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RECEIVED 30 December 2023

ACCEPTED 18 January 2024

PUBLISHED 02 February 2024

CITATION

Zhang Y, Mei Q and Zhang Z (2024),
Advancements in microemulsion-based
fabrication of upconversion-mediated
multifunctional materials.
Front. Photonics 5:1363223.
doi: 10.3389/fphot.2024.1363223

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Advancements in microemulsion-based fabrication of upconversion-mediated multifunctional materials

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Upconversion nanoparticles (UCNPs) have experienced significant advancements, finding applications in diverse fields over the past decade. The growing demand for UCNP-based nanoplatforms with multifunctionality to address complex scenarios has led to the emergence of the microemulsion confined self-assembly method, which allows for the integration of different UCNPs or UCNPs with additional functional materials within a single entity, resulting in a nanoplatform that possesses a wide range of properties suitable for specific applications. This comprehensive review aimed to summarize recent developments in the design of UCNP assemblies using the microemulsion confined self-assembly method, which focused on exploring their applications in critical areas such as color encoding, bioimaging, and programmable therapeutics. Furthermore, the review acknowledged the existing limitations associated with the microemulsion confined self-assembly method and provided an in-depth discussion of potential solutions to overcome these challenges, aiming to foster further progress and innovation in the design and application of UCNP assemblies.

KEYWORDS

upconversion, microemulsion, self-assembly, bioimaging, molecular delivery, programmed therapeutics

1 Introduction

The utilization of near-infrared (NIR) light-excitabile upconversion nanoparticles (UCNPs) has garnered significant attention in recent times due to their distinctive capability as on-demand energy transducers to convert low-energy NIR light to high-energy ultraviolet (UV)/visible light (Chen et al., 2015a; Idris et al., 2015; Li et al., 2015; Zhou et al., 2015; Zhu et al., 2017b; Zheng et al., 2019; Chen and Wang, 2020a; Chen and Wang, 2020b; Cheng et al., 2020; Dong et al., 2020; Nonat and Charbonnière, 2020), thereby enabling a range of applications such as molecular detection (Zheng et al., 2015; Chen et al., 2016; Shikha et al., 2017; Gu and Zhang, 2018; Gao et al., 2019), drug delivery (Yan et al., 2012; Li et al., 2013; Liu et al., 2013; Yang et al., 2013; Bansal and Zhang, 2014; Zhao et al., 2014; Yang et al., 2015; Wang et al., 2016), optogenetics (Wu et al., 2016; Chen et al., 2018; Liang Zou, 2020), and photodynamic therapy (PDT) (Wang et al., 2011; Idris et al., 2012; Cui et al., 2013; Liang et al., 2016; Bansal et al., 2018; Qiu et al., 2018; Liu et al., 2019). However, the limited extinction coefficients, quantum efficiency, and fixed energy levels of UCNPs hindered their broader applications in specific multiplexed scenarios. To

circumvent these limitations, researchers have focused on designing and synthesizing UCNPs with increasingly complex structures, involving multi-step and time-consuming procedures (Chen et al., 2015a; Wang et al., 2015a; Chen et al., 2015b; Wang et al., 2016; Ju et al., 2018; Leng et al., 2018; Fan et al., 2019). To resolve these problems, UCNP hybrid assemblies containing various UCNPs or UCNPs and other functional counterparts were developed to achieve desired properties tailored to specific applications, such as cell imaging (Li et al., 2013; Li and Lu, 2015; Xue et al., 2019), drug delivery (Cai et al., 2017; Zhang et al., 2019; Zhang et al., 2020a; Zhang et al., 2020b; Zhang et al., 2021a; Zhang and Zhang, 2021), molecular detection (Wang and Li, 2006; Liu et al., 2018), and programmed therapy (Zhang et al., 2019; Zhang et al., 2020a). The UCNP assembly not only preserves the inherent upconverting characteristics of UCNPs but also possesses additional variable functional properties, including environmental responsiveness, magnetic targeting, and catalytic activity, which assist in enhancing performance and overcoming the limitations of traditional UCNPs. Moreover, the composition and assembly approach of individual components could be finely tuned to obtain desired properties and adapt to specific environmental conditions as needed.

