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Controlling Cellular Endocytosis at the Nanoscale

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One of the most challenging aspects of drug delivery is the intra-cellular delivery of active agents. Several drugs and especially nucleic acids all need to be delivered within the cell interior to exert their therapeutic action. Small hydrophobic molecules can permeate cell membranes with relative ease, but hydrophilic molecules and especially large macromolecules such as proteins and nucleic acids require a vector to assist their transport across the cell membrane. This must be designed so as to ensure intracellular delivery without compromising cell viability. We have recently achieved this by using pH-sensitive poly(2-(methacryloyloxy)ethyl-phosphorylcholine)- co -poly(2-(diisopropylamino)ethyl methacrylate) (PMPC-PDPA) and poly(ethylene oxide)-co- poly(2-(diisopropylamino)ethyl methacrylate) (PEO-PDPA) diblock copolymers that self-assemble to form vesicles in aqueous solution. These vesicles combine a non-fouling PMPC or PEO block with a pH-sensitive PDPA block and have the ability to encapsulate both hydrophobic molecules within the vesicular membrane and hydrophilic molecules within their aqueous cores. The pH sensitive nature of the PDPA blocks make the diblock copolymers forming stable vesicles at physiological pH but that rapid dissociation of these vesicles occurs between pH 5 and pH 6 to form molecularly dissolved copolymer chains (unimers). We used these vesicles to encapsulate small and large macromolecules and these were successfully delivered intracellularly including nucleic acid, drugs, quantum dots, and antibodies. Dynamic light scattering, zeta potential measurements, and transmission electron microscopy were used to study and optimise the encapsulation processes. Confocal laser scanning microscopy, fluorescence flow cytometry and lysates analysis were used to quantify cellular uptake and to study the kinetics of this process in vitro and in vivo. We show the effective cytosolic delivery of nucleic acids, proteins, hydrophobic molecules, amphiphilic molecules, and hydrophilic molecules without affecting the viability of cells or even triggering inflammatory pathways. Finally we show how size, surface chemistry and surface topology of the vesicles affect their interaction with the cell membrane and hence their cellular uptake.

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