Janus Particles

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Janus particles have emerged as a novel and smart material that could improve pharmaceutical formulation, drug delivery, and theranostics. Janus particles have two distinct compartments that differ in functionality, physicochemical properties, and morphological characteristics, among other conventional particles.

Keywords: drug delivery ; Janus particle ; formulation

1. Introduction

Janus particles are a special type of nanoparticles or microparticles with surfaces having two or more different physical properties [1]. The term “Janus particle” was coined by Leonard Wibberley in his novel named ‘The Mouse on the Moon’ in 1962 as a science fiction device for space travel [2]. In 1991, Pierre-Gilles de Gennes mentioned the term “Janus” particles in his Nobel lecture, which popularized the term [3]. Janus particles are identified to be advantageous for novel biomedical applications over the past two decades due to their exclusive anisotropic properties, the synergistic ability for combinatorial therapies, and potential multilevel targeting effects [1]. Thus, Janus particles have been developed as an ideal single-carrier system for multiple drugs by dissolving them in solvents of distinct solubilities, which has been attributed to their unique properties of functionalization and asymmetric structure [4].

Janus particles react similarly to amphiphilic molecules with a spatial separation of two physiochemically as well as functionally distinct parts on their surfaces and also within the particles [5]. Thus, a Janus particle can bear hydrophilic groups on one-half of its surface and hydrophobic groups on the other half, resulting in a multicompartmental surface with unique physical and chemical properties [6]. The novel surface of Janus particles makes it possible to incorporate a variety of active ingredients into their structure [7]. Moreover, the simplest form of Janus particles can be developed by dividing the particle into two separate compartments, each composed of distinct materials and/or possessing different functional groups, as well as physical and chemical properties [8]. Consequently, anisotropic or separate compartments can be created on two sides of the particle [9]. In short, Janus particles possess multiple characteristics in terms of chemical composition, shape, polarity, and other physicochemical properties [10]. These unique features of Janus particles enhance their potential applications in various fields, including controlled drug delivery, nanocatalysis, diagnostics, and separation technology [11][12].

In general, Janus particles are classified into polymer-polymer, polymer-inorganic, lipid, metallic, organic-inorganic, organic-organic, and inorganic-inorganic particles based on the materials used for their synthesis [10]. Moreover, Janus particles are synthesized by various techniques, such as solvent evaporation, polymerization, self-assembly, microfluidics, masking, and phase separation [13]. In addition, they can be designed or tuned to have interesting properties, such as magnetic, surface, and optical features [14]. They can also be fabricated to exhibit a wide range of morphologies, including spherical, non-spherical, mushroom, snowman, and dumbbell shapes. Hence, Janus particles are gaining significant attention as promising bio-agents and are fabricated in nano size with uniform distribution [11].

2. Overview of Janus Particles

Janus particles were discovered and developed in the search for a novel drug vehicle that can accommodate multiple drugs via double emulsion systems. This class of particles refers to colloidal particles with anisotropic properties and an asymmetric geometry due to chemical and/or polarity variations [15][16].Cho and Lee (1985) reported and generated the first Janus nanoparticles using poly(methyl methacrylate)-polystyrene composite particles via a seeded emulsion polymerization approach [17]. Subsequently, Casagrande and his team developed spherical glass particles called “Janus beads”, which consist of hydrophobic and hydrophilic hemispheres and exhibit specific properties at their water-oil interfaces, compared with other solid particles [18].

In general, Janus particles are divided into two main groups, such as compartmentalized and patchy forms, based on their morphology. Compartmentalized Janus is a complex particle consisting of various phase-divided domains within a core, whereas patchy Janus particles have precisely controlled patches with different surface structures [19]. The advantageous properties and functions of Janus particles in applications have not been completely exploited due to the complications in the successful synthesis of particles of controlled size, purity, and shape. In addition, the interparticle interaction at fluid interfaces has been identified to be essential for the stability of Janus particles. The advancements in material synthesis and characterization research have led to numerous techniques to produce Janus particles, including solvent evaporation, polymerization, self-assembly, microfluidics, masking, and phase separation.