Several synthesis methods have been developed for UCNP assemblies, including interface-based approaches (Ye et al., 2010; Ren et al., 2012; Liu et al., 2016), microemulsion confined self-assembly (Bai et al., 2007; Wang et al., 2013a; Wang et al., 2013b), and polymer/DNA-mediated methods (Li et al., 2013; Chen et al., 2019; Zhang et al., 2020b). Among these methods, due to its superior versatility and efficiency, microemulsion confined self-assembly has demonstrated exceptional potential for fabricating highly useful UCNP-based nanoplatforms, particularly in emerging fields such as bioimaging, controllable molecular delivery, and programmable therapeutics. A comprehensive overview of recent developments and achievements in UCNP assemblies reported in the past years would facilitate the effective utilization of UCNP-based materials. Accordingly, Section 2 provides a concise introduction to the microemulsion confined self-assembly of UCNP-based multifunctional materials. Additionally, Section 3 discusses related applications, as well as the challenges and perspectives of UCNP assemblies are summarized in Section 4.

2 Advancements in microemulsion-based fabrication of UCNP-based multifunctional materials

Microemulsion is a process in which the continuous phase, comprising either an organic or aqueous medium, undergoes fragmentation, leading to the dispersion of oil or water droplets within an aqueous or oil solution containing surfactants (Bai et al., 2007; Lu and Yin, 2012; Wang et al., 2013a; Lee et al., 2015; Boles et al., 2016; Xiao et al., 2017; Liu et al., 2022; Zhang et al., 2022; Zhou et al., 2023). In a typical oil-in-water (O/W) microemulsion system, for instance, emulsification is achieved by subjecting the oil phase to mechanical stirring or sonication in the presence of surfactants. Subsequently, the low-temperature boiling oil phase is eliminated through evaporation, causing the materials within the oil droplets to

aggregate and form larger assemblies exhibiting a 3D spherical morphology (Figure 1A).

