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Magnetic microscale polymeric nanocomposites in drug delivery: advances and challenges

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Magnetic polymeric nanocomposites are a modern class of materials in which magnetic nanoparticles are embedded in a polymeric matrix. This combination of magnetic responsiveness and tuneable properties bestows versatility on this class of polymer nanocomposite material, which has potentially broad applications in drug delivery, imaging, environmental remediation and beyond. This review covers the uses of magnetic polymeric nanocomposites in drug delivery, discussing magnetic micelles, magnetic liposomes, magnetic hydrogels, magnetic sponges, magnetic mesoporous silica nanoparticles, magnetic microrobots, magnetic elastomers and magnetic scaffolds. The focus is on the role that might be played by magnetic nanocomposites as an interface between the magnetic and polymeric domains in the establishment of a new generation of advanced materials.

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Keywords: magnetic polymeric nanocomposites; drug delivery; magnetic field; magnetic nanoparticles; microscale magnetic drug delivery systems

Introduction

The use of magnetic material to aid targeted drug delivery has gained considerable interest in recent years. Magnetic drug delivery takes advantage of the ease of manipulation and the directionality property of the magnetic material, which can be activated within (an external) safe magnetic field to direct the material (and the accompanying drug) to target tissues. Such delivery systems are versatile and can encompass (normally inorganic) magnetic microspheres with hollow, cage-like structures that can incorporate a drug, and magnetic nanoparticles (MNPs)

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with an inorganic magnetic core that is functionalised or coated with polymers and other organic entities. Microspheres and MNPs can be further formulated and incorporated into other complex systems, such as liposomes or micelles.

The magnetic component of MNPs confers the ability to be manipulated by external magnetic fields, while functional groups add versatility for various applications. MNPs have been widely applied in various fields, including bioseparation, cell labelling, targeted therapeutic hyperthermia of tumours, magnetic microdevices, magnetic resonance imaging (MRI) and drug delivery. This is due to the various physical and chemical properties that are characteristic of their 'nano' size, such as their large surface area, low intraparticle diffusion rate and high loading capacity,[(p1),(p2),(p3)] combined with their activity within magnetic fields.

MNPs facilitate several modes of targeted drug delivery through their magnetism. The advantages of some of these systems include good compatibility, ease of fabrication and modification, and the potential to reduce the risk of systemic distribution of drugs and the resulting side effects.[(p4),(p5),(p6),(p7)] The response of MNPs to magnetic fields is achieved through an equilibrium between the magnetic force along the magnetic field and the viscous force arising from the fluid flow.[(p8),(p9)] The magnetic core in MNPs is a magnetic iron oxide such as magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3), which has superparamagnetic properties when it is produced at nanoparticle size. The superior magnetic behaviour, size- and material-dependent physicochemical properties and stability of superparamagnetic iron oxide nanoparticles (SPIONs) result in this material being widely used in drug delivery systems (DDSs).[(p10),(p11),(p12)] The size of nanoparticles in general, and MNPs in particular, is most important for controlling the distribution kinetics in various tissues, the movement of particles in the vasculature and through membranes, drug release profiles and the interaction of particles with biological molecules. Additionally, the MNP's size affects its magnetic behaviour and its response to magnetic fields. Moreover, the magnetisation of sufficiently small nanoparticles is thermally fluctuated, a behaviour known as superparamagnetism, which is size dependent. Superparamagnetic MNPs such as SPIONs are single domain: that is, their particle size is small enough to exhibit a single large magnetic domain at temperatures above the blocking temperature.[(p11),(p13),(p14)] The particle size distribution of MNPs is crucial for tissue targeting by external magnetic fields, because those magnetic particles with a size larger than the superparamagnetic radius normally exhibit a multidomain structure (with the magnetic domains separated by domain walls).[(p5),(p15)] Moreover, very small MNPs below a critical size possess a weaker magnetic moment, and show less reaction with the magnetic fields.[(p16)] As the particle size reduces, the coercivity (H_c) increases to the maximum and then drops to zero.[(p5)] In addition, the relatively long blood half-life and lower toxicity of SPIONs make them a promising candidate in theranostic nanoplatforms for drug delivery.[(p17)]

Smaller MNPs can exhibit better tumour penetration and longer half-life; however, the magnetic force of such particles can decrease with the reduction in size.[(p18),(p19)] Therefore, it is essential to strike a balance between the magnetic force requirements and the physiological behaviour (and stability) to determine the optimal size of MNPs.[(p19)] For *in vivo* applications, MNPs used in drug delivery are often injected intravenously or intra-arterially and are guided to the target site, such as a tumour, by a magnet.[(p4),(p20)] In simulation experiments, sample containers and a permanent magnet can be used to assess these DDSs.[(p21)] Targeted drug delivery using MNPs can occur through (i) using the MNPs as propellers to direct the drug to the target via convection, or (ii) conjugating MNPs with a targeting group, such as antibodies, that specifically binds to the target site. Additionally, in chemotherapy, the drug delivery efficiency of MNPs can be improved by the enhanced permeability of endothelial membranes in cancerous tissues.[(p22)] The incorporation of drug-loaded MNPs and magnetic forces increases the delivery of therapeutic agent to the targeted tumour tissue and boosts tumour cell killing.[(p23)]

One potential challenge is the low colloidal stability of MNPs in biological fluids and their rapid clearance from the bloodstream, which can limit the drug's bioavailability.[(p24)] Therefore, optimising the biological stability of MNPs is crucial when designing these DDSs. Additional potential drawbacks of MNPs in clinical applications include their relatively short half-life, chemical and metabolic instability, high tendency to agglomerate, low drug loading capacity and poor targeting specificity. To address these issues, various strategies can be employed, such as encapsulation, implementing navigation systems and modifying surfaces with surfactants, polymeric materials and thiol groups.[(p25),(p26)] For instance, PEGylation can enhance MNP stability, reduce clearance from circulation and improve accumulation at the target site owing to the stability, biocompatibility and hydrophilicity of polyethylene glycol (PEG).[(p27)] Some physical parameters, such as magnetic field strength, field geometry, magnetic properties, particle size and drug loading capacity, need to be optimised when designing an MNP-based targeted DDS, taking into consideration the physiological parameters, blood volume, blood flow rate, cardiac output, the distance from the skin surface to the target, and body weight.[(p4),(p16),(p28)]

The drug–MNP complex can be attracted to an external magnetic field by a magnetic force (F_{mag}) proportional to the magnetic field gradient, as described in Equation (1).[(p4),(p21)] According to Equation (1), the magnetic force is determined by the magnetic field strength in Tesla (B), the field gradient (∇B), the volume of the MNPs (V), the magnetic permeability of free space (μ_0), the magnetic susceptibility of the magnetic particle (χ_2) and the magnetic susceptibility of the medium (χ_1).

$$F_{mag} = (\chi_2 - \chi_1)V\frac{1}{\mu_0}B(\nabla B) \quad (1)$$

Therefore, only gradient, and not homogenous, magnetic fields can generate a magnetic force on MNPs. Furthermore, it can be seen from Equation (1) that a stronger F_{mag} is achieved by MNPs with larger size and stronger magnetic properties, exposed to magnetic fields with higher strength and gradient.[(p4)] Consequently, larger particles can move faster, and a higher concentration of particles also move faster owing to the longer chains or needle-like aggregates formed.[(p29)] Several strategies are employed in developing nanoscale DDSs using MNPs. These include: (i) modifying the size and shape of MNPs and the type of matrix or medium used; (ii) encapsulating MNPs with an exter-

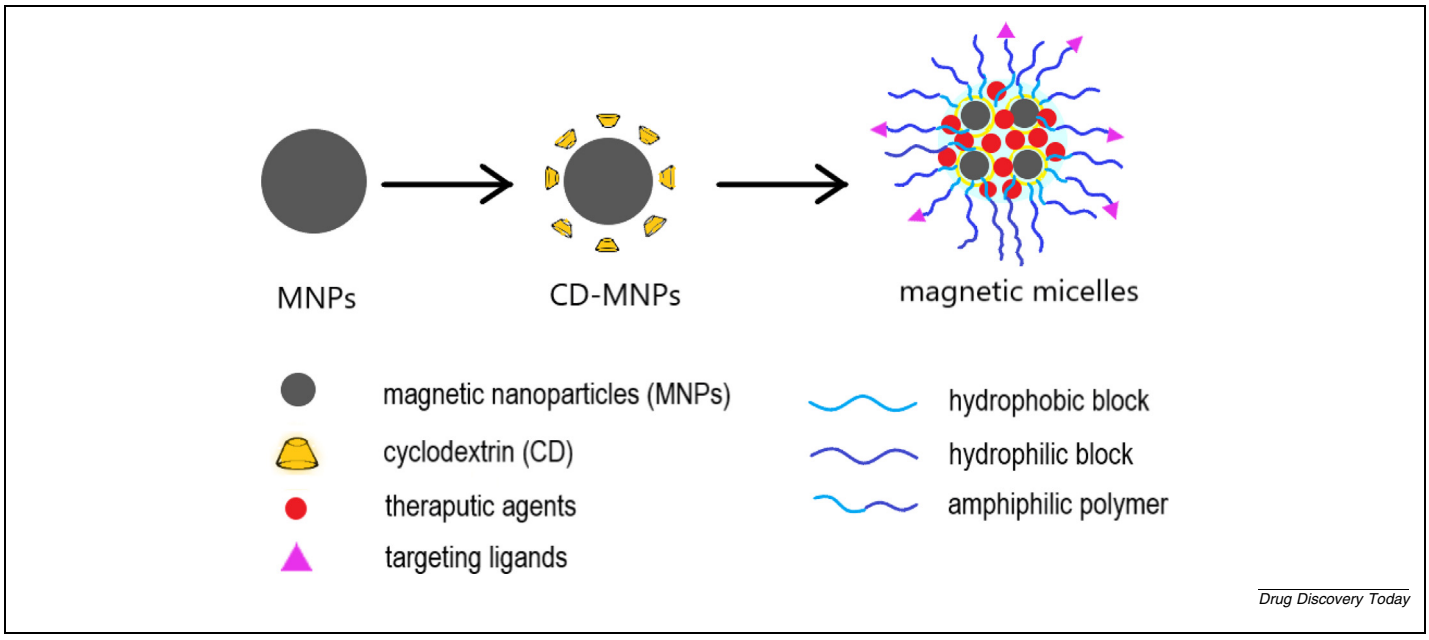

FIGURE 1

Schematic illustration of the preparing process of magnetic micelles composed of MNPs, therapeutic agents, amphiphilic polymer, cyclodextrin and targeting ligands.

