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Nanocomposites For Biomedical Applications

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ABSTRACT

Nanotechnologies represent an unprecedented recent advance which is revolutionizing core areas of biology and medicine. In recent years there has been a rapid increase in applications of nanotechnology in medicine in order to prevent and treat diseases in the human body. Biomedical nano - composites have potential to become critically important to the development of biomedical applications, ranging from diagnostic and therapeutic devices, tissue regeneration and drug delivery matrixes to various bio-technologies that are inspired by biology but have only indirect biomedical relation.Nano - diagnostic is the term used for the application of nano - biotechnology in molecular diagnosis, which is important for developing personalized therapy. Nanotechnology is based on pharmaco-genomics, and pharmaco-proteomic information but it also consider environmental factors which influence the therapy response. This article discusses current efforts and focuses on key research challenges in the emerging use of nano - composites for potential biomedical applications.

KEY WORDS: Nano - composites, Biomedical Applications, Nanotechnologies

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INTRODUCTION

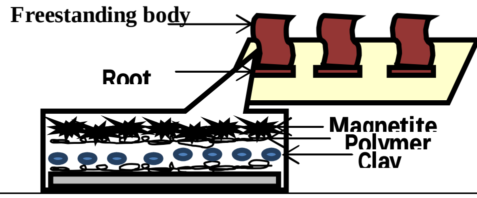
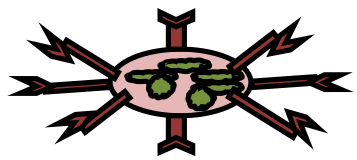
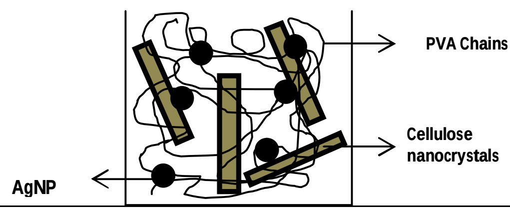
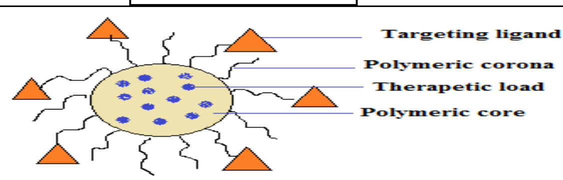
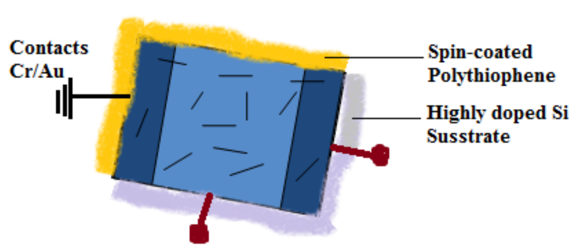
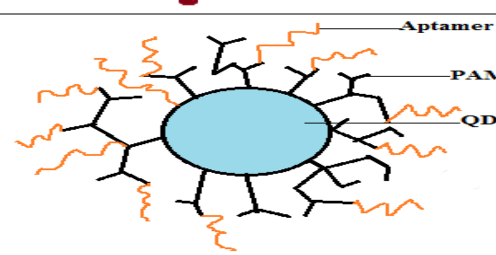
Early nanomaterials were produced without the capacity of controlling their structure and morphology and without a full understanding of what gives nanoparticles their unique properties. The dawn of modern nanotechnology can be traced to Richard Feynman's 1959 Caltech speech, "There's Plenty of Room at the Bottom ***"Nano-composite''*** is a multiphase solid material which have one, two or three dimensional phases less than 100 nanometers (nm), or structures having nano-scale repeat distances between the different phases that make up the material".[1]