2.1 Assemblies of UCNPs in various types

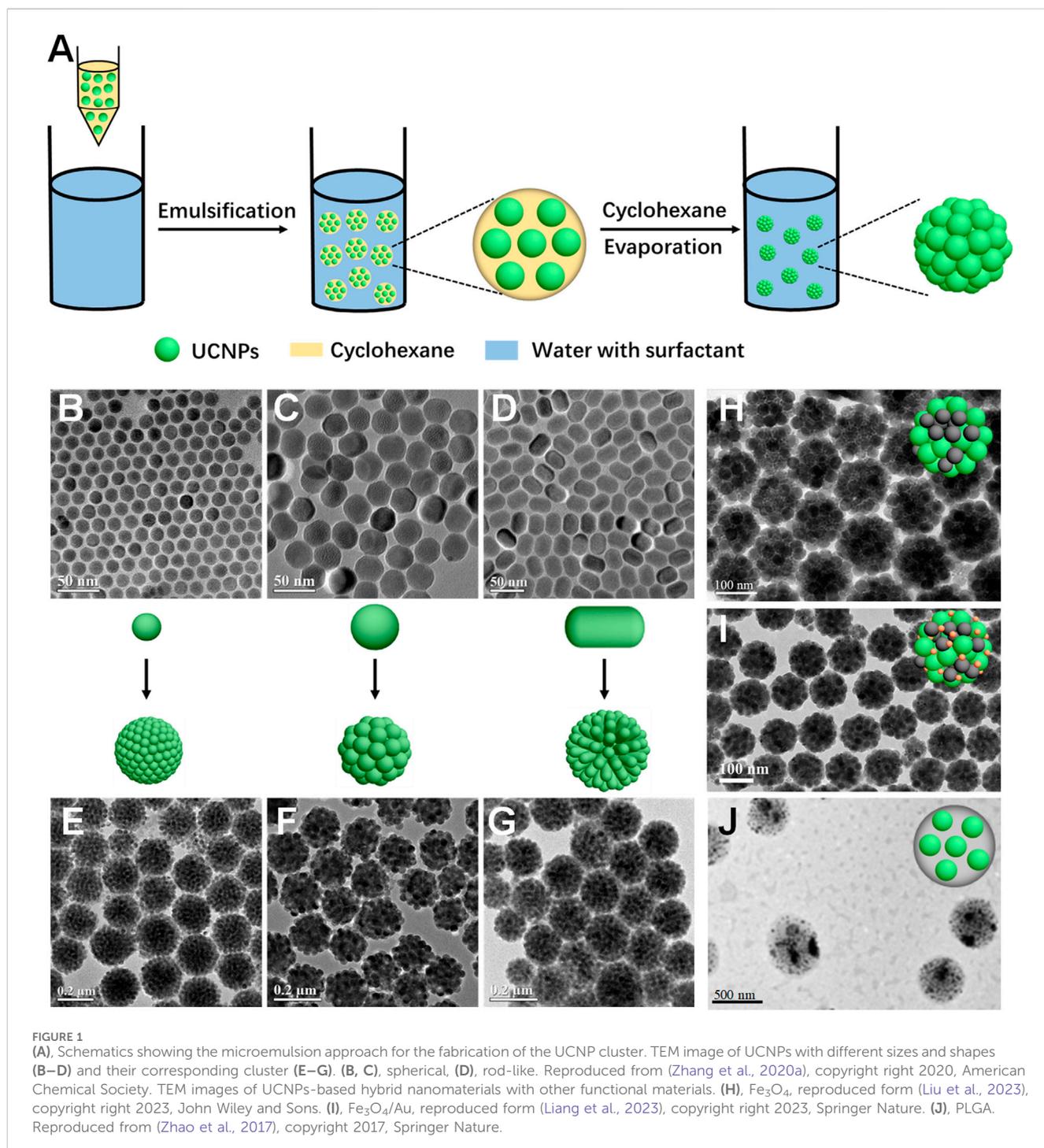
Taking advantage of the microemulsion confined self-assembly method, Zhang's group assembled various UCNPs into UCNP clusters, demonstrating the broad applicability of this approach. Initially, a set of spherical UCNPs (diameter is about 17 and 34 nm) and rod-shaped UCNPs (length about 34 nm) were selected to form spherical UCNP clusters (Figures 1B–G) (Zhang et al., 2020a). The size, composition, and surface charge of these 3D colloidal spheres can be precisely controlled by manipulating experiment parameters. This approach paves the way for the preparation of a 3D UCNP assembly derived from a single UCNP.

2.2 Assemblies of UCNPs and other inorganic nanoparticles

After a thorough exploration of the principles behind the microemulsion confined self-assembly method, Zhang's group recognized the potential for other functional inorganic materials, possessing similar surface properties as OA-capped UCNPs, to form their own assemblies or hybrid assemblies. Therefore, Fe_3O_4 nanoparticles were selected and combined with UCNPs to construct multifunctional superparticles (MFSPs), exhibiting both upconversion and magnetic targeting capabilities, which significantly highlighted the versatility of the microemulsion confined self-assembly method (Figure 1H) (Liu et al., 2023). The synthesized MFSPs, comprising two distinct types of functional nanoparticles, demonstrated remarkable performance in terms of green-colored upconversion luminescence upon excitation with a 980 nm laser. Additionally, under the influence of a magnetic field, the MFSPs exhibited controlled and directed movement. The simultaneous manifestation of both functionalities in all MFSPs provided strong evidence for the successful combination of UCNPs and Fe_3O_4 nanoparticles within a single MFSP. Expanding on this concept, Zhang and his collaborators aimed to enhance the versatility of the microemulsion approach by incorporating Au nanoparticles into the UCNPs/ Fe_3O_4 MFSPs system (Figure 1I) (Liang et al., 2023), which further demonstrated that tailored nanoplatforms with enhanced functionalities can be achieved according to the specific requirements of practical applications.

