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Controlled release of drugs in electrosprayed nanoparticles for bone tissue engineering☆

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ABSTRACT

Generating porous topographic substrates, by mimicking the native extracellular matrix (ECM) to promote the regeneration of damaged bone tissues, is a challenging process. Generally, scaffolds developed for bone tissue regeneration support bone cell growth and induce bone-forming cells by natural proteins and growth factors. Limitations are often associated with these approaches such as improper scaffold stability, and insufficient cell adhesion, proliferation, differentiation, and mineralization with less growth factor expression. Therefore, the use of engineered nanoparticles has been rapidly increasing in bone tissue engineering (BTE) applications. The electrospray technique is advantageous over other conventional methods as it generates nanomaterials of particle sizes in the micro/nanoscale range. The size and charge of the particles are controlled by regulating the polymer solution flow rate and electric voltage. The unique properties of nanoparticles such as large surface area-to-volume ratio, small size, and higher reactivity make them promising candidates in the field of biomedical engineering. These nanomaterials are extensively used as therapeutic agents and for drug delivery, mimicking ECM, and restoring and improving the functions of damaged organs. The controlled and sustained release of encapsulated drugs, proteins, vaccines, growth factors, cells, and nucleotides from nanoparticles has been well developed in nanomedicine. This review provides an insight into the preparation of nanoparticles by electrospraying technique and illustrates the use of nanoparticles in drug delivery for promoting bone tissue regeneration.

Contents

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1. Introduction

Nanotechnology is a multidisciplinary branch of science including biomedical, pharmaceutical, chemical, material, polymer, optical, and electrical engineering. In the biomedical field, it has a vital role in drug delivery, diagnostic imaging, and regenerative medicine [1]. In particular, nanotechnology has been developed in regenerative medicine to improve BTE. It aims to overcome some of the limitations related to bone tissue regeneration techniques such as inadequate mechanical strength of temporary frameworks (scaffolds), unstable production of growth factors, lack of stimulation of cell adhesion, and osteogenic differentiation at the damaged site. The gap between conventional medicine and engineering aspects has been filled by biomedical engineering. The size, structure, and surface area-to-volume ratio of nanoparticles are interrelated with the biological activity and functionalization. Nanoparticle research is therefore an area of great scientific interest due to its potential applications in tissue engineering, and many research articles (>1000) related to regenerative medicine have been published over the past few decades [2].

Bone regeneration is a well-structured, complex physiological process in normal fracture healing and includes a series of events involving various cell types, intra- and extra-cellular signaling pathways that follow a defined temporal and spatial sequence to restore and remodel the structure of skeleton [3]. There are several potential problems associated with bone tissue regeneration including osteoporosis, avascular necrosis, and atrophic nonunion. The treatment methods currently applied to overcome these issues include traditional autologous bone graft, allograft implants, free fibula vascularized grafts, application of growth factors to stimulate differentiation of cells, distraction osteogenesis and application of osteoconductive scaffolds [4]. When there are large defects, a two-step process called the Masquelet technique is used as an alternative method to promote bone tissue regeneration. This technique involves radical debridement of the soft tissue and insertion of a cement spacer into the defect in the bone region. After about 6–8 weeks, the inserted spacer is removed and the membrane, which has formed around it, acts as a chamber for the insertion of nonvascularized autografts [5]. During distraction osteogenesis, regeneration of bone is induced between slowly distracted osseous surfaces. This technique has been applied to treat limb length deformities, bone loss, or any other bone discrepancies involving external fixators. However, these approaches have certain problems associated with the psychology of patients undergoing lengthy and painful treatments of bone distraction osteogenesis [6]. In the autologous bone grafting method, the patient's own tissues, which are histocompatible and non-immunogenic, are used to reduce the possibility of immunoreactions of the grafted tissues. However, harvesting of a patient's own tissues requires further surgical procedures with potential complications and discomfort faced in addition to quantity restrictions and associated costs. Allogenic bone grafts are acquired from living donors or human cadavers and are used to overcome the limitations related to harvesting process and graft material quality, but are susceptible to rejection. Bone graft substitutes are the alternatives for autologous or allogeneic grafts. The bone grafts are generally made using natural or synthetic biomaterials that enhance the migration, adhesion, growth, and differentiation of cultured bone cells for bone tissue regeneration. The commonly used bone substitutes are made of hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), collagen (Col), glass ceramics, and calcium phosphate cements [4]. For reconstructing large bone defects or failures, there is a requirement for considerable structural scaffold, which is an alternative for cortical auto-allografts made of cylindrical titanium or metallic mesh cages combined with autologous bone grafts or demineralized bone matrix and cancellous allografts [7].

