



Enhanced solubilization of curcumin in mixed surfactant vesicles



Arun Kumar^a, Gurpreet Kaur^a, S.K. Kansal^b, Ganga Ram Chaudhary^a, S.K. Mehta^{a,*}

^a Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh 160 014, India

^b Dr. SSB University Institute of Chemical Engineering & Technology, Panjab University, Chandigarh 160 014, India

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ABSTRACT

Self-assemblies of equimolar double and single chain mixed ionic surfactants, with increasing numbers of carbon atoms of double chain surfactant, were analyzed on the basis of fluorescence and conductivity results. Attempts were also made to enhance the solubilization of curcumin in aqueous equimolar mixed surfactant systems. Mixed surfactant assembly was successful in retarding the degradation of curcumin in alkaline media (only 25–28 40% degraded in 10 h at pH 13). Fluorescence spectroscopy and fluorescence quenching methods were employed to predict the binding position and mechanism of curcumin with self-assemblies. Results indicate that the interactions take place according to both dynamic and static quenching mechanisms and curcumin was distributed in a palisade layer of mixed aggregates. Antioxidant activity (using DPPH radical) and biocompatibility (using calf-thymus DNA) of curcumin-loaded mixed surfactant formulations were also evaluated. The prepared systems improved the stability, solubility and antioxidant activity of curcumin and additionally are biocompatible.

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1. Introduction

Double chain surfactants form bilayer structures (vesicles) in aqueous medium at critical vesicle concentration (cvc). The addition of a single-chain surfactant to the vesicles results in the formation of a mixed system with the appearance of many stable mixed vesicles (Ollivon, Lesieur, Grabielle-Madelmont, & Paternostre, 2000). Such kinds of mixed systems are important, since they provide interesting information for understanding purification, solubilization, and reconstitution processes of biological membranes (Deo & Somasundaran, 2003a, 2003b; Majhi & Blume, 2002; Peter, Nikolai, & Denkov, 2005).

Aqueous solubilization of water-insoluble materials is highly important for pharmaceuticals, detergency, emulsion polymerization, enhanced oil recovery, and textile dyeing. Among colloidal self assembled structures, micelles/vesicles are efficiently used solubilizers (Maswal, Pandith, Islam, & Dar, 2013; Ribeiro et al., 2012; Wong et al., 2004), but the solubilization properties of bilayers of vesicles are superior (Lawrence, 1994).

Curcumin is a hydrophobic natural product extracted from turmeric (*Curcuma longa*), a principal ingredient of foodstuffs with many reported medicinal properties (Deters et al., 2008). Studies have shown that curcumin possesses anticancer (Shi et al., 2006), anti-inflammatory (Lantz, Chen, Solyom, Jolad, & Timmermann,

2005) and antioxidant (Ruby, Kuttan, Babu, Rajasekharan, & Kuttan, 1995) properties and is active against Alzheimer's disease (Yang et al., 2005). A primary challenge that significantly restricts its bioavailability, is poor aqueous solubility (~20 µg/ml) (Wang et al., 1997). Another major challenge is alkaline instability; it undergoes rapid degradation by alkaline hydrolysis, followed by molecular fragmentation. An attractive approach to address the poor aqueous solubility and stability issues is to encapsulate curcumin in surfactant aggregates. Several studies have shown that curcumin has significantly higher solubility and stability in micellar solutions (Chignell et al., 1994; Tønnesen, 2002; Zhou, Yang, & Wang, 2014).

The target of the present work is to utilize aggregates of the double and single chained mixed cationic surfactants to enhance solubility, alkaline stability and antioxidant properties of curcumin. The mixed surfactant aggregates offer advantages over single surfactant systems in that (i) they provide more hydrophobic environment (bilayer structure) than do single surfactant systems, (ii) the charges on the surface as well as at the centre of the mixed vesicles are exceptionally helpful for solubilization and (iii) they are more stable aggregates than are single surfactant systems. To achieve this goal, a series of double chained surfactants, with increasing chain length (C12–18), have been mixed with single chained dodecylethyldimethylammonium bromide (DDAB). First, the aggregation behavior of didodecyldimethylammonium bromide (DiDDAB), dimethylditetradecylammonium bromide (DMDTAB), dihexadecyldimethylammonium bromide (DiCTAB)

* Corresponding author.

E-mail address: skmehta@pu.ac.in (S.K. Mehta).

and dioctadecyldimethylammonium bromide (DODAB) at 1:1 ratio with DDAB has been explored. Second, the prepared assemblies were utilised for aqueous solubilization and stabilization of curcumin, especially in alkaline media. Third, efforts were made to evaluate the effect of formulations on germinal cells, and specifically, DNA.

2. Materials and methods

2.1. Materials

Dodecylethyldimethylammonium bromide (DDAB $\geq 98\%$), didodecyldimethylammonium bromide (DiDDAB $\geq 98\%$), ditetradecyldimethylammonium bromide (DMDTAB $\geq 97\%$), and dihexadecyldimethylammonium bromide (DiCTAB $\geq 97\%$) were purchased from Fluka. Dioctadecyldimethylammonium bromide (DODAB $\geq 98\%$), curcumin ($\geq 99\%$), sodium hydroxide (NaOH), cetylpyridinium chloride (CPC $\geq 98\%$), anilino-naphthalene-8-sulfonic acid (ANS $\geq 99\%$), acrylamide ($\geq 99\%$), ct-DNA (purity $\geq 98\%$), ethidium bromide (EB) (purity $\approx 95\%$) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) (purity $\geq 98\%$) were procured from Sigma Aldrich. Potassium dihydrogen phosphate (KH_2PO_4) (purity 98%) and disodium hydrogen phosphate (Na_2HPO_4) (99%) were obtained from Merck. Potassium iodide (ultra pure) was purchased from Sarabhai M. Chemicals, Limited India. Absolute ethanol (purity $\geq 96\%$) and methanol (purity $\geq 99\%$) were purchased from Chang Shu Gshu Yang Yuan and Fisher scientific, respectively. Water used for the preparation of samples was de-ionized and triple-distilled (conductivity $\leq 3 \mu\text{S}$ at 298.15 K).