2.3 Assemblies of UCNPs with organic materials

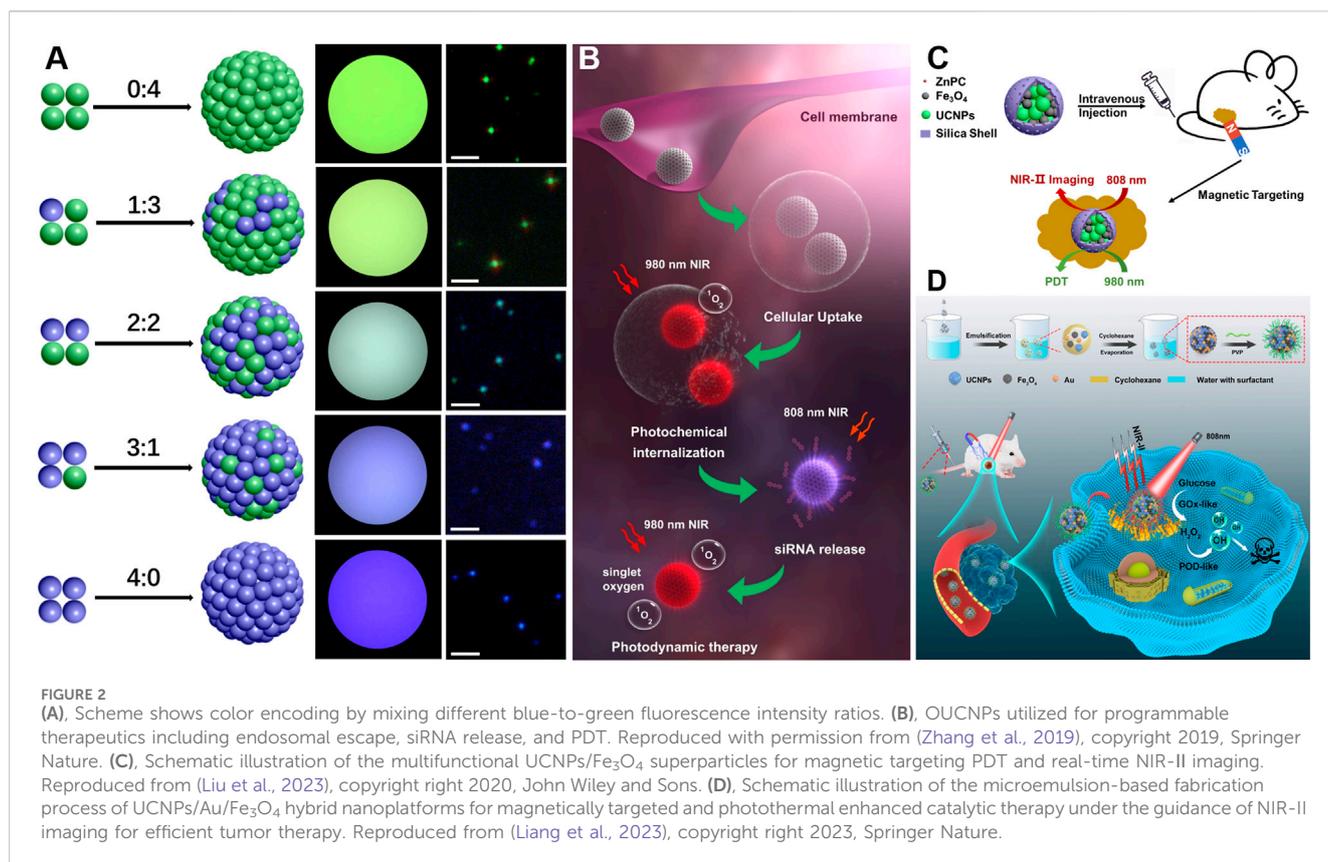
The microemulsion method offers a versatile approach not only for constructing UCNP-inorganic nanoparticle assemblies but also for combining UCNPs with other materials such as organic small molecules and polymers to create UCNP-based inorganic/organic hybrid nanosystems. Dai's group reported a facile and straightforward synthesis of $\text{ZnPc}/\text{NaGdF}_4:\text{Yb}$, Er clusters, utilizing an amphiphilic copolymer, PMAO-PEG (poly (maleic anhydride-alt-1-octadecen-poly (ethylene glycol))) as an additive



