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Calcium Carbonate Nanoparticles; Potential in Bone and Tooth Disorders

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ABSTRACT

Background: Inorganic nanoparticles for biomedical applications have undergone extensive investigations in recent years. Among different inorganic drug carriers, calcium carbonate ($CaCO_3$) nanoparticles show unique advantages due to their ideal biocompatibility and the potential as delivery system for loading different categories of drugs. The accessibility, low cost, safety, biocompability, pH-sensitive properties, osteoconductivity and slow biodegradability of $CaCO_3$ particles nominate it to be a suitable drug delivery carrier. Due to slow degradation of $CaCO_3$ matrices, these nanoparticles can be used as sustained release systems to retain cargo for longer times after administration. The osteoconductivity and bioresorbability may offer these nanoparticles as proper candidate for dual application as bone substitution and drug release in the bone related disease such as osteomyelitis. Filling bone defects, treatment of early dental caries lesions and generating neoformed bone tissue using by different types of nanoparticulate calcium carbonate has also shown notable applications. According to reviewed literature, $CaCO_3$ nanoparticles because of their special characteristics show a potential dual application as bone substitution and drug carrier in the bone related disease/defects.

Introduction

Calcium derivatives are the most important natural constituents of bone and teeth. In fact, the primary tissues of bone, osseous tissue is mostly made up of a composite material consist of the inorganic mineral calcium derivatives.[1] Furthermore, tooth enamel is one of the four tissues that composes the tooth which contains the highest percentage of mineral mostly Calcium.[2] Therefore, different calcium derivatives have been shown great potentials to be applied in bone and teeth related disorders due to their ideal biocompability with the natural bone and teeth structures and the biodegradability as well.[3,4] Filling dental caries, treatment of early dental caries lesions and generating neo-formed bone tissue using by different types of calcium derivatives has also shown notable applications.[5,6]

One of the most common calcium derivatives with long history of applications in various fields is $CaCO_3$. It has been used in plastics, paint, paper, inks, food as well as pharmaceutical industries.[4,7,8] Medical applications of $CaCO_3$ in modern health care systems have attracted the attention of researches due to its great potentials and capabilities. This material is low cost, safe, accessible, biocompatible, bioresorptive and osteoconductive.[9-12] Furthermore, due to the slow degradation and pH-sensitive properties, this material can be used as controlled release systems to maintain the drugs in targeted sites for extended times after administration.[13,14] According to researches, calcium carbonate materials can be proper to increase biomedical cement resorption rates and to initiate its replacement by bone tissue.[15] Designing the drug loaded resorbable bone filling materials using by calcium carbonate will provide a dual therapeutic scheme (drug release and bone substitution) in the one stage.

Osteomyelitis (OM) is infection and inflammation of bone that is originated by a variety of pathogens most commonly *Staphylococcus aureus*.[16] *S aureus* is normal oral and nasal flora. It can penetrate into endothelial, epithelial and osteoblastic cells[17,18] and therefore can be protected from the host immune system to provide a reservoir of bacteria in recurring osteomyelitis. Then its targeting by the antibiotic may be more important for treating chronic bone infection than physically eliminating only pathogens colonizing from the bone.[19]

Dental caries, also known as tooth decay or cavities is a disorder of teeth due to the activities of bacteria.[20,21] Its complications may contain inflammation of the tissue around the tooth, tooth loss, and infection or abscess formation.[22] *Mutans Streptococci* of oral flora in

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particular are the main cause of dental decay. Acidic substances as the metabolites of bacteria corrode the surface of the enamel and breaking down its components. From the enamel, dental decay can proceed to the dentin and all the way to the pulp. Because of softer structure of dentine, decay advances more rapidly in it.

Pharmaceutical nanoparticles are ultrafine colloidal particles with size range between 10-1000 nm, commonly 5 – 350 nm in diameter, and show different properties compared to own original materials.[23-26] Nanoparticulate systems can valuably improve therapeutic efficacy by producing more favorable drug bioavailability, serum stability and pharmacokinetics.[25,27] These novel and innovative systems can increase therapeutic efficacy and also decrease side-effects by concentrating the therapeutic agents at specific target sites in the body.[6,9,28,29] Different kinds of nanoparticulate for drug delivery purposes have been investigated so far[26,30-32] especially in the complex structure of bone and teeth.