Bio-nano-composites add a new dimension to the properties of nano-composites, in that they are biocompatible and/or biodegradable materials. Bio-nano-composites forms combinations of multiple areas that brings together biology, materials science, and nanotechnology. New bio-nano-composites are impacting diverse areas, in particular, biomedical science.[2]In this review, biodegradable materials can be described as materials degraded and gradually absorbed and/or eliminated by the body, where degradation is caused mainly by hydrolysis or mediated by metabolic processes. These nanocomposites are extremely useful in diagnostic purposes yielding fast and accurate results.[3] Therefore, these nanocomposites are of immense interest to biomedical technologies such as tissue engineering, bone replacement / repair, dental applications, and controlled drug delivery.[4,5]

Structures of Nan composites:

The nanocomposites have similar size and structure as most of the biological molecules; therefore, nonmaterial's can be useful for both in vivo and in vitro biomedical research and applications. The integration of nanocomposite with biology has led to the development of diagnostic devices, contrast agents, analytical tools, physical therapy applications, and drug delivery vehicles.[2,3,4]Nanoparticles possess certain size-dependent properties and particularly with respect to optical and magnetic parameters. Now the size and shape of nano particles can be tailor made too.[6]The structure of nanocomposites usually consists of the matrix material containing the nano-sized reinforcement components in the form of particles, whiskers, fibers, nanotubes etc.[1]Table 1 presents the detail list of different Nano-composites.

Table 1: Nano-compositesStructure and Applications

Nano-composites	Structures	Applications
Nano composite cantilevers-Ultrathin[7]		-High-throughput screening -DNA mutation detection -Diseases protein biomarker detection - provide sensor arrays
Nano composite Carbon nanotubes[8]		-DNA mutation detection -Disease protein biomarker detection -Tissue engineering -Drug delivery
Nano composite Dendrimers Eg.cisplatin and PLK-1 siRNA loaded PLGA dendrimer immune nano-composites[9]		-Image contrast detection - Cancer therapy
Nano composite crystals Eg.Cellulose nano-crystal with PVA and AgNP[10]		- Increased the modulus and tensile strength of the films - Decreased the brittleness of the films. -Biocompatible materials in tissue engineering
Nano composite Eg.Nano-shells[11]		-Tumor-specific imaging - Therapy
Nano composite Nanowire Eg.nanocomposite of silicon nanowire and polythiophene[12]		-High-throughtput screening -Disease protein biomarker detection -DNA mutation detection
Nano composite Quantum dots- Eg.CdS QDs–PAMAM–Apt). nano-composites[13]		-Optical detection of gene and protein in animal model and bioassay -Tumor and lymph node visualization

SCOPE

The nano-composite plays an important role in biomedical application as drug carriers, wound healing agents due to their high water/solvent holding capacity. Multilevel imaging by advanced nano size fluorophores vindicates the need for the development of these which can be used in all kinds of labelling (cellular and in-vitro labeling for diagnosis and studies concerning metabolic pathways) and imaging techniques, such as PET, SPECT, MRI, CT, TEM and co focal microscopy etc.Fluorescent Nan composites of noble metals and quantum dots find a wide range of applications in multiplex bioimaging, biolebelling and as biosensors. This is possible due to their unique properties such as tunable shape, size, spectral and fluorescence emissions, stability to photo bleaching and biocompatibility, nontoxic nature.[14]

Currently used procedures of detection and identification of bacterial infections are laborious, time-consuming, and require a high workload and well-equipped laboratories. Therefore by using nanotechnology new method was developed based on hydroxypeptite nanoparticles with fluorogenic substrate which is simple, fast, and low cost method of bacterial detection.

For early detection of bacteria by visual and fluorescence spectroscopy techniques the calcium phosphate ceramic nanoparticles were characterized and integrated with a nutritive mixture. This method involves the enzyme β-glucuronidase which cleave the substrate, 4-methylumbelliferyl-p-D-glucuronide (MUG).[1,3]Figure 1 representing the mechanism of bacterial detection by production of fluorescence signal.