in the organic phase to form a microemulsion (Wang et al., 2013b). After complete evaporation of the organic solvent, the UCNPs, ZnPc, and PMAO-PEG aggregated together, forming a 3D hybrid cluster. The hydrophilic PEG molecules extended to the outside of the cluster, ensuring its stability, dispersivity and biocompatibility for *in vitro* and *in vivo* applications. In 2017, Wang et al. introduced pH-dependent multifunctional nanocapsules based on pH-simultaneous PLGA and UCNPs (NaYF₄:Yb,Er@NaGdF₄) for drug delivery of an antitumor drug (DOX) (Figure 11) (Zhao et al., 2017).

3 Advancements in applications of UCNPs-based multifunctional materials

In recent years, UCNPs assemblies with diverse functionalities have found application in various practical scenarios, such as dual-modality cell imaging, controllable drug delivery, and programmable therapeutics, *etc.* Summarizing the achievements in these applications over the past few years can provide valuable insights into the self-assembly of UCNPs and facilitate the exploration of more useful and desired applications of



UCNP-based nanoplatforms through microemulsion-based fabrication methods.

3.1 Color encoding

Traditional methods for tuning the color emissions of UCNPs typically involve complex and time-consuming fabrication processes, which require multiple synthesis steps and precise control over the composition and thickness of each layer. However, by utilizing the microemulsion system, UCNPs with different emission characteristics can be easily incorporated into a single hybrid cluster, allowing for color encoding without the need for complex structural modifications. For instance, by mixing UCNPs with blue and green emission in different intensity ratios and exciting them with 980 nm excitation, diverse UCNP cluster solutions with varying blue-to-green fluorescence ratios at 450 nm and 550 nm were successfully created (Figure 2A) (Zhang et al., 2020a).

Besides, recent studies have focused on the development of UCNPs with orthogonal emissive emissions (OUCNPs) to meet the complex requirements of various applications, due to their superior temporal separation and precise molecular photoactivations. However, the synthesis of OUCNPs requires multi-core-shell structures, where different lanthanide activator/emitter cations are doped in isolated shells, and an inert shell is desired to prevent energy transfer between the shells. The behavior of these multi-core-shell OUCNPs is often limited in quantum yield and

luminescence stability. Zhang's group addressed this challenge by modularly assembling two types of UCNPs, namely, spherical UCNPs A (NaYF₄:60%Yb,20%Gd,2%Er@NaLuF₄:25%Y) and dumbbell-like UCNPs B (NaYF₄:30Yb,0.5%Tm@NaYF₄:10%Yb@NaNbF₄:10%Yb), which emits red light upon excitation at 980 nm and UV/blue light when exposed to 808 nm irradiation, respectively (Zhang et al., 2019; Zhang et al., 2020a). This approach focused on synthesizing individual UCNPs with a simple structure containing a single activator and then assembling them while maintaining their individual luminescence properties. Just by changing the laser power ratio of 980 nm–808 nm, different colors from blue to orange could be achieved easily.

3.2 Bioimaging

UCNPs have emerged as promising candidates for bioimaging applications, due to their remarkable optical properties, including large anti-Stokes shift, long lifetime emission, and narrow band emission (Wang et al., 2010; Zhou et al., 2012; Park et al., 2015; Wolfbeis, 2015; Wang et al., 2019). Moreover, the microemulsion method allows for the combination of UCNPs with other materials possessing different properties, resulting in hybrid systems with enhanced functionalities for bioimaging. One promising candidate among these functional counterparts is persistent luminescence (PL), which exhibits the ability to emit light for several minutes or even hours after the excitation source has been removed (Zhou et al., 2023). Li's group utilized the microemulsion confined method

to construct UCNP/PL hybrid cluster which involved the combination of UCNPs ($\text{NaYbF}_4:\text{Tm}@(\text{NaYF}_4)$) with PL nanoparticles ($\text{Zn}_{1.1}\text{Ga}_{1.8}\text{Ge}_{0.1}\text{O}_4:0.5\%\text{Cr}$) in a hybrid nanocluster (Xue et al., 2019). In this hybrid system, the UV light generated by a 980 nm laser served as a secondary excitation source for the PL nanoparticles, resulting in afterglow emission at 700 nm. This NIR-to-NIR bioimaging hybrid cluster exhibited remarkable reactivation capabilities even covered by a 10 mm layer of pork, showcasing its high tissue penetration ability in the NIR range for bioimaging *in vivo*.