Structural and Functional Characteristics of Janus Particles

Janus particles are structurally distinguished by the presence of two distinct hemispheres with unique properties, such as morphologies, physiochemical characteristics, and functionalities in a single entity [20]. Numerous Janus particles are recently produced with controllable chemical and topological anisotropy. For example, Janus particles with one hemisphere of cationic surface charge and the other with anionic surface charges were synthesized. This is possible by precise adjustment of the nature and concentration of the monomer under optimized polymerization conditions, resulting in an enriched Janus community with different charges (positive, negative, or neutral). In addition, various fabrication techniques enable the formation of Janus particles with exclusive sizes ranging from the nanoscale to the microscale [21]. For instance, crosslinking and self-assembly methods enable the formation of nano-sized Janus NP, while microfluidic techniques can produce micron-sized Janus formulations [22]. Various fabrication techniques and their significance are briefly discussed in Section 3. Janus particles can be fabricated in a variety of shapes, such as rods, tubes, disks, cylinders, spheres, ellipses, acorn-like shapes, and hamburger-like shapes [22][23]. Their bifunctional properties offer significant opportunities for broad applications in the pharmaceutical and biomedical industries to improve disease diagnosis, increase the efficiency of drug encapsulation and target specific cellular sites [24]. Similarly, Janus particles can also be used in applications, such as textiles, sensors, bioimaging, and catalysis [14].

It is worth noting that different structures of Janus particles can lead to unique physicochemical and functional properties [25]. For example, an inorganic-polymer hybrid can be used to improve the surface functionalization, biocompatibility, and stability of Janus particles [26][27]. Further, Janus particles composed of purely inorganic materials, such as inorganic-inorganic complexes, are promising candidates for biomedical applications as their region-specific functionalization makes them an ideal tool for bioimaging, in vivo diagnostics, delivery, and treatment [28][29][30]. Polymer-polymer hybrids are highly desirable as Janus particles, as they can be easily tuned to exhibit a variety of shapes and surface properties [31]. Winkler et al. (2019) synthesized bicompartmental poly(lactic-*co*-glycol)-(PLGA)/polycaprolactone (PCL) Janus particles for the successful delivery of both hydrophilic and hydrophobic drug molecules. They applied a novel double emulsion technique to encapsulate two drugs with different water solubility into biocompatible Janus particles and deliver them together. They demonstrated staggered release of the drug molecules with independent release kinetics. The staggered release of drugs is particularly advantageous in treatments that require the administration of multiple drugs sequentially at specific rates over a limited period. This allows pre-programmed release characteristics of Janus particles to meet different therapeutic requirements. Results showed excellent encapsulation efficiency (85–94% for hydrophobic and 68% for hydrophilic agents), successful compartmentalization of agents within the carrier to avoid interference, and controlled release of two agents over time [15].

In another study, advances in dual-reacting Janus particles for biomedical applications have been demonstrated by the carriage and release of payloads with stimuli-only behavior. This release pattern cannot be achieved with core-shell or monomorphic nanoparticles. A thermo-reactive polymer named poly(2-hydroxyethyl methacrylate) (PHEMA) and a pH-sensitive polyelectrolyte called poly(2-dimethylaminoethyl methacrylate) (PDAMEMA) were used as carriers for doxorubicin and ibuprofen, respectively. The resultant Janus particles have two different morphologies (snowman-like and dumbbell-like shapes), with different loading capacities for both drugs. The study showed that doxorubicin was rapidly released under low pH conditions due to its high solubility, while the release of ibuprofen was higher under neutral pH conditions (~7.4) [32]. This tunable property is particularly useful for drug delivery and release at specific cellular targets, such as the endoplasmic reticulum and intestine. Thus, it is evident that the drug release by Janus particles is more advanced, compared to other conventional drug release systems, and is beneficial for desired therapeutic applications [33][34][35][36].

