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Last Advances on Hydrogel Nanoparticles Composites in Medicine: An Overview with Focus on Gold Nanoparticles

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Hydrogel nanocomposites have lately taken part in the biomaterials scenario for several applications in the biomedical field, e.g., drug delivery, biosensing and cancer therapy. The inclusion of a broad variety of nanomaterials inside the hydrogel matrix leads to the successful development of hybrid platforms with superior and advantageous features. In this way, finely designed nano-systems can be obtained, which are able to overcome the intrinsic limitations of conventional hydrogels, such as weak mechanical properties, burst drug delivery, extremely high hydrophilicity and lack of multifunctionality. This review aims to outline the last advances in the manufacturing of nanocomposite systems and their novel applications to the biomedical field, providing an overview of the most used nanoparticles with a special focus on gold nanoparticles.

1. Introduction

In the last decades, hydrogels have increasingly attracted the attention of researchers from many different fields. Thanks to their versatility, these materials find applications in several areas, including drug delivery,[1,2] tissue engineering,[3,4] biosensing,[5,6] actuators production,[7] wastewater treatment,[8] to mention a few.

Hydrogels are characterized by a three-dimensional network made through the crosslinking of polymers bearing hydrophilic groups. The uniqueness of these materials is given by the ability to retain large amounts of aqueous solutions (generally more than 95% of the total composition). As a result of this property, hydrogels feature good biocompatibility, biodegradability, and excellent swelling capacities.[9–13] Nevertheless, their composition and physico-chemical properties constitute both an advantage and a disadvantage, depending on their specific application.[14] For instance, the extremely hydrophilic nature of the gel building blocks represents an issue in most of the drug delivery applications,[15] as the majority of the discovered active molecules for the current treatments are hydrophobic,[16] resulting in poor drug solubility, drug aggregation or drug non-controlled release from the system.[17,18] To overcome these limitations, the synthesis of hydrogel nanocomposites (HNCs) has paved the way for the development of new multifunctional materials with tailored behaviors, thanks to the inclusion of additional nanostructures, e.g., nanoparticles (NPs), inside the gel matrix. In this context, this review aims to report recent biomedical (and related) applications and fabrication methods of hydrogels containing various types of NPs with particular attention to systems based on inorganic and polymeric nanoparticles (PNPs), in light of their outstanding properties.

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2. Hydrogels: Main Properties and Current Limitations

Hydrogels are defined as hydrophilic networks characterized by the presence of a high amount of aqueous solution, which makes them a suitable environment to mimic biological fluids (e.g., extracellular matrix, ECM).[19] By selecting the polymeric materials, the crosslinking mechanism and density, as well as the final formulation, it is possible to finely tune the hydrogel features, obtaining a wide range of different behaviors tailored to specific applications. Hydrogel classification has been carried out according to different properties. They can be divided into natural, synthetic and hybrid, based on the nature of the polymers employed. Among the most used natural materials there are alginate, gelatin, chitosan, DNA, hyaluronic acid, agarose, and many others.[20–23] On the other hand, the mainly employed synthetic ones are polyacrylic acid (PAA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyacrylamide (PAM), Pluronic F127, etc.[24–26] To obtain specific properties of the final product, it is required an accurate selection of the polymers to use. The natural components generally provide the material with fast degradation properties, biocompatibility, good cellular interactions and low toxicity,[27,28] yet they usually suffer from drawbacks related to poor mechanical strength.

On the other hand, synthetic polymers are easy to be functionalized and more flexible,[29] endowing the hydrogel with better mechanical properties, as well as better swelling abilities.[30] Hence, the use of both synthetic and natural sources to build hydrogel networks is one of the strategies to obtain optimal functional properties with molecular design.[31] Following a second criterion, gels can be divided into chemically or physically crosslinked. The physical gels are dominated by non-

covalent linkages between the polymeric chains (i.e., hydrogen bonds, ionic interactions, hydrophobic interactions, π-π stacking)[20,32,33] and hence are characterized by weak and reversible interactions between these chains. As a result, gel properties like self-healing or shear-thinning can be obtained,[34] as well as the possibility to tune these gels' characteristics by modulation of external stimuli, e.g., pH, temperature or light, which can alter the intermolecular forces between the hydrogel constituents.[35] Conversely, the three-dimensional matrix of the chemical gels is formed by chemical bonds between single or multiple monomers present in the system,[36] conferring a stable chemical structure to the hydrogel. In this way, the final gels display stronger mechanical properties and lower degradation kinetics, whereas they are still degradable.[37] Hydrogels have found applications in many fields, especially in the biomedical one. Some examples are wound healing, tissue engineering, cell proliferation, and drug delivery.[38–40] Despite being highly attractive thanks to the abovementioned properties, hydrogels still lack multifunctionality, in terms of stimuli-responsiveness or additional functions, poor mechanical properties and scarce interaction with hydrophobic substances. For this reason, the scientific community has started to turn its attention to the development of hydrogel-based systems capable of overcoming these intrinsic limits.

3. Hydrogel Nanocomposites: A New Frontier for Multifunctional Approaches

The definition of "hydrogel nanocomposite" refers to heterogeneous hybrid materials composed of a hydrogel matrix in which additional nanomaterials, usually NPs, are embedded. In particular, the NPs can have different morphologies or architectures, encompassing, e.g., nanotubes, nanospheres, nanorods, nanocages, etc. The establishment of this new class of materials has opened the possibility of overcoming the limitations of hydrogels, as the NPs can give specific functionalities, depending on the type of material used. The formation of nanocomposite systems can be achieved by using several methods: i) NPs dispersion into the polymeric solution at sol state right before gelation; ii) NPs incorporation after the gelation process takes place; iii) NPs synthesis inside the gel matrix starting from a chemical precursor; iv) NPs used as crosslinker agent during the gelation mechanism.[41] Table 1 reports a detailed list of some examples of HNCs containing different NPs described in this review.

3.1. Hydrogel Nanoparticles Composites: Classification and Functions Based on the Types of NPs

NPs are generally classified upon their nature and chemical composition in two different classes: organic and inorganic. Organic NPs are all those nanostructures composed by self-assembling of organic molecules. In this category are included polymeric nanoparticles, liposomes, dendrimers, solid-lipid nanoparticles, polymer or protein-conjugates, protein nanoparticles, vesicles and nanogels. On the other hand, the inorganic NPs category encompasses carbon-based NPs, ceramic NPs, silver NPs (Ag NPs) and gold NPs (Au NPs). Each of these NPs holds unique properties, depending on their chemical constituent, morphology and surface properties.[79,80] A complete description of all the classes of NPs is beyond the purpose of this review. On the contrary, the scope of this report is to propose a classification of the most studied HNCs based on the NPs type employed. Therefore, only a short description of the most used NPs in HNCs will be given, focusing then on a comprehensive study of the most recent applications of each corresponding composite system.

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Filippo Rossi received his MSc and then PhD in chemical engineering from Politecnico di Milano. Then he spent research periods at Uppsala University (2012) and Mario Negri Institute for Pharmacological Research (2013–2015). In 2015 he joined the Department of Chemistry, Materials and Chemical Engineering "Giulio Natta" of Politecnico di Milano as an Assistant Professor and since 2019 he has been working as an Associate Professor of Applied Physical Chemistry. His group's research program is focused on developing novel technologies to solve problems associated with health and the environment using functionalized polymers in bulk and colloidal forms.

Table 1. Examples of HNCs designed with the most relevant NPs types and their corresponding application field.

Nanoparticles material and type	Hydrogel material	Application	Reference
Polymeric nanoparticles			
Eudragit L100	Polyacrylic acid	Drug delivery	[42]
Poly(3,4-ethylenedioxythiophene) (PEDOT)	Poly-γ-glutamic acid	Drug delivery	[43]
Poly(lactic-co-glycolic) acid (PLGA) and dioleoyl-Trimethylammonium propane (DOTAP) coated with hyaluronic acid (HA)	Poloxamer 407 and HA	Drug delivery	[44]
poly (lactide–co–glycolide) (PLGA)	Modified HA	Drug delivery	[45]
Mesoporous polydopamine (MPDA) NPs were wrapped by polyethyleneimine-modified cellulose nanocrystals (PCNC)	Cellulose nanofibrils (CNF)	Drug delivery	[46]
Alginate-chitosan	Carboxymethyl chitosan (CMC)-methylcellulose (MC)-Pluronic	Drug delivery	[24]
Poly(ethylene glycol)-block-poly(−lactic acid) (PEG-b-PLA)	Agarose-carbomer	Drug delivery	[36]
Poly(ε-caprolactone) (PCL) - based polyurethane	Poloxamer 407	Drug delivery	[47,48]
Poly (ε-caprolactone)-poly (ethylene glycol)-poly (ε-caprolactone) (PCL-PEG-PCL)	Pluronic F127	Drug delivery	[48]
PLGA	Gelatin	Drug delivery	[49]
Ceramic nanoparticles			
Wilmette (Zn_2SiO_4)	Oxidized alginate and gelatin	Hydrogel reinforcement	[50]
(3-Glycidoxypropyl) trimethoxysilane functionalized glycidoxypropyl-silica	Plasma-derived	Hydrogel reinforcement	[51]
Fe_3O_4@SiO_2 core-shell	Carboxymethyl cellulose	Drug delivery	[52]
SiO_2	Pluronic F127/HA	Drug delivery	[53]
TiO_2	Chitosan/polypropylene glycol hydrogel	Scaffold design	[54]
Hollow mesoporous SiO_2	poly(D,L-lactide)-poly(ethylene glycol)-poly(D,L-lactide) (PDLLA-PEG-PDLLA)	Drug delivery	[55]
Silver nanoparticles			
Mercaptossucinic acid-protected silver nanoparticles (Ag NPs)	Poly(methacrylic acid)-(acrylamide) poly(mAA-co-AAm)	Antibacterial properties	[56]
Iota carrageenan AuAg NPs	Poloxamer 407/polyvinylpyrrolidone (PVP) and boronic acid	Photothermal therapy; antibacterial properties	[57]
Silver nanorods (Ag NRs) and Ag NPs mesoporous SiO_2	Gelatin	Photothermal therapy; antibacterial properties	[58]
Ag NPs	Peptide-based	Antibacterial properties	[59,60]
Gold nanoparticles			
miRNA-gold nanoparticles (Au NPs) and PEG-b-PLA	PEG-**b**-PLA and hydroxypropyl methyl cellulose (HPMC) functionalized C_{12}	Therapeutic stabilization; Gene delivery	[61]
Spyropyran complexed Au NPs	N-isopropylacrylamide and N,N-methylenebisacrylamide	Therapeutic stabilization; Drug delivery	[62]
Liposomes complexed with SiO_2-coated Au NRs	Glucono-d-lactone based	Drug delivery	[63]
Ultrasmall Au NPs containing metal organic frameworks (MOF)	CMC	Photothermal therapy; Drug delivery	[64]
Au NPs	Poly(ethylene glycol) diacrylate (PEGDA)	Biosensing	[65–67]
Gap containing core-shell Au NPs	DNA based	Biosensing; SERS	[67]
Au NPs	Poly(vinyl alcohol) (PVA) –gallic acid (GA)	SERS	[68]

