Experimental report

10/04/2016

Proposal: 9-10-1435 **Council:** 4/2015

Title: Location of steroidal molecules inmonolayers of anionic and cationicsurfactant

Research area: Chemistry

This proposal is a continuation of 9-10-1348

Main proposer: Jayne LAWRENCE

Experimental team: Andrea TUMMINO
YANAN SHAO
Jayne LAWRENCE
Hisham AL-OBAIDI

Local contacts: Richard CAMPBELL

Samples: Sodium dodecyl sulphate (protiated and deuterated)
Dodecyl trimethylammonium bromide (protiated and (deuterated)
4-cholesten-3-one
testosterone heptanoate

Instrument	Requested days	Allocated days	From	To
FIGARO	5	5	30/10/2015	04/11/2015

Abstract:

Many drug molecules are very water-insoluble which limits their commercialisation and use by the patient. Solubilisation in surfactant micelles is an attractive means of increasing the apparent aqueous solubility thereby ensuring their delivery and ultimate use by patients. Surprisingly, however, very little is understood about the relationship between surfactant and drug structure and the micelle's ability to solubilise drugs. As a drug's incorporation into surfactant monolayers mirrors its distribution in surfactant micelles, here we focus on the study of drug distribution into surfactant monolayers. The present study aims to determine the level of incorporation and the extent of penetration of two hydrophobic drugs, 4-cholesten-3-one and testosterone heptanoate into monolayers formed by the surfactants sodium dodecyl sulphate and dodecyltrimethylammonium bromide using neutron reflectivity in combination with contrast variation. The results will be correlated with SANS and MD studies determining the location of the drugs in the surfactant micelles and thereby aid a better understanding of the relationship between surfactant and drug structure and micelle solubilisation capacity.

Location of various steroidal molecules in monolayers of surfactant

(9-10-1435: FIGARO: 31/10/2015-4/11/2015)

Experimental team Yanan Shao, Richard Campbell and Jayne Lawrence

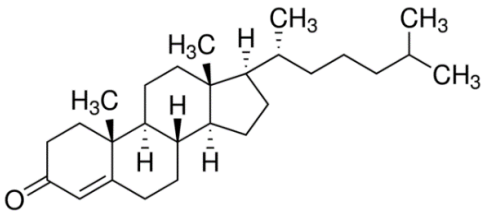
Background Many new drug molecules currently in development are very poorly soluble in water, with up to 70% of all potential new drugs being reported to exhibit extremely poor aqueous solubility. Poor water-solubility is a serious limitation when attempting to formulate the drug as a medicine because it frequently results in insufficient drug being absorbed from the gastrointestinal tract – thereby rendering the drug candidate unsuitable for development into a medicine, meaning that the patient will not benefit from the drug. Solubilisation of poorly-water soluble drug in surfactant micelles is an attractive means of increasing the apparent aqueous solubility of such drugs for the purposes of formulating a drug. Surprisingly little is known, however, about the relationship between surfactant and drug molecule structure and the ability of the micelle to solubilise drug. Consequently we have embarked on a study to understand the relationship between a drug and the extent and preferred site of its solubilisation in a surfactant micelle.

To date we have established (using a combination of small angle neutron scattering and molecular dynamic simulations) that the major site of solubilisation of the hydrophobic steroidal drug, testosterone propionate (TP), in a sodium dodecyl sulphate (SDS) micelle is the polar head group region. We have recently embarked on a study to use SNR to understand how a drug's distribution in a surfactant monolayer is related to its distribution in the micelles it forms, and thereby determination of this profile will provide valuable information about the micellar solubilisation of the drug and aid in the design of novel micelles as drug delivery vehicles. When studying drug solubilisation in a surfactant monolayer, two features are of interest:

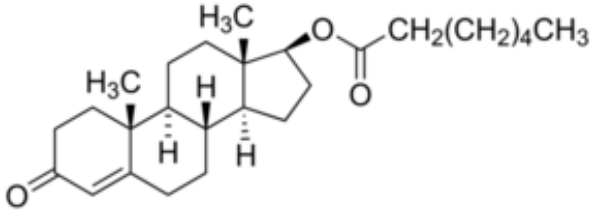
(a) the level of incorporation of drug in the surfactant monolayer, and

(b) the location of drug in the monolayer.

