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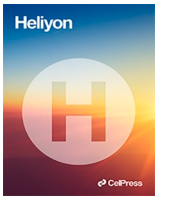

Review article

Polymeric biomaterials: Advanced drug delivery systems in osteoarthritis treatment

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ABSTRACT

Polymeric biomaterials have emerged as a highly promising candidate for drug delivery systems (DDS), exhibiting significant potential to enhance the therapeutic landscape of osteoarthritis (OA) therapy. Their remarkable capacity to manifest desirable physicochemical attributes, coupled with their excellent biocompatibility and biodegradability, has greatly expanded their utility in pharmacotherapeutic applications. Nevertheless, an urgent necessity exists for a comprehensive synthesis of the most recent advances in polymeric DDS, providing valuable guidance for their implementation in the context of OA therapy. This review is dedicated to summarizing and examining recent developments in the utilization of polymeric DDS for OA therapy. Initially, we present an overview of the intricate pathophysiology characterizing OA and underscore the prevailing limitations inherent to current treatment modalities. Subsequently, we introduce diverse categories of polymeric DDS, including hydrogels, nanofibers, and microspheres, elucidating their inherent advantages and limitations. Moreover, we discuss and summarize the delivery of bioactive agents through polymeric biomaterials for OA therapy, emphasizing key findings and emerging trends. Finally, we highlight prospective directions for advancing polymeric DDS, offering a promising approach to enhance their translational potential for OA therapy.

1. Introduction

Osteoarthritis (OA) is a prevalent and debilitating joint condition characterized by progressive cartilage degeneration, leading to pain, stiffness, and functional limitations. It affects a significant portion of the population and poses a substantial burden on the quality of life and healthcare systems [1]. Focusing primarily on the articular cartilage, OA necessitates the development of efficacious treatment modalities that extend beyond mere symptom alleviation. Regrettably, existing interventions such as exercise, weight management, physical therapy, and pharmacological measures can provide only transient respite and are incapable of addressing the fundamental etiology of this incapacitating ailment [2,3]. Recently, with the rapid development of novel biomaterials-based therapies, polymeric drug delivery systems (DDS) have attracted considerable interest and providing new chances for OA treatment [4].

Polymeric biomaterials have emerged as a promising frontier in the pursuit of advanced DDS for OA treatment (Fig. 1) [5,6]. Their outstanding biocompatibility, coupled with their ability to modulate mechanical properties and orchestrate the controlled release of therapeutic agents, has garnered significant attention for their application in biomedicine [7]. Within the intricate architecture of these polymeric biomaterials lies a compelling rationale—a resemblance to the native extracellular matrix (ECM) residing within cartilage [8]. These unique attributes endow them with the capability not only to provide structural support but also to promote cellular

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adhesion and proliferation, rendering them ideal candidates for DDS.

Polymeric biomaterials possess the ability to exhibit a variety of forms, each suited to address specific therapeutic demands. Hydrogels, nanofibers, and microspheres stand as testaments to the versatility of these biomaterials, each capable of embodying tailored characteristics to facilitate tissue regeneration [9]. Furthermore, the functionalization of polymeric biomaterials with pharmaceuticals, growth factors, and cells presents extraordinary potential for pharmacotherapy in the context of OA [9,10]. Through the encapsulation of these biomaterials with such bioactive agents, we can enhance their regenerative capabilities, thereby ensuring a more robust and targeted approach to OA treatment. Nevertheless, comprehensive studies are warranted to fully unveil the potential of polymeric DDS in OA therapy. In addition, our current knowledge remains insufficient to differentiate the varying therapeutic efficacies among distinct polymeric biomaterials.

Herein, we summarize the advanced strategies developed for improving the outcome of OA therapy based on the utilization of polymeric DDS. First, we elucidate the pathological characteristics intrinsic to OA. Subsequently, we undertake an in-depth examination of the current state of knowledge regarding to the advantages and constraints associated with diverse polymeric DDS. Moreover, we proceed to analyze recently developed therapeutic approaches that leverage functional polymeric DDS within the context of OA. Finally, advanced OA therapy with their potential for clinical translation and emerging polymeric DDS directions for OA therapy are discussed.

2. Intricate pathophysiology of OA

OA is a degenerative joint disorder characterized by progressive articular cartilage degradation, synovial inflammation, and structural changes in the affected joint. It is one of the leading causes of chronic joint pain and disability, particularly among the elderly population. The pathophysiology of OA is a complex interplay of various factors, involving articular cartilage degradation, subchondral bone alterations, synovial inflammation, mechanical stress, and genetic susceptibilities (Fig. 2) [11]. Understanding these intricate mechanisms is essential for developing targeted interventions and therapies to mitigate the progression of OA and alleviate the associated pain and disability.

2.1. Articular cartilage degeneration

Central to the pathophysiology of OA is the gradual and complex breakdown of articular cartilage, which serves as the specialized connective tissue covering the ends of bones within synovial joints [12]. This intricate degenerative process arises from a delicate balance disrupted between cartilage degradation and repair mechanisms. The degradation of articular cartilage involves several key factors, with a prominent role played by matrix metalloproteinases (MMPs). Among them, MMP-1, MMP-3, and MMP-13 stand out as critical contributors to the degradation of the cartilage matrix [13]. These enzymes are responsible for breaking down essential components of cartilage, including collagen and proteoglycans, which are vital for maintaining its structural integrity and mechanical properties.

Within the cartilage tissue, chondrocytes are the resident cells responsible for maintaining cartilage homeostasis. In OA, these chondrocytes undergo phenotypic changes, leading to a diminished capacity for matrix synthesis and repair [14]. This altered

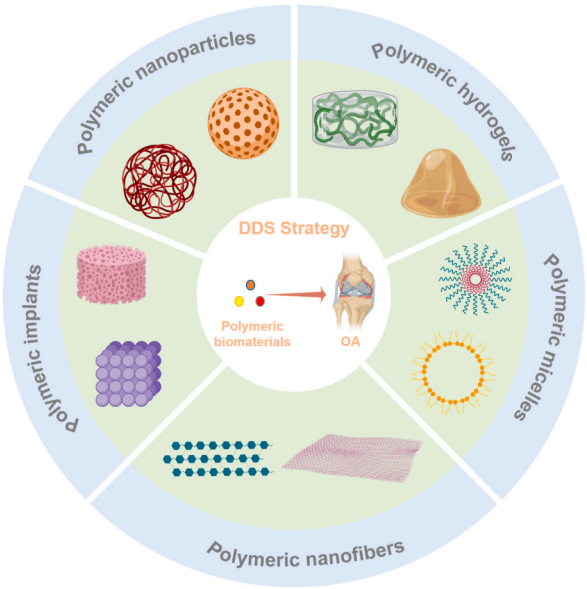

Fig. 1. Illustration of the application of polymeric DDS in the treatment of OA. Created with Medpeer (https://image.medpeer.cn/).

