

151f Colloidal Polyelectrolyte Complexes for Drug Delivery: Implications of Molecular Characteristics on Targeting and Uptake by Vascular Endothelial Cells

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Many current nanoparticle preparations used as drug delivery vehicles employ harmful solvents and mineral oils as reaction environments, leading to potentially toxic properties and technological obstacles. The development of water-soluble, biodegradable, polymeric, polyelectrolyte nanoparticles is advantageous due to the biocompatibility and biodegradation of the constituent polymers. The use of water as a solvent presents a major advantage for products that may be used as drug delivery systems. Both rationalizing the assembly mechanisms and tailoring the size, charge, and loading capability to desirable levels are essential goals needed to advance biodegradable, polymeric, polyelectrolyte nanoparticles as efficient drug delivery vehicles. Polyelectrolyte-based nanoparticles, also termed polyelectrolyte complex dispersions (PECs), are created by mixing oppositely charged molecules. The technology applied in this study produced PECs under the prevailing assembly and complexation theory by employing a four-component system, which provided both versatility and thermodynamic stability.

According to the literature, there are several PEC characteristics favorable for cellular uptake and colloidal stability, including hydrodynamic diameter less than 200 nm and zeta potential >30 mV or <-30 mV. The PEC properties of size, charge, polydispersity index (PDI), and morphology, were highly dependent on concentration, ionic strength, pH, and molecular parameters of the polyions used. In particular, the complexation process between polyelectrolytes having significantly different molecular weights lead to the formation of water-insoluble aggregates. Using this fact as a starting point, PECs were prepared and compared using systems with similar and dissimilar molecular weights, with the primary goal of producing under simple stream mixing conditions a PEC system with desirable features that will effectively target and allow uptake by cells. The working hypothesis was that PECs created from components with similar molecular dimensions may provide more uniform, attractive size distributions (monodisperse and mean size consistently <200 nm), increased stability in biological and pH environments, and efficient uptake by endothelial cells. Endothelial cells provide a model for active and passive targeting to vasculature.

Results show that PECs formulated from precursors with similar, low molecular weights yielded delivery vehicles with suitable physicochemical characteristics as verified by both photon correlation spectroscopy and TEM most likely due to efficient ion pairing. Low molecular weight precursors also lead to stability, verified by zeta potential and size measurements, across a wide pH spectrum. The effect of passive versus active targeting to endothelial cells for complexes with appropriate properties was demonstrated using fluorescent labeling and well plate technology. Cellular uptake was monitored to further understand the predominant endocytotic mechanisms. The ultimate goal of these studies is to establish the link between physicochemical and biological properties of PEC in order to further these biocompatible products as alternatives to current technologies.