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# Exploring drug-surfactant interactions and their impact on the intrinsic surface properties of aqueous dissolution media

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SUMMARY

Surfactants are often used to improve the solubility of a compound for dissolution studies in aqueous media. Having observed non-linear solubility enhancement with increasing surfactant concentration, this study investigated the effect of a poorly soluble, zwitterionic, moderately lipophilic drug, Compound A, on the critical micelle concentration (CMC) of sodium lauryl sulfate (SLS) in phosphate buffer. A force tensiometer was used to measure the surface tension of the solutions over a range of surfactant concentrations. The presence of Compound A demonstrated a decrease in the CMC, suggesting that the solution favours micellisation at lower surfactant concentrations in the presence of the drug. Future studies will use a fully saturated solution of Compound A to explore this observation further. Additional experiments will also investigate micelle formation of SLS with other compounds. 

## INTRODUCTION

The use of standardised *in vitro* dissolution testing which reflects *in vivo* performance is a major component of the drug development process. For relevant dissolution characterisation, it is desirable that sink conditions are maintained. This means that the dissolution media must be able to dissolve at least 3 times the amount of active pharmaceutical ingredient (API) in the dosage form in one vessel. However, for poorly water-soluble compounds it can be challenging to attain adequate dissolution in aqueous solutions at physiological pH. Solubility modifiers, such as surfactants, are often added to avoid the sink limitation and improve the rate of dissolution (Shah et al., 1989). Surfactants are added to dissolution media above the critical micelle concentration (CMC) and work by improving hydrophilicity, increasing micellar solubilisation, and acting as a wetting agent.

While developing a dissolution method for Compound A, it was found that at least 5-fold increase in solubility was required to achieve sink conditions for the highest tablet strength. Therefore, a surfactant-buffer combination was investigated using an anionic surfactant, sodium lauryl sulfate (SLS). At pH 4.5, a linear response was observed between the surfactant concentration and Compound A solubility enhancement. However, at pH 6.8, a non-linear response was seen. It was hypothesised that this was caused by a self-aggregating system, such that the structure of the micelles changes in the presence of the API, causing changes to the intrinsic surface properties of the dissolution media. To provide insight into drug-surfactant interaction, this study investigates the surface properties of SLS with and without Compound A present in phosphate buffer.

## MATERIALS AND METHODS

Sodium phosphate buffer solution (pH 6.8 ± 0.05) was prepared at 50 mM concentration, using Dilut-It

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concentrate (Dissolution Accessories, Oosterhout, The Netherlands) quantitatively diluted with distilled water. Compound A (Pfizer Ltd, Sandwich, UK) was added to obtain a 0.01 mg/mL concentration and stirred overnight. The pH was measured using a calibrated probe and adjusted using phosphoric acid to reach the target pH. A surfactant-buffer combination was prepared at 14 mg/mL SLS from the phosphate buffer containing 0.01 mg/mL Compound A, using SLS (Sigma-Aldrich, Darmstadt, Germany).

The K100 force tensiometer (Kruss, Hamburg, Germany) was used to perform surface tension measurements, using the Wilhelmy plate method and automatic dispensing unit. Measurements were performed in triplicate at 37 °C (± 0.5), across a range of 30 concentrations of SLS from 0 to 1000 mg/mL. The reported CMC values correspond to the intercept of the extrapolated slope of the curve, and the plateau at the minimal surface tension.

## RESULTS AND DISCUSSION

As shown in Figure 1 and Table 1, the presence of the Compound A causes a decrease in the CMC of SLS in sodium phosphate buffer, from 483 to 400 mg/L.

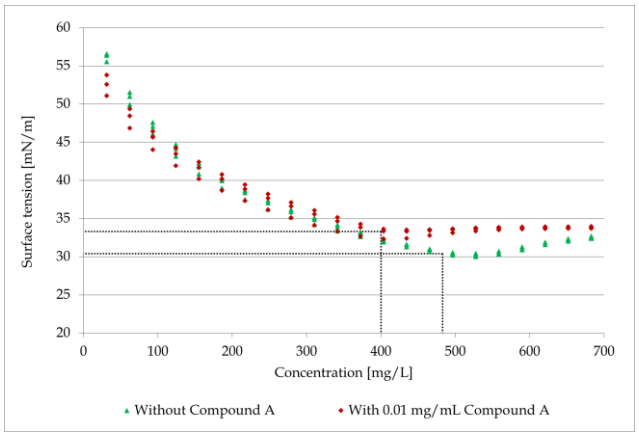


***Fig. 1.*** *Comparison of surface tension profiles for SLS with and without Compound A present (n = 3, pH 6.8 and 37 °C). Dotted lines depict the derivation of the CMC values.*

These findings could be attributed to the weakly negative charge of Compound A. When dissolved in water below CMC, SLS exists as negatively charged monomers. Thus, some repulsion between the SLS monomers and Compound A may drive the drug to reside within the core of the micelles. As a result, SLS may favour micellisation in the presence of Compound A, leading to lower CMC values.

***Table 1.*** *Overview of CMC values for SLS with and without Compound A present (n = 3, pH 6.8 and 37 °C).*

| 0.01 mg/mL Compound A present | Mean CMC (mM) | Mean CMC (% *w/v*) | RSD (%) |
|---|---|---|---|
| No | 1.673 | 0.0483 | 0.394 |
| Yes | 1.388 | 0.0400 | 1.252 |

Rajesh (2000) made similar observations when investigating interactions between simvastatin and SLS. CMC decreased in the presence of the drug; however, it was also noted that the final surface tension was reduced. In our study, this was not the case, instead observing a slightly higher minimal interfacial tension at CMC, as shown in Figure 1.

## CONCLUSIONS

During solubility studies for Compound A, it was noted that increasing SLS concentration gives rise to a non-linear solubility enhancement at pH 6.8. With no evidence of API degradation, investigations have been carried out to examine the surface properties of the dissolution media in the presence and absence of Compound A. At 0.01 mg/mL, Compound A demonstrated a decrease in the average CMC for SLS at pH 6.8. This may be attributed to increased micellisation of SLS in the presence of the drug, altering the surface properties. This could provide the scientific basis for more thorough surfactant selection based on the physicochemical properties of both drug and surfactant.

## ACKNOWLEDGEMENTS

The authors declare no conflicts of interest or competing financial interests.

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