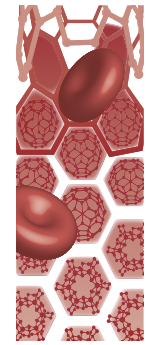
Commentary

For reprint orders, please contact: reprints@futuremedicine.com

Nanomedicine



Can nanoparticles enhance drug-delivery performance of hydrogels?

Filippo Rossi*[,1], Yuta Kurashina[2] & Hiroaki Onoe[3]

[1]Department of Chemistry, Materials & Chemical Engineering "Giulio Natta", Politecnico di Milano, via Mancinelli 7, 20131, Milan, Italy

[2]Division of Advanced Mechanical Systems Engineering, Institute of Engineering, Tokyo University of Agriculture & Technology, Koganei-shi, Tokyo, 184-0012, Japan

[3]Department of Mechanical Engineering, Keio University, Yokohama, Kanagawa, 223-8522, Japan

*Author for correspondence: Tel.: +39 022 399 3145; filippo.rossi@polimi.it

First draft submitted: 17 March 2023; Accepted for publication: 25 April 2023; Published online: 1 June 2023

Keywords: drug delivery • hydrogels • laser • nanoparticles • ultrasound

Hydrogels & drug delivery

For the past four decades, both academia and industry have paid much attention to the promise of designing smart drug-delivery carriers [1]. The need to overcome the main issues of traditional routes such as oral and intravenous administration has caused advancements in the medical field. While pills and injections represented a substantial improvement in medicine, they cannot address the main medical challenges of today. These challenges include the need for controlled release kinetics and reductions in the number of doses required, drug drawbacks due to overdosing differing from drug-to-drug and the use of drugs that have short half-lives and show toxicity if administered without control [2]. These conditions caused the development of a discipline dedicated to the development of controlled drug-delivery systems. This field brings together historically multidisciplinary topics across engineering, biology, chemistry, pharmacology and medicine, facilitating the ability to guarantee an effective plasma drug level for a therapeutic time period, avoiding over- and underdosing [3]. Novel controlled delivery systems should also allow protection of the drug from hostile environments, stimuli-responsive behavior and cell selectivity for targeted therapies. Among the possibilities in the biomaterials field for drug-delivery purposes, one of the most promising is hydrogels. These are hydrophilic polymeric networks that have found many applications in the medical field due to their elasticity, biocompatibility and ability to load aqueous solution in a semisolid state. Drug molecules can be loaded either before the gelation is complete and the system is still in a liquid state with consequent entrapment within the polymeric network or after gelation, which takes advantage of the sponge ability of hydrogel systems at their dry state. Despite good results obtained in many hydrogel applications, there are several critical issues linked to high burst release and uncontrolled delivery kinetics, which are driven almost entirely by Fickian diffusion. The drug flux related to this phenomenon is very fast due to the high *in vivo* clearance typical of body fluids [4]. In addition, the hydrophilicity of the loaded drug molecules, if they are not somehow confined, plays a key role in causing uncontrolled release kinetics and a high burst effect. Over the past 15 years, many strategies have been developed to slow release rates and guarantee a controlled and sustained release of drugs. Among them, postpolymer functionalization seemed extremely promising. It was initially developed to introduce additional properties to polymeric networks using chemical reactions compatible with biological systems, without toxic solvents and reagents and with mild reaction conditions [5]. This topic can be considered one of the precursors of sustainable chemistry, now applied in all research fields. The properties added to the polymeric networks were, in the beginning, limited to peptide sequences to improve cell attachment and growth or tracking agents to monitor materials' fate and degradation in living systems [6]. It was also successfully applied to improve the drug-delivery performance of hydrogels by linking drug molecules to their networks with cleavable bonds. This increases the stability of polymer–drug chemical bonds and slows release kinetics. The main drawback of this approach is that the chemical modification of a drug can permanently reduce or eliminate its pharmacological activity. Even if it is maintained, as observed in many papers, this approach would limit materials' translatability and increase the

Future Medicine

amount of money needed to reach the market [7]. In this commentary, we focus on alternatives to this strategy with high clinical potential without involving chemical reactions or polymer functionalization. The main focus is strategies where drug molecules are physically entrapped within the polymeric network and their release is triggered by an external stimulus that is able to change the network conformation and allow sustained release with reduced burst effect. Considering common medical practice, external stimuli that can be used to avoid patient-related pain and drawbacks are light (at different wavelengths), magnetism and ultrasound [8].

