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Review Article

DEVELOPMENT STATUS IN THE MEADOW OF NANOSTRUCTURE MAGNETIC DRUG DELIVERY SYSTEM AND ITS PROMISING APPLICATIONS

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ABSTRACT

This article discusses about magnetic nanoparticles, their physicochemical properties various applications in medicinal sectors and technology advancements. Superparamagnetic, high magnetic susceptibility, non-toxicity, and biocompatibility and less Curie temperature are critical characteristics of magnetic nanoparticles which make them suitable for assorted medical applications. Now a day's magnetic particles play a significant role in diverse technological areas with potential applications in fields such as electronics, energy biomedicine and diagnosis. Magnetic nanoparticles have been a vivacious topic of extreme research for the last fifty years due to its top-down approaches. The perspective of magnetic nanoparticles stems from the fundamental characteristics of their magnetic cores collective with their drug loading capability, biochemical properties. This article review the modern advancement of magnetic nanoparticles for drug delivery, focusing chiefly on the impending applications like targeted drug delivery, bioseparation, magnetic resonance and cancer diagnosis, induction of hyperthermia, induction of hyperthermia, nanorobotic agents, tissue engineering, artificial muscle, magnetically activated polymers, controlled tissue assembly, control cell function, bone regeneration scaffold, destruction of blood clots, labeling stem cells with magnetic nanoparticles, implant-assisted intrathecal magnetic drug targeting, biodegradable magnetic nano-composite stent, local drug delivery etc.

Keywords: Magnetic nanoparticles, Drug delivery system, Applications, Drug targeting

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INTRODUCTION

There is an ongoing struggle to develop efficient drug delivery scheme and targeting methods for diverse life-threatening diseases like cancer. Magnetic particles, ranging from nanometer-size to 1 micron, are being used in an escalating number of therapeutic applications.

Magnetism has applications in numerous sectors like diagnostics, targeting drug delivery system, molecular biology, cell isolation, cellular proteomics, cell purification, tissue engineering, detoxification of biological fluid, hyperthermia, radioimmunoassay, magnetic resonance imaging, gene delivery, minimally invasive surgery, radionuclide therapy, stem cell tracking, contraceptive drug delivery, infusion pumps and artificial muscle applications [1-2].

In biology, magneto tactic bacteria which contain miniature magnetite particles chains with the help of those responding to a magnetic field and can navigate to the surface or bottom of the pools. Magnetic separation process after disruption of the cell wall utilized for isolation of tiny magnetic particles.

The existence of the lipid layer makes them biocompatible which can be readily engineered for a multiplicity of biomedical (bio-magnetism) or therapeutic applications like cell biology, cardiology, neurosurgery, oncology and radiology.

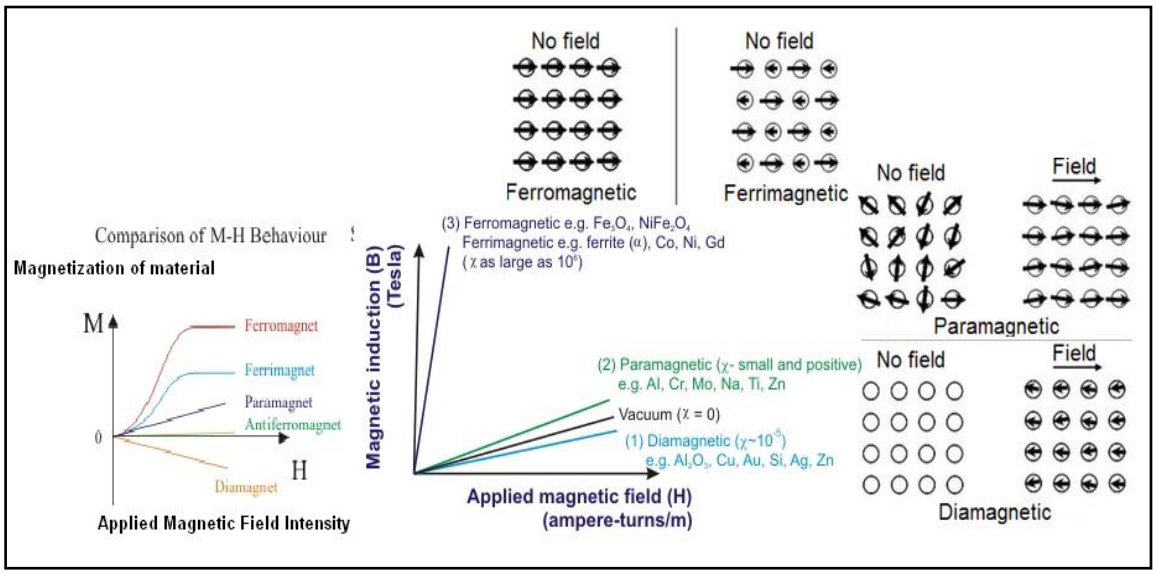

Fig. 1: Classification of magnetic materials and comparison of magnetization behaviour of each class [3]

As discussed in fig. 1 magnetic materials can be classified as

- **Diamagnetic material**: Very weak and not permanent magnetism; it persists only in a presence of external field. Due to the external magnetic field and opposite directed magnetic moment, electron's orbital motion changes.

