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Advancement of magnetic nanoparticles in bone tissue engineering

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Abstract

Novel strategies that utilizes magnetic nanoparticles (MNPs) and that is how magnetic fields are being developed to enhance the efficacy of bone tissue engineering. The current developments in the field of magnetic strategies to improve the cells, scaffolds, growth factor and gene deliveries are described. The magnetic field has been proven to enhance bone tissue repair by affecting cell metabolic behavior. Magnetic nanoparticles are used as biomaterials due because of their unique magnetic properties and good biocompatibility. Once the magnetic particles are exposed to an external magnetic field, they will be rapidly magnetized. Through endocytosis, entering the cell makes it easier to affect the physiological function of the cell. The magnetic nanoparticles and the magnetic field work together to enhance the effectiveness of their bone tissue repair treatment and bone regeneration. Potential clinical applications of magnetic nanoparticles and scaffolds with magnetic fields and stem cells in orthopedic treatments with substantially increased bone repair and regeneration efficacy.

1. Introduction

Bone is a natural complex composed of organic and inorganic materials. The main component of the inorganic material is crystalline hydroxyapatite and the organic material is fibrous collagen. Bone itself has the capacity to regenerate and repair by itself. But, in cases such as bone defects that can be caused by the external damage or because of the bone diseases, tumors, and also due to abnormal bone growth, the self-repairing ability of the bone is lost. It is necessary to resort to medical materials including autologous bone tissue, allogeneic bone tissue and bone tissue substitutes (Loi *et al*., 2016). Either method requires the regeneration of local bone tissue. Repair of bone due to the mentioned factors is a complex process which includes bone regeneration, reconstitution of bone excrescence and nonunion, including the structural and functional reconstruction of bones. Physical triggers such as the tensile and compressive stresses, fluid shear stresses and heat, are known to be able to significantly enhance bone regeneration and fracture-healing are also considered (Daoyang *et al*., 2020).

Materials that are used for bone fracture repair includes autografts, allografts, xenografts, and synthetic bone materials. Among them, autografts is mostly used and termed as “gold standard” in bone tissue repair but, it is limited as it causes trauma and some complications. The implantation of allografts and xenografts may be prone to trigger immune rejection; though the bone fracture repair may not need supportive materials other than implants, bone defects or large tissue voids may require materials as supporters (Xu *et al*., 2014). As a result, a variety of synthetic bone materials have been developed and have shown great promise in bone tissue repair. Factors such as external stimulations including stress stimulation, chemical stimulation, biological factor stimulation, magnetic field, electric field, *etc*., are necessary conditions to be considered.

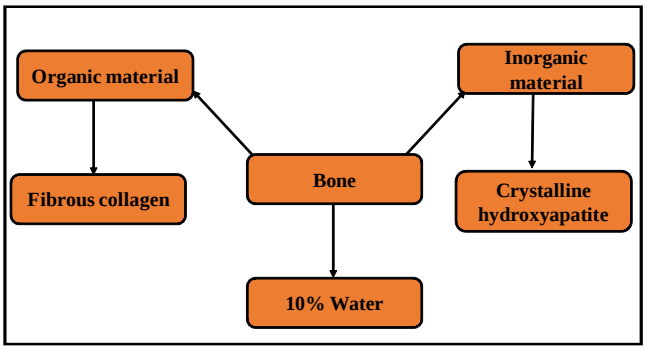

Figure 1: Composition of bone, it consists of organic and inorganic materials (Pawan Kumar *et al*., 2020).

The magnetic field had been proved to enhance repair bone tissue by affecting cell metabolic behavior. In recent researches, iron is the most usual material with its para-magnetism is been used. The unpaired electrons of the outermost layer spin to make the atom maintains a certain magnetic moment. This atomic magnetic moment is aligned along the magnetic field under the effect of an external magnetic field, showing a weak magnetic force that follow to the magnetic field. This substance is called paramagnetic substance (Oh *et al*., 2011). Ferromagnetic substances have atomic magnetic moments composed of unpaired spin electrons. In the absence of the magnetic field, the atomic magnetic moments are also neatly arranged, showing strong magnetism to the outside. Containing a small amount of paramagnetic iron, the bone is magnetically

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conductive. Furthermore, magnetic stimulations from static magnetic fields (SMFs) and electromagnetic fields (EMFs) can also substantially improve bone repair and regeneration.