Table 1. continued

Nanoparticles material and type	Hydrogel material	Application	Reference
Polymeric nanoparticles			
Gold nanorods (Au NRs)	PEG	Cell actuation activation	[69]
Ag-coated Au NRs	Chitosan/PVA	Wound healing	[70]
Hollow Au NPs	Fibrin	Protein delivery	[71]
Au NPs and Au NRs	DNA-based	Drug delivery	[72]
Au NPs and Au NRs	Pluronic F127	Wound healing; NPs delivery	[73]
Au NPs	Alginate	Drug delivery; Photothermal therapy; Radiotherapy	[74,75]
Methoxy poly(ethylene glycol)-**b**-poly(ε-caprolactone-**co**-1,4,8-trioxa[4.6]spiro-9-undecanone) (mPECT) Au NRs and mPECT NPs	mPECT NPs and α-cyclodextrin (α-CD)	Drug delivery; Photothermal therapy	[75]
Au NRs	Gellan gum	Drug delivery; Photothermal therapy; Photodynamic therapy	[76]
Gold nanostars (Au NSs)	Cellulose	Biosensing; SERS	[77,78]
Branched polyethyleneimine-Au NPs	Collagen	Drug delivery; Tissue engineering	[78]
Au NPs	DNA	Biosensing	[5]

3.1.1. Polymeric Nanoparticles Loaded HNCs

Polymeric NPs are constituted by self-assembled copolymer chains with different domains, mainly a hydrophilic and a hydrophobic one. It is possible to design these NPs by polymer engineering approaches, selecting a specific architecture and repetition of monomer units, so as to obtain peculiar structures, and hence specific polymers' properties. Such NPs are generally synthesized by exploiting methods like nanoprecipitation[42,47] or solvent removal.[48] In the field of HNCs, the incorporation of polymeric NPs inside the hydrogel is mostly justified by the attempt to overcome the limitations of conventional hydrogel for drug delivery applications, such as limited release performances or in-situ delivery of active substances.[81] Moreover, another reason for fabricating these HNCs is to promote gelification by the viscosity increase, which is indeed achieved through interactions between the hydrogel constituents and the NPs.[82] Earlier works on this topic showed the possibility of designing a system where poly(methyl methacrylate) (PMMA) NPs are used at the same time as drug delivery means themselves and to delay the release of active substances loaded inside the hydrogel matrix. In this way, the gel acted as a depot of NPs and active substances, reducing the problem of fast clearance of the NPs from the body, and slowing down the drug release over time.[83] Later from the same research group, Mauri et al. investigated the role of surface charge on polymeric NPs with poly(ethylene glycol)-block-poly(-lactic acid) (PEG-b-PLA) copolymer NPs. They designed an HNC able to release NPs upon pH changes in the release medium. They found that in the presence of acidic pH, their hydrogel formulation (named AC6) was not able to release positively charged NPs, while negatively charged were rapidly released.[36] Besides these reports, many HNCs with polymeric NPs have been lately used in drug delivery systems for cancer treatment.

Lee and coworkers prepared an injectable HNC for bortezomib (BTZ) delivery, based on a gelification process driven by the coacervation of two triblock copolymers (ABA); the B block consisted of poly(ethylene glycol) (PEG), while the A group was changed between phenylboronic acid (PBA) functionalized polycarbonate and guanidinium functionalized polycarbonate. The BTZ-loaded polymeric micelles, made of diblock copolymer (AB), were inserted inside the physical hydrogel. The micelles were made of PEG and catechol, and the drug was loaded through the formation of a pH-sensitive boronate ester bond. For this reason, the prolonged release profile was effective for 9 days, releasing almost 85% of the loaded BTZ in vitro, only under acidic conditions, preventing unwanted drug release before reaching the cancer cells. In vivo results

showed that the tumor size decreased when treated with the injectable hydrogel, while showed no increase over the first 8 days post-treatment.[84] Another example of cancer treatment was reported in the work of Brachi et al., where the HNC was directly injected at the tumor site of some mice, for glioblastoma drug delivery. The system was designed as a reservoir of drug-loaded polycaprolactone (PCL) based polyurethane NPs, through the gelification driven by the thermo-responsiveness of the poloxamer 407. The NPs could be released from the gel matrix at a slow rate, locally delivering the model drug for 5 days.[47] HNC for co-delivery of multiple anti-cancer drugs injected at the tumor site has been recently developed for hepatocellular carcinoma treatment. An example is given by a system composed of PCL-PEG-PCL NPs loaded with norcantharidin (NCTD), inserted inside a Pluronic F127 hydrogel during its sol-gel transition. Together with the NPs, the doxorubicin (DOX) was dissolved inside the gel. This platform for in-situ tumor treatment demonstrated a release of almost 97% of the DOX from the gel and 47.8% of NCTD from the NPs loaded within 7 days in vivo, showing low cytotoxicity in vitro and good antitumor ability in vivo within 13 days.[48] On the other hand, some formulations of HNCs with hydrogel based on hyaluronic acid seem to be promising in ocular drug delivery. As an example, a recent platform has been proposed, made of a chemically crosslinked hyaluronic acid hydrogel loaded with poly (lactide–co–glycolide) (PLGA) NPs, for ocular delivery of protein drugs. The developed composite system led to a prolonged drug release, avoiding fast clearance of drug-laden NPs and cytotoxicity. Nevertheless, further studies lack on the stability of the protein drugs, together with the demonstration of a higher drug delivery efficiency, which has been reported to be around 20%, due to the loss of NPs during the loading procedure.[45] Likewise, using the same combination of hyaluronic acid and PLGA-based NPs, Ottonelli et al. developed a similar nanocomposite to deliver retinal-targeted hybrid NPs.

The difference with the system reported by Hsu and coworkers,[45] lies in the hyaluronan-based coating onto the lipid-modified PLGA NPs surface, to increase their biocompatibility and motility through the retina, together with the thermo-responsivity of the hydrogel. Indeed, thanks to the addition of poloxamer 407, the so-obtained hydrogel underwent sol-gel transition at 35 °C, a feature which decelerates the release of NPs and makes the hybrid system suitable for acting as a potential ocular drug delivery storage.[44] Additionally, multi-responsive stimuli HNCs have been developed using polymeric NPs, where NPs provide different functionalities to the system. In the works of Liu and coworkers, the HNC was designed and optimized. Indeed, the mesoporous polymeric NPs formed by polydopamine (MPDA) showed high drug loading, and thanks to the graphene oxide (GO) coating,[85] or the polyethyleneimine-modified cellulose nanocrystals (PCNC) coating,[46] the HNC based on cellulose nanofibrils (CNF) exhibited improved mechanical stability and drug release properties. The work demonstrated a smart multi-responsive system for drug delivery, triggered by acid pH and near-infrared (NIR) irradiation, thanks to the polydopamine photothermal properties. Despite GO having higher toxicity, the HNC with MPDA@GO NPs showed better performances both in terms of drug delivery and mechanical strength. Under NIR light irradiation, the drug release was around 70% at pH 5 over 120 minutes, whereas almost 80% of the drug was released over 72 hours in the absence of NIR irradiation, with better performances than the case at pH 7.4. Moreover, the MDPS@GO NPs gave a mechanical strength to the HNC 5 times higher than the pristine CNF hydrogel.

3.1.2. Liposomes Loaded HNCs

Liposomes are spherical hollow NPs obtained from the self-assembling of phospholipids, in a double-layer structure with the hydrophilic heads in contact with water, and the hydrophobic tails forming an internal spherical compartment. Thanks to this structure, liposomes have both a water internal environment, in which hydrophilic substances can be encapsulated, and an interconnected hydrophobic structure, in which lipophilic molecules can be entrapped.[86] They have found applications in several biomedical fields and have been used to create HNCs,[87] some also where they can create compartmentalized zones inside the HNCs to tune drug release.[88,87] As well as PNPs, liposomes' ability to target tissues is limited by their accumulation in filtration organs (such as the liver, spleen and others).[89] In this perspective, the use of injectable HNCs with liposomes would solve this drawback, employing minimally invasive therapies with injectable systems into the tissues.[88] An example of HNC containing liposomes is described in the work by Cao and coworkers for local breast cancer treatment. The analyzed system consisted of an injectable hydrogel made of a PLGA-PEG-PLGA hermos-responsive polymer chain turning into hydrogel at around 37 °C. In this formulation, the polymer is dissolved in a DOX-loaded liposomes solution.

