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Organic Chemistry 2018- Synthesis of Multi-Compartment Nanoemulsions for Localized Co-delivery of Different Classes of Oil-soluble Drug Molecules

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Using two different highly non-equilibrium synthetic approaches, we have created new kinds of stable oil-in-water nanoemulsions composed of complex multi-compartment nanoscale droplets. Each nanodroplet contains three different types of mutually immisible oils in separate internal compartments. Consequently, each internal compartment can hold a different class of oil-soluble drug molecules. By analogy to Janus droplets, which contain two different immiscible oil types and are named after the mythological two-faced deity of doorways, we call these compartmentalized triple-oil droplets “Cerberus” droplets, after three-headed watch-dog in the same mythology. In a first synthetic approach, we combine three simple microscale oil-in-water emulsions, each made using a different oil type (aliphatic, aromatic, or fluoro siloxanes), and subject this mixed microscale emulsion to extreme flow conditions using a high-pressure microfluidic homogenizer. In addition to causing droplet rupturing towards the nanoscale, the extreme flow also overcomes the stabilizing interfacial repulsion of the water-soluble ionic surfactant, leading to flow-induced droplet fusion. The multi-compartment nanodroplets in these complex oil-in-water nanoemulsions are so small that optical microscopy methods cannot resolve the internal interfaces that separate the internal compartments. So, instead, we have developed the use of cryogenic transmission electron microscopy (*C-TEM*) to reveal the compartmentalization of these three oils inside the resulting Cerberus nanodroplets. In a second approach, we create Cerberus droplets using self-limiting droplet fusion reactions obtained by transiently destabilizing a mixed emulsion containing droplets of the three different oil types using an ionic amphiphile having the opposite charge. Based on these results, we create a classification scheme for different kinds of Cerberus droplet morphologies. In pharmaceutical applications, Cerberus nanoemulsions can be tailored to provide local co-delivery of a wide range of non-aqueous drug molecules, thereby overcoming limitations related to poor molecular solubility in certain oil types.

Nanoemulsions are pharmaceutical formulations composed of particles within a nanometer range. They possess the capacity to encapsulate drugs that are poorly water soluble due to their hydrophobic core nature. Additionally, they are also composed of safe gradient excipients, which makes them a stable and safe option to deliver drugs. Cancer therapy has been an issue for several decades. Drugs developed to treat this disease are not always successful or end up failing, mainly due to low solubility, multidrug resistance (MDR), and unspecific toxicity. Nanoemulsions might be the solution to achieve efficient and safe tumor treatment. These formulations not only solve water-solubility problems but also provide specific targeting to cancer cells and might even be designed to overcome MDR. Nanoemulsions can be modified using ligands of different natures to target components present in tumor cells surface or to escape MDR mechanisms. Multifunctional nanoemulsions are being studied by a wide variety of researchers in different research areas mainly for the treatment of different types of cancer. All of these studies demonstrate that nanoemulsions are efficiently taken by the tumoral cells, reduce tumor growth, eliminate toxicity to healthy cells, and decrease migration of cancer cells to other organs.

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