

## Nanoparticles for drug delivery across the blood-brain barrier: a cell culture study

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**Background:** Efficient drug delivery across the blood-brain barriers (BBB) is a central problem in pharmaceutical treatment of neurological diseases. Most pharmaceutical drug candidates including hydrophilic molecules, biopharmaceuticals, and efflux transporter ligands have a low permeability across barriers. To solve this unmet therapeutical need vesicular or solid nanoparticle drug delivery systems targeting physiological transporters of the BBB hold a great promise. Curcumin extracted from the plant turmeric possesses anti-oxidative, anti-inflammatory and neuroprotective properties and is a potential treatment for different cerebral diseases. However, the clinical application of this natural compound is hampered by its poor water solubility and absorption, rapid metabolism and systemic elimination resulting in low bioavailability. Nanosized, biocompatible and biodegradable vesicles containing Evans blue-albumin as a model molecule and a hydrophobic therapeutic biomolecule, curcumin were prepared and characterized. In addition, fluorescent solid nanoparticles were also examined. The aim of our study was to test the cellular toxicity and penetration of nanovesicles loaded with albumin or curcumin and fluorescent nanoparticles all containing ligands for transporters on culture models of the BBB.

**Methods:** The nanovesicles and fluorescent solid nanoparticles were labelled with different ligands, biotin, a glucose analogue and glutathione. Primary rat and human hCMEC/D3 brain endothelial cells were used as in vitro model systems of the BBB. The cellular toxicity of the nanoparticles was measured by real-time cell microelectric sensing (RTCA-SP, ACEA Biosciences) and MTT assay. The permeability tests were performed on triple co-culture BBB model and hCMEC/D3 cells using Transwell inserts. Brain endothelial uptake of nanoparticles was quantified by fluorescent spectroscopy and visualized by confocal microscopy.

**Results:** No toxicity for loaded or unloaded nanovesicles or solid nanoparticles was found by MTT assay and impedance measurements. The loading of curcumin into liposomes significantly decreased its toxicity for brain endothelial cells at high concentrations. The presence of a glucose analogue in nanovesicles increased the uptake of the model molecule to cultured brain endothelial cells. The brain endothelial uptake of both loaded nanovesicles and solid nanoparticles could be followed by confocal microscopy.

**Conclusion:** Our data indicate that encapsulation of lipophilic or macromolecular drugs into nanovesicles may decrease cellular toxicity and increase uptake and transport at the BBB, however the type of the targeting ligand and its coupling to the nanoparticle may be crucial for efficacy.

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