A prolonged DOX release over 11 days was achieved from the lipo-gel system, having a limited burst release of only 20% of the loaded drug within the first 12 hours, and promoting a good tumor size decrease during the treatment (Figure 1).[90] Moreover, some interesting outcomes have been reported showing the potential of coupling liposomes and gold colloids in HNCs.[1] A dehydropeptide hydrogel was self-assembled with dipalmitoyl phosphatidylcholine (DPPC) liposomes and silica-coated gold nanorods (Au NRs), with a silica layer thickness larger than 20 nm, to prevent their aggregation onto the liposomes' surface inside the HNC. The system developed displayed various mechanisms for controllable sustained release, including drug-loaded liposomes release, drug release through diffusion towards the gel matrix, fast release from non-encapsulated amount and NIR-irradiation-driven drug release.[63] Similarly, a system for combined chemo- and immunotherapy using chitosan injectable hydrogel with gold-labeled liposomal DOX was designed by Won et al. Also in this case, DPPC liposomes were used, while Au NPs were synthesized starting from the liposomes solution, obtaining gold NPs coated liposomes. The liposomes have been physically entrapped inside the chitosan hydrogel through interaction between the liposomes' negative charges and positive ones of chitosan. The

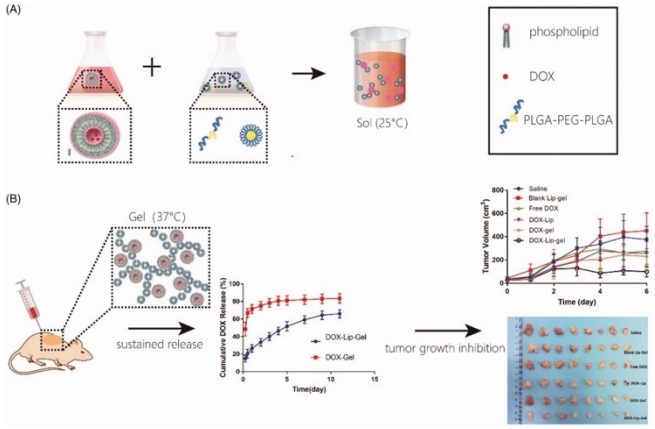

Figure 1. (A) PLGA-PEG-PLGA copolymer was dissolved into DOX liposomes suspension to form DOX-Lip-Gel, which was in a sol state at 25 °C. (B) DOX-Lip-Gel solution was injected peritumorally and transformed into a solid gel in situ at body temperature (37 °C), enabling the sustained release of DOX and significant inhibition of tumor growth. Reproduced under terms of the CC-BY license.[90] © 2019, The Authors, Informa UK Limited, trading as Taylor & Francis Group.

proposed approach demonstrated liposomes' retention, while the DOX delivery was driven by NIR irradiation. It was found that the nanocomposite was able to deliver the DOX only if irradiated with the laser light. When combined with PLGA-NPs incorporating a tumor antigen (TRP2) and a dendritic cell activation adjuvant, the HNC showed a significant immune response compared to the controls, with a substantially higher amount of damaged tumor cells.[91]

3.1.3. Carbon-Based Nanoparticles Loaded HNCs

Carbon is widely known for the different molecular assemblies that it can assume, also known as carbon allotropes, arising from the different shapes and configurations of the carbon atoms during the formation of carbon bonds.[92] Among the possible structures, the most interesting in the biomedical fields are carbon nanotubes, graphene, fullerenes, and carbon nanodiamonds. Such carbon-based configurations have indeed attracted much attention as they are soluble in both water and organic solvents, have potential antibacterial and photothermal properties, and are prone to be functionalized, finding their application in theranostic[93] and in the gene therapy field.[94] However, they show severe problems related to toxicity,[95] due to migration properties through the tissues and immunological responses that can occur from their interactions with the human body. In the HNC field, carbon-based NPs are mostly used for their antioxidant ability[96] and antibacterial potential.[97]

3.1.4. Ceramic Nanoparticles Loaded HNCs

The class of ceramic NPs encompasses all those nanostructures in the nano-size range composed of oxides, carbides, and phosphates of metals such as silicon, calcium, titanium and others.[98] These NPs have become very attractive in several fields including the biomedical one, thanks to their strong inertness, drug delivery ability and properties like porosity and high surface-to-volume ratio.[99] Their use in HNCs has been widely explored to improve physical, mechanical and chemical properties[51] of the hydrogels, e.g. in bone tissue engineering,[50,100] or to enhance the hydrogels' properties in drug delivery applications.[53,55] In this direction, some interesting studies have been recently published in the field of drug delivery for cancer treatment using ceramic NPs included in HNCs. For instance, in the work by de Melo et al.,[52,53] a system for simultaneous delivery of nitric oxide (NO) and an anticancer drug was designed by using a Pluronic F127/hyaluronic acid hydrogel containing cisplatin-loaded SiO_2 NPs for breast cancer treatment. The system showed reduced cytotoxicity and effectiveness in killing cancer cells, with a prolonged release of NO and cisplatin. Interestingly, ceramic NPs can also be coupled with other nanostructures. An exemplary configuration is represented by core-shell NPs. Mahdi Eshaghi and coworkers detailed a carboxymethyl cellulose-based hydrogel containing Fe_3O_4@SiO_2 core-shell NPs for encapsulation of quercetin. Indeed, the porosity of the silica shell was used as a depot for hydrophobic drugs, which otherwise would not be easily entrapped in the hydrogel matrix. The coupling of the systems led to improved drug encapsulation and release abilities and demonstrated pH-responsiveness for drug release.[52]

3.1.5. Silver Nanoparticles Loaded HNCs

Silver NPs belong, together with the gold-based ones, to the class of noble metal NPs. In the last years, Ag NPs have been exploited in biomedical applications and beyond,[101] given their biocompatibility, optical properties, and antibacterial nature.[102] In HNCs, they have been mainly used to confine the antibacterial properties in specific regions, for wound healing applications,[56] for NPs stabilization without further functionalization[103] or, coupled with Au NPs, to modify the system plasmonic properties (more details on the peculiar optical response of these noble metal NPs are provided in the following section).[70] The Ag NPs can be designed in different shapes, by tuning the chemical synthesis. For instance, mesoporous structures as NRs (to restrain aggregation) have been synthesized and then entrapped in a gelatin hydrogel matrix as antibacterial agents under light irradiation.[58,60]

In other works, the synthesis of Ag NPs inside the hydrogels has been studied using green and more sustainable methods, which led to improved stability and antibacterial properties of the so-obtained HNCs.[59,60] The most interesting results have been observed when coupling Au and Ag NPs. On this subject, in the work by Milanesi et al., the purpose was to combine the plasmonic features of Au NRs with the antimicrobial and germicidal activity of Ag cations. In this way, core-shell Au–Ag nanorods with a blue shift of the longitudinal plasmonic peak have been obtained and inserted in chitosan hydrogels for wound healing applications.[70] In the same fashion, the coupling of Au and Ag NPs in HNCs has been exploited for

anticancer and antibacterial coupled treatment of melanoma breast tumor. In the work by Chen et al., the authors created an HNC made of polyvinylpyrrolidone (PVP), poloxamer 407 and boric acid, where iota carrageenan stabilized NPs were inserted. The system showed a temperature increase upon 808 nm laser irradiation, reducing the tumor and promoting an anti-proliferative effect, also with hemostatic abilities thanks to the surface charge and antibacterial properties when irradiated (Figure 2).[57]

3.1.6. Gold Nanoparticles Loaded HNCs

Gold NPs are the most widespread and commonly used among the noble metal NPs, which exhibit unique optical properties when interacting with (typically visible/NIR) light. Indeed, similarly to Ag NPs, Au nanostructures can sustain coherent collective oscillations of the metal-free electrons, the so-called localized surface plasmons,[104] resonantly excited by an external electromagnetic field.[105,106] This phenomenon, named localized surface plasmon resonance (LSPR), is strongly dependent on the shape and configuration (isolated, aggregated in colloidal solutions, ordered in arrays) of the NPs,[107] as well as on their local environment. Thanks to this optical property, the colloidal gold solutions are characterized by a visible color, ranging from red to blue, according to their specific configurations. Specifically in biomedicine, the highly attractive effects of inducing LSPRs in Au NPs have been recently reviewed,[108] including their potential for photothermal therapy (PTT). In PPT, upon external light stimuli, the photoexcited NPs' electrons rapidly convert the photon energy into heat, generating a localized increase of temperature in their vicinity. For this reason, Au NPs found

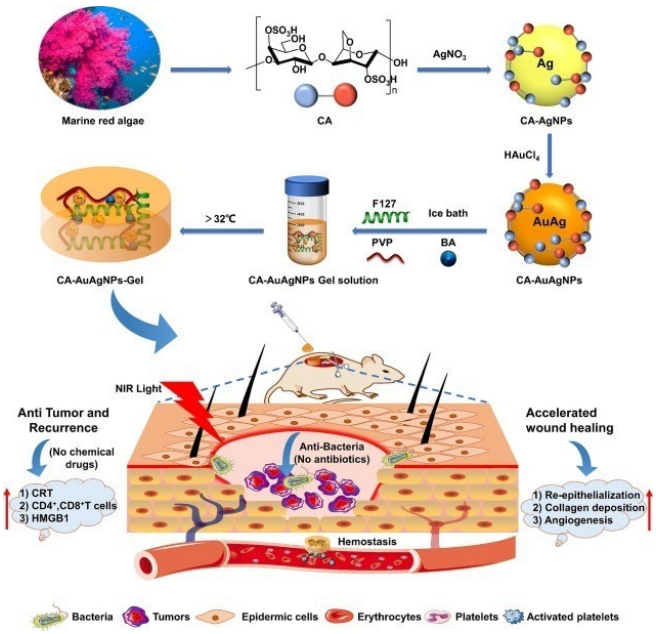

Figure 2. Schematic illustration of the preparation of CA-AuAg NPs-Gel and treatment of residual tumor and recurrence, hemostasis, as well as promoting infected wound healing after tumor surgery. Reproduced with permission.[57] © 2022, Elsevier Inc.

applications in a wide variety of biomedical applications[109] and beyond,[101,110] thanks to their finely controlled shapes and architectures, which give access to specific, tunable optical properties and heating phenomena.[111,112] The most studied Au NPs architectures are nanospheres (NSPs), NRs and nanostars (NSs).

The coupling of hydrogel and Au NPs can produce a final composite structure featuring light responsivity and unique photothermal properties for the control over the temperature changes across the system via light stimulation. Thereby, Au NPs loaded HNCs have been intensively investigated for different bio-related applications, the most attractive ones being, e.g., active substances delivery, biosensing, tissue engineering and cancer treatment. The HNCs containing Au NPs have shown great potential not only for the delivery of pharmaceutical drugs, but also for genetic therapeutics, and growth factors. The main advantages of including Au NPs in the gel for these purposes are the stabilization of the compound to be delivered, the plasmonic-induced drug delivery, or the direct delivery of the Au NPs.

In this last section, the review will cover the main recent advances in the use of Au NPs-based HNCs for the exemplary applications listed above. Evidence in literature has highlighted the benefits arising from the use of different Au NPs architectures, especially Au NRs. Besides the architectures, several studies on the different possible surface functionalizations of the particles have been reported.[73,76] A relevant example with an injectable PNPs hydrogel has been developed by van der Ven et al., containing Au NPs to improve miRNA biostability. The hydrogel was formed by non-covalent interactions between the hydroxypropyl methylcellulose derivative (HPMC-C_{12}) and core–shell poly (ethylene glycol)-block-poly(lactic acid) (PEG-b-PLA) NPs, while the Au NPs were inserted after the gelation.

