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Regenerative medicine: Hydrogels and mesoporous silica nanoparticles

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ABSTRACT

Hydrogels, that are crosslinked polymer networks, can absorb huge quantities of water and/or biological fluids. Their physical properties, such as elasticity and soft tissue, together with their biocompatibility and biodegradability, closely resemble living tissues. The versatility of hydrogels has fuelled their application in various fields, such as agriculture, biomaterials, the food industry, drug delivery, tissue engineering, and regenerative medicine. Their combination with nanoparticles, specifically with Mesoporous Silica Nanoparticles (MSNs), have elevated these composites to the next level, since MSNs could improve the hydrogel mechanical properties, their ability to encapsulate and controlled release great amounts of different therapeutic agents, and their responsiveness to a variety of external and internal stimuli. In this review, the main features of both MSNs and hydrogels are introduced, followed by the discussion of different hydrogels-MSNs structures and an overview of their use in different applications, such as drug delivery technologies and tissue engineering.

1. Introduction

Nanoscale materials have significantly transformed both research and industry, particularly in the biomedical field [1,2]. The rise of nanomaterials for many biomedical applications comes from the unique ability to control the characteristics, properties, and behaviour of the particles in several physiological environments. This advancement has given rise to a new discipline known as nanomedicine, marked by the development of nanoparticles that exhibit revolutionary physico-chemical characteristics, specific applicability, and predictable outcomes [3].

Despite these advancements, a universal nanocarrier that can effectively treat all diseases in all patients remains missing. In this sense, the most popular nanoparticles in the biomedical arena include liposomes, lipid nanoparticles, polymer nanoparticles, and inorganic nanoparticles, such as those made of gold, iron oxide or silica [4]. Among the later, mesoporous silica nanoparticles (MSNs) are a class of porous silica-based nanoparticles with pore sizes between 2 and 50 nm that exhibit a unique combination of well-defined and tuneable physico-chemical properties. Their unique porous structure and tunable properties has inspired their application in many different scientific areas. Among them, drug delivery technologies have been explored thanks to the MSNs biocompatibility, ease of surface functionalization, and ability to encapsulate and deliver a variety of payloads. In this regard, MSNs can transport huge loads of therapeutic bioactive molecules to precise locations in the body for disease treatments with higher efficacies and much lower side effects than the free drug treatment [5,6]. MSNs are promising nanomedicines compared to other nanomaterials for three main reasons: (i) their unique physico-chemical properties, such as high surface area and tuneable pore sizes, (ii) their targeted drug delivery capabilities that enhance therapeutic efficacy, and (iii) their consistent and controllable release profiles that improve treatment predictability [7].

Focusing first on their physico-chemical properties, MSNs have a highly ordered, three-dimensional porous structure with pore sizes ranging from 2 to 50 nm. This mesoporous structure originates during their synthesis, that is commonly based in the combination of three techniques: (a) the *sol-gel* process, which is a versatile method for synthesizing silica materials by undergoing hydrolysis and condensation reactions of a silicon alkoxide precursor; (b) the surfactant-templated synthesis that employs surfactants as structure-directing agents to achieve mesoporous silica with well-defined pore structures; and (c) a modification of the Stöber method conducted under dilute conditions to generate monodisperse, spherical silica nanoparticles [8–11].

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Moreover, the unique properties of MSNs, including controllable size, composition, and surface chemistry, have rendered them attractive for numerous applications. Their porous architecture facilitates the encapsulation and release of a wide variety of biomolecules and therapeutic agents, thereby enhancing their potential as drug delivery systems (Fig. 1) [6,12–17].

Additionally, the chemistry of the MSNs surface can be easily tuned thanks to the presence of silanol groups located at the surface of the matrices. The literature has described many surface modification strategies to covalently attach almost any functional group [18]. Consequently, the host–guest interaction can be designed on-demand allowing the engineering of versatile nanocarriers.

The second advantage of MSNs lies in their adaptability regarding surface chemistry. The functionalization of silanol groups on the silica walls allows for the engineering of host-guest interactions, which are critical for the effective delivery of therapeutic agents. This interaction not only prevents premature leakage but also enables the transport of large biomolecules, such as proteins and DNA, protecting them from biodegradation during their journey within the body.

Third, MSNs are particularly appealing due to their predictable biological outcomes. In this sense, a critical consideration for all nanoparticles employed in drug delivery, regardless of nanocarrier type, is their ability to deliver payloads to specific locations within the body. This targeted delivery enhances therapeutic efficacy while minimizing potential side effects. Consequently, the design of any nanocarrier necessitates careful evaluation of its in vivo biological behaviour [19,20]. Importantly, MSNs should be robust enough to protect the loaded cargo during the journey and degrade upon accomplishing their mission. The literature has demonstrated the biodegradability and clearance of silica-based nanomaterials [21]. In this regard, the kinetics of degradability and clearance of nanosilica can be tuned from a few days to weeks [22]. All these features make MSNs unique nanocarriers that combine the chemical and physical stability of silica, and the great potential derived from their network of cavities [6,23,24].

However, and despite these strengths, there are several biological barriers that MSNs would encounter when administered to a patient, which constitute a major bottleneck of nanoparticle mediated drug delivery, reducing their therapeutic profile and, consequently, preventing their successful translation into the clinic [25].

A possible way to overcome these obstacles might be based on using biomaterials, specifically hydrogels, as potential nanoparticle administration vehicles (Fig. 2). In this sense, the combination of MSNs and hydrogels offers a versatile platform for various biomedical applications, including drug delivery, regenerative medicine, cancer therapy, and tissue engineering, as it would be described throughout this review.

Hydrogels are three-dimensional hydrophilic polymer networks that can absorb large quantities of water, with porous structure that permits NPs encapsulation. They present good biocompatibility, outstanding flexibility, and functional adjustability. These MSNs-hydrogel hybrid systems leverage the unique properties of both components to achieve enhanced performance and functionality. The combination of MSNs with hydrogels leads to the creation of multifunctional biomaterials with enhanced mechanical properties, self-healing capabilities, and stimuli-responsive behaviours, among other features, making them highly suitable for applications in regenerative medicine. This strategy would provide a localized and controlled nanoparticle administration system that can improve the therapeutic efficacy of those specific nanoparticles.

Regarding the potential applications, the combination of MSNs and hydrogels has fuelled significant interest in different research areas, particularly in drug delivery technologies, tissue engineering and other biomedical imaging applications.

Among drug delivery systems, the porosity and surface area of MSNs allows for efficient loading of therapeutic agents, while the hydrophilic nature of hydrogels can modulate the release kinetics of the cargo, that could be released in response to certain environmental triggers. The combination of both mechanisms might improve the solubility and stability of poorly water-soluble therapeutic agents. Additionally, this combination can provide sustained and controlled release profiles, reducing the potential burst effects and triggering the delivery in response to specific stimuli, such as pH, temperature or physiological environment.

Tissue engineering research has also taken advantage from the combination of hydrogels with MSNs thanks to their combined properties of biocompatibility, mechanical features and controlled release of certain biomolecules. In this sense, Hydrogels provide a favourable environment for cell attachment and proliferation, while MSNs can enhance mechanical properties. These features have fuelled the creation of multifunctional scaffolds with enhanced mechanical properties, able to provide a controlled delivery of growth factors or bioactive molecules that promote tissue regeneration and stimuli-responsive behaviour. Altogether, has allowed the development of scaffolds for cell growth and bone regeneration.

Last, but not least, this MSNs-hydrogel combination has showed interest in the field of infection, both as antibacterial coatings and for developing wound healing materials. The mechanisms of this combination are based on the controlled release of several pharmaceutical agents, since MSNs can be loaded with antibiotics or antimicrobial agents, while the hydrogel matrix provide a sustained release of other antimicrobial agents over time, reducing bacterial load while promoting tissue repair. This synergistic effect allows the combination of different cargoes to enhance the antibacterial effect compared to individual components.

This review would focus on the different strategies employed for loading MSNs in different hydrogels for many different biomedical

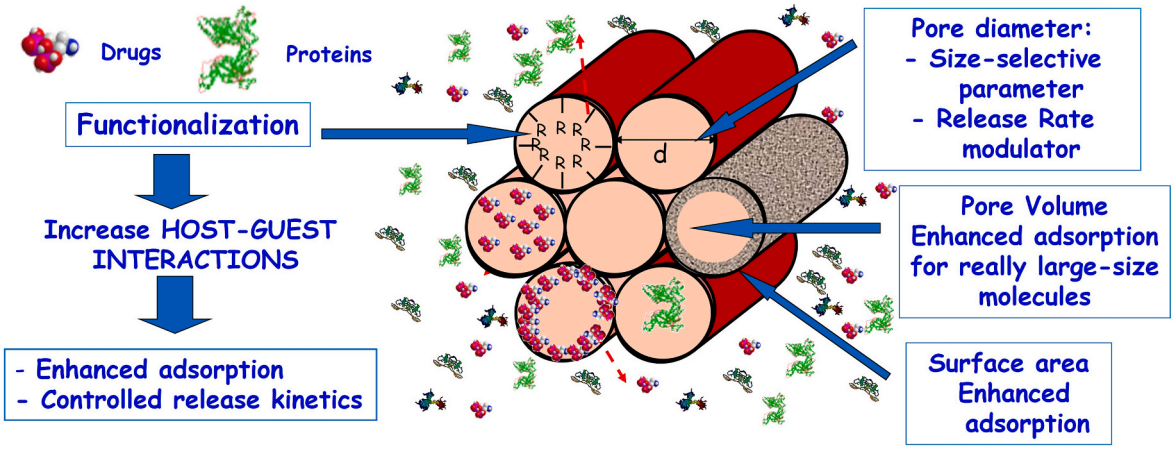

Fig. 1. Schematic representation showing how the textural and chemical characteristics of mesoporous materials make them ideal for controlled drug delivery.

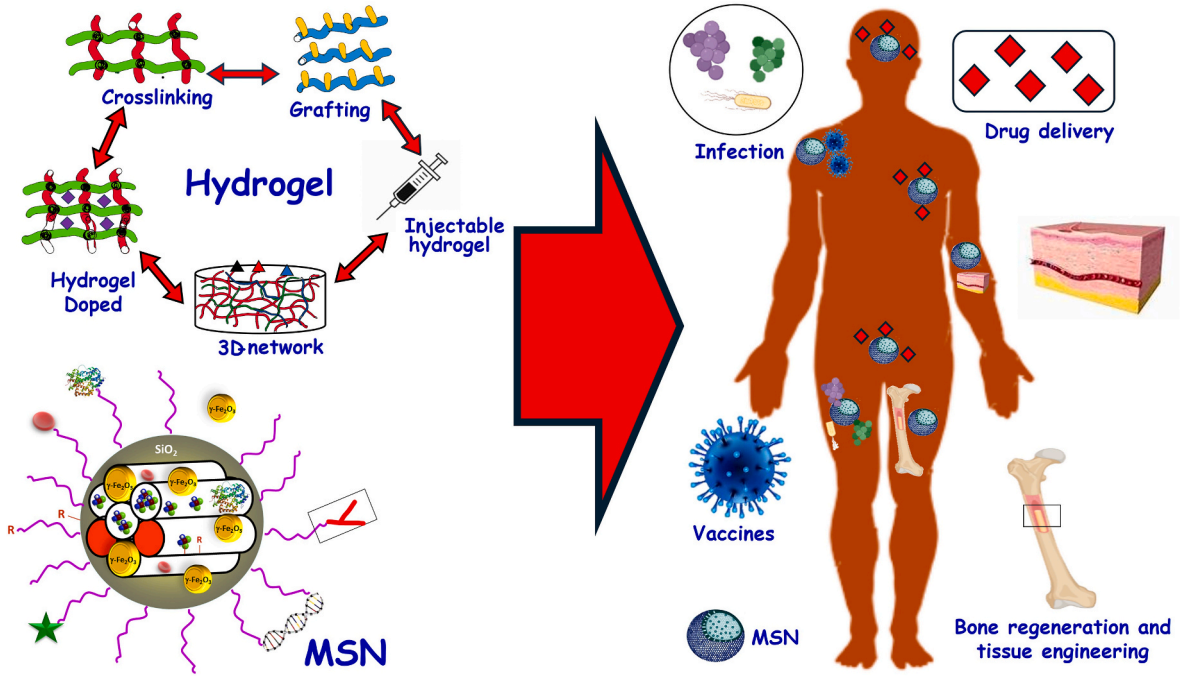

Fig. 2. Schematic representation of different hydrogels and mesoporous silica nanoparticles (MSN, left) and some potential biomedical applications (right) to infection, drug delivery, wound healing, vaccines, bone regeneration and tissue engineering.

applications. The synergistic combination of MSNs and hydrogels offers a versatile platform for various applications across multiple fields. Their unique properties allow for enhanced performance in drug delivery and tissue engineering, among other applications, as it will be here reviewed.

