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Review Article

Advancements In Calcium Carbonate Nanoparticles: Novel Strategies For Osteomyelitis Treatment

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ABSTRACT

Osteomyelitis, an inflammatory bone infection, poses significant challenges in diagnosis and treatment due to compromised vasculature and bacterial resistance. This review explores the potential of calcium carbonate nanoparticles (CaCO3 NPs) in addressing these challenges. CaCO3 NPs exhibit excellent biocompatibility, pH sensitivity, and ease of modification, making them promising candidates for biomedical applications. Recent advancements include enhancing antimicrobial properties, utilizing CaCO3 NPs as drug carriers, and leveraging their immunomodulatory effects. Future trends suggest potential applications in oral osteoporosis treatment, localized antibiotic delivery, and solid cancer therapy. Additionally, CaCO3 NPs hold promise for bone tissue regeneration and scaffold development. Despite progress, further research is needed to optimize CaCO3 NP formulations and explore their full potential in osteomyelitis management. Overall, CaCO3 NPs offer a versatile platform for improving diagnosis, treatment, and therapeutic outcomes in osteomyelitis and other bone-related disorders.

INTRODUCTION

Naturally, bone is a highly vascularized connective tissue that exhibits a unique angiogenic pattern and frequently develops in tandem with the mineralization of bone (1). However, the vasculature of bone can become compromised due to ageing, trauma, or infection, creating a nearly perfect environment for opportunistic bacteria to adhere to and grow. This damaged vasculature not only creates an environment that is ideal for bacterial growth (lower oxygen, a more alkaline pH, etc.), but it also prevents antibiotics from being delivered. This confluence of ailments results in bone infections, including diabetic foot

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osteomyelitis, septic arthritis, spinal infections, and osteomyelitis, which can cause severe trauma and result in lifelong disabilities. A novel strategy for quick diagnosis and treatment may be needed for the clinical management of such infections.

OSTEOMYELITIS

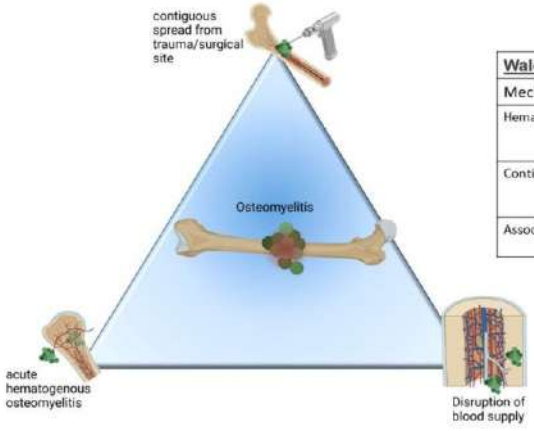
The definition of osteomyelitis is "inflammation of the bone," usually brought on by an infection of the bone marrow and surrounding osseous structures, which may also affect the surrounding soft tissue (2). Up to 75% of these infections are caused by staphylococci overall, with S. aureus being the primary pathogen in 30% to 60% of cases (3).

CAUSES

The kinds of infections are as follows: (1) Blood-borne infection: This type of infection, also known as bloodborne osteomyelitis, occurs when pathogenic bacteria are carried from distant infection foci to the bone tissue through the blood circulation; (2) Post-traumatic infection, also called post-traumatic osteomyelitis, involves direct contamination of open fractures or bone infection following fracture surgery, particularly following internal fixation or prosthesis implantation; and (3) Adjacent infection, which includes pressure ulcers, foreign body infections, and other infections that spread to the bone tissue, including ulcers brought on by diabetes and arteriosclerosis, and osteomyelitis brought on by tissue necrosis. The metaphysis of the long bones (proximal tibia and distal femur) or penetrating bone injury because of trauma is the most common site in children (4-7).

TYPES

Osteomyelitis is classified into (1Acute hematogenous osteomyelitis, which is primarily observed in children under the age of seventeen; (2) contiguous osteomyelitis, which arises from adjacent infection sites (like those resulting from trauma or surgery) or an orthopaedic implant (8) or (3) secondary osteomyelitis, which is caused by vascular insufficiency or neuropathy, as observed in diabetic foot ulcers(9,10).



Waldovogel's Classification of Osteomyelitis:

Mechanism of Bone infection	Characteristics
Hematogenous	Occurs via bacterial transport in the blood. Accounts for the majority of osteomyelitis in children under 5
Contiguous	Adjacent tissue allowing bacterial inoculation (e.g., post-traumatic, open wound, joint replacement/prosthesis
Associated with vascular insufficiency	Diabetic patients with foot infections or peripheral vascular disease

Figure 1: Osteomyelitis arises in one of three primary ways. Regardless of the underlying cause, vascular disruption due to the formation of sequestra can occur, making treatment very difficult (10). Waldvogel's classification of osteomyelitis (3) describes characteristics of each of these ways. Figure created with BioRender.com.