Aim The aim of the present study was to determine the level of incorporation and the extent of penetration of the lipophilic drugs, 4-cholesterone (4-CHOL) and adrenosterone (ADRENO) into monolayers formed by the ionic surfactant, sodium dodecyl-sulphate (SDS).



4-CHOL



ADRENO

The effect of the presence of a saturation amount of drug on the surface tension behaviour of SDS is shown in Figure 1 and Table 1. As can be seen the neither of the drugs affect the critical micelle concentration (CMC) of SDS. Note that the surfactant tension of water saturated by drug was 44.2 mN/m and 68 mN/m when saturated with 4-CHOL and ADRENO, respectively.

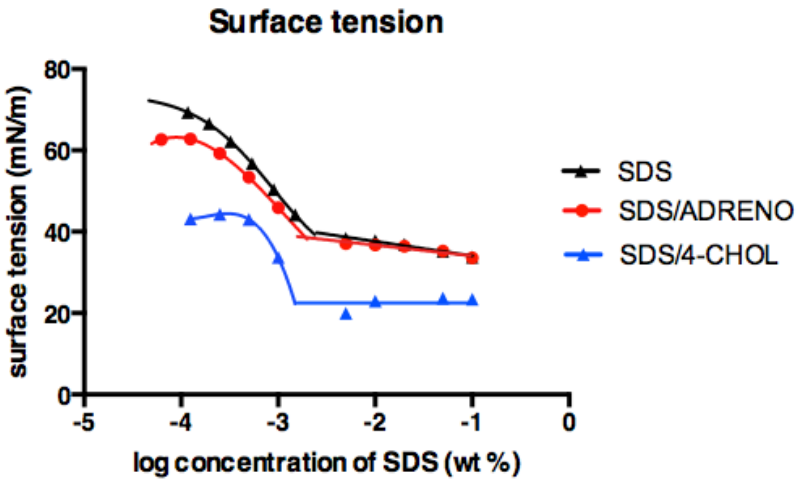


Figure 1 Variation in surface tension of SDS with concentration and the absence and presence of saturated amount of drug

Table 1 CMC of SDS in the absence and presence of saturated amount of drug

SAMPLE	CMC %w/w
SDS	0.21
SDS/4-CHOL	0.23
SDS/ADRENO	0.22

Neutron Reflectivity Experiments For each SDS concentration studied, 4 contrasts namely h-SDS/H_2O, h-SDS/D_2O, d-SDS/H_2O, d-SDS/D_2O were measured at 3 concentrations below the CMC, namely 0.1, 0.2 and 0.5 times the experimentally determined CMC of SDS and 3 concentrations above the CMC, namely 1, 1.5 and 2 times the CMC. For each system the aqueous phase was saturated with 4-CHOL and ADRENO before adding the SDS and measuring its behaviour at the air-water interface using neutron reflectivity. After which 10 times the amount of 4-CHOL and ADRENO required to saturate the monolayer was added to its surface by the careful addition of an aliquot of 5 mg/mL 4-CHOL and ADRENO in hexane and the behaviour of the surface characterised using neutron reflectivity.

Above SDS concentrations above the CMC, we measured the neutron reflectivity profile in the presence and of a saturated amount of 4-CHOL and ADRENO (taking into account here micelle formation). Thereafter, we added sufficient of a 5 mg/mL 4-CHOL and ADRENO in hexane solution to the interface in order to saturate the monolayer with 4-CHOL and ADRENO. The neutron reflectivity data was simultaneously fitting using MOTOFIT. The figure below shows a fit obtained to the data above and below the CMC.

