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Advancement of magnetic nanoparticles in bone tissue engineering: A review

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Abstract

Novel strategies that uses magnetic nanoparticles (MNPs) and that is how magnetic fields are designed to increase the efficiency of bone tissue repair. The current growth in the field of magnetic field based strategies to improve the cells, scaffolds, growth factor and gene deliveries are illustrated. The magnetic field has been proved to increase the bone tissue renovation by acting on the cell metabolites. Magnetic nanoparticles are used as biomaterials because of their unique magnetic properties and good biocompatibility. Once the magnetic particles are subjected to an external magnetic field, they will be fastly magnetized. Through endocytosis, MNPs enters the cell and affects the physiological function of the cell very easily. The magnetic nanoparticles and the magnetic field works together to increase the efficacy of their bone tissue renovation and bone regeneration. Magnetic nanoparticles and scaffolds with magnetic fields and stem cells in orthotic treatments with substantially enhanced bone repair and regeneration efficiency are used.

1. Introduction

Bone is a natural convoluted organ composed of organic and inorganic components. The main constituent of the inorganic material is crystalline hydroxyapatite and the organic material is fibrous collagen. Bone has the ability to self- regenerate and self-reconvulate. But in some cases like bone deformity that is usually caused by the external injury or due to the bone disorders, cancers, and also because of the abnormal bone generation, the self-repairing ability of the bone will be lost. It is essential to resort the medical substances including homologous bone tissue, allogeneic bone tissue and bone tissue substitutes (Loi *et al*., 2016). Either methods is used for the regeneration of local bone tissue. Repair of bone due to the mentioned factors is a large process which involves the bone regeneration, reconstitution of bone outgrowth and nonunion, that includes the structural and functional reconstitution of bones. Physical substances such as the tensile and compressive stresses, fluid shear stresses and heat, are known to be able to significantly trigger the bone regeneration and fracture-healing are included. (Daoyang *et al*., 2020).

Materials such as autografts, allografts, xenografts, and synthetic bone materials are used for bone fracture repair. Amonst, autografts are most commonly used and are termed as "gold standard" in bone tissue repair but, it is limited as it causes injury and some complications. The use of allografts and xenografts may trigger the immune rejection; though the bone fracture repair may not require any supportive materials other than implants, bone defects or large tissue voids requires materials as supporters (Xu *et al*., 2014). Due to this, a various synthetic bone materials are developed and showed great bone tissue repair. Factors such as external stimulations including stress stimulation, chemical stimulation, biological factor stimulation, magnetic field, electric field, *etc*., are the conditions required for consideration.

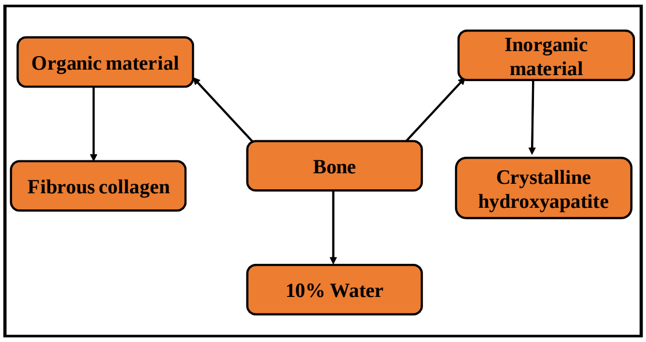

Figure 1: Composition of bone, it consists of organic and inorganic materials (Pawan Kumar *et al*., 2020).

The magnetic field has proven to increase the repair of bone tissue by acting on the cell metabolic behavior. In recent researches, iron is mostly used as usual material with its para-magnetism. The unpaired electrons of the outer layer spin to make the atom to maintain some magnetic moment. This atomic magnetic moment is aligned along the magnetic field by the effect of an external magnetic field, showing a weak magnetic force. These substances are called paramagnetic substances (Oh *et al*., 2011). Ferromagnetic substances have the atomic magnetic moments composed of the unpaired spin electrons. In the absence of magnetic field, the atomic magnetic moments are arranged, shows strong magnetism outside. It contains little amount of paramagnetic iron, thereby the bone is

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magnetically conductive. Then, the magnetic stimulations from static magnetic fields (SMFs) and electromagnetic fields (EMFs) will substantially improve bone repair and regeneration.

