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Review

Small is beautiful: Surprising nanoparticles

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ABSTRACT

In the preparation of nanoparticles for drug delivery, it is well known that their size as well as their surface decorations can play a major role in interaction with living media. It is less known that their shape and internal structure can interplay with cellular and *in vivo* fate. The scientific literature is full of a large variety of surprising terms referring to their shape and structure. The aim of this review is to present some examples of the most often encountered surprising nanoparticles prepared and usable in the pharmaceutical technology domain. They are presented in two main groups related to their physical aspects: 1) smooth surface particles, such as Janus particles, “snowmen”, “dumbbells”, “rattles”, and “onions” and 2) branched particles, such as “flowers”, “stars” and “urchins”. The mode of preparation and potential applications are briefly presented. The topic has a serious, wider importance, namely in opportunity these structures have to allow exploration of the role of shape and structure on the utility (and perhaps toxicity) of these nanostructures.

1. Introduction

Nowadays, the comparison in the literature of nanoparticles (NPs) decorated with specific targeting moieties, biocompatible polymers, cell penetrating, stealth, stimulus-sensitive or imaging agents, to objects such as Swiss army knifes equipped with several blades, corkscrews, scissors, saws, tweezers or toothpicks, is no longer surprising (Fig. 1). On the other hand, naming NPs as Janus particles, dumbbells, snowmen, Mickey Mouse, rattles, yolk-shells, raspberries, onions, stars, flowers or sea urchins, is still rather surprising, at least in the domain of drug delivery, drug targeting or theranostics.

It is well known that the biological activity of NPs is significantly dependent on their size (Shang et al., 2014) and surface decoration. It is less known that the cellular and *in vivo* fate of NPs is influenced by their internal structure and external shape (Ma et al., 2013).

The aim of this article is not to provide an extensive review of the different types of “surprising” NPs, because this could be the topic for a voluminous book. Its aim is to present some examples of the most often encountered surprising NPs, prepared and usable in the pharmaceutical technology domain. These NPs will be presented in two main groups related to their shape: 1) smooth surface particles, such as Janus particles, “snowmen”, “dumbbells”, “rattles”, and “onions”, 2) branched particles, such as “stars”, “flowers” and “urchins”.

2. Smooth surface nanoparticles

2.1. Janus nanoparticles

These NPs have been named after the Roman god Janus whose head is represented bearing two opposite faces (Fig. 2A). Thus, true

Abbreviations: APTMS, 3-aminopropyltrimethoxysilane; Bis-GMA, bisphenol A glycidyl methacrylate; BTME, 1,3-bis(trimethoxysilyl) ethane; CS, chitosan; CTAB, cethyltrimethyl ammonium bromide; CUR, curcumin; DCC, dicyclohexylcarbodiimide; DOX, doxorubicin; DTX, docetaxel; FITC, fluorescein 5(6)-isothiocyanate; FNDs, fluorescent nanodiamonds; FPX, fondaparinux; HA, hyaluronic acid; Hap, hydroxyapatite; HF, hydrofluoric acid; KPS, potassium persulfate; LSPR, localized surface plasmon resonance; MPS, 3-(trimethoxysilyl) propyl methacrylate; MPs, microparticles; MR, magnetic resonance; MRI, magnetic resonance imaging; MRTN, multifunctional theranostic rattle-type nanoparticle; MTT, methylthiazoyltetrazolium; NHS, hydroxysuccinimide; NIR, near-infrared; NIRF, near-infrared fluorescence; NPs, nanoparticles; OA, oleic acid; PAA, poly(acrylic acid); PEO, poly(ethylene oxide); PEO-*b*-PAA, poly(ethylene oxide)-*b*-poly(acrylic acid); P2VN-*b*-PAA, poly(2-vinylnaphtalene)-*b*-poly(acrylic acid); PEG, polyethylene glycol; PGMA, poly(glycidyl methacrylate); PLGA, poly(lactic-*co*-glycolic acid); PMDC, poly(methyl dichloride); PMMA/P4VP, poly(methyl methacrylate)/poly(4vinyl pyridine); PMMA/P4VP, poly(methyl methacrylate)/poly(4vinyl pyridine); PS, polystyrene; PSMA, poly(styrene-alt-maleic); PTX, paclitaxel; PVP, polyvinylpyrrolidone; RITC, rhodamine B isocyanate; SDS, sodium dodecyl sulphate; SERS, surface-enhanced Raman scattering; SPION, superparamagnetic iron oxide nanoparticle; SPR, surface plasmon resonance; St, styrene; TEA, triethanolamine; TEGDMA, triethylene glycol dimethacrylate; TEOS, tetraethoxysilane; TPP, tripolyphosphate; TSD, *N*-[3-(trimethoxysilyl) propyl]ethylenediamine; TX, Triton X-100.