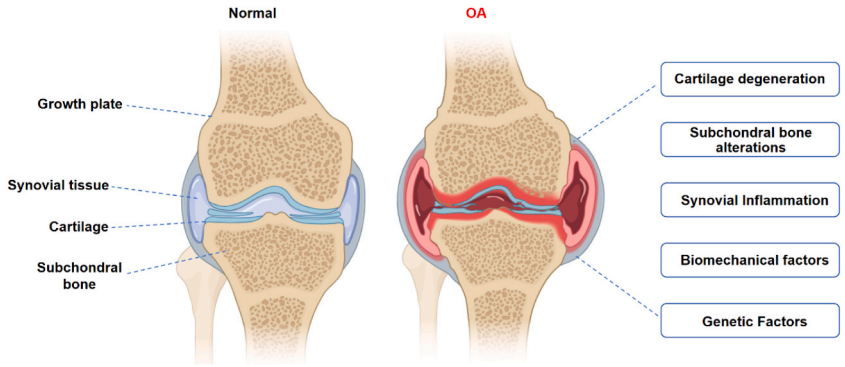

Fig. 2. Schematic illustration of the intricate interplay among biochemical, biomechanical, and genetic factors in the pathophysiology of OA. In contrast to a healthy knee joint, an OA-affected joint exhibits numerous pathological changes, such as cartilage degeneration, modifications in subchondral bone, synovial inflammation, biomechanical influences, and genetic factors. Created with Medpeer (https://image.medpeer.cn/).

chondrocyte function further exacerbates the progressive degradation of articular cartilage.

The inflammatory milieu within the OA joint is characterized by the presence of proinflammatory cytokines, notably interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) [15]. These cytokines play a pivotal role in driving cartilage degradation while simultaneously inhibiting anabolic processes within the cartilage tissue. Their presence triggers a cascade of events that perpetuate the cycle of cartilage breakdown, further compromising joint function and perpetuating the OA pathology [15]. The intricate interplay of these molecular and cellular events underscores the complexity of articular cartilage degeneration in OA, making it a critical target for therapeutic interventions aimed at halting or slowing the progression of this debilitating joint disease.

2.2. Subchondral bone alterations

Subchondral bone alterations represent another pivotal aspect of the complex pathophysiology associated with OA. This facet of OA involves a dynamic interplay between various cellular and molecular processes, which, when disrupted, can significantly contribute to the disease's progression [16].

One notable subchondral bone alteration in OA is the occurrence of increased bone resorption. This process is primarily driven by the excessive activity of osteoclasts, specialized cells responsible for breaking down bone tissue [17]. When osteoclast activity outweighs that of osteoblasts, the cells responsible for bone formation, it results in a net loss of bone density. This imbalance, in turn, can lead to subchondral bone thinning and weakening.

Conversely, subchondral bone sclerosis is another noteworthy alteration observed in OA [18]. This phenomenon is characterized by the abnormal thickening and hardening of the subchondral bone, which is the layer of bone just beneath the articular cartilage. Subchondral bone sclerosis can result from an increased deposition of bone matrix or a reduction in bone resorption [19]. This densification of subchondral bone can have significant implications for joint biomechanics and contribute to the pain and functional limitations experienced by OA patients.

Additionally, microscopic fractures or microcracks in the subchondral bone are a common occurrence in OA [20]. These small fractures may develop due to repetitive mechanical stress and can lead to localized pain within the affected joint. Moreover, the presence of these microcracks can further compromise the structural integrity of the subchondral bone and contribute to joint instability [21].

2.3. Synovial inflammation

Synovial inflammation plays a pivotal role in the progression of OA and is characterized by specific changes in the synovial membrane that contribute to the disease's pathophysiology [22]. This inflammatory process encompasses several key components and interactions within the affected joint.

One hallmark of synovial inflammation in OA is the increased production of synovial fluid, a lubricating and nourishing fluid that normally helps maintain joint health [23]. In OA, this process becomes dysregulated, leading to an excessive production of synovial fluid. This fluid overload can contribute to joint swelling, pain, and stiffness, further compromising joint function.

Furthermore, synovial inflammation involves the infiltration of immune cells into the synovium. Immune cells, such as macrophages and lymphocytes, become activated within the synovial membrane in response to inflammatory signals [24]. These immune cells release proinflammatory cytokines, including interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), as well as enzymes like matrix metalloproteinases (MMPs) [22]. These molecular mediators perpetuate cartilage degradation by promoting the breakdown of essential components of the cartilage matrix.

Importantly, genetic factors can influence the extent and severity of synovial inflammation in OA. Genetic variants within cytokine genes, which encode for proinflammatory molecules, may predispose individuals to heightened inflammatory responses within the synovium [25]. This genetic susceptibility can contribute to the heterogeneity observed in OA, where some individuals experience

more pronounced synovial inflammation and joint damage than others.

Understanding the intricate interplay between genetic factors, immune cell infiltration, and the production of inflammatory mediators in the synovium is crucial for unraveling the complexities of OA pathophysiology [25]. It highlights the potential for personalized approaches to OA management, where interventions can be developed based on an individual's genetic predisposition and the specific inflammatory processes occurring within their affected joints.

2.4. Mechanical stress and biomechanical factors

Biomechanical factors hold a central position in the pathophysiology of OA, especially in weight-bearing joints. These factors encompass the mechanical forces exerted on joints during everyday activities and are significant contributors to the development and progression of the disease [26]. Several critical aspects of this relationship between biomechanical factors and OA merit exploration.