nal polymer coating; (iii) creating porous nanocomposites composed of MNPs and polymers; and (iv) grafting drug molecules onto the surface of MNPs within a polymer matrix.[p6] Methods for conjugating therapeutic agents to nanocarriers include absorption, covalent attachment and encapsulation.[p30] Targeting strategies are generally categorised into active mechanisms, which involve the use of specific ligands and physical stimuli, and passive mechanisms, which rely on enhanced permeability and retention (EPR) effects.[p30]

This review summarises the various approaches and formulations developed for magnetic polymeric nanocomposites in diagnosis and drug delivery, including magnetic micelles, magnetic liposomes, magnetic hydrogels, magnetic sponges, magnetic mesoporous silica nanoparticles (MSNs), magnetic microrobots, magnetic elastomers and magnetic scaffolds.[p31]

Magnetic nanocomposites

Nanocomposites are composed of organic and inorganic materials: for example, MNPs embedded in various polymer scaffolds.[p32] In recent years, the adjustable chemical structure, good safety and biological assimilation of polymer nanocomposites have made them promising candidates for developing controlled drug release systems.[p33] In addition, nanocomposites can significantly increase the absorption of poorly water-soluble drugs.[p34] The magnetic properties of nanocomposites, which include saturation magnetisation intensity and coercivity, can be influenced by the synthesis approach and chemical structure.[p35] Different MNPs with ferromagnetic or superparamagnetic properties have been used to prepare magnetic nanocomposites that can target the release of drugs more effectively, minimise potential side effects and decrease the required drug concentration.[p33],[p36]

Magnetic micelles

Micelles are commonly used to encapsulate hydrophobic drugs as drug carriers. Typically, a micelle is a kind of supramolecular colloidal particle with a hydrophobic core head and a hydrophilic shell tail.[p37] According to this theory, the hydrophobic core is a perfect compartment for the storage of hydrophobic drugs, whereas the hydrophilic shell stabilises the encapsulated particles in aqueous solutions.[p38] Indeed, polymeric micelles have been proven to possess great potential for enhancing the bioactivity, stability, tissue permeability, drug delivery efficiency and solubility of hydrophobic drugs.[p39] Micelles are in dynamic equilibrium and form reproducibly above a particular concentration of the surfactant or amphiphile, referred to as the critical micelle concentration (CMC).[p40] The CMC can be affected by the hydrophobicity of the block, as well as the molecular weight of the hydrophobic component.[p41] These are multicompetent drug carriers of interest because they store and transport therapeutic substances with MNPs, and target cancer cell surface receptors.[p42] It is possible to make amphiphilic polymers respond to external stimuli such as pH, temperature and magnetic field by chemical modification when developing micelles for controlled drug release.[p39]

MNPs can be engineered to reside at the interface between the outer hydrophilic shell and the inner hydrophobic core of magnetic micelles, as shown in Figure 1. Such micelles exhibit the ability to manipulate magnetic fields, which can provide excellent chemical stability, biocompatibility, direct actuation, solubility and drug-loading efficiency.[p39] Guest molecules grafted onto the surface of β-cyclodextrin (β-CD) MNPs through inclusion complexation between β-CD and Fc groups were demonstrated by Zhang *et al.*[p43] For the fabrication of multi-stimuli-responsive DDSs (Table 1), various polymers can be conjugated

to MNPs, including poly(N-isopropyl acrylamide) (PNIPAM), β-CD and glycerol monooleate.[p7],[p43],[p44] Of these, β-CD is an especially common drug carrier and gatekeeper owing to its amphiphilic hollow structure and excellent compatibility.[p7],[p45] That is to say, the ligands conjugated with micelles targeting certain receptors on the tumour cell surface would increase the specificity and efficacy of micelles by facilitating receptor-mediated endocytosis in cancer therapy.[p41] In addition, the multivalent inclusion complexes between β-CD and drugs could potentially improve stability, biological activity and water solubility, while preventing unwanted drug release.[p25],[p46] Such properties can be optimised by adjusting the SPION/PEG ratio: for example, the size of SPIONs strongly influences pharmacokinetics, tissue distribution and saturation magnetisation.[p25] Moreover, encapsulated drugs can be released via micellar disassembly caused by external stimuli. Thus, the parameters involved in drug release from micelles include the stability of the micelle, the rate of copolymer biodegradation, the rate of diffusion of the drug, the partition coefficient, and the drug concentration and localisation within micelles.[p41] Furthermore, it is possible to optimise the drug-loading capacity via modification of the hydrophobic block length and the volume of the micelle.[p42] Therefore, these nanocarriers have shown outstanding potential in targeting for cancer therapy and hyperthermia treatment,[p44],[p47]–[p49] and many hydrophobic anticancer drugs have been successfully encapsulated into the micelle core to facilitate drug solubility and increase the rate of release.[p38]

However, the manufacturing procedure for magnetic micelles is complex, hard to scale up and time-consuming, and it could result in changes to the magnetic properties of MNPs.[p25],[p39],[p50] In addition, it is difficult to control the size of magnetic micelles.[p50] For such DDSs, more attention should be paid to drug loading capacity, drug release rate and saturation magnetisation.[p25],[p43]

Magnetoliposomes

Liposomes consist of an aqueous core enclosed within a phospholipid bilayer, and they have been utilised as nanoscale DDSs.[p11] The composition of this bilayer has a crucial role in determining liposome properties, because the membrane must remain stable in the bloodstream while becoming permeable at the target site.[p51] Therefore, controlling membrane permeability, fusion and destabilisation is key to regulating drug release. The size, structure and chemical makeup of liposomes significantly influence their membrane fluidity, charge density and permeability.[p52]

Moreover, the permeability and drug release rate, which depend on lateral compressibility, can be adjusted through factors such as increased temperature (lipid melting temperature), pH changes, the inclusion of large headgroup amphiphiles and the presence of defects or pores in the formulation.[p26],[p53],[p54] At temperatures above the lipid melting point (T_m), the membrane adopts a liquid phase (thin and disordered), whereas it shifts to a gel phase (thicker and more rigid) below T_m.[p54],[p55] This temperature-dependent phase transition results in increased membrane permeability and a burst release of encapsulated drugs.[p56]

Liposomes offer several advantages, such as modulating drug circulation *in vivo*, protecting and solubilising drugs or nanoparticles by encapsulating them to prevent biomolecular adsorption.[p16],[p54] The drugs are primarily released via transmembrane diffusion, but achieving prolonged release can be challenging.[p53],[p56] Intravenously administered liposomes face limited delivery efficiency due to the reticuloendothelial system, but this can be improved by functionalising the lipid headgroups with molecules such as PEG.[p16],[p57]

PEGylation extends the storage and circulation time of liposomes in the bloodstream, reduces liver accumulation and decreases uptake by macrophages by preventing plasma protein adsorption and shielding the complex from the reticuloendothelial system.[p6],[p54],[p58] Additionally, bioactive molecules such as enzymes and antibodies can be conjugated to the phospholipid layer, granting the liposomes biological specificity and selectivity through interactions between ligands and cell-specific receptors.[p26],[p58] This interaction ensures the targeting capabilities of liposomes for specific cells.