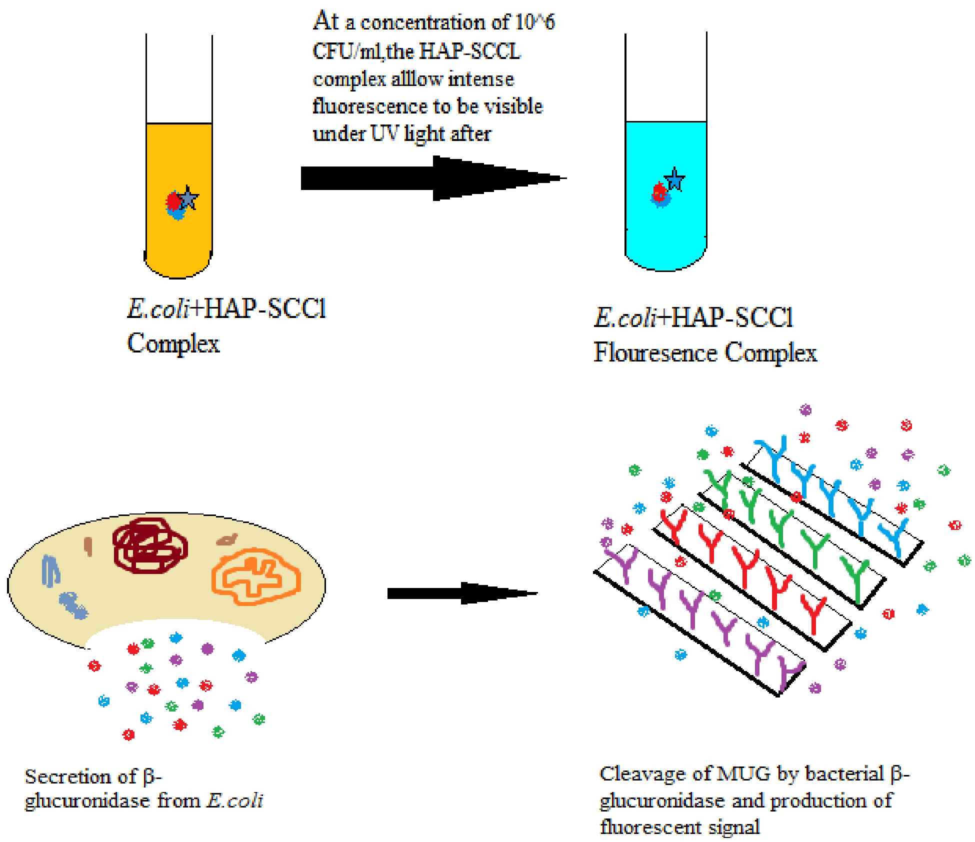


Fig 1: Mechanism of production of fluorescent signal

A study on the antibacterial activity of copper nanostructures combined with biopolymers such as cellulose was carried out for *Staphylococcus aureus* and *Klebsiella pneumoniae*, as pathogens. The results showed that the chemical nature and morphology of the nano-fillers have great effect on the antibacterial activity, which increases with increasing CuNP content in the composites.[8]

Eco-friendly synthesis of Chitosan-PVA-Silver (CPSNP) nanocomposite was achieved for sustained release of aspirin which only reaffirms their increasing biomedical applications especially for therapeutic purposes. The swelling capacity and anti-microbial activity was appreciable in view of their wound healing applications and demonstrated significant effects against *E. coli*, *Pseudomonas* sp., *Staphylococcus* sp. and *Klebsiella* sp. Drug loading efficiency (LE), encapsulation efficiency (EE) and i*n vitro* drug release of aspirin as the model drug from the nanocomposite was highly efficient. Thus the Chitosan-PVA-Silver (CPSNP) nanocomposite as a controlled drug delivery system is a workable model.[2]

For enhanced targeted therapeutic efficacy and safety purpose,combination of therapeutic and diagnostic which results in 'Theranostics' was developed.Integrated theranostic nanoagents can deliver diagnostic imaging agents capable of detecting and monitoring the early onset of diseases and simultaneously transport suitable therapeutics over a prolonged period in order to enhance therapeutic efficacy.[4]

Several Nanocomposite-Polymer complexes (Table 2) and Metal nanocomposites (Table 3) are listed with their multifaceted applications.