Biomechanical forces, including compressive and shear forces, play a pivotal role in the initiation and progression of OA [27]. These forces can lead to the mechanical wear and tear of articular cartilage, which is a hallmark feature of OA. Over time, the repetitive loading and mechanical stress on the joint surfaces can cause structural damage to the cartilage, resulting in its degradation and thinning.

Mechanical stress on the joint tissues triggers an inflammatory response [28]. This response involves the release of proinflammatory cytokines and enzymes within the joint, such as IL-1β and MMPs. These inflammatory mediators contribute to cartilage degradation and further perpetuate the disease process.

Biomechanical factors also have a significant impact on the composition of synovial fluid [28]. Synovial fluid serves as a lubricant and shock absorber within the joint. Mechanical stress can alter the viscosity and molecular composition of this fluid, affecting its lubricating properties. Changes in synovial fluid viscosity can reduce its ability to effectively lubricate and cushion the joint surfaces, leading to increased friction and further cartilage damage.

2.5. Genetic factors

Although OA is primarily characterized as a degenerative disorder, the role of genetic factors in its pathogenesis is substantial and cannot be overlooked [29]. A growing body of research has identified various genetic markers and susceptibility genes that play a significant role in shaping the disease's onset and progression. These genetic determinants encompass diverse aspects of OA pathophysiology, including alterations in extracellular matrix components and inflammation-related genes [30].

Genetic variants in genes encoding collagen and proteoglycan molecules, which are critical components of the articular cartilage matrix, have been associated with OA susceptibility. These variants may influence the structural integrity and biomechanical properties of cartilage [30]. Mutations or polymorphisms in collagen and proteoglycan genes can compromise the cartilage's ability to withstand mechanical stress and maintain its resilience, thereby contributing to cartilage degradation in OA.

Genetic factors related to inflammation play a pivotal role in OA pathogenesis. Polymorphisms in genes associated with proinflammatory cytokines, such as IL-1β and TNF-α, can influence an individual's propensity to develop synovial inflammation and cartilage degradation [31]. These genetic predispositions may contribute to the heterogeneity observed in OA, with some individuals experiencing more severe inflammatory responses than others.

Several susceptibility genes have been identified through genetic association studies in OA. These genes may not have a direct mechanistic link to cartilage biology or inflammation but can still modulate an individual's risk of developing OA [29,31]. Genetic predispositions conferred by these susceptibility genes can interact with environmental factors, such as mechanical stress or joint injury, to influence disease development and progression.

3. Different types of polymeric DDS

Polymeric DDS have attracted significant attention in the pharmaceutical field due to their versatility in delivering medications. They provide precise control over the rate of drug release, can be customized for specific purposes, and hold potential in enhancing treatment effectiveness. Various types of polymeric DDS, such as hydrogels, nanofibers, and microspheres, come with their own advantages and limitations, which affect their suitability for drug delivery functions (Table 1). The selection of the appropriate polymeric system should be a thoughtful decision, taking into account the particular therapeutic objectives, drug characteristics, and

Table 1
Overview of different polymeric DDS.

Type of DDS	Advantages	Limitations	References
Hydrogels	High biocompatibility and tissue tolerance; Biomimicry and enhanced bioavailability; Precise control of drug release profiles for various pharmacokinetic needs	Limited mechanical strength; Potential for burst release	[32–36]
Nanofibers	High surface area-to-volume ratio; Distinctive porous structure; Mimicry of native tissue structure	Specialized production methods that may not be universally accessible or scalable; Polymer choice and fabrication impact biocompatibility	[37–40]
Microspheres	Prolonged and sustained drug release; Versatility in encapsulating therapeutic compounds	Inconsistent size distribution; Agglomeration tendency	[41–46]

administration method. Ongoing developments in materials science and engineering are continuously expanding the capabilities of these polymeric DDS, driving innovation in drug delivery and ultimately improving patient outcomes.

3.1. Hydrogels

Hydrogels represent a class of polymeric biomaterials that have garnered considerable attention in the field of drug delivery and biomedical applications due to their unique characteristics. These three-dimensional networks consist of hydrophilic polymer chains, which imbue them with a high water content, typically ranging from 90 % to 99 % [32]. This remarkable feature renders hydrogels highly biocompatible and well-tolerated by living tissues, making them particularly suitable for a wide array of medical applications.

One of the most noteworthy advantages of hydrogels is their ability to create an environment that closely mimics the natural milieu of many biological tissues. This high water content within hydrogels facilitates the diffusion of drugs and essential nutrients, a critical factor in their application as drug delivery vehicles [33]. Such biomimicry plays a pivotal role in enhancing the bioavailability of drugs and promoting therapeutic efficacy, as it allows for the establishment of an environment conducive to cellular and tissue responses.

Furthermore, hydrogels offer a distinct advantage in drug delivery by virtue of their tunable properties. Researchers can adjust the characteristics of hydrogels to meet specific requirements for drug release profiles. For instance, the swelling behavior of hydrogels can be precisely controlled through the selection of polymer types and crosslinking density [34]. Additionally, their degradation rates can be manipulated to enable sustained, controlled drug release over extended periods, aligning with the pharmacokinetic needs of various drugs.

However, it is important to recognize the limitations of hydrogels as DDS. One of the primary challenges associated with hydrogels is their inherent limited mechanical strength [35]. This drawback can impose restrictions on their applicability in load-bearing or mechanically demanding applications, such as orthopedic implants. The need to balance mechanical integrity with drug release capabilities often necessitates thorogh consideration in the design of hydrogel-based DDS.

Another concern relates to the potential for excessive swelling and erosion of hydrogels, which can lead to burst release of encapsulated drugs [36]. This phenomenon can undermine the intended therapeutic outcomes, as it may result in a rapid and uncontrolled release of the drug payload. Researchers should address this issue through thoughtful formulation and engineering approaches to ensure the predictability and consistency of drug release profiles from hydrogels.

3.2. Nanofibers

Nanofibers, a compelling class of polymeric biomaterials, have attracted significant interest in the realm of drug delivery and tissue engineering due to their distinctive attributes. These nanostructured materials exhibit an exceptionally high surface area-to-volume ratio, a critical feature that profoundly affects their drug delivery capabilities [37]. This property, stemming from their nanoscale dimensions, affords nanofibers a remarkable capacity for rapid drug release and efficient drug loading.