Other studies have also shown the promising potential of Janus particles. Studies show gold-nickel Janus nanorods for non-viral delivery of vaccines and genes with higher transfection efficiency [37]; polymer-inorganic Janus particles composed of gold nanospheres and poly(styrene)-block poly(acrylic acid) (PS-PAA) to target tumor cells [38]; and multifunctional Janus nanoparticles based on superparamagnetic iron oxide nanoparticles (SPION) for the treatment of

glioblastoma which suggested that Janus nanoparticles are a potential candidate for the development of new therapeutic formulations and delivery methods for the treatment of brain cancer [39]. Further, Janus nanoparticles of gold-iron oxide are used as imaging agents for in vivo multimodal imaging due to their anisotropic structure [40]; and Janus nanoparticles of gold-mesoporous silica loaded with doxorubicin are used for theranostics and selective chemotherapy in addition to specific imaging and drug release monitoring application [41].

3. Fabrication of Janus Particles

Masking, self-assembly, microfluidic approach, and phase separation are the common methods for the fabrication of Janus particles.

3.1. Masking

Masking is a manufacturing technique based on the chemical alteration of one side or compartment of particles to create asymmetric Janus particles. It is a simple method that allows the coupling of different functional groups to generate Janus particles. In this method, Janus particles are formed when the uncovered hemisphere is masked by chemical reagents, which later trigger their unique properties, or when the particles are confined at the interface of two immiscible mixtures [42]. The masking procedure for the formation of Janus particles consists of four main steps, such as (i) exposure of a hemisphere of homogeneous nanoparticles; (ii) application of masking techniques, such as evaporative deposition and suspension of nanoparticles at the interface of two phases, where the chemically inert “blocking” surfaces can be either solid (e.g., polymer crystal) or liquid (e.g., Pickering emulsion) [8][43]; (iii) chemical modification of particle properties by the masking process; and (iv) removal of the masking agent, resulting in the formation of Janus particles [5].

3.2. Self-Assembly

The self-assembly approach is widely used for the competitive surface assimilation of incompatible ligands, such as hydrophobic and hydrophilic ligands, on particle surfaces and for block copolymer formation, including di- and tri-block copolymers [44][45][46]. Gold nanocrystals with their thiol-binding affinity are widely used to perform competitive adsorption of incompatible ligands onto particles via self-assembly [47]. However, there have been few reports on this type of self-assembly technique. Self-assembly of block copolymers usually occurs by radical polymerization. The process is initiated by preparing the copolymers in an ordinary solvent and modifying the solvent to proceed with the self-assembly process [11][48]. The effectiveness of the self-assembly process can be influenced by several factors, including pH, ionic strength, and temperature [49]. Generally, self-assembly is limited to a few sample quantities, as it is unstable at high concentrations of copolymers. The first tri-block copolymers used to form Janus particles were presented by Erhardt and his team in 2001. They developed Janus particles with a southern and a northern hemisphere along with a cross-linked core using techniques, such as solution casting, cross-linking, and redissolution processes in a selected solvent [50]. The solution casting step has led to the preparation of ABC-type triblock copolymers with embedded spherical domains of the central block, crosslinking the spherical domains and using a good solvent to redissolve the main phase. The results demonstrated an equilibrium between the molecularly dissolved Janus micelles and aggregates. Moreover, Janus particles can be generated by preserving the molecular superstructure of a microphase-separated ABC triblock copolymer are showed.

