RECENT ADVANCES OF MAGNETIC NANOPARTICLES IN BIOMEDICAL APPLICATIONS: A REVIEW

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Abstract: **MNP-based nano-emulsion formulations provide a strong platform for the straightforward administration of complex and high molecular weight medications. The formula is a versatile distribution strategy that can accommodate a wide range of therapeutic compounds with varying physical and chemical properties. The primary purpose of this article is to demonstrate the potential of MNP Technology for drug administration with minimum solubility in the aqueous and oil phases, as well as the product's optimal site penetration and stability.**

Index Terms**: Green chemistry, Benign Chemistry,Environment, Sustainability.**

INTRODUCTION

MNP is an abbreviation for Micellar Nano Particles, a multiphasic nano-emulsion, nanoengineered, and nanotechnology-based formulation used primarily in the domains of efficient ophthalmic and transdermal drug administration. The application of a pharmacologically active chemical to the skin/eye to obtain therapeutic levels of medication in the skin/receptors in order to treat disorders far from the site of application is known as ophthalmic and topical delivery. MNP-based nanoemulsions are suitable for systemic medication delivery via topical administration. The method enables appropriate medication concentrations to permeate the skin/cornea and generate a drug depot in the stratum corneum, epidermis, or corneal receptors. These MNP-based nano-emulsions are often constructed to have a diameter of 100 nanometers or less in order to allow for simple penetration.

Background of MNP [1,2,3]

For many years, it has been known that tiny particles, such as those less than one millimetre in diameter, allow for faster skin penetration than bigger ones. The limited amount of medicine delivered in minuscule particles, on the other hand, has its own set of constraints. Many APIs, such as natural and synthetic hormones, are poorly soluble, making it difficult to create a stable particulate system. Micellar nanoparticles are very useful in developing stable formulations that can deliver both hydrophilic and lipophilic medicines topically through the skin or ocular surface. These MNP are oil-encapsulated submicron-sized particles that are stable in emulsion forms and may be designed to achieve the appropriate release profile.

Rationalization [1,2]

MNP formulations are founded on the premise that a multiphasic formulation includes nano-sized particles capable of delivering a wide range of material classes. MNP formulations are ideal for delivering compounds that are soluble in alcohol but have low solubility in aqueous and oil systems. MNP technology is suited for creating particles with diameters less than 500 nanometers that may be developed for targeted medication delivery. MNP technology can potentially be used to deliver medications with a high molecular weight.

MNP Structures[1]

There are five basic components of an MNP system:

- One or more APIs
- Solvent
- Stabilizer
- Oil
- Aqueous medium

The aforesaid blend's strong milling operation will allow the medication to be present in one or more composite fractions. This will generate consistent nano-sized globules with particle sizes ranging from 100 to 500 nm. The pressure supplied to the mixers ranges from 10,000 to 20,000 psi with varying cycles depending on the blend qualities.

Characterization of MNP Technology

Parameters to be evaluated in MNP formulations are:

- Globule Size Distribution:
- Average Globule Diameter: Polydispersity Index
- Surface Charge: Zeta Potential
- Viscosity Determination: By Brookfield Viscometer.
- Refractive Index
- Drug Content: By HPLC
- Morphology and Structure analysis: By TEM
- Thermodynamic Stability Studies: By Stress test

- In vitro Skin Permeation Studies

SYNTHESIS OF MNPs

The creation of nanoparticles requires careful attention throughout its multistep process. The process must be adjusted throughout the early stages of synthesis since even little changes in the overall process might result in a significant change in the desired product. [17] As a result, the chemical and physical characteristics of the manufactured nanoparticle must be closely regulated to assure success HIGHLIGHTS analysed recent advances in the synthesis and functionalization of magnetic nanoparticles (MNPs) analysed the toxicity of MNPs in biomedical applications analysed the current state of FDA approved MNPs in the biomedical field emphasised the challenges and research scope of MNPs in the biomedical field.