Table 2: Nan composite-Polymer complexes and their Applications

NANOPARTICLES	POLYMER	APPLICATIONS
Cloisite[15]	Ethylene vinyl Acetate	Used to increase adhesion and growth of human dermal fibroblasts
Cloisite [15]	Polyurethanes	5 fold lower permeability towards water vapor and enhanced mechanical properties
Laponite[15]	poly(N-isopropylacrylamide) hydro gels (PNIPAM)	Ultrahigh elongation with near-complete recovery, rapid de-swelling responses to temperature changes and large equilibrium swellings were observed due to addition of Limonite to the polymeric matrix.
Laponite[15] Laponite[15]	PNIPAM poly(ethylene oxide)(PEO)	Cell sheet easily detached by changing temperature. Cells cultured on the surfaces of PEO-Laponite gels attached and proliferated easily.
Cloisite[15]	Poly(ethylene-co-vinyl acetate)	Used for drug delivery- Addition of nanoparticle resulted in slower release ofdexamethasone. Moreover, release kinetics were dependent on the aspect ratio and degree of dispersion of thenanoparticle
Laponite[15]	Pluronic	Used for drug delivery- A temperature dependent sol-gel transition was observed in the nanocomposites. Laponite enhanced the dissolution resistant properties of the hydro gels and release of entrapped macromolecular drug was slowed down
Bentonite[15]	Acrylic acid-PEG methyl ether acrylate	Used for drug delivery- Elution kinetics strongly depended on the interactions between the surface charges of the clay and the drug
Laponite[15]	PEO-Polyamide	Used for drug delivery- Molecular interactions between Laponite and drug resulted in sustained release profiles
Cellulose and Copper[16]	Poly(vinyl alcohol)(PVA)	Similar to Ciprofloxacin and used for wound dressing. Antibacterial Activity of Nan composites of Copper and Cellulose
Flax cellulose nanocrystals[17]	Starch	Used to improve the mechanical properties and water resistance of the starch-based materials
Silver Nanoparticles[18]	Chitin	Used in wound healing applications
Cellulose nanofibres[19]	Poly(vinyl alcohol) (PVA)	Applications in cosmetic industries
Silver nanoparticles[20]	Chitin	Antimicrobial activity and Wound healing
Silver nanoparticles[21]	Chitosan/ polyethylene glycol	Drug Delivery system
Silver Nanoparticles[2]	Chitosan- Poly(vinyl alcohol) (PVA)	Drug Delivery system
Cellulose[15]	Polyvinyl alcohol	As taste sensing material
Silicon oxide(SiO_2)[22]	Polylactic acid	For Tissue engineering
Metal nanoparticles[23]	Hydroxyl petite polymer	Tissue engineering

Silica[15]	Chitin	Chitinous organic matrix provided a template for bio-directed deposition of the silicate mineral phase.
Silica[15]	Chitosan	Improved mechanical properties observed due to addition of bioglass. Bioglass aided in significant increase in cell adhesion, proliferation and alkaline phosphatase activity. Enhanced bone regeneration observed when the nanocomposite was implanted in vivo.
Silica[15]	Collagen	Improved bioactivity of the material; accelerated the formation of bone-like apatite and led to the differentiation of human monocytes into osteoclast-like cells.
Bioglass[15] Bio glass[15]	PLA Poly L-lactide	Addition of bioglass fiber enhanced in vitro bioactivity of the nanocomposite. Significant increase in alkaline phosphatase activity observed in nanocomposite compared to pure PLA. Increase in bioglass concentration reduced water absorption capacity but enhanced degradation rate.
Bioglass[15]	Chitosan & Chitosan-Gelatin	Bioactive nanocomposite scaffolds promoted osteoblast cell adhesion and spreading.