- **Paramagnetic material**: Due to the incomplete cancellation of electron magnetic moments. When a field is applied to these atomic dipoles individually tend to align with the field. Examples: montmorillonite (clay), nontronite (Fe-rich clay), biotite (silicate), siderite (carbonate), pyrite (sulfide).

- **Ferromagnetic material**: It is the basic mechanism by which materials like iron form permanent magnets. Ferromagnetism is the strongest type magnetism.

- **Ferrimagnetic material**: These material possessing atoms with opposing magnetic moments, as in anti-ferromagnetism; which are unequal, spontaneous magnetization. This happens when diverse materials or ions are presents (such as Fe^{2+}, Fe^{3+}). Examples of ferrimagnetic materials are magnetite (iron oxide; Fe_3O_4), YIG (yttrium iron garnet), cubic ferrites, hexagonal ferrites such as $PbFe_{12}O_{19}$ and $BaFe_{12}O_{19}$, and pyrrhotite, Fe1-xS.

- **Antiferromagnetism**: Sublattice moments are exactly equal but opposite, the net moment is zero.

Magnetic drug delivery system is a superlative approach to the deliverance of diverse drug using smart engineered microcarriers which can conquer a number of limitations facing by Conventional drug delivery system which generate the need of novel drug delivery system. Magnetic drug implant or magnetically targeted drug delivery carriers that can be an exceptional substitute to diabetic's patients, who are struggling with numerous pills or intravenous injections or localized disease sites such as tumors. It can be used for delivery of analgesic agents, chemotherapeutic agents, hormones, imaging agents and other treatments for a broad range of health conditions.

The important properties of magnetic particles as follows

- Nontoxic to normal tissue
- Bio-compatibility which decreases risk of immune responses and phagocytosis
- Injectability
- High-level accumulation/Bioavailability in the target tissue or organ.

Medical Application of magnetic particles as follows

Targeted drug delivery

Injecting of drug-coated with magnetic particles (100-250 nm size) like polymer capsule, polymeric micelle, microsphere, liposomes, iron oxide nanoparticles, polymeric matrix, resealed erythrocytes; into a blood vessel and then apply a magnetic field externally near diseased site [4-5]. The polymers used for the formulation of mentioned delivery carrier system should be compatible, non-toxicity, non-antigenicity and biodegradable. Polymeric inactive ingredients for FDA-approved drug products. This external magnetic field exerts a pull on these magnetic particles loaded with therapeutic agents and retains them at the site of the disease or effecter area. The blood vessel express a paramagnetic response to magnetic field created from blood entities like hemoglobin and proteins (include carbon, hydrogen, nitrogen, oxygen atoms) demonstrate a diamagnetic response [6].

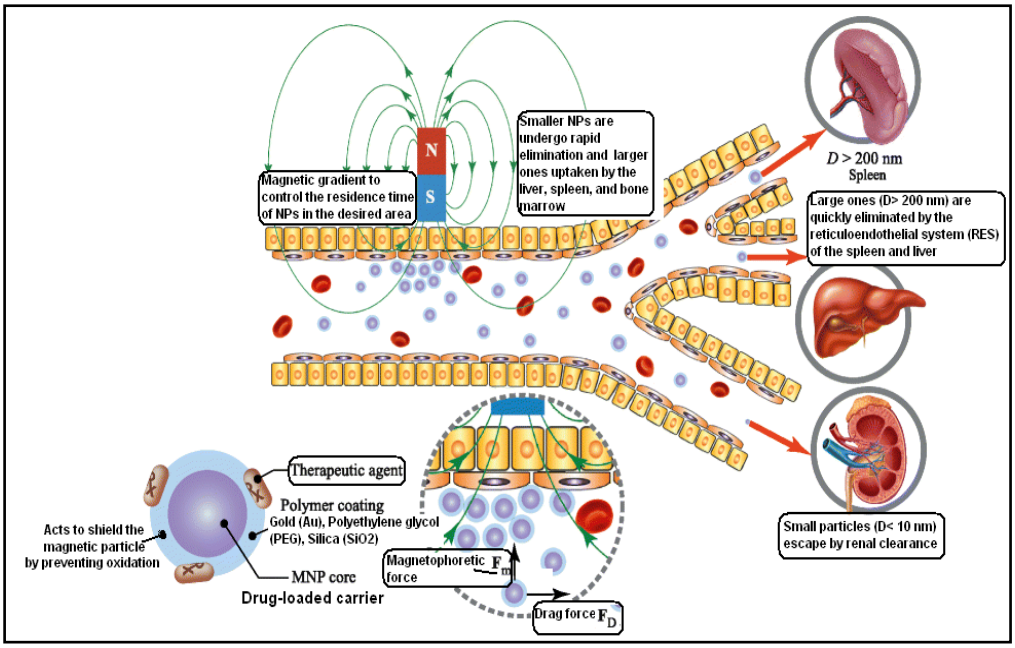

Fig. 2: Principle of targeted drug delivery [4-5]