The distinctive porous structure of nanofibers significantly enhances their attractiveness as drug delivery platforms. This inherent porosity not only allows for the precise modulation of drug release kinetics but also enables the modulation of release profiles to achieve sustained or pulsatile drug delivery, a critical consideration when addressing the pharmacokinetic needs of various therapeutic agents [38]. Such functional control over drug release is of paramount importance in optimizing therapeutic outcomes.

Beyond their drug delivery potential, nanofibrous scaffolds exhibit a remarkable capacity to emulate the structural properties of native tissues [40]. This mimicry arises from the nanoscale features of the fibers, which closely resemble the ECM found in biological tissues. Consequently, nanofiber-based scaffolds have emerged as invaluable tools in tissue engineering and regenerative medicine applications [39]. They provide an ideal microenvironment for cell attachment, proliferation, and differentiation, fostering tissue regeneration and repair.

Nonetheless, it is imperative to acknowledge the complexities and hurdles associated with the production and integration of nanofibers into biomedical applications. Fabricating nanofibers often necessitates specialized equipment and techniques, such as electrospinning or meltblowing, which may not be readily accessible or scalable for all research or manufacturing settings. The choice of polymer for nanofiber fabrication and the specific manufacturing methods employed can significantly influence biocompatibility, potentially affecting the response of cells and tissues when in contact with these materials. Therefore, a thorough evaluation of polymer selection and fabrication processes is crucial to ensure that nanofiber-based systems meet the stringent requirements of biocompatibility and safety.

3.3. Microspheres

Microspheres, as versatile polymeric biomaterials, play a pivotal role in a diverse spectrum of drug delivery contexts encompassing oral, parenteral, and controlled-release systems. Their exceptional versatility derives from their capacity to achieve prolonged and sustained drug release profiles, ultimately diminishing the need for frequent drug administrations, a hallmark achievement in optimizing patient compliance and therapeutic effectiveness [43].

One of the paramount advantages of microspheres is their proficiency to encapsulate a wide array of therapeutic compounds, comprising both small molecules and biologics [44]. This encapsulation ability transcends conventional boundaries, rendering microspheres a versatile platform for drug delivery across various therapeutic modalities. This versatility is particularly invaluable in the context of precision medicine, where tailored drug release profiles are essential to address the unique pharmacokinetic requirements of individual patients [45].

Table 2
The application of polymeric DDS in OA therapy.

Polymeric DDS	Role in OA therapy	Mechanisms	References
Polymeric nanoparticles	Offer controlled release kinetics and precise delivery of therapeutic agents to the desired site of action; Enhanced penetration within complex joint spaces	Promote cartilage regeneration, reduce inflammation; Alleviate pain	[47–50]
Polymeric hydrogels	Resemble the hydrated and gel-like nature of joint tissue' ECM; Provide sustained and controlled release of bioactive agents; Offer specific mechanical properties, degradation kinetics, and release profiles	Prevent bone destruction; Promote cartilage repair; Suppress synovial hyperplasia	[9,51–54]
Polymeric micelles	Enable sustained release of therapeutic agents; Provide specific advantages in terms of stability, biocompatibility, and drug-loading capacity; Enhanced drug solubility and stability	Alleviate synovial hyperplasia; Suppress inflammation; Enhance cartilage repair	[55–60]
Polymeric nanofibers	Provide a supportive environment for cell adhesion and growth; Controlled release ensures sustained exposure to these molecules; Highly porous structure allows efficient loading and sustained release of therapeutic molecules	Enhance cell proliferation; Promote cartilage regeneration, and reduce inflammation; Alleviate pain; Alleviate synovial hyperplasia	[61–66]
Polymeric implants	Provide sustained release of bioactive molecules over an extended period; Offer localized and targeted drug delivery	Support tissue regeneration; Suppress relentless inflammation; Induce cartilage regeneration	[67–71]

However, it is crucial to recognize the inherent challenges entailed in the production and implementation of microspheres in drug delivery systems. Achieving a consistent size distribution of microspheres represents a considerable challenge, owing to the intricacies of the manufacturing processes involved [41]. Variations in size can exert a profound impact on drug release uniformity, potentially resulting in erratic therapeutic outcomes [42]. In particular, microspheres have a propensity to agglomerate, a phenomenon characterized by the clustering of individual particles into larger aggregates. Such agglomeration events can lead to an uneven distribution of the encapsulated drug within the microsphere matrix, thereby compromising the precise control over drug release kinetics [46].

Addressing these challenges necessitates a meticulous approach to microsphere formulation and manufacturing, with a focus on optimizing particle size distribution and minimizing agglomeration tendencies [45]. Advanced manufacturing techniques and process controls have been developed to enhance the reproducibility and uniformity of microsphere production. Additionally, innovative strategies involving surface modification and encapsulation techniques are continually evolving to mitigate agglomeration-related issues.

4. Application of polymeric DDS in OA treatment

The utilization of polymeric biomaterials for the delivery of bioactive agents has emerged as a highly promising strategy in the treatment of OA (Table 2). This approach harnesses the capabilities of small molecule delivery systems, enabling the controlled and sustained release of bioactive agents precisely at the site of injury. This precise orchestration plays a significant role in driving tissue regeneration, mitigating inflammation, and alleviating pain. In the following section, we introduce and explore a diverse range of polymeric DDS that have been developed to address the specific requirements of small molecule delivery within the context of OA treatment.