Table 3: Metal nanocomposites and their Applications

NANOCOMPOSITES	APPLICATIONS
Fe/MgO[24]	Catalysts, magnetic devices.
Ni/PZT[24]	Wear resistant coatings and thermally graded coatings.
Ni/$_{TiO2}$[24]	Photo-electrochemical applications.
Al/SiC[24]	Aerospace, naval and automotive structures.
Cu/Al_2O_3[24]	Electronic packaging.
Al/AlN[24]	Microelectronic industry.
Ni/TiN, Ni/ZrN[24]	High speed machinery, tooling.
Cu/ZrN[24]	Optical and magnetic storage materials.
Nb/Cu[24]	Structural materials for high temperature applications.
$Fe/Fe_{23}C_6/Fe_3B$[24]	Structural materials.
Fe/TiN[24]	Catalysts.
Al/ Al_2O_3[24]	Microelectronic industry.
Au/Ag[24]	Microelectronics, optical devices, light energy conversion
Pd/Chitosan[25]	Catalytic and antibacterial activity
Pd-Chitosan/Starch[25]	Suzuki-Miyaura reaction
Au/Pt[25]	Measles virus diagnosis

Highlights of different applications of nanocomposites[15] are shown in Figure 2.

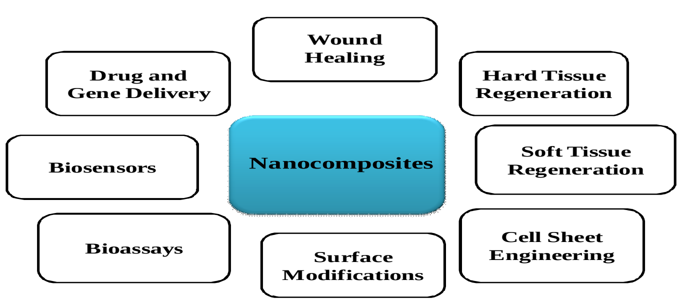


Fig 2:Applications of Nanocomposites

1. **Rapid and Economical**: Nan composites are widely applied in clinical laboratories for bacterial detection in human samples due to the reduced costs of reagents and equipment. In addition, chromogenic and fluorogenic methods have been developed for faster and more accurate detection and identification of microbes. These methods can provide data in a shorter time with higher accuracy (95%–100%) than those based on current methods.[24]

2. **Antibacterial activity**: Antimicrobial tests revealed that the Cu nanocomposites have antibacterial action for both bacteria, though with a more pronounced effect in respect to *Staphylococcus aureus* and *Klebsiella pneumonia*.[26]It has been also reported that photosynthesized palladium nanoparticles showed the bactericidal activity against both Gram Negative as well as Gram Positive bacteria.Polyaniline/Pd-Pt nanocomposite are showing the superior antimicrobial activity.[27]

3. **Drug Delivery and Thermal Ablation**: Gold nanoshells-hydrogels composite materials have been located with protein and then illuminated at the Plasmon resonancestimulate release and shrinking the hydrogels. The nanoshells caused enhanced drug release and enable multiple bursts of protein by modulated heating. Such devices could have significant drug delivery applications, especially if the stimulant radiation can be administered exogenously to NIR resonant nanoparticles.[28]It is reported thatChitosan-montmorillonite (Cs-Mnt) nanocomposite showed increased drug release profile.Mantmorillonite is a clay of soft phylosilicate mineral group.Some properties of mantmorillonite clay which are contributing to drug delivery are-large surface area which shows good cation exchange capacity, adsorption capacity, adhesive ability and drug carrying capability.[29]

4. **Biomedical imaging contrast**: From a single gold nanoparticle the Plasmon resonant scattering produces brighter signal as compared to other single fluorophores,fluorescent beads or quantum dots in microscopic imaging application. The large nanoparticle size relative to fluorophores and quantum dots may limit intracellular imaging application. The two-photon luminescence from NIR resonant gold nanorods has been used to monitor microscopic blood flow in vivo.[28]