3.3. Microfluidic

Microfluidics is a method that requires an organic solvent (dispersed phase) to dissolve both hydrophilic and hydrophobic compounds. Later, the dispersed phase is injected into an aqueous phase to create amphiphilic droplets by controlling the flow rate of both the dispersed and aqueous phases. This technique allows equal quantities of different polymers to be encapsulated in the resultant droplet as the dispersing phase exerts the same shear force, resulting in the formation of Janus beads. Subsequently, polymerization is initiated by thermal initiation or UV irradiation [11]. A modified fluidic nanoprecipitation system was used to generate PLGA Janus particles with both hydrophobic and hydrophilic agents in exclusive compartments. The system allowed for a one-step manufacturing approach with two inlets for the Janus components to be introduced into the precipitation stream. In this method, the release properties of hydrophobic agents were improved, compared with monomorphic particles [51]. In addition, a simple droplet-based microfluidic fabrication technique was developed to produce hybrid (gold nanorods @ silver)-polyaniline (PANI) Janus nanoparticles, which was identified to be beneficial as sensors for surface-enhanced Raman scattering application. The technique enabled the production of Janus particles with uniform size, excellent dispersion, and short response time [52].

3.4. Phase Separation

The concept of the phase separation technique is based on an oil-in-water emulsion, where the oil phase consists of two incompatible polymers, that are homogeneously mixed with the help of a co-solvent and dispersed dropwise in a water phase, followed by precipitation of Janus particles after evaporation of the solvent [5][53]. This approach can produce Janus particles with excellent colloidal stability. Liu and team (2013) reported the preparation of non-spherical and amphiphilic Janus particles by a reaction-controlled phase separation technique with kinetic control [54]. A direct synthesis technique to prepare hydrophilic inorganic silica/hydrophobic polystyrene (PS) polymeric Janus particles using a mixture of styrene (St) and octadecyltrimethoxylsilane (ODTS) was developed. The structural features of the particles could be tuned by modification and kinetic control of ODTS hydrolysis and St polymerization. This technique is scalable and applicable to all mixtures, including organic/organic, inorganic/inorganic, and organic/inorganic systems [5]. Emulsion polymerization is a partial phase separation technique that enables colloidal dispersions of latex polymer formulations in water with improved stability. In addition, emulsion polymerization allows better control of the morphological properties of the particles, and the particle size is usually in the range of 0.05 to 1 µm [55][56].

3.5. Factors Affecting the Fabrication of Janus Particles

Several factors must be considered while synthesizing Janus particles with symmetrical compartments, which include the degree of incompatibility and the molecular weights of the two compounds, as well as the interfacial tension at the water-solvent interface. It has been reported that compounds with a high degree of incompatibility and a high molecular weight in addition to a low interfacial tension can produce more symmetric Janus particles [57][58]. Thus, the efficiency of the self-assembly process can be influenced by various factors, such as pH, ionic strength, and temperature. The “Janus equilibrium” is also a significant factor to be considered in the synthesis of perfectly biphasic Janus particles with the desired anisotropic structures [59]. Various fabrication techniques can be used to control the physical properties, surface chemistry, and material composition to produce the desired Janus particles [60]. Nucleation growth and surface nucleation methods are primarily used to generate complex Janus morphologies [61]. Other factors can influence the effectiveness of the various manufacturing processes. For example, the conductivity of polymer masks plays a critical role in achieving evenly distributed compartments on the Janus microspheres [7]. The slow feed rate of the monomers and the high degree of crosslinking are also essential parameters that affect the structure of the resultant anisotropic particles [62].

4. Biomedical Applications of Janus Particles

Recently, several effective drugs have become available on the pharmaceutical market. However, their efficacy in the treatment of common diseases, such as cancer, diabetes, and neurodegenerative diseases is still hampered by factors, including low targeting, systemic cytotoxicity to other normal cells, poor solubility and hydrophobicity, excessive and frequent dosing, and rapid renal filtration [63][64][65]. Therefore, it is crucial to design the drug delivery system at the molecular level to improve its therapeutic indices, targeting, pharmacokinetics, and pharmacodynamics. Hence, Janus particles have been introduced as an effective system for targeted and controlled drug delivery. In addition, they are also used as biomarkers for targeted cancer chemotherapy and various other biomedical applications. **Table 1** provides an overview of various Janus particles that have been extensively studied for other biomedical applications.

Table 1. Janus particles as an effective drug-delivery system for the treatment of various diseases.