Magnetoliposomes have been developed to combine the physical and magnetic properties of MNPs with the drug delivery capabilities of liposomal nanocarriers. This combination serves various purposes, such as enhancing multivalent properties, pre-

TABLE 1

Examples in the literature of magnetic micellar formulations

Stimulus	MNPs	Drug	Block copolymer	Targeting ligand	Refs
Magnetic field, tumour cells	SPIONs	Paclitaxel	PEG; β-CD	Arg–Gly–Asp (tumour targeting)	(p25)
Temperature, pH, H_2O_2, magnetic field	Fe_3O_4	Doxorubicin	PEG/PNIPAM/CD-MNP; PNIPAM (thermoresponsive); β-CD and Fc pair (redox responsive)	–	(p43)
Temperature, pH, magnetic field	Fe_3O_4	Doxorubicin	PNIPAM@β-CD-BI-Fe_3O_4@mSiO_2; PNIPAM (thermoresponsive); β-CD (pH-responsive)	–	(p44)
Magnetic field	Fe_3O_4	Paclitaxel	pPTX/CD-SPION	–	(p46)
Magnetic field, acid, tumour cells	Fe_3O_4	Doxorubicin	PEG-P(GA-DIP); poly(L-glutamic acid) (acid-sensitive)	Folate (tumour targeting)	(p42)
Magnetic field, pH	Fe_3O_4	Paclitaxel	Amphipathic chitosan derivatives; PEG	–	(p39)
Magnetic field	Magnetic beads	Paclitaxel or curcumin	p(HPMAm)-b-p(HPMAm-Bz)	–	(p48)
Magnetic field, temperature	Fe_3O_4	Doxorubicin	Poly(phenyl isocyanide)	–	(p49)

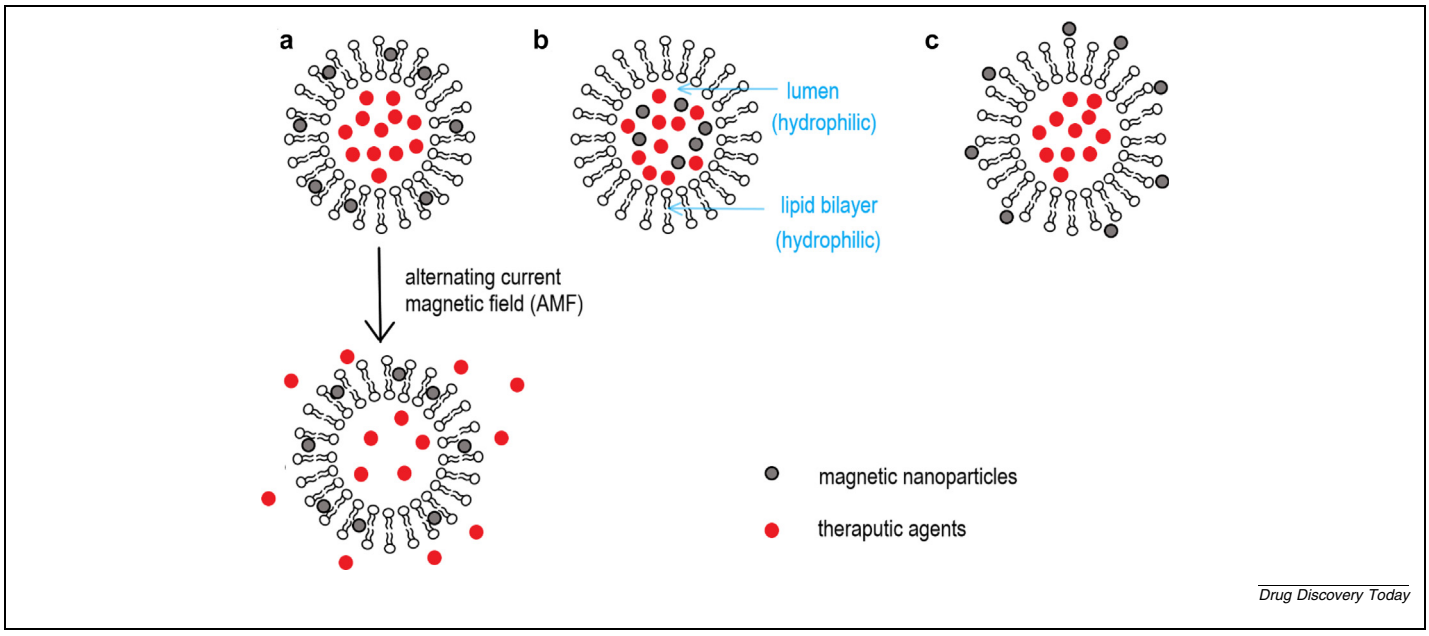

FIGURE 2

Schematic description of magnetoliposomes when MNPs were (A) located in the lipid bilayer, (B) the lumen (middle) or (C) attached on the surface of the liposome.

venting the aggregation and oxidation of MNPs, improving bioavailability, and enabling targeted delivery for biological applications.[p11],[p16],[p26] There are three main methods for integrating MNPs with liposomes: encapsulating hydrophilic MNPs within the liposome's aqueous core, embedding hydrophobic MNPs between the lipid bilayers and attaching MNPs to the outer surface of the bilayer using polymers, lipids or surfactants (Figure 2).[p11],[p16],[p58],[p59]

The surface properties of MNPs determine their spatial location in these MNP–liposome hybrids.[p11] Because MNPs can interact directly with the liposome membrane, the second approach (embedding MNPs between the lipid bilayers) is preferred for DDSs.[p16] The encapsulation efficiency largely depends on the size of the MNPs. However, embedding MNPs in the lipid bilayer increases membrane rigidity, which can reduce drug diffusion.[p58] The first approach (encapsulating MNPs within the liposome core) also has limitations, such as leakage caused by interactions between unstable MNPs and the liposome membrane, and heat generation from SPIONs.[p16]

The lipid composition plays a key part in the successful incorporation of drugs into magnetoliposomes, because excess physical ligands can lead to drug leakage.[p16],[p59] The third approach, which involves MNP conjugation to the outer bilayer surface, has seen limited use.[p16] The number of MNPs incorporated, which affects the saturation magnetisation of magnetoliposomes, is determined by the composition of their bilayers.[p59] In general, rapid and high drug release from magnetoliposomes is associated with high drug loading capacity, strong magnetic fields, larger MNP sizes and extended exposure to magnetic fields.[p53]

Under the exposure of alternating current magnetic field (AMF), the magnetically induced heat rises and the temperature increase of the magnetoliposomes can drive microstructure changes in the phospholipid bilayer from the gel to liquid phase; this increases membrane permeability and results in the diffusive release of encapsulated drugs.[p55],[p56] Once the AMF is switched off, the temperature of the membranes cools down below T_m owing to the superparamagnetic behaviour. Otherwise, the membrane would revert to the gel phase and drug release would be prevented.[p55]

The investigation and development of magnetoliposomes involves several challenges, including the inhibition of cell function, MNP clustering, micelle formation and increased passive drug release.[p54],[p57] Thus, balancing the concentration of encapsulated MNPs with effective cellular targeting is crucial.[p57] Notably, incorporating larger MNPs (greater than 5 nm) into the membrane can lead to the formation of magnetic micelles.[p16] Additionally, the density and stability of MNPs can influence both the overall stability and the membrane permeability of the liposomes.

Thermal and magnetic stimuli pose another concern, because they can cause damage to surrounding tissues as a result of temperature increases and magnetically induced eddy currents, thereby limiting the clinical use of magnetoliposomes.[p56] The method of preparation also has a significant role in determining the final characteristics of magnetoliposomes, such as their shape, size distribution, surface chemistry and magnetic properties.[p16]

During magnetoliposome development, it is essential to focus on selecting appropriate synthesis and surface-coating methods for MNPs, as well as optimising the composition of the liposome bilayers to ensure the desired functionality.[p11],[p60]

Ferrogels (magnetic hydrogels)

Under conditions of specific deformation, gels can act like a solid state.[p61] Hydrogels consist of crosslinked 3D polymeric net-

works that show high swellability in water due to the hydrophilic chains.[p15],[p62] This includes various crosslinking methods such as covalent bonds, crystallisation and hydrophobic interaction.[p63] With their dual nature of solid and liquid, high water content, softness, elasticity and diffusion ability, the structure of hydrogels resembles that of living tissues.[p60],[p61],[p63] Hydrogels can be divided into synthetic and natural polymers[p60]; natural hydrogels are regarded as more suitable for biocompatible applications owing to their environmentally friendly and sustainable properties, whereas synthetic hydrogels have excellent processability and long service life. These synthetic hydrogels have many similarities with biological objects in both structure and performance, although common hydrogels usually have weak mechanical strength.[p64],[p65]

Crosslinkers have been adopted in hydrogel preparation to enhance their mechanical properties and stability and minimise their viscosity and insolubility, as well as providing strength.[p66]

As one of the most common drug delivery carriers, hydrogels have played an important role in sustained-release and controlled-release dosage forms owing to their good biocompatibility, excellent mechanical properties, high water content and flexible physicochemical structures.[p10],[p67] However, conventional hydrogels suffer from several drawbacks, including unfavourable mechanical properties in terms of stiffness and strength; insufficient functionality, such as conductivity, poor sensitivity and responsiveness; fatigue deterioration after multiple operations; and inaccurate drug release. In fact, a passive mechanism represents the major pattern of drug release from hydrogels.[p63],[p68]

Because of their great potential for real-time alternation in swellability, permeability and elasticity in response to various environmental conditions, the applications of hydrogels as sensors have recently come under much attention.[p68] Because the channels and pores of hydrogels are the reservoirs and diffusion pathways for drugs, traditional hydrogels mainly modulate drug release behaviour via variations in pore size.[p60] With the manipulation of physical and chemical stimuli such as pH, temperature, magnetic field, electric field, changes in solvent composition and pressure, various types of stimulus-sensitive hydrogels (smart hydrogels) show obvious, reversible changes in volume and shape to achieve pulsatile release and position control.[p61],[p64],[p67],[p69] Among these various stimuli, pH- and temperature-stimulated hydrogels have been widely used in cancer therapy owing to the relatively low pH of about 5–6 and high temperature of about 40–42 °C in cancerous cells.[p70] For application in DDSs, these stimuli-sensitive hydrogels must be biocompatible and biodegradable.[p71] In the past few years, 3D printing has been widely applied to fabricate smart hydrogels.[p72]

