Advances and challenges in hydrogel microspheres for biomedical applications

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Hydrogel microspheres, with their high water content and tunable physicochemical properties, have emerged as a promising class of materials for a myriad of biomedical applications.[1] These microscale particles, which can be fabricated from both natural and synthetic polymers, exhibit diverse properties and bear a striking resemblance to the native extracellular matrix.[2] This makes them highly suitable as substrates for cell culture, templates for tissue engineering, and vehicles for drug and protein delivery.

Traditional hydrogels are typically crosslinked into bulk forms with dimensions at the millimetre scale and a mesh size at the nanometre scale, which allows for molecule diffusion. However, the limitations of bulk hydrogels, particularly in applications requiring injection or smaller sizes, have led to the development of hydrogel microspheres.[2] These microparticles, with dimensions ranging from 1 to 1000 μm, can be produced using a variety of techniques that are often compatible with the encapsulation of biologics, such as cells and drugs.[1]

The fabrication of hydrogel microspheres encompasses methods like batch emulsion, microfluidics, lithography, electrohydrodynamic spraying, and mechanical fragmentation.[3] Each technique has its strengths and limitations, with factors, such as particle size distribution, production rate, and the ability to control particle geometry being critical considerations. For instance, microfluidic emulsions offer precise control over particle formation, enabling the production of monodisperse hydrogel microspheres with specific internal and external architectures, while batch emulsions and mechanical fragmentation are favoured for their simplicity and speed.[1]

Hydrogel microspheres possess unique properties that distinguish them from their bulk counterparts. Their small size facilitates minimally invasive delivery through needles and catheters, and they can be formulated in suspensions or as aggregates to form microporous scaffolds that promote cell infiltration. The modular nature of hydrogel microsphere systems allows for the mixing of multiple hydrogel microsphere populations with varying compositions, sizes, and contents, creating diverse materials tailored for specific applications.

In terms of applications, hydrogel microspheres have been extensively explored for cell delivery, where they can enhance cell survival and integration at the target site. They have been used in tissue repair and biofabrication, offering a platform for the development of three-dimensional tissue models and the delivery of therapeutic cells to damaged tissues.[4] In drug delivery, hydrogel microspheres provide a controlled release system for various bioactive factors, with the ability to tailor the release profile to match the biological signalling cascades during tissue repair.[5,6]

Scaffolding with hydrogel microspheres leverages their microporous nature, which supports cell infiltration and proliferation without the need for degradation. These granular scaffolds can be annealed to form microporous annealed particle scaffolds, offering improved mechanical properties and stability.[7] The design of these scaffolds can be tailored to modulate the mechanical properties, degradation behaviour, and biological cues presented to cells.

Biofabrication using hydrogel microspheres takes advantage of their modularity and the ability to create complex three-dimensional structures using extrusion-based and lithography-based printing techniques. Hydrogel microspheres can be used as building blocks in automated assembly processes or as components of bioinks for three-dimensional printing, enabling the creation of constructs that mimic the complexity of native tissues.[8]

Despite the significant advancements in the field, challenges remain. These challenges span across

material synthesis, nano-micron combination strategies, regulatory mechanisms, and clinical translation. Here, we discuss these challenges and future perspectives to provide insights for the advancement of hydrogel microspheres in biomedical research:

1. Challenges in material synthesis and functionalisation

One of the main challenges lies in the precise synthesis of hydrogel microspheres with tailored physicochemical properties to meet specific biomedical needs. The biofunctionalities of current hydrogel microspheres are often limited, necessitating the development of versatile and efficient crosslinking techniques that can accommodate a broader range of biomaterials. Additionally, the integration of functional molecules, such as growth factors and small molecules with biomimetic features, into hydrogel microspheres requires innovative approaches to enhance their bioactivity and therapeutic efficacy.

2. Strategies for nano-micron combination

The combination of nanomaterials with hydrogel microspheres, while offering multifunctional capabilities, also presents challenges in achieving uniform dispersion and stable integration. The development of strategies that allow for the controlled loading and release of nanomaterials from hydrogel microspheres, without compromising their integrity or bioactivity, is crucial. Furthermore, the potential cytotoxicity and immunogenicity of some nanomaterials when integrated into hydrogels need thorough evaluation.

3. Regulation of microenvironment for tissue regeneration

The microenvironment in tissue regeneration is complex, involving various physiological, chemical, and physical factors. Hydrogel microspheres must be designed to respond and adapt to these dynamic conditions. The challenge is to create hydrogel microspheres that can actively regulate the microenvironment by modulating factors such as pH, oxygen levels, and cytokine release profiles to facilitate tissue repair and regeneration.

4. Clinical translation and commercialisation

The transition from laboratory research to clinical applications is fraught with challenges, including scalability, cost-effectiveness, and regulatory approval. The development of scalable and cost-effective manufacturing processes for hydrogel microspheres is essential for their widespread use. Moreover, rigorous preclinical and clinical studies are required to establish safety, biocompatibility, and efficacy profiles that meet regulatory standards.

To address these challenges, future research should focus on the following perspectives:

1. Material innovation

The exploration of new biomaterials and crosslinking chemistries that enhance the mechanical properties, biocompatibility, and biodegradability of hydrogel microspheres is vital.

2. Multifunctional integration

Strategies for the integration of multiple functionalities within hydrogel microspheres, such as stimuli-responsive drug release, targeted delivery, and imaging capabilities, should be developed.

3. Microenvironment regulation

Designing hydrogel microspheres that can dynamically interact with the microenvironment, including the ability to modulate immune responses and promote cell-cell interactions, is an important direction for research.

4. Clinically relevant studies

More translational studies are needed to evaluate the performance of hydrogel microspheres in clinically relevant models, addressing issues like long-term safety, efficacy, and integration into existing healthcare practices.

5. Manufacturing and commercialisation

Collaboration between researchers, industry, and regulators is essential to establish standardized protocols for manufacturing and commercialising hydrogel microspheres.

6. Ethical and regulatory considerations

As with any new medical technology, ethical considerations and regulatory guidelines must be addressed to ensure the responsible development and application of hydrogel microspheres.

In conclusion, while hydrogel microspheres offer a versatile platform for biomedical applications, there is a need for continued innovation and rigorous evaluation to fully realise their potential. By addressing the aforementioned challenges and embracing future perspectives, the field can progress towards the development of safe, effective, and clinically viable hydrogel microspheres for tissue regeneration and beyond.

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