PATHOPHYSIOLOGY OF OSTEOMYELITIS

The location of the bone, its structural variation according to the patient's age, and the underlying source of the infection all affect the pathophysiology of osteomyelitis. According to recent research, ageing may cause changes in both the vascular and mineral structures of bone, with the impaired endothelial Notch signalling appearing to be the primary cause of these changes (11, 12). This change in blood flow may impair osteogenesis and bone healing, making it more

susceptible to infection, especially following trauma, surgery, or injury (13). It is evident how both contiguous spread and disruption of the blood supply result in osteomyelitis given the vital role that the vasculature plays in bone regeneration; however, osteomyelitis resulting from acute hematogenous spread of infection in pediatric patients does not initially appear to fit that pattern. Upon closer inspection, however, acute hematogenous osteomyelitis is frequently linked to the venous architecture in pediatric patients, which is linked to more turbulent blood flow at the metaphyseal vessel loop, which is found in the vicinity of the pediatric patient's growth pates and lumbar spine (9). This turbulent flow, in conjunction with a transient bacteremia frequently brought on by trauma, results in venous pooling of blood close to the metaphysis of bone, which permits bacterial deposition close to the growth plate and starts the osteomyelitic progression (Figure 2) (2). Osteomyelitis can be particularly difficult to diagnose, regardless of its pathophysiology.

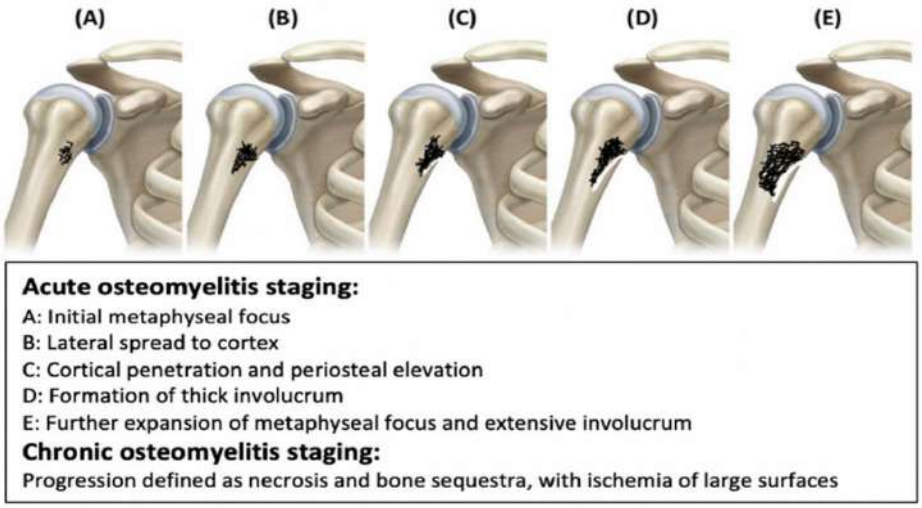


Figure 2: Progression of either (A) acute or (B) chronic osteomyelitis (C) Cortical penetration and periosteal elevation (D) Formation of thick involucrum (E) Further expansion of methaphyseal focus and extensive involucrum. Two significant differences between acute and chronic osteomyelitis should be noted: the formation of a biofilm and the infiltration of the bacteria into host cells, both of which happen in chronic osteomyelitis (2).

EPIDEMIOLOGY OF OSTEOMYELITIS

The use of prosthetic implants in orthopedic surgery, the advancement of diagnostic technology, and the rise in diabetes have all contributed to an increase in the incidence of osteomyelitis. For instance, a statistical analysis of osteomyelitis patients by German researchers revealed that the overall incidence of the disease increased by 10.44%, from 15.5/100000 people/year to 16.7/100000 people/year, compared with a decade ago; this increase was more pronounced in developing countries than in undeveloped ones(4,14,15).The total yearly incidence of osteomyelitis from January 1969 to December 2009 was determined to be 21.8/100000 persons/year(16). However, women had a lower annual incidence of osteomyelitis than men did, and the infection rate rose with age. From 11.4/100000 person-years in 1969–1979 to 24.4/100000 person-years in 2000–2009, there was a notable increase in the incidence. The rates were consistent in young adults and children, but nearly three times higher in those over 60. This could be linked to a significant rise in diabetes-related osteomyelitis cases(17), of which 44% included S. aureus infections. The incidence of

diabetic foot ulcers was found to be 25%, and the incidence of diabetic foot infections was found to be 36.5 per 1000 people/year in diabetic foot-related osteomyelitis. Osteomyelitis may be linked to between 20% and 68% of diabetic foot ulcers (18). Following osteomyelitis in diabetic foot infections, 66% of cases result in amputation. Diabetes was linked in one study to a 1.6% hospital death rate from osteomyelitis (19).