Magnetic nanoparticles (MNPs) are used as biomaterials because of their unique magnetic properties and good biocompatibility. Recently, they are widely applied in drug transportation, magnetic hyperthermia, nuclear magnetic imaging, and biological separation. The magnetic particles are slowly deposited on the cell membrane under the effect of the magnetic field. The cells engulf the magnetic particles through endocytosis (Aliramaji *et al*., 2017; Brett *et al*., 2017). Entering the cell makes it easier to affect the physiological function of the cell. If a magnetic field is applied, each magnetic particle will become a magnetic source, which will enable the magnetic scaffold material to play the function of bone tissue repair therapy. Once the magnetic particles are exposed to an external magnetic field, they will be rapidly magnetized. The magnetic nanoparticles and the magnetic field work together to enhance the effectiveness of their bone tissue repair treatment. Magnetic fields can influence the ion channels and biochemical pathways of the cells. Magnetic-cell strategies include cell labeling, targeting, patterning, and gene modification (Yang *et al*., 2019). Magnetic scaffolds can be prepared with the aid of MNPs and magnetic fields; they can also be actuated by a magnetic field to enhance the cells *via* magneto-mechanical stimulations. MNPs can also serve as delivery methods for the growth factors, drugs and gene transfections. This article reviews on the osteogenic effect of magnetic nanomaterials, its preparation and evaluation which are used for bone repair or bone cell regeneration.

2. Few traditional methods of bone repair

The ideal requirements for bone fracture repair should possess the following characteristics:

2.1 Good biocompatibility

The material itself and its degradation substances should be non-toxic.

2.2 Appropriate biodegradability

The material should be able to degrade after fulfilling its targeted mission and its degradation rate should match the tissue growth rate.

2.3 Optimal plasticity and mechanical properties

The material can be made into desired shapes and gives support for new tissue growth until the repair process is complete.

2.4 Good osteoinductivity and osteoconductivity

The material is expected to show osteogenesis and to stimulate bone growth.

2.5 A three-dimensional (3D) porous structure

The material is desirable, if it can be processed into a three-dimensional porous model which mimics the structure of bones and is conducive for cell adhesion and extracellular matrix deposition and has passages for nutrients and oxygen.

2.6 Easily sterilized

The material should be suitable for sterilization by currently available approaches while maintaining its mechanical and biological properties. (Qifei *et al*., 2016).

Table 1: Traditional methods of bone repair (Qifei *et al*., 2016)

Material		Advantage	Disadvantage
Bone cement	Bioactive or non-bioactive cement	Easy to fit high stability, hood hardening thereby good strength, Better bone setting action	Expensive very less biocompatibility, Insufficient mechanical property
Metal	Stainless steel titanium alloy	Inexpensive good biocompatibility, Very easy process, corrosion resistant	Very less ductility, Poor wear resistance, High stiffness
Ceramic	Aluminum oxide glass ceramic	Good biological activity, Low expansion, High corrosion resistant	High elastic modules, Brittleness, Poor flexibility, Causes local stress
Polymer	Polymethyl methacrylate chitosan alginate	Easy fit biodegradable, Good mechanical property, Nontoxic	Possibility of disruption, Poor biocompatibility, Low solubility, Very less mechanical stability

3. Advantages of using modern method of bone repair over the traditional method of bone repair (using MNPs) are as follows:

(i) Nanomaterials have shown improved bone cell functions compared to their micron-sized counterparts and have been emerging as a new viable class of materials for bone fracture repair.

(ii) Nanomaterials may also precisely mimic the hierarchical and nanoscale features of bones and nanomaterials and the introduction of magnetic nanoparticles may provide mechanical stimuli as needed or provide unique ‘smart’ functions.

(iii) MNPs can be formulated not only drugs but they can be loaded with growth promoters and genetic materials that can help for bone repair (Sterling *et al*., 2014).

4. Preparation of magnetic nanoparticles

Various elemental compositions have been used in magnetic nanomaterials, including Fe_3O_4, Fe, Co, Ni, $MgFe_2O_4$, and Co Fe_2O_4.

