Editorial

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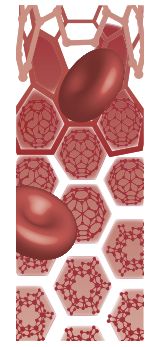

Hydrogel–nanoparticle hybrids for biomedical applications: principles and advantages

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> "Although the application of hydrogel–nanoparticle hybrids offers vast potential in improving medical treatment, there are few drawbacks and challenges to overcome, with most of the research discoveries in this area often not proceeding to industrial usage."

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The utilization of nanotechnology to develop competent drug delivery system for the treatment of diseases is widely researched. This is due to the fact that nano-sized particles can easily penetrate into, and be internalized by cells [1]. Drug-loaded nanoparticles can be incorporated into various structures and one of the most common structures into which they can be incorporated are hydrogel. Hydrogels are composed of a network of hydrophilic polymeric chains that dissipate in water [2]. Their 3D network allows the structure to retain water or biological fluids, they therefore have a great potential to be used for biomedical purposes [3–5]. The versatility of both nanoparticle and hydrogel structures make them a robust system if they are combined together as a hydrogel–nanoparticle hybrid. The aim of this article is to discuss the methods available to formulate the hybrids, their advantages and their potential applications in the biomedical field.

Hydrogel–nanoparticle hybrids

The versatility of hydrogels & their improvisation

Hydrogels have sparked interest among researchers in the field of drug delivery as they provide a convenient approach to deliver drugs efficiently. A typical hydrogel has sturdy interconnected hydrophilic chains, which give it the ability to resist dissolution in water [6]. The motion and relaxation of the hydrated network of the fully swollen hydrogel makes it elastic under external forces. This elasticity makes it highly biocompatible as it mimics the mechanical properties of the extracellular matrix of many living tissues, thus giving less irritation when it is applied *in vivo* [3,7]. In addition, hydrogels can be used to transport and release the materials it carries in a versatile way as its structure can be altered to suit its final purpose. Efficient drug loading, with an extended period of drug release, can be achieved using hydrogels. This is possible due to their uniquely porous structure which can be easily tuned according to the density of chain cross-linking [8]. The release mechanism of hydrogels is typically controlled by diffusion processes, chemical bonding and environmental stimuli, such as pH, temperature or glucose concentration [6].

However, difficulties in using hydrogels to deliver hydrophobic drugs, due to its hydrophilic properties [9]. Hydrophobic drugs play a critical role in the pharmaceutical industry, especially in cancer therapy where most of the anticancer drugs, such as paclitaxel, doxorubicin and camptothecin, are insoluble in water [10]. To overcome

this limitation, hybridization is one of the strategies that has been adopted by researchers to improvise the functionality of hydrogels [4,11]. Hydrogel hybrids are comprised of more than one different building blocks, each with various functionalities, morphologies and chemical structures that are interconnected through physical or chemical approaches [5]. One of these hybrid modifications includes the addition of nanoparticles in the hydrogel. The nanoparticles act as a carrier for hydrophobic drug molecules in the hydrophilic environment of the hydrogel [12,13]. Nanostructures incorporated in hydrogels are also able to enhance its mechanical structure, increase its stability and improve drug penetration into the cellular matrix [14,15].

Methods available to form hydrogel–nanoparticle hybrids

There are various approaches available for the construction of hydrogel–nanoparticle composites. These different methods are vary by the use of different frameworks of the hydrogel bulk being combined with diverse forms of nanoparticles, which either *via* covalent or noncovalent binding strategies [16]. To date, there are five different methods available to synthesize homogeneous forms of hydrogel–nanoparticle hybrids. The first one is by physically embedding the nanoparticles into the hydrogel following the gelation process. In this method, the nanoparticles are inserted in the hydrogel through a 'breathing in' mechanism of the gel. The swollen gel is placed in an aprotic solvent causing it to shrink (the 'breathing out' step). After that, the shrunken hydrogel is placed in an aqueous solution containing the nanoparticles to be swollen again by 'breathing in' the solution and nanoparticles [17].

The second method is by direct formation of the hydrogel in a nanoparticle suspension. This strategy was pioneered by Haraguchi *et al.* and involves polymerization of monomers into a network in the presence of preformed nanoparticles accompanied by gelators or cross-linkers [11,18]. The synthesis of hydrogel–nanoparticle hybrids can also be achieved by the formation of reactive nanoparticle precursors within a prefabricated gel. This can be done by crosslinking the monomers with co-monomers containing thiol groups that will enable the modulation of nanoparticle formulation with the addition of reducing agent, such as sodium borohydride. The nanoparticles will be completely formed once inside the gel [19].