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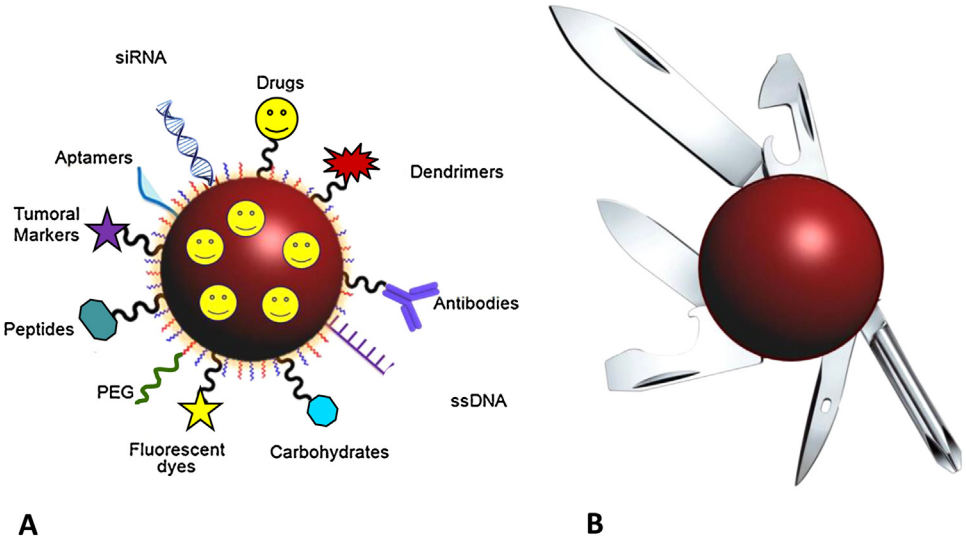

Fig. 1. Decorated nanoparticle (A) compared with Swiss knife (B).

Janus NPs are constituted by asymmetric spheres with two incompatible or different faces, for example hydrophilic (polar) and hydrophobic (non-polar). A number of papers have been devoted to their preparation (Perro et al., 2005; Wurm and Kilbinger, 2009; Tran et al., 2014) that determine their constitution.

Based on recent developments regarding the synthesis and design of Janus nanoparticles, they have attracted increased scientific interest due to their outstanding properties. There are several combinations of multicomponent hetero-nanostructures including either purely organic or inorganic, as well as composite organic–inorganic compounds.

Janus NPs are interconnected by solid state interfaces and, therefore, are distinguished by two physically or chemically distinct surfaces, making them particularly appealing for biomedical applications mainly for theranostics (Schick et al., 2014). A plethora of combinations were described, resulting in structures for instance, being hydrophilic on one side and hydrophobic on the other, conferring versatility in terms of physico-chemical properties such as optical properties based on plasmonic resonance, two-photon activity, as well as magnetic, and superficial properties.

2.1.1. Preparation of Janus nanoparticles

It seems difficult to obtain spherical particles from polymer Janus assemblies. Cheng et al. (2008) reported the preparation of Janus micelles by mixing two diblock copolymers, poly(ethylene oxide)-*b*-poly(acrylic acid) (PEO-*b*-PAA) and poly(2-vinylnaphtalene)-*b*-poly(acrylic acid) (P2VN-*b*-PAA). After intra-molecular complexation of the poly(acrylic acid) (PAA) based polymers, Janus NPs possessing a PEO shell were obtained. Interestingly, the hydrophobic P2VN was on one side whereas the hydrophilic PAA stayed on the other. However, these amphiphilic micelles aggregate in tubular structures. In a more or less similar manner, Yang et al. (2009) prepared amphiphilic diblock codendrimers with Janus faces, constituted of a third generation poly(methyl dichloride) end-capped with 8 hydroxyl groups ($PMDC(OH)_8$) and a second generation poly(urethane amide) end-capped with 4 alkyls groups ($PUA(C16)_4$) which self-assembled at an air/water interface. Anyhow, ribbons and not NPs were obtained. Voets et al. (2006) mixed two aqueous solutions of diblock copolymers: poly (acrylic acid)-*b*-poly(acrylamide) and poly(2-methylvinylpyridinium iodide)-*b*-poly(ethylene oxide) which spontaneously led to the formation of Janus NPs with a disc-like shape . . .

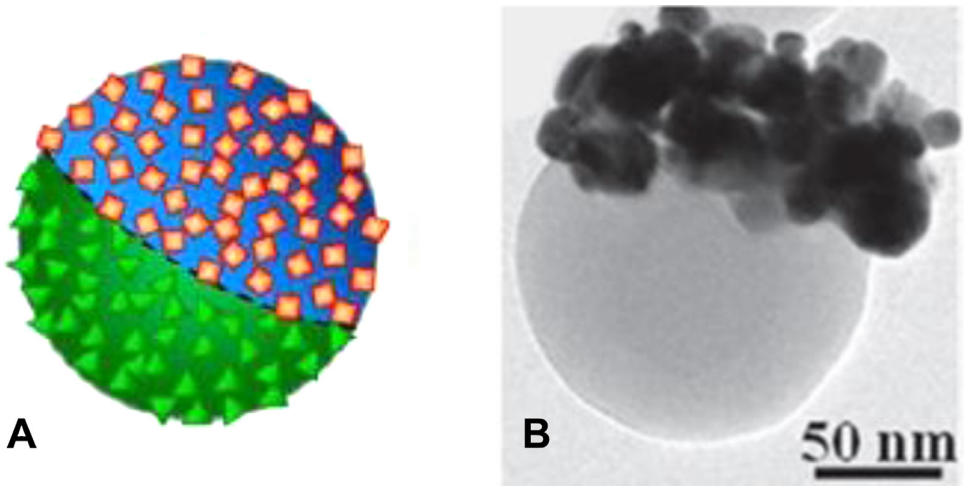

Fig. 2. Janus nanoparticles. (A) Janus nanoparticle, from Chao et al. (2014); with permission from The American Society Publications. (B) Raspberry-like Janus nanoparticle, from Li et al. (2013d) with permission from The Royal Society of Chemistry Publishing.