NANOMATERIALS FOR DIAGNOSIS AND TREATMENT OF OSTEOMYELITIS

NANOTECHNOLOGY:

Material scientists have spent the last fifty years researching various applications for nanoparticles and nanostructured materials in the biomedical and healthcare industries (20). Numerous fields have adopted the term "nanotechnology," which is quickly developing because of the creation of nanoproducts with unique size-related physicochemical characteristics that set them apart from larger matter. Processing, separating, combining, and forming materials with a single atom or molecule is the main objective of nanotechnology (21). A few industries where nanotechnology is gaining traction are medicine, food, cosmetics, natural health, biomedical sciences, mechanics, optoelectronics, substance enterprises, energy science, nonlinear optical devices, single electron transistors, catalysis, space industries, chemical industries, gadgets, light producers, and photoelectrochemical applications (22). Larger particles (up to 500 nm in diameter) can be referred to by different names, but the term "Nano Particle" typically refers to very small particles of matter (1 to 100 nm in diameter). As an illustration, nanorods, nanowires, and nanofibers are nanoparticles having one dimension outside of the nanoscale range and a diameter between one and one hundred nm (23, 24). Materials that are composed of one or more materials and have one dimension within the nanoscale range (less than 100 nm) are referred to as nanostructured materials. As a result, nanostructured materials are made up of linked nanoscale components. "NMs can exhibit unique properties dissimilar than the equivalent chemical compound in a larger dimension," according to the Environmental Protection Agency (EPA) (25). Simple materials (such as metal, carbon, or polymer) (26), composite materials (such as polymer-metal, silica-metal, or graphene-metal), or core-shell materials (27,28) can all be used to create nanoparticles and nanostructured materials.

- Nanoscale: Approximately 1 to 1000 nm size range.
- Nanoscience: The science and study of matter at the nanoscale that deals with understanding their size and structure-dependent properties and compares the emergence of individual atoms or molecules or bulk material related differences.
- Nanotechnology: Manipulation and control of matter on the nanoscale dimension by using scientific knowledge of various industrial and biomedical applications.
- Nanomaterial: Material with any internal or external structures on the nanoscale dimension.
- Nano-object: Material that possesses one or more peripheral nanoscale dimensions.
- Nanoparticle: Nano-object with three external nanoscales dimensions. The terms nanorod or nanoplate are employed, instead of nanoparticle (NP) when the longest and the shortest axes lengths of a nano-object are different.
- Nanofiber: When two similar exterior nanoscale dimensions and a third larger dimension are present in a nanomaterial, it is referred to as nanofiber.
- Nanocomposite: Multiphase structure with at least one phase on the nanoscale dimension.

- Nanostructure: Composition of interconnected constituent parts in the nanoscale region.
- Nanostructured materials: Materials containing internal or surface nanostructure (25).

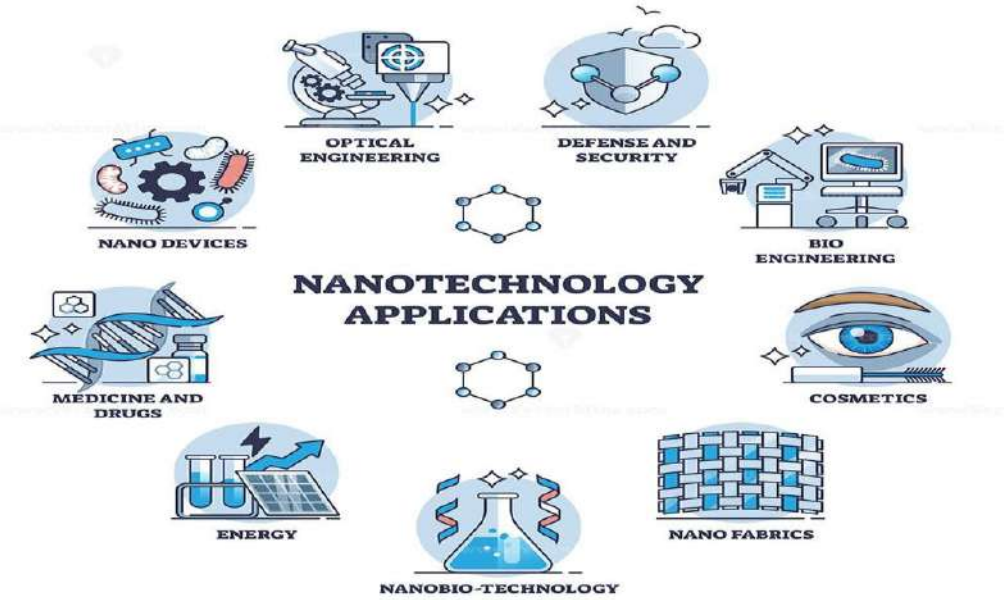


Figure 3.: Applications of Nanotechnology

NANOPARTICLES

The basic building block of nanotechnology is nanoparticles (NPs). Particulate matter with at least one dimension smaller than 100 nm is referred to as a nanoparticle. They may consist of organic materials, metal, metal oxides, or carbon (29).

