Journal of Materials Chemistry B

ROYAL SOCIETY OF CHEMISTRY

EDITORIAL

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Cite this: *J. Mater. Chem. B*, 2024, **12**, 5571

An introduction to injectable hydrogels

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Injectable hydrogels have emerged as intelligent and versatile materials that have been proven to possess huge potential for many biomedical applications including drug delivery, tissue engineering, and regenerative medicine. Hydrogels are a class of polymers with highly hydrated 3D networks that have microenvironmental properties such as oxygen/nutrient permeability that are similar to the native extracellular matrix. In addition to possessing the typical advantages of conventional hydrogels, injectable hydrogels offer extra unique features, enabling minimally invasive injectability and durability for irregularly shaped sites, and the possibility of processing these materials *via*, *e.g.*, additive manufacturing techniques. As such, there has been a growing interest in using injectable hydrogels as scaffolds/carriers for therapeutic agents, including but not limited to drugs, cells, proteins, and bioactive molecules, targeted to treat chronic diseases including cancer, but also to facilitate the repair and regeneration of damaged organs/tissues. In this themed collection of *Journal of Materials Chemistry B* and *Biomaterials Science*, we include outstanding contributions covering recent developments in this rapidly evolving field of injectable hydrogels including emerging chemistries, synthesis pathways, fabrication methods, cell–material interaction, *in vitro*, *ex vivo* and *in vivo* performances, and subsequent targeted applications (drug delivery, tissue engineering and regenerative medicine) of injectable hydrogels.

DOI: 10.1039/d4tb90085e

rsc.li/materials-b

In this collection, Selvam *et al.* provided an interesting perspective on the adaptation of click chemistry in developing injectable organo-hydrogels in revolutionizing pharmaceutical research and development (https://doi.org/10.1039/D3TB01674A). The pathway towards clinical advancements of such injectable hydrogels is clearly articulated, building on current clinical progress of injectable organo-hydrogels in the market, targeted for a range of biomedical applications. Throughout the various examples, hyaluronic acid (HA) is showcased as one of the most widely used biomaterials as the main polymer backbone in designing intelligent injectable

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hydrogels, mainly due to its native extracellular matrix mimicry (structural and mechanical properties). It is however noted that any bench-to-bedside translation is heavily reliant on regulatory boards such as the Food and Drug Administration (FDA) and the European Medical Agency (EMA), where regulatory requirements should be considered during the injectable hydrogel design process. Furthermore, Morel *et al.* reported on using other chemical modification processes beyond click chemistry to further improve functionality of injectable HA hydrogels (**https://doi.org/10.1039/D3TB02108D**). In their study, thermoresponsive polyoxazoline was grafted onto HA, resulting in injectable hydrogels that undergo a reversible sol–gel transition at 25 °C. These hydrogels demonstrated enhanced robustness, thermal stability, and resistance to enzymatic degradation, showing great potential in therapeutic drug delivery applications.

In terms of applications, Xie *et al.* focussed on designing injectable hydrogels as long-lasting dermal fillers (**https://doi.org/10.1039/D3BM01488F**). Silk fibroin was used as their biomaterial of interest, fabricated into hydrogels which were then mechanically fragmented into microparticles. Interestingly, these silk microparticles had to be dispersed in HA solution prior to subcutaneous injection in a rat model. Subsequent functional evaluation showed lasting filler performance after 2 months, with good tissue infiltration and blood vessel in-growth. These results are highly promising, demonstrating that the injectable silk dermal fillers can be used to increase soft tissue volume in a minimally invasive procedure, further implying quick recovery, cost effectiveness and long-lasting aesthetic improvement. On the other hand, Han *et al.* explored the use of injectable hydrogels as bioinks for cutting-edge 3D bioprinting technologies (**https://doi.org/10.1039/D3BM02111D**). Injectable materials that exhibit a shear-thinning behaviour have been widely adopted as bioinks for extrusion-based bioprinting modalities. In this case, the authors were interested in decellularized extracellular matrix (dECM) due to its tissue-specific nature but were also challenged with its unsuitable inherent rheological properties. Therefore, they specifically developed gelatinized-dECM (GeldECM) through heat-induced denaturation of dECM, which was then used as a rheological modifier to improve injectability of dECM bioinks. Through mixing dECM and GeldECM, they proposed a triple crosslinking process – physical entanglement, photo-oxidation of di-tyrosine bonds, and thermal crosslinking of collagen fibrils, which enabled microextrusion of cm-scale, tough and resilient tissue constructs. This study showed the feasibility of gelatinized-dECM as a strategy to impart injectability into native dECM, further paving the way for development of tissue-specific bioinks. In another study, Piglionico *et al.* developed fibrinogen–blood injectable hydrogels as scaffolds for dental pulp regeneration (**https://doi.org/10.1039/D3BM00515A**). Biologics contained in blood favored the tissue regeneration, while a high concentration of fibrinogen in the formulation enabled tuning of the mechanical and degradability properties of the matrices. These hydrogels supported survival and proliferation of dental pulp cells as well as demonstrated angiogenic potential, as tested in an *ex vivo* rat aortic ring assay. These results are promising to support the revascularization of newly formed tissue and pave the way for the use of these materials in regenerative endodontic treatment.

The articles highlighted here are only a selected few out of a collection of exciting contributions from leading researchers working on injectable hydrogels. We hope this themed collection will inspire the community to explore and harness the exciting and versatile features of injectable hydrogels, to further generate significant impact in the multiple fields of application demonstrated in the articles included in this themed collection. We would also like to thank the editorial staff at the Royal Society of Chemistry, editorial staff, for their assistance throughout commissioning this themed collection.