The system demonstrated a sustained release of miRNA–Au NPs of 20% within 5 days, caused by erosion of the PNPs gel. Besides, it was found from in vivo analyses that the Au NPs could be totally excreted from the body in 11 days.[61] In the work by Moretti et al., an agarose-carbomer based hydrogel loaded with Au NPs for plasmonic-induced drug delivery was presented, using model drugs of different sizes. Authors found that NPs assemblies into the hydrogel are more efficient compared to isolated Au NPs in locally increasing the temperature, and hence in stretching the hydrogel mesh, thus enabling the dextran 70 kDa release only under laser irradiation.[113] As regards protein delivery instead, Sanchez-Casanova and coworkers developed an HNC able to combine gene expression by a heat-inducible dimerizer and NIR light-induced hyperthermia. Authors used hollow Au NPs for bone morphogenetic protein (BMP-2) production. Au NPs were dissolved in the fibrin gel precursor before the gelation process and the cells started the production of BMP-2 after activation in the presence of rapamycin under irradiation for 10 minutes, reaching a maximum temperature Increase of $11.2 \pm 0.6\,^{\circ}C$. The hydrogel could act then as a time- and space-activated reservoir of the morphogenetic proteins.[71] Among the preparation of HNCs formulations for drug delivery, there are examples where

the Au NPs are maintained inside the gel through bonds and interactions. For instance, Veloso et al. compared two systems made by a dehydropeptide-based hydrogel containing Au-decorated or core/shell manganese-ferrite NPs. The employed hydrogel self-assembled at acid pH and the formulation contained methionine to inhibit the escape of Au NPs through S–Au bonding. The system has demonstrated the ability to release curcumin both under light irradiation and in the dark, showing the best performances in the case of Au-decorated manganese NPs.[114]

In some other cases, the advantages of HNCs lay in the possibility of using them as depots of Au NPs, which can be possibly delivered for multiple purposes. In the work by Huang et al., a bilayer HNC containing two different functionalized Au NRs was produced. The HNCs allowed the release of Au NRs in a multistage procedure, in a way that, taking advantage of the different NRs functionalization, the antibacterial effect takes place first, and then the pro-angiogenic effect is exerted. Besides, the application of NIR laser light enhanced the antibacterial killing effect by the application of hyperthermia. The designed system showed promising results in diabetic chronic wound healing applications (Figure 3).[115]

Moreover, Au NPs have been used not only for their plasmonic features but also for their electroconductive nature.[116] Recently, a nanocomposite system has been developed for tissue engineering and drug delivery by Roshanbinfar et al., for cardiovascular system treatment. Specifically, the authors created a collagen hydrogel in which Au NPs, synthesized using branched polyethyleneimine (bPEI) as a reducing and stabilizing agent, are present inside. The system was characterized by a final overall positive surface charge, improved mechanical and electrical properties, and low cytotoxicity. Furthermore, the analyzed HNC allowed the delivery of different active substances useful for cardiovascular treatments, showing release profiles dependent on the drug net charge. Lastly, the system showed promising potential to load several peptides or nucleotides bearing negative charges and in the treatment of several cardiac diseases (Figure 4).[78]

Nowadays, a great number of studies have remarked the potential of Au NPs, and therefore HNCs loaded with Au NPs, in killing cancer by PTT. The colloidal Au NPs suffer from limitations related to colloidal stability, immune system recognition, opsonization and accumulation in organs when used in biomedical applications.[117–120] The advantage of HNC systems lies in the hydrogel's ability to entrap the Au NPs in a localized region after body injection or implantation of the gel, overcoming the commonly known drawbacks of the colloidal solutions. In addition, most of the studies focused on the combination of multiple factors to treat cancer, such as PTT and photodynamic therapy (PDT)[76] or PTT and anti-tumoral drugs release from the HNCs. Several approaches have been tested for chemo-photothermal therapy, with most of the examples corroborated by in vivo analyses. For instance, Liu and co-workers developed an injectable HNC made by self-assembling of methoxy poly(ethylene glycol-b-poly(ε-caprolactone-co-1,4,8-trioxa[4.6]spiro-9-un-decanone)) (mPECT) decorated with Au NRs and mPECT NPs by addition of an α-cyclodextrin (α-CD),

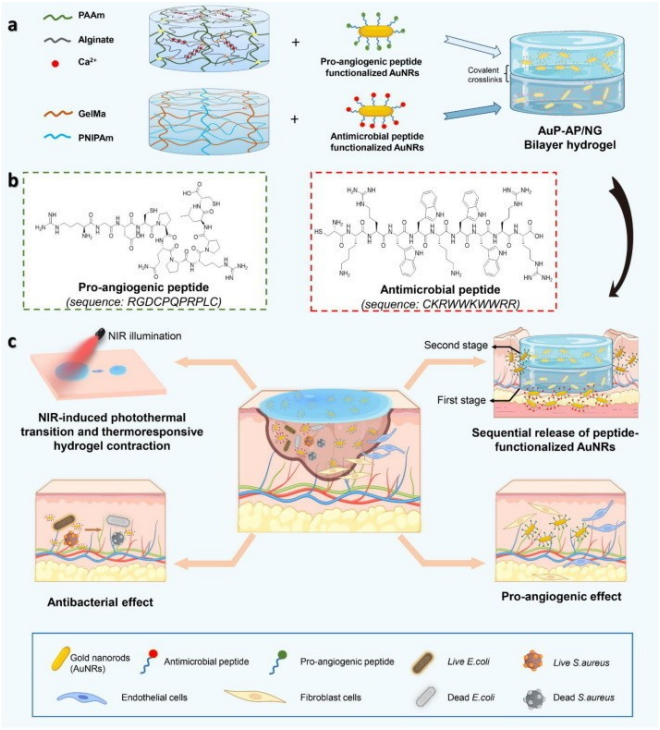

Figure 3. Schematic illustration of bilayer hydrogels for diabetic wound healing applications. (a) Design of the Au P-AP/NG hydrogel. Different peptide-functionalized Au NRs were embedded in the corresponding layers. (b) The chemical formulas of the functional peptides. (c) The AuP-AP/NG hydrogel obtained under NIR irradiation was capable of NIR-induced thermoresponsive contraction, sequential drug release, as well as antibacterial and pro-angiogenesis effects. Reproduced with permission.[115] © 2023, Elsevier Inc.

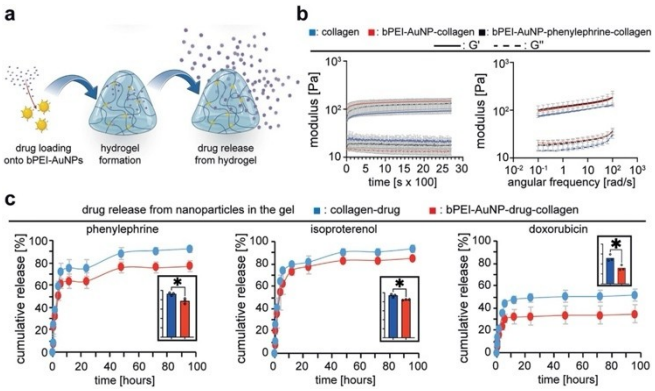

Figure 4. bPEI-Au NPs function as drug carriers and allow release of drugs from 3D hydrogels. A) Schematic illustration of loading NPs with drugs and subsequent drug release. B) Quantitative rheometric analysis of mechanical properties of hydrogels over time during the gelation process and quantitative post-gelation rheometric analysis of hydrogels as a function of angular frequency (n = 3, data regarding collagen and bPEI-AuNP-collagen is the same as Figure 3 and are provided for comparison purposes). C) Representative graphs of quantitative analyses of drug release from different hydrogels. Measurements were performed based on UV–vis absorption of samples of medium in which hydrogels were incubated (n = 3). Inserted bar graphs show the statistical analysis of the end point release of drugs (n = 3). Data are mean ± SD and compared based on a two-tailed t-test. Reproduced under terms of the CC-BY license.[78] © 2023, The Authors, Advanced Healthcare Materials published by Wiley-VCH GmbH

where Au NPs are part of the gelling system. The mPECT NPs were loaded with paclitaxel (PTX), demonstrating a prolonged release within 2 weeks in vitro. The Au NRs were exploited for PTT in vivo, irradiated for 5 min with an NIR laser, and displayed a decrease in tumor volume over the treatment.[75] A relevant system showing multimodal treatment has been presented by Mirrahimi et al., where an HNC combines chemotherapy, radiotherapy and PTT.[74] The system was composed of an alginate hydrogel loaded with Au NPs and cisplatin. The drug was almost 100% released after 2 hours under laser irradiation, as a consequence of the HNC degradation at high temperatures. Mice treated with the photoactivated HNC showed an increase in the tumor tissue temperature and a decrease in the tumor volume growth after 21 days of treatment, with the best performances for the case of chemo-photo-radiotherapy. Not only drugs or active substances are released by HNCs systems directly to the site of application. Indeed, in a recently published work, a photosensitizer agent (merocyanine) promoting the production of reactive oxygen species (ROS) against β-amyloid aggregation has been stabilized by the presence of Au NPs into a hydrogel. The system made its delivery possible in the active form to the intracellular environment.[62]

More generally, Au NPs alone have been widely employed not only in disease treatments but also in sensor chemistry, thanks to the tunability of their optoelectrical properties as well as the easy functionalization of their surface.[121,122] The benefit of detecting extremely low quantities of a compound has been exploited both in the pollutant, pesticides and metal ions detection, as well as in the biomedical field. This last application is usually named biosensing, where biomolecules can be detected mainly by observing the NPs' optical response (changes in the LSPR), colorimetry changes, surface-enhanced Raman scattering (SERS) or plasmon-enhanced fluorescence (PEF).[123] Examples using functionalized Au NPs have been recently proposed as colorimetric assays based on LSPR for rapid detection of SARS-Cov-2 by the naked eye assisted by the CRISPR-Cas system.[124] The CRISPR-Cas system allows enhanced specificity in the detection of specific RNA sequences. Indeed, the same technology has been also used in metallic electrochemical biosensors composite with Au NPs, for high-sensitivity detection of mutations in SARS-Cov-2 variants.[125] The development of HNCs containing Au NPs is a lately emerging strategy to fabricate smart and highly sensitive biosensors, where the hydrogel serves as a stable platform to contain Au NPs.

