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In vitro studies of the release of doxorubicin and other amphiphilic drugs from microgels: Improved mechanistic understanding

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Statement of the Problem: Microgels have the capacity to store large amounts of amphiphilic, peptide and protein drugs. This makes them interesting as delivery systems for drugs needing protection against degradation, and as components of slow-release and depot formulations for parenteral administration. Despite the fact that microgels are used clinically, e.g., to deliver doxorubicin in the treatment of liver cancer [1], little attention has been given to how the drug self-assembly inside microgels affects the release properties. The purpose of this study is to show that that the release of amphiphilic drugs is strongly influenced by self-assembly [2] and its effect on the swelling of the microgel network.

Methodology & Theory: Loading and release of cationic amphiphilic drugs are investigate by means of micropipette-assisted microscopy of single microgels [2, 3] (Fig. 1) and μDiss apparatus studies. We have developed and evaluated two new models combining transport dynamics and thermodynamics of drug self-assembly, one for non- swelling responsive microgels based on the Nernst-Planck equation [2], and one for responsive networks handling coexisting phases with different degrees of network swelling.

Findings: For two polyelectrolyte microgel systems, DC bead® used clinically, and polyacrylate microspheres (diameter: ~100 μm), the drug self-assembly has a profound effect on the loading and release kinetics as well as on the distribution of the drug inside the beads and the distribution between different beads in a suspension. The roles played by salt in the release medium and the responsiveness of the polymer network are highlighted. The micropipette technique is found to be a powerful *in vitro* method.

Conclusions & Significance: The results highlight the importance of the electric coupling of diffusive fluxes, the amphiphilic self-assembly and the responsiveness of the microgel. The results are important for the development of microgel drug delivery systems with improved release kinetics.

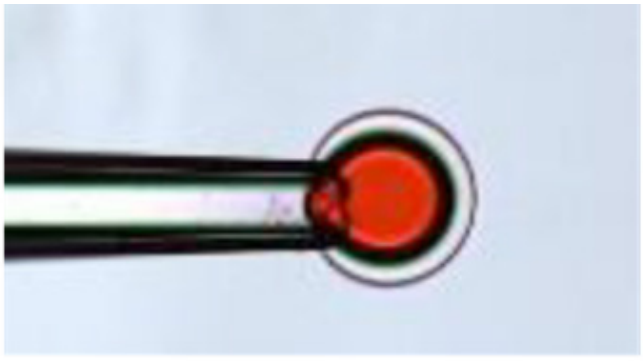

Figure 1: Microscopy image of doxorubicin-loaded microgel during release in *in vitro* study.

Recent Publications

1. Ahnfelt E, Sjögren E, Hansson P, Lennernäs H (2016) *In vitro* release mechanisms of doxorubicin from a clinical bead-delivery system. Journal of Pharmaceutical Sciences 105: 3387-3398
2. Ahnfelt E, Gernandt J, Al-Tikriti Y, Sjögren E, , Lennernäs H, Hansson P (2018) Single bead investigation of a clinical drug delivery system – A novel release mechanism. Journal of Controlled Release 292: 235-247
3. Jidheden C, Hansson P (2016) Single microgels in core/shell equilibrium: A novel method for limited volume studies. Journal of Physical Chemistry B 120: 10030−10042
4. Andersson M, Hansson P (2017) Phase behavior of salt-free polyelectrolyte gel – surfactant systems. Journal of Physical Chemistry B 121: 6064-6080
5. Gernandt J, Hansson P (2016) Surfactant induced core/shell phase equilibrium in hydrogels. Journal of Chemical Physics 144: 064902

Biography

Per Hansson has his expertise in colloidal systems of relevance for developing drug delivery systems. Most of his studies have dealt with polyelectrolytes and their interaction with colloids of opposite charge, in particularly phase transitions and phase separation in polyelectrolyte hydrogels in relation to the loading and release of amphiphilic drugs, proteins and peptides. He is currently investigating the self-assembling properties of amphiphilic drugs, and the fate of biomacromolecular drug formulations after injection into the subcutaneous tissue. This involves the development of *in vitro* methods to study the release from formulations and transport through the extracellular matrix. Hansson is leading the Pharmaceutical Physical Chemistry group at the Department of Pharmacy, Uppsala University, and the Parenteral Drug Delivery Platform of the Swedish Drug Delivery Forum.

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