2. Hydrogels

The term *hydrogel* is closely associated with the concept of biomaterial and is often regarded as a pivotal solution for bridging the gap between physical and biological systems. One of the major healthcare problems is related to tissue loss and organ failure. Their unique ability to mimic the extracellular matrix, promote cell adhesion, and facilitate tissue regeneration positions them as effective solutions for addressing the potential complications resulting from damaged tissues and organs.

The hydrogel concept was first introduced by Wichterle and Lim in 1960 [26] with the synthesis of poly(hydroxyethyl methacrylate) used in the manufacture of contact lens to increase the wettability while maintaining their structural conformation. Hydrogels can be synthesized via crosslinking of monomers or polymers, employing either covalent or non-covalent interactions, such as hydrogen bonding and electrostatic forces [27].

One of the most remarkable properties of hydrogels is their ability to swell significantly by absorbing large volumes of water or biological fluids while maintaining their original structure. Water can be absorbed thanks to the presence of polar hydrophilic groups attached to the polymer framework, such as, primary amines, carboxylic acid groups or amides, among others. Consequently, their water absorption ability is closely related to their chemical composition, that can be designed to fulfil any specific requirements depending on the application. This results in a tuneable swelling character pointed out by the hydrophilic character of those groups, the swelling media and the crosslinking degree.

The physical properties of hydrogels are characterized by their elasticity, resilience, and soft assembly, along with versatile structural designs and adjustable functionalities. Their high-water content and porosity closely resemble natural tissues and confer good biocompatibility, typically exhibiting low toxicity and gradual biodegradability in physiological environments [28,29]. This adaptability makes hydrogels suitable for various biomedical applications, including tissue engineering [30], disease therapies [31], wound healing [32], controlled drug delivery [33], 3D printing [34] or biosensing applications [35], as it will be described in this review. Additionally, hydrogels might provide a versatile platform for biomedical material fabrication depending on the final application. In this sense, they can be designed as implantable, injectable, or sprayable hydrogels, which has fuelled their application in many biomedical areas [36–39].

Regarding biodegradability, crosslinked chains of biodegradable hydrogels can be degraded through contact with enzymes, microorganisms or water molecules which makes them excellent candidates to be used as implant devices. Examples of biodegradable polymers typically used in drug delivery applications include Poly(vinyl alcohol) (PVA), Poly(lactic) acid and Poly(Lactic-co-Glycolic) Acid (PLGA) [40,41].

Furthermore, hydrogel-based biomaterials should be compatible with the immune system, which is an aspect linked to the hydrophilic character of hydrogels and the potential irritation to the nearby tissues. Additionally, hydrogels can act as drug release systems with a tuneable release rate. For example, pH responsiveness for specific drug delivery or the presence of different ions and drug molecules that results in a slower release rate.

2.1. Hydrogels classification

Hydrogels can be classified according to different factors, including the polymer source and composition (materials involved in hydrogel formation), the crosslinking method employed for the synthesis, their network charge, durability, or their potential responsiveness to certain stimuli. (Table 1). For instance, hydrogels can be derived from natural polymers (e.g., polysaccharides, polypeptides) or synthetic polymers (e.g., PVA poly(ethylene glycol)). Natural hydrogels are often biocompatible and biodegradable but may lack mechanical strength. In contrast, synthetic hydrogels offer better stability and mechanical properties but generally exhibit lower biological activity.

Table 1
Hydrogels classification according to different factors. (IPN: Interpenetrating Network).

Hydrogels classification			
Polymer source and composition	Crosslinking method	Network charge	Stimulus response
Natural or synthetic hydrogels Homopolymers, copolymers, semi-IPN or IPNs	Chemical crosslinking Physical crosslinking	Non-ionic, ionic (cationic and anionic) and ampholytic hydrogels	Physical, chemical and biochemical response

2.1.1. Classification based on polymeric composition

Hydrogels can be obtained from natural polymers (*natural hydrogels*), synthetic polymers (*synthetic hydrogels*), or a combination of both (*hybrid hydrogels*). Typically used natural polymers include polypeptides, polysaccharides, or even nucleic acids [42,43]. These have the advantage of their appealing biological properties, such as innate bioactivity, non-toxicity, biocompatibility, and biodegradability. Furthermore, these are accessible, abundant, and relatively inexpensive. In contrast they possess relatively poor mechanical strength and weak stability which limits their applicability.

Typical examples of synthetic polymers employed for the production of hydrogels are PVA, poly(ethylene glycol) (PEG), poly(2-hydroxyethyl methacrylate) (PHEMA), poly-N-isopropyl acrylamide (PNIPAM), poly (acrylic acid) (PAA) or poly(acrylamide) (PAAM) [44]. They show dimensional stability together with a good control in their physical and excellent chemical properties and mechanical strength. In contrast, their biological activity and biocompatibility is generally lower than natural polymers. In addition, this type of polymer does not usually induce the regeneration of new tissue as quickly and effectively as natural polymers when implanted [43].

The combination of natural and synthetic polymers includes natural polymers that have been chemically modified, as methacryloyl gelatine [45], or a combination of both natural and synthetic components that will present the main characteristics of both components: the bioactivity and biocompatibility of natural polymers together with the versatility of synthetic polymers.

Hydrogels can also be classified as homopolymers (one type of monomer), copolymers (two or more monomers, where at least one is hydrophilic), semi-interpenetrating networks (semi-IPNs), formed when lineal polymer chains are enclosed into a polymer network without any crosslinker agent, or IPN hydrogels (when several polymer networks are crosslinked between them by a crosslinker agent, either synthetic or/and natural polymers) [46].

2.1.2. Classification based on crosslinking method

Crosslinking is defined as the process of chemically linking two or more molecules through a covalent bond leading to three-dimensional structures. Hydrogels are considered as hydrophilic polymeric gels obtained from crosslinking of monomers or polymer chains to provide those three-dimensional structures. The type of crosslinking employed for the synthesis of hydrogels is crucial, since it will have a significant impact on the properties of final hydrogel in terms of elasticity, viscosity, toughness, rigidity, hardness, or thermal behaviour [47]. Additionally, the crosslinking would have a strong influence on their swelling degree and the maintenance of the 3D-network structure when swollen [48]. Therefore, in general, as the degree of crosslinking increases, an increase in mechanical properties is observed, along with a lower equilibrium swelling rate. In addition, another key parameter to be considered, which is closely related to the degree of crosslinking, is the adhesion, which decreases with the crosslinking degree due to the restrictions in mobility of hydrogel chains [49].

In view of the crosslinking method, there are two types of hydrogels: Chemical and physical hydrogels. In the case of *physical hydrogels*, crosslinking occurs through weak and temporary non-covalent interactions, such as hydrogen bonds, hydrophobic, ionic or Van der Waals interactions [50]. These interactions may be reversible by environmental changes, such as pH, temperature, and simple mixing of components. Their importance lies in the lack of cross-linking agents for their obtention, which might be of interest from the economic and/or environmental point of view. They are usually soluble in water or organic solvents when heated due to the breakdown of those weak interactions. In relation to their mechanical properties, they are fragile and weak, since the 3D polymer network is formed by purely physical weak interactions [51,52].

On the other hand, *chemical hydrogels* are characterized by permanent and strong covalent linkages between the polymer chains. This means that chemically crosslinked hydrogels would not show a reversible response and will be non-soluble in aqueous media. This results in outstanding thermal, mechanical, and chemical properties, that offer very versatile and selective systems.

2.2. Mechanical properties of hydrogels

Hydrogels possess multiple properties such as biodegradability or biocompatibility together with optimal mechanical properties, that make them excellent candidates for a wide variety of biomedical applications. When it comes to mechanical strength in hydrogels, this is defined as the ability to maintain their structural integrity under mechanical forces. Thus, every hydrogel will have different and exclusive characteristics which makes them suitable for multiple applications in relation with their properties. From the point of view of their mechanical properties, hydrogels are versatile due to their flexibility, elasticity, stiffness and deformation properties. In this sense, stiffness properties of hydrogels are a crucial parameter in hydrogels for tissue engineering. The rigidity and the viscoelastic and mechanical properties of hydrogel scaffolds will define their performance and stability together with their injectability or gelation ability. In addition, the mechanical properties will have a great impact on their in vivo and in vitro behaviours and some biological parameters such as cellular microenvironment, cell adhesion, cell proliferation, differentiation or even cellular morphology. Moreover, when it comes to therapeutic drug delivery, their flowable nature is an important parameter. Therefore, they can be customized by modifying the cross-linking density or the polymer chain length with the main objective to control parameters such as their mechanical strength, their shear modulus or stiffness [53]. In relation to the measurement of the mechanical properties of hydrogels, the two most common methods most used are rheometry and dynamic mechanical analysis (DMA). Thus, it is possible to obtain their rheological properties in terms of viscoelastic behaviour or their response to deformation forces (strain and stress). In this way, it will be possible to obtain hydrogels with the appropriate characteristics for the multiple applications of these systems in biomedicine, such as, for example, tissue engineering/regeneration and drug release.

2.2.1. Mechanical properties in drug delivery systems

When talking about drug delivery systems, the main objective of these is to deliver a therapeutic amount of drug to the affected site in the body in order to obtain rapid drug action. Regularly, hydrogels have been routinely used to develop drug delivery systems due to their outstanding properties, such as their porous structure, tissue compatibility, ease of functionalization and permeability to solutes. In relation to mechanical strength, it is crucial to avoid failures in the structure to ensure that the hydrogel behaves intact throughout the process of drug delivery. To deliver drugs to the desired site, the porous structure of the hydrogel provides an optimal matrix for drug loading, so that the drug encapsulated in the hydrogel dissolves as soon as water enters the system and leaks into the surrounding aqueous medium by diffusion. Therefore, an optimal design of hydrogels with application in drug delivery must consider factors such as drug encapsulation, drug release and the release kinetic and in addition, the composition (density,

crosslinking or strengthening fillers) of the polymers that constitute the hydrogel. Among the most relevant mechanical characteristics of hydrogels with application in drug delivery, it can be included the following.

- Elasticity and flexibility, related to the ability to conform and adhere to the irregular surfaces of tissues with hard mechanical stresses. The main purpose is to obtain optimal contacts at the target locations avoiding hydrogel's deterioration.
- Viscoelasticity, related to their capacity of exhibiting viscous and elastic behaviour during mechanical stress during stages of compression or tissue movement [54].
- Adhesion, related to an optimal integration of hydrogel and tissue in the surrounding environment, allowing closer contact between them and improving drug delivery efficiency [55].

2.2.2. *Mechanical properties in tissue engineering*

The main purpose of hydrogels with application in tissue engineering is the reparation of injured tissues due to their structural similarity to the extracellular matrix. Among their usual features, it is possible to highlight by their hydrophilicity, biodegradability, biocompatibility, porosity and viscoelasticity.

In the design of hydrogel-based scaffold for regeneration of bone, cartilage, or other damaged tissues, the most important challenge is to ensure that the scaffold can withstand and support the internal stress–strain of tissues. While being able to create an appropriate environment for cell growth.

Another key aspect is centred in resorbable scaffolds. When these are implanted, the main objective is achieve a beginning of cell growth at the same speed as the degradation of the scaffold happens. If the scaffold undergoes a too rapid degradation with insufficient cell growth could translate into a failure of the hydrogel based scaffold. But on the other hand, an excessive stability may retard and could result in a failure of the remodelling process of the damaged tissue. This translates into negative responses in terms of fibrosis and encapsulation [56].

2.3. *Hydrogels as therapeutic agents in biomedicine*

Hydrogels have shown great promise as bio-compatible materials in a wide range of therapeutic applications. The unique properties of hydrogels, such as water content, softness, flexibility, porosity, permeability and biocompatibility, together with their great affinity towards water and other physiological fluids, resemble those of many soft living tissues, which has inspired their use in the biomedical field. In this regard, hydrogels have shown great promise in a wide range of therapeutic applications, although both natural and synthetic hydrogels present pros and cons. In this sense, they can be modified to emphasize the optimal properties of its constituent elements, in terms of biocompatibility, encapsulability and plasticity, which results in a precise control over their therapeutic outcomes.

