M1323

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Universal Potentiometric Sensors:

Fast determination of the free ionized drug concentration in micellar solutions with the aim of analyzing drug distribution during *in vitro* lipolysis of self nano-emulsifying drug delivery systems

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Background and purpose

Recently developed specialized ion selective potentiometric sensors detect free ionized molecules that can pass from the solution into the sensor membrane [1, 2]. In theory, such free drug sensors (FDS) are supposed to detect only dissolved molecules that are not solubilized in micelles since such complexes cannot penetrate the sensors membrane.

In this study, the potential of the FDS to differentiate between free drug and drug bound in micelles was investigated with the aim of real-time monitoring the concentration of free drug during *in vitro* lipolysis of lipid formulations.

Materials and methods

The model drugs are diphenhydramine hydrochloride (DPH) and loperamide hydrochloride (LOD). The chemical structures are shown in Figure 1. The total concentration of drug in buffer or micellar solutions was obtained by adding known amounts of stock solution with known drug concentrations. The concentration of free ionized drug was determined by exposing the FDS in the solutions. The digestion medium used contained 2.95 mM sodium taurodeoxycholate (TDC), 0.26 mM phosphatidylcholine (PC), 2.0 mM Trizma® maleate, 1.4 mM calcium chloride, 94.3 mM sodium chloride (pH 6.5). The self-nanoemulsifying drug delivery system (SNEDDS) used consisted of corn oil (32.5% w/w), Maisine 35-1(32.5% w/w), Kolliphor EL (35% w/w). Self-diffusion nuclear magnetic resonance (NMR) was performed on a 600 MHz Bruker Avance III HD equipped with a cryogenically cooled 5 mm dual probe. *In vitro* lipolysis was performed on a Metrohm titrando system.

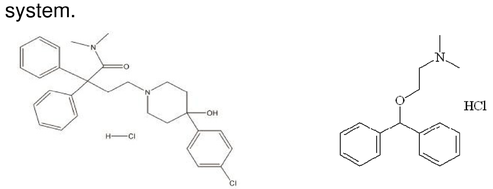

Figure 1. Chemical structure of LOD (left) and DPH (right).

Results

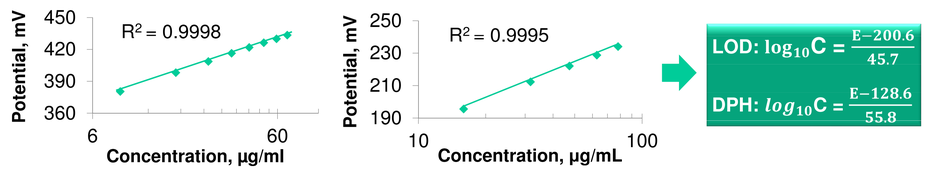

Figure 1. Calibration curves for determining the concentration of free ionized drugs in buffer pH 6.5. Left: LOD, Right: DPH.

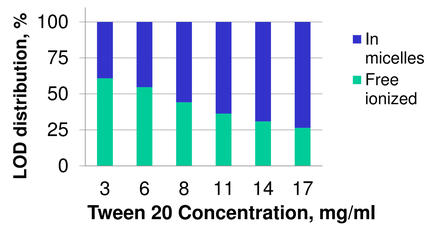

Figure 3. Distribution of LOD in free ionized form and in micelles when solubilized in Tween 20 micellar solution.

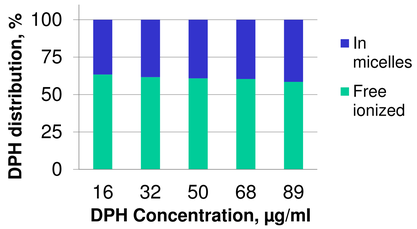

Figure 4. Distribution of DPH in free ionized form and in TDC/PC micelles when solubilized in digestion medium.

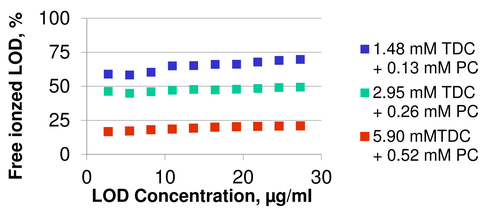

Figure 5. Percentage of free ionized LOD in micellar solutions containing different concentrations of TDC/PC micelles

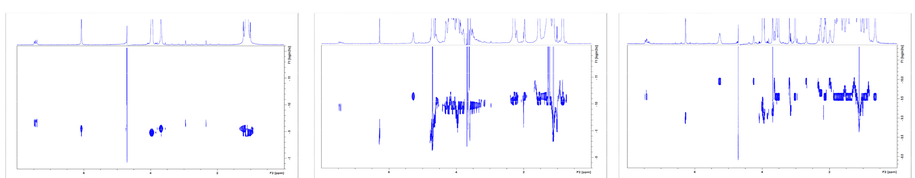

Figure 6. Self-diffusion NMR spectra of LOD in buffer (left), LOD in Tween 20 micellar solution (middle) and LOD in digestion medium (right) showing the coexistance of free and bound in micelles LOD in micellar solutions.

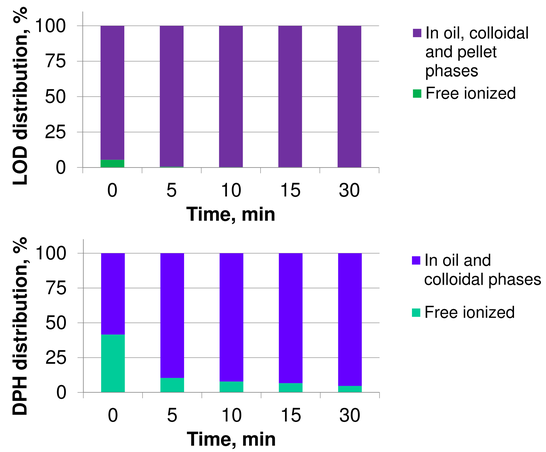

Figure 7. Drug distribution during *in vitro* lipolysis of SNEDDS containing LOD (up) and SNEDDS containing DPH (down).

Conclusions

This study indicated that the FDS could monitor the actual free ionized drug concentration in micellar solutions, where the drug distributed both outside and inside the micelles, as shown in self-diffusion NMR spectra. This makes the FDS an addition in the toolkit for *in situ* concentration measurements.

Additional studies are required to further investigate applicability, accuracy and precision of measurements in such complex media. More data of *in vitro* lipolysis and the corresponding *in vivo* study need to be investigated to study the relationship between the concentration of free ionized drugs and oral absorption.

REFERENCES

1. Mostafa GA et al., (2008) Journal of pharmaceutical and biomedical analysis.
2. Bohets et al., (2007) Analytica Chimica Acta