REVIEW PAPER

Architectural fabrication of multifunctional janus nanostructures for biomedical applications

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ABSTRACT

The domain of Janus nanoparticles (JNPs) has seen a surge in research and development during the last decade. JNPs are anisotropic composite innovations with remarkable characteristics that depict a peculiar class of particles, which integrate the features and functions of multiple materials into a single unit. Janus particles are superior prospects for several high-end applications due to their possible modifications by "click chemistry". JNPs offer new possibilities by combining the features of components. Janus nanoparticles can pack multiple pharmaceuticals and imaging contrast agents simultaneously since they have a distinct chemical configuration on different sides. As a result, they become ideal for administration and bioimaging at once. They have sparked interest due to their exceptional architecture and their potential implications in science and engineering, biological application, and most notably, theranostics. The emphasis of this review is on the latest advancement in the fabrication and implementation of innovative Janus nanoparticles, along with their spectacular performance in therapeutic delivery applications.

Keywords: *Biomedical applications, Janus, Multifunctional, Nanoparticles*

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INTRODUCTION

In the search for novel smart materials with tailored functionalities for desired applications, scientists have been driven to nanotechnology during the last two decades. Nanoparticles feature exceptional physicochemical properties owing to their decreased unique dimensions, making them best suitable for biological applications as a theranostic agent [1-4]. Extensive research initiatives for development in the synthesis procedure of nanomaterials lead to wide applications in high-end domains such as diagnostics, drug delivery, bio-monitoring, catalysis, nanoelectronics, etc., [5-7]. The most widely used technique for synthesis falls under the bottom-up approach, where the precursor molecules such as building blocks can be used to build nanoparticles with desired characteristics by self-assembly. Hence, the application designed decides the building blocks that are to be used for the preparation of new material. The objective is to acquire a greater degree of control on the properties of materials, which can be achieved by minimizing the scale of nanoparticles. The key obstacle for any researcher is to figure out new different ways to manufacture nanostructures and build those with the features as per requirement. The synthesis procedures that currently exist usually yield spherical-shaped particles with surface modifications. This is due to the isotropic behavior of the precursor bulk material. The limited range of possible behavior and configurations associated with isotropic bulk materials is one of their shortcomings [8, 9]. Since size and shape can alter the functionalities, shape anisotropy is the primary approach in the synthesis method of nanoparticles, which involves anisotropic bulk material. Particles can be prepared with structures

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exhibiting anisotropic behavior or with irregular arrangements of functional groups. Anisotropic architecture can be accomplished generally by splitting a nanoparticle into two categories: which can be built of a composite design or can contain a set of distinct functional groups [10, 11]. During the noble lecture in 1991, the French physicist Pierre-Gilles de Gennes coined the particle name as "Janus" since it mimics the Janus god of Greek mythology by having two non-identical faces. From then, the nanoparticles with two different compositions and functions are called Janus nanoparticles (JNP). However, the word Janus and the original work was earlier carried out by his colleagues and was published in 1989 [12]. The biomedical applications of these JNPs are emerging as the need for theranostic increases. As they exhibit two different functions in one single particle, they can be used as agents for diagnosis and therapy simultaneously. The ease of production, multiple applications, and minimal toxicity inside the biological system made the JNP a potential interest in biomedical applications [13]. Besides that, they are stable and capable of forming clusters by self-assembly having control over size, morphology, and surface properties. The synthesis procedure, if modified, can yield JNP with stimuli-responsive behavior. The most biomedical application uses homogenous nanoparticles due to their stability. In addition, the synthesis of the heterogeneous nanoparticle is difficult as it involves multiple steps where the possibility to cross the permissible limit is high [14, 15]. However, in the case of JNP, the synthesis methods are as easy as creating homogenous material, and the capability is even higher. Both the hydrophilic and hydrophobic ligands can be attached to JNPs simultaneously, making them multifunctional [16]. The morphology of a commonly synthesized JNP is a sphere sharing equal halves of hydrophilic and hydrophobic structures. Due to their unique hierarchy of structural compositions, they offer broad potential biomedical applications. The targeting of the drug can be improved by incorporating alternative chemistry to produce JNP by asymmetrizing the surface of symmetric particles. The objective of this article is to provide a detailed review of types, salient features, and some of the most effective approaches towards the fabrication of JNPs that have been proposed in recent studies. Furthermore, the possible implications of JNP in the future are reviewed to provide insight for the researchers.