Another method to form the hybrids is gelation *via* interconnection of hydrogel polymers and nanoparticles in the presence of gelator molecules. This scalable solution-phase synthesis methods involves mixing polymers and nanoparticles with gelling agent molecules [20]. The fifth method is through using nanoparticles as cross-linkers in the gel in which the cross-linking group is present on the surface of the nanoparticles. The ability of the nanoparticles to act as cross-linkers to link multiple bonds within the hydrogel network is a great advantage compared with the conventional hydrogel formation reaction which involves only two covalent bonds [13,16]. These methods predominantly will be chosen depending on the materials used to form the hybrid and final usage of the formulation

The advantages & applications of hydrogel–nanoparticle hybridization

Chemical enhancements enable hydrogels to increase their functional and structural versatility, making them suitable for nanoparticle incorporation [5]. Drug-loaded nanoparticles that are infused in hydrogels have a number of advantages; they can enhance the drug penetration through the skin and modify the drug activation activity, which consequently will optimizes drug efficacy [21]. In addition, the porosity of hydrogel structure for the drug loading is also able to protect the drug from unstable environment [3]. Several studies have reported that drug-loaded nanocapsules incorporated in hydrogels demonstrated a sustained release of the drug through topical application and the hydrogel's pseudo plastic behavior showed no changes after the nanocapsules being incorporated in it [4,15,22].

Hybrid-nanoparticle hydrogels have been widely studied for the treatment of brain cancer to improve the poor delivery of anticancer drugs into brain cells in cellular and animal models [23,24]. The implantation of a hydrogel that is incorporated with nanoparticles in the brain through an *in situ* injection can prolong sustained release of the drug to the targeted site and due to the nano-sized drug carrier structure, it grants them access across the blood brain barrier efficiently [23]. For example, a hydrogel containing the anticancer prodrug lauroyl-gemcitabine loaded in lipid nanocapsules was found to be a suitable local treatment for glioblastoma as it was shown to significantly reduce the size of a subcutaneous human glioblastoma tumor in an *in vivo* model [24]. This hydrogel was formed directly by the linking of the lipid nanocapsules themselves which made it convenient to formulate without the need of any gelling agent, polymers or external stimuli.

Magnetic guiding can be applied to hydrogel–nanoparticle hybrids, together with ligand conjugation targeting. This allows formation of a dual-targeting system with active targeting ability. A study by Kim *et al.* showed that systems like these are promising as a future anticancer treatment [14]. They managed to incorporate magnetic

nanoparticles loaded with doxorubicin hydrochloride in a crosslinked poly(N-isopropylacrylamide) hydrogel with folic acid. This formulation showed increased intracellular uptake of the drug by HeLa cancer cells *via* receptor-mediated endocytosis which was enhanced by the specific targeting of the nanoparticles and magnetic attraction working synergically to localize the drug at the targeted site. In addition, the formulation also provided efficient cytotoxicity and enhanced the apoptotic activity of HeLa cells.

Incorporation of nanoparticles in hydrogels can improve the hydrogel structure as well. A thermosensitive hydrogel formed by combination of chitosan and β-glycerophosphate showed increased mechanical strength following incorporation of nanoparticles [25]. The nanoparticles acted as cross linkers that strengthened and supported the dissipative network of the gel [7]. In this study, conducted by Saeednia *et al.* they also discovered that the inclusion of carbon nanotubes loaded with methotrexate in chitosan-β-glycerophosphate hydrogel improved the swelling behavior of the formulation and prolonged drug release, enhancing death of MCF-7 breast cancer cells [25].

Besides medication, hydrogel–nanoparticle hybrids have been discovered to be useful for application in tumor resection. An injectable polyamidoamine hydrogel containing silica nanocapsules was found to be an efficient structure to form a submucosal fluid cushion to facilitate resection of a mucosal tumor in endoscopic submucosal dissection [26]. This formation of submucosal fluid cushion is needed to separate the cancer cells from the underlying muscle during the tumor resection when the tumor is located in or near to an organ that can be easily damaged by perforation. This hydrogel hybrid showed a long-lasting gelation, which helped to prolong the mucosal elevation to facilitate the dissection and it can be degraded in the body cells itself by secretion of glutathione.

Challenges & future outlook

Although the application of hydrogel–nanoparticle hybrids offers vast potential in improving medical treatment, there are few drawbacks and challenges to overcome, with most of the research discoveries in this area often not proceeding to industrial usage. This is because, the delicateness and complexity of the formulation process itself makes it hard to be reproducible in larger scale. Most studies only available at preclinical stages that only limited up to *in vivo* studies. In addition, the stability of the hydrogel nanoparticles hybrid is also a major concern. The leaching of nanoparticles over time could affect the performance of the formulation and ruin its efficiency. Thus, to bring the findings from the laboratory to become a safely functional medication for the patients, collaborations across different field of academia and industry should be well planned and structured accordingly. An invention of Avant-grade method strategy will provide a better quality of the formulation in both research-scale and industrial-scale quantity. Apart from that, it also opens a new level of understanding and knowledge for more sophisticated application of this hybrid.

Author contributions

I certify that each coauthor listed participated sufficiently in the work to take responsibility for the content and that all those who qualify are listed.

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