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Structure-Property Relationship in $CaCO_3$ for Developing pH-sensitive Drug Delivery Vehicles

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Extended Abstract

The quantitative relationship "chemical composition–structure–physical property" is a well-established area of research, which allows to evaluate the prospects for the application of crystalline materials in various fields. Study of the relationship between structural features and crystal properties becomes even more essential for crystals with complex polymorph behaviour, which include $CaCO_3$ [1], [2]. Due to its versality, $CaCO_3$ is widely used in various industrial fields such as contamination removal in wastewater [3], ceramic industry [4], food packaging [5], and medical treatments [6]. $CaCO_3$ availability, simple synthesis, low cost, surface area, biocompatibility and physiologically driven biodegradability make it an excellent candidate for loading and delivery of various drugs [2], [7], [8]. Importantly, the use of calcium carbonate as a food and pharmaceutical ingredient is approved by the Food and Drug Administration Agency (FDA). The metastable $CaCO_3$ micron and submicron particles have been successfully applied in various methods of drug administration, e.g., injections, oral, nasal, and through other parenteral routes [9]–[11]. Additional benefits of $CaCO_3$-based delivery systems include stimuli-responsive properties, namely pH-sensitivity of $CaCO_3$ polymorphs which demonstrate a pH-dependant cargo release [12], [13]. Moreover, as an ultra pH-sensitive material, $CaCO_3$ particles can serve as sacrificial templates to form other nanostructured drug delivery vehicles, such as polyelectrolyte capsules and alginate particles [14]–[16].

Although the pH-sensitive potential of particles is fairly well explored, important details about how pH-sensitivity and the degree of release of encapsulated molecules correlate with crystal polymorphism and particle size are missing. Continuing to develop this area, here we demonstrate the effect of the size (50 – 500 nm) and structure of $CaCO_3$ particles (amorphous, vaterite or calcite) on the efficiency of their loading with doxorubicin, as well as its release under model neutral and acidic conditions. The doxorubicin loading up to 4-5 wt.% was achieved. As the particles are expected to be intravenously administered to the body, we modified their surface with a number of biocompatible polymers to achieve better dispersancy and improve the stability of their suspension. We optimize the concentration of submicroparticles in saline in terms of maximum concentration while maintaining colloidal stability. The effect of coating on the rate of internalization and accumulation of particles by cells was established.

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