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Optimizing $CaCO_3$ Matrix Might Allow To Raise Their Potential Use In Biomedical Application

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Abstract

The significant step in $CaCO_3$ fabrication is to obtain homogenous population. There is a wide application in biomedical and industry market, since many reports have been investigated possible control of its diameter and shape during fabrication. Nowadays, $CaCO_3$ template can be synthesised in diameter near or less than 120 nm. Control factors affected $CaCO_3$ nucleation with integration of polymer inside were the main purpose in $CaCO_3$ modification. In spite of great work that was done, designing of $CaCO_3$ matrix as a way to be more attractive for hydrophobic cargo molecules could need a second eye for other investigation. The modification of $CaCO_3$ matrix not only can provide mechanical support of all of $CaCO_3$ architecture, or as a vehicle for hydrophobic molecules but also can be used as a smart vector for integration other drug delivery system such as liposome, micelles or even lipid nanoparticles.

Keywords: $CaCO_3$ fabrication; Homogenous population; Liposome; Micelle; Polymers

Introduction

$CaCO_3$ crystals were considered as one of important inorganic materials for producing drug delivery carriers [1-4] for several advantages as following:

1) There is no any sign for histological toxicity after core removal with EDTA and it is safer in handling than other templates [5].

2) The natural porosity of $CaCO_3$ micro/nanoparticles has provided them with great advantages for layer by layer adsorption [6]. Hence polymers used in polyelectrolyte multilayer assembly, will diffuse through these porous forming interior polyelectrolyte network complexes having the same materials presented in the shell after the core removal [2,7]. These connected networks might provide mechanical and protective support for capsules architecture [8] allowing for long storage and can cause good stability in blood stream.

3) $CaCO_3$ crystals can be formed with simple mixing of inexpensive and widely accessible salt precursors, $CaCl_2$ and Na_2CO_3 and the core can be removed by EDTA with no more effect on layer by layer capsules [4,9]. Cargo molecules could be encapsulated inside $CaCO_3$ matrix by either using co-precipitation in its porous (Figure 1A, pre loading method) [1] or by loading cargo molecule inside Layer by Layer (LbL) capsules after core removal (Figure 1, post loading method) [2].

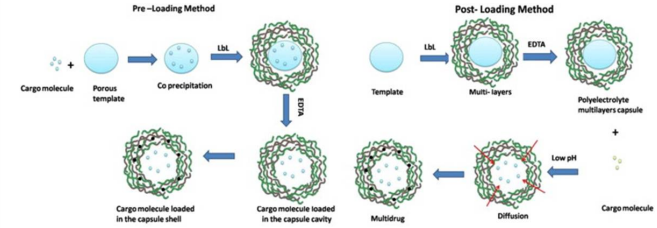

Figure 1: Drug encapsulation schemes (reproduced with permission from Ref [10]).

The above notable advantages give $CaCO_3$ template much important use in medical applications and also can be considered as a good example to study mechanical and physical properties in carrier fabrication. Although $CaCO_3$ has attracted many attentions and used in wide applications, the matrix of $CaCO_3$ is still under optimization. Previously its aggregated state, polymorphism crystallization and its micrometer diameter were completely solved [10]. The nucleation process of $CaCO_3$ during fabrication becomes a way for improving the final $CaCO_3$ template. Indeed, the quality of the resultant microparticles is introduced to be strongly dependent on the experimental conditions such as the type of the used salts, their concentration, pH, temperature, rate of mixing solutions and the intensity of agitation of the reaction mixture [11-14]. In addition, inclusion of various additives, such as divalent cations, organic solvents and macromolecules (synthetic or natural) added to the reaction mixture, are shown to exert a strong effect on the morphology of the formed $CaCO_3$ microparticles [15-18].

Control of $CaCO_3$ Fabrication

In previous reports, $CaCO_3$ synthesis was controlled by adding organic materials and its derivatives during fabrication. These materials might strongly influence the crystallization of $CaCO_3$ whereas, stabilized amorphous $CaCO_3$ could be formed due to the functional groups of organic material leading to control nucleation, growth, and alignment of the crystals [19,20]. Currently, simple polyelectrolytes have been used to control the crystallization of calcium carbonates during synthesis [21]. The functional group of polyelectrolyte allows to control strongly nucleation and crystals agglomeration. Hence the single particle of $CaCO_3$ is agglomerated by tiny smaller crystals resulting from attachment of Ca^{2+} and CO^{3-} nuclei. In case of absence of electrostatic balance, these nuclei tend to bind with other in the same solution causing aggregation and growth in diameter. Furthermore, their aggregation is not easily separated by using mechanical separation (example: vortex and shaker or even physical separation like sonication). The active group of both polyelectrolyte cationic and anionic polymers could contribute to keep balance among nuclei. This could be explained from the fact that Ca^{2+} and CO^{3-} nucleation can accept the active group of polymers to keep them in most case under electrostatic balance. This property allows to reduce growth of crystal, furthermore leading to diameter control (Figure 2) [10].