Bioseparation

Magnetic nanoparticles can be utilized for separation of diverse entities, also used in DNA/RNA purification, bioengineering, removal of a specific cell from blood, removal of cytokines/interlukin-1/necrosis factor and immunoassay [7]. This method has been proficient for the selection of tumor cells from blood, isolate enzymes, isolate DNA or RNA.

Magnetic resonance and cancer diagnosis

A magnetic resonance imaging (MRI) scanner includes a gigantic magnet of 1.5 to 7-tesla strength (without radiation). Radio waves, external magnetic field are applying to excite the protons present in the body or body fluid. These protons relax after excitation process which offers magnetic movement and this proton excitation and relaxation data is transformed into cross-sectional pictures of human tissue by a computerized scheme. Diseased and normal tissues propose dissimilar relaxation rates of water molecules that can be interpreted by the light (higher water content body area) and dark contrast images in Magnetic resonance imaging. Paramagnetic gadolinium-based materials are used (super-paramagnetic iron oxide particles which coated with dextran) for this principle. Magnetic nanoparticles also used for the detection of growth of the local tumor by the administration in the body. Such magnetic

nanoparticles collect in lymph nodes. Magnetic resonance tomography (MRT) recognition of nanoparticles makes it possible to visualize abnormalities in the lymph node structure caused by a growing tumor [8].

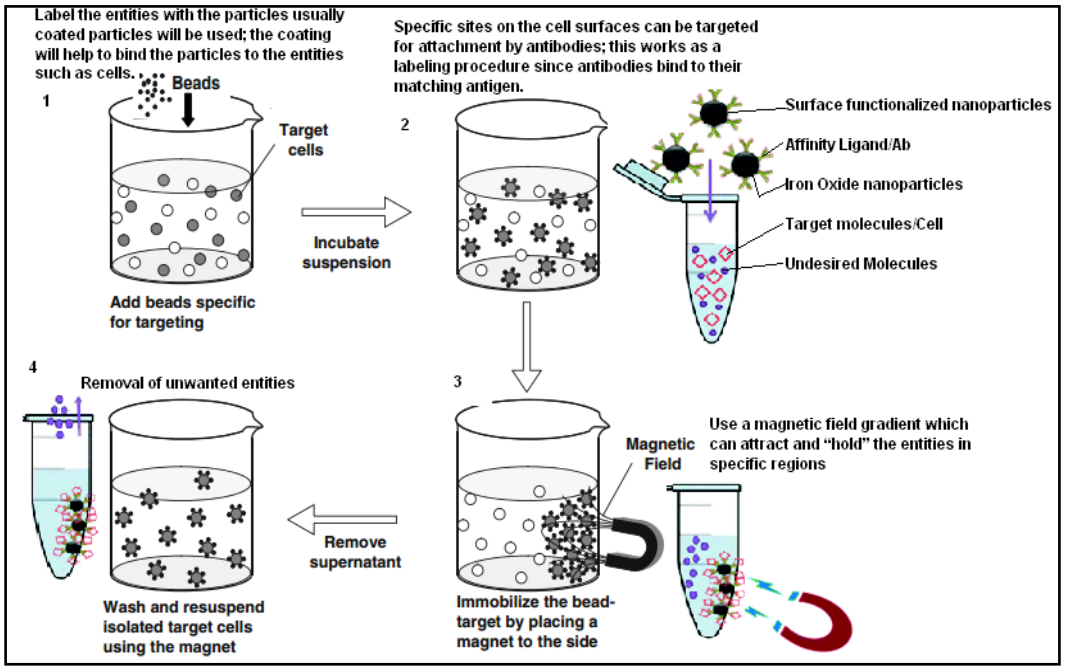

Fig. 3: Steps for bio separation [7]

