Encapsulation of magnetic nanocubes in core-shell polymeric nanoparticles for their application in hyperthermia

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Cancer is still considered one of the leading causes of death worldwide. Current treatments, like surgery or chemotherapy, have the critical inconveniences of being invasive, not localized, with limited effectiveness, and leading to severe side effects for the patients [1]. Nanoparticles are a powerful tool to overcome these limitations, improving drugs' bioavailability and enhancing their stability, presenting a high loading capacity. Stimuli-responsive nanoparticles that can change their physicochemical properties under the influence of an external or internal stimulus are of particular interest [2]. In cancer therapy, nanomaterials able to generate heat under certain stimulus have gained great attention in recent decades. Indeed, hyperthermia, defined as the increase of cells' temperature above 40 °C, is considered a promising treatment used alone or in combination with other traditional ones. This increase in temperature can directly induce cancer cells' death or provoke harmful side effects, making them less resistant to the immune system or chemotherapeutic drugs. Localizing this heating effect only to the cancer region is crucial to avoid damage to healthy tissues [3]. Two main strategies can be recognized: photothermia and magnetic hyperthermia. The photothermal effect is achieved when nanomaterials, able to convert the absorbed light into heat, are used. In this case, near infrared (NIR) radiation is commonly used as the source of light because it penetrates deeper into tissues without causing side effects. Indeed, in certain NIR regions, neither water nor biomolecules absorb or scatter the light [4]. On the other side, magnetic hyperthermia is accomplished when magnetic nanomaterials are used, generating a temperature increase under an alternating magnetic field. If the amplitude and frequency of the field are low, no damage to healthy tissues is caused. Therefore, it is possible to treat tumors located deeply in the body since a magnetic field penetrates better than light, which can only reach superficial tumors [5]. In both photothermia and magnetic hyperthermia, the amplitude of the external stimulus and its time of application influence cells' death.

Among stimuli-responsive nanoparticles, biocompatible magnetic iron oxide nanoparticles (IONPs) are very promising as they respond to both NIR and magnetic fields. Moreover, they can be easily located in the tumor by guiding them with an external static magnetic field. Additionally, they can be used as a contrast agent in MRI [6]. However, parameters such as particles' composition, morphology, size, shape, and magnetic anisotropy, must be tuned to improve the heating efficiency. It has been demonstrated that cubic-shaped IONPs present a higher magnetization and heating efficiency than their spherical counterparts [7]. However, when IONPs are dispersed in water or physiological media, they drastically suffer aggregation, losing their physicochemical properties. IONPs can be coated or encapsulated with organic materials to prevent aggregation and improve their biodistribution. In addition, with IONPs, it would be possible to encapsulate biomolecules or drugs that could be delivered to the tumor. In most studies, they have been encapsulated in silica nanoparticles [8] or polymeric solid nanoparticles [9], which, due to the material rigidity might alter the properties of the magnetic nanoparticles

In this work, we have successfully encapsulated cubic superparamagnetic magnetite nanocrystals (NCs) in biocompatible polymeric nanoparticles. Furthermore, we have been able to confine NCs in the liquid core of polymeric capsules, which is made of viscous oil. This encapsulation would not only ensure NCs' stability, providing a positive effect on their biodistribution but would let the NCs to be free to rotate, preserving their excellent magneto-optic properties. The morphology of both polymeric particles (average size ~200 nm) and NCs (average size ~16 nm) has been evaluated by transmission electron microscopy (TEM). Moreover, TEM results corroborated the presence of an oil core and a polymeric shell in the case of nanocapsules, which was further demonstrated by differential scanning calorimetry (DSC). The amount of encapsulated oil was determined via nuclear magnetic resonance spectroscopy (NMR), while the quantity of encapsulated NCs was estimated by thermogravimetric analysis (TGA) and magnetometry. Finally, the efficiency of the NCs-loaded polymeric nanocapsules as a photothermal agent was demonstrated by the temperature increase of nanocapsules' suspension irradiated with a NIR light source. Interestingly, temperatures above 40 °C were reached upon NIR irradiation.

On top of that, we have induced an external anisotropy by modifying the shape of polymeric nanoparticles or nanocapsules. The resulting ellipsoidal nanoparticles containing NCs are able to orient in the direction of an applied static magnetic field. When the magnetic field is moved, the ellipsoidal NPs rotate to follow it. This system would represent a promising strategy against cancer, acting as a powerful photothermal agent that can be easily guided and oriented.

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Figures

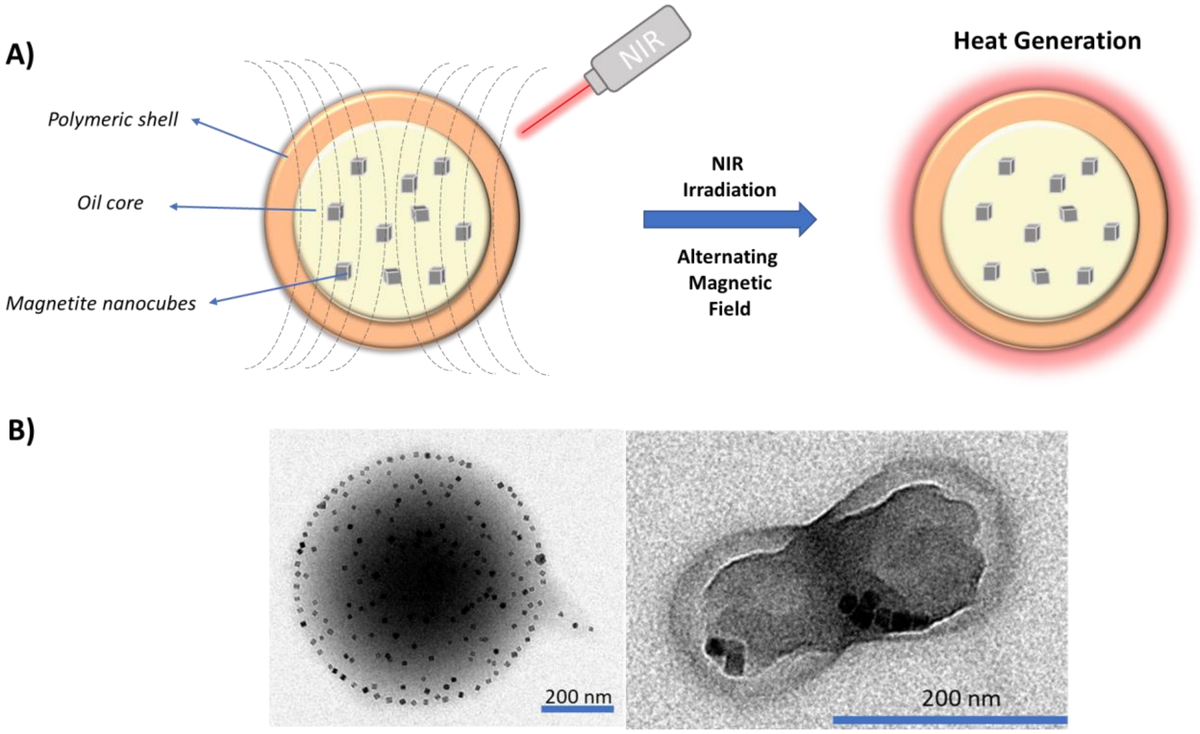

Figure 1. A) Schematic representation of magnetic core shell nanoparticles and heating generation after external stimuli application. B) TEM images of nanocubes encapsulated in core-shell polymeric nanoparticles.