Neutron Reflectivity Results and Discussion

Figure 2 shows the neutron reflectivity data and the corresponding fit to the 4 contrasts measured at 2 x CMC in the presence of a saturated amount of drug. As can be seen the fits to the neutron reflectivity data were excellent. The neutron reflectivity data were fitted assuming the drug was incorporated into the surfactant monolayer in the hydrophobic

region of the micelle. All 4 data sets could not be fitted using any other model of the drug containing SDS monolayer

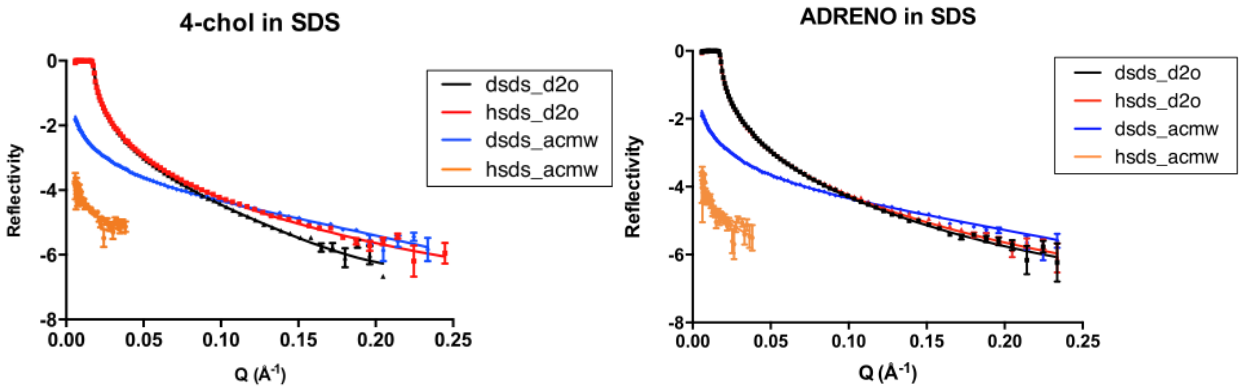


Figure 2 Measured and fitted neutron 2 x CMC (a) 4-CHOL and (b) ADRENO in SDS (drug saturated on surface)

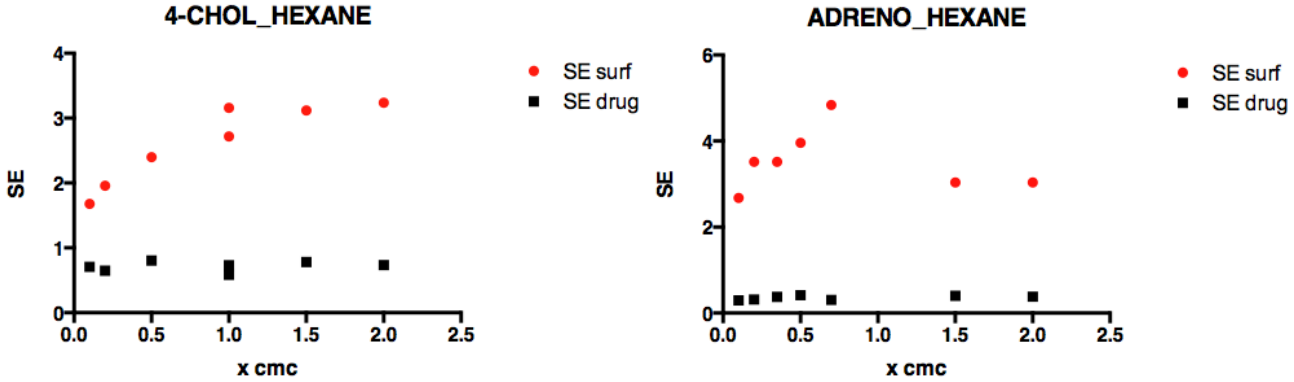


Figure 3 Variation in surface excess obtained from fitted neutron data with SDS CMC.

The modelling allowed both the level of incorporation of drug into the surfactant monolayer, and the location of drug in the monolayer to be established.