STRUCTURE OF NANOPARTICLES:

The structures of nanoparticles (NPs) are intricate. There are two or three layers to them:(i) a surface layer that has been functionalized by metal ions, surfactants, polymers, or a range of small molecules (ii) The core material, which is the central component of NPs; (iii) The shell layer, which is chemically distinct from the core and can be added on purpose. The core material is usually responsible for the distinctive characteristics of NPs. As a result, NPs are frequently only referred to by their core material (30).

CLASSIFICATION OF NANOPARTICLES:

Based on dimensions NPs can be classified into (31,32):

1. Zero dimensional (0D) with length, breadth & height Corresponding Author fixed at a single point. E.g. Nano dots
2. One dimensional (1D) which possess only one parameter. E.g. Graphene
3. Two dimensional (2D) which possess only two parameters i.e., length & breadth. E.g. Carbon nanotubes
4. Three dimensional (3D) possessing all three parameters viz. length, breadth & height. E.g. Gold nanoparticles.

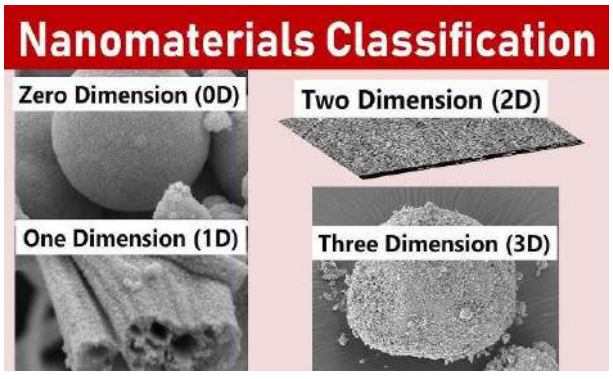


Figure 4: Classification of nanoparticles based on dimension.

The main criteria used to classify nanoparticles (NPs) are their size, shape, and physical and

chemical characteristics. They are primarily divided into carbon-based, inorganic, and organic NPs.

Organic-based nanomaterials:

These are nanomaterials primarily derived from organic matter; they do not include inorganic or carbon-based nanomaterials. Noncovalent (weak) interactions are used in molecular design and self-assembly to help convert organic nanoparticles (NMs) into desired structures like polymer NPs, dendrimers, micelles, and liposomes.

Inorganic-based nanomaterials (NMs):

These comprise NSMs and NPs made of metal and metal oxide. Metals like Au or Ag NPs, metal oxides like TiO2 and ZnO NPs, and semiconductors like silicon and ceramics can all be created using these NMs.

Carbon-based nanomaterials:

These NMs typically consist of carbon and can take the form of hollow tubes, ellipsoids, or spheres. The category of carbon-based NMs includes fullerenes (C60), carbon nanotubes (CNTs), carbon nanofibers, carbon black, graphene (Gr), and carbon onions. The main production techniques for these carbon-based materials (apart from carbon black) are chemical vapour deposition (CVD), arc discharge, and laser ablation (33).

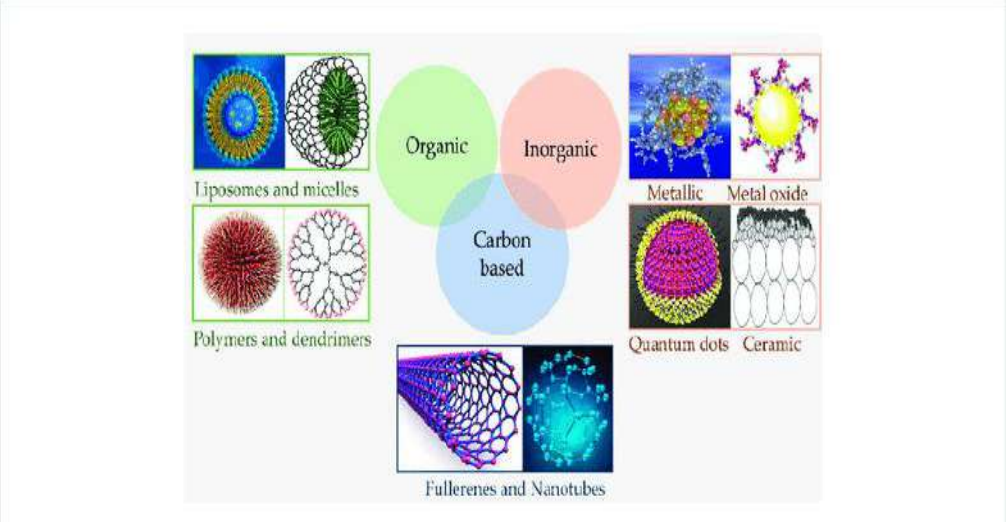


Figure 5: Classification of nanoparticles based on their morphology, size, physical & chemical properties.