Having in mind the great potential of $CaCO_3$ in bone and teeth complications as well as the advantages of nanoparticle based drug delivery systems, in this review; we address the current state of $CaCO_3$ nanoparticles with focusing on their application in bone and teeth.

$CaCO_3$ nanoparticle

$CaCO_3$ is one of the most common inorganic materials that has been used as a viscosity modifier in many industrial areas such as; rubber, plastics, paint, paper, inks and food.[33] Owing to the availability, safety and slow biodegradability of $CaCO_3$ nanoparticles, it has been used for controlled drug delivery and encapsulation of different kinds of drugs such as bioactive proteins in pharmaceutics.[12,34-36] Toxicological tests by Zhang et al. on HeLa cells showed that calcium carbonate particles could be used as moderately nontoxic drug carrier.[37] Combes et al also evaluated the cytotoxicity of calcium carbonate cement compositions on osteoprogenitor cells obtained from human bone marrow and showed no cytotoxicity effect of calcium carbonate based cements.[38] However, as a noticeable point, the generation of reactive oxygen species (ROS) in high concentrations should be considered.[37,38]

$CaCO_3$ has three anhydrous crystalline polymorphs include calcite, aragonite and vaterite.[39,40] These differences in morphological forms of calcium carbonate is related to the synthesis conditions.[41] Calcite is the stable form and exists as trigonal crystalline form in nature. Its thermodynamic stability and mechanical properties in blending with polymeric micelles have recently been investigated for sustained and targeted drug release into cancerous cells.[42] Also a direct contact between the bone and polycrystalin, metamorphic calcite $CaCO_3$ without interposition of soft tissue at the interface has reported.[15] Vaterite has the least stability and belongs to the hexagonal crystal system. In contact with water, vaterite can slowly dissolve and recrystallizes to stable form.[43] Owing to its large porosity and surface area, as well as rapid disintegration under relatively mild conditions, vaterite can use as an ideal nominate for preparation of a controlled drug delivery carrier.[44,45] Aragonite type occurs in orthorhombic system[46] and has got exclusive research attention because of its biocompatible properties.[47,48] According to literature, aragonite can be resolved, integrated and replaced by bone.[49] Aragonite polymorph is denser than calcite and has also been used for the designing of the anticancer drug carrier and scaffolds for bone repair and tissue engineering.[50] Three polymorphs of calcium carbonate were shown in figure 1.

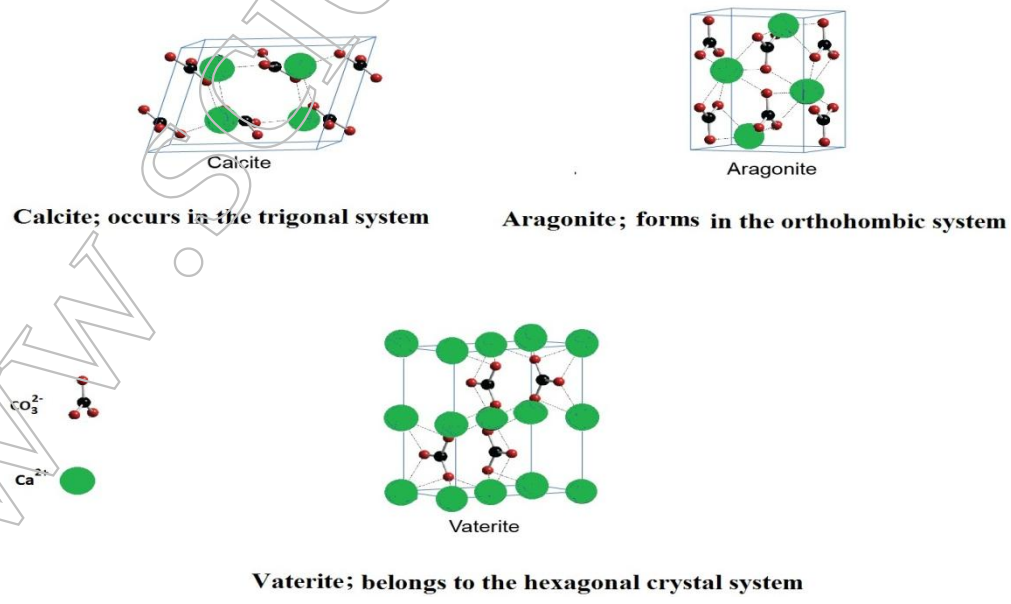

Figure 1. Three polymorphs of calcium carbonate; Calcite, Aragonite and Vaterite.