5.Biosensors: An important goal for biosensors is the capability of continuously monitoring concentrations of specific targets in a simple and reliable manner within the physico-chemical and biological constrains of their microenvironment .Recognition-based biosensors capable of specifically detecting chemical and bio-agents in their environment are under active development using fluorescent metal nanos. Huang et al. developed new competitive homogeneous for analyzing proteins using bioconjugated photoluminescent Au nanodots as donors and bioconjugated spherical Au nanoparticles as accepters. An oligonucleotide Aptamer(Apt) has a higher affinity for specific proteins such as a breast cancer marker protein, platelet-derived growth factor (PDGF).Nanoclusters of PDGF-modified fluorescent gold nanoparticles can attach onto Apt-modified particles, consequently resulting in fluorescence quenching ("off" state) through resonance energy transfer. Addition of free PDGF can further recover the fluorescence of PDGF-modified nanoclusters through the competitive binding, releasing the quenched nanocluster to "on" state.Another example of sensing proteins, are capable of sensing concanavalin A with high sensitivity and remarkable selectivity over other proteins and lectins also has the capability of binding, yielding brightly fluorescent cell.[28] Different Nanocomposites are used as biosensor by various techniques (Table 4)

Table 4: List of Nanocopmosite biosensors

NANOCOMPOSITE BIOSENSOR	SUBSTANCE TO BE MONITORED	TECHNIQUE
Fluorescent gold NC(AuNC@MUA)[1]	Mercury Hg(II)	FluorescenceQuenching
glutathione-protected gold nano(AuNC@GSH)[1]	Calcium Ca2+	FluorescenceQuenching
fluorescent mannose-protected Au NCs AuNC@Man[1]	FimH of type 1 in E. coli	Fluorescence microscopy
Aptamer modified NCs[1]	PDGF (a breast cancer marker)	Fluorescence microscopy
Reduced graphene oxide-Chitosan NCs[27]	Hydrogen peroxide	Electrochemical detection
Chitosan-graphene/glucose oxidase NCs[27]	Glucose	Electrochemical detection

6. Bioimaging: Multilevel imaging from molecular to medical scales demonstrates the need for the development of advanced nano-size florophores that can be used in all kinds of labelling and imaging techniques, such as PET, SPECT, MRI, CT, TEM and confocal microscopy etc. Tunablefluorescence, strong quantum-size confinement ,stability to photo bleaching, higher biocompatibility these novel optical properties render the fluorescent noble-metal ,quantum dots(QD's) ideal fluorophores for multicolor and multiplexing applications in biomedical engineering and molecular biotechnology.[8,14]The semiconductor quantum dots (QDs) have already become a new class of fluorescent labels due to their unique optical properties as well as offering potential invaluable benefits such as cancer targeting and biomedical imaging. QDs containing heavy metals are unsuitable for in vivo clinical use because of their toxic, and may pose risks to human health as well as the environment under certain conditions. In contrast to QDs and organic dyes noble metal nano-clusters (NCs) are highly attractive for bioimaging and bio labeling applications due to their low toxicity as well as its ultra-fine size.The labeling of endothelial cells with fluorescent gold NCs was found to detect cellular functions including angiogenesis, vasodilatation, coagulation, adhesion, and junction integrity. Humanfluorescent gold nanocluster-labeled late endothelial progenitor cells also possessed angiogenic potential in vitro and in vivo.[28]Various Magnetic Fluorescent nanocomposites are depicted in Fig.3.