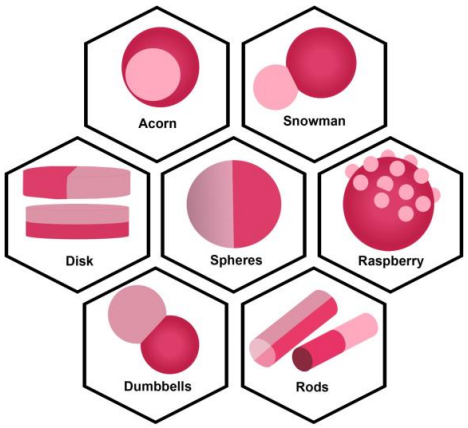

Fig. 1. Widely use morphologies of JNPs

Morphological types

The JNP can be produced with two distinct morphologies, namely, Patchy and Compartment particles with different shapes (Fig. 1).

Patchy JNPs

Patchy particles are termed as nanostructures of finely regulated portions of the variable surface, mostly consisting of structures with anisotropic behavior. A recent study by Biswas et al., in 2020 developed a facile synthesis procedure for the fabrication of JNP with the combination of silver (Ag) and copper (Cu). The seed-mediated technique used in this study is the first reported facile synthesis procedure for metal-based JNPs. The patchy structure was formed due to the reduction potential exhibited between Ag and Cu. Thus, formed particles showed better results in the antifungal behavioral study against rice pathogen [17]. Zhang et al. in 2020 used interface evaporation and emulsification technique and synthesized iron oxide nanocubes patched onto the Janus magnetic nano-based drug carrier (IONCs-P-JMNC). The synthesized particle was anisotropic and showed significant T2 contrast in MRI examination. The drug-carrying capacity, magnetic properties, and multifunctionality of the IONCs were readily enhanced. As a result, it was anticipated that it could be used as a novel nanoplatforms for theranostics [18]. Another group of researchers, Sologan et al. in 2017, validated the viability of the synthesis approach, which incorporated multiscale molecular simulation and NMR investigations. They have grafted the

Hydrogenated and Fluorinated Alkanethiolates onto the surface of gold nanoparticles (AuNp). The prepared JNP was evaluated under computational studies and showed successful demonstration on the self-assembly behaviour of numerous insoluble ligand compounds on AuNp. The outcomes of this detailed investigation can be used to understand the principles of cellular design to gain accurate control over inorganic nanoparticles [19]. McConnell et al., in 2010, developed a novel approach to fabricate JNP with tunable optical properties through the hierarchy of self-assembly. The patchy JNP synthesized was with gold and silica, which were covalently attached to each other. The particle they prepared showed excellent tunable optical properties with the change in surface energy, which was accomplished during annihilation [20].

Compartment JNPs

Compartmented particles, on the other hand, are core nanostructures with numerous phase-separated regions. Since the structure contains two separate parts with different behavior, compartmented particles can function as a dual drug delivery vehicle. This was proved from the study conducted by Chen et al. in 2020. The study comprised designing of OA-UCNPs/PDA- gold nanoflowers JNPs, application for multimodal imaging, and tested for dual anticancer activity. The *in vivo* investigation on mice showed a significant therapeutic effect against hepatocellular carcinoma [21]. Kemel et al. in 2020 have studied the potential of compartmented JNPs in skin penetration. *In vitro* investigations using AFM-IR on Franz cells offered a clear understanding of the local penetration effect of JNP. It was concluded that future research on JNP might improve the transdermal fluxes of any active substances [22]. Another research group consisting of Li et al. in 2014 successfully synthesized the mesoporous structure of Janus silica nanocomposite through island nucleation growth method. The experiments on the optical property revealed that the dual compartment JNP synthesized here showed two folds greater carcinoma cell killing capacity (around 50 %) than single triggered delivery vehicles (approximately 25%) [23]. Truong-Cong et al. in 2018, conducted research regarding dual drug delivery of compartmented JNP. The prepared lipid-based JNPs showed a greater possibility of co-administration of two different drugs at once. The synthesis procedure comprising FDA-approved pharmaceutical and lipid-based JNPs showed long-term stability [24]. Yang et al. in 2017 tested JNP for catalytic activity by producing mesoporous-carbon and organosilica JNPs via a wet chemical approach. The prepared JNPs exhibited three-fold superior catalytic activity in comparison to the Pt-loaded carbon sphere catalyst [25]. Figure 1 shows the different morphologies of JNPs.

Compositions

The JNPs can be distinguished by their compositions, i.e., the sharing of hydrophilic and hydrophobic characteristics. The particles can be tailored with any composition in terms of their applications. JNPs were developed for different sorts of applications, and the fabrication technique used were tabulated in Table 1, including recent findings.

