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Significance of Size, Surface Chemistry and Morphology in Nanodrugs Behavior: A Mini-review

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Abstract

Nanoparticles (NPs) have increasingly captured attention as high potential anticancer drugs over the years. A categorization of this landscape can immensely propel organized comparative research in the future and bring deeper understanding of nanomaterials' comportment in biological settings. Although diverse, all nano platforms pursue similar goals of increasing efficacy in the four domains of oncology known as; diagnosis, treatment, drug delivery, and detection of biomarkers. In this review, we have gathered and provided a class-affiliated rendering of the most recent wet-lab research exploring the impacts of size, surface chemistry, and morphology in various aspects of cancer care. Efforts here are focused on defining parameters for physicochemical properties of NPs and demonstrating variable attributes of them with regard to each. The said goal is achieved by i) grouping NPs under parameters of size, surface properties, and shape, ii) listing major types of NPs within each group, and iii) arranging diverse and well-trusted original research done on cancer control over the past years.

Key words: Nanoparticle, Nanodrug, Physio-chemical properties

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Introduction

The prefix nano—meaning dwarf in Greek, refers to material (particles) within the range of 1-100 nm in at least one dimension. Nanoparticles (NPs) are engineered material at said scale with a wide array of applications, arguably most important of which to be oncology, birthing nanodrugs. This rapidly growing area of research investigates the use of the said platforms in the all domains of various cancers. 2843 papers were published on gynecologic cancers in this area alone through 2004 to 2024 (Gospodinova et al., 2025). Similar studies report 3683 papers on colorectal cancer (M. Lu et al., 2025) and 1624 other solely focused on albumin NPs published over 24 years, averaging 68 papers published per year (Liu et al., 2024). The staggering extent of focus of researchers on this matter highlights a twinkle of hope for NPs to become our go-to tool for treating not only cancer but many other medical conditions. However, this enormous body of research can make it confusing for new audiences. Therefore, the need for an overarching, well-organized picture of the landscape of developed nanotechnologies in oncology is beckoning. Physicochemical properties of NPs determine their behavior during interface with biological systems. Understanding their properties is vital for fit application of varied tools. A requirement to that on the other hand is a comprehensive classification of said properties, arranged in such a way that would lay the ground work for comparative study of different NPs in each modality of cancer therapy based on their nature of interaction with biological systems. The current paper is expected to be lucrative to fresh audiences and lay the ground work for future investigations and picturing a higher resolution image of the research field.

Nanoparticle Properties

What ultimately sets one research done on developing a NP apart from another is the success rate of the particular NP in performing the expected results, tightly associated with the content and arrangement of its constituent elements. The most important form of this arrangement emerges as the particles size being at the nanoscale as opposed to micrometer or bulk dimension. Next comes the morphology of NPs dictating their functionality for different purposes. Porous NPs, for example, are more suited for carrying loads, while different shapes of gold nanoparticles change their surface plasmonic resonance (SPR) value, making them more effective in photothermal therapy (PTT). At last, nature of constituents of NP systems—be pure or modular complexes, determines their chemical effects important in localized targeting and drug internalization, and their physical properties like magnetism and interaction with infrared (IR) light, which are subsequently exploited for different forms of therapy and/or diagnosis.

Size

At the nanoscale, the surface-to-volume ratio factor increases, meaning there is more surface area available compared to the volume that the number of atoms occupies in the space. This simple factor can lead to changes in: magnetism of iron oxides (Lavín Flores et al., 2024), optical bandgap of copper oxides (Zhakypov et al., 2023), black phosphorous (Guo et al., 2016), optical emission of semiconductor Quantum Dots (QDs) (Eroglu et al., 2023), plasmonic resonance of silver, gold, and their alloy (Kshirsagar et al., 2023). However, utilizing any of these effects for biomedical applications requires a thorough understanding of particle behavior in live systems, referred to as nano-bio interactions. At the physiological level, achieving an effective concentration of NPs at the tumor site is a vital index of success. Numerous administration approaches of nanoparticles, such as subcutaneous injection (Jiang et al., 2025), pulmonary (Cojocaru et al., 2024) and oral administration (Y. Lu et al., 2023), and intratumoral injection(Yue et al., 2016), have been developed, most prominent being intravenous (IV) injection