Magnetic nanoparticles (MNPs) can be used as biomaterials because of their distinctive magnetic properties and good biostability. Recently, they are broadly applied in drug transportation, magnetic hyperthermia, nuclear magnetic imaging, and biological separation. The magnetic particles slowly deposits on the cell membrane *via* effect of the magnetic field. The cells swallow up the magnetic particles through endocytosis (Aliramaji *et al*., 2017; Brett *et al*., 2017). Thereby enters the cell and makes it easier to affect the physiological purpose of the cell. If, the magnetic field is applied, each magnetic particle will become a source of magnet, which enables the magnetic scaffolds that plays the function as the bone tissue repair. Once the magnetic particles are subjected to an external magnetic field, they will rapidly gets magnetized. The magnetic nanoparticles and the magnetic field work together to increase the efficancy of the bone tissue repair treatment. Magnetic fields can affect the ion channels and biochemical pathways of the cells. Magnetic-cell schemes includes cell labeling, targeting, patterning, and gene modification (Yang *et al*., 2019). Magnetic scaffolds are prepared by the help of MNPs and magnetic fields; they can also be activated by a magnetic field to increase the cells *via* magneto-mechanical stimulations. MNPs serves as the delivery methods for the growth factors, drugs and gene transformations. This article reviews on the osteogenic effect of magnetic nanomaterials, its methods of preparation and evaluation which are been used for the bone tissue repair or bone cell regeneration.

2. Few traditional methods of bone repair

The ideal conditions for bone tissue repair should require the following characteristics:

2.1 Good biocompatibility

The material and its metabolites should not be toxic.

2.2 Suitable biodegradability

The material should have ability to metabolise itself after fulfilling its targeted mission and its metabolism rate should be same as that of the tissue growth rate.

2.3 Optimal plasticity and mechanical properties

The materials should have ability to make into desired shapes which gives the support for new tissue growth until the repair process gets 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 is same as the structure of bones and is helpful for the cell adhesion and extracellular matrix deposition and has ability for passaging the nutrients and oxygen.

2.6 Easily sterilizable

The materials should be suitable for sterilization by currently available approaches which help in 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, good hardening there by 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 show improvised bone cell functions when compared to their micron-sized counterparts and is emerging as a new viable class of materials for bone fracture repair.

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

(iii) MNPs can be formulated with only drugs which can be loaded with growth promoters and genetic materials that helps for the bone repair (Sterling *et al*., 2014).

4. Preparation of magnetic nanoparticles

Various elemental configurationsare used in magnetic nanomaterials, that includes Fe_3O_4, Fe, Co, Ni, $MgFe_2O_4$, and Co Fe_2O_4. The most classic and common configuration of magnetic nanomaterials is Fe_3O_4. Two main types of magnetic Fe_3O_4 preparation methods are used such as dry method and wet method. Amongst which, the wet method is most commonly applied, that is done by using methods such as hydrothermal method, solvent - thermal method, chemical co-precipitation method, ball milling method, sol-gel method and atomic layer deposition method. In the synthesis of MNPs, various preparation conditions, different preparation methods and different catalysts, turnover number (TON) and turnover frequency (TOF) are usually different. The formulation of MNPs for bone repair are done with the help of different catalysts such as the Suzuki reaction and Heck reaction of halogenated benzene that can be carried out efficiently. The overall TON and TOF can reach more than 30,000 mol and 50,000 mol per hour, respectively. (Singh *et al*., 2012; Maleki, 2014).

