Nanosized Janus and Dendrimer Particles

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Nanosized Janus and dendrimer particles have emerged as promising nanocarriers for the target-specific delivery and improved bioavailability of pharmaceuticals. Janus particles, with two distinct regions exhibiting different physical and chemical properties, provide a unique platform for the simultaneous delivery of multiple drugs or tissue-specific targeting. Conversely, dendrimers are branched, nanoscale polymers with well-defined surface functionalities that can be designed for improved drug targeting and release. Both Janus particles and dendrimers have demonstrated their potential to improve the solubility and stability of poorly water-soluble drugs, increase the intracellular uptake of drugs, and reduce their toxicity by controlling the release rate.

Keywords: Janus nanoparticles ; drug ; dendrimers ; particles

1. Introduction

Nanoparticles have gained considerable attention among researchers as a potential drug delivery system due to their unique properties, such as their high surface-to-volume ratio and surface charge-dependent behavior, compared to their bulk counterparts [1][2][3]. The properties of nanoparticles depend on their size and shape, which can be tailored by selecting an appropriate synthesis approach [4]. Dendrimers, micelles, liposomes, and biopolymers are the most commonly used drug-delivery nanoparticles [5]. Micelles are colloidal suspensions formed by the dispersion of amphiphilic lipid molecules in a liquid and have a hydrophilic head and a hydrophobic tail [6]. Micelles as a drug delivery system have advantages such as improved solubility of highly lipophilic drugs, controlled drug release, the ability to adjust their physiochemical properties, and protection of the drug from environmental factors. However, they have limitations such as low drug-loading capacity, high dependence on critical micelle concentration, and limited applicability to only lipophilic drugs [7]. Liposomes are small artificial spherical vesicles formed using natural, nontoxic phospholipids and cholesterol and have benefits such as biocompatibility and hydrophilic/hydrophobic characteristics [8]. However, liposomes as a drug delivery system face limitations such as high production cost, limited shelf life, vulnerability to oxidation and hydrolysis of phospholipids in certain conditions, instability, fusion, and potential release of encapsulated drugs [9]. Biopolymers (polymers synthesized or extracted from biological source) have also been used for drug formulation, but they often lack solubility or have pH-dependent solubility, which limits their use [10][11].

Dendrimers are synthetic, tree-like hyperbranched polymers with a high number of functional groups and an open molecular structure. They are designed as artificial macromolecules with void spaces for drug storage and targeted release [12][13][14]. However, dendrimers have limitations such as high non-specific toxicity, drawbacks during scale-up experiments, and low hydro-solubility [15]. Despite these limitations, they have potential as nanoparticles for drug delivery. Janus nanoparticles are a recent addition to the range of nanoparticles, featuring the integration of two or more chemically distinct components into a single structure. They possess unique properties based on their synthesis approaches and the materials infused into the Janus structure [16][17][18][19]. However, the complex synthesis process and toxicity due to chemicals involved in the synthesis approach are limitations of Janus nanoparticles [17][20].

2. Janus Nanoparticles

Janus nanoparticles were first discovered by Pierre-Gilles de Gennes, the Nobel Laureate who pioneered fabricating microparticles ‘Janus grains’ with an apolar and polar side [21]. The word ‘Janus’ comes from the two-faced Roman God of gates, which defines Janus nanoparticles as anisotropic particles that possess two different compartments with varying functionalities, material compositions, morphology, size, shape, and biochemical properties. Janus nanoparticles are originally from polymeride but can be subcategorized as organic/polymeric, inorganic, or hybrid of organic and inorganic Janus particles [22][23][24][25]. In addition to the typical spherical shape, Janus nanoparticles can be fabricated into different conformations, which include rod [26], dumbbell [27], platelet [28], and snowman [29][30].

Due to their asymmetric faces, Janus nanoparticles can improve the stability of different phases [31]. This has then broadened their biomedical and clinical applications from emulsion stabilizer, bio-sensing, bio-catalysis, molecular imaging, and diagnostic tools to pharmaceutical targeted drug delivery systems [32], offering significant benefits over the conventional mono-functional particles. This is highly ascribed to the tunable properties of Janus nanoparticles whereby their different surfaces or compartments can be modified with individual functionality. This includes hybrid particles with one amphiphilic surface and another stimuli-responsive surface [19]; Janus nanoparticles made of organic and inorganic compartments [33]; or biocompatible particles [34] for targeted medical treatments.

This enables Janus nanoparticles to be utilized as delivery carriers to carry different drug molecules with the combination of various functionalities. Otherwise, as a delivery system, one hemisphere can load medical drug molecules while another side acts as a targeting element with high specificity toward targeted cells. Janus nanoparticles have practical medical and environmental applications, such as detecting water contaminants and environmental pollutants and serving as superior candidates for cancer theranostics due to their high loading capacity and tunable properties. Janus nanoparticles made of silver/chitosan have also been reported to exhibit high antimicrobial effects against bacteria such as *Escherichia coli*, *Salmonella choleraesuis*, *Bacillus subtilis*, *Staphylococcus aureus*, indicating their potential applications in food sector [35]. Interestingly, there are Janus nanoparticles used to detect DNA and metals for monitoring applications. A streptavidin-modified retroreflective Janus particle can selectively sense the presence of mercury ions with up to 0.027 nM detection limit [36] whilst a hybrid of gold-silver nanorod and polyaniline has also been developed as a Janus nanoparticle, serving as a surface-enhanced Raman scattering sensor for the detection of mercury [37]. In addition, gold-silver Janus nanoparticles have been exploited as aptasensor to detect toxins such as Ochratoxin A quantitatively, which can be widely used in real systems, including red wine monitoring [38]. The above examples highlight the vast potential of Janus nanoparticles for a broad range of applications, offering numerous benefits to various industries.