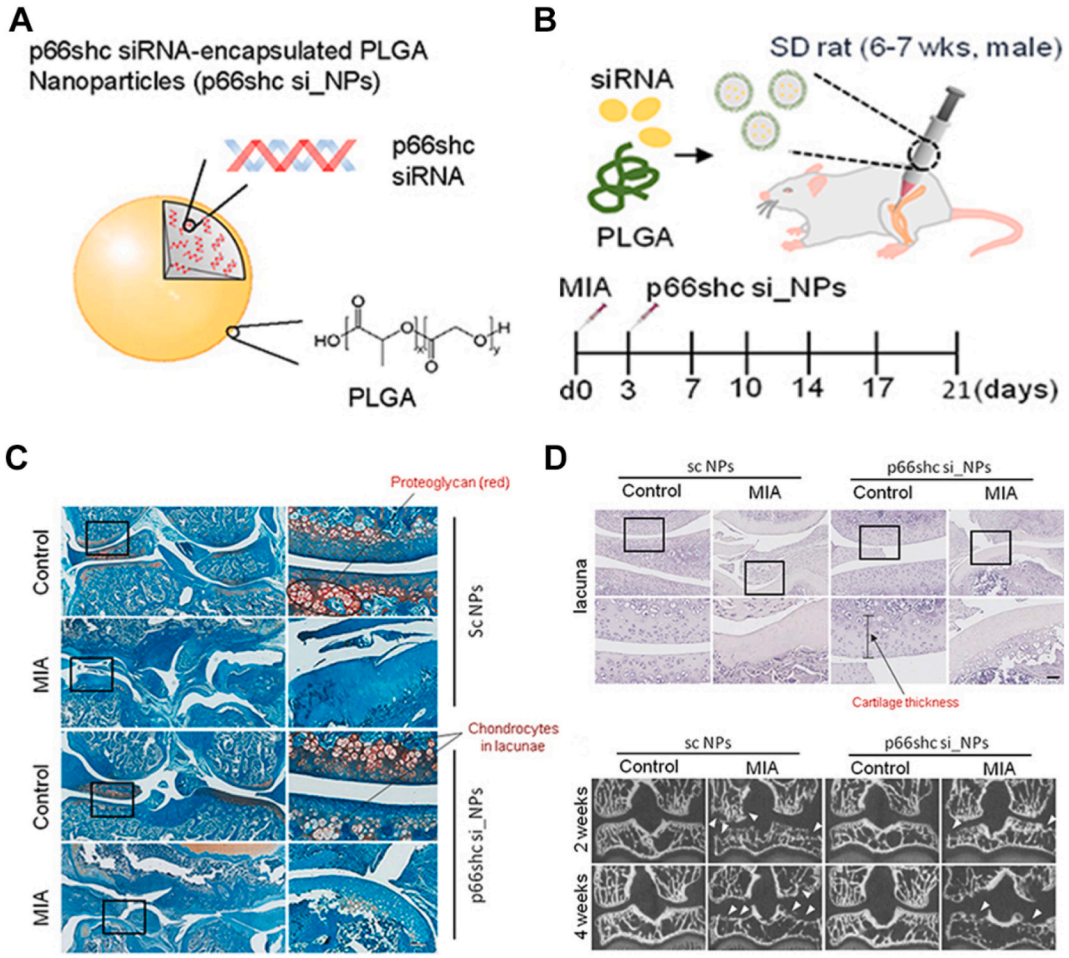

Fig. 3. A. Schematic illustration of fabrication of the p66shc siRNA-loaded nanoparticles. B. Protocol of the administration of the functional nanoparticles to the rat model. C. Safranin-O and Fast Green staining of knee joints from rats in the different groups. D. Hematoxylin staining of paraffin-embedded sections of the knee joint, and the representative micro-CT images of tibial subchondral bony destruction at 3 weeks after injection with the functional nanoparticles. Reproduce with permission [49]. Copyright 2020, Dove Press. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4.1. Polymeric nanoparticles

Polymeric nanoparticles have emerged as a versatile and effective strategy for the delivery of small molecules in OA treatment. These nanoparticles present a sophisticated platform for the encapsulation and precise delivery of therapeutic agents, affording enhanced control and accuracy [8]. The distinctive attributes of polymeric nanoparticles, encompassing dimensions, surface charge, and hydrophobicity, allow for tailoring to enhance performance and maximize therapeutic efficacy.

Among the various polymers used for fabricating polymeric nanoparticles, PLGA represents a widely employed and well-characterized choice. This polymer possesses excellent biocompatibility and biodegradability, making it suitable for biomedical applications [47]. PLGA nanoparticles have demonstrated exceptional potential in the targeted delivery of small molecules for OA treatment [48]. For instance, Kim et al. synthesized rebamipide-loaded nanoparticles using methoxy poly(ethylene glycol)-b-poly(D, L-lactide) (mPEG-PDLLA) and PLGA polymers to achieve sustained release of rebamipide. Results revealed that *in vitro*, rebamipide/nanoparticles demonstrated a dose-dependent reduction in mRNA levels of pro-inflammatory mediators, including IL-1β, IL-6, TNF-α, MMP-3, MMP-13, and cyclo-oxygenase-2. *In vivo*, the intra-articular injection of rebamipide/nanoparticles led to the most significant decrease in mRNA levels of pro-inflammatory components compared to other groups. Macroscopic, radiographic, and histological assessments demonstrated that intra-articular rebamipide/NPs administration effectively inhibited cartilage degeneration compared to rebamipide solution or oral administration of rebamipide. All these results indicated that intra-articular delivery of rebamipide, particularly when encapsulated in PLGA nanoparticles, led to reduced local and systemic inflammation, decreased joint degradation, and slowed the progression of OA [50].

Moreover, PLGA nanoparticles have been functionally engineered to enhance the efficacy of essential molecules involved in chondrogenesis and cartilage regeneration. P-p66shc was previously well-documented highly expressed in cartilage from OA patients, and play vital roles in OA development. The incorporation of p66shc small interfering RNA (siRNA) into PLGA nanoparticles enables sustained release, allowing for their prolonged presence within the joint environment (Fig. 3A). *In vivo* results indicated that inhibition of p66shc via siRNA delivered using PLGA-based nanoparticles alleviated pain behavior, cartilage damage, and inflammatory cytokine production in the knee joints of OA rats (Fig. 3B–D). Theses results suggested p66shc siRNA PLGA nanoparticles represent a promising therapeutic strategy for OA [49].

In addition to their exceptional capabilities in delivering specific therapeutic agents, polymeric nanoparticles have several advantages for OA treatment [51]. Their small size enables efficient penetration into the complex and crowded joint space, facilitating targeted delivery to the desired site of action. The controlled release kinetics of the nanoparticles ensure a sustained and controlled therapeutic effect, reducing the frequency of dosing and optimizing the drug's bioavailability. Furthermore, the surface properties of the nanoparticles can be modified to enhance their stability, cellular uptake, and interaction with the joint tissues, further augmenting their therapeutic potential.