Drug delivery systems include the release of encapsulated therapeutic agents into the body by improving its efficiency and controlling the site, rate, and time of drug release. The controlled delivery of drugs in an adequate time period without degradation of non-released drugs is essential for tissue regeneration. Drugs within the optimal concentration range provide maximum benefit, but outside that range are toxic or of limited therapeutic benefit. The conventional methods of drug administration include injection, oral ingestion, implantation, and transdermal delivery. Pharmaceutical industries spend a huge amount of money in developing new and more efficient methods for delivering successful drugs. The average cost and duration for developing a drug delivery system is $20–30 million and about 3–4 years, respectively. However, formulation of a new drug requires ~$500 million and about 10–12 years. The global cost of drug delivery products was estimated to be more than $130 billion in 2012 and $220 billion in 2015 with an annual increase rate of 37% [2,8]. The need for efficient delivery of drugs with fewer side effects has driven researchers to innovate new drug delivery systems with an emphasis on the emerging technologies. They focus mainly on minimizing drug degradation or loss, increasing the bioavailability of drug, preventing side effects, and improving drug accumulation in the targeted zone. Drug carriers are the substances used to improve the effectiveness of drug delivery and target the damaged sites. They can be made stimuli responsive, slowly degradable, and also capable of directing the drug-loaded system to the targeted site either by active or passive targeting mechanisms. These drug carriers comprise soluble synthetic polymers, biodegradable liposomes, micro/nanoparticle, nanofibers, dendrimers, and micelles. Nanoparticles derived from poly(lactic-co-glycolic) acid (PLGA), polyglycolic acid (PGA), and polylactic acid (PLA) are commonly applied biomaterials for delivering osteoinductive factors, plasmid DNA (for gene therapy), or anti-inflammatory drugs to enhance bone tissue regeneration [9–11]. The size of a molecule plays a significant role in effective drug delivery to the target site.

Pharmaceutical industries face major challenges due to rapid degradation of large molecules in the bloodstream or gut when delivered orally or failure of transdermal delivery of drugs of molecular size above 500 Da. These drawbacks can be overcome by the active or passive targeted delivery of drug carrier systems. These targeting mechanisms are designed to regulate the drug release kinetics, and to avoid nonspecific delivery of drugs and the consequent side effects, thereby increasing therapeutic efficiency. In some cases, like pain, the sustained release of drugs is not effective and instead pulse release is more desirable. This review summarizes the recent progress of electrohydrodynamics atomization (EHDA) method applied for the nanoformulation of micro/nanoparticles using electrospraying. This technique has been applied for the encapsulation of several therapeutic agents onto the surface of biodegradable polymeric nanoparticles to provide sustained and control release profiles with improved encapsulation efficiency. The fabrication of particulate materials using electrospray methods including the size, shape, composition, structure, and morphology has also been discussed for BTE.

2. Fabrication of nanoparticles

Synthesis of nanoparticles involves various methodologies such as solvent evaporation, precipitation, single and double emulsion, electrospraying, porous glass membrane emulsification, sol–gel, and coacervation are used for fabricating micro/nanostructures. The most popular among these techniques is the emulsion method, which involves