The most classic and common composition of magnetic nanomaterials is Fe_3O_4. Two main types of magnetic Fe_3O_4 preparation methods are dry method and wet method. Among them, the wet method is more commonly applied, mainly including the following method, hydrothermal method, solvothermal method, chemical co-precipitation method, ball milling method, sol-gel method and atomic layer deposition method. In the synthesis of MNPs, with various preparation conditions, different preparation methods and different catalysts, turnover number (TON) and turnover frequency (TOF) could be largely different. In the formulation of MNPs for bone repair, with the help of different catalysts, the Suzuki reaction and Heck reaction of halogenated benzene can be carried out efficiently. The overall TON and TOF and TOF can reach more than 30 000 moll and 50,000 per hour respectively. (Singh *et al*., 2012; Maleki, 2014).

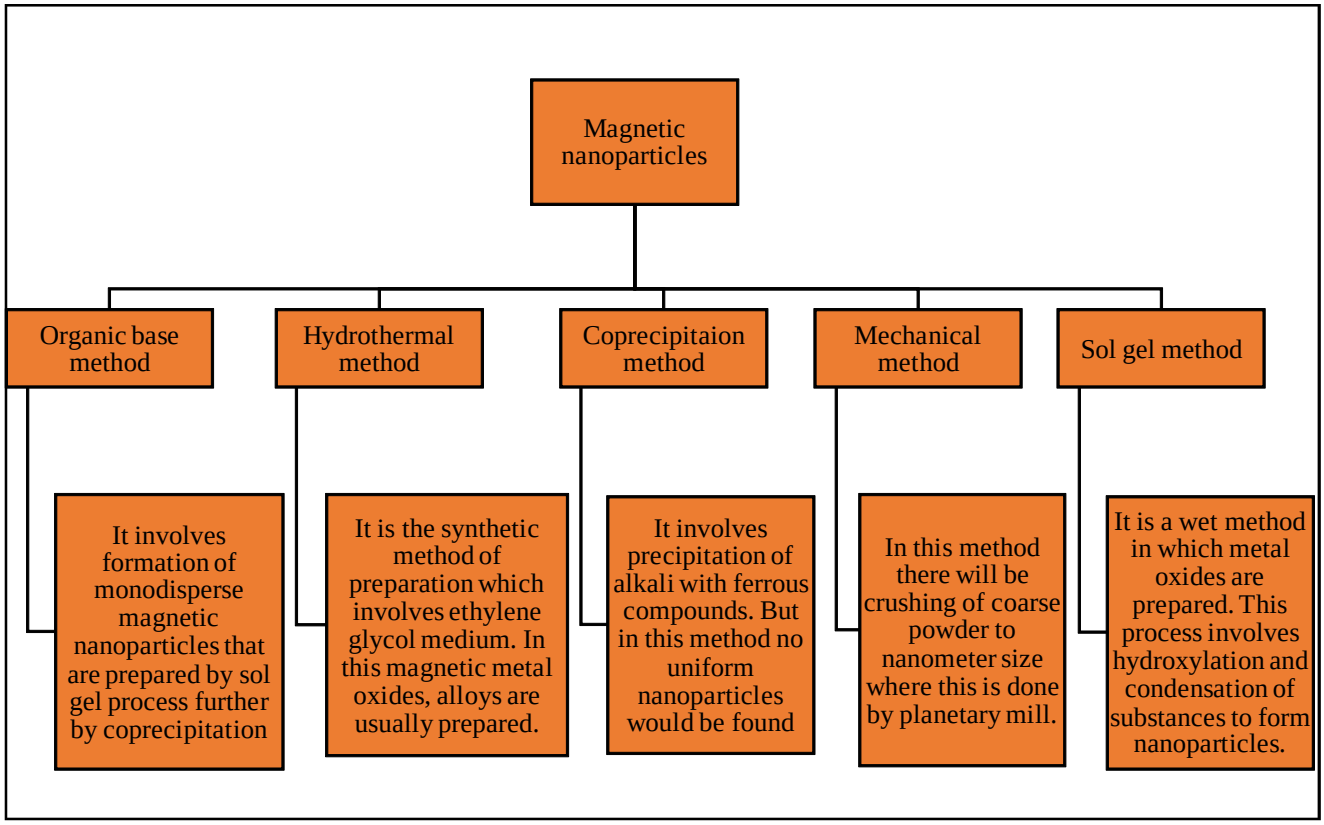

Figure 2: Method of preparation of MNPs (1. Organic base method; 2. Hydrothermal method; 3. Coprecipitation method; 4. Method; 5. Sol-gel method).