2.2. Methods

To measure critical aggregation concentration (cac) of mixed surfactant systems, at equimolar ratio 1:1, conductivity measurements were carried out, using a Pico conductivity meter from Labindia and thermostatic glass cell with two platinum electrodes. The glass cell was connected to the RE320 Ecoline thermostat controlled to better than $\pm 0.01 \text{ K}$ temperature variations. The constant of the cell used was 1.11 cm^{-1} . The measurement of conductivity was carried out with absolute accuracy to $\pm 3\%$. Measurement was carried out volumetrically with increasing total concentrations of equimolar surfactant concentrations in triple-distilled water. The cac of mixed surfactants was also determined, using fluorescence (Hitachi-F7000) with quartz cells. ANS was used as a probe with an excitation at 330 nm, scan rate 1200 nm/min and emission collection range of 340–650 nm. Excitation and emission slits were fixed at 5 nm. For solubility studies, UV–vis. spectra were recorded with a Thermo Scientific Evolution 160 UV–vis. spectrophotometer using quartz cells and absorbance spectra were collected in the range of 350–650 nm. All the experiments were performed in duplicate to assess the reproducibility. Position of the curcumin in vesicles was evaluated by a fluorescence quenching technique, where excitation was done at 425 nm, with slit widths at 5 nm, and collection range was from 430–700 nm. Concentration of each of the quenchers (potassium iodide and acrylamide) was varied from 0 to 0.15 M. Aggregation number of mixed surfactant systems was also determined by the fluorescence quenching technique. Instrument settings were the same as for above measurement, using stock solutions of curcumin (20 μM) and potassium iodide (KI) as quenchers. Stability of curcumin in alkaline medium, in the presence of pure as well as in mixed surfactant formulations, was assessed by UV–vis. spectroscopy for up to 10 h. Scavenging radical activity of curcumin with and without mixed surfactants was analysed by UV–vis. spectrophotometry, using the DPPH ($\lambda_{\text{max}} = 535 \text{ nm}$) method. ct-DNA binding studies were carried out

using fluorescence quenching of ethidium bromide (EB) (4 μM). Two sets of experiments were performed, one with increasing surfactant (0–2 mM) and the second with increasing curcumin concentrations (0–25 μM). The concentration of mixed surfactant was constant at 2 mM for the second experiment. Excitation wavelength was set at 450 nm, with a slit width of 10 nm and range of observation was from 500 to 700 nm. Hydrodynamic radii of the mixed surfactants and curcumin-loaded mixed surfactant systems were measured by dynamic light scattering (DLS), using Malvern zetasizer Nano-S.

2.3. Sample preparation for solubility, stability and radical-scavenging experiments

Accurately weighed double chain and single chain surfactants (in equimolar concentrations) were sonicated in aqueous medium for 15 min at 45 °C. Batch tests for solubilization of curcumin in equimolar combination of DDAB, with a series of double chain cationic surfactants (DiDDAB, DMDTAB, DiCTAB and DODAB), were done. Equimolar concentrations of each surfactant, in the concentration range above their cac values, containing 4 ml of surfactant solution, were prepared. Curcumin was separately added to each vial in amounts slightly more than required to saturate the solution. The sample vials, after sealing with screw caps, were then agitated for a period of 24 h on a magnetic stirrer at 850 rpm maintained at 25 °C. The vials were left, for sedimentation, for a period of 2–3 h and then decanted. The decanted samples were subjected to centrifugation for 15 min at 500 rpm so as to remove the undissolved solid curcumin. The samples were further filtered through a 0.45 μm membrane. The concentration of dissolved curcumin was determined, using UV–vis spectroscopy ($\lambda_{\text{max}} = 425 \text{ nm}$), following appropriate dilution of an aliquot of the 7 supernatants with the respective concentrations of the surfactants. The surfactant concentration was kept the same in both reference and measurement cells, to eliminate the effect of surfactant on UV–vis. absorbance. For stability studies, stock solution of curcumin (1 mM) were prepared in methanol (MeOH). Then a small volume of stock solution was added to the surfactant solutions and UV–vis. spectra were observed with respect to time. Scavenging radical experiments were carried out with preparation of DPPH stock solution in ethanol (1 mg/ml). Further dilutions were made in surfactant solutions, where curcumin concentration was fixed at 20 μM . For ct-DNA binding studies, 4 μM ct-DNA solution was prepared in double distilled water; to that, EB was added and maintained 4 μM EB concentration. EB stock solution was prepared in absolute ethanol. Simultaneously, Curcumin stock solutions were prepared in methanol and added to the mixed surfactant solutions in which curcumin concentration was 25 μM . For all the above studies, the minimum volume of methanol and ethanol was maintained (i.e. $\leq 5\%$ of total solution volume to avoid cytotoxicity).

3. Results and discussion

3.1. Aggregates

Conductivity and fluorescence measurements were carried, with increasing concentration of equimolar mixed surfactants, to obtain its critical aggregation concentration (cac). Fig. S1 depicts variation of conductivity as a function of volume of mixed surfactant. With increase in total concentration of mixed surfactants, conductivity increases up to a certain range and then becomes nearly constant due to aggregation. The slope change in conductivity vs volume plot (Fig. S1) represents the critical aggregation concentration (cac). It varies in the order DiDDAB + DDAB > DMDTAB

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