Nanodrug delivery enhancers using optics

Light is one of the most frequently used external stimuli in medicine and has been reported in many drug-delivery systems integrated with technologies like lasers, lamps and light-emitting diodes (LEDs). The intrinsic characteristics of light make the corresponding responsive devices both temporally and spatially tunable and may be used in a wide range of therapeutic applications. To induce light responsivity to hydrogels, it is necessary to introduce, within the polymeric network, nanostructures able to respond to a wide range of light wavelengths, from microwave to infrared. Therefore, depending on the type of light-emitting instrument, the effect of the therapy will be triggered, taking into consideration the balance between the effect caused by nanostructures and the penetration ability associated with the light emitted. It is indeed well known that UV light presents high energy but extremely poor penetration ability. To have an optimal drug dosage using UV sources, mechanisms like photocrosslinking, photoisomerization and photocleavage can be used [9]. The results of this interaction are changes in conformation and covalent bonding. Attention should also be paid to the interactions between UV light and organic molecules, like polymers that form the hydrogel 3D network or drug molecules. For example, UV light can cause the production of reactive oxygen species, conformational change and bond cleavage. Regarding therapeutic applications, the most widely used light source is near-infrared (NIR), which is in the range of 700 nm and 1 mm. The penetration ability of NIR is higher than UV and is able to reach deep areas in the human body, but the energy is generally lower. Other advantages include its better safety compared with UV light, capacity as a remote stimulus, noninvasiveness and ease of use with standard medical instruments. Several studies underlined the importance of semiconductor-based, carbon-based and plasmonic metal-based nanoparticles that can convert excitation energy into heat. Nanoparticles embedded in the polymeric network can sustain release rates and, more importantly, allow the on/off release of a loaded drug. This is possible because the interaction between NIR light and nanoparticles can trigger hydrogels to change conformation either cyclically or on a one-off basis, enlarging their pores and allowing the release of their content. Indeed, plasmonic nanoparticles can concentrate light, with a consequent local heating effect, working as nanoheaters [10]. In this framework, gold nanoparticles (spheres, stars or rods) can be entrapped within a composite (natural/synthetic) hydrogel and can regulate the release of drug molecules dispersed within the 3D network [11]. The use of NIR light is also extremely promising, as found by Takatsuka *et al.* [12], in therapies where the active agent should be protected from the immune system, such as for gene therapies based on adeno-associated viruses.

They can also be loaded within microsystems such that their release is regulated by the interaction between NIR light and Fe_3O_4 microparticles entrapped within the hydrogel network. Indeed, by irradiating alginate hydrogel systems with an NIR source, adeno-associated viruses were released on demand, maintained their activity and consequently induced gene transfection to cell culture. Among medical applications, the use of enhancers that use light showed great promise in cancer treatment with many preclinical and clinical studies in solid tumors [13]. Light-activated systems can work either as photodynamic therapy with localized chemical damage in the target lesion or as photothermal therapy causing localized thermal damage. In addition, research has evidenced the formation of an antitumor immune response. However, some drawbacks should be addressed before considering them common medical practice, particularly thermal damage directed to other tissues, multiple drug loading within drug-delivery systems to obtain a synergistic effect and formation of reactive oxygen species.

Nanodrug delivery enhancers using magnetism

The use of magnetic fields in medicine involves the application of high- or low-frequency alternating magnetic fields. These are able to penetrate deeply into human tissues while avoiding interactions with biological matter, which makes this technique extremely promising for clinical applications [14]. Using this technique, magnetic materials can be tracked using a static magnetic field, and their release can be tuned using an alternating field. In general, this function comes from the ability of magnetic nanoparticles to convert the electromagnetic input into thermal energy to work as nanoheaters. As a result, magnetic nanoparticles that are able to change their structure

in a temperature-responsive way can be linked or embedded within hydrogel polymeric networks. Depending on the physicochemical properties of the polymeric network, magnetic nanoparticles that work as nanoheaters can induce changes in the 3D structures to open pores and favor the release of their drug-molecule contents. For example, different systems, based on breaking thermocleavable bonds like aliphatic azo linkers or Diels Alder-based bonds, have been reported to be successful in triggering drug delivery. The main advantage is that the drug can be entrapped within the network because these bonds are not cleavable at body temperature, while the high local temperature induced by the nanoheaters causes their rupture with consequent drug release. Loading iron oxide nano- and microparticles within hydrogel networks can make them magnetic and thus control drug release using static magnetic fields. Applying a low-frequency alternating magnetic field increases the release rates of the loaded drug while it can be reduced using a static magnetic field [15]. With the sequential application of alternate cycles of static magnetic field and low-frequency alternating magnetic field, it is possible to obtain sustained release that can be remotely triggered and tuned. This function is possible because hydrogel networks swell or shrink depending on the type of magnetic field applied. Low-frequency alternating fields have been shown to be an extremely promising treatment for cancer, and importance is given to the stability of nanoparticles to facilitate efficient response to external treatment for a long period of time. However, the need for expensive magnets or coils to generate the required field is a significant limit on the easy use of this release strategy.