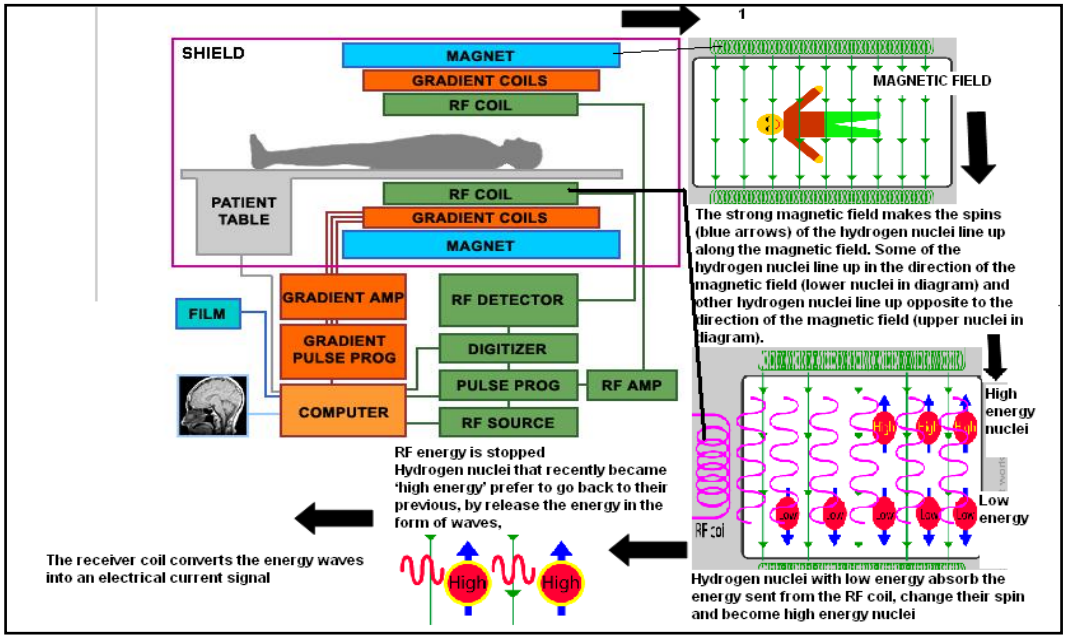

Fig. 4: Principle and working of magnetic resonance [8]

Principle and working of magnetic resonance

- Apply a steady field of about 1 tesla which causes a very small fraction of protons to line up in a parallel direction to the field as per their energy is shown in fig. 4. And due to this positioning of hydrogen nuclei, made them to absorb and then radiate energy at the larmor precession frequency of the hydrogen nuclei present in water.

- To quantify the signal created as a result of this alignment, apply a transverse radio frequency magnetic field with the assist of Radiofrequency coils (RF coil).

- When second field produce by Radiofrequency coils is switched off, the amplitudes of the magnetic moments relax back to their original values.

- This relaxation of the response is calculated by pick-up coils. The intensity emitted radiation by the body is recorded and transformed by the magnetic resonance imaging scanner which delivers an image of the body portion on its monitor.

- Thus if an area is tagged by magnetic particles, the less relaxation time as compared to the untagged area; and thus these particle acts as a contrast agent.

Induction of hyperthermia

1. Hyperthermia is a promising approach for Cancer therapy in which localized enhance in temperature upto 42.5 to 44° C which can be used to destroy malignant cells selectively is called as hyperthermia; this method of treatment can be effected by magnetic particles (dextran magnetic nanoparticles by Gordon) which is referred as intracellular hyperthermia. Hyperthermia produces by hysteresis losses, relaxation losses and eddy current effect [9-11]

2. Hyperthermia can be used against parasitic infections caused by a drug-resistant microbe.

Numerous approaches for the development of hyperthermia explained as follows:

➢ **Magnetic nanoparticles induced hyperthermia**

The elementary idea is that magnetic material can be heated by uneven magnetic field. The mechanisms of generation of heat by ferromagnetic materials comprise hysteresis losses. In the case of super paramagnetic particles (e. g. dextran magnetite), heating can be occur due to the rotation of the particles themselves or by the rotation of the atomic magnetic moments. Hyperthermia induces cellular apoptosis, cell cycle detain and improves the effects of radiotherapy, chemotherapy in the treatment of cancer; as diverse mechanism explained in fig. 5. This method is non-toxic, biocompatible, enhance bioavailability, accumulation nanoparticles at the diseased site, can cross blood-brain barrier. The killing of tumor cells principle as shown in the following fig. 5 [12-19].