NANOPARTICLES SYNTHESIS

A crucial component of both nanotechnology and nanoscience is the synthesis of nanomaterials. Several factors are involved in the nucleation and subsequent production of stabilised nanoparticles during the synthesis of nanomaterials. Temperature, reactant concentrations, reaction time, and pH are some of these variables. Studies have shown that changing the pH of the reaction medium often results in differences in the size and shape of the synthesised nanoparticles. Larger particles are likely to be produced by lower acidic pH values and smaller particles by higher pH values (34,35). In less than two minutes, nanoparticles emerged from the quickly reduced reaction medium. Temperature: temperature has a major impact on the creation of nanoparticles. There are many different forms that nanoparticles can take, such as hexagonal, circular, triangle, and chain-like structures (36,37). Historically, there have been two approaches to producing nanoparticles that can be categorised according to how they are assembled, namely the Top-down and Bottom-up approaches (38) that are schematically depicted in Figure 6.

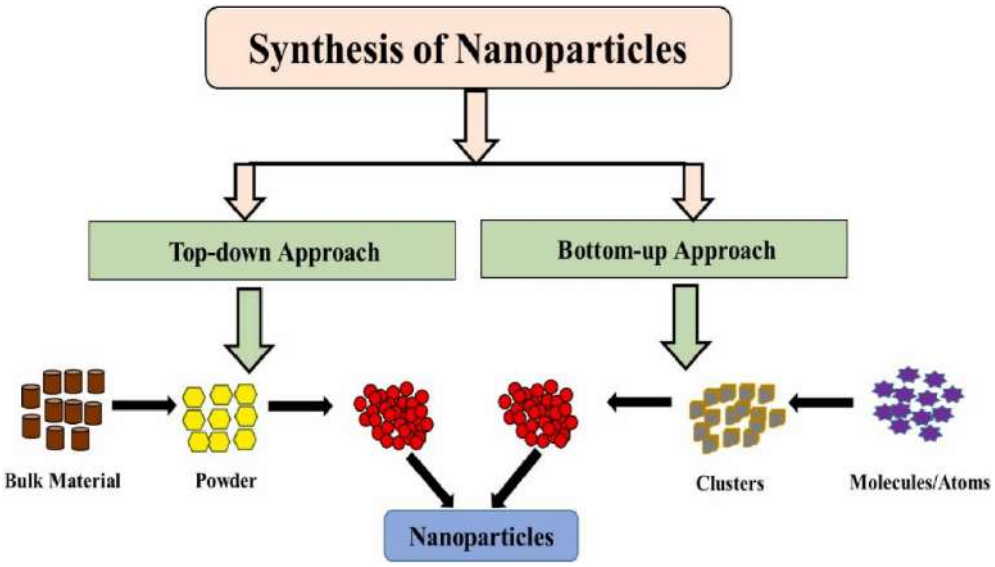


Figure 6: Schematic representation of 'top-down approach' and 'bottom-up approach' for synthesis of nanoparticles.

DIFFERENT METHODS FOR SYNTHESIS OF NANOPARTICLES

Various chemical, physical, biological techniques are presently accessible to create various varieties of nanoparticles (39-42) as depicted in Fig. 7.

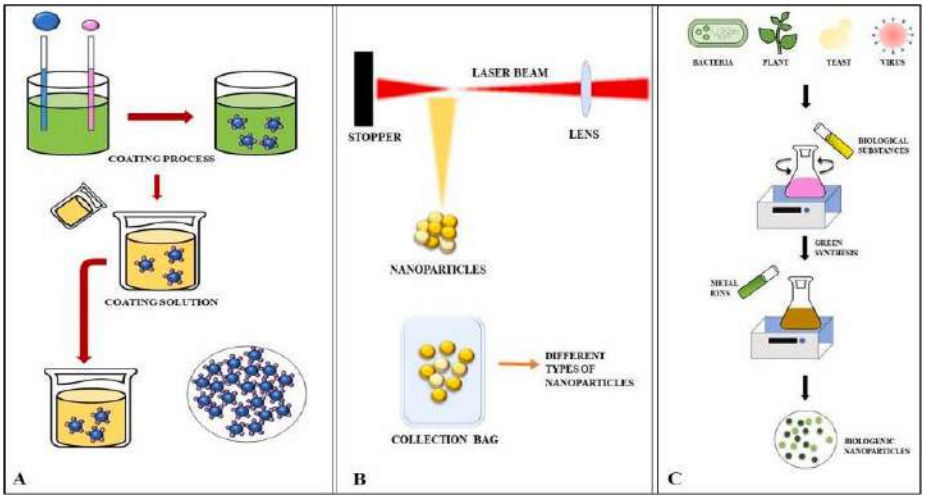


Figure 7: Methods of synthesis of Nanoparticles (A) Chemical synthesis by the means of reduction/precipitation reactions (B) Physical synthesis of nanoparticles, and (C) Biological synthesis utilizing microorganisms or plant extracts as reducing agents.

Although the synthesis of nanoparticles is more frequently accomplished by chemical and physical methods, their applicability is constrained using hazardous compounds and yields (43, 44). Because of their unique physical, chemical, and biological characteristics, nanoparticles are perfect for a wide range of uses in the biomedical and industrial sectors (45). As seen in Fig. 8, a variety of methods are used in the synthesis of nanoparticles.

