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Can a catanionic surfactant mixture act as a drug delivery vehicle?

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ABSTRACT

Surfactants can self-assemble in dilute aqueous solutions into a variety of microstructures, including micelles, vesicles, and bilayers. Recently, there has been an increasing interest in unilamellar vesicles, which are composed of a closed bilayer that separates an inner aqueous compartment from the outer aqueous environment. This interest is motivated by their potential to be applied as vehicles for active agents in drug delivery via several routes of administration. Active drug molecules can be encapsulated in the bilayer membrane if they are lipophilic or in the core of the vesicle if they are hydrophilic. Furthermore vesicles formed by mixing of cationic and anionic surfactants (so called 'catanionic' systems) can be used as models for biological membranes as they have low critical micelle concentration (*cmc*) and are highly biocompatible. In this work the formation of amino acid based mixed surfactant vesicles and their stabilization and biocompatibility were studied systematically using several instrumental techniques.

1. Introduction

Drug delivery is an interdisciplinary area of research in which people from almost every scientific discipline can make a significant contribution. Catanionic vesicles have already been applied as templates for drug-delivery applications as well as in nano-drug carrier synthesis [1–5]. Catanionic vesicles can be tailored in size and bi-layer thickness by changing the characteristics of the two surfactants, such as the type of the polar head and chain length, presence of salt and cholesterol, etc [6]. Owing to the vesicle structure, they compartmentalize the aqueous domain in the inner core of the vesicles which is separated from the outer water by a hydrophobic bi-layer [7]. They display therefore, interesting features like pH sensitivity as far as the synthesis of different stable vesicles of finite size is involved [8]. Greater the sensitivity of the vesicle architecture in differing pH in the local environment greater is the use as the template for drug delivery systems. However, as technology has advanced over the past few decades, methods of drug delivery became more sophisticated and rational, and people incite new strategies, including novel liposomes or vesicles for drug administration.

Attempts have been made to explore the potential applications of the vesicular systems to act as drug carriers in pharmaceutical industries. The formation, stability and biocompatibility studies of the mixed surfactant vesicles were thus examined in terms of different characterization techniques, hemolysis and MTT (3-(4,5 dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide) assay. Although this type of mixed surfactant vesicle applied here exhibits enhanced stability in the presence of external stimuli, like salt, cholesterol, pH it is expected to encapsulate drugs in its core [6]. The drugs encapsulated in the

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aqueous core of the vesicles are also stable over a certain period of time in the physiological pH-temperature ranges, and can be considered as an effective drug delivery vehicle. Therefore, the main objective of the present study is to investigate the vesicle stability, pH-induced release of model drugs, hemocompatibility and cytotoxicity of the mixed surfactant vesicles using amino acid based carboxylate surfactants sodium *N*-alkanoyl-L-sarcosinate (SOS, SDS, SLS, and STS) of varying chain length and two commercial cationic surfactants cetyltrimethylammonium hydroxide (CTAOH) and dodecyltrimethylammonium hydroxide (DTAOH).

2. Experimental section

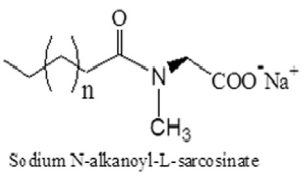
2.1. Materials

Sodium *N*-alkanoyl-L-sarcosinate (SAS) surfactants with different chain lengths (see Fig. 1 for structure) employed in this work were synthesized according to the reported methods [9,10]. L-alanine was obtained from SRL (Mumbai, India) and was used without further purification. The cationic surfactants, CTAOH and DTAOH, were prepared from CTAB and DTAB, respectively, by using anionic ion exchanger resin, where the ion exchange capacity of the anionic exchanger was fixed at $\geq$0.9 mM/ml. The model drug calcein (a fluorescent dye) was purchased from Aldrich (Milwaukee, WI, USA) and was used after recrystallization at least three times from an ethanol or acetone–ethanol (1:1) mixture. All the reagents and solvents used in this experiment were of good quality commercially available and were purified or distilled fresh whenever required.

