicles formed from surfactants of classical type; in this study we have explored the

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use of a conventional surfactant in combination with an oppositely charged, surface active, drug substance.

In earlier studies by this research group the drug containing catanionic aggregates, have been incorporated within a conventional, preformed, gel. Usually, a covalently cross-linked gel has been used, and the catanionic aggregates have then been enclosed in these structures [7–11]. The conventional gels typically remain intact at the site of application also after the drug substance has escaped the gel and been absorbed. In this study we explore the possibilities of using the interactions between the catanionic vesicles and the polymers for the actual gel formation. Since the catanionic vesicles most likely form the cross-links that give rise to the gel formation, the gel is expected to break down as the drug substance and the oppositely charged surfactant diffuses from the vesicles. These systems are interesting from a pharmaceutical point of view, since after the active ingredient is removed from the vehicle there is not an "empty" gel left at the application site.

2. Materials and methods

2.1. Materials

Sodium chloride, sodium dodecyl sulfate (SDS), alprenolol hydrochloride and tetracaine hydrochloride was purchased from Sigma Chemical Co. (St. Louis, MO, USA). All substances were of analytic grade or "Ultra" quality. The cationic polymers UCARE JR-400 and SoftCAT SK-MH were kind gifts of The Dow Chemical Company. The uncharged polymer HM(C16-18)-PEG was a kind gift of Akzo Nobel Sweden. The polymers were used as received, without further purification. Carbopol polymers 940 and 1342 were kind gifts of Noveon, Inc. (Breeksville, OH, USA). Millipore water (Millipore, France) was used in all experiments.

JR-400 and SK-MH are hydroxyethylcellulose derivates; JR-400 is an *N*,*N*,*N*-trimenthylammonium derivative and SK-MH is an *N*,*N*-dimethyl-*N*-dodecylammonium derivative, structures are displayed in Fig. 1a and b. JR-400 has a higher degree of cationic substitution and charge density than SK-MH, JR-400 has a nitrogen content of 1.5–2.2% [22] and SK-MH has a nitrogen content of 0.8–1.10% [23]. HM(C16-18)-PEG is an uncharged poly (ethylene glycol), modified with hydophobic hydrocarbon chains comprised of C_{16-18}, the hydrophilic part between these hydrocarbon chains are composed of approximately 280 oxyethylene units, the structure displayed in Fig. 1c. Carbopol 1342 has a lipophilic graft on its backbone, a long chain alkyl acrylate [24].

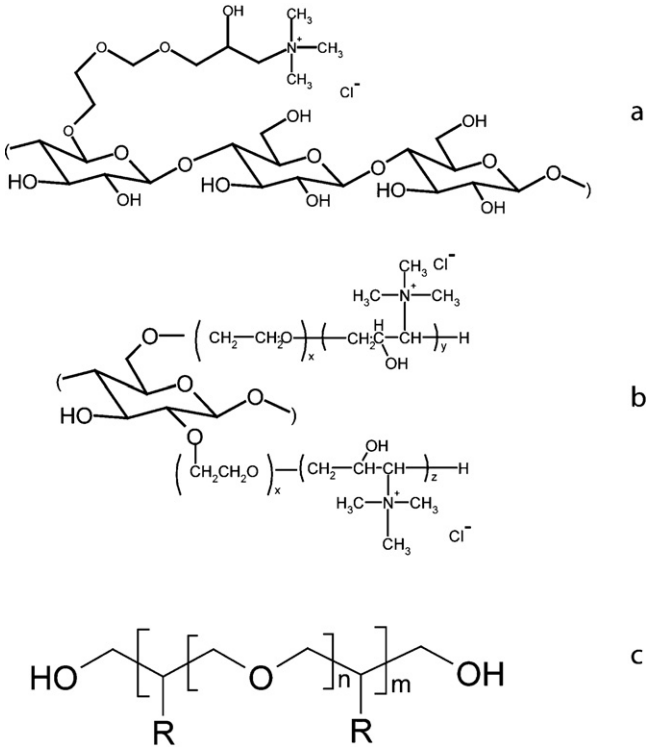

Fig. 1. Molecular structures of (a) JR-400, positively charged polymer and (b) molecular structure of SK-MH, positively charged polymer bearing lipophilic modifications. Both redrawn from DOW product information; (c) HM(C16-18)-PEG. *n* is approximately 280, *R* is 16–18 and *m* is not disclosed, according to Akzo Nobel Sweden.

2.2. Sample preparation and phase studies

2.2.1. Catanionic phase study

The first part of the phase studies consisted of exploring the phase behavior in mixtures of oppositely charged surfactants, where one of the surfactants is a drug substance. Catanionic aggregate mixtures were prepared by mixing solutions of drug substance and oppositely charged surfactant. The proportions of drug substance and surfactant were varied, keeping the total concentration constant; then the total concentrations were varied between 5 and 160 mM. The total surfactant concentration will henceforth be referred to as the vesicle concentration. All mixtures were made with 0.9% sodium chloride solution. The mixtures were allowed to equilibrate for at least 48 h before visual inspection, allowing phase separated mixtures to set. The physical long-term stability was controlled after 5 months. To confirm findings in the visual study solutions containing vesicles were investigated using cryogenic transmission electron microscopy (cryo-TEM). The phase behavior of tetracaine and SDS has previously been studied thoroughly by this research group [9] and those results were used to find suitable ratios and concentrations where vesicle content was observed in non-phase separated samples. A more detailed presentation of those results can be found elsewhere [9]. The alprenolol and SDS phase table explored and used in this study is presented in this work.

2.2.2. Vesicle–polymer gel formation study

To study if gel formation could occur, catanionic vesicle containing solutions and polymer solutions were mixed. Three different polymers were used; one bearing positive charges, one uncharged polymer bearing lipophilic modifications, and one polymer bearing lipophilic modifications and positive charges. These variations were included to show which type, or types, of properties that are important for gel formation. In the vesicle–polymer study the vesicle containing solutions were mixed with polymer solutions of different concentrations, both of double the intended final concentrations, so that when equal volumes were mixed the desired concentrations were obtained. These samples were mixed with magnetic stirrers for several days before evaluation as the polymer solutions were very viscous. Samples containing large amounts of trapped air were centrifuged before evaluation. Mixtures appearing to have resulted in gel formation were examined further using rheological measurements and cryo-TEM.

2.3. Cryogenic transmission electron spectroscopy

Cryo-TEM was used to confirm the results of the visual phase studies. A drop of the sample was deposited on a holey polymer film covered grid. Excess sample was blotted away with filter paper and the remaining liquid was vitrified by plunging the grid into liquid ethane held at a temperature of −170 °C. After transfer to a Zeiss EM 902 transmission electron microscope the films were kept below −165 °C for the viewing process. All observations were made in the zero-loss bright-field mode at an accelerating