4.2. Polymeric hydrogels

Polymeric hydrogels have emerged as a promising and versatile platform for small molecule delivery in the treatment of OA. These hydrogels, 3D networks of crosslinked polymers, possess unique properties that make them highly suitable for this application. With their biocompatibility, resemblance to the natural ECM, and ability to retain and release bioactive molecules, polymeric hydrogels have obtained significant attention and have been extensively studied in the context of OA treatment [9].

One of the eminent features of polymeric hydrogels is their ability to absorb and retain large amounts of water. This characteristic allows the hydrogels to provide an environment that closely mimics the hydrated and gel-like nature of the ECM in joint tissues. By encapsulating and entrapping small molecules within their hydrophilic network, these hydrogels enable sustained and controlled release of bioactive agents, ensuring a prolonged and localized therapeutic effect.

In the pursuit of effective small molecule delivery for OA, researchers have developed a diverse range of polymeric hydrogels [52]. These hydrogels have been employed to deliver platelet-derived growth factor (PDGF), a potent growth factor involved in chondrogenesis and cartilage regeneration [53]. By encapsulating PDGF within polymeric hydrogels, sustained release profiles can be achieved, facilitating the stimulation of chondrogenic processes and promoting the regeneration of damaged cartilage. The controlled release of PDGF from the hydrogel provides a continuous and localized supply of this growth factor, enhancing its therapeutic efficacy and facilitating tissue repair.

Similarly, Zhou et al. developed a hydrogel encapsulating MnO_2 nanozymes by dispersing bovine serum albumin (BSA)-MnO_2 (BM) nanoparticles within a hyaluronic acid (HA)/platelet-rich plasma (PRP) gel network crosslinked through Schiff base reactions [54]. Leveraging the self-healing and pH-responsive properties of Schiff base bonds, this hydrogel served not only as a viscosupplement but also demonstrated pH-responsive release of BM nanoparticles and growth factors from PRP. The BM nanoparticles played a crucial role in mitigating severe oxidative stress, while PRP promoted chondrocyte proliferation. In a rat OA model, the HA/PRP/BM hydrogel significantly mitigated the degradation of cartilage matrix. Results from both *in vitro* and *in vivo* investigations highlighted the potential of this innovative hydrogel platform to inhibit OA progression through a synergistic mechanism involving mechanical dissipation, inflammation reduction, cartilage repair promotion, thus indicating promising applications in OA therapy.

4.3. Polymeric micelles

Polymeric micelles have also emerged as a highly promising and versatile platform for the delivery of small molecules in the treatment of OA [55]. These self-assembling structures, composed of amphiphilic polymers, possess unique properties that make them

feasible for improving the solubility, stability, and sustained release of hydrophobic drugs in OA treatment.

One of the eminent features of polymeric micelles is their ability to encapsulate hydrophobic small molecules within their core. By self-assembling in an aqueous environment, the hydrophobic segments of the amphiphilic polymers aggregate to form a core, while the hydrophilic segments surround the core, forming a stabilizing shell [56]. This core-shell structure allows hydrophobic drugs to be efficiently loaded within the micelles, enhancing their solubility and protecting them from degradation or premature release. PEG micelles have attracted significant attention for small molecule delivery in OA treatment [57]. These micelles combine the hydrophilic properties of PEG and the biodegradable nature of PLA. PEG-PLA provides a protective shell that improves the stability and circulation time of the micelles in the body, while PLA forms the hydrophobic core that encapsulates the small molecules. Dexamethasone, a potent anti-inflammatory agent, has been successfully loaded into PEG-PLA micelles for the inhibition of inflammation and reduction of pain in OA [58]. The micelles enable the sustained release of dexamethasone, ensuring a prolonged and localized therapeutic effect within the affected joint.

Similarly, poly(ethylene glycol)-b-poly(caprolactone) (PEG-PCL) micelles have shown great potential for small molecule delivery in OA treatment [59]. These micelles combine the advantages of PEG, which improves stability and biocompatibility, with the biodegradability and drug-loading capacity of poly(caprolactone) (PCL). 9-aminoacridine (9AA) and the natural compound caffeic acid (CA), robust anti-inflammation factors and key molecule involved in cartilage regeneration, has been successfully loaded into PEG-PCL nanomicelles to promote chondrogenesis and facilitate cartilage regeneration [60]. The nanomicelles protect 9AA and CA from enzymatic degradation and enable its controlled release, providing a sustained supply of this important molecule in the joint environment (Fig. 4).

4.4. Polymeric nanofibers

Polymeric nanofibers have emerged as a remarkable and versatile platform for the delivery of small molecules in the treatment of OA [61]. These nanofibers, with their intricate structure and unique properties, have attracted considerable attention for their ability to enhance cell proliferation, and promote tissue regeneration.

One of the key advantages of polymeric nanofibers is their large surface area-to-volume ratio, which allows for increased interactions with the surrounding tissues and cells. This property is particularly advantageous in OA treatment, as it facilitates the attachment and proliferation of cells crucial for tissue regeneration [62]. The nanofiber architecture mimics the natural ECM, providing a supportive environment for cell adhesion and growth.

Furthermore, polymeric nanofibers can be functionalized with bioactive molecules and stem cells to enhance their therapeutic potential. These bioactive factors can be incorporated within the polymeric matrix or coated onto the nanofiber surface [63]. For instance, a prior study reported a nanofibrous scaffold (NFS) using a synthetic biodegradable polymer, poly(-caprolactone) (PCL), and assessed its ability to support *in vitro* chondrogenesis of MSCs. The electrospun PCL porous scaffold was constructed from uniform, randomly oriented nanofibers with a diameter of 700 nm, and it maintained its structural integrity throughout a 21-day culture period.