From an engineering perspective, hydrogels can be divided into two main categories based on their application: *injectable* and *non-injectable hydrogels* (Fig. 3). Injectable hydrogels are generally based on the idea that the 3D polymer networks can be injected as liquid into the body, to then form in-situ a solid hydrogel. They are characterized by an easy and minimally invasive way of administration, representing a less aggressive method for the patient. On the other hand, non-injectable hydrogels are usually produced before being implanted, so they must be moulded to the appropriate size and shape, and then implanted through surgery, with the subsequent potential complications of this procedure. This approach represents a more aggressive option for the patient since injectable biomaterials facilitate spontaneous in situ gelling.

Hydrogels have been explored for various biomedical applications, including tissue engineering and drug delivery. In tissue engineering, hydrogels can mimic the extracellular matrix, facilitating cell attachment and promoting tissue regeneration. Their versatility enables the development of multifunctional hydrogels capable of restoring and maintaining damaged tissues, with improved properties (mechanical behaviour, biocompatibility, therapeutic benefits, or antibacterial activity), have significant implications in biomedicine and healthcare. Some of their main applications include bone regeneration, cardiac repair, cartilage repair, nerve regeneration, skin trauma, osteoarthritis or even hair regeneration. The literature contains numerous examples of functional hydrogels that exhibit enhanced properties, such as increased mechanical strength, improved biocompatibility, and greater responsiveness to environmental stimuli. From the point of view of functionalized natural polymers, 3D printed scaffolds of collagen-chitosan are a promising and innovative therapeutic approach in spinal cord injury and can be used in regeneration of axonal nerve fibres. Furthermore, these scaffolds decrease the formation of scar and cavity, together with functional recovery observed in animal model tests [57]. Another example in relation to nerve tissue regeneration is the combination of hyaluronic acid (HA) with fibrin and a RGD (Arg-Gly-Asp) peptide modified alginate and fibrin, obtaining printed scaffolds with application in nerve regeneration together with the orientation of dorsal root ganglia (DRG) neurons [58].

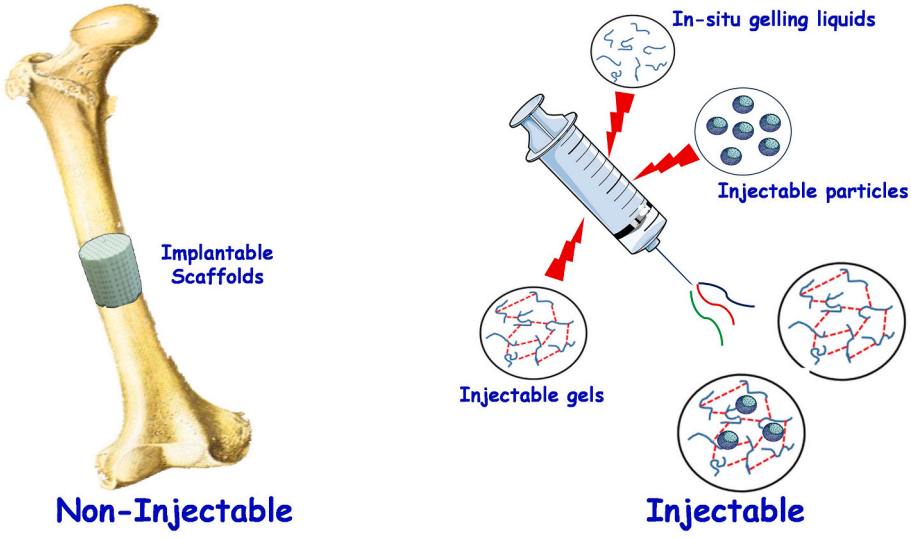

Fig. 3. Schematic representation of non-injectable and injectable hydrogels employed in biomedicine.

In relation to bone and cartilage diseases (bone fractures, tumours or osteoarthritis), and their healing and regeneration process, hydrogels are presented as versatile and promising candidates in applications for tissue engineering and regenerative medicine. Hydrogels can be used to provide 3D scaffolds that allow cell growth and thus promote bone regeneration by mimicking the structure of natural bone to promote bone regeneration [59]. In this field, it can be emphasized HA based hydrogels, with excellent performance in their properties, such as swelling degree, water retention, biocompatibility and osteogenic activity [60].

Regarding to cartilage tissue engineering and the ability to form structures close to natural cartilage, hydrogels based on chondrocyte spheroids loaded in gelatin methacrylate crosslinked with HA methacrylate are able to improve the production of cartilage extracellular matrix, enhancing the cell proliferation, aggregation and morphology in vivo and promoting chondrogenic differentiation [61,62]. In addition, Shi et al. demonstrated that hydrogels with that mixture of functionalized natural polymers, could reduce the levels of reactive oxygen species (ROS) in the inflammatory microenvironment present in the implanted injured area. In this way, it is damped this critical factor which may affect the regeneration efficacy [63].

Another challenge faced by hydrogels is the wound healing. Skin is one of the largest human organs and is usually attached by multiple damages, that trigger a series of physiological responses that induce wound repair (wound healing). This is a dynamic and complicated process that involves four well differentiate phases that will allow the wound to heal. In connection with the ideal characteristics for wound dressing, this should provide a moist environment, with an adequate transmission of gases and the capacity of remove exudates from the injured area, promote angiogenesis and moreover, present low toxicity and biocompatibility and biodegradability [64].

Most used hydrogels as wound dressings are those derived from natural polymers such as cellulose, chitosan, HA or collagen. Ying et al. describe injectable hydrogels composed of collagen-HA covalently crosslinked that allows vascular cell growing and promotes the formation of collagen fibre spontaneously together with good biocompatibility and biodegradability [65]. PEG-modified collagen-chitosan injectable hydrogel described by Ding, C. et al. showed self-healing capacity, haemostatic ability, antibacterial properties and injectability. Furthermore, these hydrogels can be applied as sensitive epidermal sensors, promoting the wound healing [66].

Hydrogels can also be applied as drug delivery systems in tissue engineering, providing a controlled spatio-temporal control over the release of multiple therapeutic agents to the injury site or even designed to target specific cells or tissues through the incorporation of specific ligands and molecules in hydrogel structure. Additionally, hydrogels protect and stabilize the encapsulated drugs from inactivation or degradation due to variations in pH or degradation by enzymes until their release towards the target site [67]. Among the most common mechanisms used in hydrogels for drug delivery in biomedical applications, it is worth mentioning those who exhibit responsive behaviour towards exterior stimuli such as pH, temperature, exposure to light or specific biomolecules.

Regarding pH-sensitive hydrogels, these represent intelligent carriers with swelling and shrinking properties against changes in pH values. For this purpose, it can be employed hydrogels with ionizable moieties (carboxylic acids and amines), which can be deprotonated or protonated at pH variations or hydrogels that contain acid-labile linkages, with the aim of enhance their biocompatibility and drug loading capacity. Typical examples of such hydrogels are those based on natural polymers such as alginate, chitosan or hydroxy-propyl cellulose. Zhu et al. developed a pH-sensitive hydrogel composed of carboxymethylated konjac glucomannan and sodium Tri metaphosphate with application in intestinal targeted delivery system. These hydrogels showed a variation in their swelling behaviour due to pH value changes [68,69].

On the other hand, hydrogels that show a response to changes in temperature can be described. In this way and taking into account both the lower critical temperature of the solution and the upper critical temperature, it is possible to observe the changes produced due to interactions between its hydrophilic and hydrophobic segments, thus modifying the solubility of the cross-linked network, as well as allowing phase transitions from sol to gel. Among monomers typically used in the production of temperature-sensitive hydrogels are included N-isopropylacrylamide and cross-linkers such as poly-ethylene glycol or methylene bis-acrylamide, with optimal adjustability in their mechanical and physical properties [70].

Tang et al. developed thermosensitive biocompatible hydrogels based on N-isopropylacrylamide monomer crosslinked with a new diacrylate derivative with a lower critical solution temperature. These hydrogels showed a temperature-dependent swelling profile, with reversible temperature response from high values at lower temperatures to temperatures of 50 °C, where the hydrogel showed the lowest swelling value [71]. Zhao et al. developed studies focused on the system HPMA-copolymer-based dexamethasone, with the ability to form solid hydrogel at 30 °C after intraarticular administration, with anti-inflammatory properties in arthritis and osteoarthritis diseases [72].

Furthermore, it can be detailed the natural thermo-responsive polymers with chemical modifications to improve their temperature response. Examples of those are certain polysaccharides such as amylose, cellulose derivatives, agarose, amylopectin) or even protein derivates like collagen, elastin-like polypeptides or gelatin. These natural polymers are able to form thermo-reversible hydrogels, but with the limitation of poor mechanical strength.

The exposure to light (ultraviolet, visible or infrared lights) also can serve as a non-invasive and efficient stimulus in the drug release from hydrogels in a wide range of medical applications (wound healing, chemo-therapy or photodynamic therapy). In this way, these hydrogels undergo processes such as phase transitions, alteration of their mechanical properties, such as stiffness, or biochemical activation after exposure to light, leading to the release of drugs. In this way, with a controlled distribution of the drug in the body, therapeutic efficacy is increased, along with the reduction of possible side effects. In this sense, Li Z et al. developed a new hydrogel system that upon visible irradiation light was able to seal an irregular wound in situ and after that, upon UV irradiation light, dissolve the hydrogel on demand to improved healing process in diabetic chronic wound [73,74].

Despite all these advantages and multiple applications, and even though hydrogels are widely used in the research field of biomedicine, some of them still have certain limitations that restrict their applications in this area. In this sense, their clinical applications have been limited by some pitfalls, such as low thermal stability, poor mechanical properties, and their random biodegradation profiles [75]. As the properties of hydrogels are highly dependent on their chemical composition, pure hydrogels have often shown limited mechanical performance, among other limitations. In this sense, the potential combination of hydrogels with nanoparticles in a single platform to crosslink the polymer networks might allow the formation of composite gels mechanically stronger. In addition, the incorporation of NPs into hydrogels has also broadened the properties of the composites and subsequently expanded their field of applications. This is of particular importance in the biomedical area, where NPs are great assets and their incorporation into hydrogels has given then access to a whole new world of applications and possibilities, such as drug delivery technologies, as it will be reviewed here.

3. The synergistic power of nanoparticles and hydrogels

The combination of nanoparticles and hydrogels leverages their unique properties for cutting-edge diagnostic and therapeutic applications in various biomedical fields, such as drug delivery and tissue engineering, among others. The combination of hydrogel and nanoparticle

components creates synergies that enhance the performance of these composites in applications were using each component separately may yield suboptimal outcomes. As a result, research and applications involving these biomaterial-based platforms are advancing rapidly, demonstrating significant improvements in areas such as drug delivery, tissue engineering, and biosensing. While numerous variations exist based on the chosen nanoparticle or hydrogel, they typically comprise NPs embedded into hydrated and cross-linked polymeric networks [76–78]. A wide variety of nanoparticles have been incorporated into hydrogels to enhance their performance and expand their applications in fields such as drug delivery, tissue engineering, and regenerative medicine. In this review, we will focus primarily on mesoporous silica materials integrated with hydrogels, highlighting their promising applications.

Recent advancements in MSNs have significantly fuelled a range of biomedical applications, both in vitro and in vivo [6,79–81] thanks to their unique physico-chemical properties, as it has been mentioned above. However, some critical challenges remain to be solved. Safety concerns, potential toxicity, and unintended systemic effects pose significant hurdles to their widespread clinical translation [82]. In addition, similar limitations plague hydrogels in the biomaterials field, such as, inherent characteristics like hydrophilicity, compressibility, and mechanical properties that often complicate the loading and release of therapeutic agents [76,83–85]. However, the combination of two remarkable biomaterials into a single integrated structure leverages the strengths of both platforms to overcome their individual limitations.

3.1. Benefits of hydrogel-nanoparticles hybrid systems

The strategic integration of nanoparticles and hydrogels marks a major advancement in biomaterials science. This combination effectively addresses the limitations of each component, enhancing their collective performance and offering substantial potential to transform various biomedical applications. Ultimately, this synergistic approach facilitates the development of safer, more targeted, and more effective therapeutic interventions, such as improved drug delivery systems and advanced wound healing strategies.

The hydrogel component plays a multifaceted and essential role in nanoparticle-based drug delivery. It could ensure biocompatibility, minimizing tissue reactions and inflammation, allowing for safe and extended therapeutic interventions. The hydrogel matrix could also act as a shield, protecting encapsulated nanoparticles from degradation and premature release, guaranteeing their stability and effectiveness within the body [86,87]. Additionally, due to its inherent hydrophilicity, the hydrogel can facilitate the loading of hydrophilic drugs, enabling efficient loading and sustained release of a broad spectrum of different payloads. Furthermore, hydrogels could be designed to respond to specific stimuli like pH, temperature, or enzymes, triggering the precise release of drugs at the target site. In this sense, the hydrogel can modulate release kinetics, maximizing the concentration of therapeutic agents at the desired location and minimizing systemic side effects [76–78].