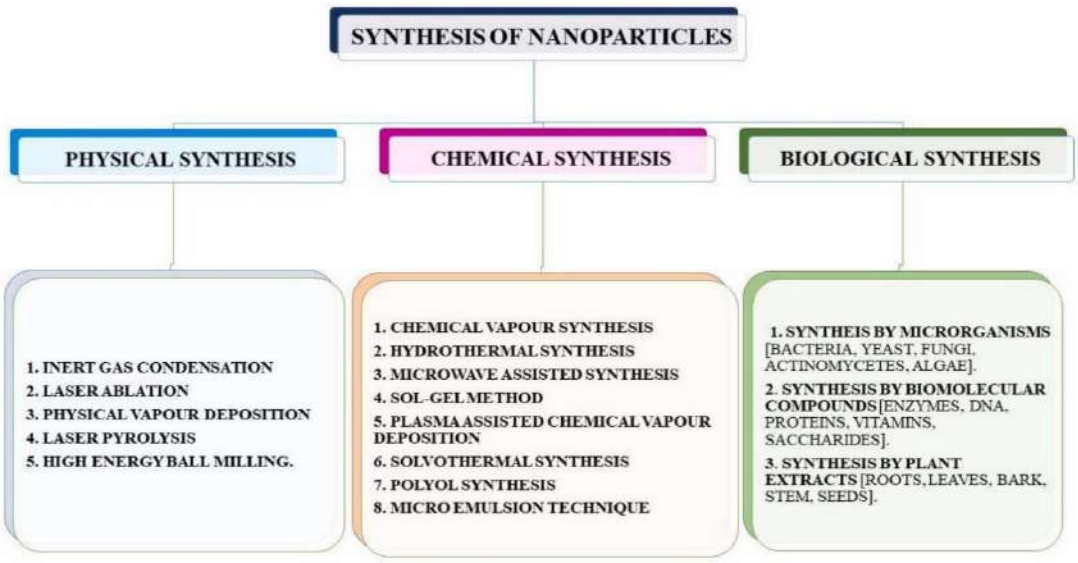


Figure 8: Various techniques for synthesis of Nanoparticles

CALCIUM CARBONATE NANOPARTICLES

Calcium carbonate (CaCO3) nanoparticles (NPs) have drawn a lot of interest among various inorganic materials because of their superior biocompatibility and biodegradability, as well as their ease of preparation and pH sensitivity (46). Three anhydrous crystalline polymorphs (calcite, aragonite, and vaterite) and two hydrated metastable phases (calcium carbonate hexahydrate and monohydrocalcite) are the known forms of CaCO3 (47). The most soluble of them all is the ACC phase, which also happens to be the progenitor of anhydrous crystalline polymorphs that crystallise readily in solutions to create polymorphs (48).

The Advantages of CaCO3 NPs

Excellent Biocompatibility/Biodegradability and pH-Sensitive Property

Calcium phosphate and carbonate are essential building blocks of teeth, shells, and bones in biological systems (49). Because CaCO3 and tissues have similar chemical compositions, it is thought that CaCO3-based drug delivery systems have excellent biocompatibility. Moreover, it has been shown that several common NPs, including Au, Ag, Se, Cr, TiO2, and ZnO, increase the frequency of mutations and the production of reactive oxygen species, which causes cell apoptosis (50, 51). On the other hand, because only two of their byproducts, Ca2+ and CO32−, are already present in blood, CaCO3 NPs are among the safest biomaterials. Furthermore, CaCO3 NPs degrade rapidly in an acidic tumour microenvironment but remain stable at normal blood pH (7.4), allowing for tumor-targeted delivery (52).

Ease of Preparation and Surface Modification

CaCO3 NPs are inexpensive because they can be prepared using common salts alone, typically without the need for organic solvents (53). Additionally, CaCO3 NPs can have their surface modified with a targeted moiety, which facilitates their arrival at the target sites (54).

The Preparation Methods and Controlled Release of CaCO3 NPs

As of right now, the precipitation method (55), gas diffusion (56), flame synthesis (57), breakdown of cockle shells (58), biomineralization, and so forth are the frequently employed techniques for preparing CaCO3 NPs (59,60). For CaCO3 NP-based drug delivery systems, solution precipitation, microemulsion, and gas diffusion methods have been extensively utilised.

Solution Precipitation Method

The most well-known method for preparing CaCO3 NP is the solution precipitation method, which makes use of the reaction between the Ca2+ and CO32− aqueous solution. The cost of production could be decreased by using this method to produce large amounts of CaCO3 NPs without the need for a surfactant. Numerous bioactive species, such as genes, proteins, and small molecule drugs, could load into CaCO3 NPs during the precipitation process due to the mild preparation conditions (46). Notably, the size, shape, and phase of CaCO3 NPs are frequently controlled by the synthesis parameters, which include pH, temperature, ion concentration, stirring speed, solvent species, and additives (55).

