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Characterization of Colloidal Drug Delivery Systems via Atomic Force Microscopy

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Colloidal Drug Delivery Systems

The concept of colloidal drug delivery is inspired by biomimikry and nanotechnologyl, and comprises the administration of a pharmaceutically active compound entrapped in the matrix of a biodegradable micro- or nanometer sized particle. In addition to a controllable release rate according to the matrix composition, this offers the striking advantage to specifically exert influence on the particles distribution pattern in the human body, which means the targeted delivery to the site of disease becomes feasible. By appropriate tuning of surface features and covalent immobilization of receptor-specific biomolecules, the preferential binding to a certain cell population can be achieved. However, despite tremendous advancements the field of colloidal drug delivery still could not reach its full potential, also due to the fact that any analytical description is intrinsically difficult in this small size range. There is a urgent need for methods that can accurately characterize the biophysical properties of the particulate formulations and the intended target cells, which can be fulfilled by applying biologically adapted Atomic Force Microscopy as a highly valuable tool for interdisciplinary research.

Atomic Force Microscopy

- Resolution in the nanometer scale
- Operates in physiological environment
- No sample preperation (dye etc.) required
- Provides mechanical information
- Measurement of piconewton forces
- Dynamic binding experiments possible

Particle Characterization

Several influencing factors (Fig.1) are known to determine a particles binding pattern, which can be selectively manipulated (Fig2). Every modification applied has to be thoroughly monitored to achieve correct results and allow for optimization.

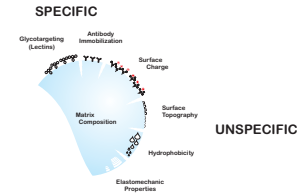

Fig. 1: Different specific or unspecific particle modifications can be exploited to achieve advantageous distribution patterns in the body

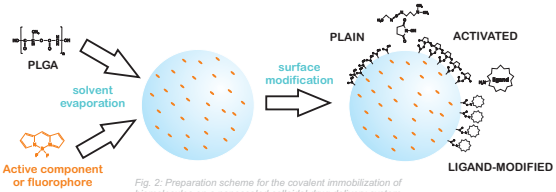

Fig. 2: Preparation scheme for the covalent immobilization of biomolecules on a nanoscaled colloidal drug delivery system

Cell Characterization

For successful implementation of targeting strategies, a detailed knowledge of the cell population in focus is necessarily required. AFM permits high resolution imaging in near natural environment. Mechanic probing relveals dynamic changes in the intracellular cytoskeletal organization, which is of relevance for binding and uptake processes at the plasmatic membrane.

For cell imaging, different preperation procedures have been tested and compared for their tendency to generate artifacts (Fig 4a+b).

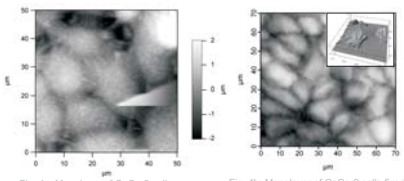

Fig. 4a: Monolayer of CaCo-2 cells showing interlinked artifacts upon preperation with Glutaraldehyde 0,5%

Fig. 4b: Monolayer of CaCo-2 cells fixed in MeOH, without artifacts. Inset: 3D-pictuer of a single CaCo-2 cell in subconfluent state

Cell Binding Experiments

Fig. 3: Principle of Colloidal Probe Microscopy: A single particle is immobilized on the cantilever tip and raster-scanned across the surface of living cells

Drug carriers with tailored properties can be tested for their adhesive potential by colloidal probe microscopy (Fig 3). The direct measurement of binding strength yields comparable data and helps finding the optimum vehicle for delivery.

- Detection of binding events on the cell membrane with high lateral resolution
- *In situ* evaluation of different targeting strategies in terms of selectivity and efficiency

Outlook

In an interdisciplinary research project of engineering and life science groups in Vienna the method of biological AFM is to be adapted for *in situ* characterization of colloidal drug delivery systems. Focus will be layed on biomaterials and targeting strategies originating from application-oriented pharmaceutical research, which are to be screened for bioadhesive properties and selectivity on medical cell culture models.

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