On the other hand, nanoparticles are revolutionizing the capabilities of composite systems by acting as multi-functional tools. Firstly, they boost the system's capacity to store therapeutic agents maximizing the impact of the drugs and paves the way for more potent treatments [6,79–81]. Secondly, the conductivity of the entire system can be fine-tuned by selecting specific nanoparticle materials, opening doors for applications in areas like biosensing, electroceuticals, and targeted drug delivery [6,85]. Furthermore, nanoparticles offer precise control over the release of therapeutic agents. This is achieved through mechanisms like triggered degradation or stimuli-responsive release such as light-responsive nanoparticles, which can be incorporated to trigger drug release using external light, offering unparalleled precision in therapeutic interventions [88] and ensuring they reach their target locations, minimizing unwanted side effects [6,79–81]. Additionally, certain nanoparticles function as efficient crosslinking agents, strengthening the composite system's mechanical stability and integrity, making it suitable for in vivo applications.

Some of the straightforward advantages of nanoparticle-hydrogel systems can be exploited in drug delivery technologies. Encapsulating nanoparticles with drugs inside a hydrogel delay the release of the drug, avoiding its premature release. The localized administration of the hydrogel allows targeting the drug to a specific affected area, improving the efficacy of the treatment [89]. In addition, platforms can be designed to release the drug in response to specific stimuli, such as pH changes or irradiation with near-infrared light, in the so-called stimuli responsive drug delivery platforms [76]. Fig. 4 describes a scheme of general properties of hydrogels and nanoparticles, and the benefits of these hybrid systems.

3.2. Hydrogels with mesoporous silica nanoparticles

The combination of MSNs and hydrogels has been explored in various biomedical applications due to their complementary properties. The reason for that relay on the above-mentioned characteristics of MSNs and hydrogels. Some relevant applications of this combination include drug delivery systems, regenerative medicine, cancer therapy, and a variety of other biomedical applications, such as tissue engineering, wound healing, or biosensing.

From the synthesis perspective, there are several methods of crosslinking between the hydrogel and MSNs (Fig. 5). However, most of the examples refer to either physical or chemical encapsulation of nanoparticles within the hydrogels. The former is based on weak physical interactions to promote crosslinking. On the other hand, nanoparticles could participate in the crosslinking process so they would be directly integrated and linked to the hydrogel network in what is known as chemical crosslinking, where nanoparticles are contributing to the formation of the crosslinked hydrogel network.

3.2.1. Physical crosslinking in hydrogels with MSNs

The physical crosslinking of hydrogels with MSNs is based on non-covalent interactions between the polymer chains and the nanoparticles in terms of hydrogen or coordination bonding and hydrophobic or electrostatic interactions [90]. In this case, the primary role of nanoparticles is normally based on improving the therapeutic properties rather than structural duties. The absence of an initiator could be considered as an advantage since it leads to a reduction in the toxicity.

In a different approach, MSNs can be adsorbed into polymer gels to act as connectors between polymer chains. In fact, the adsorption of polymers at the surface of MSNs can improve the adhesion between hydrogels and/or biological tissues. The high specific surface area of MSNs can enhance the adhesiveness of hydrogel polymer chains. Thus, adhesion energy of hydrogels of PDMA can be increased with the deposition of little amounts of MSNs, which improves when using spherical aggregates of MSNs [91]. In relation with this concept, the adhesive properties of MSNs can be modulated by varying their average particle diameter along with their pore size, being important factors on their interaction with the PDMA matrix [92]. Another evidence of strong intermolecular interactions between MSNs and hydrogels is described in Chitosan/MSNs composites, where the mesoporous structure of MSNs improves the sustained release of active components together with an enhancement of their strength and physicochemical properties [93]. In this sense, the drug delivery applications of these hydrogel-MSNs composites will be reviewed below.

3.2.2. Chemical crosslinking in hydrogels with MSNs

The chemical crosslinking of hydrogels with MSNs can be explained in two possible crosslinking methods. For one side, the crosslinker method and on the other, the chemical reaction method. Chemically crosslinked hydrogels-MSNs composites are very versatile since both MSNs and polymers can be functionalized with a plethora of chemical

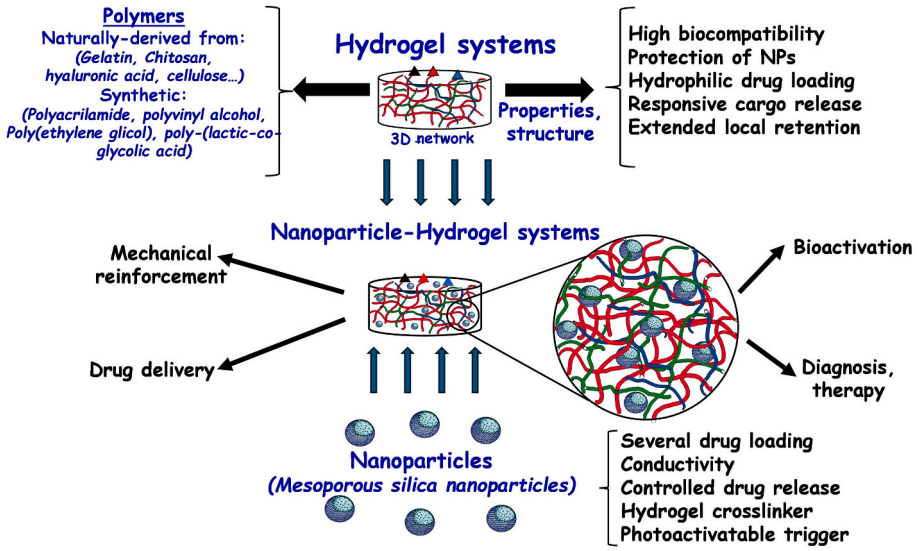

Fig. 4. General properties of hydrogel systems and nanoparticles. Description of how these hybrid systems present multiple advantages.

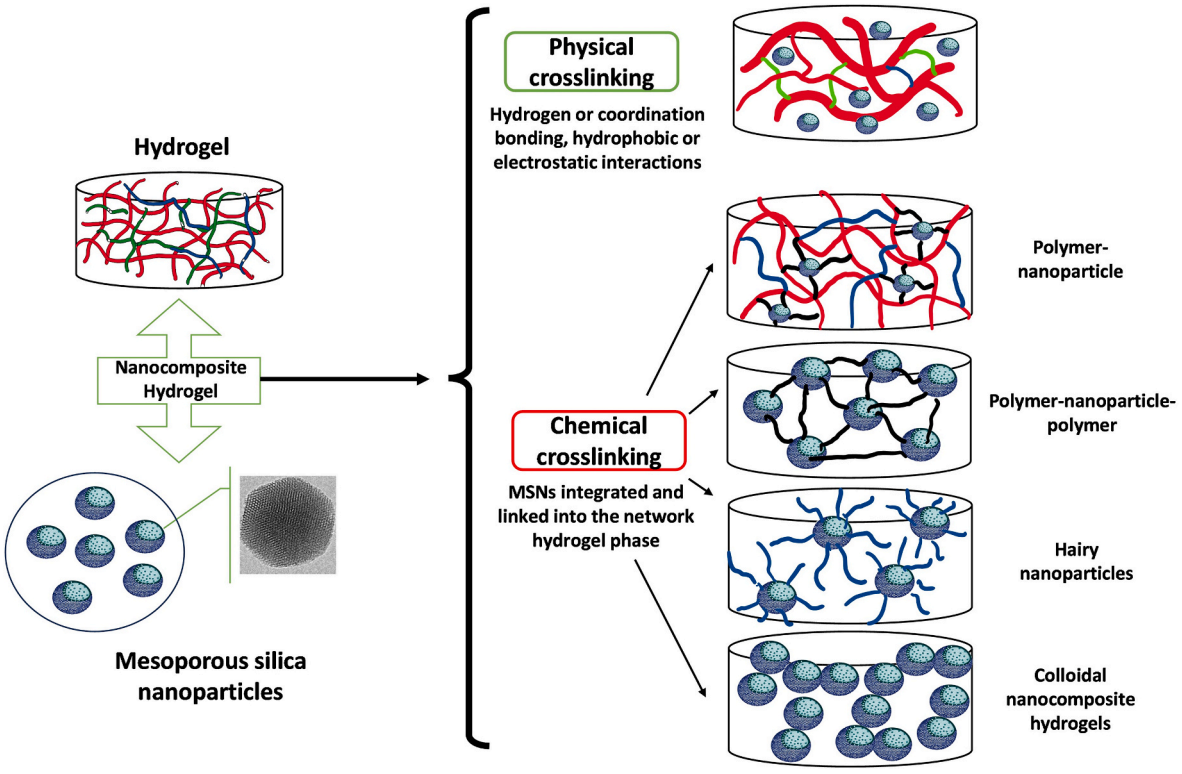

Fig. 5. Different crosslinking methods between hydrogels and MSNs.

groups, such as nucleophilic moieties as thiol, amine, or hydrazide functional groups to react with electrophiles such as aldehydes, ketones, vinyl or methacrylate groups.

When it comes to crosslinker method, nanocomposite hydrogels are obtained by chemical crosslinking through covalent bonds, using a chemical crosslinker between MSNs and polymer chains that could be previously formed or in-situ polymerized to form a network structure. Thus, a crosslinked polymer structure can be obtained from either in-situ polymerization of precursor monomers. In relation to chemical reaction methods, chemical crosslinked hybrid hydrogel is obtained from chemical reactions between functional groups present in the molecular chain of a polymer that react with another polymer chain through the formation of covalent bonds.

In both cases, strong covalent bonds are formed through free radical polymerization [94], thiolene click reactions [95] or Schiff base reactions, among others. In this way, compared to physically crosslinked hydrogels, it is possible to obtain a highly crosslinked system, with improved mechanical properties, self-healing properties, in vivo stability, and a tuneable degradation behaviour based on crosslinker concentration.

The simplest approach is to use a small molecule as crosslinking agent between nanoparticles and polymer or precursor monomers, since the hydrogel network can be formed in-situ with the NPs present in the polymerization reaction. Among all of them, methacrylic derivates are

one of the most usual ways to obtain chemical crosslinking, since the characteristic double bound of methacrylate compounds is suitable to polymerize by free radical polymerization to obtain the hydrogel in the easy and rapid way [76,96]. The use of methacrylic comonomers is one of the most used strategies to obtain chemical crosslinking. The presence of methacrylic carbon double bonds enable to perform free-radical polymerization (photo or thermal polymerization), with the use of a biocompatible radical initiator, leading to the formation of crosslinked hydrogels. Among the advantages of free-radical polymerization, it should be emphasized a facile and rapid synthesis that allows to yield heterogeneous network structures. Dextran, natural polysaccharide polymer, was functionalized with glycidyl methacrylate to obtain an easily polymerizable system in aqueous phase with a wide range of applications in tissue engineering [97]. The use of MSNs functionalized with carboxylic acids and loaded with pinacidil (vasodilator drug) allowed to obtain a reinforced nanocomposite hydrogel with a functionalized natural polymer, gelatin methacryloyl through radical photopolymerization and physical and chemical interactions between polymer network and functionalized nanoparticles with promising applications in tissue engineering, functional integration and optimal differentiation of stem cells after transplantation [98].

In relation to self-healing polymers, an ongoing challenge is the obtention of hydrogels with a rapid self-healing capacity and optimal mechanical strength to be used in regenerative medicine applications. The incorporation of MSNs is a promising strategy to improve the mechanical properties of hydrogel, together with some additional functionalities such as bioactivity or controlled drug release. The use of MSNs with a thiol surface functionalization that acts as chemical crosslinker together with a hydrophilic polymer such as polyethylene glycol also functionalized with thiol groups (PEG-SH) allows to obtain hybrid systems through dynamic thiol-disulfide covalent interactions.

The combination of a crosslinked hydrogel based on aldehyde HA and chitosan with modified MSNs with alginate/chitosan polyelectrolyte allowed to obtain a reinforced hybrid hydrogel due to the Schiff base reaction between the amino group of chitosan and the aldehyde group of HA. Thus, the nanocomposite hydrogel showed as an optimal support for a sustained drug release profile of angiogenic drugs and a favourable support for cell adhesion and proliferation for vascularized bone regeneration application [99]. As a result, it is possible to obtain mechanically robust systems and with self-healing properties, good biocompatibility, and tuneable properties in terms of their chemical structure [100].