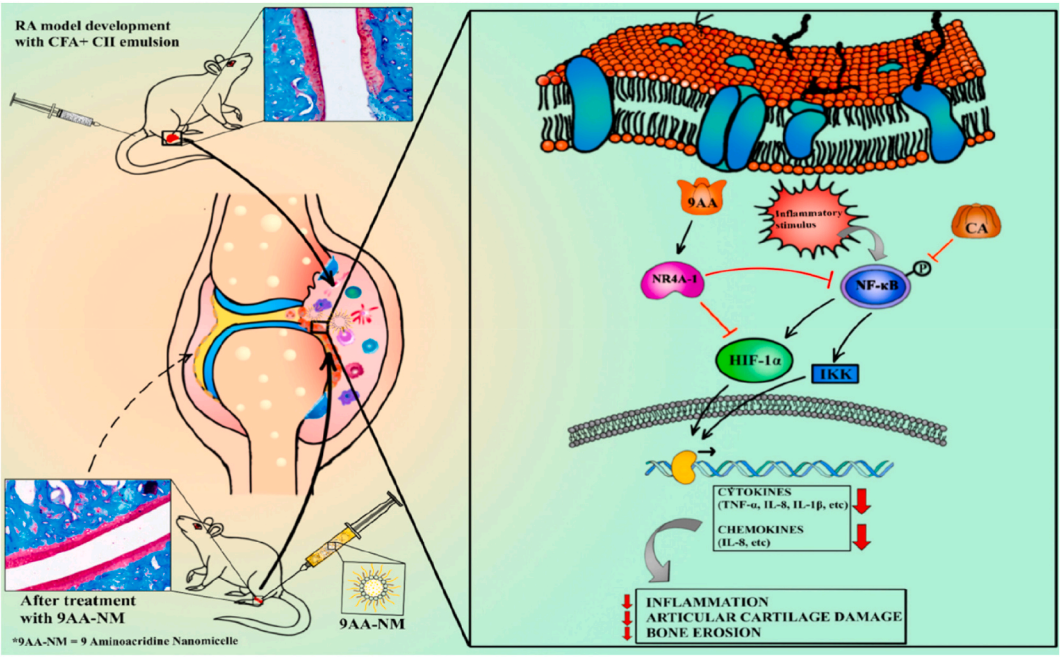

Fig. 4. Schematic illustration of 9AA-CA loaded nanomicelles in promotion of cartilage regeneration. Reproduced with permission [60]. Copyright 2022, American Chemical Society.

MSCs cultured within NFSs in the presence of TGF-β1 exhibited differentiation towards a chondrocytic phenotype. Due to the physical properties and enhanced mechanical characteristics of NFSs, these findings suggest that the PCL NFS serves as a practical vehicle for for cell-based tissue engineering strategies aimed at cartilage repair [64]. Similarly, nanofibers composed of PCL and HA have been designed to deliver TGF-β3, a molecule involved in cartilage regeneration [65]. The incorporation of TGF-β3 within the nanofiber structure improves its efficacy in promoting cartilage regeneration and enhancing the extracellular matrix synthesis.

Polymeric nanofibers present a range of advantageous attributes as small molecule delivery systems for the treatment of OA [66]. Their exceptional porosity facilitates efficient loading and the sustained release of therapeutic molecules, ensuring a prolonged therapeutic impact at the precise site of injury. Moreover, the electrospinning technique offers an adaptable means to adjust the size, morphology, and composition of the nanofibers. This level of control affords precise modulation of their properties and performance to meet the specific demands of OA therapy.

4.5. Polymeric implants

Polymeric implants have emerged as a significant advancement in the field of OA treatment, offering a promising approach for the controlled and sustained delivery of small molecules [69]. These implants serve as localized depots of bioactive molecules, providing a tailored therapeutic strategy to address the specific needs of individual patients.

One of the significant advantages of polymeric implants is their ability to achieve sustained release of bioactive molecules over an extended period [68]. By encapsulating the therapeutic agents within a biocompatible and biodegradable polymeric matrix, the implants ensure a controlled and continuous release, maintaining therapeutic concentrations at the site of injury. This sustained release enables long-lasting effects and reduces the need for frequent administration of drugs, enhancing patient convenience and compliance. PLGA implants represent a noteworthy example in small molecule delivery for OA treatment. These implants, loaded with IGF-1, have been developed to promote chondrogenesis and stimulate cartilage regeneration. The sustained release of IGF-1 from the PLGA implants provides a favorable microenvironment for chondrocyte proliferation and extracellular matrix synthesis, facilitating the restoration of damaged cartilage and improving joint function [70].

Moreover, chitosan-based implants loaded with TGF-β1 have achieved significant attention for their potential to inhibit inflammation and alleviate pain in OA [71]. Chitosan, sourced from natural origins like crustacean shells, boasts exceptional biocompatibility and biodegradability, rendering it a suitable material for the fabrication of implants. The deliberate release of TGF-β1 from these implants serves to regulate the inflammatory response, thereby reducing the production of pro-inflammatory cytokines and alleviating the pain associated with OA.

Polymeric implants offer several advantages in OA treatment [67]. These implants offer localized and targeted drug delivery, thereby minimizing the systemic side effects typically associated with conventional drug administration methods. Moreover, the capacity to adjust the composition, size, and shape of these implants enables the development of customized treatment strategies that cater to the distinctive characteristics and requirements of individual patients. This adaptability allows the implants to be modified to align with the specific anatomical attributes of the affected joint, ensuring optimal placement and effectiveness.

5. Challenges and future directions

Polymeric biomaterials have emerged as highly promising candidates for advancing the treatment of OA due to their inherent biocompatibility, customizable attributes, and adaptability in design [4,7,8]. However, the clinical translation of these materials into widespread therapeutic use is impeded by several substantial limitations and technical challenges, which necessitate careful consideration and innovative solutions.

One of the primary challenges in harnessing the potential of polymeric biomaterials for OA treatment is achieving mechanical properties that can withstand the demanding physiological loading conditions within the joint. An ideal biomaterial-based scaffold should offer robust support and stability while maintaining structural integrity over extended periods. This challenge remains a critical point, demanding the development of materials that can endure the demanding mechanical stress encountered within the joint.

Moreover, the endeavor to design a biomaterial capable of accurately replicating the intricate and dynamic ECM of native tissue poses a considerable obstacle. The ECM plays a pivotal role in tissue regeneration and function, making it essential to strive for the accurate emulation of its intricate structure and composition within biomaterial constructs [72]. This objective necessitates further exploration and innovation in biomaterial design.

