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Calcium Phosphate Nanoparticles as Potent Adjuvant and Drug Delivery Agent

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Abstract

Nanotechnology comprises of technological developments at scales less than 1μm. Nanoscience and nanotechnology have been diversely explored for extensive research and development in several medical, agricultural, pharmaceutical and biological arenas. Presently, nanoparticle-based products are widely and commercially available and are being used as sunscreens, electronics, stain, wrinkle resistant textiles, paints, varnishes fabrics and etc. Most recently, Biodegradable nanoparticles with enhanced biocompatibility factors have been postulated for usage in biosciences for drug delivery and as drug or vaccine adjuvants. Nanoparticulate formulations being cost effective, penetrable and significantly reduced risks of toxicity make it an even more interesting field to explore. Nanoencapsulation of medicinal drugs (nanomedicines) has been found to improve drug efficacy, specificity, tolerability and therapeutic index of corresponding drugs. Both organic and inorganic nanoparticles have been used for drug delivery purpose. Various Polymeric Nanoparticles have been studied for the treatment of cancer, diabetes, malaria, etc. such as PLA, PLGA, PCL, chitosan, gelatin, and poly-alkyl-acyanoacrylate. Easy surface modification of polymeric nanoparticles has made them very much capable of improvisation. On another hand, Inorganic Nanoparticles has gained a deep interest as drug delivery agent due to their hydrophilic nature, better stability, easy synthesis, and much higher biocompatibility.

Keywords: Nanotechnology; Nanoparticles; Biocompatible; Drug delivery

Abbreviations: PLA: Poly Lactic Acid; PLGA: Poly Lactic-Co-Glycolic Acid; PCL: Polycaprolactone

Introduction

A large number of inorganic nanoparticles had already been used for biosciences. Other than drug delivery agent nanoparticles can be used for diagnostic technique, body implants, humoral immune response induction, biomineralization and as biomaterials. Ferro oxides, Calcium phosphate nanoparticles, Gold nanoparticles, layered double hydroxides, Silver nanoparticles, mesoporous silica and Silicon are commonly used nanoparticles.

Among these nanoparticles, Calcium Phosphate nanoparticles have developed immense interest above all, due to its biocompatibility which is a result of chemical similarity to human hard tissue (bone and teeth) in the form of hydroxyapatite (HAP). Calcium Phosphate Nanoparticles causes very less inflammation to human muscles as compare to other nanoparticles used in drug delivery system. It is non-toxic to CNS. Calcium phosphate nanoparticles were primitively examined as an adjuvant to stimulate immunoregulatory responses and results were found that it was better adjuvant as compared to aluminum (alum) [1]. Calcium phosphate macroparticle is not approved as an adjuvant for vaccine due to site specific inflammatory response but according to study calcium phosphate nanoparticle has shown less irritation than macroparticles. It has been studied with immunogenic recombinant protein Omp87 [2]. Further CPNPs were studied for successful adjuvant with DNA vaccines [3] and Bovine Serum Albumin (BSA) encapsulated in CPNPs on rat muscle cell. It is illustrated that Calcium Phosphate nanoparticles are excellent protein carrier and have very good stability [4]. Nano-sized Calcium Phosphates are not only capable of entrapping protein and nucleic acid but can also be used for encapsulating antibiotics, insulin has studied Zinc Calcium Phosphate nanoparticles coated with alginate as a successful delivery of Insulin in the human body [5-7].

Several adjuvants have been approved for human use in European countries like MF59, alum, compounds and virosomes [8] among which alum compounds have been extensively used for many licensed vaccines. Despite their approval, they suffer from certain drawbacks [9]. It was observed that Alum based vaccine adjuvants induce local tissue irritation. Although, the duration of inflammatory reactions is longer at the injection site, induction of cell-mediated immunity in minimal with a high probability to induce IgE responses [10,11].

Biodegradable calcium phosphate nanoparticles have revealed a new highly interesting and novel platform for adjuvant development and designing. Being safer than alum-based adjuvant systems [12], calcium phosphate nanoparticles are simple to synthesize and commercially manufacture with lower batch variability in quality and physiochemical properties [13,14]. He et al. [15] reported that calcium phosphate nanoparticle did not elicit IgE response. Although the exact mechanism is still unraveled, it is hypothesized the slow release of antigen may correspond to its potential adjuvant property. Calcium phosphate nanoparticle being in nano-size (less than 1.2μm size) are capable of stimulating strong cellular immunity as they are effectively taken up by dendritic cells, macrophages and local lymph nodes.