The main challenges of these chemically crosslinked systems are focused in two main objectives: firstly, the obtention of an environmentally sensitive crosslinking to be able to control more precisely their administration and their undesired degradation [101] and secondly, in the improvement of their properties for multiple applications, from drug loading, biosensing or tumour therapy and cell encapsulation together with better physicochemical properties in tissue engineering applications.

4. Biomedical applications of hydrogels loaded with mesoporous silica nanoparticles

As previously discussed, hydrogels offer numerous advantages in biomedical applications; however, they also face challenges such as weak adhesion, poor mechanical properties, and uncontrolled degradation. The integration of MSNs might mitigate these drawbacks, enhancing the performance of these hybrid systems for applications in drug delivery and tissue engineering, among others. A summary of the systems described together with their main features and applications for their application in drug delivery and tissue engineering is described in Tables 2 and 3 respectively.

4.1. Drug delivery

Nanoparticles offer unmatched versatility for encapsulating therapeutic agents, protecting them from degradation, and facilitating site-specific delivery. When integrated within hydrogels, these nanocarriers benefit from a sustained release profile, appropriated targeting at the site of interest, extended residence time at the target site, and improved bioavailability. This synergy enables to overcome limitations like premature drug release, off-target effects, and systemic toxicity, paving the way for more effective and personalized therapies (Fig. 6).

Considering their drug delivery applications, the main goal of the design of these hydrogel-MSNs hybrid composites is to develop a system with low toxicity, high biocompatibility and high efficiency, both in terms of drug encapsulation and release kinetics. On the one hand, although hydrogels have good properties from the point of view of their application in drug delivery as described in section 2.2, in most cases hydrogels alone are not commonly capable of meeting the demands of control release kinetics because they normally present a large initial

Table 2
Nanocomposite hydrogels with application in drug delivery.

Type of Hydrogel	MSNs drug loaded	Nanocomposite hydrogel improvement	Biomedical application	Cite
Natural polymer: Alginate	Prednisolone	Regulate uncontrolled and fast drug release	Rheumatoid arthritis and multiple sclerosis	[104]
pHEMA	Estrogen	Precise drug delivery-controlled system	Treatment and reparation of damaged tissues after surgical procedures or infections	[105]
Natural polymer: Chitosan	Antibiotics or biomacromolecules: Gentamicin and BSA	Precise drug delivery-controlled system together with their protection toward degradation of biomolecules or antibiotics	Cartilage regeneration through a sustained co-delivery of both biomacromolecules and small chemical drugs	[98]
Natural polymer: Chitosan	Curcumin	Deal with the drawback related to the water insolubility and low bioavailability	Revert the cognitive deficit produced in Alzheimer's disease	[106]
Thermosensitive poly(d,l-lactide)-poly(ethylene glycol)-poly(d,l-lactide) hydrogel	Erlotinib	Deal with the drawback related to the water insolubility and low bioavailability	Delivery nanosystem for localized anticancer therapies	[107]
Natural polymer: Chitosan	Colchicine	Deal with the drawback related to the water insolubility and low bioavailability	High potential in osteoarthritis treatment	[108]
Modified agar, natural polymer, with vinyl-caprolactam	Doxorubicin	Release only under the simulated cancer tissue conditions (pH 4.0 and 40 °C)	Model for parenteral chemotherapy and high haemolytic potential	[109]
Physically crosslinked PNIPAM - MSNs	Mock drug: BSA	controlled drug delivery systems	Potential as temperature-sensitive composite hydrogels for drug delivery and controlled drug release.	[110]
Gelatin methacrylated (GelMa)	Co-administration of drug molecules (Rutin) and oxygen (O_2)	Dual delivery of different bioactive molecules	Local area delivery and tissue regeneration for implantation or even with applications as wound dressings	[111]
Hyaluronic acid (HA)	use of fluorescent probes and release of rich anticancer drugs	Tumour marker detection and local controlled drug release	Location of tumoral cells together with the release of rich anticancer drugs around tumour tissue	[112]

Table 3
Nanocomposite hydrogels with application in tissue engineering.

Type of Hydrogel	MSNs drug loaded/ functionalization	Nanocomposite hydrogel improvement	Biomedical application	Cite
Natural polymer: Aldehyde hyaluronic acid/chitosan	Sphingosine 1-phosphate (S1P)-modified MSNs	Sustained release profile of the angiogenic drug and improvement of mechanical properties	Great potential for vascularized bone regeneration application	[138]
Core-shell nanocomposites, based on poly N-isopropylacrylamide (PNIPAM) and polyacrylic acid (PAA)	Anti-tumor drugs and growth factors	Maintain a sustained release of anti-tumour drugs loaded in the hydrogel, but limited the leakage of growth factors from MSNs.	Trigger the release of growth factors and produce suitable pores with sufficient size for healthy cell growth after tumour chemotherapy	[139]
Hydrogel based on human modified platelet lysates (PLMA)	Osteoinductive MSNs functionalized with bioactive ions, Ca^{2+} and PO_4^{3-} ions	Precise drug delivery-controlled system together with their protection toward degradation of biomolecules or antibiotics	Induce osteogenic differentiation, without loss in the mechanical and biological properties	[141]
Alginate/gelatin hydrogel with Human adipose-derived mesenchymal stem cells (hASCs) encapsulated	MSNs of varying surface chemistry	Improved the stability of the hydrogel beads	Enhances both the proliferation hASCs. Inflammation suppression	[143]
PEG	Thiol surface-functionalized MSNs capable of acting as chemical crosslinkers	Mechanically stronger nanocomposites and rapid self-healing capabilities	Creation of multifunctional self-healing biomaterials for a wider range of applications in regenerative medicine.	[102]
Alginate Dialdehyde-Gelatine	Lysozyme Loaded Cerium Doped Mesoporous Silica-Calcia Nanoparticles	Bioactivity. Co-delivery of beneficial ions for bone regeneration as well as biological agents with anticancer and antibacterial properties.	Customizable, multifunctional scaffolds for bone tissue engineering.	[146]
Collagen/chitosan/hyaluronic acid hydrogel-	Mesoporous silica particles decorated with hydroxyapatite and loaded with alendronate	Minimized burst release	High-potential formulation for safe and effective osteoporosis therapy	[149]
Chitosan/hydroxyethyl cellulose	Puerarin loaded MSNs	Integration of drug delivery and structural matrix, coupled with outstanding biocompatibility	Tendon Healing via Immunomodulatory and pro-regenerative Effects	[151]
Methacrylated gelatin, methacrylate hyaluronic acid	Artemisia argyi extract	Carriers for sustained drug release, ensuring a continuous supply of the bioactive compound to the wound site	Treatment of chronic wounds	[152]
				112

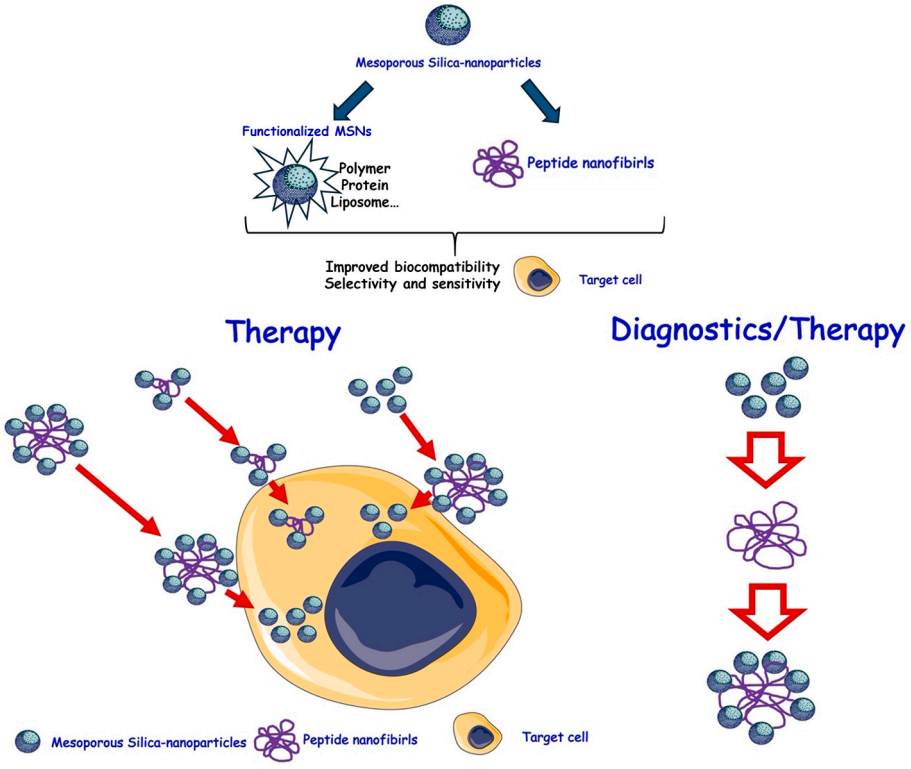

Fig. 6. Different ways in which hydrogels can serve as a vehicle source for MSNs for therapy and diagnosis.

burst of uncontrolled release. On the other hand, MSNs are ideal for drug encapsulation and release, as it has been commented before. Therefore, to compensate for the disadvantages of hydrogels, the addition of mesoporous nanosystems was initially conceived to regulate the uncontrolled and fast release of drugs from hydrogels, to improve the system stability from the drug delivery perspective in biomedical applications related to pharmaceutical active compounds release. A summary is shown in Table 2.

In relation to control drug release in the treatment of inflammatory and autoimmune disease disorders, the research in this topic revealed that the presence of these activated MSNs in alginate hydrogels result in an advanced hybrid biomaterial that could efficiently reduce excessive and uncontrolled initial drug release. For this purpose, Lima et al. reported the characterization of the release profile of prednisolone, corticosteroid drug used for treating rheumatoid arthritis and multiple sclerosis, with a combination of MSNs with a natural polymer (alginate) to obtain modulated properties adapted to the specific microenvironment. Thus, it was possible to obtain biomaterials with an inhibition of nearly 90 % of initial burst effect due to the determinant presence of nanosystem. This effect is attributed to the reduction in the movements in the polymer chains and the distribution of MSNs that make drug release less accessible in the surrounding environment. An all of this with an improvement in mechanical properties with an interconnected pore hybrid polymer network, with make them suitable candidates for physiological and pathological applications in biomedicine [102]. Another example is focused on the treatment and reparation of damaged tissues after surgical procedures or infections, such as damaged endometrium in intrauterine adhesions and formation of fibrous tissue. However, the treatment of this type of problem requires overcoming a series of physical, pharmacological and biological barriers. Physical barriers are related to the inability to promote the proliferation of endometrial cells. Pharmacological barriers imply the lack of local administration of estrogen, the most used drug in those diseases. It is crucial to ensure the required local drug concentration in the affected tissue and avoiding the potential side effects of the increased dosage of estrogen. Thus, the design of the precise drug delivery-controlled system with an improvement in drug efficacy, reduced side effects and optimal mechanical properties is a key factor. For one side, it is crucial the use of hydrogel scaffolds with these 3 characteristics: adequate mechanical properties, good biocompatibility and controlled drug release kinetics. For this purpose, a robust and stable hydrogel based on physically and chemically crosslinked poly(hydroxyethyl methacrylate) and estradiol-loaded mesoporous silica has been successfully explored to promote the vascularization and proliferation of endometrial and stromal cells and then inhibit the progression of fibrosis. This polymer network results in excellent mechanical properties combined with a controlled and sustained release of selected drug to achieve the optimal treatment [103]. And continuing to discuss drug delivery technologies, these have become important assets to deliver antibiotics or biomacromolecules that could be degraded when being freely administered, in a highly sustained manner. Thus, the combination of nanocarriers with hydrogels has also been explored to deliver macromolecules. This is the case of the development of nanocomposite biocompatible hydrogels of chitosan with MSNs to deliver biomacromolecules such as gentamicin and BSA steadily, with application in cartilage regeneration through a sustained co-delivery of both biomacromolecules and small chemical drugs. This translates into chondrocyte proliferation and growth and can be considered as a promising alternative in the non-invasive therapy of cartilage regeneration [93].