Microemulsion Method

For the preparation of CaCO3 NP and gene encapsulation, the microemulsion methods are a popular extension of the precipitation method (61, 62). The reversed microemulsion (water in oil, or W/O) method and the double emulsion method are examples of microemulsion techniques. The W/O microemulsion droplets were employed as nano-reactors in the reversed microemulsion technique (61). Initially, the "calcium microemulsion" and "carbonate microemulsion" were created by mixing an organic phase with the Ca2+ or CO32- aqueous phase, respectively. Then, to create CaCO3 NPs, "calcium microemulsion" and "carbonate microemulsion" were combined. Ultimately, the CaCO3 NPs were separated using a centrifuge. For the treatment of lung cancer, CaCO3 NP loading with the therapeutic peptide was developed using the reversed microemulsion method (63). The reversed microemulsion method and the double emulsion method are similar (62). First, the preparation of W/O "calcium microemulsion" was identical to that of the reversed microemulsion technique. Subsequently, a substantial amount of CO32−-containing aqueous phase was combined with “calcium microemulsion” to create the W/O/W double emulsion. In the W/O/W double emulsion, the Ca2+ and CO32− reaction produced CaCO3 NPs. The surfactants, temperature, pH, and ion concentration could all be optimised through the microemulsion method to control the structure, size, and crystallinity of CaCO3 NPs (64).

Gas Diffusion Method

Preparing ACC loading with small molecule drugs is the primary application of the gas diffusion method(56). CaCl2 was dissolved in ethanol and put into a glass bottle, as seen in Figure 9. After that, the bottle and another bottle of ammonia bicarbonate were placed in a desiccator. Ammonium bicarbonate was used to create CO2 and NH3, which were subsequently dissolved in the ethanol solution to produce CO32− and NH4+. NH4+ produced an alkaline environment in which CO32− and Ca2+ reacted to form ACC. By adjusting the additives, temperature, and Ca2+ concentration, it was possible to control the size, shape, and polymorph of the prepared ACC using this method (65).

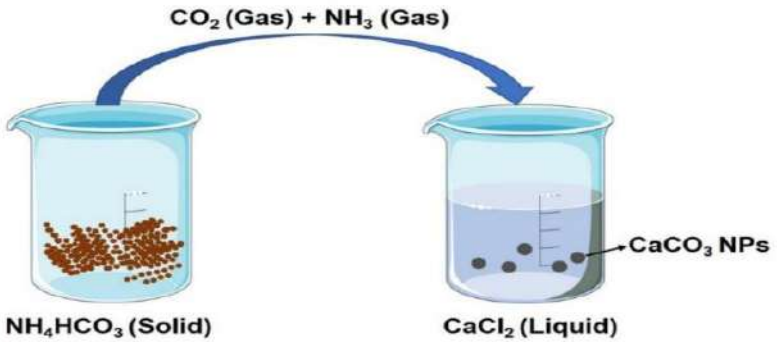


Figure 9: Illustration of the gas diffusion method. CO2 and NH3 were generated from ammonium bicarbonate, which then dissolved in the ethanol solution and reacted with Ca2+ to form CaCO3 NPs.

Controlled Release of CaCO3 NPs

Through a controlled release, CaCO3 NPs may enhance the pharmacokinetics of drug loading, thereby mitigating side effects and improving therapeutic effect. Three methods are used by CaCO3 NPs to release the drugs: diffusion, carrier dissolution, and recrystallization (66). The most important factor in the controlled release of CaCO3 NPs is pH. Free protons react with CO32− in an acidic environment to form HCO3-, which dissolves CaCO3 NPs and speeds up the release of loading drugs (67).

The Biomedical Applications of CaCO3 NPs

CaCO3 NPs for Treatment

CaCO3 NPs have been widely used as carriers for a variety of treatments, including chemical therapy (68), gene therapy (63), PTT/PDT (69), and combination therapy (70), due to their excellent biocompatibility / biodegradability, pH-sensitive property, ease of preparation, and surface modification. Additionally, CaCO3 NPs themselves may be employed as Ca2+ generators to trigger autophagy and immunogenic cell death (ICD) to initiate immunotherapy (54).

CaCO3 NPs as an Antimicrobial Agent

The well-known, extremely strong antibacterial effect of inorganic NPs, such as metal and metal oxides, has led to their effective use as antimicrobial agents. The mechanism of ion (s) release and reactive oxygen species (ROS) generation represents the bactericidal properties of most metal oxide nanoparticles (NPs). Antibiotic-containing CaCO3-NPs may be directly phagocytosed by intracellular microbes, which would allow the release of the antibiotic to continue against the intracellular microbes until the microbe's developed resistance. Agrobacterium tumefaciens and Staphylococcus aureus are two examples of gram-positive and gram-negative bacteria that CaCO3-NPs effectively combat. These results have demonstrated a promising use of CaCO3-NPs as antimicrobial agents, which may offer remedies for illnesses associated with microbial infections (71). Osteomyelitis is one of the infectious diseases of the bones that is thought to be difficult to treat with traditional medicine. In addition to antimicrobial treatment with high serum concentration, debridement of the surrounding tissue and amputation of the infected bone may be linked to high resistance levels and patient discomfort.