Nanodrug delivery enhancers using ultrasound

Ultrasound is a technology that has been incorporated into many conventional medical techniques, such as contrast imaging and tissue healing. Compared with optics, ultrasound reaches deeper into the body because of its lower attenuation and is promising for the treatment of diseases deep within the body. Ultrasound-based drug-delivery systems have conventionally used nanosized drug carriers. These include phase-change droplets releasing the drug from a liquid to a gas by applying heat with ultrasound [16], and liposomes dissolving the gas in the inner water layer to disrupt the lipid membrane [17], which has been developed as an efficient method of drug release by Orita *et al.* Recently, hydrogels were also used to actively release drugs by ultrasound irradiation. The drug-release mechanisms for ultrasound-responsive hydrogels can be divided into two main categories, similar to those for ultrasound-responsive release from nano-sized drug carriers. One is to control the drug release from thermosensitive hydrogels by the thermal effect generated by ultrasound. The other releases the drug by changing or destroying the hydrogel structure using vibration or cavitation. An *et al.* showed that hyaluronic acid-based hydrogels with gold cross-links are ultrasound-responsive and can significantly increase their temperature, leading to the dissociation of gold clusters and subsequent drug release [18]. While such drug release by thermal effect is easy to design for hydrogel materials, there is a risk of damaging other biological tissues.

Therefore, a combination with high-intensity focused ultrasound is effective. In the latter method, a self-healing gel for injection has been reported by Meng *et al.* [19] in which nanovaccines are encapsulated in a precursor solution containing polymer monomers and physical cross-linking agents, cleverly utilizing ultrasound-induced sol–gel transition. The hydrogel is transformed into a viscous flow sol by ultrasonic treatment, which results in the controlled release of the nano-vaccines. When not irradiated with ultrasound, the gel self-repairs and maintains its shape. In this method of changing or destroying the hydrogel structure, it is necessary to pay attention to the ultrasonic permeability of the hydrogel. Since the acoustic impedance of hydrogel is almost the same as that of biological tissue, more than 90% of the ultrasound is transmitted through the hydrogel, so it cannot efficiently react to irradiating ultrasound. Encapsulating particles as a vibration enhancer in hydrogel improved drug-release efficiency [20]. However, ultrasound, reaching deep into the body, has a longer wavelength, which results in a lower resolution. In addition, the ultrasound applied must be powerful enough to release the drug, which causes thermal damage and the formation of reactive oxygen species, in a similar manner to optical irradiation. Therefore, the development of better ultrasonic transducers and hydrogel nanocomposites is expected.

Conclusions & future perspectives

In recent years, nanotechnology has been responsible for many significant improvements in different fields including medicine, where it was utilized to overcome the limits of previous technologies and reach the market with commercial products. In addition, in the last decade, in many other medical applications, great attention was dedicated to the advantages of these new formulations able to overcome the drawbacks of classic treatments: inability to cross biological barriers, toxicity and quick clearance by body fluids. In this field, the possibility of working as nanoactuators, typical of magnetic and photonic nanoparticles, opened the door to their use as drug-delivery

10.2217/nnm-2023-0081

enhancers when coupled with hydrogel systems. This combination can ensure a more sustained release together with the ability to tune drug-release rates in time as well as in space. Indeed, the use of external stimuli on these nano-objects can induce molecular and physicochemical changes in the 3D hydrogel network and guarantee an engineered and tunable release of their contents. In particular, nanomaterials responsive to magnetic fields, NIR irradiation or ultrasound exhibited better outcomes in terms of the reduction of side effects and improvement of treatment efficacy. Although the literature is full of examples of preclinical studies, only a few have begun clinical trials. Their translation is hampered by various factors, including a lack of standardized procedures, regulatory problems and the uncertain fate of nanoparticles in the tissues. Consequently, regulatory organizations in many different countries are moving to build a standardized compendium to improve the safety and reproducibility of these nanoparticles for clinical use. Indeed, uniform legislation will help facilitate translation from *in vitro* studies to preclinical studies, toward the complexity of clinical trials.