3.3 Programmable therapeutics

Traditional UCNPs with fixed emissions pose limitations in performing multiple tasks, while utilizing UCNPs with orthogonal emissive emissions (OUCNPs) makes it possible to independently control the photoactivation of different functions by simply adjusting the external excitation light. This capability allows for precise temporal control and targeting of multiple specific biological processes (Boyer et al., 2010; Wang et al., 2014; Wang et al., 2015b; Huang et al., 2018; Zheng et al., 2018; Zhang et al., 2021b; Zhang and Zhang, 2021). So far, the synthesis of OUCNPs is complicated and tedious because different lanthanides need to be incorporated into the different shells (Boyer et al., 2010; Lai et al., 2014; Wang et al., 2015b; Li et al., 2016; Dong et al., 2017; Mei et al., 2019; Lei et al., 2020). To address these bottleneck problems, Zhang et al. utilized the microemulsion method to assemble two distinct UCNPs with different emissions into OUCNP clusters (Zhang et al., 2020a). These UCNPs can be individually activated by irradiation with the 980 and 808 nm light, resulting in red and UV/blue emission, respectively, which were applied for cell imaging and drug delivery in a controllable manner. Furthermore, the same group achieved enhanced PDT using OUCNP clusters through programmed photoactivation of multiple therapeutic processes, including endosomal escape through photochemical internalization for enhancing cellular uptake, gene knockdown of superoxide dismutase-1 to increase sensitivity to reactive oxygen species, and PDT to ensure a higher therapeutic efficacy (Figure 2B) (Zhang et al., 2019).

In addition to the controlled photoactivation of OUCNP clusters through external excitation light, hybrid nanoplatforms combining UCNPs with other materials could be programmed to suit various practical applications. Zhang's research group utilized the microemulsion based method to assemble UCNPs and Fe_3O_4 nanoparticles into multifunctional UCNP/ Fe_3O_4 superparticles with highly integrated functionalities including magnetic targeting, PDT and real-time NIR-II imaging, which allows for the guidance of PDT using 980 nm and 808 nm excitations (Figure 2C) (Liu et al., 2023). In order to further enhance the efficacy of tumor theragnostic, Zhang's group incorporated Au nanoparticles into the superparticles, which act as catalysts for the conversion of glucose to gluconic acid and H_2O_2 . Importantly, the generated H_2O_2 serves as a reactant source for the production of $\cdot\text{OH}$ due to the nanoenzyme-like peroxidase activity of Fe_3O_4 nanoparticles. Furthermore, under 808 nm irradiation, the Au nanoparticles exhibit enhanced catalytic properties due to their photothermal conversion capability (Liang et al., 2023). This multifunctional nanoplatform demonstrates a synergistic effect of different nanoparticles for cancer treatment. By

utilizing the microemulsion confined modular assembly technology, the construction of such multifunctional intelligent systems brings us closer to the realization of effective cancer diagnosis and therapy integration.