Another vital aspect demanding attention is the long-term stability and durability of implanted polymeric DDS in OA treatment. The materials should exhibit resilience against degradation processes and maintain structural integrity, especially in the context of OA, where the joint endures repetitive mechanical stress. Achieving precise control over the release kinetics of bioactive molecules from these biomaterials represents another significant challenge, as it directly affects tissue regeneration, inflammation reduction, and therapeutic effectiveness.

The clinical translation of polymeric DDS for OA treatment also hinges upon stringent safety and regulatory considerations. Factors such as biocompatibility, immunogenicity, and the risk of infection are paramount and necessitate comprehensive assessment. While polymeric biomaterials are generally regarded as biocompatible, potential inflammatory responses and local tissue toxicity stemming from degradation byproducts should be thoroughly evaluated through rigorous biocompatibility and toxicity assessments. Regulatory approvals from agencies like the FDA are imperative to ensure compliance and patient safety.

In preclinical studies, various polymeric biomaterials have been extensively investigated in animal models of OA. These studies have provided valuable insights into their potential for OA management. For instance, a study by Diaz-Rodriguez et al. demonstrated

that intra-articular injections of a hyaluronic acid-based hydrogel significantly reduced cartilage degradation and improved joint function *in vivo* [73]. This finding highlights the chondroprotective effects of polymeric biomaterials. Furthermore, the use of drug-loaded polymeric nanoparticles has shown promise in preclinical studies. Research conducted by Ai et al. revealed that sustained release of bioactive agents from polymeric nanoparticles effectively reduces cartilage damage and alleviates the disease severity in the mice with collagenase-induced OA [74]. These results underscore the potential of polymeric biomaterials not only as structural support but also as drug delivery platforms for OA treatment.

Furthermore, numerous investigations have undertaken the assessment of safety and efficacy associated with polymeric biomaterials in patients with OA. For instance, Utamawatin et al. conducted a comparative study evaluating the effectiveness of intra-articular triamcinolone acetonide at dosages of 10 mg and 40 mg in individuals suffering from knee OA [75]. Their findings indicate that the 10 mg triamcinolone acetonide dosage demonstrates non-inferiority to the 40 mg dosage in terms of alleviating pain in symptomatic knee OA patients. Significantly, both the 10 mg and 40 mg triamcinolone acetonide dosages exhibit substantial improvements in pain reduction and overall quality of life for these individuals.

On the contrary, in a preceding investigation, McAlindon et al. conducted a randomized clinical trial to evaluate the effects of administering intra-articular injections of 40 mg of triamcinolone acetonide every three months on the progression of cartilage loss and knee pain [76]. The study's outcomes reveal that, among patients afflicted with symptomatic knee OA, the administration of intra-articular triamcinolone over a two-year duration did not yield a significant improvement in knee pain when compared to the control group receiving intra-articular saline injections. Notably, the study discerned that patients subjected to triamcinolone treatment experienced a notable increase in cartilage volume loss, implying a potential adverse impact on the joint's structural integrity. In light of these findings, it is reasonable to conclude that the use of intra-articular triamcinolone may not represent an efficacious or advisable treatment modality for individuals suffering from symptomatic knee osteoarthritis. This underscores the critical importance of prudently weighing the potential risks and benefits associated with various therapeutic approaches for osteoarthritis and emphasizes the necessity for further research to identify more suitable interventions for effectively managing this condition.

It is imperative to acknowledge the inherent heterogeneity in clinical studies, encompassing disparities in patient cohorts, study methodologies, and duration of follow-up. Thus, there is an imperative need for further extensive, long-term clinical trials on a larger scale to substantiate the sustained benefits and safety profiles of polymeric biomaterials in the management of OA. Meanwhile, the future directions of polymeric DDS in OA therapy offer great promise for advancing the treatment of this debilitating condition. Several key directions of exploration include.

(i) Personalized medicine: Tailoring polymeric DDS to the unique profiles of individual patients by considering factors such as genetics, disease stage, and joint characteristics can significantly enhance therapeutic outcomes. Advances in biomarker identification and diagnostic techniques will further support the customization of DDS formulations to address the specific needs of each patient.

(ii) Targeted drug delivery: Future research will place a strong emphasis on enhancing targeting strategies. Polymeric DDS can be meticulously engineered to deliver drugs precisely to the affected joint, thereby minimizing systemic exposure and potential side effects. Utilizing ligands, nanoparticles, or other targeting moieties with an affinity for OA-specific markers will be pivotal in achieving this goal.

(iii) Combination therapies: OA is a complex disease with multiple underlying mechanisms. Future polymeric DDS may involve the delivery of multiple therapeutic agents simultaneously, addressing various aspects of OA pathology. This approach can include anti-inflammatory drugs, disease-modifying agents, and pain management medications in a single DDS, offering a more comprehensive and effective treatment strategy.

(iv) Smart and responsive DDS: The development of smart DDS that can respond to disease cues within the joint environment is an emerging area. These systems can release drugs in response to changes in pH, temperature, or other OA-related factors. Such responsive DDS can provide on-demand drug delivery, optimizing therapeutic efficacy while minimizing side effects.

(v) Long-term durability: Ensuring the long-term stability and durability of polymeric DDS within the joint is crucial. Research efforts will focus on designing materials and formulations that can withstand the mechanical stresses and enzymatic degradation associated with OA over extended periods. Advances in polymer science and engineering will play a vital role in achieving this objective.

In summary, while polymeric biomaterials hold substantial promise for advancing OA therapies, they are currently constrained by noteworthy technical challenges and limitations. The optimization of mechanical and biological properties, alongside enhanced biocompatibility and comprehensive safety and regulatory assessments, stands as imperative steps toward harnessing the full therapeutic potential of polymeric biomaterials in OA treatment. As research and development in polymeric DDS continue to evolve, these biomaterials are promising for offering more effective and enduring solutions for managing this debilitating disease.

CRediT authorship contribution statement

Lin Liu: Methodology, Software, Writing – original draft. **Haifeng Tang:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Yanjun Wang:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Validation, Visualization, Writing – review & editing.

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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Appendix A. Supplementary data

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