3. Dendrimers

The Greek phrase ‘dendron’, which means trees or branches, is the source for the word ‘dendrimer’. Dendrimers are symmetrical, generation-dependent spherical polymers consisting of a core and dendrons (branches), possessing a hyperbranched, three-dimensional structure [13]. In 1941, Paul John Flory and colleagues (Nobel Prize in Chemistry 1974) introduced the theory of highly branched polymers [39][40], which can be synthesized through polycondensation of a monomer with one or more functional groups, avoiding the gelation process [41]. However, it was not stable and are without a cavity. Later, Vogtle and his team (1978) reported the formation of the first non-skid chain-like and cascade-like molecules with the topology of the molecular cavity, which is considered the earliest dendritic polymer form. The term “hyperbranched polymer” was first coined by Kim and Webster in 1988 in reference to the synthesis of soluble hyperbranched polyphenylene. This term was later used to describe the structure of dendrimers [42]. However, these particular types of polymers attract the academy’s attention only with the work of Tomalia et al. (1985) [43] and Newkome et al. (1985) [44]. Further, Tomalia not only coined the term “dendrimer” as made a drastic breakthrough in dendrimers field by forming in a controlled manner using divergent synthesis, poly(amidoamine) (PAMAM) dendrimers with a hollow core in the center and outward branches of tendrils [45]. Currently, there are about 100 dendrimer families, which include beyond poly(amidoamine) (PAMAM) dendrimers, among others, polypropyleneimine (PPI), polyester-, polyamide-, phosphorus, and polyether-based dendrimers [12].

Dendrimers’ molecular mass and size are specifically controlled during the polymerization process, which is not possible during linear polymer formation [46]. The unique molecular architecture of dendrimers results in improved physical and chemical properties compared to traditional linear polymers [47]. In general, dendrimers have a tightly packed spherical structure with excellent rheological properties and low viscosity than linear polymers [48][49]. It’s worth mentioning that the intrinsic viscosity of a dendrimer reaches its peak at the fourth generation as its molecular mass increases [49][50]. The high solubility, miscibility, and reactivity of dendrimers can be attributed to the multiple chain-ends present in their structure [51]. Similarly, the solubility of the dendrimers depends on their surface group, where dendrimers with hydrophilic and hydrophobic terminations are soluble in both polar and nonpolar solvents, respectively [52]. Furthermore, the spherical shape and presence of internal cavities in dendrimers make them ideal for encapsulating desired molecules or drugs within the macromolecules [53]. These novel polymers are further sub-classified into cationic, neutral and anionic dendrimers, based on their surface charge [54]. It is worth noting that cationic dendrimers are cytotoxic and hemolytic, whereas dendrimers with carboxylate surfaces that are anionic are considered nontoxic for a broad range of concentrations [55][56]. However, the properties of dendrimers are significantly influenced by factors such as pH, solvent, precursor salt, and concentration [57]. Moreover, preparation of dendrimer in the nano-regime will further enhance their properties, due to their exceptional high surface-to-volume ratio and unique structure [58][59]. **Figure 1** shows the structural aspects of Janus and dendrimer particles.

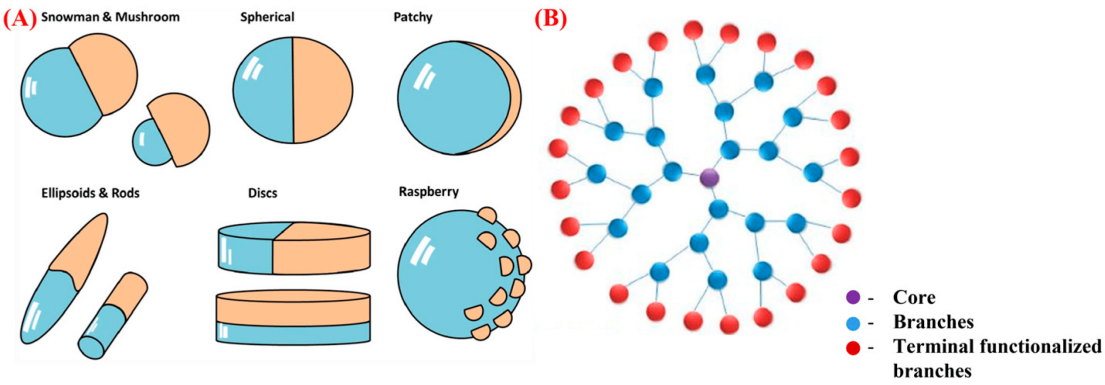

Figure 1. The general structure of (**A**) Janus, Adapted with permission from Honciuc Ref. [60]. Copyright 2019 Springer and (**B**) dendrimer particles, Adapted with permission from Araujo et al. Ref. [61]. Copyright 2018 MDPI.

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