The nanoparticle-based adjuvant systems have been broadly classified being organic and Inorganic. The organic nanoparticle formulations include polymers (PLG copolymers) which have been successfully elucidated with subunit vaccines against Herpes Simplex Virus [8]. It was reported that PLG based nanoparticle adjuvants induced intense antibody production and higher Th1 response, the major drawback being their extensive preparation protocols and sophistication. Such polymeric particles have been explored for potential applications in medical and veterinary sciences [16-18]. The inorganic nanoparticles have an upper hand over their organic counterparts, with better storage properties, stability, and resistance from microbial attack. They can be prepared at low temperature and are relatively inexpensive. These inorganic compounds have been explored in various veteran-medical applications such as vaccination, drug delivery system and gene therapy vectors [18,19,20]. Various inorganic nanoparticles have been synthesized by many workers such as silica nanoparticles [21], inorganic nanorods [22], nanotubes and other inorganic compounds [23].

Calcium phosphate nanoparticles are the most commonly used adjuvant and delivery system that was first developed by He et al. [12,15]. Biodegradable calcium phosphate has been investigated as an alternative to aluminum adjuvants for the parenteral vaccine. Clinical studies conducted in France described the use of calcium phosphate adjuvant for secondary or booster immunization against diphtheria and tetanus [10]. Earlier studies indicate that calcium phosphate particles produce strong adjuvant effects induce less IgE than aluminum adjuvants and elicited only minimal local irritation in animals experiments and human clinical trials [10-11]. He et al. [15] for the first time developed calcium phosphate nanoparticle adjuvant and He et al. [15] used it as an adjuvant with subunit vaccine against HSV-2 virus. They concluded that calcium phosphate nanoparticle-induced systemic immunity against HSV-2 virus in mice apart from that they demonstrated that calcium phosphate nanoparticles show great potential as a safe and effective vaccine adjuvant for humans and animals, given its relative absence of side effects and lack of IgE antibody induction. The exact mechanism of adjuvant action of calcium phosphate nanoparticles is still a mystery, however, it is believed that antigen presenting cells are more efficient in taking up the nanoparticle than the microparticles [24].

Bajpai et al. [10] has prepared swellable Gelatin nanoparticles encapsulating anti-cancer drugs. It is one of the major advantages of Nanoparticle medication that it can be easily administered in the system. Thus, incorporation of these biocompatibility factors and further coating with polymers may be explored to substantially enhance the stability and biocompatibility. Apart from drug delivery and adjuvant CPNPs can be used as biomaterials. Calcium phosphate nanoparticles (CPNPs) used for drug delivery gets deposited to our bones and teeth and strengthen them. Use of CPNPs are demonstrated in biomineralization and as biomaterials due to their biocompatibility plays an important role in the formation of hard tissues in nature. Due to this fact, CPNPs have been used for bone repair, enamel repair, and bone tissue engineering [7].

Discussion

Biocompatible and Biodegradable calcium phosphate nanoparticles have a great futuristic scope in targeted drug delivery agents or site targeted drug carrier. Easier delivery, reduced cost of synthesis and improved penetrability allows the extensive use of these strategies for encapsulation of biomolecules. Surface modification facilitates us in increasing loading and releasing capacity of the drug in nanoparticles and surface modifiers such as Cellobiose, Alginate, Gelatin and other materials can be used. By the help of Nano-particles the sensitive biomolecules or drugs can be immobilized and targeted to a specific site and due to nano size, they have high penetrability acting directly at cellular level. These targeting capabilities of nanomedicines are influenced by particle size, surface charge, surface modification, and hydrophobicity.

Conclusion

Calcium Phosphate nanoparticles have proved its excellence in bioscience it is a very good adjuvant, delivery agent, and biomaterial. Calcium phosphate nanoparticle can play an important part in site specific drug delivery system specifically in the case of anti-cancerous and antiviral drugs where drugs have to act on a cellular level and on specific cells. CPNP has adjuvanted insulin, protein and DNA vaccine very well and it can be further examined on antibiotics and another type of drugs as an adjuvant.

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