Ferrogels, which consist of magnetic particles embedded in polymer hydrogels, have been extensively studied as a smart material for drug delivery because of their macroscopic changes in shape under magnetic fields.[p68],[p73],[p74] Ferrogels refer mainly to magnetic gels that are prepared with MNPs rather than microparticles.[p75] Because ferrogels show a rapid response and can be controlled remotely by adjusting magnetic fields, they have been investigated for their use in controlled drug release and dialysis membranes. MNPs loaded ferrogel matrices have also been used with a micro- and macrovascular catheter that has facilitated targeted drug delivery at remote sites.[p60],[p76] Blending, grafting and precipitation methods have been commonly utilised for the integration of MNPs into hydrogels.[p60],[p63] MNPs attached to the crosslinked polymeric chains of hydrogels can respond to external magnetic fields by producing localised heat through magnetic hyperthermia, and they can enable the remote delivery of encapsulated drugs while the hydrogel protects biological tissues from direct exposure to inorganic particles.[p61],[p77],[p78] During exposure to a magnetic field, the mechanical properties of the polymeric matrix can be enhanced, and the deformation can be adjustable with different types of MNPs incorporation.[p75] Thus, these materials with mechanical softness, a viscoelastic nature and magnetosensitivity have been used most commonly as carriers for the delivery of drugs, proteins and cells.[p10],[p61] The production of ferrogels with a 4D structure, indicating sensitivity to magnetic fields, has recently emerged as a new area of research activity.[p72]

The major components of ferrogels are MNPs and a polymeric matrix, which usually consists of poly(vinyl alcohol) (PVA), alginate, NIPAM, polysaccharides and polydimethylsiloxane (PDMS), as shown in Table 2. The properties of ferrogels rely on the sizes and distribution of MNPs, as well as the type and concentration of gels and MNPs.[p60] Indeed, a larger radius of ferrogels might result in a stronger magnetic force and faster movement, which leads to a shorter time to reach the target site.[p9] Ferrogels with small dimensions show a higher swelling rate because of their larger surface/volume ratios and their greater contact with the surrounding solvent.[p9] Moreover, the types and concentrations of base materials and MNPs have an essential role in the swelling behaviour of ferrogels, because the ratio of ionic and non-ionic functional groups in ferrogels determines their ability to swell.[p61],[p79] Loosely structured ferrogels with high swellability and low crosslinking extent can retain more fluids for the development of DDSs.[p61] It has been proved that as a result of coating MNPs with polymers, ferrogels can have higher biocompatibility, pre-programming, self-regulation and precise actuation, and it also reduces the risk of particle aggregation.[p10],[p80] This work shows that the extent of crosslinking, the intensity of the applied magnetic field and the concentration of MNPs are crucial factors that affect the elastic modulus of prepared ferrogels.[p75] The high tendency of MNPs to aggregate is one of the main challenges with the encapsulation of MNPs within the polymer matrix.[p81] Thus, it is mainly the compatibility of the polymer matrix with the encapsulated MNPs that presents the key challenge in achieving ferrogels with good mechanical properties as well as magnetic sensitivity.[p75]

Ferrogels have obvious advantages in specific locations because of their rapid deformation and their dynamic microstructural changes when external magnetic fields are exerted.[p10],[p61],[p80] They primarily spread through diffusion, but the extent and velocity of this diffusion can be modulated using externally applied magnetic fields.[p10] For example, direct actuation can be achieved through the physical deformation of ferrogels (Figure 3a). Furthermore, because the MNPs will be aligned under the applied magnetic field, the ferrogels are likely to acquire a magnetic macro-response.[p13],[p63]

As a result of fluid convection, drug release can be easily triggered from ferrogels.[p73] Ferrogels will stretch immediately in the

TABLE 2

Examples in the literature of ferrogel formulations

Stimulus	Base material	Crosslinker	Drug	MNPs	Refs
Magnetic field, pH	Methacrylic acid or 2-aminoethyl methacrylate hydrochloride and N,N′-dimethylacrylamide	N,N′-methylene bisacrylamide	5-fluorouracil	Fe_3O_4	(p61)
Magnetic field	Acrylamide	PEG	–	$CoFe_2O_4$	(p82)
Magnetic field	PVA	Polyethylenimine	–	Fe_3O_4	(p83)
Magnetic field, pH	PVA; κ-carrageenan	–	Diclofenac sodium	Fe_3O_4	(p79)
Magnetic field	Alginate	Calcium sulfate	Doxorubicin	SPIONs	(p67)
Magnetic field, temperature	NIPAM	N,N′-methylene bisacrylamide	Doxorubicin	$Mn_{0.6}Zn_{0.4}Fe_2O_4$ SPIONs	(p80)
Magnetic field	PAAm	N,N′-methylene bisacrylamide	–	γ-Fe_2O_3	(p64)
Magnetic field	GC; OHA	–	–	SPIONs	(p65)
Magnetic field, temperature, pH	NIPAM	N,N′-methylene bisacrylamide	Doxorubicin	Fe_3O_4	(p70)
Magnetic field, pH	Chitosan	Glyoxal	Doxorubicin	Iron (III) chloride hexahydrate	(p84)
Magnetic field	GC	–	–	SPIONs	(p72)
Magnetic field, pH, temperature	Polyhexamethylene guanidine; κ-carrageenan	–	Curcumin	Iron (III) chloride	(p85)
Magnetic field	Chitosan	Terephthaloyl thiourea	–	Fe_3O_4	(p66)
Magnetic field, pH	Xylan hemicellulose	Poly(ethylene glycol) diacrylate	Acetylsalicylic acid; theophylline	Fe_3O_4	(p77)
Magnetic field	Chitosan; alginate	Sodium tripolyphosphate; calcium chloride	5-fluorouracil	Fe_3O_4	(p32)
Magnetic field	PVA Scleroglucan	Glutaraldehyde –	Theophylline	Fe_3O_4	(p71), (p86)

direction of the magnetic field, then return to their previous form after the disappearance of the magnetic field.[(p1)] This mechanical deformation property can therefore be controlled by adjusting the number of magnetic particles in order to manage drug release from ferrogels.[(p13)] Making ferrogels smaller will lead to a decrease in the size of the inner pore, shifting the drug release mechanism from diffusion to magnetic field activation.[(p13)] In order to realise this goal, MNPs of sizes between 5 and 500 nm are regarded as the most appropriate for ferrogels.[(p1)]

Interestingly, the size of MNPs has a significant effect on the deformation of ferrogels under a moderate magnetic field, because larger particles have higher saturation magnetisation values than smaller particles.[(p73)] Importantly, all MNP sizes, along with the frequency of magnetic treatment and the switching duration time, have crucial effects on the drug release behaviour of ferrogels under magnetic fields.[(p82)–(p87)], Ferrogels composed of MNPs with larger particle sizes present better magnetic sensitivity because they exhibit higher saturation magnetisation and weaker coercive force.[(p83)] The role of MNP concentration on the elastic properties of ferrogels has also been addressed by a lot of researchers, who have found that an increased concentration of MNPs enhances the density of the ferrogel matrix and prohibits the swelling process in some cases.[(p64)] Moreover, the roughness of the ferrogel surface is related to the concentration of the embedded MNPs, and the surface roughness can influence the ferrogel's cell adhesion and proliferation abilities.[(p64)]

Ferrogels can be designed to be multifunctional via conjunction with biological ligands or encapsulation with polymers for MNPs.[(p1)] However, Zhao *et al.* have pointed out that the range of deformation and volumetric change of the typical, nanoporous ferrogels used in drug delivery is limited, and the pore sizes are almost within the nanometre scale.[(p74)] This might limit the transport of large molecules and cells through gels (Figure 3a).