Organic JNPs

Organic Janus nanoparticles are classic examples that share equal halves of hydrophilic and hydrophobic groups. These organic JNPs are pure polymers. Thus, prepared particles can be used for several applications ranging from biomonitoring to therapeutics. The polymers-based organic JNPs are otherwise called soft systems, which are highly efficient in terms of theranostic application compared to other systems due to their excellent stability. Cong Wei et al., in 2019 have, synthesized organic fluorescent JNPs doped equally with hydrophobic and hydrophilic dyes and were used as lasers. Thus, the fabricated nanophotonic particles were assured to provide insight for optoelectronic applications [26]. Lingyu Zhang et al. in 2018 have fabricated UFO-like cyclodextrin-Pd Nanosheet/ZIF-8 JNPs. The *in vivo* and *in vitro* investigations conducted in the study have concluded that the prepared organic JNPs showed a synergistic effect on cancer therapy. Their diverse properties were combined to achieve multiple applications, including a vehicle for dual drug delivery, stimuli-responsive carrier, and chemo-photothermal therapy with minimal toxic effects [27].

Inorganic JNPs

Inorganic JNPs are, called hard systems or pure inorganics, have a wide application in the biomedical field, which was discussed by Isabel et al. in 2014. This study talks about the synthetic route to synthesize different shaped

Table 1. A literature review of the JNPs developed for diverse biomedical applications

S.No	Composition	Types	Components	Morphology	Fabrication strategy	Applications	Ref.
1.	Organic	Patchy	Poly(4- vinylpyridine)-based block copolymers	Dumbbell	Solvent evaporation induced assembly	Facile synthesis approach	[35]
2.	Hybrid	-	Poly(acrylic acid)-mesoporous calcium phosphate/polydopamine (PAA-mCaP/PDA) JNPs	Acorn	-	Photoacoustic (PA) imaging-guided synergistic cancer chemo-phototherapy	[36]
3.	Inorganic	-	Gold-Mesoporous Silica Nanoparticles	Spherical	Pickering emulsion method	Cancer therapeutics	[37]
4.	Hybrid	Compartment	UCNP@SiO2@mSiO2&PMO	Ball-shaped depression	Anisotropic island nucleation and growth method	Bimodal Triggered Drugs Delivery	[23]
5.	Organic	-	Poly(4-vinyl benzyl chloride) (PVBC)	Ball and stick structure	-	pH-responsive delivery to tumor cells	[38]
6.	Hybrid	-	Rhodamine doped silica (SiO2) nanoparticles	Spherical	Pickering emulsion method	Extended cell surface attachment	[39]
7.	Inorganic	Patchy	Ag-Cu	Spherical	Seed mediated method	Antifungal activity against the potent rice pathogen R. solani and potential protective agents for rice crop production	[17]
8.	Hybrid	-	DMAEMA-MAA	Snowman-like Janus particles	Seed mediated method	Drug carrier for anticancer agent	[40]
9.	Inorganic	-	Ag-MoS2	Snowman-like Janus particles	Hydrothermal method	Nanomotors for investigation of active colloids.	[41]
10.	Organic	Patchy	Carboxylated Polystyrene-*PVDF/PVP*	Dumbbell	Seeded emulsion polymerization	Compatibilizer for polymer blends	[42]

JNP. They have studied the optical characteristics of inorganic JNPs. JNPs showed better emission of photoluminescence, which makes them the best suitable contrast agent for multimodal imaging. The surface modification in JNP is so facile that the properties can be tailored as per requirements and possibly can be applied in theranostics [28]. Wei Xue et al. in 2017 have, successfully fabricated novel inorganic JNPs with two different mixtures using regioselective modifications. The JNPs thus prepared was used as a solid emulsifier in order to better understand the interfacial assembly behavior. The prepared JNP exhibited a pH-sensitive release of payloads. They had concluded that the theoretical explanations were experimentally proved to be the same for the first time when JNPs were applied in the place of homogenous particles [29]. Another group of researchers, including Xiaowei et al., has developed inorganic JNPs with dual imaging properties for simultaneous applications on chemotherapy and hyperthermia. The *in vivo* investigation on the mouse model has shown a complete tumor inhibition with minimal detrimental effects when irradiated with AMF plus laser as by which the ROS production increases. The study results showed an alternative method for treating cancer, especially breast tumor cells, and can also be used in theranostics [30].