Author contributions

F Rossi, Y Kurashina and H Onoe wrote the first draft and final version of the manuscript.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1. Liu D, Yang F, Xiong F, Gu N. The smart drug delivery system and its clinical potential. *Theranostics* 6(9), 1306–1323 (2016).
2. Zhang DX, Esser L, Vasani RB, Thissen H, Voelcker NH. Porous silicon nanomaterials: recent advances in surface engineering for controlled drug-delivery applications. *Nanomedicine* 14(24), 3213–3230 (2019).
3. Park K. Controlled drug delivery systems: past forward and future back. *J. Control. Rel.* 190(9), 3–8 (2014).
4. Jacob S, Nair AB, Shah J, Sreeharsha N, Gupta S, Shinu P. Emerging role of hydrogels in drug delivery systems, tissue engineering and wound management. *Pharmaceutics* 13(3), 357 (2021).
5. Gauthier MA, Gibson MI, Klok HA. Synthesis of functional polymers by post-polymerization modification. *Angew. Chem. Int. Edit.* 48(1), 48–58 (2008).
6. Hersel U, Dahmen C, Kessler H. RGD modified polymers: biomaterials for stimulated cell adhesion and beyond. *Biomaterials* 24(24), 4385–4415 (2003).
7. Mauri E, Chincarini GMF, Rigamonti R, Magagnin L, Sacchetti A, Rossi F. Modulation of electrostatic interactions to improve controlled drug delivery from nanogels. *Mater. Sci. Eng. C* 72(3), 308–315 (2017).
8. Armenia I, Ayllon CC, Herrero BT *et al.* Photonic and magnetic materials for on-demand local drug delivery. *Adv. Drug Deliv. Rev.* 191(12), 114584 (2022).
9. Karisma VW, Wu W, Lei M *et al.* UVA-triggered drug release and photo-protection of skin. *Front. Cell Dev. Biol.* 9(2), 598717 (2021).
10. Lee JH, Choi JW. Application of plasmonic gold nanoparticle for drug delivery system. *Curr. Drug Targets* 19(3), 271–280 (2018).
11. Moretti L, Mazzanti A, Rossetti A *et al.* Plasmonic control of drug release efficiency in agarose gel loaded with gold nanoparticle assemblies. *Nanophotonics* 10(1), 247–257 (2021).
12. Takatsuka S, Kubota T, Kurashina Y, Onoe H. Near-infrared-triggered on-demand controlled release of adeno-associated virus from alginate hydrogel microbeads with heat transducer for gene therapy. *Small* 19(7), 2204139 (2023).
13. Dai X, Li X, Liu Y, Yan F. Recent advances in nanoparticles-based photothermal therapy synergizing with immune checkpoint blockade therapy. *Mater. Des.* 217(5), 110656 (2022).
14. Price PM, Mahmoud WE, Al-Ghamdi AA, Bronstein LM. Magnetic drug delivery: where the field is going. *Front. Chem.* 6(12), 619 (2018).
15. Wang Y, Li B, Xu F *et al.* Tough magnetic chitosan hydrogel nanocomposites for remotely stimulated drug release. *Biomacromolecules* 19(8), 3351–3360 (2018).
16. Lea-Banks H, O'Reilly MA, Hynynen K. Ultrasound-responsive droplets for therapy: a review. *J. Control. Rel.* 293(1), 144–154 (2019).
17. Orita Y, Shimanuki S, Okada S *et al.* Acoustic-responsive carbon dioxide-loaded liposomes for efficient drug release. *Ultrason. Sonochem.* 94(3), 106326 (2023).
18. An JY, Um W, You DG *et al.* Gold-installed hyaluronic acid hydrogel for ultrasound-triggered thermal elevation and on-demand cargo release. *Int. J. Biol. Macromol.* 193(12), 553–561 (2021).

19. Meng Z, Zhang Y, She J *et al.* Ultrasound-mediated remotely controlled nanovaccine delivery for tumor vaccination and individualized cancer immunotherapy. *Nano Lett.* 21(3), 1228–1237 (2021).

20. Kubota T, Kurashina Y, Zhao JY, Ando K, Onoe H. Ultrasound-triggered on-demand drug delivery using hydrogel microbeads with release enhancer. *Mater. Des.* 203(5), 109580 (2021).

10.2217/nnm-2023-0081