The main advantage is represented by the possibility of having In situ applicable devices with enhanced stability, e.g., by preventing Au NPs uncontrolled aggregation,[126] where the biomolecules can easily diffuse and be detected. Many examples of biosensors have been developed based on HNCs. In the past years, Ma et al. designed a hydrogel system containing Au NPs for quantitative and qualitative visible detection of glucose, by the release of Au NPs in solution. The HNC has been made by a DNA-based hydrogel crosslinked by the glucose complex with Shrinkai-receptor target aptamer, containing Au NPs. In the presence of the glucose complex, the aptamer selectively bound to the analyte, with the result of breaking the hydrogel matrix and therefore releasing the encapsulated Au NPs. In this way, the supernatant solution shifted the color to the characteristic red color given by the optical properties linked to the LSPR of colloidal gold. The amount of Au NPs released in the solution is directly related to the glucose concentration present in the sample, making detection possible.[5] Miranda and coworkers recently published a work where a poly-(ethylene glycol) diacrylate (PEGDA) hydrogel containing Au NPs was designed and fabricated using UV light as reaction initiator. This biosensing platform included pre-synthesized citrate stabilized Au NPs inside the hydrogel matrix to prevent NPs aggregation. The aim was to study the sensing abilities with biotin and Au NPs at different sizes, by monitoring the LSPR peak shift after biomolecules binding with the NPs.[66] From another report, the designed biosensor patches have shown absorption increase or decrease according to the concentration of the analyte molecule and the hydrophobic or hydrophilic nature of the substance. It demonstrated good results also in the detection of biotin-streptavidin interaction, up to picomolar concentrations in the case of both LPSR and PEF detection, decreasing the limit of detection compared to a blank sample (Figure 5).[65,127] The versatility of PEGMA hydrogels has been also exploited for

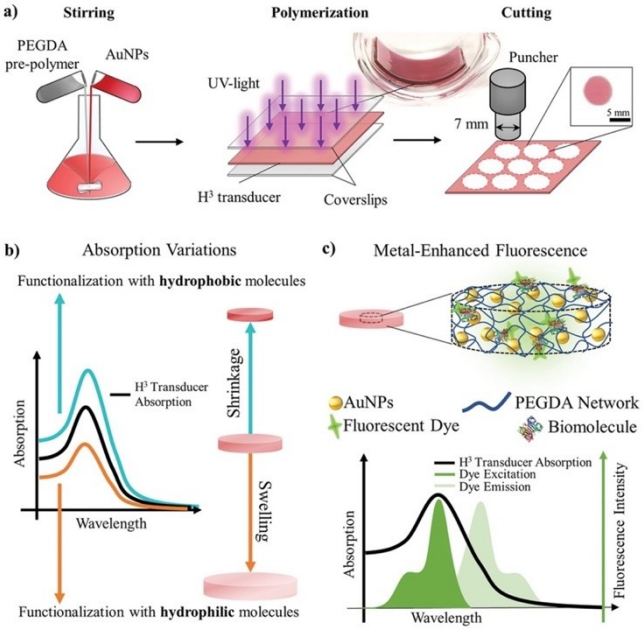

Figure 5. (a) Schematic representation of the simple fabrication strategy of the plasmonic hydrogel-based (H3) transducers, based on prepolymer solution preparation, photopolymerization, and accurate cutting of the resulting patch. B) Absorption intensity variations due to shrinkage/swelling capability of the hydrogel when the embedded Au NPs are functionalized with hydrophobic/hydrophilic molecules. The functionalization of the H3 transducer with hydrophobic molecules leads to an increase of the absorption spectrum intensity due to the hydrogel shrinkage (blue line) compared to the bare transducer (black line). On the contrary, the modification of the H3 transducer with hydrophilic molecules results in a decrease of the absorption spectrum intensity due to the hydrogel swelling (orange line). C) Metal-enhanced fluorescence is obtained by the overlap of the Au NPs absorption and fluorescent dye excitation spectra when the distance between the metal and fluorescent dye is lower than 10 nm. A significant enhancement of the fluorescence can be achieved by immobilizing the labeled-target analyte onto the Au NPs surface within the hydrogel. Reproduced under terms of the CC-BY license.[65] © 2022, The Authors, Advanced Materials Technologies published by Wiley-VCH GmbH

biosensing applications and for tuning the diffusivity of molecules inside the gel matrix. For instance, Muranaka et al. proposed a platform where Au NPs are grown in a specific hydrogel region by photoreduction of $AuCl_4$ driven by femtosecond laser pulses. The selective growth was performed by the presence of glutamine which inhibited the formation of aggregated Au NPs in favor of the small NPs. The system was used for the detection of compounds contained in the sweat, but it demonstrated to be effective only for urea. This may be due to the urea ability to act as H-bonds breaker, which promoted the mesh size increase of the hydrogel, hence a higher dispersion of the Au NPs, resulting in a blue-shift of the LSPR peak.[127]

Among others, SERS represents an up-to-date technique employed for several applications, thanks to the augmented sensitivity that plasmonic structures can give for the detection of small quantities of analytes.[128]

In this perspective, hydrogels combined with metal NPs have attracted attention as support for SERS platforms, since they can prevent NPs aggregation and promote the analyte diffusion inside the network, thanks to their physico-chemical properties.[129] Recent examples have revealed how HNCs containing Au NPs can be applied as SERS scaffolds in biosensing applications. García Schejtman et al. designed a supramolecular hydrogel based on PVA and gallic acid (GA) with Au NPs. More specifically, GA was exploited both as a crosslinker for the hydrogel and as a reducing agent and stabilizer for Au NPs, creating an HNC without the use of any other chemical agent and stabilizer to prevent Au NPs aggregation. With a concentration of 50 mM Au^{3+}, the plasmonic HNC showed a distribution of aggregated Au NPs inside the gel and demonstrated a very high analytical enhancement factor of the Rhodamine 6G compound in SERS.[68] Always in the same context, Chen and coworkers presented a DNA-based nanocomposite as SERS detector. The system was composed of different parts: i) gap-containing core-shell Au NPs with P-nitrothiophenol as Raman reporter molecule; ii) primer functionalized magnetic beads complemented to the kanamycin aptamer. In the presence of kanamycin, the aptamer released the primer, which hybridized with two DNA strands modified with phosphate. In this way, two circular padlocks, partially complemented one to the other, could form a hydrogel by physical entanglement after the initiation of the rolling circle amplification reaction, creating a trap for Au NPs which act as SERS detector of kanamycin even at low concentration. The strategy exhibited high sensitivity to the molecule, lower limit of detection ($\simeq$2.3 femtoM) than previous methods and acceptable accuracy and precision.[67] Gold nanostars (Au NSs) are known as one of the possible structures that can be obtained by tuning the synthesis procedure from gold reduction. They are of particular interest due to the augmented electromagnetic field enhancement at the tips (also called hot spots) that characterize this structure.[111,130] This also provides a larger surface area for plasmon resonance.[111] Thanks to these features, Au NSs have attracted attention in SERS, to improve the sensitivity of molecules' detection.[131] In the framework of HNCs, the use of Au NSs is not very common yet, and indeed, to the best of our knowledge, few systems with NSs have been developed. An interesting example has been recently presented by Oliveira et al., regarding a point-of-care testing immunosensor device, based on cellulose hydrogel containing Au NSs as SERS enhancer.[77] The system is composed of a sandwich complex formed between the functionalized Au NSs and the counterpart hydrogel, both able to capture the horseradish peroxidase, used as a proof-of-concept for the strategy. The complex platform has demonstrated excellent reproducibility, sensitivity, and specificity, overcoming the limitations arising from common commercial systems, such as enzyme-linked immunosorbent assay (ELISA). Furthermore, it showed an increased limit of detection using SERS, and a potential in multiple cycles application, thanks to the possibility of washing the device.

3.2. HNCs Limitations and Challenges

Significant progress has been achieved with the employment of HNCs in biomedical applications during the last decades. These polyvalent structures have been indeed finely designed to improve the weaknesses associated with the single systems, i.e., NPs and hydrogels alone. The HNCs have shown several advantages among which we highlighted: NPs stabilization and in situ application, cargo protection, cargo sustained release, increase of hydrogel mechanical properties, stimuli-responsiveness, and localized drug delivery.

Despite the outstanding advantages reported as examples, HNCs still suffer from limitations related to the global arrangement of the different components, which hinders their translation to clinical applications. HNCs' lack of commercial formulations arises from the unrevealed interaction mechanisms between the single building blocks of the overall systems.[63] The macroscopic properties of the composite structure are indeed strongly dependent on the preparation methods, as well as on the synthetic pathways of all the components. A batch-to-batch reproducibility is a primary need for these systems to be commercially reproduced together with a scalable synthesis and formulation process[132] Trying to overcome these obstacles, scientists have been lately focusing on inorganic NPs synthetical pathways directly inside hydrogels, obtaining increased reproducibility and better NPs dispersion.[68] Meanwhile, alternative solutions for organic-loaded HNCs rely on hydrogel matrix formation upon NPs self-assembly of NPs after their synthesis.[133]

Furthermore, being the nanocomposites made by the combination of known elements, their toxicity is strictly related to each of the constituents. Although the single parts exhibit a biocompatible nature, the long retention of the whole system inside the body could cause a foreign-body response.[134] Hydrogels can be easily designed to tune their biocompatibility, biodegradability, and reduced cytotoxicity through the use of natural polymers and cleavable moieties. Likewise, considerable ongoing works have been established on a harmless design of NPs, as they have been found to cause adverse toxicological effects on human bodies.[135] Nevertheless, NPs accumulation

can still be considered the principal drawback, which has a direct impact on NPs fate after HNCs degradation. In particular inorganic NPs cannot be degraded and tend to accumulate, if not properly sized to escape the biological filtration barriers. On the contrary organic NPs, comprehending liposomes, are easier to be excreted although their elimination could take time. In recent works the cytotoxicity of the HNCs has been checked as well as NPs retention ability, showing great results.[136]

However, the HNCs require optimizations and further developments to overcome the main constraints yet to reach suitable benchmark solutions, although they represent a simple appealing solution endowing multifunctional properties.