Hybrid JNPs

Hybrid JNPs are composite materials consisting of a combination of organic and inorganic materials in every single particle. Zhang et al. in 2019 synthesized 2D JNPs - Black phosphorus Nanosheets (BPNs)/ quantum dots (BPQDs) to provide better photocatalytic activity in photodynamic therapy against cancer. This investigation showed that when a laser at 670 nm irradiates these particles, the interaction with O_2 increases, leading to high production of singlet oxygen. The antitumor effect of the prepared particle was tested on tumor-induced mice and compared with nude BPQDs. The BPQDs treated mice group showed minimal delay of tumor growth, whereas the mice group treated with the prepared JNPs featured excellent tumor growth delay. Later, it was confirmed that, this sort of activity is due to the Cu^{2+} release. This acts as Fenton like agent against tumor growth. The environmental stability is also high compared to BPQDs [31]. JNPs are concluded as the best catalyst in the study done by Wang et al. in 2015. The catalytic activity of the prepared JNPs through sprout growth technique was evaluated by acid-base deacetalization, i.e., Henry cascade reaction. The functionalization of NH_2 and SO_3H groups on the surface was confirmed by Fourier transform

infrared spectroscopy. Any Janus nanostructures can be functionalized with three or more functional groups. However, the tagging of these two groups on mesoporous silica nanoparticles showed better acidic catalytic activity. Therefore, these JNPs can be used for nanocatalytic applications [32]. The composite Janus nanomaterial synthesized by Zhang et al. in 2021 has concluded that JNP can serve as probe in photoacoustic imaging for the detection of biomarkers and other radicals. The gold nanoparticles were coated with two pH responsive polymers through Surface-initiated atom transfer radical polymerization method. The assembly mechanism of the polymer and the nanoparticle was studied using dissipative particle dynamics (DPD) simulations. Thus prepared JNPs was tested on tumor induced mice model and exhibited high biocompatibility and deeper penetration making them best suitable probe for *in vivo* applications [33]. Ali et al. in 2014 demonstrated a facile method for the fabrication of hybrid JNPs via solvothermal synthesis technique. The magnetic property of the nanoparticle was evaluated by vibrating sample magnetometer and their structures were studied using X-ray Diffractometer. The particles prepared through this route possessed higher surface tunable property and super paramagnetic property with an increased amount of magnetite [34].

Fabrication techniques

There are three major techniques involved in the fabrication of JNPS (Figure 2).

Self-assembly

Self-assembly is a simple and robust strategy that involves a simultaneous arrangement of various di or triblock copolymers to synthesize JNPs. They are categorized under the bottom-up approach since they deal with the built-up of bulk material from monomers [13, 43]. The solubility of the precursors can be adjusted to control the morphology and porous structure. As a result, a range of different configurations can be constructed. The most prevalent form obtained is the dumbbell. Self-assembly was the first known synthesis approach for creating Janus nanoparticles. They are the beneficial synthesis method since the primary and secondary precursors have strong intermolecular interactions. Self-assembly typically involves two sorts of materials: pre-synthesized core nanoparticle and secondary precursor molecule [9]. The second precursor is then allowed to envelope the core by altering the synthesis environment. Depending upon the difference in surface energy between the two materials, three distinct growth modes can be observed: Frank-van der Merwe growth mode (layer-by-layer deposition), Volmer-Weber growth mode (island growth), and Stranski-Krastanov growth mode (combination of the above growth modes) [44]. In case the surface energy of the second precursor is low than the core, then the precursor undergoes Frank-van der Merwe growth mode. When the surface energy of the core is lower than that of the precursor, then it undergoes Volmer-Weber growth mode. Whereas in Stranski-Krastanov growth mode, the precursor primarily undergoes Frank-van der Merwe growth mode followed by Volmer-Weber growth mode after it reaches saturation point (typically means the thickness of the layer). As a consequence of the deposition, JNPs with a broad range of functionalities are generated.

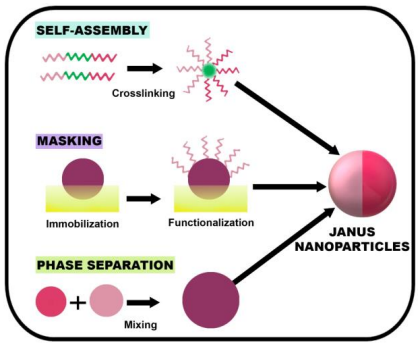

Fig. 2. Fabrication strategies involved for the preparation of JNPs

Wen et al., in 2021, synthesized single-chain JNPs that were then modified to obtain photo responsiveness. The block copolymer with azobenzene was prepared by crosslinking of separate polymer chains and their liquid crystalline behaviour was studied using differential scanning calorimetric technique. These particles are believed to broaden their application in nanomedicine [45]. Kang et al., in 2019, studied the self-assembly behavior of polymers to prepare JNPs, which can carry two different payloads simultaneously. The monomer of siloxane derivative namely TMPT [3-(trimethoxysilyl)- propane-1-thiol] tagged with thiol group was used as a precursor molecule to prepare JNPs. The triblock JNPs featured chemical versatility denoting that the individual structure can be altered with various chemical