Investigated current advancements in MNP-assisted CRISPR-Cas9-mediated gene editing Reviewed the present status of imaging modalities in biological applications such as MRI, MPI, CT, and PET. Magnetic nanoparticles may be created in a variety of methods. The particles can be created in either a "top-down" or a "bottom-up" manner. The "top-down" approach entails high intensity ball milling of a magnetic sample until the appropriate nanoscale size is obtained. [18] The benefit of the "top-down" technique is that a large number of particles may be produced in a single batch; however, control over particle shape and size is impaired, which is critical in biological applications. [18] Starting with a salt of ferrous (Fe2+) or ferric (Fe3+) ion and going through a distinct chemical process to nucleate and stimulate seeded development to grow particles to the appropriate hydrodynamic diameter, the "bottom-up" approach is used. [19] Various "bottom-up" techniques have been mentioned in the literature. [20–22] Co-precipitation,[23-27] hydrothermal technique,[28-31] thermal decomposition method,[32-39] and polyol method are the most often described methods. [40–43] Flow injection technique, microwave-assisted, solvothermal, sol-gel, sonochemical, chemical vapour deposition, physical vapour deposition, electrodeposition, combustion, laser pyrolysis, preparation inside micelles, carbon ARC, and microemulsion are some of the other ways. [44] However, several technologies have been used to create nanoparticles of diverse sizes and forms, such as spherical, pallet, hierarchical superstructures, nanorods, nanotubes, and so on. [17]

Co-precipitation

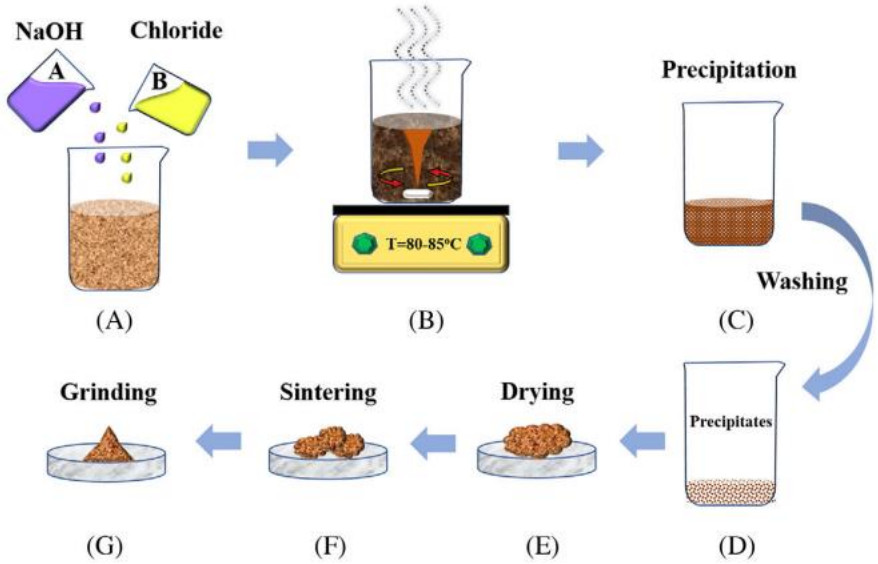

Fig 1: Steps to synthesize ferrite nanoparticles using co-precipitation method: (A) solution of NaOH and chloride precursors, (B) stirring at 80–85°C for 1 hour, (C) precipitation, (D) precipitates after washing, (E) drying at 80°C, (F) sintering at 1100°C, and (G) grinded final product

In general, the co-precipitation process begins with a 2:1 ratio of ferrous and ferric salts and a basic condition at ambient temperature or high temperature (80-85C). [49] Various bases, such as NaOH or NH4Cl, are used to create the basic state. [50] When the reaction is finished, precipitation develops in the bottom of the reactor, and further washing, drying, sintering, and grinding results in MNPs. [51] The coprecipitation technique of nanoparticle creation is depicted in Figure 1. The reaction may be represented as Equations (1)-(3) during the co-precipitation method:

$$Fe2+ + 2OH- \rightarrow Fe(OH)2 \quad (1)$$

$$Fe3+ + 3OH- \rightarrow Fe(OH)3 \quad (2)$$

$$Fe(OH)2 + 2Fe(OH)3 \rightarrow Fe3O4 + 4H2O \quad (3)$$

The aggregation of nanoparticles is quite typical during this preparation procedure because nanoparticles have a higher specific surface and a high surface energy due to their small particle size. In addition, the impact of alkali, reaction temperature, and emulsifier should be well monitored since they dominate the created nanoparticles. [17] Furthermore, maintaining a homogeneous and monodisperse particle shape during both the synthesis and purification processes is extremely difficult. [47]

Hydrothermal

The hydrothermal method (also called solvothermal method) is considered the most popular wet chemical approach to produce inorganic nanoparticles, particularly metal and oxides.[17]