When ferrogels are exposed to magnetic fields, the magnetic moments of MNPs can be aligned together, and the aggregation of MNPs will result in a 'close' configuration.[(p79)] The application of a magnetic field will reduce drug release kinetics owing to the significant reduction in pore size and the increase in tortuosity of the diffusion channels of ferrogels.[(p71),(p86)] In cases in which the size of the drug molecules is smaller than the pore size of ferrogels, the diffusion coefficients are inversely proportional to the tortuosity of the gels.[(p86)] Conversely, the application of macroporous ferrogels with micrometre scale interconnected pores can overcome those problems owing to simultaneous scaffold collapse and on-demand release of loaded drugs in response to magnetic fields (Figure 3a).[(p1),(p74)]

Ferrogels of various formulations have been used in a number of clinical applications, including drug-delivery modulation, MRI, *in vivo* cell tracking and heat treatment, as a result of the promising combination of a safer stimulus with biocompatible magnetic particles, especially iron oxide nanoparticles. It is intriguing to note that reducing the size of ferrogels will lead to reduced ferrogel deformation as a result of the lower numbers of MNPs.[(p73)]

PVA can be crosslinked with MNPs due to its amphiphilicity for encapsulating drugs in either aqueous or organic solvent and its ability to disperse MNPs uniformly.[(p83)] Glycol chitosan

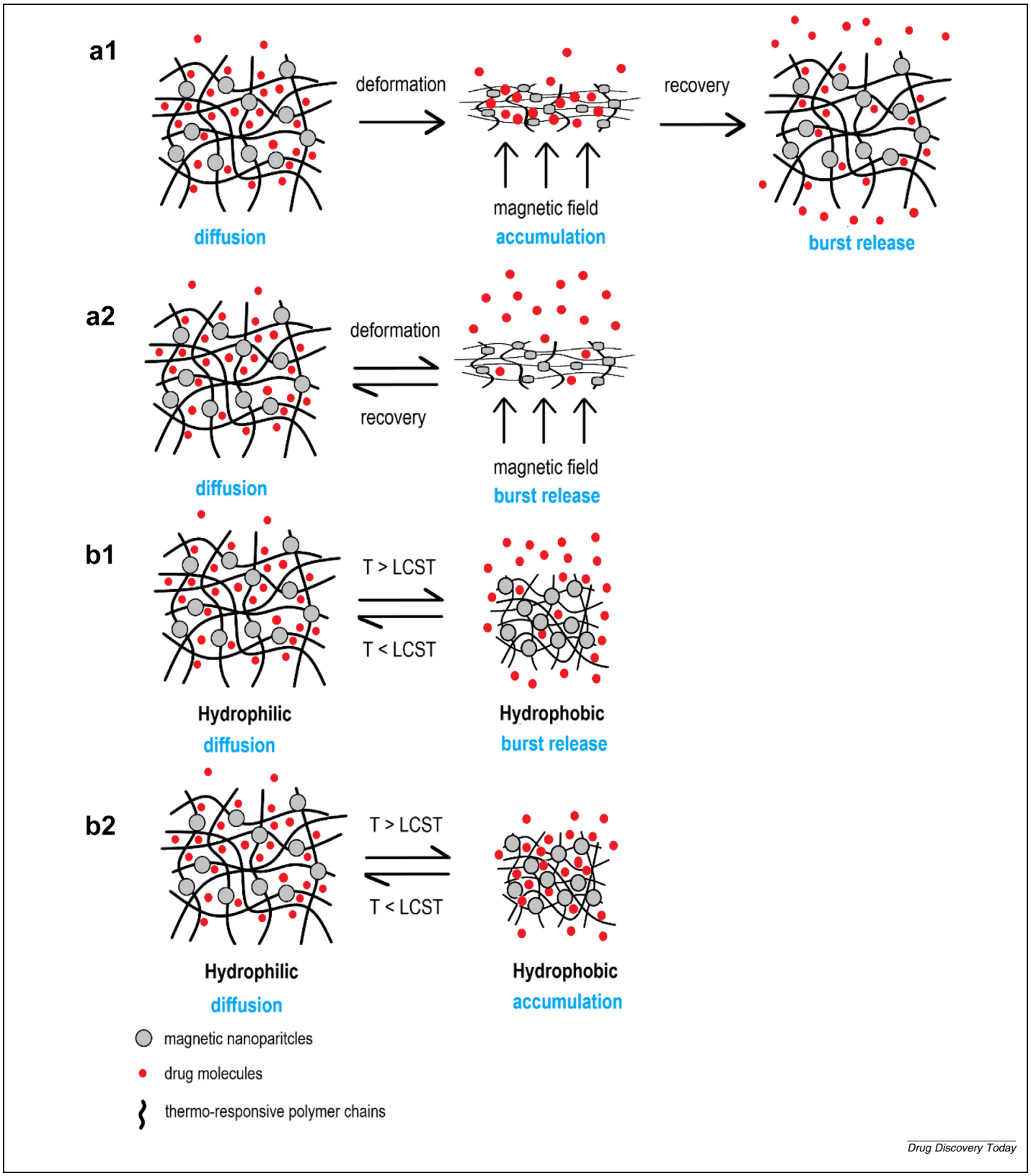

FIGURE 3

Schematic description of the drug release mechanisms of ferrogels: (A) matrix deformation induced by externally applied magnetic fields and (B) gelation induced by the association of polymeric chains beyond LCST.

(GC) and oxidised hyaluronate (OHA) solution (without extra chemical crosslinkers) could be used to fabricate ferrogels with the addition of SPIONs.[p65]

Polyacrylamide (PAAm) gels, which are one of the most common hydrogels, have been employed to fabricate ferrogel networks with varied crosslinking densities as a result of their low toxicity, cell compatibility and high elasticity.[p64] However, the addition of a crosslinking agent, initiator and catalyst is necessary for the synthesis of PAAm hydrogels.[p64] As a kind of physical crosslinking method, freezing–thawing has been used for the preparation of PVA-based hydrogels owing to its simplicity.[p79] Ferrogels have also been prepared using other polymer systems such as gelatin-ferrite. In addition, injectable temperature-sensitive hydrogels have been coupled with ferromagnetic particles.[p13]

Besides magnetically induced matrix deformation, the other mechanism for releasing drugs from ferrogels involves degelling as a result of the conversion of high-frequency magnetic fields to heat (Figure 3b).[p1],[p63] When the temperature is below the lower critical solution temperature (LCST), the polymer chains of ferrogels can absorb water and swell.[p10] Then, under an oscillating magnetic field, the MNPs will heat inductively because of power absorption and the subsequent magnetic relaxation of single-domain nanoparticles.[p10],[p87] The produced heat can enhance the degradation rate of these thermo-responsive ferrogels because of their reversible phase transition characteristics.[p80] The polymer chains will de-swell and aggregate into a 'gel' phase because of switching from hydrophilicity to hydrophobicity once the temperature is higher than the LCST.[p80] The porosity and diffusive pathways of ferrogels can be influenced by tremendous volume fluctuations at various temperatures.[p10] Once the magnetic field is switched off, the ferrogels can cool down, and the phase transition reverses.[p69],[p87]

PNIPAM is the most commonly used polymer, because its LCST is about 32 °C.[p47] Hydroxypropyl cellulose and poly (dimethyl aminoethyl methacrylate) also exhibit thermosensitivity,[p47] with a higher temperature leading to hydrogel collapse and the release of encapsulated drug molecules (Figure 3b).[p1],[p88]

This squeezing-controlled release is regarded as superior to magnetically controlled matrix deformation in terms of targeted treatment, because a large number of therapeutic agents can be released simultaneously.[p47] However, the collapse of the hydrogel matrix can also prevent drug release as a result of the immense reduction in diffusive pathways (Figure 3b).[p1],[p13] Given this, ferrogels are potential candidates for use in non-invasive and precise implantable devices with tuneable pharmacokinetics.[p47]

The LCST of hydrogels can be modified by altering the hydrophilicity of the polymers[p47]: for example, the LSCT could be increased by blending in hydrophilic comonomers, such as acrylic acid and acrylamide.[p10],[p47] Thus, the LSCT of thermo-responsive polymers could be controlled easily, along with the grafting of MNPs.[p10]

The spatial distribution of MNPs in magnetic matrices aligns with the direction of the magnetic field.[p89] Thereby, depending on whether they are randomly distributed or laid in a parallel or perpendicular chain-like structure, the distribution of MNPs can affect the mechanical properties of composites in terms of, for example, the elastic modulus, shear modulus and Young's modulus.[p89],[p90] In addition, by controlling the nanochannels in ferrogels along different directions of the externally applied magnetic field, the diffusion behaviour of ferrogels can be adjusted.[p76]

In anisotropic ferrogels, MNPs are aligned in an end-to-end configuration, whereas in isotropic ferrogels, MNPs are distributed randomly, as shown in Figure 4. Thus, the ferrogel nanochannels can be controlled according to the fabricated pearl-chain structure of ferrogels. The drug release rate of ferrogels is controlled by the drug diffusion direction, and the nanochannels are decided by the direction of the magnetic field, which is in the order of anisotropic perpendicular-aligned ferrogels < isotropic ferrogels < anisotropic parallel-aligned ferrogels. In conclusion, the switch between 'on' and 'off' for drug release from hydrogels can be manipulated by different magnetic field directions.