Another aspect of crucial importance, together with the control of the initial burst of uncontrolled release drug release, is the possibility of dealing with the drawback related to the water insolubility and low bioavailability due to the inability to cross the blood barrier of biomedical interest. This is the case of curcumin, an encouraging compound on Alzheimer's disease treatment, that is water insoluble, presents poor bioavailability and is instable in biological environments. These characteristics have limited biological applicability. However, a potential solution might be found in the combination of MSNs with hydrogels. Curcumin can be loaded into MSNs with high encapsulation efficiency and dispersed in a thermo-responsive chitosan-based hydrogel to obtain biocompatible nanocomposite hydrogels with excellent viscoelastic and mechanical properties oriented to intranasal administration increasing the ex vivo permeation and able to revert the cognitive deficit in mice with induced Alzheimer's disease [104]. Another example in which hollow MSNs have also been employed to load and release non-soluble drugs is related to the encapsulation of the hydrophobic drug, Erlotinib, together with a thermosensitive poly(d,l-lactide)-poly(ethylene glycol)-poly(d,l-lactide) hydrogel. The hybrid hydrogel was obtained by simple mixing to form of an injectable system with application against non-small cell lung cancer, providing an ideal platform for the obtention of a delivery nanosystem for localized anticancer therapies [105]. Another outstanding example related to a reduced cargo solubility and applied to bone and cartilage tissue engineering is referred to colchicine, with limited bioavailability together with side effects on the intestinal tract if administered orally but high potential in osteoarthritis treatment. Encapsulation of this bioactive compound in MSNs together with a self-healing hydrogel based on pullulan and chitosan, natural, biodegradable, and biocompatible polymer and loaded on cotton fabrics, allows the promotion of colchicine through the skin by modulating the release and the skin permeation. These approach opens new strategies for osteoarthritis therapy with a prolonged, efficient, localized, and friendly trans-dermal delivery [106].

The combination of nanocarriers with hydrogels is also advantageous for delivering antibiotics or biomacromolecules susceptible to degradation. For instance, nanocomposite hydrogels composed of chitosan and MSNs have been developed to steadily deliver biomacromolecules like gentamicin and BSA [93].

A key aspect to keep in mind is the responsiveness of these hybrid systems to certain stimuli with multiple applications in biomedical field. The literature is full of examples showing the importance of smart nanocarriers able to release their cargo only in response to certain stimuli, both internal and external. This technology ensures the efficacy and efficiency of the potential treatment, avoiding many side effects. In this sense, it is important to highlight the pH or thermo-responsive systems which allow to control the release kinetic of bioactive compounds or drugs; variations in pH or temperature in environmental conditions would trigger their release rate [94]. An example of this approach of hydrogel-functionalized MSNs, is the use of modified agar, natural polymer derived of marine polysaccharides, with vinyl-caprolactam, that can govern the drug release in response to the environmental temperature and pH. This modified natural polymer can act as backbone for mesoporous silica system by using carboxylic acid modified MSNs, loaded with doxorubicin, hydrophobic drug, as model for parenteral chemotherapy and high haemolytic potential. The main objective of these hybrid systems is to allow a complete doxorubicin release only under the simulated cancer tissue conditions (pH 4.0 and 40 °C) [107]. Within the thermo-responsive polymers for controlled drug-delivery systems with a sustained drug release, the nanocomposite hydrogels composed of physically crosslinked PNIPAM - MSNs, present great potential in temperature-dependent drug release [108]. The addition of MSNs improves the network structure and adjust the size of the hole while maintaining the thermal properties of PNIPAM, with a phase transition at 33.7 °C. On the other hand, the presence of mesopores of MSNs, allows to enhance the drug loading capacity and a sustained release, which can be controlled with temperature variations. And all this while maintaining good biocompatibility together with a controlled drug delivery system which showed great potential as temperature-sensitive nanocomposite hydrogels for controlled drug delivery systems.

Another significant strategy in biomedical applications is to achieve a dual delivery of different bioactive molecules with the purpose of

obtaining a synergetic therapeutic effect. One example of this strategy is referred to the co-administration of drug molecules (Rutin) and oxygen (O_2) in MSNs, and in this way, thus, improving the cell viability and also reducing the damage produced by hypoxia. This system along with a 3D printable hydrogel (GelMa) allows us to obtain 3D nanocomposite hydrogel scaffolds that enhance cell-viability under hypoxia and/or normoxia conditions. Furthermore, the introduction of nanosystems allowed to improve the rheological properties, mechanical properties and 3D printability or injectability of nanocomposite hydrogels. Thus, it is possible to obtain systems with potential applications as artificial tissue constructs as an alternative route in the obtention of injectable hydrogels with use in a local area delivery and tissue regeneration for implantation or even with applications as wound dressings [109].

From the point of view of biomedical applications of nanocomposite hydrogels, it is important to highlight the use of fluorescent probes to indicate the location of tumoral cells together with the release of rich anticancer drugs around tumour tissue. An example of this approach is the formation of physically crosslinked composite hydrogels that is referred to injectable hydrogels composed of MSN labelled with a fluorescent probe and end capped with HA. The gelation of the system is assisted by the presence of HA as gate cap, targeting agent and cross-linker agent in combination with nanosystems. This nanosystem interacts easily during its synthesis process with the multiple hydroxyl groups present in HA to obtain HA-silica composite hydrogel, since combines the interactions in form of hydrogen bonds due to pH changes that allow this injectable and pH responsive HA hydrogel to self-assemble in situ around the tumoral tissue and MSNs fluorescent labelled for tumour-cell targeting together with the capacity as anti-cancer drug container. This system provides targeted cell labelling to cancer cells for a long time along with a targeted controlled drug delivery system for cancer treatments [110]. In connection with the improvement of selectivity and sensitivity in systems applied in tumour marker detection, magnetic core-shell structure MSNs loaded with a signal molecule and with a surface modification based on amine groups subsequently activated, can be anchored to modified polyacrylamide DNA strand crosslinked to obtain a new biosensor based on a crosslinked nanocomposite hydrogel [111].

There are different ways in which hydrogels can serve as a vehicle source for MSNs to achieve better internalization to improve therapy [112]. First, for scenarios aiming for sustained drug release outside the cells, larger aggregates formed through strong interactions between MSNs and peptide fibrils can function as drug reservoirs, gradually releasing the payload over time. Secondly, it must be noted that aggregates of 100 nm in size can be directly internalized by cells, achieving a more immediate therapeutic effect. Third, direct binding of fibril aggregates to cells creates another pathway for internalization, where MSNs can subsequently attach and accumulate for uptake. This level of control over internalization enables targeted delivery and minimizes potential off-target effects. On the other hand, to optimize approaches for diagnosis and therapy, the best internalization strategy depends on the intended application [112,113]. For therapeutic purposes, the focus lies on maximizing cellular uptake of MSNs to deliver the therapeutic cargo effectively. However, in the context of diagnosing diseases associated with fibrils, attaching MSNs directly to the fibrils without targeting the cells might be more relevant (Fig. 6). This highlights the remarkable versatility of hydrogel-MSN systems, making them adaptable to address various biomedical needs, encompassing both diagnostic and therapeutic goals [112].

4.2. Tissue engineering

Tissue engineering is currently an effective tool in regenerative medicine and its clinical application. It has been based on the creation of three-dimensional scaffolds that serve as matrices for cell growth and differentiation, allowing the formation of new and functional tissues. The scope of tissue engineering has increased considerably, incorporating an interdisciplinary approach including the use of state-of-the-art biomaterials, cell therapies and bioactive molecules [114]. The design of biocompatible and biodegradable biomaterials that mimic the natural tissue environment is critical to provide the structural support and biochemical signals necessary for tissue regeneration [115]. The use of stem cells, such as human mesenchymal stem cells, now offer significant therapeutic potential for the repair and regeneration of damaged tissues [116]. Finally, the integration of bioactive molecules, such as growth factors and cytokines, into scaffolds or cultured cells can modulate the cellular response and promote targeted tissue regeneration [117]. In this regard, in recent years there have been several advances in tissue engineering and its potential to address various medical conditions [118,119]. On the one hand, the type of cells used has evolved and expanded, and on the other hand, the biomaterials chosen as matrix.

A summary of main examples described below are shown in Table 3.

On the cellular side, the methodology for the isolation and culture of human mesenchymal stem cells, with a high capacity to differentiate into various types of tissue cells, has been improved, opening a promising field for personalized medicine in orthopaedics and implant development [116]. In addition, autologous corneal epithelium cultured from the patient's own tissue is being used as an innovative treatment for unilateral limbal stem cell deficiency, a rare disease affecting the ocular surface [120]. As for biomaterials, there are several examples of improvement in the field of tissue engineering. For example, bioartificial autologous skin substitute materials such as antibacterial treatments that replace skin damaged by severe burns [121]. Furthermore, tissue-engineered vascular grafts that offer a promising alternative to traditional vascular grafts, aiming to improve the success rate and reduce postoperative complications [114]. In addition, the development of three-dimensional lung tissue substitutes for next-generation therapies has evolved [122]. In addition, the application of polymer nanocarriers for targeted drug delivery, a novel strategy to improve the efficacy of drugs such as statins in the treatment of hypercholesterolemia, is also being explored [123].

In addition, the applications of tissue engineering have increased considerably in recent years. The use of biodegradable scaffolds for bone regeneration offers a promising alternative to traditional bone grafting, with the potential to improve bone healing and reduce recovery time in patients with fractures or bone defects. On the other hand, the 3D printing of personalized tissues, using the patient's own cells, opens new possibilities for the creation of tailor-made implants for various applications, such as facial reconstruction or heart valve repair [124]. Finally, tissue engineering strategies have the potential to significantly reduce the incidence of transplant rejection using the patient's own cells to grow tissues or organs [114,125,126]. This could mean transplant patients wouldn't need to take immunosuppressive drugs for as long. These drugs can cause side effects, and by avoiding them, patients would have a better quality of life.

The latest findings support the integration of tissue engineering solutions into current medical practice, combining the reduction of healthcare costs with the improvement of patient quality of life [114,127]. In this regard, a particularly outstanding recent development in this field is the use of gene-editing technologies, such as CRISPR/Cas9, to create scaffolds that can actively participate in tissue healing and regeneration [128] These scaffolds are no longer inert structures but are now designed to release growth factors or genetic material at the site of injury, thereby improving tissue integration and function. Another remarkable advance is the emergence of organ-on-chip technology, which involves creating models of human organs on microchips. These chips mimic the complex biological functions of specific organ systems and are revolutionizing drug testing. This technology could significantly reduce the need for animal experimentation and provide a more accurate representation of human physiology, leading to better patient outcomes [129]. For example, the use of biodegradable scaffolds for bone regeneration laid the groundwork for today's gene-edited scaffolds. The principles remain the same (facilitating tissue growth and integration),

but the methods have become more sophisticated, precise and customized. Conversely, while organ-on-chip technology represents a leap forward in the field, it also highlights a gap that exists in current tissue engineering applications: the transition from two-dimensional to three-dimensional complexity. These recent developments discussed together with the above findings reflect both the evolution of established techniques and the beginning of completely novel approaches in the field of tissue engineering.

Tissue engineering attempts to replicate complex tissue structures and functions such as the liver or kidneys faces major challenges. Vascularization, or the formation of blood vessels within engineered tissues, represents another difficulty. Without adequate blood flow, even the best engineered tissues cannot survive and function after transplantation [130]. In addition, the regulatory scenery adds to another level of complexity. Ensuring the safety and efficacy of new tissue-engineered products requires processes that can be slow and costly. However, this approach is necessary to ensure patient safety and treatment efficacy. Despite this, the convergence of bioengineering, materials science and digital technology is opening the way for new approaches [131]. Another frontier to consider is the development of smart biomaterials that can respond to their biological environment, providing signals for healing or tissue regeneration as needed [132]. The integration of these materials with emerging technologies such as nano- and microtechnology could lead to the development of next-generation implants that are tailored to the needs of individual patients.

In this context, hydrogels, with their tuneable structure and biomimetic properties offer ideal scaffolds for tissue regeneration. They promote cell growth, differentiation, and blood vessel formation (neovascularization) while providing structural support for organized cell growth [133]. Additionally, hydrogels can encapsulate and deliver cells, serve as reservoirs for therapeutic agents, and mimic the extracellular matrix due to their tuneable biodegradability. However, limitations like inadequate mechanical strength and limited cell infiltration can hinder their efficacy. The incorporation of nanoparticles, particularly those with bioactive cues or regenerative properties, addresses these challenges. Recent advancements incorporate nanoparticles into hydrogels, enabling tailored biological function, controlled mechanics, and electrical conductivity [76,134]. These composite scaffolds provide structural support, enhance cell adhesion and proliferation, and can even deliver growth factors or other regenerative molecules directly to the target site, promoting optimal tissue repair and regeneration [76]. In this sense, hydrogels are a promising avenue for bone healing research. However, their weak mechanics and limited mineralization post-implantation hinder their application in weight-bearing bone defects. A successful strategy involves incorporating inorganic nanoparticles, particularly mesoporous materials [135,136]. By incorporating MSNs loaded with therapeutic agents, researchers aim to achieve a two-pronged effect: providing a supportive scaffold for tissue growth and simultaneously delivering potent biomolecules to accelerate regeneration. These hydrogels serve as a dual-action platform, providing both mechanical support for tissue regeneration and a means to deliver therapeutic agents [135,136].