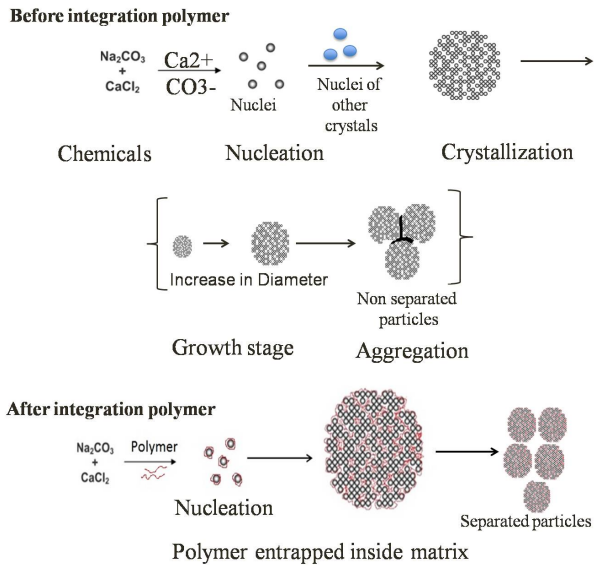

Figure 2: Scheme of control of $CaCO_3$ crystallization by integration polymer inside matrix of $CaCO_3$ (reproduced with permission from Ref [10].

Many polymers have been used to control $CaCO_3$ during fabrication such as poly (sodium 4-styrene-sulfonate) PSS [22,23], Poly (allylamine hydrochloride PAH [24], Poly acrylic acid (PAA) and Chitosan [10] (CH), poly (vinyl alcohol) (PVA), polyacrylamide, poly(N-isopropyl acrylamide), poly(N-vinyl pyrrolidone), and poly(ethylene oxide) [10]. From previous studies, it is indicated that any peptides can influence strongly on $CaCO_3$ nucleation, should certainly alter the morphology of $CaCO_3$ [25].The demission of $CaCO_3$ from diameter and shape is already studied and the both are completely controlled by adding polymers during fabrication. As example, PAA can reduce diameter of $CaCO_3$ to less than 200 nm and PAH can control morphology of $CaCO_3$ toward elongated shape like rods. It could be concluded that $CaCO_3$ mineralization can accept physicochemical properties of used polymers.

Drawback of $CaCO_3$ Controlled by Polymers

As a rule, the spherical $CaCO_3$ microparticles that were obtained by simple mixing of Ca^{2+} and CO^{3-} can be turned into rhombohedral calcite microcrystal after several weeks of storage in water at room temperature because of re-crystallization [1]. In case of used polymer, there is no shape change during successive six months of storage[14]. Since the negatively charged of PSS are adsorbed on the matrix of carbonate nanoparticles constituting the porous $CaCO_3$ microparticles and prevents the re-crystallizations. High stability of the $CaCO_3$ microparticles in water is very important for the successive LbL assembly. However this storage is linked much with distilled water, milli Q water or buffer pH 7.2. In case $CaCO_3$ kept at solution having ionic salts, acidic solution, or strong minerals, Its morphology can be changed and re-crystallization is expected. Indeed the polymer entrapped $CaCO_3$ matrix could answer the ionic stress allowing to modify $CaCO_3$ configuration. Chitosan, poly acrylic acid [26], poly allylamine hydrochloride [27] are known with their answer for ionic stress and they could modulate their chain after they are crystallized inside matrix of $CaCO_3$. It is proven in case of polymer integrated in a matrix of $CaCO_3$ to coat them with layer-by-layer alternate adsorption or to keep them as dried particles at room temperature or to keep them in water. This environment could prevent $CaCO_3$ re-crystallization.

Designing Matrix of $CaCO_3$

Recently the porous channel of $CaCO_3$ was employed completely as a safe vector for protein encapsulation (Figure 3) [1].

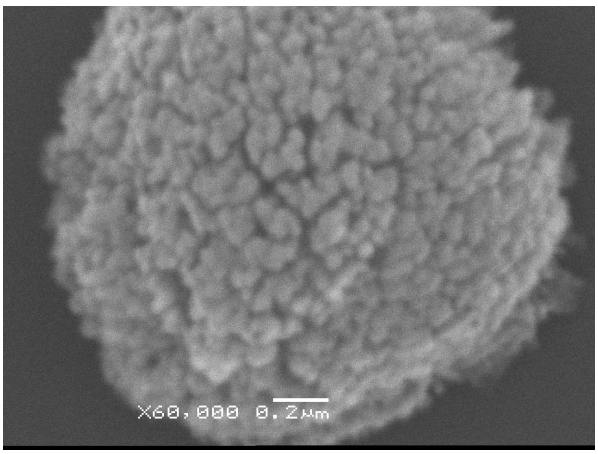

Figure 3: Scanning Electron Microscopy image of $CaCO_3$ showing Pores. (reproduced with permission from Ref [10]).