4.1 Organic base method

MNPs can be prepared in sol-gel processes in aqueous solutions, such as co-precipitation methods, microwave synthesis, and hydrothermal reactions MNPs can also be prepared in organic solution reactions. Organic phase synthesis has been used to prepare MNPs based on Fe, Co, and Ni alloys, oxides, core/shell and dumbbell structures. The size, shape, and composition of MNPs are affected by reactant concentration, solvent polarity, and reaction temperature/ time. Here, usually focus is on the synthesis of monodisperse MNPs (Maleki *et al*., 2013).

4.2 Hydrothermal/solvothermal method

Hydrothermal process is a widely used synthetic method of magnetic nanoparticles. The reaction is generally, carried out in a reactor, with many advantages, such as simple operation and high reacting efficiency. The metastable phase and nanomorphology obtained by hydrothermal/solvothermal methods are difficult to obtain in other ways. Generally, Fe_3O_4 is synthesized by hydrothermal method using $FeCl_2$, $FeCl_3$; and NaOH (Pandi *et al*., 2019) at high temperature in a high-pressure reactor. The reaction principle of solvothermal method and hydrothermal method is similar, with differences in application of ethylene glycol medium. The method is suitable for a wider temperature range as the solvent used has a higher boiling point than water. With reducing solvents, products could be protected from oxidation during high-temperature preparation. Researchers have successfully prepared magnetic metal oxides, elemental metals and alloys using hydrothermal/solvothermal methods.

4.3 Co-precipitation method

The most usually used preparation method of Fe_3O_4 magnetic nanoparticles is chemical co-precipitation method. Alkaline substance is added to the soluble iron salt and ferrous salt solution, getting a precipitate or hydrated precursor. Followed by washing, drying and burning procedures, magnetic nanoparticles would be synthesized. This method is easy to operate and can produce a large number of nanoparticles (Nosrati *et al*., 2018). The limitation

of this method is the poor controllability of its particle size and distribution, because the kinetic factor is the only controllable factor in the grain growth process.

4.4 Ball milling method mechanical grinding

It is a method of crushing coarse particles through strong plastic deformation to the nanometer level. In the planetary ball mill, the coarse-grained material is refined mainly by the collision between the steel balls or between the steel balls and the inner wall of the grinding tank. Using the dry grinding process, nanoparticles can be prepared, but due to repeat crushing-cold welding, the final result is micron-sized particle aggregates with nanograin structure. To obtain highly dispersed nanoparticles, a wet grinding process is required, which has a better grinding and crushing effect. Compared with metal, ceramic powder is more conducive to ball milling due to its brittleness (Narayanaswamy *et al*., 2019). The physical ball milling method has good reproducibility of particle size. With expensive equipment, long production cycle, and low efficacy, it is difficult to get industrial production.

4.5 Sol-gel method

Sol-gel method for preparing nano metal oxide is an ideal wet method. This method is based on the hydroxylation and condensation of molecular precursors in solution to form a "sol" of nanoparticles. Prepared Fe_3O_4 nanoparticles under supercritical conditions by the sol-gel method. The results it showed that the particles have a monodisperse distribution with a mean size of nearly 8 nm. Due to the small particle size and good dispersion, the researchers suggested that the particles could have been used in biomedical magnetic therapy. It was reported that monodisperse spherical Co-Cr-ferrite nanomaterials can be easily prepared by co-condensation of Co $(NO_3)_2 \cdot 6H_2O$, chromium nitrate, Cr $(NO_3)_3 \cdot 9H_2O$ and iron nitrate using the sol-gel method. Co-Cr-ferrite nanomaterials were prepared with excellent magnetic properties with stable monodisperse distribution. (Gao *et al*., 2019). Atomic layer deposition method recently, atomic layer deposition (ALD) has become an important thin film deposition technology that is widely used in thin film deposition on the surface of various semiconductors, metal oxides and polymers. This method has many advantages, including precise control of product thickness, excellent uniformity. It is a good method for synthesizing multi-component structure controllable composite materials. Alessandro ponti synthesized SiO_2-coated α-Fe_2O_3 nanofibers (NFs) with ALD method (Ponti *et al*., 2020). It was used for electromagnetic wave absorption. The results showed that the magnetic carbon nanowires obtained have a uniform morphology, which has lower magnetic reflection loss and higher frequency absorption range than simple carbon nanowires. This means better electromagnetic wave absorption capacity.

