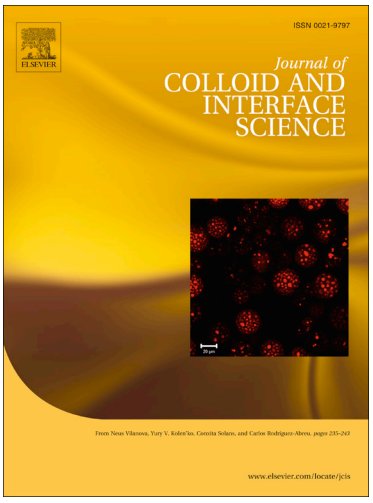

Regular Article

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Impact of the Strategy Adopted for Drug Loading in Nonporous Silica Nanoparticles on the Drug Release and Cytotoxic Activity

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Abstract: Nanoparticles are normally classified as "hard", mainly consisting of metal or metal oxide cores, or "soft", including polymer-based, liposomes and biomimetic nanoparticles. Soft nanoparticles have been studied in depth for drug formulation and therapeutic delivery applications, albeit hard nanoparticles may offer easier synthesis, smaller size and more effective tumor penetration. Among them, silica nanoparticles maintain excellent biocompatibility and biodegradability and can be finely adjusted in size and shape, easily produced in a large scale and functionalized or loaded with active molecules. To help filling the gap of a poor clinical translation of hard nanoparticles, we have designed and developed three different nonporous silica nanocarriers loading the chemotherapeutic doxorubicin within the core matrix, on the surface or both inside and outside, respectively. A comparative study was performed on drug loading and drug release, silica matrix degradation and nanodrug cytotoxic activity, highlighting unexpected correlation between the strategy adopted for drug incorporation and nanoparticle behavior in a physiological environment. This study offers a new insight on the impact of the choice of the prodrug nanoparticles on the kinetics and efficacy of drug delivery, which may encourage the scientific community in developing a new generation of drug delivery systems based on hard nanocarriers.

Keywords: hard nanoparticles; nonporous silica nanoparticles; drug delivery systems; drug conjugation; chemotherapy; doxorubicin.

1. INTRODUCTION

The advent of nanotechnology in biomedicine is expected to revolutionize the classical approaches to chemotherapy, making an impact on drug discovery [1]. In principle, the use of nanoparticles is estimated to allow researchers to overcome several hurdles that have hindered the development of reliable drug treatments, including targeted action at the malignant cells and tissues, crossing the biological barriers, such as the blood brain barrier, prolonged circulation, improved drug bioavailability, and restricted systemic side effects [2]. In a basic classification, nanoparticles can be split out into two distinct categories, namely "hard", frequently consisting of metal nanoparticles and referred to as "colloidal", and "soft", which include polymer-based, liposomes/micelles and bioorganic nanoparticles [3,4]. While in soft nanoparticles drug cargo can be loaded both inside the core and on the surface, hard nanoparticles usually allow immobilizing the active molecules exclusively on the outer surface due to the inorganic nature of the core. As all current FDA-approved nanodrugs fall within the "soft" category, our knowledge of the actual efficacy of nanoparticle formulation of drugs in curing malignant diseases comes from the contribution of clinical studies limited to soft nanoparticles [5,6]. The low rate to translation associated to hard nanoparticles is mainly attributable to a lack of data on the potential of colloidal nanocarriers to reproducibly load, transport and release their cargo in a controllable manner. However, filling up this gap has become increasingly urgent in the light of several advantages that hard nanoparticles exhibit over soft. Indeed, the latter ones often suffer from large size (~100-200 nm) and broad size distribution, which limit their penetration into the dense stromal tissue typical of several human cancers, often characterized by high interstitial pressure and poor spatiotemporal control over therapeutics deployment [7-9]. In