4.2.1. Musculoskeletal diseases

There are a variety of applications of nanosystems based on MSNs embedded in hydrogels for applications related to bone and musculoskeletal diseases. Loading bioactive compounds such as proteins that can promote osteogenesis for bone regeneration, into designed core/shell mesoporous silica carriers and then, adding them to injectable hydrogels, allows to obtain release kinetics of zero-order that are favourable in tissue engineering [137]. In this sense, osteoinductive MSNs functionalized with bioactive ions, Ca^{2+} and PO_4^{3-} ions can be incorporated in a hydrogel based on human modified platelet lysates (PLMA) with the aim to induce osteogenic differentiation [138].

Hydrogels for bone tissue regeneration must provide stem cell adhesion and proliferation, together with osteogenic differentiation. In this case, hydrogels of human modified platelet lysates have mechanical stability and excellent biocompatibility; the combination with osteoinductive nanoparticles allows the obtention of a multifunctional bioactive system, able to support stem cell culture and to induce osteogenic differentiation, without loss in the mechanical and biological properties.

While polymeric hydrogels offer established platforms for stem cell cultivation and differentiation, the search continues for scalable systems that mimic the native cellular environment with optimal biological and physical properties for tissue engineering [112,139]. In this regard, a study explored the influence of incorporating MSNs on these factors [140]. Alginate/gelatin hydrogel beads loaded with MSNs of varying surface chemistries (amine- and carboxyl-functionalized, A-MSNs and C-MSNs, respectively) were prepared. Human adipose-derived mesenchymal stem cells (hASCs) were then encapsulated within these alginate/gelatin/silica hydrogels. The inclusion of MSNs significantly improved the stability of the hydrogel beads. Additionally, the expression levels of Nanog and OCT4, key stem cell markers, suggest that A-MSN incorporation enhances both the proliferation and stemless of encapsulated hASCs. Notably, in vivo studies revealed that A-MSNs slightly suppress inflammation. In contrast, C-MSNs appear to influence hASC differentiation. Marker gene expression analyses indicate that culturing hASCs in alginate beads loaded with 10 % w/w C-MSNs leads to a heterogeneous mix of differentiated cells, including osteocytes, chondrocytes, and adipocytes. While this might be beneficial for specific applications, it's not ideal for general cell culture and differentiation purposes. These findings highlight the potential of A-MSNs in engineering biomimetic scaffolds that promote hASC growth and stemless while suppressing inflammation [140]. Another example was the study where mesoporous cerium-doped silica-calcium nanoparticles enhance the composite hydrogel's mechanical strength, promote apatite mineralization on the surface, and stimulate preosteoblasts growth, adhesion, and differentiation in pre-osteoblast cell [141].

In order to improve the engineering of biomimetic hydrogel scaffolds for bone repair, there is the possibility of generating a double network hydrogel with MSNs with improved properties [142,143]. In this sense, a study evaluated a hydrogel combines poly(ethylene glycol) diacrylate and chitosan for a robust structure, achieved through a combination of UV polymerization and ionic crosslinking [142]. Additionally, copper-doped mesoporous silica nanospheres were synthesized and modified with an apatite layer via in-situ biomineralization and polydopamine coating. The composite hydrogels were formulated by incorporating different concentrations of those nanospheres. Analysis revealed the formation of interconnected porous structures within the hydrogels. Notably, the compressive strength significantly increased compared to pure hydrogels. In vitro experiments demonstrated excellent biocompatibility of the composite hydrogels, with high cell viability and significant cell proliferation over a 7-day period. Furthermore, the hydrogels promoted osteogenic differentiation, as evidenced by an increase in ALP expression and a remarkable rise in ARS staining. Additionally, the expression of key osteogenic genes, including RUNX2, Col1a1, and Spp1, was significantly upregulated. These findings suggest the promising potential of this hydrogel as a scaffold for bone regeneration, which results in a composite material with superior mechanical properties and enhanced ability to promote bone cell growth and differentiation (Fig. 7).

In the last few years, bone tissue engineering has become a very hot topic because of the ageing population. In one of those approaches to improve bone repair and the treatment limitations of osteoporosis with bisphosphonates, a multifunctional hybrid system for alendronate (ALN) delivery was investigated [144]. These systems consisted of MSNs decorated with hydroxyapatite, the inorganic fraction of natural bone, and loaded with ALN, immobilized within a collagen/chitosan/HA hydrogel matrix crosslinked with genipin. The hybrid systems exhibited prolonged ALN release (up to 20 days) with minimal initial burst effect. The hybrids also displayed no hemolytic effects and were biocompatible with immune cells, liver cells, and human bone marrow mesenchymal

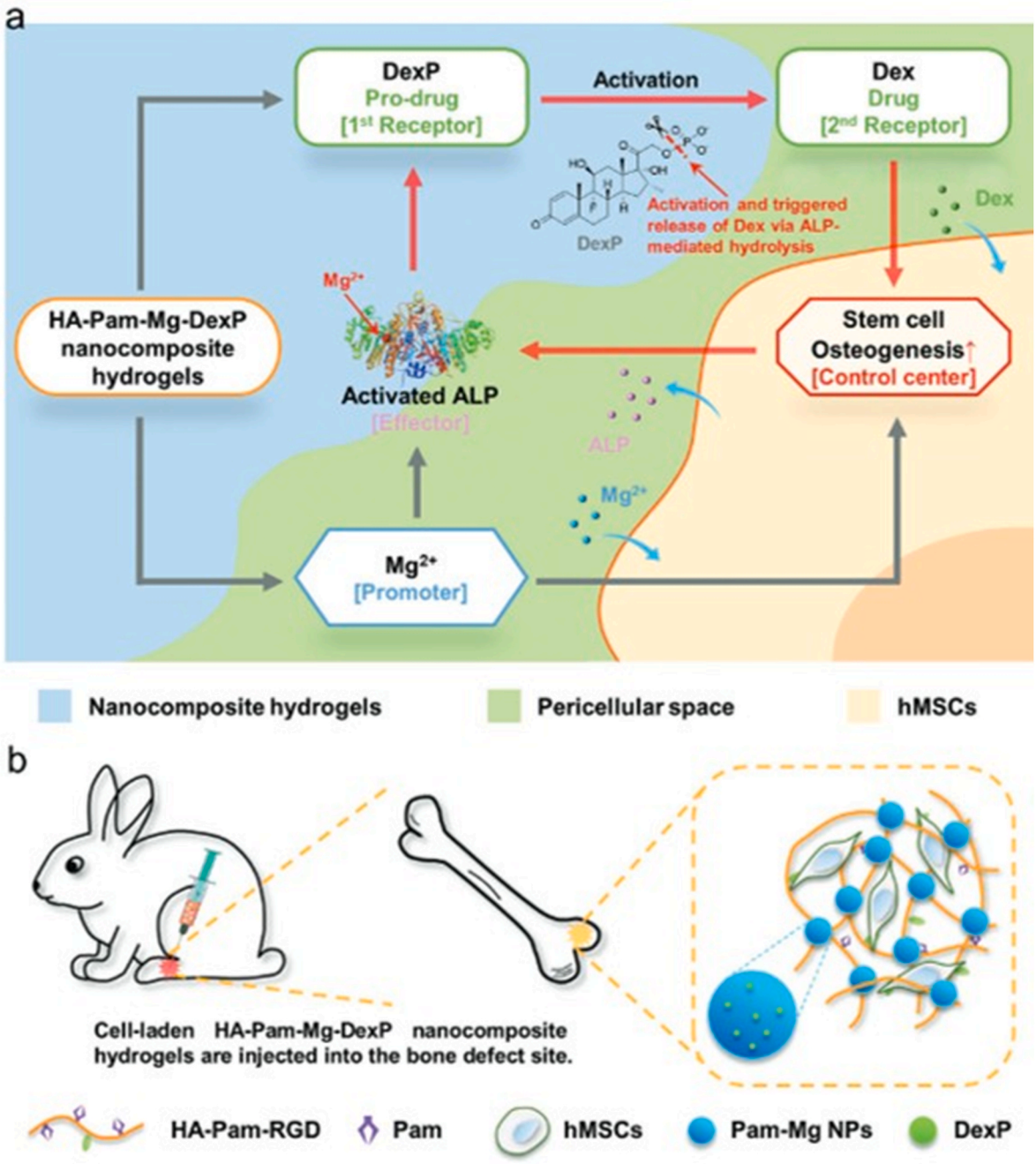

Fig. 7. a) A diagram illustrating smart hydrogels that facilitate the cofactor-assisted activation of drug delivery responsive to biomarkers through a positive feedback loop (marked in red), aimed at improving the osteogenesis of encapsulated human mesenchymal stem cells (hMSCs). b) The injection of nanocomposite hydrogels containing hMSCs supports in situ bone regeneration. Reproduced with permission from ref. 141. Copyright 2018, Wile-VCH GmbH on behalf of Advanced Healthcare Materials.

stem cells. Hydrogels with the lowest drug concentration showed reduced toxicity towards bone-forming cell precursors and induced osteoblast differentiation gene expression. Therefore, these hybrid MSNs-hydrogel composites hold great promise for osteoporosis treatment and tissue engineering because they are biocompatible, exhibit prolonged ALN release, and demonstrate therapeutic activity in vitro [144].

The field of tissue engineering encompasses a multitude of approaches, one of which targets the intricate issues associated with severe tendon injuries, such as Achilles tendon ruptures, which often demonstrate restricted recovery [145,146]. Although certain biomaterials could offer a potential solution, the current tissue engineering approaches face limitations [147]. In this sense, a possible solution could be based on novel injectable hydrogel-MSNs composite that combines puerarin, a bioactive compound, with chitosan through self-assembly and incorporates MSNs [148] This hydrogel enhanced cell proliferation and differentiation of tendon-derived stem cells, reduced inflammation and improved biomechanical properties as the hydrogel-injected tendons demonstrated a significantly higher load-to-fracture ratio, indicating stronger tissue. A comprehensive in vivo study using a tendon injury model confirmed its efficacy in tendon repair through histological analysis and behavioural observations (Fig. 8).

The development of self-healing hydrogels for regenerative medicine

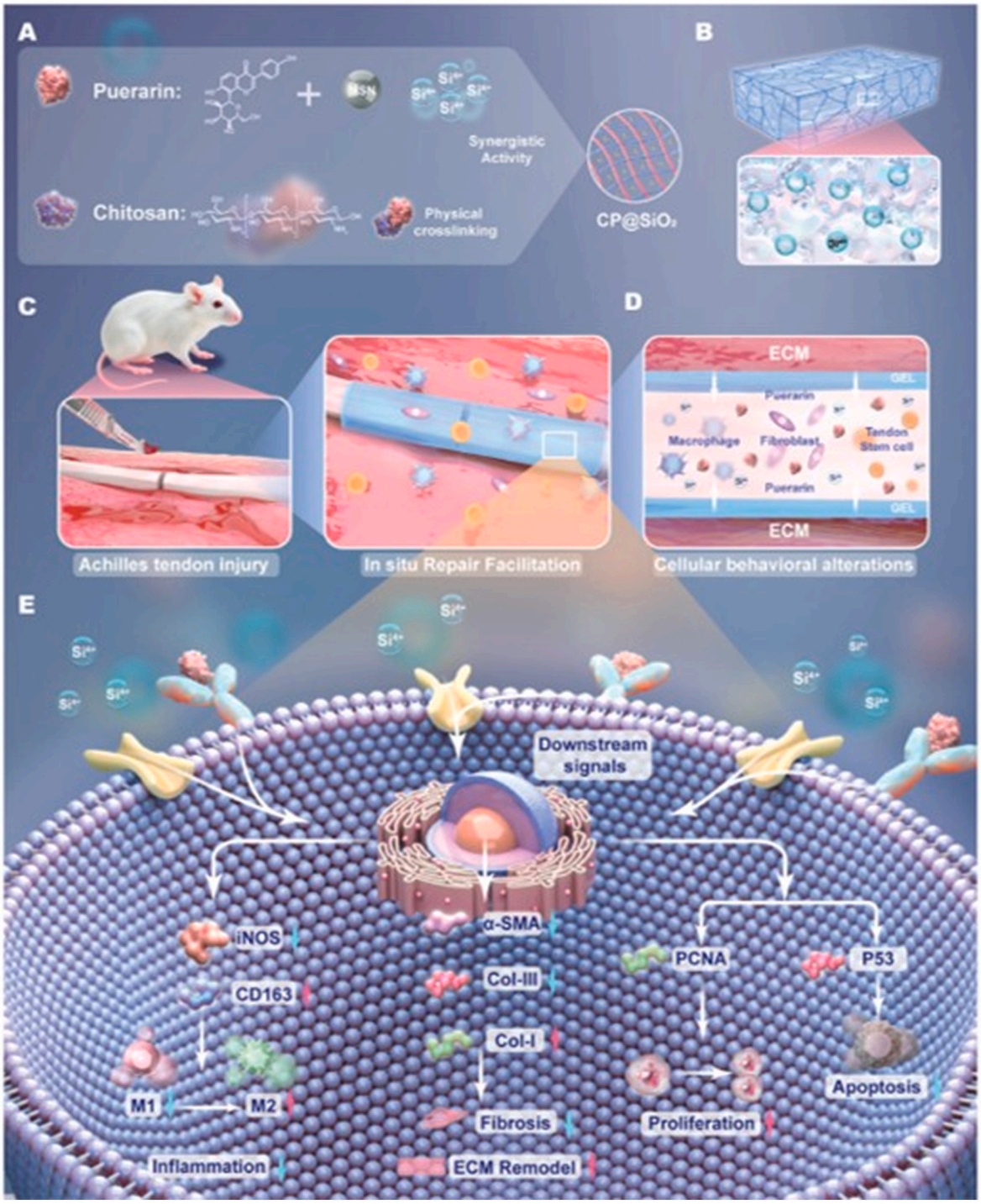

Fig. 8. Illustrative representation of how CP@SiO2 hydrogel is utilized to enhance tendon regeneration from different perspectives. Reproduced with permission from ref. 147. Copyright 2024, Wile-VCH GmbH on behalf of Advanced Healthcare Materials.