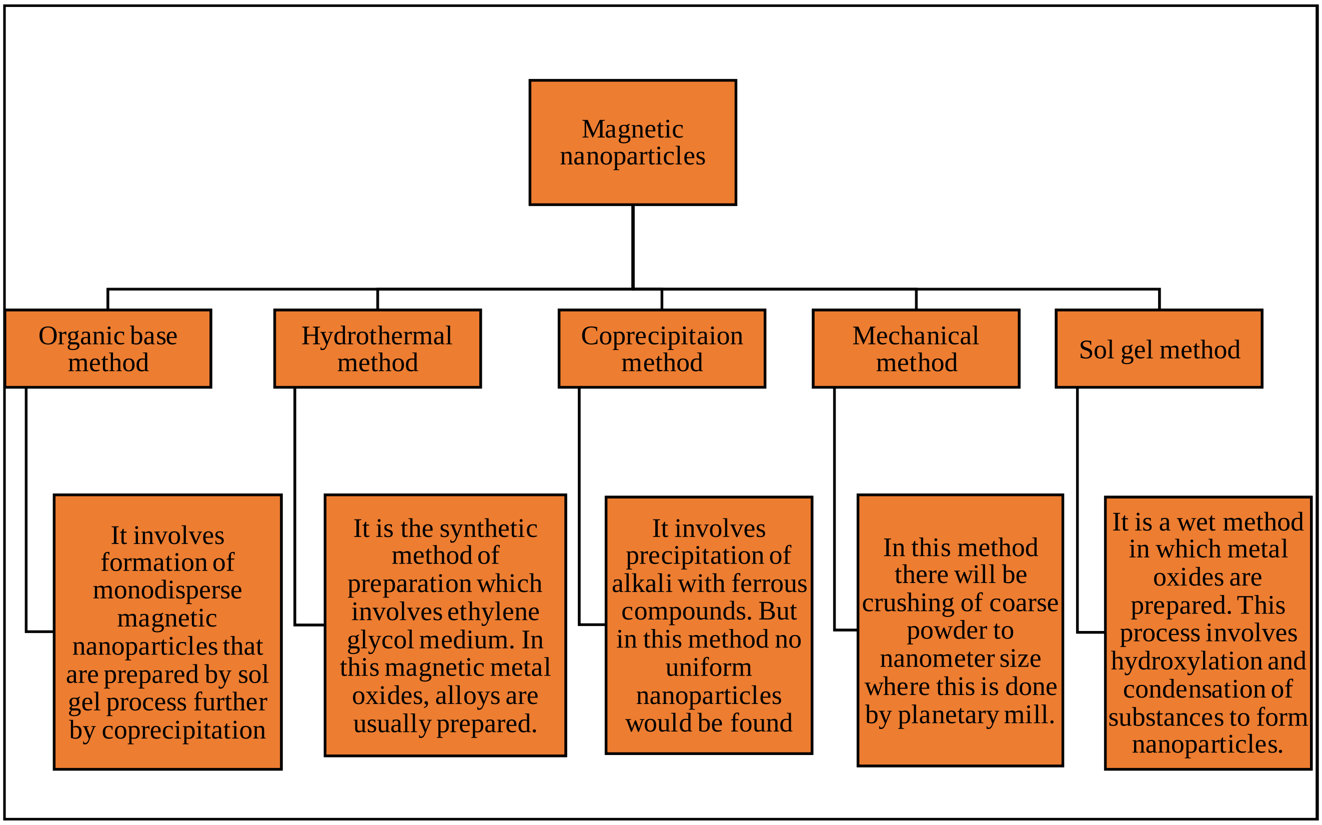

Figure 2: **Method of preparation of MNPs, 1. Organic base method; 2. Hydrothermal method; 3. Coprecipitation method; 4. Mechanical method; 5. Sol-gel method.**

4.1 Organic base method

MNPs arecomposed using various methods such as sol-gel processes in aqueous solutions, co-precipitation methods, microwave synthesis, and hydrothermal reactions.The mentioned methods are organic solution reactions. Organic phase synthesis are 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 influenced by the reactant concentration, solvent polarity, reaction temperature and reaction time. Here, usually synthesis is done of monodisperse MNPs (Maleki *et al*., 2013).

4.2 Hydrothermal/solvothermal method

Hydrothermal process is a commonly used synthetic method of magnetic nanoparticles. The reaction is generally carried out in a reactor, which includes various advantages, such as simple operation and high reacting efficacy. The metastable phase that is obtained by hydrothermal/solvothermal methods are difficult. Generally, Fe_3O_4 nanoparticles 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, which is differentiated only by application of ethylene glycol medium for preparation. The method is applicable for a wider temperature range solvents that has a higher boiling point than that of water. With using reducing solvents, products could be protected from oxidation during high-temperature preparation. Many 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 that is done by crushing coarse particles *via* strong plastic deformation to the nanosize level. This process is done in a planetary ball mill, where the coarse-grained particals are purified mainly by the collision within 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 and cold welding, the final result is micron-sized particles gets clogged with nanosized particles. To obtain highly dispersed nanoparticles, a wet grinding process is essential, which has the 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 an expensive equipment, long production cycle is done but shows low efficacy, thereby it is difficult to get industrial production.