(Deivayanai et al., 2025). However, each may come with a cost ranging from risk of disrupting tumor vasculature to poor absorption in the gastrointestinal tract; thus the correlation between nanoparticle size and suitable administration process is undoubtable. Apart from administration, once entered the body, NPs face a multitude of hurdles. Renal clearance cut-off for particles to pass through the glomerular filtration barrier (GFB) is known to be 6-8nm, meaning particles smaller than this size will most certainly not have enough blood circulation time to accumulate at the cancer inflicted tissue and are cleared by the kidneys (Wang & Liu, 2018). However, reports have been made on particles larger than 100nm to have been found in urine bypassing GFB through Proximal Convoluted Tubules (PCT) specialized for reabsorption of beneficial ions (Curthoys & Moe, 2014; Naumenko et al., 2019; Williams et al., 2015, 2018). Thus, NPs administered through systemic delivery (IV, pulmonary, and oral) methods face the risk of insufficient blood circulation time. Another systemic clearance pathway is the Reticuloendothelial System (RES), a group of phagocytic cells located in liver, spleen, lymph nodes and bone marrow. As the size of NPs increase, macrohpages uptake rate increases disproportionately with a statistically significant value (Soni et al., 2024). This leads to major localization of designed NPs in vital organs like liver, raising long term safety concerns for particles larger than 100nm. Although Korangath et al have demonstrate enhanced tumor accumulation mediated by innate immunity cells (Korangath et al., 2020). In this work, they highlight the dominating effect of RES cells absorbing and carrying these large NPs to the tumor, a localization that was not predominantly a result of direct interaction of antibodies functionalized on the surface of bionized nanoferrite (BNF) NPs and cancer membrane antigens. The diversity in size among different nanodrugs determine the interplay of these with the cell membrane too. There are four major cellular internalization pathways: phagocytosis, macropinocytosis, Caveoleae and Clathrin mediated endocytosis, each of which is size and cell dependent. In a study, the best uptake efficiency was witnessed for 30nm particles by endothelial cells when compared to the uptake rate of 50 and 70 nm particles by fibroblasts and macrophages (Gimondi et al., 2023). In another instance, particles under 50nm were observed to be internalized via Clathrin-mediated pathway, while those within the 50-100nm range were internalized via Caveoleae pathway. Particles within 200-500 were macropinocytosed, and anything beyond that phagocytosed (Murugan et al., 2015). However, these values can overlap and hugely depend on the nature of the NP and the type of the targeted cell as well (Behzadi et al., 2017). Despite these strict conditions, numerous studies have found 50nm spherical NPs to have optimal cellular internalization (Cybulski et al., 2025a; Foroozandeh & Aziz, 2018; Peng et al., 2024; H. Shin et al., 2020; H. J. Shin et al., 2022). This can help as a reference point for quick comparison on the uptake performance of other particles. Ultimately, the size of the particle determines its fate with regard to its interaction and absorption by biological entities, as simplified in Figure 1.

Surface properties

Two of the most basic attributes of NPs' surface are charge and water affinity. Adsorption of proteins onto NPs in biological fluids forms a structure known as Protein Corona (PC) (Lynn et al., 2025). Hydrophobic and charged interactions of serum protein with NPs' surface leads to reversible/irreversible attachment of proteins to them, hampering their biodistribution profile (Bertrand et al., 2017). Surface hydration of NPs is demonstrated to be the solution through different means, from dense coatings of hydrophilic polymers like Polyethylene glycol (PEG) to nanogels and zwitterionic shells to mitigate this effect (Barz et al., 2024).