5. Mechanism of MNPs on bone cells

5.1 Effect on bone tissue repair

Due to some of the conditions of external magnetic field, they have ability of act on the cell surface by which they control the function and regulate the mesenchymal stem cells in the bone marrow. This results in the deposition of magnetic nanoparticles in the cell of about 20 pg/cell where they do not show any toxic effects such as differentiation and cell proliferation. Then under the force of external magnetic field there will be the proliferation of the mesenchymal stem cells in the bone marrow (Qian *et al*., 2018).

During this process, the distribution of the nanoparticles has to be maintained uniform among the MNPs. If it is not there, then it might be disturbances in the cell permeation and the action on the cell wall due to change in the particle size of the molecules (Tang *et al*., 2017). The forces that act during this process is van der Waals dispersion force and Coulomb force which are very strong forces.

5.2 Effect on the bone cell growth

Usually medium strength magnetic field is used for the growth of cells. They increase by promoting the formation of biominerals such as calcium, phosphate, *i.e*., termed as biomineralisation. This occurs in the osteoblasts. That is how it causes the proliferation of the cells and also it alters the calcium channels in the cell surface. It does not only promotes the biomeneralization processes but also affects the osteoblast gene and the proteins in the late stages; where the early stage (biomineralization) is proportional to the late stage (protein formation) (Rotherham *et al*., 2018). Due to the process of biomineralization, there is change in the special arrangement of proteins in the cytoskeleton and also affects the structure and crystallinity of the repaired bone.

6. Magnetic nanoparticles on bone regeneration

Usually superparamagnetic iron oxide nanoparticles termed as 'SPION' are usually used for bone tissue repair. They alone, even without a magnetic field, were able to enhance the tissue repair efficacy, provide dynamic mechanical stimulations for bone formation, promote osteogenic differentiation of bone marrow stem cells, and enhance bone regeneration *in vivo*. For understanding the molecular mechanisms on why and how spions promoted the osteogenic differentiation of MSCS, gene microarray assay and bioinformatics analyses were performed. The results showed that the gene expression was regulated, and the classic MAPK signal pathway was activated by the spions. Therefore, the downstream genes of this pathway were modulated to enhance the osteogenic differentiation. At the molecular level, spions upregulated the long noncoding RNA INZEB2, which was critically important for sustaining the osteogenesis by mscs. There were results provided insights into the mechanisms of spions at the molecular level, which can facilitate the application of spions to enhance the regenerative medicine efficacy *via* stem cells (Xiong *et al*., 2015).

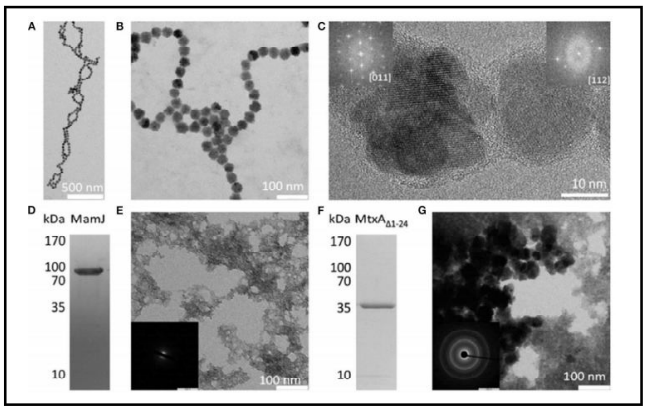

Figure 3: The growth of bone cells *via* polypeptide chain and bone regeneration using MNPs (Mirabello *et al*., 2016).

In another study using a Sprague-Dawley rat model, SPION-containing gelatin sponges were implanted in the incisor sockets, which enhanced bone regeneration, with about 1.5-fold increases in BMD and bone volume per tissue volume (BV/TV), is compared with gelatin sponge control without spions (Wang *et al*., 2016).