4. Summary and Perspectives

The main advances in the field of HNCs with NPs have been pointed out throughout the text, aiming to classify the type of composite materials on the basis of the NPs used. We believe this classification could create awareness in understanding which are the advantages emerging from the presence of each NP in the hydrogels. Overall, the combination of NPs and hydrogels has led to two main achievements: i) the acquisition of further properties, from the hydrogel point of view; and ii) the colloidal stabilization and spatial restriction in a confined region, from the NPs side instead. The published results have led to beneficial outcomes in drug delivery, tissue engineering, biosensing, and cancer treatment. Organic NPs incorporation has led to final formulations exhibiting higher stability, stronger mechanical properties, controlled therapeutics co-delivery, improved target treatments, and decreased burst release.[34,137,138] The amphiphilic nature of these nanocarriers allowed the delivery of hydrophilic as well as hydrophobic drugs, creating physical compartments inside the hydrogel for improved control of the drug delivery mechanisms.[88]

On the other hand, inorganic NPs incorporation has imparted the HNCs with external light and/or magnetic field responsivity, optical properties, antibacterial activity, and improved mechanical stability. These results have produced valuable effects within drug, protein and gene delivery, tissue engineering and biosensing.

The presence of ceramic-based NPs has provided enhanced mechanical properties, augmented drug encapsulation and stimuli-responsiveness, e.g., pH. Noble metal NPs have been instead responsible for the modification of the optical properties and thermal phenomena occurring in the final formulation. Specifically focusing on Au NPs loaded HNCs, they have been extensively exploited for photothermal therapy and localized temperature increase after light irradiation, which causes beneficial effects in drug delivery and cancer treatment.

HNCs containing all the aforementioned nanostructures have been studied both in vitro and in vivo, demonstrating acceptable cytotoxicity, good biocompatibility and potential immunotherapy effects as well as the ability to lower tumor volumes. Notwithstanding the late studies, new perspectives on these highly promising materials could include the understanding of the principles of assembling and formation of HNCs. In this way, it would be possible to develop better tailored-to-application solutions. Furthermore, as a large variety of NPs has been described, the use of different NPs together inside the hydrogel could be investigated. Early studies presented some examples using liposomes with Au NPs, Au NRs with Au NPs or core-shell noble metal NPs to tune the properties.[63,70,115] Future directions on the combination of different NPs inside hydrogels could give rise to cascade reactions in response to constructive interfering stimuli, for the design of multi-purpose systems.

Besides, the use of ultrasmall or fast degrading NPs in HNCs would be beneficial to avoid accumulation, obtaining faster NPs body clearance. For the specific case of Au NPs loaded HNCs, recent works studied the thermal performances of the nanocomposite. However, information regarding the NPs architecture-dependent thermal heating of the HNCs is lacking. Indeed, a better clarification of the physical phenomena together with mathematical models to predict the photothermal heating of such structures would be beneficial to precisely design HNCs with specific drug delivery behaviors, based on the thermal heating knowledge.

This field is still under continuous evolution, therefore advances in this area would conduct to well-designed complex systems for additional research and to reach the clinical stages. The interdisciplinary coupling of material science and nanomedicine is indeed a promising strategy to build up the future of human health and tackle the most severe diseases of the current society.

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Conflict of Interests

The authors declare no conflict of interest.

Keywords: hydrogels · nanoparticles · nanocomposites · gold nanoparticles · polymer nanoparticles

[1] S. Baseeruddin Alvi, R. P. S. N. Begum, A. B. Jogdand, B. Veeresh, A. K. Rengan, *ACS Appl. Mater. Interfaces* **2021**, *13*, 55862.
[2] B. Yan, J.-C. Boyer, D. Habault, N. R. Branda, Y. Zhao, *J. Am. Chem. Soc.* **2012**, *134*, 16558.
[3] E. Bari, I. Roato, G. Perale, F. Rossi, T. Genova, F. Mussano, R. Ferracini, M. Sorlini, M. L. Torre, S. Perteghella, *Int. J. Mol. Sci.* **2021**, *22*, 4064.