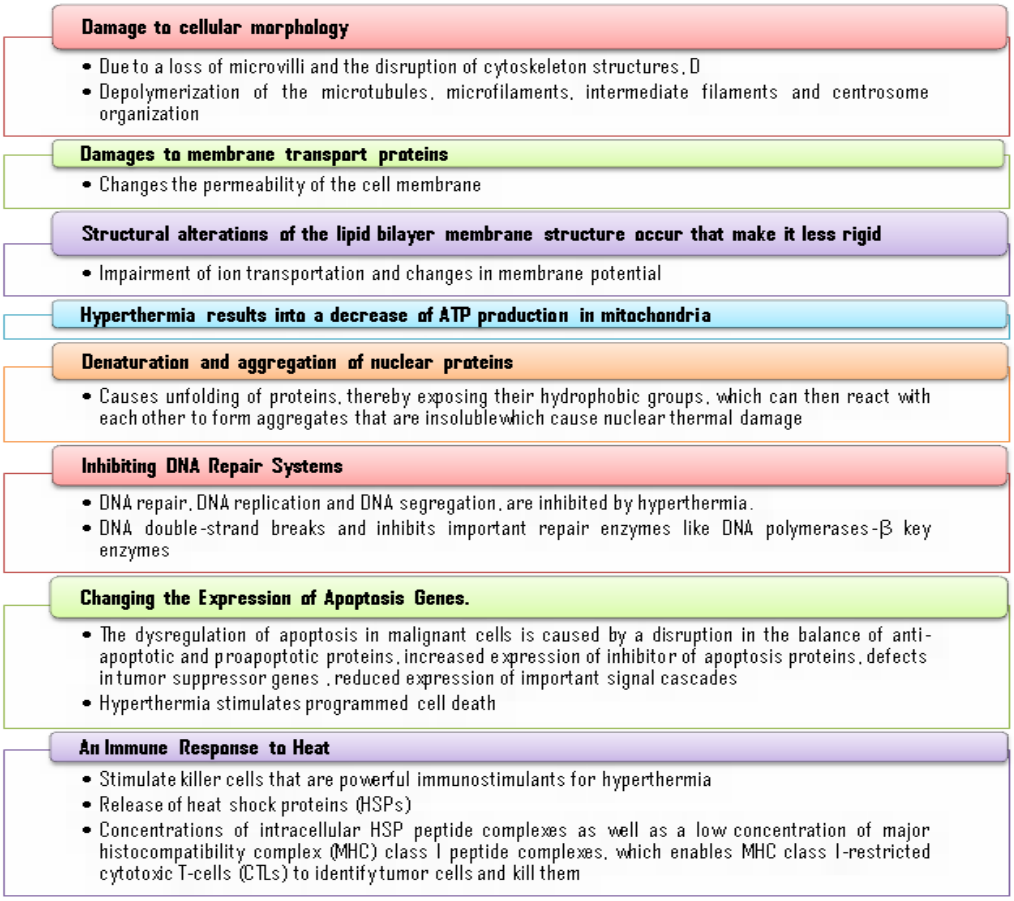

Fig. 5: Principle of killing of tumor cells by Hyperthermia [12-19]

➢ **Antibody conjugated magnetic nanoparticles induced hyperthermia**

Magnetic cationic liposomes directly injected intravenously, in tumor tissue. Which used for magnetic resonance imaging recognition of cancer and induce hyperthermia. It has been documented that an interactive therapy shows synergistic effect, additive effect or antagonistic effect and theranostics [20]. Magnetic nanoparticles coated with polyethene glycol which avoid the identification or capture by reticuloendothelial system, due to opsonin absorbance onto magnetic nanoparticles and phagocytosis carried out by macrophagic cells [21-22]. Antibody targeting of tumour-associated antigens or cell surface protein like tumor necrosis factor receptor enhances the selectivity or targeting effect in cancer tissues like renal cell carcinoma [23].

Use of magneto tactic bacteria

Bacteria which synthesize magnetosomes were also useful in the battle against parasitic infections under shifting magnetic field. These magneto-aerotactic bacteria contain magnetite (Fe_3O_4) or greigite (Fe_3S_4) nanocrystals that are enveloped by biomembranes. Biosynthesis of these nanocrystals is genetically controlled and is enzyme-catalyzed process. Magnetosomes arrange in a chain or chains, conferring to bacteria a magnetic dipolar moment that allows them to give magnetotaxis movement. Cancer cells consume huge amounts of oxygen and parts of a tumour will become ravenous for oxygen which creates the hypoxic situation.

It is dreadfully difficult to deliver anti-tumour drugs to hypoxic regions using conventional drug delivery system, therefore, magneto-aerotactic bacteria or magnetosomes can be utilized to transmit drug-loaded nano-liposomes into the hypoxic area of a tumour which amplify therapeutic index of diverse nano-carriers in targeted regions [24].

Nanorobotic agents (nanobots or nanoids)

Nanorobots are characteristically devices with size from 0.1-10 micrometres. Researchers from Polytechnique Montreal, University de Montreal and McGill University have constructed novel nanorobotic agents having the capacity for navigation through the

bloodstream to administer a drug with precision for targeting the active cancerous cells with less toxicity [25-26].

Tissue engineering in presence of magnetic force Mag-TE

Magnetic micro particles and nanoparticles utilized in a multiplicity of tissues to influence cell seeding, cell growth and mechano-transduction for regenerative medicine strategies. A magnetic nanoparticle-labeled cells enables manipulation and organization of cell functions by applying an external magnetic field [27]. *In vitro* fabrication of scaffold-free tissue-engineered constructs with programmed cellular alignment, additionally magnetic cell levitation with thermo-responsive nanofabricated substratum (TNFS) based cell sheet engineering technique [28].

The temperature-mediated alteration in surface wettability of the thermo-responsive poly (N-isopropylacrylamide), substratum enables the spontaneous disconnection of the cell monolayer, which can easily remove by use of ring or disk-shaped magnet; As discussed in fig. 6 [28-29].