A study by Zhao *et al*. proposed creating an active scaffold in a macroporous ferrogel, which achieves on-demand and reversible delivery of diverse biological agents upon exposure to an external magnetic field.[p74] The alginates used to fabricate the scaffolds were covalently coupled with peptides containing the arginine-glycine-aspartic acid (RGD) amino acid sequence. Pluronic-

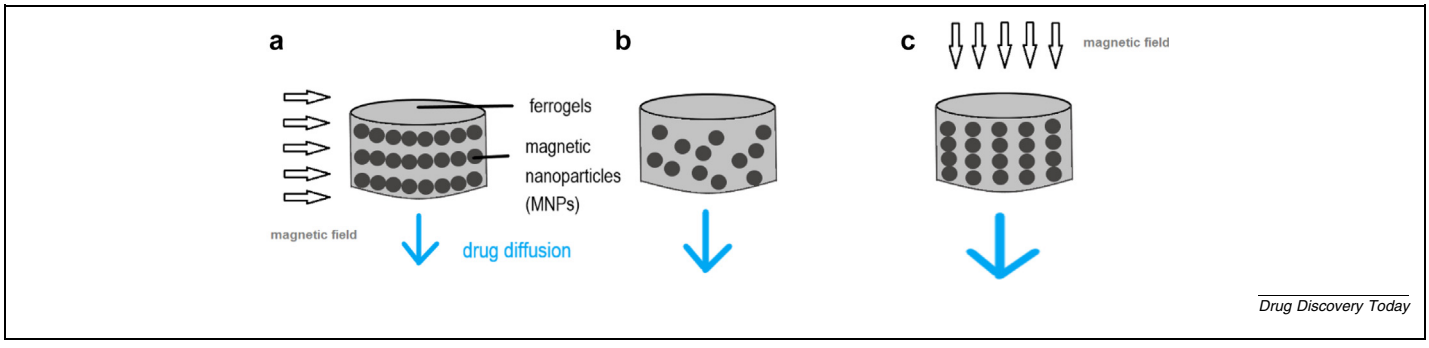

FIGURE 4

Schematic illustration of the effects of the direction of magnetic fields on the drug diffusion behaviour of anisotropic and isotropic ferrogels: (A) the ferrogels were arranged by left-to-right magnetic fields (perpendicular to the drug diffusion direction), (B) isotropic ferrogels (randomly distributed MNPs), and (C) the ferrogels were arranged by top-to-down magnetic fields (parallel to the drug diffusion direction).

coated Fe_3O_4 nanoparticles were embedded in the RGD-modified alginate, and a superparamagnetic gel was formed. These interconnected pores can allow the prompt deformation of the macroporous ferrogel under an externally applied magnetic field to trigger the release of entrapped biological substances. In ferrogel formulations, a high enough concentration of MNPs is needed to allow suitable magnetic sensitivity.[p73]

The poor drug-loading capacity of hydrogels remains the main restriction to their application.[p70] In addition, swellable hydrogels have the potential to block blood vessels.[p91] Although ferrogels have been widely investigated for controlled drug delivery, it is difficult to obtain zero-order drug release before reaching the target sites owing to the thermodynamic nature of diffusion.[p92] Also, it is of vital importance to completely entrap MNPs inside the hydrogel to ensure the attainment of a uniform dispersion and optimised performance without leakage of MNPs in the course of drug release.[p47] Excess MNPs could create an extra health burden, whereas insufficient numbers of MNPs will not be able to produce a rapid response to a magnetic field.[p60] It is therefore challenging to develop ferrogels that possess suitable physicochemical properties for the complex *in vivo* environment.[p63] Consequently, further development of magnetic elastomers is needed to provide a safer structure and composition.

Magnetic sponges (ferrosponges)

In recent years, inorganic sponges have emerged as a promising material for various applications, such as tissue engineering, drug delivery and protein separation, owing to their high porosity, large surface area, enhanced elasticity and interconnected porous structure.[p93] These sponge-like scaffolds have been extensively studied for their role in promoting tissue regeneration and repair, because their 3D porous structure closely resembles that of natural tissues.[p94] The interconnected nanopore design of ferrosponges allows them to hold a large quantity of therapeutic agents.[p68] Additionally, ferrosponges with nanoporous networks exhibit strong magnetic sensitivity, high swelling capacity, good elasticity and hydrophilicity.[p68]

The release of drugs from ferrosponges is influenced by their magnetic properties and interactions between the MNPs and the polymer matrix when exposed to magnetic fields.[p68],[p94] Although ferrosponges are similar to ferrogels, their porous structures provide superior shape recovery, higher absorbency and stronger magnetic sensitivity, because the MNPs are more densely packed within thinner polymeric walls.[p68] Moreover, the incorporation of MNPs into the polymeric walls reduces wall permeability and decreases the drug release rate under magnetic field exposure (Figure 5).[p68]

It has been demonstrated that the polymer matrix plays a more significant role than the amount of MNPs in determining the morphology and pore size of ferrosponges.[p68] Giannelli *et al.* developed magnetic hybrid 3D sponges through freeze-drying, showing that keratin sponges with magnetic MgFe hydrotalcite nanoparticles enhanced cell proliferation, controlled drug release and promoted cellular activity.[p94] Similarly, Zhang *et al.* created magnetic hydroxyapatite–Fe_3O_4 scaffolds with a sandwich structure using the freeze-drying method, demonstrating their potential as smart biomaterials for remotely controlled, on-demand drug delivery using an external magnetic field.[p93] Consequently, the formulation of ferrosponges, including factors such as porosity, crosslinking degree, polymer type and concentration, significantly affects the drug release behaviour.[p95]

Magnetic mesoporous silica nanocomposites

Magnetic compounds, such as iron oxide or gadolinium oxide MNPs and metal ions, have been widely used for designing magnetic mesoporous silica nanocomposites.[p96] These nanocomposites have served as drug delivery platforms for various therapeutic agents, including anti-inflammatory drugs, antibiotics and anticancer drugs. MSNs have gained significant attention in biomedical applications owing to their biocompatibility, large surface area, porosity, versatile functional groups, and customizable pore size and structure.[p94] These unique physicochemical properties make MSNs excellent carriers for therapeutic agents of different sizes, shapes and functionalities.[p44]

MSN surfaces have been tailored to enhance the drug reservoir capacity and to provide functionalities for selective drug loading and controlled drug release.[p97] The most common MSNs feature

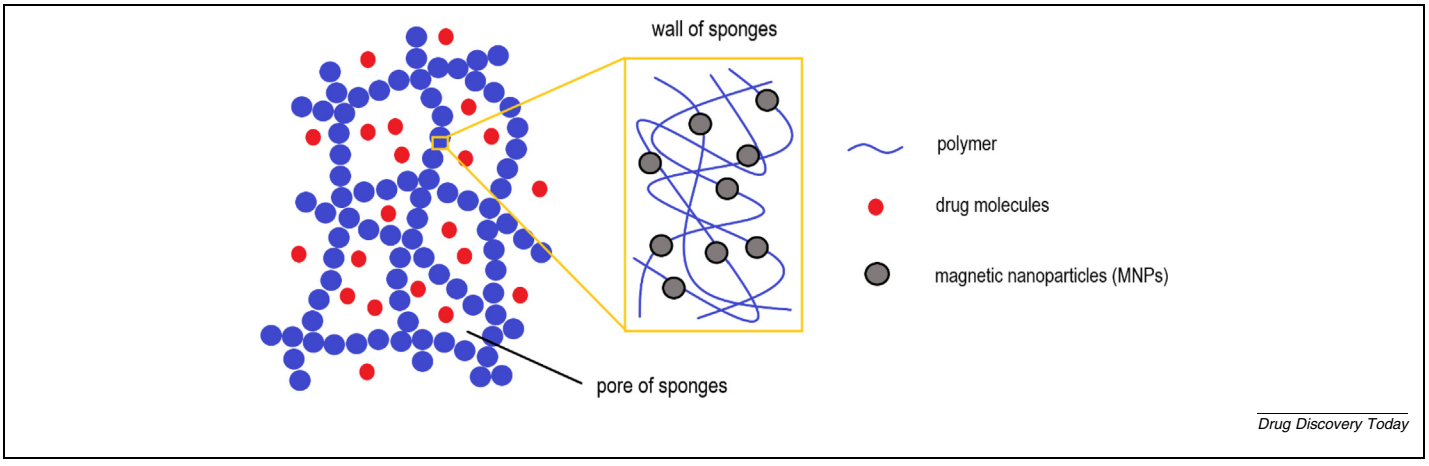

FIGURE 5
Schematic illustration of ferrosponges.

pore sizes ranging from 2 to 10 nm, as well as structural arrangements such as 2D hexagonal and 3D cubic shapes.[p15] Therapeutic agents can be trapped within the pores of the silica surface layer.[p15]

Magnetic MSNs, which consist of mesoporous silica-coated MNPs with a core–shell structure, have been extensively studied for their biocompatibility, water dispersibility and wide range of biomedical applications.[p44],[p62] The combination of MSNs with magnetic properties has been applied in magnetic targeting, MRI and magnetic fluid hyperthermia (MFH).[p15] Their advantageous structural properties for DDSs include a large surface area, modifiable surface, and uniform and large pore volume.[p62] The silica coating further prevents potential MNP toxicity by providing biochemical stability and resistance to erosion.