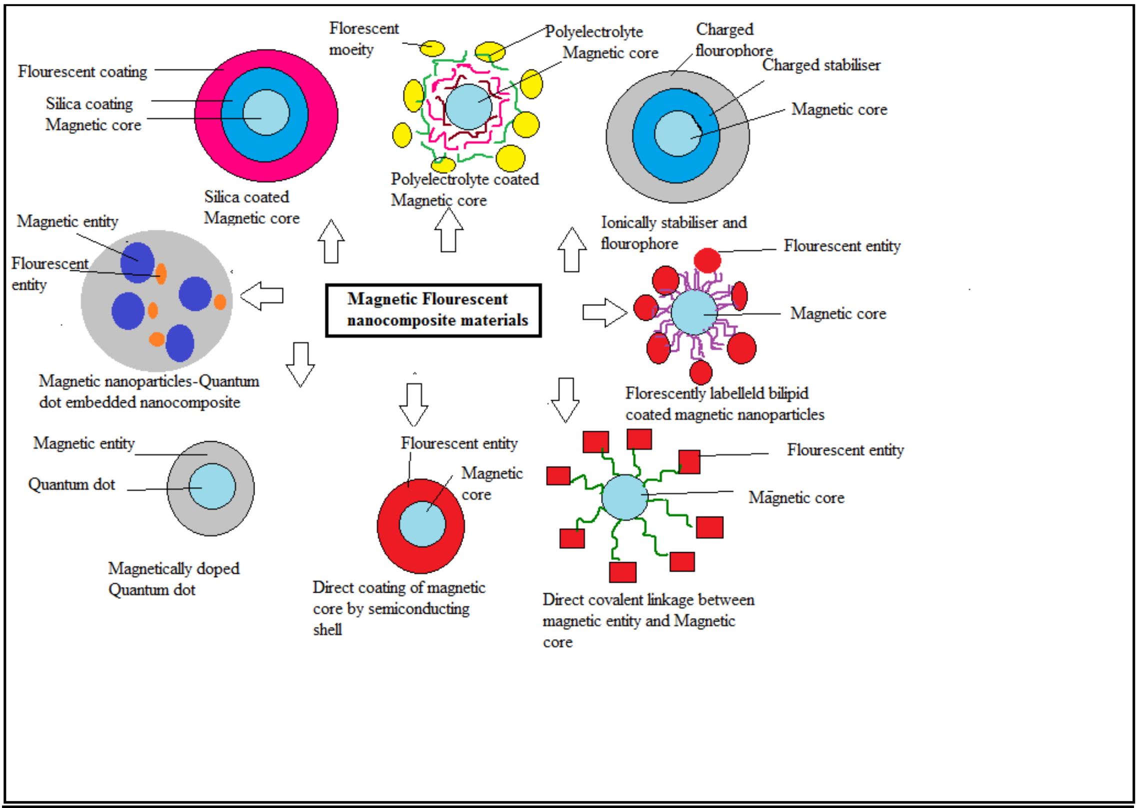


Fig 3.Magnetic-Florescent Nanocomposites Material

7. Tissueregeneration: Bone defects, ranging from small voids to large segmental defects are a prevalent and persistent problem in clinical orthopedics and dentistry. Bone defects arise from a variety of causes including fracture nonunion, dental and orthopedic implant fixation, trauma or tumor resection, periodontitis, and musculoskeletal disorders such as rheumatoid arthritis. So in these clinical circumstances, bone repair and regeneration and can be accelerated by using natural and synthetic bone grafts are desired to ensure rapid restoration of skeletal function. Hence, Nanocomposite polymer scaffolds for tissue engineering are prepared.[29]Perspective materials for production of new generation of scaffolds for bone tissue regeneration are polymeric-based nanocomposites, which plays a role of an artificial extra-cellular matrix (ECM) which serves as temporary support where isolated cells are introducedto form a tissue (Fig 4). These scaffold should be biocompatible, biodegradable, promote cell attachment andmechanically stable. The ideal scaffold should possess mechanical propertiesadequate to support growing bone tissue, degrade uponbone tissue growth and have high porosity with interconnectingpores enabling ingrowth of osteoblasts cells. The new direction in tissue engineering is modificationof a polymer matrix with nanoparticles which caninfluence on mechanical, electrical, physicochemical andbiological properties much more suitable for human body. Bioactive compounds of nanocomposite materials can be prepared with silica (SiO_2), hydroxyapatite (HA), tricalciumphosphate (TCP) or carbon nanotubes (CNT).Silica