[4] Y. Zhang, F. Rossi, S. Papa, M. B. Violatto, P. Bigini, M. Sorbona, F. Redaelli, P. Veglianese, J. Hilborn, D. A. Ossipov, *Acta Biomater.* **2016**, *30*, 188.
[5] Y. Ma, Y. Mao, Y. An, T. Tian, H. Zhang, J. Yan, Z. Zhu, C. J. Yang, *Analyst* **2018**, *143*, 1679.
[6] S. L. Lim, C.-W. Ooi, L. E. Low, W. S. Tan, E.-S. Chan, K. L. Ho, B. T. Tey, *Mater. Chem. Phys.* **2020**, *243*, 122578.
[7] Y. Zheng, H. Huang, J. Yu, Z. Hu, Y. Wang, *Chem. Eng. J.* **2023**, *454*, 140054.
[8] Q. Zhang, N. Liu, Y. Wei, L. Feng, *Soft Matter* **2018**, *14*, 2649.
[9] P. Sánchez-Cid, M. Jiménez-Rosado, J. F. Rubio-Valle, A. Romero, F. J. Ostos, M. Rafii-El-Idrissi Benhnia, V. Perez-Puyana, *Polymers (Basel).* **2022**, *14*, 272.
[10] M. N. Egorikhina, L. B. Timofeeva, D. D. Linkova, Y. P. Rubtsova, M. L. Bugrova, I. N. Charykova, M. G. Ryabkov, I. I. Kobyakova, E. A. Farafontova, D. Y. Aleynik, *Polymers (Basel).* **2023**, *15*, 1337.
[11] X. Gu, Y. Xu, S. Li, Z. Wang, Q. Meng, J. Yu, *ACS Appl. Polym. Mater.* **2021**, *3*, 3519.
[12] Y. Li, H. Y. Yang, D. S. Lee, *Biomacromolecules* **2022**, *23*, 609.
[13] F. Wu, Y. Pang, J. Liu, *Nat. Commun.* **2020**, *11*, 4502.
[14] Y. Wu, H. Wang, F. Gao, Z. Xu, F. Dai, W. Liu, *Adv. Funct. Mater.* **2018**, *28*, DOI 10.1002/adfm.201801000.
[15] J. J. Pillai, A. K. T. Thulasidasan, R. J. Anto, D. N. Chithralekha, A. Narayanan, G. S. Kumar, *J. Nanobiotechnol.* **2014**, *12*, 25.
[16] A. Fahr, X. Liu, *Expert Opin. Drug Delivery* **2007**, *4*, 403.
[17] K. Peng, I. Tomatsu, A. V. Korobko, A. Kros, *Soft Matter* **2010**, *6*, 85.
[18] C. Rodriguez-Tenreiro, C. Alvarez-Lorenzo, A. Rodriguez-Perez, A. Concheiro, J. J. Torres-Labandeira, *Pharm. Res.* **2006**, *23*, 121.
[19] E. Lacroce, F. Rossi, *Expert Opin. Drug Delivery* **2022**, *19*, 1203.
[20] X. Li, L. Shang, D. Li, W. Wang, S. Chen, H. Zhong, Y. Huang, S. Long, *Polym. Test.* **2022**, *109*, 107547.
[21] V. Vanoli, S. Delleani, M. Casalegno, F. Pizzetti, P. Makvandi, H. Haugen, A. Mele, F. Rossi, F. Castiglione, *Carbohydr. Polym.* **2023**, *301*, 120309.
[22] F. Pinelli, M. Ponti, S. Delleani, F. Pizzetti, V. Vanoli, F. B. Vangosa, F. Castiglione, H. Haugen, L. P. Nogueira, A. Rossetti, et al., *Int. J. Biol. Macromol.* **2023**, *252*, 126284.
[23] F. Pizzetti, A. Maspes, A. Rossetti, F. Rossi, *Eur. Polym. J.* **2021**, *161*, 110843.
[24] S. Fattahpour, M. Shamanian, N. Tavakoli, M. Fathi, H. Sadeghi-aliabadi, S. R. Sheykhi, M. Fesharaki, S. Fattahpour, *Int. J. Biol. Macromol.* **2020**, *151*, 220.
[25] G. Camana, M. Tavano, M. Li, F. Castiglione, F. Rossi, F. Cellesi, *Materials* **2023**, *16*, 2749.
[26] D. Mazunin, N. Broguiere, M. Zenobi-Wong, J. W. Bode, *ACS Biomater. Sci. Eng.* **2015**, *1*, 456.
[27] R. Singhal, K. Gupta, *Polym.-Plast. Technol. Eng.* **2016**, *55*, 54.
[28] M. C. Catoira, L. Fusaro, D. Di Francesco, M. Ramella, F. Boccafoschi, *J. Mater. Sci. Mater. Med.* **2019**, *30*, 115.
[29] V. Nele, J. P. Wojciechowski, J. P. K. Armstrong, M. M. Stevens, *Adv. Funct. Mater.* **2020**, *30*, 2002759.
[30] I. M. Garnica-Palafox, F. M. Sánchez-Arévalo, *Carbohydr. Polym.* **2016**, *151*, 1073.
[31] M. Nakahata, N. Tominaga, K. Saito, K. Nishiyama, Y. Tanino, K. Saiki, M. Kojima, S. Sakai, *Macromol. Biosci.* **2022**, *22*, 2200055.
[32] J. Ahn, S. Park, J. H. Lee, S. H. Jung, S.-J. Moon, J. H. Jung, *Chem. Commun.* **2013**, *49*, 2109.
[33] H. Jiang, L. Duan, X. Ren, G. Gao, *Eur. Polym. J.* **2019**, *112*, 660.
[34] E. A. Appel, J. del Barrio, X. J. Loh, O. A. Scherman, *Chem. Soc. Rev.* **2012**, *41*, 6195.
[35] S. Panja, A. Seddon, D. J. Adams, *Chem. Sci.* **2021**, *12*, 11197.
[36] E. Mauri, A. Negri, E. Rebellato, M. Masi, G. Perale, F. Rossi, *Gels* **2018**, *4*, 74.
[37] B. Hosseinzadeh, M. Ahmadi, *Materials Today Sustainability* **2023**, *23*, 100468.
[38] L. Wang, M. Zhou, T. Xu, X. Zhang, *Chem. Eng. J.* **2022**, *433*, 134625.
[39] D. Calder, A. Fathi, F. Oveissi, S. Maleknia, T. Abrams, Y. Wang, J. Maitz, K. H. Tsai, P. Maitz, W. Chrzanowski, et al., *Adv. Healthcare Mater.* **2022**, *11*, 2201714.
[40] A. L. R. Costa, S. M. Willerth, L. G. de la Torre, S. W. Han, *Mater. Today Bio.* **2022**, *13*, 100221.
[41] M. Song, J. Wang, J. He, D. Kan, K. Chen, J. Lu, *Gels* **2022**, *9*, 16.
[42] D. Khan, M. Qindeel, N. Ahmed, M. I. Asad, K. ullah Shah, Asim.ur. Rehman, *Int. J. Pharm.* **2021**, *610*, 121242.
[43] H. Muñoz-Galán, B. G. Molina, O. Bertran, M. M. Pérez-Madrigal, C. Alemán, *Eur. Polym. J.* **2022**, *181*, 111670.
[44] I. Ottonelli, A. Bighinati, E. Adani, F. Loll, R. Caraffi, M. A. Vandelli, F. Boury, G. Tosi, J. T. Duskey, V. Marigo, et al., *Pharmaceutica* **2022**, *15*, 25.
[45] X.-L. Hsu, L.-C. Wu, J.-Y. Hsieh, Y.-Y. Huang, *Polymers (Basel).* **2021**, *13*, 642.
[46] Y. Liu, Q. Fan, Y. Huo, M. Li, H. Liu, B. Li, *Cellulose* **2021**, *28*, 6953.
[47] G. Brachi, J. Ruiz-Ramírez, P. Dogra, Z. Wang, V. Cristini, G. Ciardelli, R. C. Rostomily, M. Ferrari, A. M. Mikheev, E. Blanco, et al., *Nanoscale* **2020**, *12*, 23838.
[48] B. Gao, J. Luo, Y. Liu, S. Su, S. Fu, X. Yang, B. Li, *Int. J. Nanomed.* **2021**, *16*, 4073.
[49] T. Kulsirirat, K. Sathirakul, N. Kamei, M. Takeda-Morishita, *Int. J. Pharm.* **2021**, *602*, 120618.
[50] M. Ghanbari, M. Salavati-Niasari, F. Mohandes, *Arab. J. Chem.* **2022**, *15*, 103730.
[51] Y. Galeano-Duque, P. K. Sharma, M. Mesa, *Mater. Today Commun.* **2023**, *34*, 105243.
[52] M. Mahdi Eshaghi, M. Pourmadadi, A. Rahdar, A. M. Díez-Pascual, *Materials* **2022**, *15*, 8711.
[53] B. de Melo Santana, J. C. Pieretti, R. N. Gomes, G. Cerchiaro, A. B. Seabra, *Pharmaceutica* **2022**, *14*, 2837.
[54] A. Ulu, E. Birhanlı, S. Köytepe, B. Ateş, *Int. J. Biol. Macromol.* **2020**, *163*, 529.
[55] X. Zhou, X. He, K. Shi, L. Yuan, Y. Yang, Q. Liu, Y. Ming, C. Yi, Z. Qian, *Adv. Sci.* **2020**, *7*, DOI 10.1002/advs.202001442.
[56] H. Haidari, Z. Kopecki, A. T. Sutton, S. Garg, A. J. Cowin, K. Vasilev, *Antibiotics* **2021**, *10*, 49.
[57] X. Chen, J. Tao, M. Zhang, Z. Lu, Y. Yu, P. Song, T. Wang, T. Jiang, X. Zhao, *Carbohydr. Polym.* **2022**, *298*, 120123.
[58] Y. Li, Y. Yan, J. Wang, L. Li, F. Tang, *Colloids Surf A Physicochem Eng Asp* **2022**, *648*, 129242.
[59] L. Chronopoulou, R. Binaymotlagh, S. Cerra, F. H. Haghighi, E. G. Di Domenico, F. Sivori, I. Fratoddi, S. Mignardi, C. Palocci, *Materials* **2023**, *16*, 2134.
[60] R. Binaymotlagh, A. Del Giudice, S. Mignardi, F. Amato, A. G. Marrani, F. Sivori, I. Cavallo, E. G. Di Domenico, C. Palocci, L. Chronopoulou, *Gels* **2022**, *8*, 700.
[61] C. F. T. van der Ven, M. W. Tibbitt, J. Conde, A. van Mil, J. Hjortnaes, P. A. Doevendans, J. P. G. Sluijter, E. Aikawa, R. S. Langer, *Nanoscale* **2021**, *13*, 20451.
[62] Y.-C. Wu, C.-Y. Wu, S.-W. Tsai, H.-J. Chen, W.-J. Liu, D. Lin, T. Gong, K.-T. Yong, K. V. Kong, *ACS Appl. Nano Mater.* **2022**, *5*, 17613.
[63] S. R. S. Veloso, V. Gomes, S. L. F. Mendes, L. Hilliou, R. B. Pereira, D. M. Pereira, P. J. G. Coutinho, P. M. T. Ferreira, M. A. Correa-Duarte, E. M. S. Castanheira, *Soft Matter* **2022**, *18*, 8384.
[64] N. Kaur, Mimansa, P. Sharma, P. Praveen Kumar, P. P. Neelakandan, A. Shanavas, *ACS Appl. Polym. Mater.* **2023**, *5*, 542.
[65] B. Miranda, R. Moretta, P. Dardano, I. Rea, C. Forestiere, L. De Stefano, *Adv. Mater. Technol.* **2022**, *7*, DOI 10.1002/admt.202101425.
[66] B. Miranda, R. Moretta, S. De Martino, P. Dardano, I. Rea, C. Forestiere, L. De Stefano, *J. Appl. Phys.* **2021**, *129*, DOI 10.1063/5.0033520.
[67] Q. Chen, R. Tian, G. Liu, Y. Wen, X. Bian, D. Luan, H. Wang, K. Lai, J. Yan, *Biosens. Bioelectron.* **2022**, *207*, 114187.
[68] S. D. García Schejtman, P. A. Mercadal, M. L. Picchio, A. V. Veglia, E. A. Coronado, *J. Phys. Chem. C* **2022**, *126*, 9979.
[69] W. Yu, O. Deschaume, L. Dedroog, C. J. Garcia Abrego, P. Zhang, J. Wellens, Y. de Coene, S. Jooken, K. Clays, W. Thielemans, et al., *Adv. Funct. Mater.* **2022**, *32*, DOI 10.1002/adfm.202108234.
[70] A. Milanesi, G. Magni, S. Centi, G. Schifino, A. Aluigi, B. N. Khlebtsov, L. Cavigli, A. Barucci, N. G. Khlebtsov, F. Ratto, et al., *J Biophotonics* **2020**, *13*, DOI 10.1002/jbio.202000135.
[71] S. Sanchez-Casanova, F. M. Martin-Saavedra, C. Escudero-Duch, M. I. Falguera Uceda, M. Prieto, M. Arruebo, P. Acebo, M. L. Fabiilli, R. T. Franceschi, N. Vilaboa, *Biomaterials* **2020**, *241*, 119909.
[72] C. Wang, X. Liu, V. Wulf, M. Vázquez-González, M. Fadeev, I. Willner, *ACS Nano* **2019**, *13*, 3424.
[73] N. N. Mahmoud, S. Hikmat, D. Abu Ghith, M. Hajeer, L. Hamadneh, D. Qattan, E. A. Khalil, *Int. J. Pharm.* **2019**, *565*, 174.
[74] M. Mirrahimi, J. Beik, M. Mirrahimi, Z. Alamzadeh, S. Teymouri, V. P. Mahabadi, N. Eslahi, F. Ebrahimi Tazehmahalleh, H. Ghaznavi, A. Shakeri-Zadeh, et al., *Int. J. Biol. Macromol.* **2020**, *158*, 617.
[75] M. Liu, P. Huang, W. Wang, Z. Feng, J. Zhang, L. Deng, A. Dong, *J. Mater. Chem. B* **2019**, *7*, 2667.
[76] X. Jin, S. Yao, F. Qiu, Z. Mao, B. Wang, *Colloids Surf A Physicochem Eng Asp* **2021**, *614*, 126154.