7. Magnetic nanoparticles drug loading

Targeted drug therapy is used; when compared to the traditional method of drug delivery, there is reduced dose of the drug and the reduced toxicity in targeted drug delivery. In turn this even decreases the cost of drug treatment. The nanoparticles or the microspheres of the growth molecule is prepared and they are served with the magnet thereby they serve as the magnetic nanoparticles. Antibiotics, growth factors, microrna and few agents are used for the repair of the bone (Kumari *et al*., 2016). In this sometimes they fail to target the specific site but this method is used to minimize the adverse effects and the toxicity.

Nanobiomaterials can be used for the drug delivery that can be used against the infections, bone regeneration, and also osteointegration. Carriers such as chitosan are used which act by releasing the drug in controlled manner and gets degraded by itself. Thereby, they can be used as targeted, sustain release and also controlled drug delivery. Various tools such as nanospheres, tubes, capsules are widely used. Due to its small size, it can be used for targeted and sustain drug delivery (Jung *et al*., 2018).

Few studies found that the iron oxide nanoparticles can be used as a means of delivery, which can effectively carry drug molecules under the influence of an external magnetic field and target specific parts of the body. Suspension of drug molecules on magnetic carriers or dispersion on magnetic nanoparticles is a simple and direct magnetic targeted drug delivery route (Xia *et al*., 2018). Recent studies have used solvent evaporation and lyophilization to prepare degradable polylactic acid-glycolic acid copolymer capsaicin-coated magnetic nanoparticles (Wang *et al*., 2015).

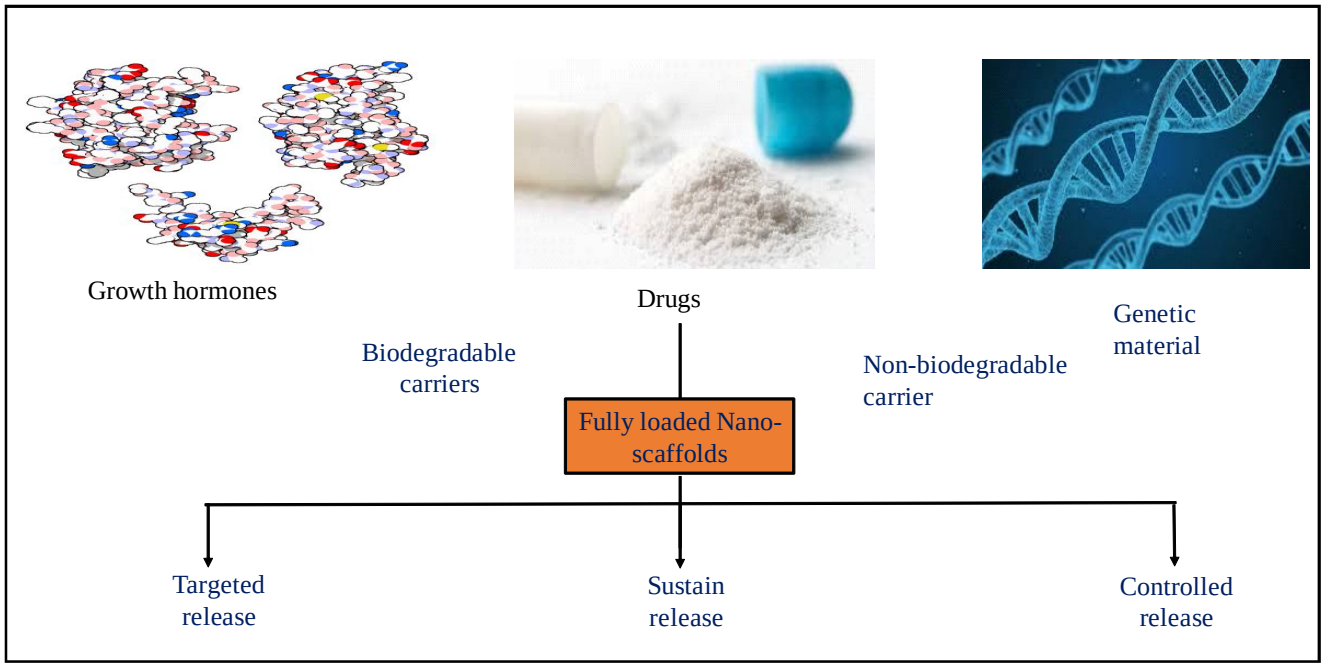

Figure 4: Methods of drug delivery using MNPs.