Magnetic MSNs can be directed to target sites in response to externally applied magnetic fields. For example, Zarkesh *et al*. synthesised ethylenediaminetetraacetic acid (EDTA)-modified magnetic and pH-responsive MSNs with hyaluronan for the delivery of cisplatin, introducing a novel method for targeted drug delivery and MRI.[p98] Similarly, the mesoporous structure of MNP surfaces enhances their drug loading capacity and targeting efficiency. Hollow mesoporous MNPs loaded with anticancer drugs can be prepared through simple methods for targeted cancer treatment.[p99]

Fuentes-García *et al*. developed magnetic cores with a core–shell mesoporous surface using sonochemical methods, resulting in doxorubicin-loaded particles that exhibited magnetic-driven and pH-triggered drug release.[p97] Al-Omoush *et al*. created cisplatin-loaded core–shell magnetic nanocomposites using Fe_3O_4 nanoparticles and a metal–organic framework for controlled drug delivery under an external magnetic field.[p78]

To further improve the targeted delivery of therapeutic agents in MSNs, several strategies have been explored, such as incorporating hyaluronic acid into mesoporous silica-coated Fe_3O_4 nanoparticles. This approach enables selective targeting of tumour cells and efficient drug release both *in vitro* and *in vivo*.[p62]

Other magnetic nanocomposites

Magnetic carbon nanotubes (CNTs), especially magnetic multiwalled CNTs, present several benefits as targeted DDSs, such as simple synthesis and longer residence time for therapeutic agents through the application of magnetic fields.[p91],[p100],[p101] Ahmadi *et al*. prepared curcumin-loaded magnetic nanocomposites through the coprecipitation method; the high release of drugs from these nanocomposites could be a promising property in cancer treatment.[p102],[p103] Sadeghi-Ghadi and colleagues fabricated magnetic nanocomposites composed of alginate, curcumin and Fe_3O_4 nanoparticles to improve the antibacterial efficiency of curcumin.[p104] Barra *et al*. developed chitosan bionanocomposite films using magnetite nanoparticles, and these nanocomposites proved to be versatile components for drug delivery applications.[p103],[p105]

Magnetic force-directed targeting of these nanoparticles to particular tissues in the human body is an intricate process that requires consideration of a variety of factors relevant to the design of the MNPs, the carriers/scaffolds and the physiological properties of the target organ and blood flow. For example, studies have investigated the movement of MNPs in the vasculature, the effects of MNP shape, size and volume fraction, and the positioning of the magnet with respect to the microvessels.[p106] A permeable microvessel of a defined radius and blood flow rheology has been modelled using a two-phase Casson fluid model with two Newtonian and non-Newtonian blood flow regions within the microvessels. A more complex estimation of the system was achieved by incorporating a non-porous MNP structure[p107] and accounting for the unsteady dispersion of MNPs due to a pulsatile pressure gradient calculated from the unsteady Darcy law.[p108] In a different approach, specific consideration has been given to various mechanisms of particle motion, including the Brownian motion, magnetic force-induced particle motion and convective blood flow. This model predicts the capture efficiency of MNPs of different sizes under the influence of a range of magnetic field strengths.[p109]

These transport models can be integrated with chemotherapy efficacy models to investigate the effect of drug dispersion on tumour-effector dynamics and cancer therapy efficacy.[p23] This is an important approach given that the MNPs are able to disrupt the endothelial permeability, thereby modifying the drug distribution into tissues,[p110] a feature that is useful in cardiovascular disease targeting.[p111]

Nowadays, polymeric multilayered nanocapsules with core–shell structures have been developed for DDSs to achieve high drug loading and surface functionalisation through the encapsulating of drugs and contrast agents in the core and shell.[p112]

Although many nanoscale magnetic DDSs have been developed targeting various diseases, only a few strategies have been translated to clinical applications and commercialisation owing to the major limitations of poor controllability, hydrophilic drug loading capability, *in vivo* circulation instability and efficiency.[p113],[p114],[p115] In addition, these strategies rely on complicated chemical syntheses and inappropriate MNP properties, complex crosslinking agents, and inadequate magnet systems.[p30],[p63],[p114] The combination of microscale DDSs and nanocomposites is considered an up-and-coming future strategy for the development of a targeted DDS.[p113]

Microscale magnetic drug delivery systems

Microscale magnetic DDSs are promising candidates in clinical therapy because of their minimal invasiveness and wireless controllability.[p113] The main problem that needs to be resolved is the controllability of microscale DDSs and the precision of drug release at the target site.[p113]

Magnetic microrobots

Microrobots, with their micrometric dimensions, minimal invasiveness and ability to access almost all places in the human body, have the potential to play an important part in biomedical applications.[p8],[p116] The use of wirelessly controlled microrobots in applications such as tumour imaging and targeted drug delivery could increase drug retention while decreasing side effects and trauma.[p117]

Magnetic actuation is the most common strategy for the design of microrobots,[p118] which exist in various forms such

as capsules, 'earthworms', crawling robots and helical shapes.[p119] As well as being used individually, microrobots can be deployed in swarms, which have many advantages such as high drug loading capacity and more flexibility for *in vivo* imaging.[p118]

Both miniature components and entire, complicated microrobot models developed using SolidWorks Software can be fabricated using 3D printing technologies.[p119],[p120],[p121] The finished device must be structurally compact and small enough to navigate within the body,[p119] and suitable and efficient actuation strategies are the determining factor for minimising microrobots; magnetic actuation has become a common strategy owing to its advantage of not requiring onboard power or computation.[p116],[p117] To maintain homeostasis, the amount of drug released from microrobots should be controlled actively in real time in response to physiological changes and therapeutic needs.[p116]

Wireless capsule endoscopes (WCEs), which consist of a miniature video camera, a battery and telemetry, have been developed to solve the problems in examining, diagnosing and curing inaccessible parts of the gastrointestinal (GI) tract.[p122],[p123] After oral administration, captured video can be sent to an external memory system by means of radio frequency signals.[p121] These systems can detect suspected diseases in a comparatively safe, non-invasive and well-tolerated way. Although conventional WCEs show many advantages in terms of swallowability, painlessness, movement inside the body, drug delivery and surgery in the GI tract, they still face many technical problems in realising active or real-time movement without causing damage *in vivo*.[p121],[p123],[p124] Therefore, effective, accurate and versatile methods of WCE actuation are required, because currently WCEs have lower diagnostic accuracy and fewer abilities than traditional endoscopes.[p125] The currently investigated approaches include magnetic actuation, battery-powered motor actuation and hybrid actuation. Microbubble-driven micromotors, for example, rely on the collapse of microbubbles and the subsequent hydrodynamic jet to create a quick inertial effect.[p126]

One issue facing microrobots is that the energy supply is expensive, and it is difficult to realise multi-directional motion or backwards movement.[p121],[p124] But it is hoped that the application of magnetic torque could solve the problem of energy supply in WCE movement. Munoz *et al*. suggest that for capsule endoscopes, an external magnetic system outside the patient's body and internal permanent magnets could interact with each other.[p127] Some commercial systems that have been used to actuate capsule endoscopes, such as the electromagnets in MRI, are too expensive for clinical applications.[p127] Therefore, the application of external permanent magnets manipulated by robotic arms is feasible, easy and cheap, with the aim of remotely triggering magnetic modules inserted in capsule endoscopes. The main challenge in this approach arises from the complicated magnetic interaction between an external and internal magnetic system.[p128]

A WCE device could be controlled actively in the GI tract with an externally applied magnetic field,[p121] and with the addition of a drug delivery module, this could be one of the most promising candidates for achieving targeted, non-invasive, pain-free drug delivery.[p121],[p123] Recent advancements have seen permanent magnets being placed within WCEs, enabling them to achieve rotation and movement with the application of an electromagnetic field generated by Helmholtz coils.[p120] Several prototypes for WCE drug delivery have been developed, but few have been able to attain full control over drug release.[p121] The major problems they face are possible damage to tissues and the difficulties of maintaining precise, real-time control over positioning and location.[p128]

Magnetic microrobots must overcome several hurdles before they can reach clinical trials and commercialisation, such as the development of multifunctional robots, tracking of the device *in vivo* and achieving real-time visualisation.[p119]

Magnetic elastomers

Magnetic elastomers are composite materials made from highly crosslinked polymer matrices containing magnetic particles.[p89],[p90] Traditional magnetic elastomers have issues such as limited flexibility and deformation, and low responsiveness to external magnetic fields. To address these challenges, a new generation of magnetic elastomers has been developed using MNPs and highly elastic polymers, offering improved deformation, adjustable elastic modulus and greater sensitivity to magnetic fields.[p89]

Although ferrogels and magnetic elastomers have certain similarities, ferrogels feature less crosslinking in their polymer matrices, giving the MNPs more freedom to move through the network and form clusters. Based on the distribution of MNPs (determined by whether the composite was exposed to a magnetic field during polymer crosslinking), magnetic elastomers are divided into two types: isotropic elastomer-ferromagnet composites and anisotropic magnetorheological elastomers. Studies show that the elastic and shear moduli of both isotropic and anisotropic magnetic elastomers increase with stronger magnetic fields.[p90] In addition to these DDSs, microbubbles containing MNPs have shown promise as effective carriers for magnetic targeting.[p129]

Although significant progress has been made in developing microscale DDSs that can be triggered by magnetic fields, several challenges persist. One major area for further research is ensuring the biocompatibility of polymer matrices used in magnetic-triggered systems. Additionally, these systems must be designed to resist degradation during repeated inductions, because unexpected degradation could compromise the functionality of the device.[p1]

Macroscale magnetic drug delivery systems

As a result of the limitation of low drug loading capacity, nanoscale and microscale DDSs often struggle to achieve prolonged drug release.[p130] Additionally, their targeting efficacy can be compromised by the complex biological environment *in vivo*. However, increasing attention is being directed towards macroscale DDSs, because these systems offer the potential for spatiotemporal control of drug release at target sites. Based on their drug release mechanisms, macroscale DDSs can be broadly categorised into two types: polymer scaffolds (passive DDSs) and stimuli-responsive devices (active DDSs).[p131]