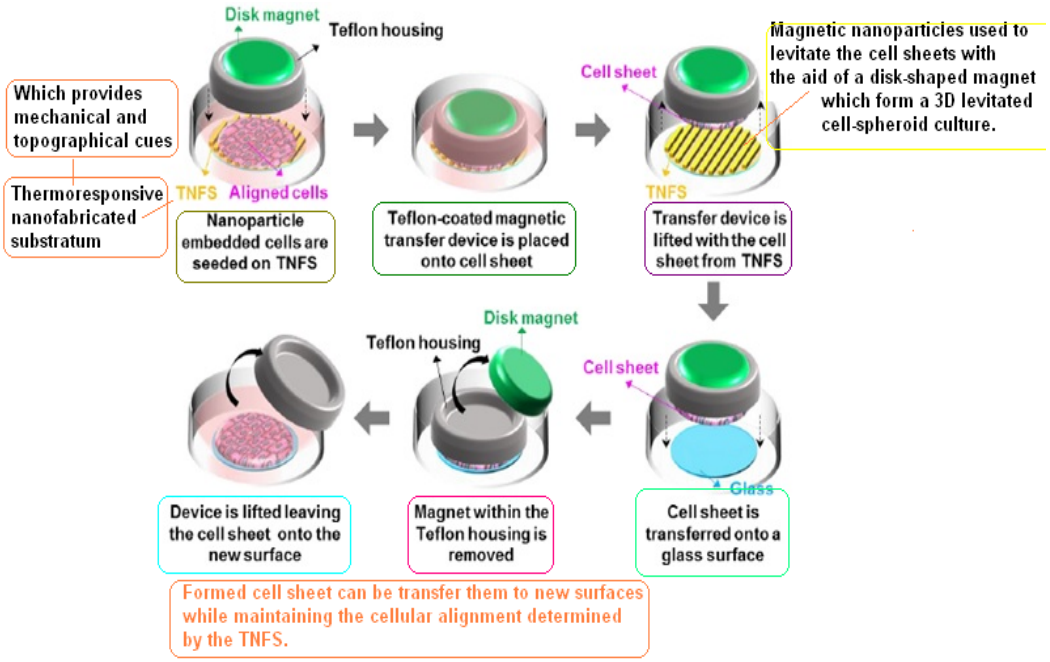

Fig. 6: Magnetic force-based tissue engineering [27-29]

Magnetic nanocomposites produced by a biodegradable poly (caprolactone) (PCL) matrix and super paramagnetic Iron doped hydroxyapatite (FeHA) nanoparticles at diverse PCL/FeHA compositions have been productively prototyped, layer on layer, through 3D bioplotting. Creating nano-sized features on the exterior to hip or knee prosthesis can lessen the peril of rejection and also stimulate the synthesis of osteoblasts which accountable for bone matrix growth. This would allow aiming longer-lasting hip/knee replacements and diminishing the probability of loss of the implant.

Artificial muscle

Cells labeled with magnetite nanoparticles were cultivated into 96 well plate or 24-well ultralow-attachment culture plates which have positioned magnet underneath each plate. The cells in wells are accumulated on the culture surface and produced multilayered cell sheets. The artificial tissue constructs shapes can be controlled by external magnetic force like cellular string-like assemblies were created by use of the linear magnetic field. Similarly, when a silicone plug was situated at the midpoint of the well for the duration of the fabrication of a cell sheet, the cell sheet shrank significantly and shaped a ring-like assembly.

Magnetically activated polymers

Magnetically activated gels are also called as ferrogels which are chemically cross-linked polymer network to the presence of a magnetic field which is nothing but the colloidal dispersion of mono-domain magnetic nanoparticles. Electric and magnetic field-induced shape and movement were obtained in a polymer gel with a complex fluid as the swelling agent. They can bend, elongate, deform, curve contract and their response is independent of particle size. Magnetic particles were incorporated into poly (N-isopropylacrylamide) and poly (vinyl alcohol) gel beads. The beads aligned as a chainlike structure inconsistent magnetic field lines, and they aggregated in a non-uniform field due to magnetophoretic force. These magnetic gels give quick and controllable changes in shape, which can be exploited in applications mimicking muscular contraction [30].

The use of polymer gels as actuators creates a quick and reliable control system, and the use of electric or magnetic stimuli facilitates the development of these control systems. Poly(vinyl alcohol) (PVA) gel, with magnetic nanoparticles, contracted in a nonuniform magnetic field [31], which is smaller than the field strength observed on the exterior of common permanent magnets. By coordinating and controlling the magnetic field, muscle-like motion can be obtained, leading to the development of artificial muscles [32].

Controlled tissue assembly

Magnetic nanoparticles have been utilized to collect more complicated tissue constructs than those that are structured by conventional scaffold-based tissue engineering strategies.