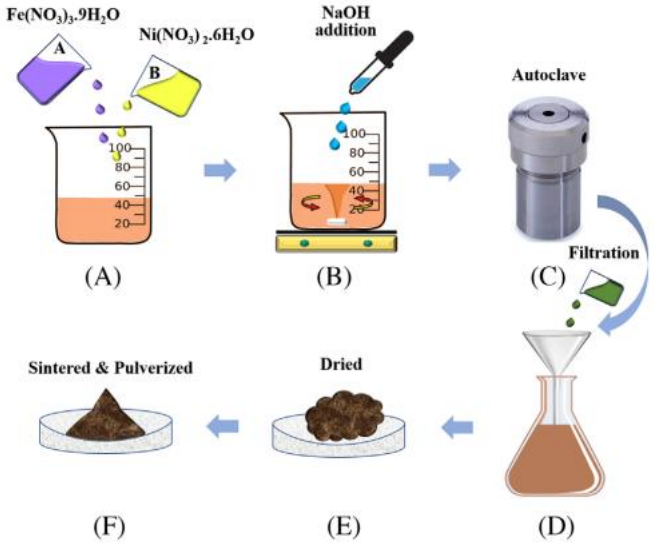

FIGURE 2 Illustration of (NiFe2O4/Fe2O3) nanocomposite synthesis via hydrothermal method: (A) addition of Fe(NO3)3·9H2O and Ni(NO3)2·6H2O precursors, (B) magnetic stirring during the addition of NaOH(1 M) until to pH 12, (C) autoclave the mixture for 20 hours at 180°C, (D) filtration, (E) drying at 100°C, and (F) annealed in the air for 2 hours at 400-800°C and pulverized to get the final product

Wet-chemical approaches for crystallisation in a sealed container are often used in the hydrothermal procedure. [17] The aqueous solution in the container is held at high pressure and temperature (130-250 C) (0.3–4 MPa). [17] The hydrothermal technique often yields bigger diameter NPs. [17] Fe3O4 NPs with a diameter of 27 nm were generated in the presence of a surfactant such as sodium bis sulfosuccinate. [17] Alternatively, at 140 C for 6 hours, Fe3O4 powder with a diameter of 40 nm was created using this procedure. [17] Tuning nanomaterials from a few nanometers to hundreds of nanometers is conceivable using the hydrothermal technique. [52–54] In general, the concentration of the precursors, the total duration of the reaction, and the reaction temperature all influence the size and dispersion of the synthesised nanoparticle.

Thermal decomposition

Thermal decomposition is a well-known process for the sequential production of different nanoparticles. [17] It also allows for fine-tuning of the mean diameter of the generated particles. [56] The two most fundamental methods of producing thermal breakdown are "heating-up" and "hot-injection." During the heating-up process, nanoparticles begin clustering and developing by continuously heating pre-mixed precursor materials, solvent, and surfactant to a particular temperature range. [33,57] When the reagent is introduced into heated surfactant via a controlled growth phase, quick and consistent nucleation occurs. [17] However, both techniques generally include the breakdown of precursors in the presence of organic surfactants to create the desired nanoparticles. [58] Acetylacetonates and iron carbonyls are the most often utilised non-magnetic precursors, as are surfactants such as fatty acids, hexadecylamine, oleic acid, and so on. The optimal temperature range for producing nanoparticles with sizes ranging from 4 to 30 nm and a high degree of homogeneity is between 100 and 350 degrees Celsius. [56,59] Alternatively, monodisperse magnetite NPs with diameters ranging from 3 to 20 nm were produced in the presence of iron (III) acetylacetonate in phenyl ether and alcohol, oleic acid, and oleylamine at high temperatures (265 C). [17] When organometallic precursors (such as Fe (CO)5) are thermally degraded, metal NPs are formed. Further oxidation, on the other hand, results in monodisperse NPs. [17] In contrast, the breakdown of cationic metal precursors (such as Fe(acac)3) results in direct MNP production. [17] To synthesised nanoparticles, this approach provides good yield amount, particle size control, fine size distribution, crystallinity, and dispersibility. [17] The size of nanoparticles is an important parameter when using MRI; hence, nanoparticles created by thermal decomposition synthesis are one of the finest possibilities for this application. [48] For perfect control of the size and shape of the produced particles, the ratio of the precursors, such as organometallic compounds, surfactant, and solvent, as well as reaction duration and temperature, ageing period is crucial. [53] The thermal breakdown technique of nanoparticle manufacturing is depicted in Figure 3. [60]