reactions. They worked on surface modification of JNPs to obtain micellar structures. The self-assembly behavior and micellar-structured JNP can be utilized for several applications [46]. The research team of Lu et al. in 2018 designed a hollow structure of gold nanoparticles with MPD ligands (3-mercapto-1,2-propanediol) attached to its surface. Biosensing requires high plasmonic circular dichroism (PCD) absorption in the visible region. The prepared JNPs showed increased absorption of PCD and hence can be used for biosensing applications [47]. In 2016, Deng et al. illustrated a facile synthesis of block copolymers based on Polyvinylpyrrolidone by emulsion solvent evaporation induced self-assembly technique. The self-assembled superstructures were efficient in changing and modifying the morphology. The desired superstructures can be formed due to the interfacial and solvent selectivity and this modification is highly affected by the janus balance [35]. Tran et al. in 2015 designed lipid-based JNPs to study the interface potential of the interconnected nanomaterials. The Pluronic F127 stabilized lipid monoolein utilized in this experiment consists of various applications including drug delivery and membrane protein crystallization. The cryo-electron microscopy (cryo-EM) investigations with the data obtained from the SAXS technique were carried out to visualize the structural arrangements. The coexistence of stable and discrete lipid based nanoparticles through self-assembly was first reported [48].

The intense interest in JNP self-assembly has contributed to the emergence of other fabrication processes as well. Fabrication can be accomplished without the requirement of a primary pre-synthesized core nanoparticle using precursors with similar reaction kinetics. Due to their same reaction kinetics, the nuclei formed by both the particle will occur at the same time. This nuclei formation occurs, dropping the surface energy and forming a single Janus particle. Due to the obvious convenience of this approach and the high scalability of the particles formed, a comprehensive investigation of self-assembly fabrication techniques for JNP synthesis has been established.

Masking

Masking is the first-ever method used to prepare JNPs and a majority of JNPs are synthesized using a masking approach. This method works by protecting and modifying the surface of the desired particle and usually yields patchy nanostructures. Asymmetric functionalization on the surface can be accomplished by adhering the particle to a surface/support or entrapping it in the interface of a fluid system. In this method, only the reaction region will be exposed to the environment, while the other half of the hemisphere will be shielded, providing safe functionalization on the desired area alone. Masking is still the most preferred fabrication method since it can construct any sort of material and offers a variety of functionalities. However, in comparison to the self-assembly strategy, it seems to have much lower scalability. This issue can be fixed by using a different platform for entrapment. This usually involves droplets or particles of the colloidal phase to attain a high yield [49]. As a result, the implementation of functional groups for surface modifications is constricted. Pickering emulsion is one of the masking methods which can be employed to resolve this difficulty and ensure a better yield. The yield of the approach can also be determined by the substrates being used. Hard and soft flat substrates are the two major types of substrates intended to immobilize nanoparticles. However, the immobilization can be carried out at the interface between air and water or between two liquids as well. The masking method can be carried out in four ways: (a) masking/unmasking, (b) printing, (c) deposition with the use of reactive fields or fluxes, (d) partial interaction with reaction medium. Kloberg et al. in 2021, constructed a Janus nanoparticle with silica and quantum dots by 2D masking technique using 2D nanosheets as substrate. The use of this substrate allowed the researchers to tag various types of functional groups (both hydrophilic and hydrophobic) without any alteration in their optoelectronic characteristics [49]. Mayol et al. in 2021, reported novel nanotools with gold and mesoporous silica functionalized with glutathione reductase for the release of anticancer agents such as doxorubicin to the tumor site. The nanodevice constructed was an enzyme controlled system which uses AND logic gate (Boolean) for the command. Glutathione disulfide and NADPH were used as input signals. The payload i.e. the anticancer drug gets delivered as output signal as changes in gating procedure due to the production of enzymes during reduction of glutathione [50]. Firozjah et al. in 2020, designed a pH-sensitive Janus nanocarrier with SPION and a polymer using the masking method. The