[77] M. J. Oliveira, I. Cunha, M. P. de Almeida, T. Calmeiro, E. Fortunato, R. Martins, L. Pereira, H. J. Byrne, E. Pereira, H. Águas, et al., *J. Mater. Chem. B* **2021**, *9*, 7516.
[78] K. Roshanbinfar, M. Kolesnik-Gray, M. Angeloni, S. Schruefer, M. Fiedler, D. W. Schubert, F. Ferrazzi, V. Krstic, F. B. Engel, *Adv. Healthcare Mater.* **2023**, *12*, DOI 10.1002/adhm.202202408.
[79] R. Ridolfo, S. Tavakoli, V. Junnuthula, D. S. Williams, A. Urtti, J. C. M. van Hest, *Biomacromolecules* **2021**, *22*, 126.
[80] K. Kobayashi, J. Wei, R. Iida, K. Ijiro, K. Niikura, *Polym. J.* **2014**, *46*, 460.
[81] D. Nunes, S. Andrade, M. J. Ramalho, J. A. Loureiro, M. C. Pereira, *Polymers (Basel).* **2022**, *14*, 1010.
[82] E. A. Appel, M. W. Tibbitt, M. J. Webber, B. A. Mattix, O. Veiseh, R. Langer, *Nat. Commun.* **2015**, *6*, 6295.
[83] F. Rossi, R. Ferrari, S. Papa, D. Moscatelli, T. Casalini, G. Forloni, G. Perale, P. Veglianese, *Colloids Surf. B* **2013**, *108*, 169.
[84] A. L. Z. Lee, Z. X. Voo, W. Chin, R. J. Ono, C. Yang, S. Gao, J. L. Hedrick, Y. Y. Yang, *ACS Appl. Mater. Interfaces* **2018**, *10*, 13274.
[85] Y. Liu, Q. Fan, Y. Huo, C. Liu, B. Li, Y. Li, *ACS Appl. Mater. Interfaces* **2020**, *12*, 57410.
[86] L. Zhang, F. Gu, J. Chan, A. Wang, R. Langer, O. Farokhzad, *Clin. Pharmacol. Ther.* **2008**, *83*, 761.
[87] L. Pourtalebi Jahromi, M. Rothammer, G. Fuhrmann, *Adv. Drug Delivery Rev.* **2023**, *200*, 115028.
[88] S. Correa, A. K. Grosskopf, J. H. Klich, H. Lopez Hernandez, E. A. Appel, *Matter* **2022**, *5*, 1816.
[89] A. A. Manzoor, L. H. Lindner, C. D. Landon, J.-Y. Park, A. J. Simnick, M. R. Dreher, S. Das, G. Hanna, W. Park, A. Chilkoti, et al., *Cancer Res.* **2012**, *72*, 5566.
[90] D. Cao, X. Zhang, M. D. Akabar, Y. Luo, H. Wu, X. Ke, T. Ci, *Artif. Cells, Nanomed., Biotechnol.* **2019**, *47*, 181.
[91] J. E. Won, T. I. Wi, C. M. Lee, J. H. Lee, T. H. Kang, J.-W. Lee, B. C. Shin, Y. Lee, Y.-M. Park, H. D. Han, *Acta Biomater.* **2021**, *136*, 508.
[92] S. Nasir, M. Hussein, Z. Zainal, N. Yusof, *Materials* **2018**, *11*, 295.
[93] S. M. Hosseini, J. Mohammadnejad, R. Najafi-Taher, Z. B. Zadeh, M. Tanhaei, S. Ramakrishna, *ACS Appl Bio Mater* **2023**, *6*, 1323.
[94] E. Mostafavi, H. Zare, *OpenNano* **2022**, *7*, 100062.
[95] M. A. Saleemi, M. Hosseini Fouladi, P. V. C. Yong, K. Chinna, N. K. Palanisamy, E. H. Wong, *Chem. Res. Toxicol.* **2021**, *34*, 24.
[96] Z. Zhou, A. Zhou, A. T. Jalil, M. M. Saleh, C. Huang, *Bioprocess Biosyst. Eng.* **2023**, *46*, 577.
[97] Y. Chao, S. Yu, H. Zhang, D. Gong, J. Li, F. Wang, J. Chen, J. Zhu, J. Chen, *ACS Appl Bio Mater* **2023**, *6*, 1525.
[98] S. Thomas, B. S. P. Harshita, P. Mishra, S. Talegaonkar, *Curr. Pharm. Des.* **2015**, *21*, 6165.
[99] G. Desante, I. Pudełko, M. Krok-Borkowicz, E. Pamuła, P. Jacobs, A. Kazek-Kęsik, J. Nießen, R. Telle, J. Gonzalez-Julian, K. Schickle, *ACS Appl. Mater. Interfaces* **2023**, *15*, 21699.
[100] Y. Pan, Y. Zhao, R. Kuang, H. Liu, D. Sun, T. Mao, K. Jiang, X. Yang, N. Watanabe, K. H. Mayo, et al., *Mater. Sci. Eng. C* **2020**, *116*, 111158.
[101] I. Vassalini, G. Ribaudo, A. Gianoncelli, M. F. Casula, I. Alessandri, *Environ. Sci.-Nano* **2020**, *7*, 3888.
[102] A.-C. Burduşel, O. Gherasim, A. M. Grumezescu, L. Mogoantă, A. Ficai, E. Andronescu, *Nanomaterials* **2018**, *8*, 681.
[103] M. A. Rojas, J. Amalraj, L. S. Santos, *Polymers (Basel).* **2023**, *15*, 3370.
[104] E. Redolfi Riva, I. Pastoriza-Santos, A. Lak, T. Pellegrino, J. Pérez-Juste, V. Mattoli, *J. Colloid Interface Sci.* **2017**, *502*, 201.
[105] C. Kohout, C. Santi, L. Polito, *Int. J. Mol. Sci.* **2018**, *19*, 3385.
[106] E. Petryayeva, U. J. Krull, *Anal. Chim. Acta* **2011**, *706*, 8.
[107] V. Amendola, R. Pilot, M. Frasconi, O. M. Maragò, M. A. Iatì, *J. Phys. Condens. Matter* **2017**, *29*, 203002.
[108] X. Ding, D. Li, J. Jiang, *Theranostics* **2020**, *10*, 8061.
[109] W.-K. Ko, S. J. Lee, S. J. Kim, G. H. Han, I. Han, J. B. Hong, S. H. Sheen, S. Sohn, *Biomacromolecules* **2021**, *22*, 2887.
[110] C. Tian, C. Li, D. Chen, Y. Li, L. Xing, X. Tian, Y. Cao, W. Huang, Z. Liu, Y. Shen, *J. Mater. Chem. A* **2021**, *9*, 15462.
[111] W. Yang, B. Xia, L. Wang, S. Ma, H. Liang, D. Wang, J. Huang, *Materials Today Sustainability* **2021**, *13*, 100078.
[112] L. Bianchi, R. Mooney, Y. R. Cornejo, E. Schena, J. M. Berlin, K. S. Aboody, P. Saccomandi, *Int. J. Hyperthermia* **2021**, *38*, 1099.
[113] L. Moretti, A. Mazzanti, A. Rossetti, A. Schirato, L. Polito, F. Pizzetti, A. Sacchetti, G. Cerullo, G. Della Valle, F. Rossi, et al., *Nat. Photonics* **2020**, *10*, 247.
[114] S. R. S. Veloso, J. A. Martins, L. Hilliou, C. O. Amorim, V. S. Amaral, B. G. Almeida, P. J. Jervis, R. Moreira, D. M. Pereira, P. J. G. Coutinho, et al., *J. Mater. Chem. B* **2020**, *8*, 45.
[115] X. Huang, L. Xu, X. Yu, Y. Li, Z. Huang, R. Xu, W. Zeng, Z. Zhang, W. Li, F. Deng, *J. Colloid Interface Sci.* **2023**, *639*, 369.
[116] K.-Y. Chan, D. Yang, B. Demir, A. P. Mouritz, H. Lin, B. Jia, K.-T. Lau, *Compos. B. Eng.* **2019**, *178*, 107480.
[117] A. Albanese, P. S. Tang, W. C. W. Chan, *Annu. Rev. Biomed. Eng.* **2012**, *14*, 1.
[118] F. Alexis, E. Pridgen, L. K. Molnar, O. C. Farokhzad, *Mol. Pharm.* **2008**, *5*, 505.
[119] C. Alric, I. Miladi, D. Kryza, J. Taleb, F. Lux, R. Bazzi, C. Billotey, M. Janier, P. Perriat, S. Roux, et al., *Nanoscale* **2013**, *5*, 5930.
[120] N. Ajdari, C. Vyas, S. L. Bogan, B. A. Lwaleed, B. G. Cousins, *Nanomedicine* **2017**, *13*, 1531.
[121] K. Saha, S. S. Agasti, C. Kim, X. Li, V. M. Rotello, *Chem. Rev.* **2012**, *112*, 2739.
[122] A. Sengupta, M. Azharuddin, N. Al-Otaibi, J. Hinkula, *Vaccine* **2022**, *10*, 505.
[123] M. Z. Quazi, T. Kim, J. Yang, N. Park, *Biosensors* **2022**, *13*, 20.
[124] Y. Jiang, M. Hu, A.-A. Liu, Y. Lin, L. Liu, B. Yu, X. Zhou, D.-W. Pang, *ACS Sens.* **2021**, *6*, 1086.
[125] Z. Chen, C. Wu, Y. Yuan, Z. Xie, T. Li, H. Huang, S. Li, J. Deng, H. Lin, Z. Shi, et al., *J. Nanobiotechnol.* **2023**, *21*, 141.
[126] K. Wang, Z. Yue, X. Fang, H. Lin, L. Wang, L. Cao, J. Sui, L. Ju, *Sci. Total Environ.* **2023**, *856*, 159108.
[127] K. Muranaka, T. Niidome, M. L. Torres-Mapa, A. Heisterkamp, M. Terakawa, *Plasmonics* **2023**, *18*, 751.
[128] H.-L. Wang, E.-M. You, R. Panneerselvam, S.-Y. Ding, Z.-Q. Tian, *Light-Sci. Appl.* **2021**, *10*, 161.
[129] Y. Li, S. Yang, C. Qu, Z. Ding, H. Liu, *Food Safety and Health* **2023**, DOI 10.1002/fsh3.12010.
[130] Y. Liu, E. Chorniak, R. Odion, W. Etienne, S. K. Nair, P. Maccarini, G. M. Palmer, B. A. Inman, T. Vo-Dinh, *Nat. Photonics* **2021**, *10*, 3295.
[131] I. B. Becerril-Castro, I. Calderon, N. Pazos-Perez, L. Guerrini, F. Schulz, N. Feliu, I. Chakraborty, V. Giannini, W. J. Parak, R. A. Alvarez-Puebla, *Analysis & Sensing* **2022**, *2*, DOI 10.1002/anse.202200005.
[132] C. Dannert, B. T. Stokke, R. S. Dias, *Polymers (Basel).* **2019**, *11*, 275.
[133] X. Wang, L. Ye, W. He, C. Teng, S. Sun, H. Lu, S. Li, L. Lv, X. Cao, H. Yin, et al., *J. Controlled Release* **2022**, *345*, 786.
[134] Y. Jiang, N. Krishnan, J. Heo, R. H. Fang, L. Zhang, *J. Controlled Release* **2020**, *324*, 505.
[135] L. Xuan, Z. Ju, M. Skonieczna, P. Zhou, R. Huang, *MedComm (Beijing)* **2023**, *4*, DOI 10.1002/mco2.327.
[136] S. C. T. Moorcroft, L. Roach, D. G. Jayne, Z. Y. Ong, S. D. Evans, *ACS Appl. Mater. Interfaces* **2020**, *12*, 24544.
[137] G. A. Roth, E. C. Gale, M. Alcántara-Hernández, W. Luo, E. Axpe, R. Verma, Q. Yin, A. C. Yu, H. Lopez Hernandez, C. L. Maikawa, et al., *ACS Cent. Sci.* **2020**, *6*, 1800.
[138] E. C. Gale, A. E. Powell, G. A. Roth, E. L. Meany, J. Yan, B. S. Ou, A. K. Grosskopf, J. Adamska, V. C. T. M. Picece, A. I. d'Aquino, et al., *Adv. Mater.* **2021**, *33*, DOI 10.1002/adma.202104362.

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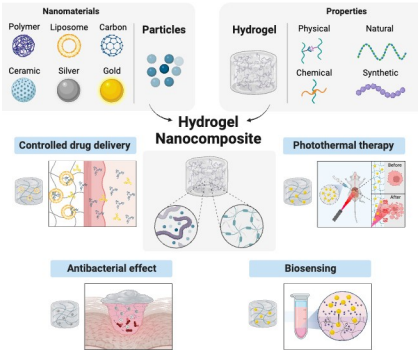
REVIEW

This review aims to give an overview of the current advances in hydrogel composite materials with nanoparticles (NPs). It focuses on the limitation of plain hydrogels, proposing the nanocomposites as a solution to overcome the limits. Then it lists and describes the main NPs used for fabrication of nanocomposites fabrication, focusing on gold nanoparticles (Au NPs) and their application fields.



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Last Advances on Hydrogel Nanoparticles Composites in Medicine: An Overview with Focus on Gold Nanoparticles