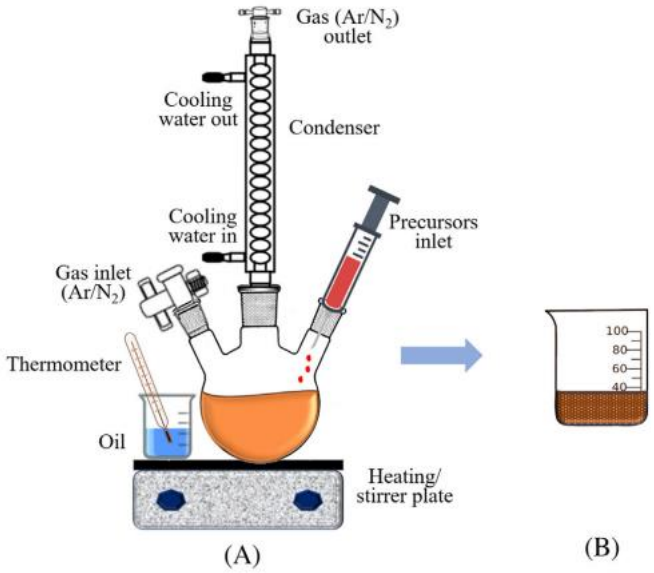

FIGURE 3 A) Experimental setup for nanoparticle synthesis following the thermal decomposition method. B) In this method, iron pentacarbonyl Fe(CO)5 was added to octyl ether, and oleic acid mixture at 100◦C then refluxed for 1 hour.

Dehydrated (CH3)3NO was added to the solution at room temperature and then again heated to 130◦C under an argon atmosphere for 2 hours. After the formation of a brown-colored solution, the temperature was increased slowly and refluxed for more than 1 hour. Ethanol was added to the mixture at room temperature to produce a black precipitate of γ-Fe2O3 nanoparticles and then separated by centrifuging[60]

Polyol method

Because polyols are water-comparable and have chelating properties, they are another extensively utilised technique for nanoparticle production. [17] . The polyol approach of nanoparticle production is depicted in Figure 4. In this technique, liquid polyol serves as a solvent for metallic precursors, a redcing agent, and, in certain situations, a cation complexing agent. [17] For less reducible metals, this solution is agitated and heated to a certain temperature (the boiling point of the polyol). [17] Heterogeneous nucleation can influence the size of these NPs (seeding the medium with foreign particles). [17] Diol dissolves or suspends precursor chemicals such as oxides and acetates (ethylene glycol or diethylene glycol). [17] The mixture is then heated to 180-199 degrees Celsius. [17] The NP size can be precisely controlled.

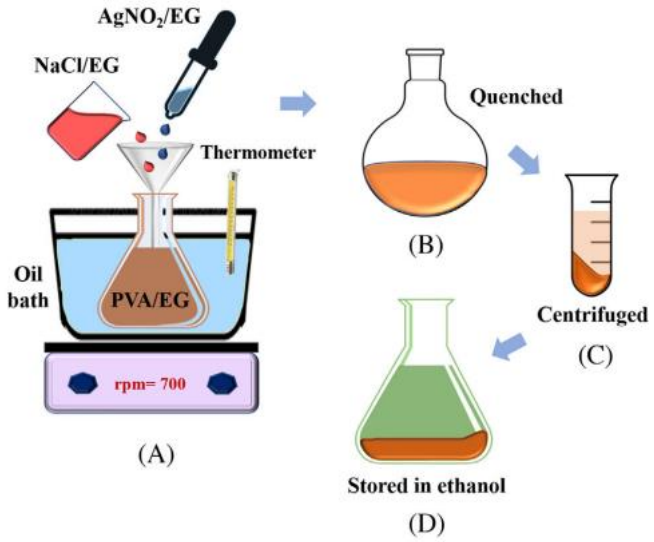

FIGURE 4 Steps to the synthesis of silver nanorods following polyol method: (A) NaCl/EG and AgNo3/EG are added to PVA/EG solution and stirred at 700 rmp using magnetic starrier, (B) quince at room temperature, (C) centrifuged at 6000 rpm, and (D) stored in ethanolby controlling the reaction temperature or nucleation process.[17]

This process may manufacture magnetic nanoparticles such as metal, metal oxides, and metal chalcogenides. This method can also yield bio-metallic clusters and nanocrystalline alloys. Using this technology, nanoparticles with uniform sizes, minimal agglomeration potential, and a high production rate may be created. The easy dissolving and suspending capabilities of oxides, acetates, and nitrates in diols allow for the production of nanoparticles at low temperatures, which is why this approach has gained popularity. This bottom-up method can produce huge batches of magnetic nanoparticles with ultra-small particle diameters ranging

from 1 nm to several microns with little or no agglomeration. [62] The particle size is determined by the organometallic precursors, polyol solvent type, water concentration, reaction duration, reaction temperature, heating technique, and so on. In general, the size of nanoparticles grows with increasing precursor concentration and water amount. Hot injection of starting materials and/or water aids in the formation of nanoparticles. [45] Polyols have been widely employed in industry because they are low-cost, environmentally friendly solvents. [17] However, re-oxidation caused by the protic polyol limits the production of less noble metals. [17] The temperature range for nanoparticle production is limited by rapid thermal breakdown around the boiling point. The solubility of the generated particles in polyol media might make the synthesis of nanoparticles with lowest size difficult at times. [45]