microgel of PMMA [poly(methyl methacrylate)]-Fe3O4[Iron oxide] -PHEMA [poly(2-hydroxyethyl methacrylate)] were subjected to ultrasound waves to PMMA-Fe3O4-PHEMA. The release rate of methotrexate (MTX) grafted on PHEMA was observed by release kinetics study. The results obtained showed the release at pH 5.8 could be controlled by the hydrolysis of bonds, especially the ester bond and further used as a potential drug carrying system instead of conventional structures such as core-shell [51]. Papan et al., in 2021, developed barium-hexaferrite/Au-JNPs through a pickering emulsion method. This novel particle showed excellent optical and magnetic properties, which can be used for *in vivo* imaging systems [52]. Khoee et al. in 2020 illustrated surface modification of SPIONs with hydrophilic and hydrophobic functional groups such as poly (2-hydroxyethyl methacrylate) (PHEMA) and polydopamine (PDA) that can work as stimuli responsive nanocarrier. The study concluded that this type for carriers would be helpful for cancer therapy [53]. Paniague et al in 2019 has reported the preparation of Janus nanocolloids of gold and mesoporous silica functionalized with biosensing element and capturing element such as horseradish peroxidase and avidin modified SPION@SiO2 respectively. The prepared particles were successfully employed for the study as electrochemical biosensors for carcino-embryonic antigen biomarker detection. The masking method here was helpful for the asymmetric bifunctionalization on the surface [54].

Phase separation

Phase separation is the third basic approach to fabricate JNPs. Originally, they were employed to prepare inorganic materials. However, recent advancements have made it possible to produce organic and hybrid materials as well. The phase separation method is commonly preferred as it allows a wide range of functionalizations on all types of materials, including organic, inorganic, and hybrid. The stability scalability acquired from the particles synthesized through this route is comparatively high. Many studies were using a microfluidic methodology based on the phase separation approach to develop Janus particles on a wide scale because of the peculiar characteristics of fluid at the micron scale level. Urban et al. in 2014, has designed polymer Janus nanoparticles through a phase separation strategy where they demonstrated that the nucleation on each phase was so facile and can be tailored according to the applications [55]. The magnetic JNPs prepared by Teo et al. in 2011 showed reversible behavior, which is demonstrated as the key advantage. This method could fabricate particles with novel symmetries to function as stabilizing agents [56]. Dehghani et al. in 2018, studied the *in vitro* simultaneous release behavior of two drugs from Janus carrier. PHEMA were used as a precursor molecule to fabricate 2-dimethylaminoethylamino methacrylate (DMAEMA) via seed emulsion polymerization technique. To conclude the best suitable morphology for the release of anticancer agents, two morphologies such as Dumbbell and snowman shape were chosen and anticancer drugs such as doxorubicin and ibuprofen were loaded to both the structures. The release rate of both was monitored. The work concluded that the snowman like morphology obtained was stable, and the release of doxorubicin was better and sensitive to stimuli such as pH [57]. Zhang et al. in 2017 fabricated polymeric JNPs in two steps process involving phase separation. The TEM results showed a well-dispersed structures of the particles. The study summarized that this could be a stable, highly efficient, and highly applicable process of synthesis for biomedical applications [58]. Polymeric JNPs constructed via phase separation by Wu et al. in 2016 have shown higher stability without any use of surfactants. Thus, the solubility issues regarding the precursor molecules were resolved [59].

The microfluidic approach based on a phase separation technique can instantly be adjusted to generate larger quantities of granules in a linear fashion. The generated particulates are big due to the comparatively larger diameter of fluidic pathways. The size of these generated particles often ranges from one to hundreds of micrometers, being a great concern and the only reason for limited works under the phase separation technique.

Applications

As discussed, JNPs exhibit various functionalities, including asymmetrical morphology, composition, and higher reactivity. JNPs effectively blend the features of elements, expanding possible outcomes for a wide range of applications (Figure 3). Because there has been a limited investigation on JNPs, their characteristics

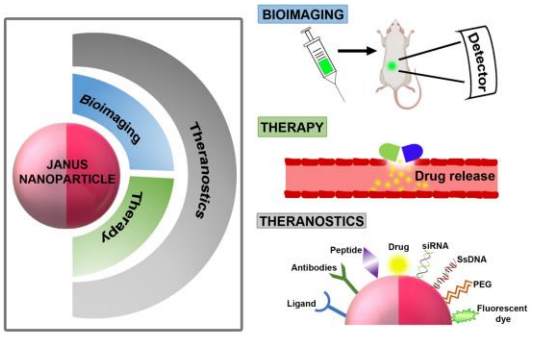

Fig. 3. Biomedical applications of multifunctional JNPs

are not well understood. Surface activity and self-assembly behavior are two of the most important features studied in JNPs.

Cellular delivery

Designing nanostructures for the delivery of therapeutic substances such as bioactive substances or drugs has experienced tremendous growth. Taking advantage of their amphiphilicity and anisotropy, site-specific delivery can be accomplished. Co-administration of drugs or imaging probes is possible due to their functionality difference on two sides. Specific modification on the surface highly influences the tagging and encapsulating multiple components of the same characteristics.