4.5 Sol-gel method

Sol-gel method is used for nanometal oxide that is done by an ideal wet method. This method is based on the hydroxylation and condensation of molecular precursors in solution to form a "sol" of nanoparticles. It is used to prepare Fe_3O_4 nanoparticles under extreme conditions by the sol-gel method. In the result it showed that the particles have a monodisperse distribution with ameash size of nearly 8 nm. Due to the small particle size and good dispersion, the researchers suggested that the particles could be used in biomedical magnetic therapy. It was reported that monodisperse spherical Co-Cr-Ferrite nanomaterials can be prepared by co-condensation of $Co(NO_3)_2 . 6H_2O$, chromium nitrate, $Cr(NO_3)_3$ $9H_2O$ and iron nitrate *via* sol-gel method. Co-Cr-Ferrite nanomaterials were prepared with excellent magnetic properties with stable monodisperse distribution (Gao *et al*., 2019). Recently, atomic layer deposition (ALD) has become one of the important thin film deposition method that is extensively used in thin film deposition on the surface of various semiconductors, metal oxides and polymers. This method has many advantages, including accurate control of product thickness, excellent uniformity. It is a good method for synthesizing multi-component structure that can be controlled by 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 that it has 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 (MSCs) 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 growth. 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.

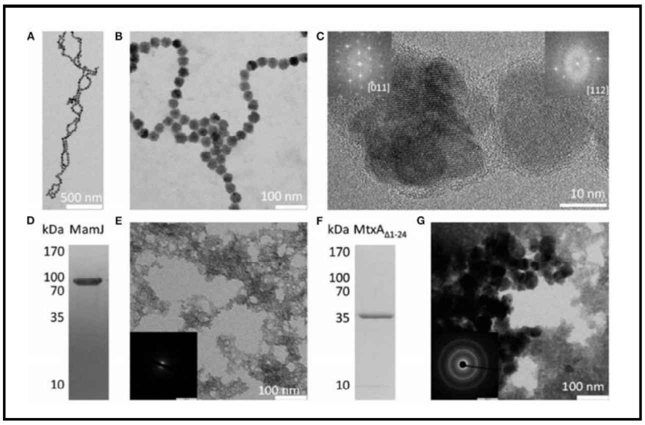

Figure 3: The growth of bone cells *via* polypeptide chain and bone regeneration using MNPs (Mirabello *et al*., 2016).

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, provided a dynamic mechanical stimulations for bone formation, that promotes osteogenic differentiation of bone marrow stem cells, and increase the bone tissue regrowth *in vivo*. For understanding, the molecular mechanisms on why and how spions are 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 action of spions. Therefore, the downstream genes of this pathway were altered to increase the osteogenic differentiation. At the molecular level, spions upregulated the long noncoding RNA INZEB[2] protein, which was critically important for sustaining the osteogenesis by MSCs. There were resulted to provide insights into the mechanisms of spions at the molecular level, which can facilitate the application of spions to increase the regenerative medicine efficiency by the stem cells (Xiong *et al*., 2015).

In another study by the use of a Sprague-Dawley rat model, SPION-containing gelatin sponges were inserted in the incisor sockets, which enhanced bone regeneration, with about 1.5-fold increases in BMD and bone volume per tissue volume (BV/TV). This 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 are used as the means of delivery, which efficiently carry the 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).