FUNCTIONALIZATION OF MNPs

Surface modification or functionalization is an essential aspect of magnetic nanoparticle (MNP) synthesis and application. Functionalized MNPs have been the focus of the biomedical application. The primary purposes of surface modification of MNPs are (1) to prevent agglomeration, (2) to improve surface catalytic activity, (3) to improve physiochemical and mechanical properties, and 4. To increase solubility and biocompatibility.[94] The functionalization process that gives MNPs their typical morphology can be one of the four types of core-shell structure, matrix dispersed structure, Janus structure, or shell-core-shell structure.[94,95] Surface functionalization can be done both in-situ (simultaneous synthesis and functionalization) and post-synthesis methods (functionalization after synthesis).[96] Surface functionalization of these MNPs is done using three mechanisms (1) ligand addition, (2) ligand exchange, (3) encapsulation.[96] The prevalence of functionalization groups facilitates the covalent bonds to the affinity ligands, and the balance between intermolecular forces drive the interaction between functional groups and nearby MNPs.[97] Between the mechanisms mentioned, encapsulation is the most widely used. It is the best method in terms of the materials available for coatingsince both organic material (polymers, surfactants) and inorganic material (silica, carbon, metal, metal oxides) can be used for encapsulation.[94] Functionalization with polymers is the most comprehensive used method for biomedical applications, especially in nanomedicine.[94] Dextran, chitosan, alginate, polyethylene glycol (PEG), polyvinyl alcohol (PVA), polydopamine (PDA), polysaccharide, polyethylenimine, polyvinylpyrrolidone (PVP), polyacid polyetherimide, and polyamidoamine (PAMAM) are the most commonly used polymers for the surface modification of MNPs.[94] PEG is a water-soluble polymer widely used for biomedical applications like magnetic resonance imaging (MRI) contrast agents for cancer visualization and biosensors.[94,98] Dextran is also a material with excellent biocompatibility, water solubility, and low cytotoxicity.[94,99] This dextran coated MNPs have been used for a biomedical application like in-vivo cancer drug carriers and MRI contrast agents.[94,100] Some polymers like PEI can be used to enhance the biocompatibility of MNPs and are used in cancer cell separation and hypothermia.[94,101] Other polymers like PVP are used to kill breast cancer agents, whereas PVA, 13olyacrylic acids are used in anticancer drug delivery applications.[94] Polydopamine formed from dopamine at a low pH has been used as a biosensor and catalyst for biological reactions.[94] Chitosan (a hydrophilic polymer) has low toxicity, good compatibility, and it can also be used with other polymers like PEG and PAA.[94] Chitosan functionalized MNPs have been used in MRI imaging, microwave therapy, hyperthermia, and tissue engineering applications.[94,102]

TABLE 1 MNP synthesis methods with their advantages and disadvantages

Method	Advantages	Disadvantages
Co-precipitation	• Rapid reaction • Mild reaction conditions • Can be produced in large batches	• Poor size distribution • Low reproducibility • Surface oxidation
Hydrothermal	• Superior control in size, shape, dispersion • Magnetic controllability • Excellent crystallinity • Eco friendly	• High temperature and pressure • Longer synthesis time • Adsorption of capping agents
Thermal decomposition	• High yield • Superior size distribution • High reproducibility	• Safety issues for high temperature andpressure • Solubility in organic solvents • Toxicity
Polyol	• Chelating effect • Bio(water)compatibility • Low cost industrial application	• Difficult to synthesize small size-particles • Instable oxidation

BIOMEDICAL APPLICATIONS OFMNPs

Magnetic nanoparticles are an excellent choice as drug delivery module due to their high surface area to volume ratio, low toxicity, and high targeting efficacy.[116] More-over, magnetic nanoparticles are being used in magnetic hyperthermia to reduce tumor volume and eradicate can- cer cells from a targeted region.[117] Magnetic biosepara- tion is useful in case of separating a specific molecule froma library of different molecules.[118] For instance, mag- netic bioseparation is being used to isolate viral RNA to further analyze using polymerase chain reaction (PCR) method.[119] Furthermore, magnetic particles have imag- ing properties that make these particles excellent choice as multimodal theranostics platform, which enables us to perform diagnostics and therapy simultaneously.[117] Mag- netic resonance imaging (MRI), magnetic particle imaging(MPI), computed tomography (CT), and positron emissiontomography (PET) are major imaging techniques that uti-lize the magnetic properties of the particles. In this section,we will briefly discuss different usage of magnetic particles in the biomedical field.