Preparation methods for $CaCO_3$ nanoparticles

Some methods generally based on emulsion techniques include reversed microemulsion[13], double emulsion[51], O/W microemulsion method using by a High Pressure Homogenization (HPH)[52], and also chemical precipitation methods[53] have been reported in the synthesis of calcium carbonate nanomaterials. Other methods including decomposition of cockle shells,[49] flame synthesis,[54] spray drying[55] and reactive precipitation using a high pressure jet homogenizer[7] has also been used for preparation of $CaCO_3$ nanoparticles.

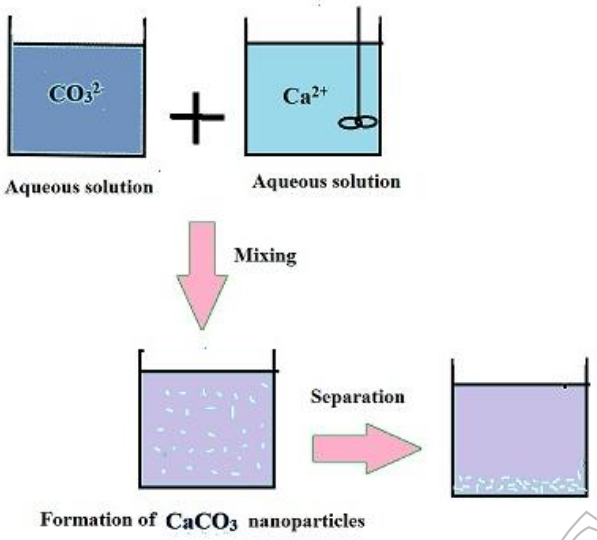

Figure 2. Chemical precipitation procedure; the reaction between calcium ions and carbonate ions (in aqueous solution) leads to preparation of calcium carbonate nanoparticles.

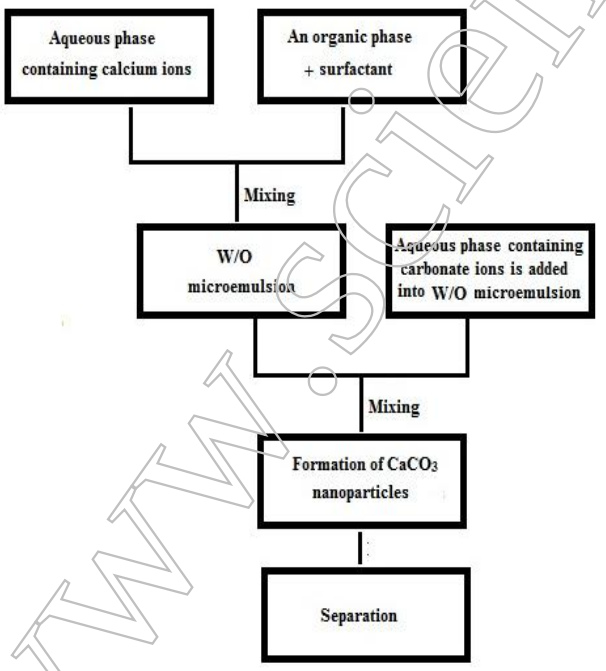

Figure 3. Preparation of $CaCO_3$ nanoparticles through W/O microemulsion; First step is mixing of an aqueous phase include calcium ions with an organic phase to produce a W/O microemulsion. Then an aqueous solution consisting of carbonate ions is added into experimental vessel and mixing is continued until $CaCO_3$ particles are formed. The final step is separation of nanoparticles from aqueous media.

Chemical precipitation procedure

In the chemical precipitation procedure, the reaction between calcium ions and carbonate ions from aqueous solutions leads to preparation of calcium carbonate nanoparticles. After the preparation of nanoparticles, the separation of nanoparticles from solution using by for example a centrifuge is done.[53] Figure 2 shows the process schematically.