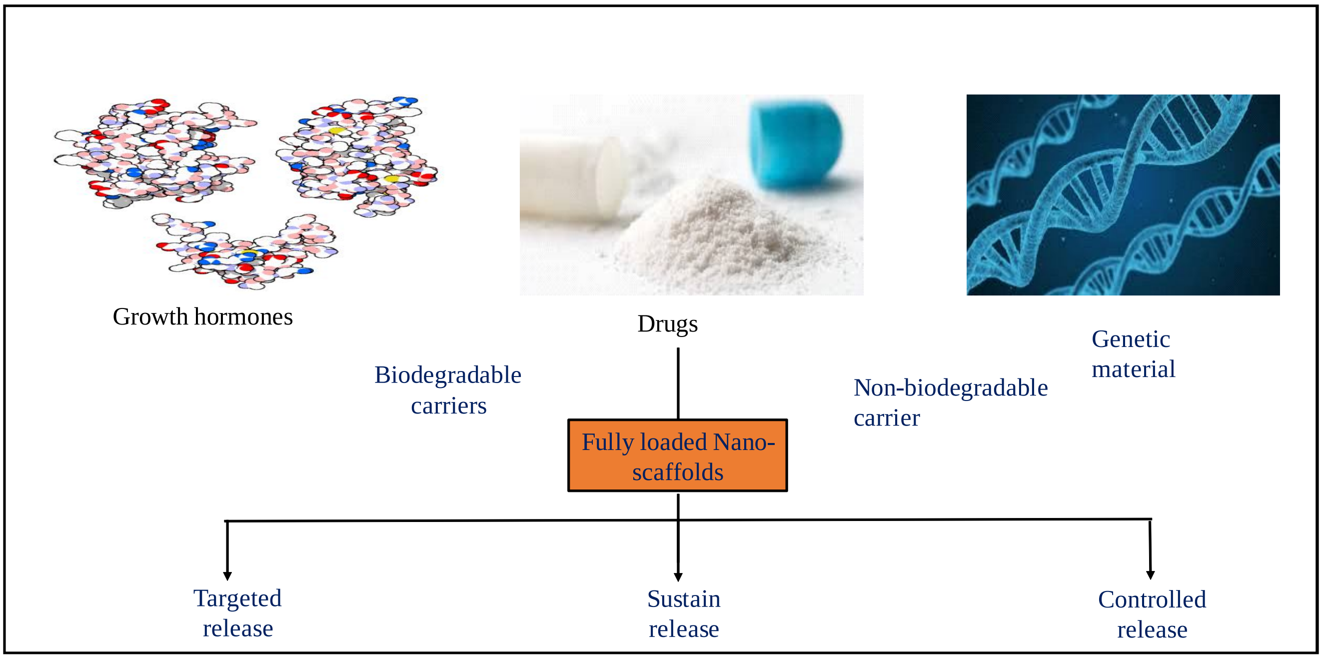

Figure 4: Methods of drug delivery using MNPs.

In few other studies, magnetic multi-walled carbon nanotubes, hydroxyapatite, and clodronate were prepared into nanoparticles. Where it found that clodronate can be continuously released from the system and discontinues the formation of osteoclast cells. The magnetic liposomes are prepared by combining iron oxide nanocomposites into a liposome membrane. When an alternating, the magnetic field is applied externally, thereby the generated heat will destroy the cell membrane and releases the drug encapsulated in the liposome to show its action. In addition to promoting osteogenic differentiation, iron oxide nanoparticles also have good bone conduction capacity. Currently in the field of bone regenerative medicine, iron oxide nanoparticle complexes are commonly 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 that improve the continuous release of gentamicin, which is helpful to reduce the fixing of bacteria and prevent biofilm formation. In addition to treat infection, the Fe_3O_4 nanoparticles are combined that can also promote the adhesion, growth, and osteogenic differentiation of bone marrow mesenchymal stem cells (Wang *et al*., 2015). Nanomaterials can be used as transporters 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 for bone defect repair.

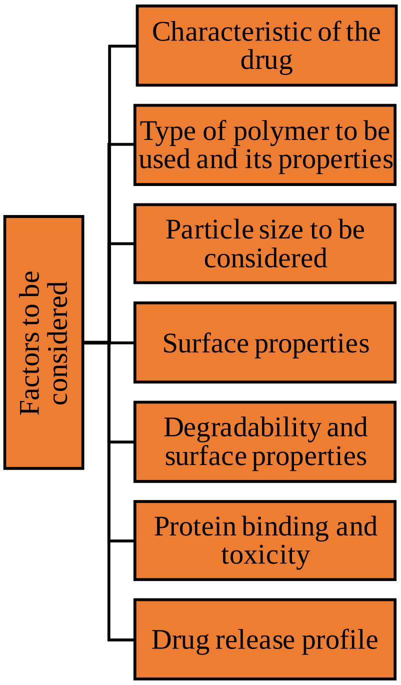

Figure 5: Factors to be considered for designing the drug delivery using MNPs.