TABLE 2 Different functionalization material and biomedical application associated with MNPs

Material	**Biomedical Applications**
Silica	Drug delivery, biosensor, toxicity studies
Carbon	Drug delivery, cancer treatment
Polyvinylvinyl pyrrolidone (PVP)	MRI contrast agent, drug delivery for breast cancer
Dextran	MRI imaging, drug delivery, diagnostic agent
Chitosan	Magnetic hypothermia, tissue engineering, imaging, drug delivery
Polyvinyl alcohol (PVA)	Imaging, drug delivery, biosensor, toxicity studies
Gelatin	MRI imaging, gelling agent, emulsifier
Amino acids	Radio-labeling for PET/CT imaging, cancer detection
Aminosilane	Drug delivery, viability studies
Lipids	Gene therapy, multi-modal imaging
Polyethylenimine (PEI)	Cell separation, hyperthermia, drug delivery
3-aminopropyltriethyloxysilane (APTES)	MRI imaging, heavy molecule adsorption

DRUG OR GENE DELIVERY

The recent progress in the field of nanoscaled drugs/gene carriers such as micelles,[120,121] liposomes,[122,123] hydrogels,[124] dendrimers,[125] and mesoporous silica nanoparticles [126] is phenomenal. Still, these nanocarrier suffers from some challenges such as off-targeting accu- mulation of carriers,[127] low penetration through blood brain barrier (BBB),[125] low circulating time in blood,[122] low physical and chemical stability,[123] premature releaseof cargo molecules [128] and low drug loading efficacy.[123] These challenges can be addressed by incorporating magnetic nanoparticles with these nanocarriers to create unique magnetic nanocomposites (MNCs). Figure 5 illustrates commonly used magnetic nanocomposites for drug and gene delivery. Drug/gene molecules can be attached to the surface ligand of magnetic nanoparticles

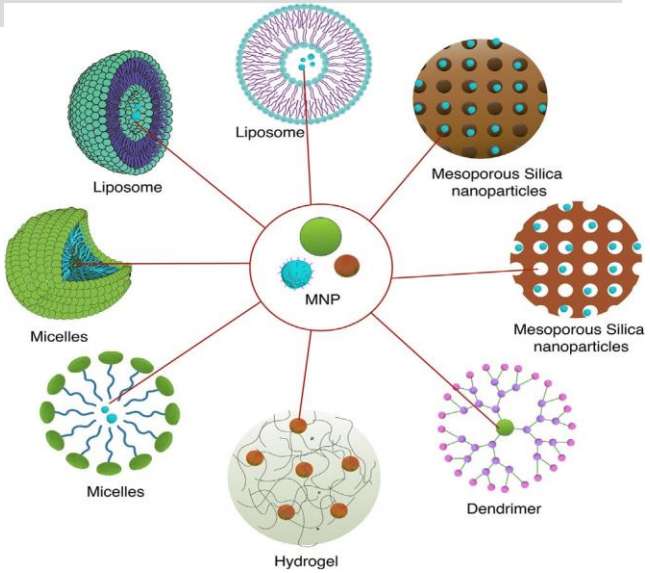

FIGURE 5 Different nanocomposite containing magnetic nanoparticles. The high surface area of the nanoparticles loaded inside the nanocarriers makes them excellent choices for drug and gene delivery module

either by physicochemical interaction or electrostatic interaction.[129] Later, these MNCs can be used to delivercargo to the targeted sites under the influence of an exter-nal magnetic field.[130] Furthermore, magnetic particles can be utilized as on demand and controlled therapeutic agent release platform into desired sites.[131] Externalstimuli such as alternating magnetic field can be usedto release attached therapeutic molecules into targetedlocalized region.[130] In this section, different types of nanocarriers incorporated with magnetic particles to increase the overall efficacy of drug/gene delivery will be discussed.