has gained significant traction [36,143,149]. However, a key challenge lies in engineering these materials to exhibit both rapid self-healing and high mechanical strength. Overcoming this hurdle is crucial for expanding their use in diverse organs and tissues. A novel type of nanocomposite hydrogel formed through thiol-disulfide exchange has been developed where thiolated MSNs act as dynamic crosslinkers, leading to self-healing biomaterials with high mechanical strength [100]. These nanocomposites exhibit fast gelation, injectability, and rapid self-healing while achieving a 25-fold increase in elastic modulus compared to pristine PEG hydrogels (significantly exceeding previous studies) [144]. Notably, high mechanical strength doesn't compromise self-healing. Additionally, the hydrogels demonstrate stability under physiological conditions but degrade in a glutathione-rich environment (beneficial for longer-term tissue regeneration). They also show tunable release of two model drugs and support human mesenchymal stem cell encapsulation, suggesting potential for 3D bioprinting applications [100]. Examples include nanocomposite hydrogels from MSNs modified with alginate/chitosan polyelectrolyte. This coating of MSNs is composed of amino groups to establish a chemical crosslinking with a hydrogel formed by aldehyde HA/N,O-carboxymethyl chitosan. Thus, it

is possible to obtain systems with better mechanical and biological properties for the required application [99].

4.2.2. Cancer

Due to their exceptional physicochemical characteristics, stimuli-responsive nanocarriers have emerged as an effective method for localized chemotherapy, providing potential answers to many of the current challenges in cancer treatment. Combining MSNs drug carriers with a responsive sol–gel system can enable localized drug delivery in response to specific stimuli, potentially preventing tumour recurrence. The three-dimensional structure of hydrogels prevents the migration of drug-loaded nanocarriers while allowing small molecule release. Most hydrogels are designed to gel rapidly when exposed to external stimuli, minimizing the free diffusion of encapsulated materials. To enhance their effectiveness in cancer treatments, it's essential to improve their mobility and tumour-targeting capabilities without compromising their drug retention.

Regarding to tumour therapy and tissue regeneration in tumour affected sites, there is a possibility to fabricate a polymer (azobenzene and α-cyclodextrin-functionalized HA) combined with gold nano bi-pyramids (AuNBs) conjugated to MSNs for an injectable drug delivery system aimed at sustained cancer treatment [150]. Due to the specific binding between the HA on MSNs and the CD44 antigen found in high levels on tumour cells, these nanoparticles can selectively target tumour cells. The nanocomposite utilizes thermos-responsive interactions between α-cyclodextrin and azobenzene, along with the photothermal properties of AuNBs, to self-assemble into a hydrogel under near-infrared (NIR) radiation. Once gelled, the drug-loaded MSNs are trapped within the HA network, and their release is triggered by the increased levels of hyaluronidase around tumour tissue, allowing the MSNs to be internalized by tumour cells and deliver the drug to their nuclei. This system creates a microenvironment rich in anticancer drugs around the tumour, providing prolonged therapeutic action to help prevent disease recurrence. The enhanced efficacy of this approach complements traditional therapies. In addition, the use of injectable core-shell nanocomposites, based on poly N-isopropylacrylamide and polyacrylic acid functionalized MSNs can be double crosslinked after injection in the tumour site to promote a compact nanocomposite hydrogel in the tumoral environment (37.5 °C and pH 6.8) [99]. MSNs also act as nanocarriers for growth factors, which are retained by the crosslinked networks. Growth factors are released gradually when the hydrogen bonds in PAA chains break, which occurs when the pH rises to 7.4 after tumour treatment. Additionally, the cleavage of these bonds leads to the swelling of the hydrogel, effectively filling tissue defects and creating numerous pores at the cellular level, providing an excellent scaffold for the attachment and growth of healthy cells [151].

4.2.3. Wound healing

In a different biomedical area, wound healing relies on coordinated biological pathways and complex biochemical cascades [152] While hydrogels excel as wound dressings for infection control, they often fail to promote chronic wound healing due to limited blood vessel formation and cell proliferation, leading to stalled inflammation [153] Therefore, hydrogels with regenerative properties are highly desirable. Incorporation of mesoporous materials holds promise for enhancing both biological activity and antimicrobial efficacy of hydrogels. These composite hydrogels demonstrate superior wound closure, increased antioxidant activity (scavenging reactive oxygen species), and significant promotion of blood vessel formation (angiogenesis). Additionally, in vivo studies show improved organization of epidermal and dermal layers in full-thickness wounds, highlighting the ability to achieve both angiogenesis and infection inhibition [154]. In this regard, a novel composite hydrogel scaffold composed of methacrylated gelatin, methacrylate HA and MSNs and incorporating Artemisia argyi extract for the treatment of chronic wounds was evaluated [155]. The gelatin provides mechanical strength and biodegradability, while methacrylate HA enhances biocompatibility and promotes cell adhesion and MSNs serve as carriers for sustained drug release, ensuring a continuous supply of the bioactive compound to the wound site. The hybrid composite exhibited a sustained release of the cargo, potent antibacterial activity against common wound pathogens, biocompatibility supporting human skin cell growth, and the ability to reprogram macrophages towards a healing promoting M2 phenotype. This combination of features suggests significant potential for promoting wound healing and reducing inflammation. In vivo studies using a rat model of full-thickness cutaneous wounds showed accelerated wound closure, reduced granulation tissue formation, and enhanced re-epithelialization, which demonstrates the efficacy of this hydrogel in promoting chronic wound healing [155].

5. Overall challenges in the field of MSNs-hydrogel composites

The integration of MSNs into hydrogels presents several challenges, primarily related to compatibility, mechanical stability, controlled release, scalability, biocompatibility, and drug loading efficiency.

The compatibility between MSNs and hydrogels is a significant challenge that comes from their differing chemical properties and structures. Such incompatibility could affect the stability and overall performance of the composite. Researchers might address this issue through chemical functionalization of the MSNs to enhance their interaction with the hydrogel matrix, improving dispersion and bonding within the composite.

Another challenge could be the mechanical stability of the resulting composites, since the incorporation of MSNs can sometimes lead to brittleness or reduced elasticity in hydrogels. Employing crosslinking agents that strengthen the network structure of the hydrogel can significantly enhance those mechanical properties. It is also important to optimize the amount of MSNs in the hydrogel to maintain a balance between mechanical integrity and functional performance.

Controlled release of therapeutic agents from MSN-hydrogel composites is another area of concern, as rapid diffusion can lead to suboptimal therapeutic outcomes. In this sense, it is well known that the organic modification of the MSNs surfaces can help to control the release kinetics from the nanocarriers. Moreover, modifying the hydrogel matrix to respond to environmental stimuli, such as pH or temperature, can enable more precise control over drug release profiles.

From a more engineering point of view, scalability and fabrication processes also present many difficult challenges, as the synthesis and incorporation of MSNs into hydrogels would difficult these processes for industrial applications. Streamlining synthesis methods is essential; employing scalable techniques such as one-pot synthesis or continuous flow methods could facilitate the production of MSN-hydrogel composites. Additionally, utilizing 3D printing technologies might allow for precise control over the architecture of the composites, enhancing their functionality and applicability.

As it has been stated throughout this review, biocompatibility and toxicity are critical considerations when developing these materials. Surface modification of MSNs with biocompatible coatings can help mitigate toxicity issues. Furthermore, conducting thorough in vitro and in vivo studies is essential to assess the safety and biocompatibility of the composites before clinical application.

Lastly, achieving high drug loading efficiency while maintaining the structural integrity of the composites is crucial for their potential translation to the clinic. This can be challenging, but optimizing the interactions between the drug, MSNs, and hydrogel matrix can enhance loading efficiency.

In conclusion, addressing these challenges requires a multidisciplinary approach that combines advances in both chemistry and engineering. By focusing on the chemical properties of MSNs and hydrogels, along with optimizing fabrication techniques, researchers can develop MSN-hydrogel composites that are effective for a wide range of biomedical applications while also being scalable for real-world use.

6. Conclusions

Hydrogels, that are cross-linked polymer networks that can adsorb large quantities of water, have been used for many biomedical applications. Their unique properties, such as flexibility, softness, biodegradability and biocompatibility, make them ideal candidates to be used in different tissue engineering and regenerative medicine disciplines. However, some of their clinical applications have been limited by poor mechanical properties and lack of control on the biodegradation and/or drug release. Their combination with nanoparticles, and particularly with MSNs, improves their mechanical properties, drug encapsulation and release capabilities and, more importantly, their stimuli-responsiveness to a variety of both internal and external stimuli. Similarly, MSNs, that might encounter several barriers on their clinical applications, are also benefited of being administered dispersed in a hydrogel, since the composite allows for a localised therapy, enhanced biocompatibility and nanocarrier protection. Thus, the hybrid hydrogel-MSNs composites are able to overcome the limitations and drawbacks associated to the use of either of them alone.

Although there is significant progress in the development of hydrogels-nanoparticles composites, their clinical applications still face many challenges that need to be addressed in the near future. The continuous development and improved understanding of the composite biomaterial and the complexity of the biological environment would ensure the success of this approach in the coming years.

7. Future outlook

Future research is expected to focus on the development of smart hydrogels that can dynamically respond to a plethora of stimuli such as pH, temperature, and light. These adaptive properties will enhance their functionality in tissue engineering applications, particularly in controlled drug release and in situ tissue regeneration. Additionally, the addition of MSNs functionalized with specific ligands is anticipated to improve the hydrogels performance in regenerative contexts. In this sense, the combination of hydrogels and MSNs is expected to lead to the creation of innovative scaffolds that could provide both structural support and controlled release of therapeutic agents. Such hydrogel-MSN composites could significantly enhance the regeneration of complex tissues, including bone and cartilage, by enabling the targeted delivery of growth factors or stem cells directly to injury sites. Moreover, ongoing research into the biocompatibility and biodegradability of these materials will enhance their applicability in *in vivo* settings, with a focus on long-term outcomes and the ability to monitor their performance within living systems.

As these technologies evolve, regulatory frameworks governing their use will also need to adapt. Collaborative and multidisciplinary efforts among researchers, clinicians, and regulatory agencies will be crucial in translating hydrogel and MSN-based therapies to the clinic. Furthermore, interdisciplinary collaborations among materials scientists, biologists, chemists, and clinicians will be essential for overcoming existing challenges and accelerating the translation of laboratory findings into clinical applications. Collectively, these advancements hold the promise of transforming regenerative medicine, ultimately improving healing processes and patient outcomes.

CRediT authorship contribution statement

Jesús L. Pablos: Writing – review & editing, Writing – original draft, Conceptualization. **Daniel Lozano:** Writing – review & editing, Writing – original draft, Conceptualization. **Miguel Manzano:** Writing – review & editing, Writing – original draft, Conceptualization. **María Vallet-Regí:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

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

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