(SiO_2) plays a fundamental role in bioactive glasses becausesilanolan groups interact with calcium and phosphate ions forming an amorphous calcium phosphate which also can be found in the natural bone. Polylactic based nanocomposite scaffolds containing SiO_2 as a ceramic bioactive nanoadditive were prepared. Preliminary studies showed that 2 wt. % of the nanofiller improves mechanical properties. It was observed that small amount of the nano-filler resulted in increasing proliferation of osteoblast-like cells contacted with PL/DLA. The studies proved that nano-SiO_2 altered so far inert polymeric material to bioactive one.[30]

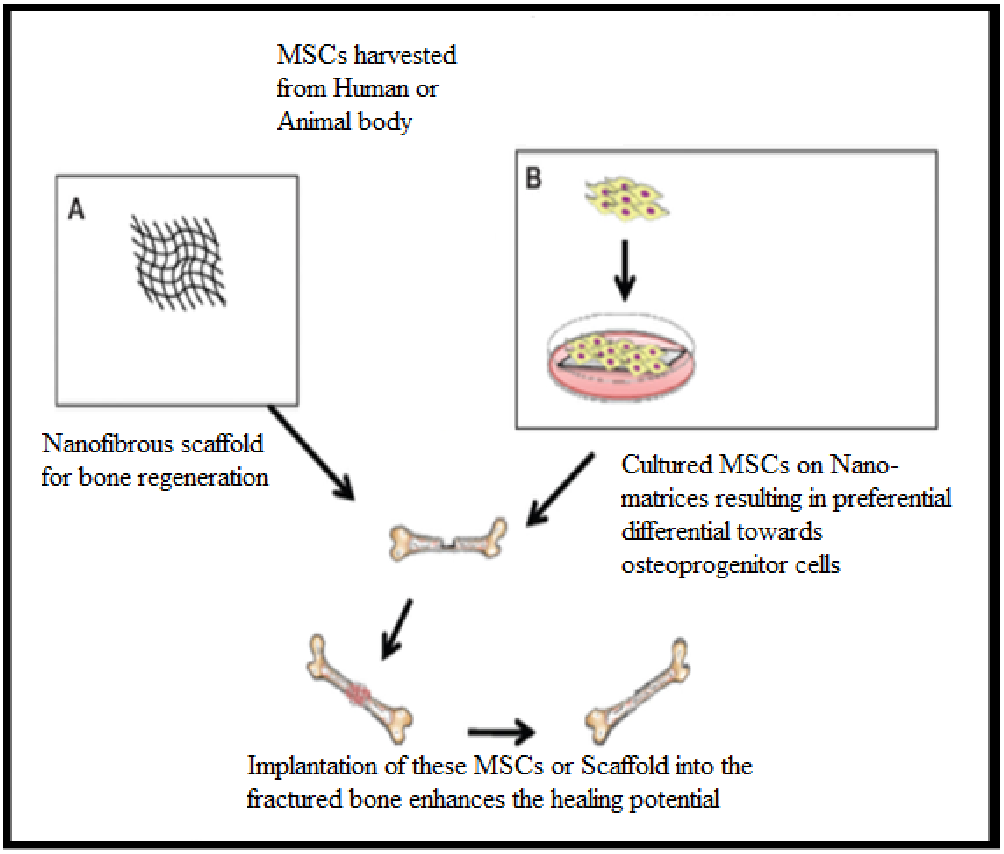


Fig 4.Tissue Regeneration by Nanotechnology

CONCLUSION

Nanotechnology is an emerging field which has immense applicationespeciallyin the field of medicine. Nanocomposites are used for diagnosis and therapy.Metal nanocomposites play different roles as optical and magnetic storage materials, structural material for high temperature appliacations.Some nanocomposites are used asbiosensors. Fluorescencelabeled magnetic nanocomposites are playing important role in bioimaging.

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