Delivery of bioactive agents

Delivering bioactive agents across the physiological barrier is another issue regarding delivery carriers. The particular carrier molecule must possess better endosomal escape to successfully transport any bioactive agents such as RNA, DNA, or protein. This way, JNPs can escape the biological barriers better compared to conventional carrier molecules. Antiviral therapy usually involves bioactive agents such as siRNA or mRNA. After the covid-19 pandemic, researchers are mostly into the development of antiviral therapy to quickly treat the diseased condition. Recently, Lee et al. developed Janus particles incorporated with RNA therapeutics to deliver across the physiological barriers. The loading of RNA therapeutics was carried out by charge interactions, and the cellular delivery of JNPs was monitored by confocal laser-scanning microscopic investigations. The cytotoxicity assay, RNA expression studies, siRNA knockdown study were clearly carried out to declare that the JNPs serve as the best carrier molecule for antiviral therapy [60]. The bioactive agent functions as therapeutics and is also used in functionalization to facilitate localized administration to target cells in conditions like solid tumors. In accordance with this hypothesis, Khezrian in 2020 developed JNPs functionalized with aptamers to specifically deliver anticancer agents for colorectal adenocarcinoma. The prepared particles were evaluated with various *in vitro* investigations such as cellular uptake study using confocal microscopy, cytotoxicity analysis using cell line etc., to demonstrate JNP as an effective delivery platform [61]. Zhang et al. in 2021, developed dendrimers like JNPs for the transport of mRNA across physiological barriers. The luciferase activity in mice model was quantified in *in vivo* study. The results obtained from *in vivo* and *in vitro* studies showed that Janus dendrimer is an efficient carrier of mRNA [62].

Delivery of drug molecules

Nanoparticles as a carrier molecule were studied by several research groups and declared as a promising way to deliver drugs at the targeted site in a controlled manner. Usually, the drug to be delivered suffers from low efficacy. As a result, tremendous effort is being carried out to develop nanostructures of delicate configurations in order to take complete control over the targeting and release of payload. As aforementioned, because the physiochemical features of JNPs are different in different sites of the same particle, they are indeed the best candidate for shipping the drug moieties to the target site. To study the potential of multifunctional JNPs as a carrier molecule, Shaghaghi et al. in 2019, prepared a pH-sensitive JNP, loaded with doxorubicin for the treatment of cancer. The prepared particle was decorated with folic acid receptors to actively target the brain tumor. The *in vitro* study was conducted on a rat C6 glioma cell line for the confirmation of efficacy and pH responsiveness. The study showed that the prepared JNP was vital for carrying drugs to the brain cortex [63]. Thus, the above study proved that the multifunctional JNP could be an ideal carrier to actively target the desired site by tagging various ligands onto them. The research team of Montoto prepared a stimuli-responsive JNP carrier with gold stars and mesoporous silica particles (AuNSt-MSNP). The study concluded that upon NIR irradiation, the payload entrapped in the carrier molecules was released effectively [64]. The photolabile compound became photo-dissociate

to form the succinic acids inducing the opening of gate-keeper and payload delivery. Llopis-Lorente et al. prepared stimuli-responsive mesoporous silica nanomotors for intracellular delivery. The system equipped with urease enzymes that act as the power supply to nanomotors. The HeLa cell line studies showed increased therapeutic effect and internalization of [Ru(bpy)3] as well as doxorubicin compared with the bulky structure in presence of biofuels urea. The pH responsiveness of the nanomotors made them unique for the site-specific delivery of drugs [65].