In few other studies, magnetic multi-walled carbon nanotubes, hydroxyapatite, and clodronate were synthesized into nanocomposites. It was found that clodronate can be continuously released from the system and cease the formation of osteoclasts. The magnetic liposomes are obtained by embedding iron oxide nanocomposites into the liposome membrane. When an alternating magnetic field is applied externally, the generated heat will destroy the cell membrane, releasing the drug encapsulated in the liposome for therapeutic purposes. In addition to promoting osteogenic differentiation, iron oxide nanoparticles also have good bone conduction ability. Currently in the field of bone regenerative medicine, iron oxide nanoparticle complexes are often used as carriers for the controlled release of drugs (Xia *et al*., 2018; Swietek *et al*., 2019)

The iron oxide nanomaterials in multifunctional magnetic mesoporous bioactive substance improve the continuous release of gentamicin, which is helpful to reduce the adhesion of bacteria and prevent biofilm formation. In addition to treating infection, the Fe_3O_4 nanoparticles in the combination can also promote the adhesion, proliferation, and osteogenic differentiation of bone marrow mesenchymal stem cells (Wang *et al*., 2015). Nanomaterials can be used as carriers to deliver therapeutic drugs in cells, including proteins, growth factors, small molecule chemicals, and DNA/RNA. This magnetic drug delivery system will provide a useful support platform for bone defect repair.

8. Magentic strategeies for growth factor

The mechanism of bone repair is complex and involves several important growth factors and small molecules, such as BMP-2, platelet-derived growth factor (PDGF) and parathyroid hormone (PTH). These molecules can act directly to positively influence the bone mass, or indirectly, by acting on negative regulators of the bone mass (Silva *et al*., 2017). Therefore, delivering growth factors

is an important approach in bone tissue repair, with the use of stem cells and scaffolds.

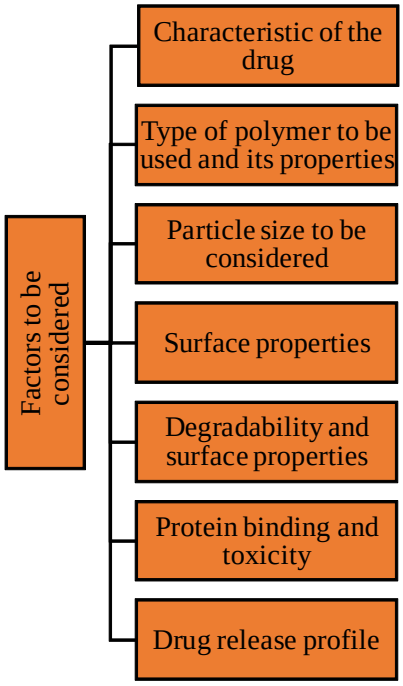

Figure 5: Factors to be considered for designing the drug delivery using MNPs.

MNPs are used as the delivery vehicles for bioactive agents such as drugs, chemotherapeutics, antibodies, peptide therapeutics, oligonucleotides, and growth factors *via* magnetic fields. Growth factors could be stabilized by conjugation to nanocomposites (Dobretsov *et al*., 2015). The growth factors immobilized to iron oxide/human serum albumin nanoparticles promoted a higher growth and differentiation of the cells, when compared to their counterparts. When applied in the deeper parts of the body, the efficiency of capturing mnps was ensured by the use of a remnant magnetic implant especially when the external magnetic field was turned off, which was a major advantage of magnetic delivery systems (Angrisani *et al*., 2013)

MNPs can be used to target mechanically-responsive receptors, like the TREK1 ion channel, PDGF receptors and integrin, and receptor. They enable the ligand-MNP complex that has to be manipulated using magnetic fields, allowing the control of ion channel stimulation. The osteogenesis of bone marrow stem cells could be significantly enhanced by mechanical stimulation *via* magnetic tagging. The application of magnetic activation was capable of initiating nuclear translocation of β-catenin to a similar level as WNT3A, which enhanced the skeletal progenitor cell proliferation, differentiation and accelerated bone repair in Auxin (Hu *et al*., 2013)