W/O microemulsion method

In the preparation of $CaCO_3$ nanoparticles via W/O microemulsion, first, an aqueous phase include calcium ions is mixed with an organic phase to produce a W/O microemulsion. Then an aqueous solution consisting of carbonate ions is added into vessel through the mixing in high speeds and mixing is continued until $CaCO_3$ particles are formed.[13] The final step is separation of nanoparticles from aqueous media. The steps of this process are shown in figure 3 schematically.

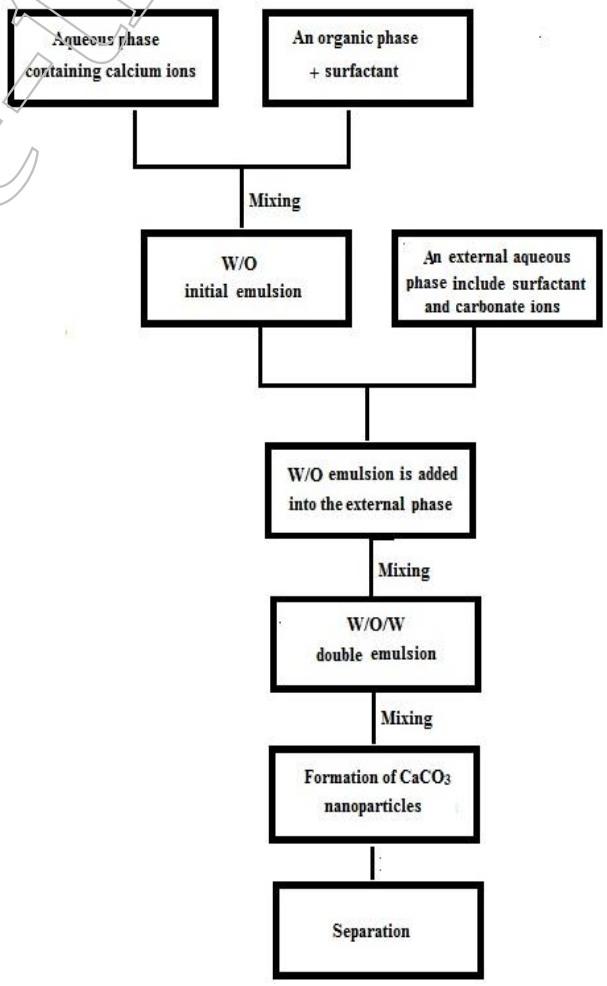

Figure 4. Preparation of $CaCO_3$ nanoparticles through a W/O/W double emulsion technique; the calcium ions and carbonate ions are reacted in W/O/W emulsion droplets. Then nanoparticles are formed and separation of nanoparticles are performed.

W/O/W double emulsion method

W/O/W double emulsion is another method to preparation of $CaCO_3$ nanoparticles which is includes four main steps. In the first step, the mixing of an aqueous internal phase (consisting calcium ions) with an organic phase leads to form a initial emulsion (W/O). This phase is then further mixed in a larger mixing container with an external aqueous phase including carbonate ions to form W/O/W double emulsion. Similar to former method, the calcium ions and carbonate ions were reacted in emulsion droplets and nanoparticles are formed and then separation of nanoparticles is performed. Indeed, the ions in the external phase can be transported across the liquid membrane to react with the internal phase.[51] Figure 4 shows the preparation steps of $CaCO_3$ nanoparticles via a W/O/W double emulsion technique.

O/W microemulsion method using by a HPH

O/W microemulsion method; Calcium carbonate nanoparticles can also be obtained via O/W microemulsion method using by a HPH.[52] In this procedure, the size of microparticulate calcium carbonate is reduced through passage from the homogenizing gap by cavitations, particle collisions, and shear forces.[56] Reduction of particle size using by High Pressure Homogenization method is shown in figure 5.