H y d r o g e l

Magnetic hydrogel nanocomposites are being evalu- ated for various biomedical applications such as wound healing,[132] nerve repair [133] and controlled drug delivery.[134–136] As mentioned earlier, magnetic particle exhibits low biotoxicity and have a high surface area to volume ratio, which makes them preeminent candidateto be used in hydrogel matrix as a carrier for therapeutic molecules. Recently, Chitosan (CS) and polyacrylic acid (PAA) coated 94 nm iron oxide magnetic nanoparticles showed promising potentiality as a drug carrier moduleto deliver anticancer drug 5- fluorouracil.[137] The drug loading capacity of CS/PAA/Fe_3O_4 was reported as 100%; however, these nanocarrier suffers from initial burst release of 40% of the loaded drugs which can introduce challenges in certain applications where sustained releaseis paramount.[138] To surmount initial burst release challenge, Hyati et al. [139] reported a temperature, pH and magnetic triple sensitive nanogel hydrogel compositefor controlled drug release to the targeted site. Briefly, Hyati et al. incorporated magnetic nanoparticles into poly(*N*-isopropylacrylamide)-co-((2-dimethylaminoethyl) methacrylate) (PNIPAM-co-PDMA) which was then grafted onto sodium alginate as a biocompatible polymer.The drug release profile of these 9-11 nm nanoparticles were studied at varying pH, varying temperatures and in the presence and absence of an alternating magnetic field (AMF). The release profile exhibits no initial burst releaseof the loaded doxorubicin (DOX) drug which overcomes the inherent challenges with many other drug carriers. Although we have mentioned one of the prominent characteristics of magnetic particles being inherently low-toxic, they still can induce toxicity in certain applica-tions, especially in sensitive areas; such as the eyes.[140] To address this challenge, Kim et al. [140] reported a bilayer hydrogel nanocomposite, composed of an MNP layer anda therapeutic layer to treat retinoblastoma Y79 cancer cells. Upon reaching the targeted site under the influence of a stagnant magnetic field, the hydrogel nanocompositewas exposed to an AMF to assist the release of PLGA-DOXdrug molecules. The MNP layer of the nanocomposite bilayer consists of PEGDA 700 and Iron oxide particles, whereas the attached therapeutic layer contains gelatin, PVA and PLGA-DOX drug particles. Once the PLGA-DOXparticles are released, the magnetic layer of the carrier canbe retrieved by using a stagnant magnetic field (Figure 6).Kim et al. [141] reported similar working principle mono- layer hydrogel nanocomposite with retrievable MNPs synthesized with gelation and PVA. The Hydrogel matrixwas loaded with MNP and PLGA-DOX nanoparticles. The nanocomposite was driven to the desired site under the influence of a stagnant magnetic field, and upon arrivalto the desired site, the hydrogel matrix decomposed upon irradiation with 808 nm NIR laser (1.65 W cm^{-2}). The decomposition of nanocomposite facilitated the releaseof the drug molecules in the target site. Once the drug molecules are released, the magnetic particles can be retrieved by using a stagnant magnetic field to reduce magnetic particle-induced toxicity to the targeted site.