By initially targeting the cell membrane receptor PDGFRA, a higher mineral content was present in the cells after 3 weeks of magneto-mechanical stimulation and osteogenic medium culture. Magnetic iron oxides and gold nanoparticles were embedded in nanosphere which was been used as the drug carrier in the human cells. The drug release inside the cells can be controlled by applying heat and a magnetic field. Moreover, the use of the magnetic field to pull the nanocomposite is promising for tissue-specific clinical applications in bone, heart, lung and brain, for targeted drug delivery and on-demand drug release. Further, more the magnetic targeting method enhanced the viral and non-viral gene delivery (Liu *et al*., 2017). This strategy can be applied to a range of viral vectors (including adenoviruses, adeno-associated viruses and lentiviruses), cationic polymers (polyethyleneimine, or PEI), as well as cationic lipids. Compared with common transfection approaches, a key advantage of the magnetic targeting method was the lower dosage of the vector, which could be applied for both *in vitro* and *in vivo* (Yang *et al*., 2018). Moreover, because of the high target site specificity, side effects for viral or non-viral gene delivery were also lowered. For magnetic transfection, various polymers, lipids, and dendrimers were developed to prepare mnps with accurate sizes, shapes, compositions, magnetization, relativity and surface charge.

To increase the cell targeting capacity, the MNP-liposome complexes were associated with transferrin. Pan and his team. synthesized cationic lipid-coated mnps and prepared transferring-coated MNP/(Plasmid DNA) complexes. The transfection using these magnetic vectors required much less incubation time in the presence of an external magnetic field, and achieved gene transfer at a high efficiency (Pan *et al*., 2008). Therefore, magnetic delivery and gene transfection would be an important future research focus, with the purpose to reduce the side effects of a specific drug for treating bone diseases, to enhance the treatment by endogenous growth factors.

Commercially MNPs available are:

PEI-coated MNPs = Polymag™ and combimag™ (OZ Biosciences, Marseille, France) (Yang *et al*., 2018).

9. Application of magnetic nanoparticles for bone repair

Magnetic nanomaterials not only have the unique properties of nanoparticle materials, but also have magnetic responsiveness and superparamagnetic. They can gather and position under a constant magnetic field and absorb electromagnetic waves to generate heat under an alternating magnetic field (Li *et al*., 2016). Among them, magnetic iron oxide nanoparticles are widely used in magnetic stimulation to promote bone formation, drug loading, bone formation with stem cells, and bone formation with scaffolds. Magnetic nanomaterials have shown good bone-promoting effects in many studies and have good application prospects

10. Future perspective

To overcome few of the difficulties in the development of MNPS; more studies should be carried out to give a combined applications of magnetically enhanced scaffolds, cells *via* noninvasive tracking of implanted cells. Biosafety issues during the application of magnetic magnetic strategies has to be overcomed. There has to *in vivo* studies conducted to know any allergic or inflammations are caused due to external factors.

However, nanomaterials have also posed new challenges. One of the main challenges is the potential toxicity related to nanomaterials or nontoxicity. Due to the nanosize, nanomaterials are expected to have different toxicity properties compared to their micron-sized counterparts. Nanoparticles could show significantly greater toxicity *in vitro* at a very less concentrations and shorter exposure times compared to micron-sized particles where nanoparticles but not micron-sized particles were internalized by lung epithelial cells.

It is known that endocytosis including clathrin-mediated endocytosis and post-endocytic trafficking is the predominant route of nanoparticle uptake, and multiple internalization mechanisms may be involved. Furthermore, nanoparticle internalization has been confirmed to contribute to cellular toxicity.

11. Conclusion

The review is about the usage of magnetic nanoparticles for bone cell, tissue repair and also for bone generation. It includes even about the effect of these particles on the bone and also the delivery of the same. The unique properties of magnetic nanomaterials have accelerated their application in medicine, especially in terms of magnetism, magnetic fields can provide remote control of drug release and biomolecule activation, generating biological reactions including cell differentiation, tissue growth, and bone defect regeneration. Homogeneous distribution of mnps resulted in faster bone regeneration but relatively immature new bone but an inhomogeneous distribution resulted in a higher level of bone maturity but with less new bone formation which has to be overcomed.

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Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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