Control cell function

Cell functions are predominantly structured by growth, bioactive factors that attach to varied membrane receptors. Controlled mechano-transduction pathway in the cells is an influential approach to transform cellular behaviour. When a magnetic field is functional, magnetic particles are drag and form ligand-receptor bond, which further trigger cellular signaling like Ca^{++} signaling, proto-oncogene tyrosine-protein kinase (SRC) Family protein kinase, mitogen-activated protein kinases (MAPK) pathaway.

Bone regeneration scaffold method

Ceramic crystals are used to achieve uniform dispersion of magnetic particle, surfactant and the specific drug was loaded as discussed in

fig. 7. The drug-loaded scaffold was positioned at the defective site in the occurrence of a magnetic field, which facilitated effortless drug release from the scaffold, serving to defend it from bacterial colonization, and the magnetic field stimulated cell proliferation of scaffold. Engineered biomaterials collective with growth factors, like bone morphogenetic protein-2, which can act as a scaffold and drug delivery system to which promote bone repair and regeneration.

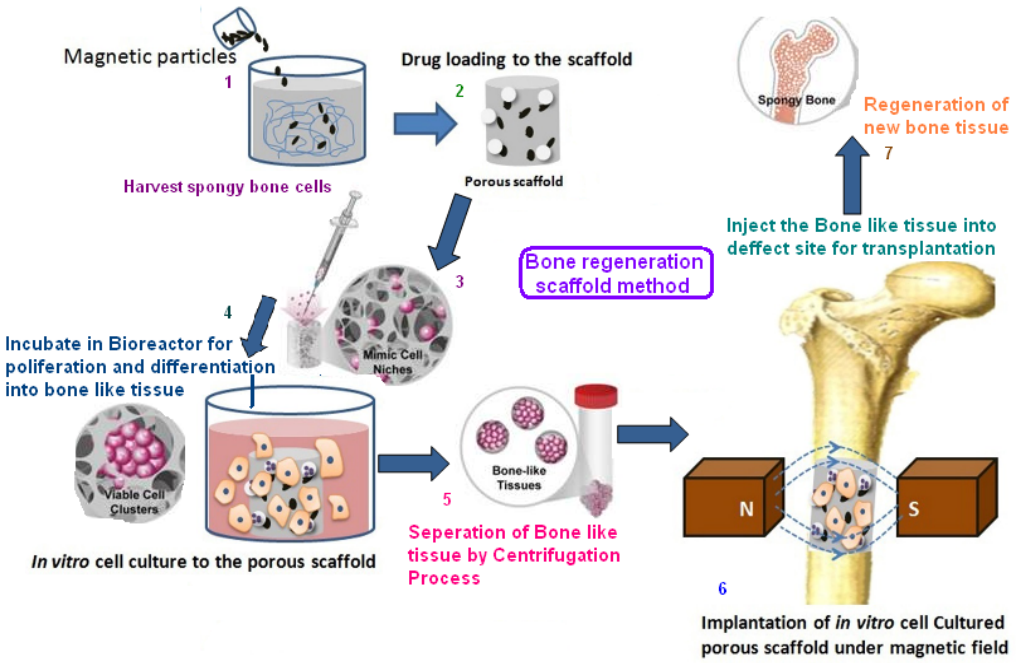

Fig. 7: Bone regeneration scaffold method [32-33]

Bone regeneration materials as follows:

- Calcium phosphate ceramics
- Porous spherical hydroxyapatite granules for drug delivery
- Demineralized bone matrix
- Carriers and delivery systems for growth factors
- Nano scaffolds
- **Magnetic nanoparticles (Fe-hydroxyapatite) [32-33]**

Iron (Fe) is a vital element in the human body, its concentration within the hard tissue is low, and its presence into the body scarcely affects bone remodeling with good biocompatibility. Hence, an iron-substituted hydroxyapatite nanocrystals (Fe-Ha) phase is nontoxic, biodegradable, super paramagnetic, magnetic nanocarrier that could be used as an active scaffold for bone and osteochondral regeneration.

Destruction of blood clots

Magnetic nanoparticles containing iron oxide deliver a lofty concentration of a drug straighty at the clot site for dissolution of a blood clot. These Nanoparticles are coated with albumin, which decreases phagocytic engulfment by phygocytic cell. These magnetic nanoparticles can observe under magnetic resonance imaging and can induce a high-frequency vibration by heating them which enhance clot dissolution rate [34].

Labeling stem cells with magnetic nanoparticles

Stem cells immensely studied for their capability to replicate, undifferentiated daughter cells that can be physiologically induced to mature under specific conditions. Characterized by pluripotency, (capacity to differentiate into a plethora of specialized cells) and confer therapeutic benefits that have catalyzed the meadow of regenerative medicine [35-36]. Their application for treatment of retinal degenerations, spinal cord injuries and brain traumas [37-39]. Magnetically responsive nanoparticles are biocompatible and employ for targeted delivery of stem cells for improvement in their retention in targeted site. Application of non-invasive cell tracking approaches is essential to establish tissue distribution at the injection site and which provide information about stem cells mechanisms of tissue repair. The physical identity (aggregated against isolated nanoparticles) and the biological identity of particles dictate the uptake by diverse cell types and the *in the vivo*-biodistribution of magnetic nanoparticles [40-43].