2.2. General instrumentation and solution preparation

All the measurements were carried out at room temperature (30 °C) unless otherwise mentioned. Temperature controlled measurements were carried out using a circulating water bath. Samples were prepared by combining the cationic and anionic surfactants at a desired concentration and mixing ratio from the individual surfactant stock solution. After sealing the samples were mixed by simple hand agitation. The composition of the mixtures thus obtained is expressed in terms of molar fraction, X_1 (=[SAS]/([SAS] + [CTAOH])) of SAS. The pH of the samples was constant (pH 7.4) at 20 mM phosphate buffer having an ionic strength of 0.0126 M. Prior to observation and measurements, the solutions were allowed to equilibrate at room temperature for a 2–3 h. Transmission electron microscopy (TEM), dye entrapment and vesicle stability determination, hemolytic assay and cytotoxicity assay (cell culture and MTT assay) were performed as per our previous investigations [11].

The phase behavior of the SAS-CTAOH (or DTAOH) mixtures at different mixing ratios and concentrations was first investigated for aqueous solubility. It was observed that binary mixtures of SAS and CTAOH produced optically isotropic clear solutions at all compositions and total concentrations tested.



n	Abbreviations
4	SOS
6	SDS
8	SLS
10	STS

Fig. 1. Chemical structure of sodium *N*-alkanoyl-L-sarcosinate (SAS).

3. Results and discussion

The catanionic mixture formed by anionic amino acid based carboxylate surfactants sodium *N*-alkanoyl-L-alaninate (SOS, SDS, SLS, and STS) of varying chain length and two commercial cationic surfactants DTAOH or CTAOH with different chain lengths forms a strong synergistic interaction and stable vesicles in different compositions as discussed earlier [12]. The presence of vesicles are mostly seen at $X_1 = 0.50$, whereas in other compositions both micelles and vesicles are found. The surface tension (also *cmc*) value of the mixed system is found to be minimum at different compositions and much lower than the pure and individual surfactants [13]. The fluorescence anisotropy values are also much higher (>0.140) in different compositions [11] which suggest the formation of vesicular systems which is further supported by the transmission electron micrograph (TEM) in Fig. 2. The TEM images show the hollow sphere structure of the vesicles and the hydrodynamic diameter (d_H) of the vesicles is in the range of ~30–200 nm. The drug molecules can easily be encapsulated in the aqueous core of these vesicles. The mixed surfactant vesicles are also stable (stability > 60 days), which can be used as drug carriers in pharmaceutical industry. The vesicles are also stable with time in the presence of additives like sodium chloride, cholesterol etc.

In order to investigate drug entrapment ability and pH-induced release by the vesicle structures, calcein was used

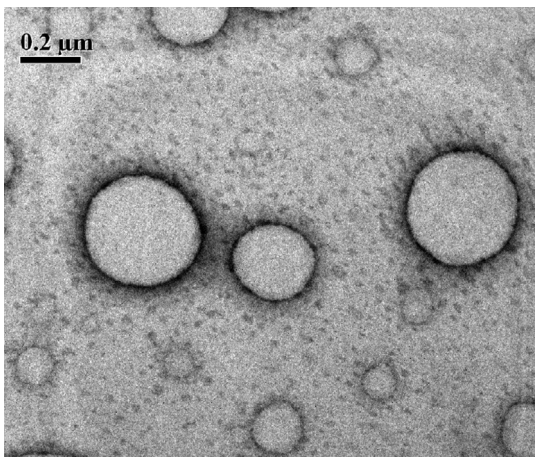


Fig. 2. Negatively strained (1% uranyl acetate) transmission electron micrograph of the SLS-CTAOH (1 mM, $X_1 = 0.2$) mixture.