Bio-Imaging

The cure rate of any ailments depends on two aspects: early detection and appropriate treatment design, which requires a non-invasive imaging technology with superior spatial resolution. The shortcomings associated with the existing techniques such as X-Ray, Computed tomography (CT), Magnetic Resonance Imaging (MRI), Sonography, etc., need to be addressed to ensure the overall effectiveness of the treatment. The limitation includes cost, quality of resolution, imaging time, the requirement of professional for handling the instrument, availability, and adverse effects. This is the reason for the development of contrast agents (CA) and multimodal imaging. CA, on the other hand, has challenges that make it less preferable. CA does have many detrimental consequences on the biological system. In this quest, nanomaterials were implemented for the betterment of CA. Among the nanostructures, JNPs are anticipated to provide better effectiveness due to the availability of many sites for surface functionalization. In this regard, researchers are working intensively to incorporate the imaging agents with JNP. Wang et al, in 2019, fabricated hybrid JNP with gold nanoparticles and polymers for CT imaging. The prepared particles were coated with folic acids and used as a targeting probe. Cellular uptake studies were conducted, which showed increased fluorescence. The work suggested that the fabricated particle can be used as diagnostic agents and also for therapy [66]. Hybrid bioresorbable JNP was prepared by Tamarov et al. in 2017 was used as a contrast agent for ultrasound imaging that has the ability to generate microbubbles under US radiation [67]. The porous morphology of the particle was introduced by nanostopper techniques to penetrate ultrasound inside them and it offers hydrophobic inner face and hydrophilic outer face. The lifetime of these particles in the systemic blood circulation was greater compared to the standard microbubbles used in sonography. Deka et al. in 2019, prepared manganese-based (MnFe2O4@MnO) JNPs enveloped with PEG (Polyethylene glycol) to increase the stability. This particle has the capability to function as a dual-mode MRI agent. The particle consists of manganese oxide (MnO) and manganese ferrite (MnFe2O4) moieties, which correspond to T1 and T2 contrast, respectively. The r2/r1 ratio justified the dual contrast ability of the MnFe2O4@MnO JNPs. The PEGylation made the particles water soluble and biocompatible for safer biomedical application. The cell viability study was performed with different metal concentrations to evaluate the cytotoxicity using HEK 293 and HEPA 1-6 cell lines. Further to study the efficiency of the particle, *in vitro* and *ex vivo* studies were conducted. All the results showed that the MnFe2O4@MnO JNPs can be an ideal diagnostic agent on MRI for dual T1 and T2 imaging [68].

Theranostic applications

To ease the existing techniques, a newer particle can be developed which could perform both diagnostics and therapy simultaneously. Theranostic applications of JNPs are being studied by various researchers as they provide multiple functionalization and tunable morphology. In this field, Iqbal et al. in 2017 used a solvothermal synthesis route to prepare Janus nanostructures, which were further processed with epitaxial growth and lattice mismatch. Microscopic analyses showed homogenous growth and the prepared JNP were tested as MRI CA and as Photosensitizer (PS) for photodynamic therapy (PDT). The study results demonstrated enhanced MRI contrast on T1 weighted image and extensive property in PDT. Thus, they concluded that the fabricated particles could be used as a flawless candidate in cancer theranostics [69]. Li et al. in 2018 fabricated ternary JNPs with Manganese dioxide (MnO2) and Gold Nanoparticle (AuNp) enveloped with Copper sulfide (CuS). The stability of the particle was enhanced by incorporating polymeric structures. The resultant particle functioned as contrast agents and showed effective CT/MR images alongside potent outcomes in chemo and photothermal therapy (PTT) [70]. Ju et al. in 2017, synthesized monodispersed 12 nm Au-Fe2C

Janus particles and demonstrated as the perfect candidate for cancer theranostics. The particle features a superior agent for triple modal MR/CT/multispectral photoacoustic tomography (MSOT) imaging and guides the PTT. The *in vivo* and *in vitro* studies showed deeper penetration and selective accumulation of affibody conjugated Au-Fe2C JNPs (Au-Fe2C-ZHER2:342) in the tumor tissues than non-targeting JNPs. The *in vivo* experiments on tumor-bearing mouse reveled the PTT efficacy of Au-Fe2C-ZHER2:342 with low side effect during the therapeutic period [71]. Recent research conducted by Li et al. in 2020 demonstrated successful CT-guided chemotherapy and PTT. The synthesis of the Prussian blue@polyacrylic acid/Au aggregate JNPs (PB@PAA/Au-A JNPs) were facile and stable. The doxorubicin-loaded PB@PAA/Au-A JNPs exhibited enhanced tumor inhibition due to the clear images obtained in CT imaging. These investigations established the new generation cancer theranostics using nanostructures [72].

CONCLUSION

JNPs are an intriguing topic since they exhibit some of the ideal properties of all the nanostructures. The morphology of JNPs is diverse, allowing researchers to select the desired design from a variety of alternatives. The surface characteristics are vast and can accommodate a wide range of targeting agents. This review discusses the four major elements of JNPs: morphology, composition, fabrication techniques, and biomedical applications. Designing a single particle with the combination of two distinct particles provides them the peculiar features compared with traditional nanostructures. The catalytic performance is one of the major modules in consideration with their theranostic applications. The optical, chemical, and electric properties of JNPs are much more effective than the other nanomaterials. The amphiphilicity of this range of particles makes them the best suitable candidate for biomedical applications. This article also summaries recent investigations and their outcomes in this field.

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CONFLICT OF INTEREST

The authors declare no competing interests.

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