Objective of cell labelling by magnetic nanoparticles

a. Numerous types of cells can be labeled

b. Achieve a reproducible and quantifiable particle uptake

c. Modulate intracellular location and distribution of magnetic nanoparticles

d. Preserve viability, proliferation capacity, phenotype and functions of labeled cells

Cell labeling is currently accomplished through probes into the cells and/or integration of the reporter genes into the genome. Surface charges can be engineered using antibodies, peptides, and aptamers. Coatings of nanoparticles can hasten the rate of internalization by passive diffusion, endocytosis, phagocytosis, macropinocytosis methods. The cell labeling policy employs a throng of imaging modalities like magnetic resonance imaging, single photon emission computed tomography, fluorescence imaging, bioluminescence imaging, positron emission tomography to detect the signal along with efficient release of stem cells at the target location [44], is a synthetic cationic polymer commonly used to improve cell adhesion to the surface of culture dishes. Use of Poly-l-lysine (PLL) has not been approved in humans and studies have shown that complexes formed by ferumoxides and Poly-l-lysine-modified iron oxide nanoparticles can be large. Such complexes do not become included into endosomes, remain attached to the cell membrane [45-46]. These formed complexes can influence cell proliferation and differentiation. Protamines are arginine-rich proteins with low-molecular-weight, which isolated from testis of mature fish. It is a clinically accepted polyatomic peptide chiefly used as for heparin anticoagulation antidote [47-49].

Magnetic implant

Magnetic drug implants can be safe, convenient and effective for treating numerous health conditions, and can adjust the dose after implantation by using different magnet strengths. Magnetic Implant drug delivery system is useful for diabetes, where the requisite dose and timing of insulin dose varies from patient to patient. Magnetic targeting is based on two prime essentials: a magnetic field source and magnetically responsive drug carrier.

Recently, a magnetic implant containing a silicone sponge with magnetic carbonyl iron particles wrapped in an encircling polymer layer, which having 6 mm in diameter were prepared which broaden the application of controlled drug delivery system. The drug is injected into the device and then surgically implanted in the area being treated. Passing a magnet over the patient's skin which activates the device.

•By deforming the sponge

•By triggering the release of the drug into surrounding tissue through a tiny opening.

The magnetic implant can be used for administering painkillers, hormones, chemotherapy drugs and other treatments for a wide range of health conditions [50-51].

Implant-assisted intrathecal magnetic drug targeting

Targeted delivery strategies have shown assurance to strengthen efficacy and diminish side effects of different classes of drug and are now budding as an essential element of novel therapies with superior safety profiles of dosage forms. Ferritic stainless steel implants were built-in subarachnoid space of *in vitro* human spine model, and targeting magnet was positioned at a physiological distance away from the model and implant to mimic the distance between the epidermis and spinal canal which is a brilliant supplementary technique which progress targeting capabilities of the delivery system.

A biodegradable magnetic nanocomposite stent: Polymer composites with iron oxide loadings were melt extruded into fibers and coiled to reproduce a ferromagnetic stent implant. An *in vitro* setup was utilized for study loading capacity of 100 nm magnetite particles (magnetic drug carrier particles) under physiological flow conditions.

Local drug delivery system

The therapeutic agents like Pharmaceutical drugs, radioactive polymers, cells can be used for various disease conditions treatment of hepatic, renal, pancreatic, prostate/other cancers, coronary atherosclerosis. Stent angioplasty is largely utilized for an obstructive vascular disease which structured to provide local release of antiproliferative drugs. Biodegradable nanoparticles can be used to magnetizable stents which enables competent localization of the drug to the stented arterial region [52]. The magnetic targeting strategy compatible with multiple drug dosing, which is potential use in stent angioplasty for the treatment of non-coronary atherosclerotic vascular disease.

CONCLUSION

Magnetic nanoparticles, by an asset of their size, magnetic characteristics; provide themselves to a variety of applications. The magnetic centre of a magnetic carrier may be used for the directing via a magnetic field. The huge surface area provided by the magnetic nanoparticles for attachment of extractable species and functionalization with particular ligands allows for targeting of a selected species or for delivery of a species to a selected location. Their ability to be effortlessly manipulated using a magnetic field makes these carriers an attractive option for use in biomedical and process engineering applications. Although certain limitations exist in terms of the range of magnetic influence and chemical resistance of carriers, much scope remains for the enlargement of a large variety of new applications using magnetic carriers.

CONFLICTS OF INTERESTS

Declared none

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