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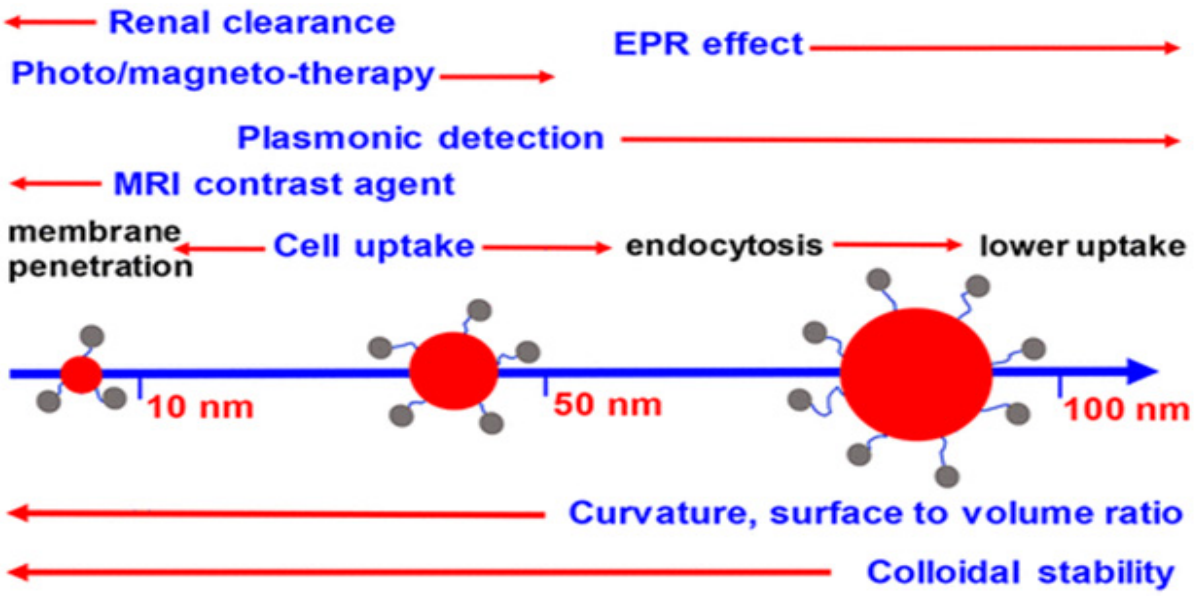

Fig 1. Impact of NP size on biological and chemical behavior at cellular and molecular level. Adapted from (Dolai et al., 2021).