Janus Particles	Characteristics Features and/or Performance	References
Hybrid plasmonic-magnetic and biocompatible SiO_2-coated Ag/Fe_2O_3 Janus particles.	• The physical characteristics and functionality of each compartment of the Janus particles demonstrated the potential for clinical applications in thermal therapy, magnetic or optical resonance imaging, and targeting drug delivery. • The in vitro experimental findings indicated their capabilities as biomarkers via specific interactions with tagged HeLa and Raji cells.	[66]

Janus Particles	Characteristics Features and/or Performance	References
Biocompatible Janus particles are made up of poly(lactic-*co*-glycolic acid) (PLGA).	• PLGA Janus particles were generated via one-step fluidic-dependent nanoprecipitation, incorporating nanoprecipitation for hydrophobic and emulsion for hydrophilic drug molecules. • The in vitro studies demonstrated that PLGA Janus nanoparticles were capable of encapsulating multiple pharmaceutical ingredients of different solubilities, such as paclitaxel (hydrophobic) and doxorubicin (hydrophilic) drug molecules, for drug delivery.	[51]
'Handbags-type' Janus particles with 2 separate oil and aqueous cores surrounded by a phospholipid.	• This positively charged Janus particle is comprised of medium-chain triglycerides, lecithin, stearyl amine, and poloxamer 188. • The Janus particles showed effectiveness in carrying both hydrophobic and hydrophilic pharmaceutical ingredients according to the in vitro examinations. • It was developed for DNA condensation and delivery transfection.	[67]
A two-in-one micelle-plex (Janus).	• Both in vitro and in vivo studies showed effective co-delivery of both siRNA and paclitaxel drug molecules to the same cancer site. • A triblock copolymer poly(ethylene glycol)-*b*-poly(ε-caprolactone)-*b*-poly(2-aminoethyl ethylene phosphate) was used to develop the Janus particles. • The findings showed promising results for the combination of SiRNA-based treatment and chemotherapy to trigger synergetic effects.	[68]
Janus nanoparticles with ice-cream coned shape.	• The Janus nanoparticles were synthesized from FDA-approved polymers such as PLGA and polyvinylpyrrolidone, and GRAS-stated lipids such as glycerol behenate and glycerol di-stearate. • The generation steps included emulsification, solvent evaporation, and phase separation. • The in vitro research findings indicated that PLGA/glycerol di-stearate Janus nanoparticles were efficient in carrying both curcumin and doxorubicin to target and treat lung tumors in vitro using A549 human lung tumor cells. No gene or cytotoxic effects were observed. • In vivo study showed the accumulation of Janus nanoparticles in the lungs of mice for at least 24 h after nasal delivery by inhalation, indicating sustained of the drug ingredient.	[69]
Amphiphilic Janus dendrimers.	• Amphiphilic Janus dendrimers were fabricated with one polar and one non-polar compartment for effective bone-targeted drug delivery. • The encapsulation efficiency of naproxen within the Janus dendrimers was 28-fold higher compared to native naproxen. • The Janus dendrimers exhibited a good binding rate of >80% towards the targeting of bone hydroxyapatite with low cytotoxicity in the in vitro study.	[70]

Janus Particles	Characteristics Features and/or Performance	References
Janus particles with differentially degradable compartments.	• The Janus particles were made up of poly(acrylamide-*co*-acrylic acid) and poly(ethylene oxide) (PEO) at one side, and poly(acrylamide-*co*-acrylic acid) and dextran at another side via electrohydrodynamic co-jetting and controlled crosslinking. • Both sides demonstrated to have different degradation kinetics and pH-stimulated degradation, allowing a more effective oral drug delivery to occur, based on in vitro analysis.	[71]
Janus particles for theranostic application.	• The Janus particle was synthesized from a hydrophilic PEI hydrogel-based release compartment and hydrophobic PLGA imaging compartment. • In vitro studies showed that it is a bi-compartmental nanoparticle carrying both diagnostic and therapeutic agents, offering multiple functionalities for biomedical applications.	[72]

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