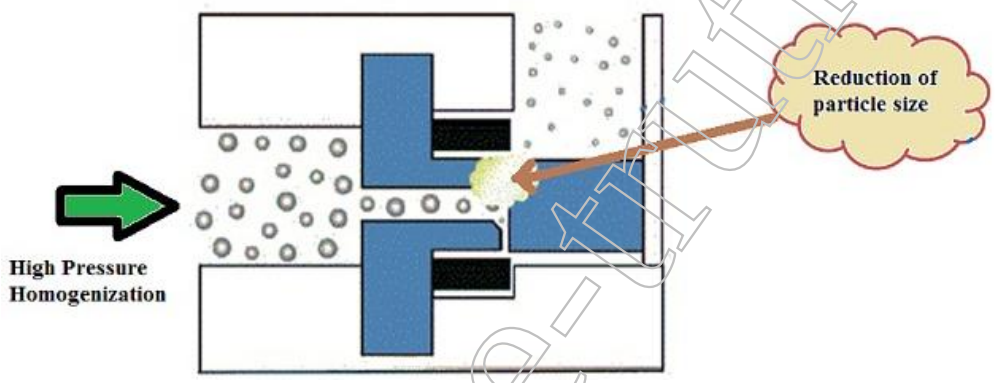

Figure 5. Reduction of particle size via High Pressure Homogenization method.

Drug loaded calcium carbonate nanoparticles

For the preparation of drug loaded calcium carbonate nanoparticles, drug can be wrapped into the nanoparticles in the process of the reaction. For example, Ueno et al prepared the calcium carbonate nanoparticles loaded with betamethasone phosphate (BP), Erythropoietin and Granulocyte-colony stimulating factor (G-CSF) by chemical precipitation method. Their drug-loaded calcium carbonate nanoparticles produced by mixing calcium chloride and sodium carbonate aqueous solutions and drug enclosed into the nanoparticles in the process of the reaction. In the other study, Qian et al using by W/O reverse microemulsion produced validamycin - calcium carbonate nanoparticles. Validamycin was wrapped into the nanoparticles in the process of the reaction between calcium chloride and sodium carbonate aqueous solutions. Drugs can also be adsorbed on or entrapped in proses nanoparticles after the preparation of $CaCO_3$ nanoparticles.[52] Shafiu Kamba et al prepared $CaCO_3$ nanocrystals using by O/W microemulsions and a HPH. Then doxorubicin hydrochloride was adsorbed on the $CaCO_3$ nanocrystals by adding the doxorubicin into suspension of the calcium carbonate nanocrystal. Suspension was continuously stirred overnight, in a dark environment at room temperature.[52]

Bone related applications of $CaCO_3$

Systemic treatment of bone infections such as osteomyelitis requires high serum concentrations of antibiotics for extended periods. Furthermore, the antibiotic overdose often has adverse side effects. In this context, local treatment seems to be proper idea with better compliance and fewer side effects. [57] So far some drug delivery systems have been used to prevent or treat chronic or implant-related osteomyelitis in bone surgery which is often composed of nonresorbable materials, need to be removed after treatment.[58-62]

An ideal bone grafting material should be replaceable by the host bone and therefore needs to be bioresorbable, osteoconductive and biodegradable.[63,64] Bioresorption is a biological mechanism by which the matrix of some ceramic materials resorbs partially or completely over a period of time in biological media.[65] Osteoconductivity provides a scaffold for the growth of bone. The porosity is the main factor in the case of osteoconductivity and bioresorbability. The pore size, the total porous volume and the interconnectivity of the pores are the important aspects of the porosity for the osteoconductive properties.[65] Larger pores are able to resorb faster and therefore develop the new bone material faster. Among the biodegradable materials, calcium carbonate has been reported to be bioresorbable, biodegradable and osteoconductive.[66-68] A direct contact between the bone and polycrystalin,

metamorphic calcite $CaCO_3$ without interposition of soft tissue at the interface has reported.[15] Lucas-Girot et al developed a synthetic aragonite-based calcium carbonate macroporous drug carrier loaded with gentamicin sulphate, an antibiotic active on *Staphylococcus aureus* responsible for osteomyelitis for dual application as bone substitution and drug release. According to authors, the resorption kinetics of this new device is faster than a common type of bioceramics (hydroxylapatite/tricalcium phosphate). They emphasized that these materials show good potential incorporate of temperature sensitive substances like antibiotics. Also, the degradation of calcium carbonate matrix can easily metabolized in osseous tissue. They concluded that compared to polymeric drug delivery systems, calcium carbonate materials (aragonite-based) integrated with gentamicin can be utilized either as a resorbable delivery sustem for release of gentamicin or for a combined therapy e.g. bone substitution, and prevention or treatment of osteomyelitis in a single stage.[69]