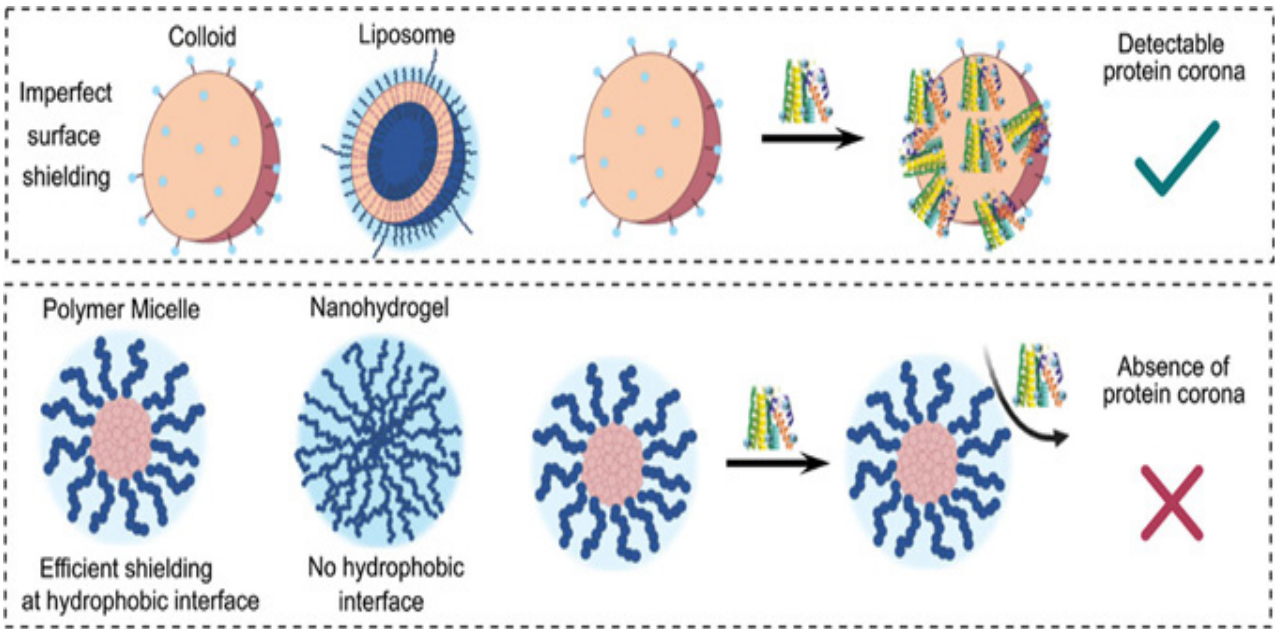

Fig 2. Inhibition of protein corona formation via surface engineering. Adapted from (Barz et al., 2024).

Surface charge of NPs—reflected in their zeta potential- can influence their behavior with cell membrane. In an effort, polystyrene nanoparticles (PS-NPs) were synthesized with spherical shapes and similar sizes ranging from ~20nm to 1 µm for positively charge particles (amine-modified) and negatively charged (carboxylate-modified) PS-NPs ranging from ~40nm to 1.7µm. Expectedly, cellular uptake by human embryonic kidney (HEK 293) revealed particles with zetapotential of +56.7 mV were absorbed more readily due to the opposite charge attractive forces (negative membrane), leading to a comprehensive cytotoxicity gap between them and negative PS-NPs with −41.3 mV electrostatic potential (Moscatiello et al., 2025). Excessive positive charge isn't always beneficial either. Pang and colleagues studied the interaction of +46.5 mV silver NPs coated with branched polyethyleneimine (BPEI AgNPs) with nucleic acids, observing strong attraction due to negative phosphate groups and fragmentation, especially on DNA, leading to genotoxicity, regarded as an alarming side effect for nonregulated delivery of said particle (Pang et al., 2015). Gold nanoclusters (AuNC) of positive and negative charges were set to interact with 20S proteosome—crucial in recycling misfolded proteins. Negative AuNCs were found to stabilize the enzyme's open conformation, rendering them neuroprotective, while positive AuNCs bound to negative sites on the protein and inhibited its function (X. Ma et al., 2020). Therefore, water affinity and surface electrostatic profile of different nanoparticles governs their nano-bio fate in an indiscriminatory fashion, prohibit naked use of such particles, and emphasize the need for more complex delivery techniques. A number of studies have demonstrated enhanced tumor localization using pH-dependent surface charge reversal (AlSawaftah et al., 2022; Sun et al., 2023; Wu et al., 2018).

Morphology and conformation

As discussed, size is the first parameter of different materials that significantly changes the particles' physicochemical properties. Particle's 3D shape can also alter these parameters. Different morphologies influence NPs' isotropy—uniformity of physicochemical characteristics of the particle regardless of orientation, resulting in anisotropy. This effect, in turn, can immensely influence NP's behavior in biological context and therefore its purposeful applicability. Spheres: Reliable cellular uptake (Y. Li et al., 2015), ease of synthesis (Singh et al., 2020). and least surface energy (Agudo-Canalejo & Lipowsky, 2016) make spherical NPs (S-NPs) the most prominent shape among nanodrugs developed so far. The extracellular matrix (ECM) of tumors is a dense, gel-like structure composed of fibrillar collagens (especially type I), adhesive glycoproteins (fibronectin, laminin), proteoglycans and other water absorbing fibers, creating steric hinderance for internalization of NPs. When tested on 3D A549 spheroid models, spherical AuNPs penetrated deeper into the ECM compared to rod-shaped particles, explained by less steric hindrance (Cybulski et al., 2025b). A systematic study had also observed a 2 to 5-fold increase in cellular uptake of S-NPs by human prostate cancer (PC-3) across different serum conditions compared to cubical NPs (Carnovale et al., 2019). Cytotoxicity is a role-defining property of NPs. In therapy, an increase in this effect is favorable; however, makes the safe delivery of particles to cancer tumor vital. While in diagnostics, where NPs are used to encapsulate and deliver signaling probes to tumor site, cytotoxic effects might not be mandatory or even unwanted depending on the case. Seemingly contrary researches, have portrayed morphology-influenced effects differently. Based on findings of (Carnovale et al., 2019) again, at 10µM concentration spherical gold NPs (AuNPS) reduced cell viability of PC-3 to ~70%. Prism-like AuNPs caused cytotoxicity too, especially at values above 10µM, while rod and cubical particles were rendered biocompatible at all concentrations. Yet in the same year, Steckiewicz et al. studied sphere, rod, and star morphologies of AuNPs on 143B (osteosarcoma) and healthy osteoblast cells and reported spherical gold to be the least cytotoxic, especially in normal cells at max concentration of 5µg/ml (Steckiewicz et al., 2019).

