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Balancing the effect of corona on therapeutic efficacy and macrophage uptake of lipid nanocapsules

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Several studies have shown the potential of biocompatible lipid nanocapsules as hydrophobic drug delivery systems. Understanding the factors that determine the interactions of these oil-in-water nanoemulsions with cells is a necessary step to guide the design of the most effective formulations. The aim of this study was to probe the ability of two surfactants with a markedly different nature, a non-ionic poloxamer, and a charged phospholipid, to prepare formulations with shells of different composition and different surface properties. Thus we determined their effects on the interaction with biological environments. In particular, we investigated how the shell formulation affected the adsorption of biomolecules from the surrounding biological fluids on the nanocapsule surface (corona formation). A complete physicochemical characterization including an isothermal titration calorimetry (ITC) study revealed that the use of poloxamer led to nanocapsules with a marked reduction in the number of protein-binding sites. Surface hydrophilicity and changes in corona formation strongly correlated to changes in uptake by cancer cells and by macrophages. Our results indicate that the nature and concentration of surfactants in the nanocapsules can be easily manipulated to effectively modulate their surface architecture with the aim of controlling the environmental interactions, thus optimizing functionality for *in vivo* applications. In particular, addition of surfactants that reduce protein binding can modulate nanoparticle clearance by the immune system, but also screens the desired interactions with cells, leading to lower uptake, thus lower therapeutic efficacy. The two effects need to be balanced in order to obtain successful formulations.

1. Introduction

The rapid advancement of nanomedicine has promoted the development of numerous nanosystems that can deliver drugs and other therapeutic agents to target tissues and that often possess complex structures and surface functionalizations [1-3].

Oil-in-water nanoemulsions, also known as lipid nanocapsules, have been studied in the pharmaceutical and medical fields because they show promise as drug carriers for their controlled and sustained release properties, subcellular size, inexpensive and easy-to-scale production, independence of dilution, and biocompatibility [4]. Generally, these lipid nanocapsules consist of a hydrophobic inner core which can incorporate lipophilic drugs, and a hydrophilic outer shell that provides stabilization and offers the possibility of chemical modifications, among other important properties [5]. Lipid nanocapsules have become increasingly important for drug delivery in the field of cancer treatment, showing greater advantages over other lipid-based nanosystems in terms of leakage and drug loading [6], and they have been shown to be effective carriers for delivering hydrophobic drugs such as docetaxel [7-9]. Due to their nanoscale size, they can accumulate in tumor tissues more than in surrounding healthy tissue through enhanced permeability and retention effect (EPR) [10], and they can also be engineered and actively targeted with different molecules against overexpressed receptors of cancer cells [11-13].

Following intravenous administration, a nanoparticle is exposed to an evolved combinatorial system containing thousands of different proteins alongside lipids and sugars which can reconfigure nanoparticle dispersion and surface characteristics, forming a "corona" [14-19]. Recently, it has been shown that a biofunctional nanoparticle, quite basic in design, while showing specific recognition of biological receptors under model *in vitro* conditions, can lose uptake and receptor specificity as the complexity of the environment is increased by introducing human plasma [20]. The proteins adsorbed onto the original nanoparticle surface can mask targeting ligands and furthermore can interact with specific plasma membrane receptors on monocytes and various subsets of tissue macrophages, promoting rapid recognition and removal of the intravenously injected nanoparticles. Therefore, pharmacokinetics and biodistribution of nanoparticles are to a large extent governed by their surface properties, which in turn depend on the shell composition [21] and can be strongly altered upon interactions with complex biological environments [22].

To prolong their half life in the bloodstream by means of avoiding recognition by the mononuclear phagocyte system (MPS), different grafting materials have been tailored in drug delivery systems by using a variety of polymers such as poly (ethylene glycol) (PEG) and triblock copolymers (poloxamers and poloxamines). PEG is a flexible, electrically neutral, and hydrophilic polymer that has been commonly used to coat nanoparticles, to decrease the interaction of the surface with serum components, and to prolong particle circulation [23-26]. Poloxamers (Pluronic®) and poloxamines (Tetronic®) have been used for the same purpose with different levels of success

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