CaCO3 NPs as Drug Nanocarriers

Long after administration, CaCO3 has also been studied in controlled drug release systems (72). Because CaCO3 nanoparticles are pH-sensitive, scientists can adjust the rate of degradation based on the intended use (73,74). Some key characteristics, like the slow degradation of CaCO3-NPs and their potential to work with targeting agents to specifically target cancer cells, enable a sustainable level of drug delivery. Creating functionalized CaCO3 nanostructures offers up fresh possibilities for cancer cell delivery methods. This combination reduces the toxicity of anticancer drugs on healthy cells and tissues while producing a targeted and effective drug carrier for cancer diagnosis and therapy (60).

RECENT ADVANCES

Utilizing calcium carbonate (CaCO3) nanoparticles to treat osteomyelitis has advanced over time, addressing the problems related to this serious bone infection. These are a few noteworthy advancements.

1. **Antibacterial Activity:**

Researchers have investigated ways to make CaCO3 nanoparticles more effective against the bacteria that cause osteomyelitis in terms of their antimicrobial properties. To increase the ability of nanoparticles to kill bacteria and eradicate strains that form biofilms, methods such as adding substances to their surface or altering it with peptides have been researched.

2. **Drug Delivery Systems:**

To deliver agents, like antibiotics or antimicrobial peptides, to the infected bone tissue, CaCO3 nanoparticles have been used as carriers. Formulations with controlled-release CaCO3 nanoparticles allow for the localized delivery of substances, increasing their effectiveness and lowering systemic side effects.

3. Immunomodulatory Properties:

Research has shown that CaCO3 nanoparticles have characteristics that can affect how the body reacts to infections and promote tissue growth and repair. These nanoparticles can control cytokine production, improve cell phagocytosis, and encourage mesenchymal stem cells to differentiate into bone-forming cells, which helps osteomyelitis patients heal their bones.

4. Biocompatibility and Safety:

Advances in nanotechnology have produced biodegradable, biocompatible CaCO3 nanoparticles with varying degrees of cytotoxicity and immunogenicity. Benefits from using CaCO3 nanoparticles in formulations include their low toxicity, easy manufacturing processes, and compatibility with the body, which makes them perfect for treating osteomyelitis.

FUTURE TRENDS

Because nanosized calcium carbonate has a higher bioavailability than micro sized calcium carbonate, it can be administered orally to osteoporotic patients with less side effects and greater levels of convenience(75). CaCO3-NPs can be used to treat infections where the necessary antibiotic needs to be delivered to tissues with specific penetration at higher serum level concentrations. At the same time, because of its controlled release property, which is characterized by CaCO3-NP adsorption on bacterial cell walls, it can replace local antibiotic delivery systems like implantable antibiotic pumps and cements. It also requires no replacement or refills and offers patients a higher level of convenience (76). The pH-sensitive CaCO3 NPs offer a window into potential future solid cancer treatment options because of their acidic microenvironment, which draws the CaCO3 NPs and allows them to specifically release their antitumor drug in a controlled-release manner due to the slow biodegradability of nanoparticles (60). It is anticipated that improvements in the management of bone infections will result from the possible application of calcium carbonate (CaCO3) nanoparticles in the treatment of osteomyelitis.

Treatment strategies that combine immunomodulators, bone regenerative drugs, or biofilm disrupting agents with therapy appear promising in improving osteomyelitis outcomes. CaCO3 nanoparticles may serve as delivery vehicles for medicinal agents, either simultaneously or sequentially, enabling synergistic effects and individualized treatment plans catered to the needs of each patient. Future developments could include creating CaCO3 nanoparticles with stimuli characteristics like enzymatic activation or pH sensitivity. This might make it possible to release drugs under control in response to signals or medical conditions. These clever nanoparticles may increase the effectiveness of medication delivery. Release antimicrobial agents precisely when and where they are most needed to minimize toxicity and maximize outcomes. Moreover, the development of implants, scaffolds, or bone substitutes using CaCO3 nanoparticles shows promise for the regeneration and repair of bone tissue damaged by osteomyelitis. In the future, it may be possible to integrate CaCO3 nanoparticles into composite materials or 3D printed structures to improve their biocompatibility, integration, and ability to promote bone healing while delivering agents directly to the infection site.

CONCLUSION

In conclusion, CaCO3 NPs' exceptional qualities—such as their pH sensitivity, surface modifications, biocompatibility and

biodegradability, and ease of preparation—make them highly promising for use in biomedical applications. Even though a lot has been done, more work is still required to address the problems. More effective CaCO3 NPs, in our opinion, will be created as secure carriers for illness diagnosis, treatment, and theranostics(77). They play a significant role in bone scaffolding, tissue engineering, gene, drug delivery, and could displace several antiquated practices and medical interventions for conditions like cancer and microbial infections. To advance knowledge in the field, more research is required (78).

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