4 Summary and outlook

Over the past few years, the synthesis of UCNPs have made tremendous progress and high-quality UCNPs greatly expand their application potential in various fields, including imaging, detection, delivery, PDT, PTT, and programmable control of therapeutic processes. Although advancements have been made, UCNPs still suffer from certain challenges, such as low quantum efficiency and extinction coefficients, and fixed emissions, which limit their broader practical applications. To address these limitations and draw inspiration from the strengths of other materials, researchers have focused on constructing UCNP nanoplatforms that incorporate different types of UCNPs or other functional counterparts. By leveraging the advantages of diverse materials, UCNP-based hybrid nanoplatforms can exhibit improved performance and overcome the inherent limitations of UCNPs alone. However, synthesizing UCNP-based hybrid nanoplatforms with different functionalities is a challenging and time-consuming process. A possible solution to this issue is the modular assembly of UCNPs with other materials through a microemulsion confined method. This approach allows for the synthesis of individual materials with simple structures, which can then be bonded together to create a complex and versatile nanoplatform that meets the requirements of various applications. By simplifying the synthesis process, this method offers a promising and efficient way to create hybrid nanoplatforms with diverse properties. Moreover, the exploration of alternative approaches for efficient and convenient synthesizing UCNP-based multifunctional materials is expected to become a key focus in future research and developments.

This review provides an overview of the recent advancements and applications of the microemulsion confined method in fabricating functional materials based on UCNPs. Despite the significant progress made in the past decade, several limitations need to be addressed before these materials can be effectively translated into practical applications. One significant factor to consider is the size of UCNP clusters, as it has a substantial impact on their interaction with biological systems (Hoshyar et al., 2016; Dolai et al., 2021), such as cellular uptake (Arnida et al., 2010; Dasgupta et al., 2014), tumor penetration (Perrault et al., 2009; Zhang et al., 2009; Huang et al., 2012), and tissue biodistribution (De Jong et al., 2008; Sonavane et al., 2008; Hirn et al., 2011; Duadi et al., 2013). Therefore, it is crucial to study the interactions between nanoparticles and cells and tissues to determine the optimal size for UCNP clusters. Previous lectures have indicated that nanoparticles should have a diameter larger than 10 nm to prevent kidney filtration (de Barros et al., 2012; Zuckerman et al., 2012). However, if the diameter exceeds 200 nm, the nanoparticles can activate the complement system, leading to their removal from the bloodstream and accumulation in the liver and spleen (Faraji and Wipf, 2009; Kulkarni and Feng, 2013). Furthermore, the colloidal properties of nanoparticles necessitate their size to be less than 200 nm, as larger nanoparticles tend to settle out due to the gravitational forces (Karagoz et al., 2014). Additionally,

nanoparticles with a size of 100–200 nm are more efficiently internalized by cancer cells (Zhu et al., 2017a). Therefore, most of the UCNP clusters described in this review have been designed to be around 100–200 nm to fulfill these size-related requirements for applications *in vitro* and *in vivo*. Achieving precise control over the microemulsion confined self-assembly while obtaining desired properties in the final nanostructures remains a major challenge. Another challenge arises from the inherent dependence on high mechanical forces such as sonication agitation, or homogenization during the process of the microemulsion-based assembly method. Therefore, a wide range of cluster sizes is often obtained, making it difficult to guarantee excellent reproducibility of the products across different batches. This poses a significant hurdle in the practical utilization of microemulsion for large-scale production of monodisperse structures at the sub-micrometer scale. In summary, the microemulsion-based method for the fabrication of UCNP-based assemblies with different functional materials has experienced rapid development in recent years. However, there are still numerous areas and directions that require further explorations to address the challenges mentioned above and unlock the full potential of microemulsion-based fabrication techniques.

Author contributions

YZ: Conceptualization, Funding acquisition, Writing–original draft, Writing–review and editing. QM: Conceptualization, Writing–original draft, Writing–review and editing, Supervision. ZZ: Conceptualization, Supervision, Writing–original draft, Writing–review and editing, Funding acquisition, Software.

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Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. We gratefully acknowledge the financial support from the Natural Science Foundation of China (No. 52103276), Guangdong Basic and Applied Basic Research Foundation (No. 2022A1515010947 and 2022A1515111012), Science and Technology Projects of Guangzhou (No. 201804010173), Science and Technology Plan of Haizhu District (No. 2022-51), Open Project Program of Jiangsu Key Laboratory of Environmentally Friendly Polymeric Materials (PML2204), Fundamental Research Funds for the Central Universities, Sun Yat-Sen University (No. 23qnp03), and China Postdoctoral Science Foundation (2023M731314).

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