The bone formation process and the nature of the interface between the bone and the calcium carbonate surface are still ambiguous.[70-72] Ohgushi et al showed that the bone forming response of $CaCO_3$ is comparable to that of the well-known bioactive hydroxyapatite. They also present a method for determining the interaction between osteogenic cells derived from marrow cells and porous $CaCO_3$, without influences from preexisting host bone.[10]

Dental applications of $CaCO_3$

Filling of bone defects with resorbable materials leads to neo-formed bone tissue and has orthopaedic and dental surgery.[6] Guided Bone Regeneration (GBR) is dental surgical procedure which utilizes barrier membranes to direct the growth of new bone and gingival tissue at sites having insufficient volumes or dimensions of bone or gingiva for proper function. In a reported study, preparation of a new type of GBR membranes using by polycaprolactone (PCL)/$CaCO_3$ composite nanofibers were reported. SEM analyses showed good cell attachment and proliferation manner. Their study showed the potential of PCL/$CaCO_3$ nanofibers for GBR membranes.[5]

An irreversible loss of hard tissue of tooth due to a chemical process without involvement of microorganisms is known as tooth erosion.[73] According to researchers, one of the important external factors in dental erosion is eating/drinking of acidic products.[74] Esmaeili Khoozani et al prepared calcium carbonate nanoparticle with milling the eggshells using by a high energy planetary ball mill. According to their results, adding calcium carbonate nanoparticles to soft drinks can reduce or prevent tooth erosion and the modification of these drinks is critical to reduce the risk of dental erosion.[75]

Treatment of early caries lesions using by different types of nanoparticulate calcium carbonate or apatite has shown noteworthy applications.[76,77] According to researches, the mechanical properties of releasing composites containing the calcium and phosphate are comparable with commercial hybrid composites.[78-80] Hydroxyapatite or calcium carbonate nanostructurs can act as a calcium and phosphate sources to retain these ions in supersaturation state in the enamel minerals. Furthermore, deposition of these ions on the surface of the demineralized enamel might support remineralization process of the outer enamel caries lesion.[6] Nakashima et al reported the preparation of an experimental dentifrice containing 1% amorphous calcium carbonate nanoparticles. They used in vitro collagen-coated wells as a model for oral mucosal surfaces and application of experimental dentifrice (twice a day over 20 days) showed significant mineral gain and remineralization of artificial caries lesions.[81] They emphasized that, this dentifrice shows good efficiency to remineralize initial enamel lesions owing to the exclusive properties of the calcium carbonate nanoparticles. Calcium carbonate nanoparticles may be reserved on the collagen-coated surfaces in the model system and then may also be retained on oral surfaces, therefore releasing of calcium ions into oral fluids for remineralization was occurred. In another study, Moreau et al prepared the nanocomposites containing amorphous calcium phosphate and calcium carbonate via a spray-drying technique which showed rapidly neutralization of the lactic acid solution (pH 4.0) by increasing the pH to 5.69 within 10 min. They concluded that these types of nanocomposites may have the potential to reduce secondary caries and restoration fracture.[78]

Conclusion

In summary, we conclude that $CaCO_3$ matterials have promising potential for dual application as bone substitution and drug release in the bone related disease. Furthermore, filling of bone defects, treatment of early dental caries lesions and producing of new bone tissue using by different types of calcium carbonate nanomaterials has also shown outstanding applications. However, $CaCO_3$ nanoparticles may show cytotoxic effects like to other nanoparticles and therefore cytoxicity tests are essential before *in vivo* evaluation of these nanoparticles. Despite their great potentials in drug delivery into bone, $CaCO_3$ nanoparticles have not been studied in desirable scale. Further studies are necessary to demonstrate the dual potential role of these nanoparticles for delivery of drugs in bone or teeth related disorders.

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