The empty pores were formed among tiny crystals of $CaCO_3$ during crystallization resulting in connected network after core removal. These networks could be occupied by cargo molecules. Hence, cargo molecule can be mixed initially with $CaCl_2$ or Na_2CO_3 according toits charge and its ability to be stable under alkaline pH of $Na2CO_3$. After reaction of the mixture, cargo molecules will be entrapped inside matrix of $CaCO_3$ [28]. In another case, biomolecules can be adsorbed

in the pores of the $CaCO_3$ crystals, after their crystallization by physical adsorption [29,14] chemical cross-linking [30] co-precipitation, [27] and trapping by coating with polyelectrolyte multilayers. In order to control the porosity of $CaCO_3$ crystal, temperature should be optimized during fabrication [9]. It is found that the $CaCO_3$ crystals with larger pores (prepared at 22 or 45°C) will be even more penetrable for molecules of interest. The designing of $CaCO_3$ porous was initially employed by adding several type of polymers during fabrication such as carboxymethyl cellulose (CMC), a negatively charged polysaccharide, which was simultaneously incorporated providing attractive force for positively charged drugs such as doxorubicin (DOX) [28,14]. Wang et al. (2006) reported that ibuprofen, a lipophilic drug, was loaded into the polystyrene sulfonate (PSS)-doped $CaCO_3$ microparticles. Due to the charge repulsion, the loading amount of ibuprofen was not very large. Moreover, the additive of PSS has some uncertainties for biomedical applications [14]. In addition, porous of $CaCO_3$ were design by Cyclodextrins to be accommodated for hydrophobic materials such as curcumin [31]. Another designing is to generate block co polymer micelles inside $CaCO_3$ matrix during fabrication. Since polystyrene-blockpoly (acrylic acid) (PS-b-PAA) was added drop wise into Na_2CO_3 aqueous solution under vigorous agitation then $CaCl_2$ was rapidly poured into the mixed solution under vigorous agitation [23]. It is found that $CaCO_3$ cores possess high connected and very stable internal area [8]. Yashchenok and co-workers have introduced liposomes for modification of $CaCO_3$ cores and demonstrated that ultrasound (US) triggered mixing of the liposome encapsulated moleculesand core-embedded molecules may be achieved in confined volumes [32]. The other modification for $CaCO_3$ matrix is to involve air bubbles inside matrix during fabrication by using Plexiglas reactor [33].

$CaCO_3$ and Biological Toxicity

Calcium carbonate nanoparticles have exhibited successful application as biological subcutaneous delivery [5,34,35]. Many reports confirmed their safe use for raise their therapeutic activity without harming biosystems [5]. Jaji and his co-workers investigated the safety of cockle shells (ANC) as a potential agent for subcutaneous delivery of biology and drug materials. Confirming that there is no mortality, it was recorded at the end of the acute and subchronic toxicity experiments for calcium carbonate injected subcutaneously. With a LD50 of 6450 mg/kg body weight, calcium carbonate merged a wide margin of safety and low acute toxicity [36]. The Single doses of 1770 and 11,800 mg/m^2 of calcium carbonate did not form any cytotoxicity while the high dose of 29,500 mg/m^2 introduced some toxic signs and lesions. Okogbue et al. (2014) showed that histological results revealed that calcium carbonate had no negative impact on the body tissues of the prawns tested both on the muscle and carapace [37]. Furthermore, the total calcium ions was higher in serum after administration of calcium carbonate powder versus calcium citrate tablets [38]. The multilayered nanocapsules produced by calcium carbonate core removal observed no evidence for any histological toxicity because $CaCO_3$ crystals can be removed completely by using disodium ethylenediaminetetraacetic acid (EDTA) and the ions formed upon dissolution can be diffused out through the capsule wall rapidly [39]. In case shell, the histological toxicity depends on the type of polymer formed layers of capsules. From the above mention, calcium carbonate could be highlighted their potential use in biomedical and industrial applications. Recently, many type of particles have been introduced as great vehicles for drug delivery system such as self assembly polymers [40,41], liposomes [42,43] and micelles [44,45], LbL $CaCO_3$ [10,46], and LbL magnetic nanoparticles [47].

Conclusion

The potential use of drug delivery system could be raised with smart modification of $CaCO_3$. In this sense, the shell and core become more efficient to encapsulate several drugs with hydrophobic and hydrophilic properties. Several studies have been confirmed that $CaCO_3$ crystallization could be acceptable for development.

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