Magnetic macroporous scaffolds

Because of their 3D structure, porous scaffolds made from natural or synthetic polymers have been extensively studied as drug carriers and tissue engineering scaffolds.[p74] Although these scaffolds are highly efficient in preserving and delivering therapeutic agents and cells, achieving precise and on-demand drug release remains challenging, because the release is primarily governed by passive mechanisms such as molecular diffusion and scaffold degradation.[p132] Based on pore size, porous networks are classified into two categories: macroporosity (100 to 200 nm) and mesoporosity (less than 100 nm).[p68] Active porous scaffolds, which respond to external stimuli, have been developed for controlled drug delivery, enabling more flexible and reproducible drug release.[p74]

Silicon, an essential trace element in mammals, is abundant in human tissues.[p133] The silicone polymer PDMS has been widely studied as a matrix material for fabricating scaffolds with random porous structures as a result of its unique properties, which include chemical inertness, elastomeric behaviour, biocompatibility, low toxicity, high flexibility, nonflammability, ease of fabrication, low production costs, optical transparency and gas permeability.[p134],[p135] PDMS sponges exhibit several attractive characteristics, such as high absorption capacity, high porosity, low density, hydrophobicity, lightweight, low surface tension, elasticity that allows deformation into any shape, repeated compressibility in both air and liquids without collapsing, and excellent recyclability.[p134],[p136]

Magnetic scaffolds can be prepared by incorporating MNPs into structured biomaterials such as polymers, bioceramics and bioglasses.[p137] Because of their 3D network, adjustable stiffness, high porosity and elasticity, magnetic scaffolds could be applied as a magneto-responsive smart carrier for remotely controlled, on-demand drug delivery.[p93] Controlled delivery of drugs via these systems requires a thorough characterisation to ensure a homogenous drug distribution. In an interesting recent development, the drug-release profiles of several designs of magnetic scaffolds have been collected from the literature and the data have been used to develop mathematical kinetics models. It was found that models based on a modified Gompertz equation can successfully describe the dissolution rates under magnetic fields.[p137]

Additionally, PDMS sponges can be produced within a few hours, and large-scale production is feasible through a sugar-templating process. When carbonyl iron (CI) microparticles are incorporated into PDMS sponges with 3D macropores, they provide tuneable forces that can trigger drug release via external magnetic stimulation.[p138] Different PDMS sponges can be fabricated with CI or Fe_3O_4 nanoparticles and varying weight ratios of PDMS prepolymer and curing agents. Optimised magnetic PDMS sponges have demonstrated great potential for delivering drug solutions.[p139]

Tolouei *et al*. developed a two-compartment biomaterial system consisting of a magnetically actuated biphasic ferrosponge enclosed within an outer macroporous gelatin hollow scaffold.[p95] The outer scaffold is designed with an interconnected macroporous structure to support cell infiltration and residence. The inner compartment includes an Fe_3O_4-loaded alginate sponge in the top section and a pure alginate sponge in the bottom section. This biphasic ferrogel system demonstrates significant deformation in response to magnetic fields and facilitates drug release from the lower compartment, enabling delayed and magnetically triggered drug delivery.[p95]

Magnetically triggerable implants

In recent years, implantable DDSs have gained significant attention for enabling controlled drug release, particularly when oral administration is not ideal.[p131],[p140] In the treatment of localised diseases, these implants offer advantages over traditional injections by bypassing physiological barriers without causing the pain associated with repeated invasive skin punctures.[p140] Research has shown that implants are highly effective in suppressing inflammation and angiogenesis.[p141]

Typically, an implantable DDS consists of a reservoir, a microscale chip and a pump.[p140] The reservoir is made from biocompatible materials with strong mechanical properties. Most clinically applied implantable DDSs are cylindrical and free of sharp edges, simplifying implantation and removal.[p140] The device's size is customised to accommodate drug administration frequency and release duration. However, challenges such as bulky design, complex electronic components, unpredictable drug delivery and the need for battery replacement or additional surgeries limit their widespread use.[p142]

Active DDSs, which are more versatile than diffusion-based systems in managing complex drug release kinetics, have been widely studied for treating conditions such as cancer, diabetes and sclerosis.[p140] For clinical applications, the ideal implants should be compact and easily retrievable, especially because most commercially available implants are made from non-biodegradable polymers.[p116],[p143] It is also crucial that therapeutic agents remain stable within the device until released.[p140]

With advancements in 3D printing, customised implantable DDSs are now possible.[p143] Magnetic actuation offers a space-saving alternative to electric power supplies and circuitry, providing wireless activation, rapid response, no need for batteries, biosafety and improved tissue permeability.[p140] Magnetically triggered implants have been extensively researched, utilising external magnetic fields to actuate drug release by moving or deforming the liquid medication-loaded magnetic components in the reservoir.[p142] One example is a magnetically triggerable DDS, which combines a drug solution-loaded magnetic PDMS sponge cylinder with a 3D-printed reservoir, enabling active and repeatable control of drug release via magnetic fields.[p144]

Shademani *et al*. introduced a novel drug delivery device, the microspouter, designed for precise, on-demand local drug delivery.[p138] Using a 3D-printed positive mould, a PDMS reservoir was fabricated, and a magnetic sponge was inserted into the de-moulded (peeled off from the mould), round reservoir (measuring 4 mm in diameter and 1.5 mm in depth), into which the drug was then loaded. To seal the device, a thin PDMS membrane was securely bonded to the top of the sponge and reservoir using plasma treatment. A small aperture 90×90 μm^2) was created in the centre of the membrane through laser ablation.

Two drugs were used to test the microspouter's drug release capabilities: methylene blue (a water-soluble model drug) and

docetaxel (a hydrophobic drug with poor solubility in water). The experiments showed that this implantable device allows for simple and precise control of both the drug release duration and dose. Moreover, the activity and efficacy of docetaxel were maintained even after more than a month of encapsulation. The microspouter also demonstrated potential for safe and long-term drug release owing to its low background leakage and high drug loading capacity.[p138]

Clinical applications of DDSs with magnetic stimuli have so far been unsuccessful as a result of their relatively low efficacy and difficulties in controlling the MNPs.[p19] More effort should be given to developing novel magnetic-field-triggerable DDSs to meet the needs brought about by personalised medicine for the safe and effective delivery of drugs to individual patients.[p145]

Future directions

Magnetic DDSs offer an unprecedented opportunity for targeted drug delivery with the aid of a magnetic field to guide the distribution of nanoparticles to the target tissue. Recent MNP designs have taken advantage of new magnetic cores, innovations in the use of polymers and various functionalisation strategies. An example is the use of thermoresponsive polymer coating along with superparamagnetic iron oxide in the design of MNPs that not only aid cancer treatment by producing hyperthermia under alternating magnetic fields, but also produce a temperature-dependent chemotherapeutic delivery.

Despite the wealth of research into the design and *in vitro* characterisation of these systems, as well as efficacy studies *in vivo*, the true potential of this technology has not been realised in terms of clinical applications. To enable translation into the clinic, there are a number of hurdles and research gaps that need to be overcome, as well as a need for technological developments. First, the targeted nature of these applications necessitates a thorough characterisation of their distribution within human body tissues, with respect to the nanoparticle characteristics, the design of the magnetic fields and the properties of the diseased tissue (e.g., the solid tumour size, vasculature and permeability). Hence, to achieve the best possible targeting outcome, unlike with other nanoparticle DDSs, there are additional characterisation and standardisation requirements with respect to the magnetic field and its utilisation. Another challenge that impedes MNP applications for targeted drug delivery is the targeting of deep tissues with an external magnetic field. Promising strategies are being developed that include robotized precision magnetic platforms.[p146]

The behaviour of magnetic polymeric composites in complex biological pathways, especially in relation to the fluid flow characteristics of blood and the dynamic cellular microenvironment, should be investigated for various MNP designs. Such designs should be optimised in terms of the magnetic core and the MNP size, shape, structure and functionalisation to achieve the desired drug release kinetics at the target site. However, the challenge of utmost importance is the scalable, standardised and homogeneous production of MNPs: a problem that can hinder dose uniformity, and hence clinical application. In addition, the targeting, drug release and pharmacodynamic properties of these delivery systems should be optimised.

Now, technological developments are beginning to enable the detection of MNPs through ultra-low magnetic field sensing (e.g., magneto relaxometry imaging), which can allow us to quantitatively characterise the spatial distribution of MNPs within human body tissues in real time.[p147] Because the tissue distribution of MNPs is still an area of concern, such technologies will be instrumental in the clinical development and safety assessment of magnetic DDSs. Progress in clinical validation, regulatory approval and cost-effectiveness will be crucial for the successful integration of magnetic DDSs into mainstream medical practice.

Conclusion

Magnetic polymeric nanocomposites are based on embedding MNPs within a polymeric matrix, and this combination of magnetic and polymeric features gives rise to new structural properties that can have applications in drug delivery and imaging. These nanocomposites are prepared by complex techniques that carefully interlink the unique properties of the magnetic elements with the adaptive nature of the polymers, allowing them unparalleled versatility. A closer look into recent progress made within the field uncovers the transformational potential of magnetic polymeric nanocomposites.

Author contributions

Conceptualisation: **A.N.** and **T.G.** Data curation: **K.S.** and **A.N.** Writing (original draft preparation): **K.S.** Writing (review and editing): **A.N.** and **T.G.** Visualisation: **A.N.** and **T.G.** Supervision: **A.N.** and **T.G.** All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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