8. Magentic strategies for growth factor

The mechanism of bone repair is complicated process which includes few important growth factors and small molecules, like BMP-2, platelet-derived growth factor (PDGF) and parathyroid hormone (PTH). These molecules can act directly to influence the bone mass, or indirectly, by acting on negative regulators of the bone mass (Silva *et al.*, 2017). Thereby, delivering growth factors is one of the important approach in bone tissue repair, with uses stem cells and scaffolds.

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 standardized by combining to nanocomposites (Dobretsov *et al.*, 2015). The growth factors that are immobilized to iron oxide/human serum albumin nanoparticles are promoted for higher growth and differentiation of the cells, when compared to their counterparts. When it is applied in the deeper parts of the body, the efficacy of capturing MNPs are ensured by the use of a residual magnetic implants that too when the external magnetic field will not be there, 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 activate the ligand-MNP complex that has to be altered using magnetic fields, by allowing the control of ion channel stimulation. The osteogenesis of bone marrow stem cells could be substantially increased by mechanical activation *via* magnetic tagging. The application of magnetic activation was able to initiate the nuclear translocation of β-catenin to a similar level as Wnt3a, thereby increases the skeletal progenitor cell proliferation, differentiation and hastens the bone repair in auxin (Hu *et al.*, 2013).

Firstly by targeting the cell membrane receptor pdgfrα, a higher mineral content was there in the cells after 3 weeks of magneto-mechanical stimulation in the osteogenic medium culture. Magnetic iron oxides and gold nanoparticles were encosed into a nanosphere which was used as the drug carrier in the human cells. The drug release inside the cells can be controlled by the application of heat and a magnetic field. Moreover, the use of the magnetic field to pull the nanocomposite is done for tissue-specific clinical applications in bone, heart, lung and brain, for targeted drug delivery and on-demand drug release. Furthermore, the magnetic targeting method increased the viral and non-viral gene delivery (Liu *et al.*, 2017). This approach can be used for a wide range of viral vectors (including adenoviruses, adeno-associated viruses and lentiviruses), cationic polymers (polyethyleneimine, or PEI), as well as cationic lipids. On comparision with common transfection strategies, a key advantage of the magnetic targeting process was developed to lower the 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 presiced sizes, shapes, compositions, magnetization, relativity and surface charge.

To enhance the cell targeting capacity, the MNP-liposome complexes were combined with transferrin (Pan *et al.*, 2018). That is synthesized cationic lipid-coated MNPs and are prepared by transferring the coated MNP/(plasmid DNA) complexes. The transfection using these magnetic vectors requires much less incubation time in the presence of an external magnetic field, and is achieved by the gene transfer at a high efficacy (Pan *et al.*, 2008). Therefore, magnetic delivery and gene transfection would be an important future research focus, with the purpose to decrease the adverse effects of a specific drug for treating bone diseases, to increase 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 with the superparamagnetic properties. They can combine and position under a constant magnetic field and absorb electromagnetic waves to create heat by alternating the magnetic field (Li *et al.*, 2016). Amongst which, magnetic iron oxide nanoparticles are extensively used in magnetic activation to initiate the 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 new challenges. One of the main challenges is the possible toxicity related to nanomaterials or nontoxicity. Due to the nanosize, nanomaterials have different toxicity properties when compared to their micron-sized composites. Nanoparticles can show greater toxicity *in vitro* at a very less concentrations and shorter exposure times when compared to micron-sized particles where nanoparticles were internalized by lung epithelial cells, but it is not seen in micron-sized particles. It is known that endocytosis including clathrin-mediated endocytosis and post-endocytic trafficking is the important route of nanoparticle usage, and multiple internalization mechanisms may be included. 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 about the effect of these particles on the bone and also the delivery of the same. The distinctive properties of magnetic nanomaterials have induced their application in medicine, that too in terms of magnetism, magnetic fields can give a remote control of drug release and biomolecule activation, thereby generating the biological reactions that includes cell differentiation, tissue growth, and bone defect regeneration. Homogeneous distribution of mnps resulted in faster bone regrowth but relatively immature new bone but an in homogeneous 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 author declares that there are no conflicts of interest relevant to this article.

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