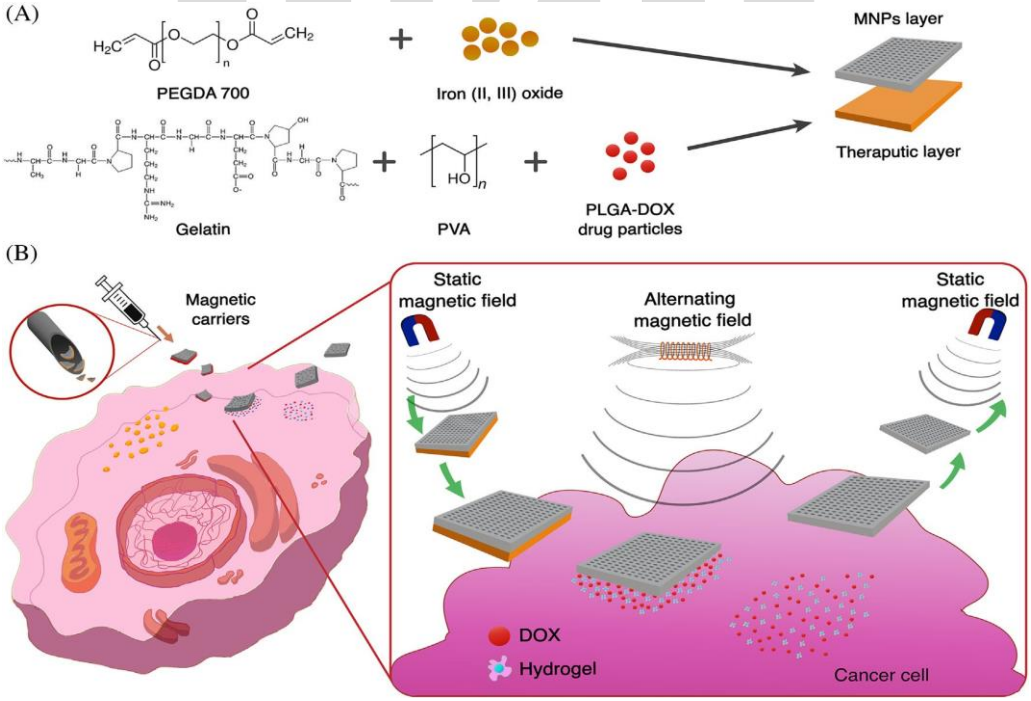

FIGURE 6 A, Structure of bilayer magnetic drug delivery vehicle. The delivery vehicle is composed of two layers with MNP layer and atherapeutic layer that contains DOX. B, The bilayer magnetic vehicles can be locally injected to the tumor

site, which will then be delivered tothe desired cancerous cell by a static magnetic field. Upon reaching the desired site the bilayer delivery vehicle will be exposed to an alternatingmagnetic field (AMF) which will facilitate an increase in temperature in the cellular microenvironment and the release of the therapeutic layer.The remaining magnetic layer will be retrieved using a static magnetic field. Recreated with permission from ref [140]

TABLE 3 Different magnetic nanoparticle-hydrogel nanocomposites for drug delivery

Hydrogel monomer	Crosslinker	Magnetic particles with size	Hydrodynamic diameter of nanocarrier	Drug	Cell line
Acryl-PEG-NHS	RGDS peptide	SPION (7.3 ± 0.7 nm)	28.5 ± 4.8 nm	Doxorubicin (DOX)	HeLa cells
Hyaluronic acid	Divinyl sulfone (DVS)	SPION (6–15 nm)	–	Trimethoprim (TMP)	–
Polyvinylpyrrolidone (PVP)	PVA	Iron oxide	35.20 ± 15.29 nm	Bleomycin	L929 cells
O-acetyl-galactoglucomannan(AcGGM)	A high concentration of NaOH was used to induce deacetylation ofAcGGM	Fe_3O_4(5.8 nm)	–	Bovine serum albumin (BSA)as a model drug	–
κ-carrageenan	Sodium alginate	Fe_3O_4 (less than 20 nm)	–	Riboflavin	–
2-hydroxyethyl methacrylate (PHEMA) and polyethylene glycol acrylate (PEGDA)	2-Hydroxyethyl methacrylate (HEMA)and ethylene glycol dimethacrylate (EDGMA)	Fe_3O_4 (>50 nm but <100 nm)	–	Docetaxel	Mammary carcinoma (4T1)
PVP	Irradiation with *γ*-ray followed by an oil-water-oil emulsion	Fe_3O_4(50 nm)	–	Bleomycin A5 hydrochloride (BLM)	VX2 squamous cell
N-isopropylacrylamide	Polyethylene glycol 400dimethacrylate	Fe_3O_4 (20–30 nm)	–	Pyrocatechol violet dye as model drug	–
N-isopropylacrylamide(NIPAM)	(2-dimethylaminoethyl) methacrylate (DMA)	Fe_3O_4(9 nm)	94 nm	Doxorubicin (DOX)	–

Marketed Nano emulsion Formulations

Drug	Brand Name	Manufacturer	Indications
Cyclosporine A	Restasis,Gengraf,Nano Tears	Allergan, Abbott, New India BioPharma Pvt. Ltd.	Immunosuppressant
Ritonavir	Norvir	Abbott	Anti retroviral
Vitamin A D E & K	Vitalipid	Fresenius Kabi	Parentral Nutrition
Acyclovir	Zovirax	Glaxo group	Anti Herpes
Estradiol	Estrasorb	Novavax, Inc	Menopausal disorder
Propofol	Diprivan, Troypofol	Astra-Zeneca, Troikaa	Anaesthetic

CONCLUSION:

MNP technology has gained notoriety following several years of painstaking research and development effort by pharmaceutical academics, which resulted in stable formulations that have previously been successfully scaled up and evaluated for stability and particle size maintenance. Because of their tiny size and compatibility with tissue, micellar nanoparticles are useful for a wide range of applications. The use of lipophilic and hydrophilic components, stabilisers, and the preferred application of sophisticated series of procedures resulted in kinetically compatible MNP formulations.

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