Concentration units of the two studies may not match, but when rod AuNPs are considered as a reference point, we can see a complete shift from being biocompatible to lowering 143B cell viability down to 50% in the second study. More recently, the toxicity of the same 3 shapes of PEG coated AuNPs was tested on 3 prostate cancer cell lines: PC-3, LNCaP, and DU145 (Soares et al., 2023). According to cell metabolic activity results, each shape had a distinct cell type-dependent degree of toxicity, with spherical particles still ranking 3rd in toxicity and rods being the most toxic.

Rod or cylindric NPs

Contrary studies have also been published on the superiority of the elongated, filamentous morphology of certain NPs over spheres in cellular uptake. Findings after coincubation of rod-shaped and spherical iron oxide particles with 3 cell types revealed uptake rates in favor of rod-like iron oxide NPs despite being 7 times larger in size (Thamizhchelvan et al., 2024). Other studies have demonstrated the subordination of spherical shape to others according to conditions and the purpose of employment. In systematic absorption of NPs by endothelial cells, short rod mPEG-PCL polymeric NPs showed increased blood vessel permeation (Uhl et al., 2018). Similarly, rod-shaped arrangement of borondipyrromethene (BDP—a biocompatible imaging agent) outperformed spherical micelles, attributed to increased surface area and higher quantum yields (C. Ma et al., 2019). Encapsulation efficiency (EE) is a relative measure of how well a NP is able to absorb valuable material like chemotherapeutics compared to the total amount added to the mixture. Paclitaxel (PTX) is an example of such a drug that is usually encapsulated by porous silica NPs. Over and over, rod morphology of mesoporous silica NPs has demonstrated promise as the most efficient drug carrier (Banerjee et al., 2016; Fan et al., 2024; Fang et al., 2024; Q. Li et al., 2024). Along with factors of size and solvent dielectric, a particle's spatial shape can impact its constituent atoms' conduction electrons, especially in certain metallic elements like gold (Kondorskiy & Lebedev, 2021). This effect becomes of critical matter in photothermal therapy (PTT)— the process of light to heat transformation. Unlike spherical AuNPs, gold nanorods have localized surface plasmonic resonance (LSPR) that resonates with 808nm light. Among all rod AuNPs, only 10×38nm particles yielded ~15°C increase in temperature, emphasizing the importance of aspect ratio under the same conditions of concentration and light intensity (Vikas et al., 2023). Another element of NP's shape is the conformation pattern of its elements. Certain material like carbon nanotubes (CNTs) bolden this effect. When a one-atom-thick sheet of graphene is rolled, a cylindrical rod is achieved with open ends known as single-walled CNT (SWCNT), and it can be enclosed to form a capsule. If multiple layers of graphene are rolled, then multi-walled CNTs (MWCNTs) result. In either case, the angle of rolling the sheet determines the spatial arrangement of carbon atoms within the body of the harvested CNT and yields distinct physicochemical properties of heat and electrical conductivity (Zhang & Li, 2009). An example of chiral semiconducting SWCNT is used for combinational photo-chemotherapy of multi drug resistant (MDR) ovarian cell lines (Bhirde et al., 2014).

Miscellaneous shapes

Nonconventional morphologies of NPs of different nature are seen scattered through the research literature more often than not. Their sizes, purpose of application, and type of cell line they interact with vary and avoid multifunctionality. In drug delivery, for example, Iqbal et al. reports lipid-coated cubical MSN to achieve 84% EE with a huge margin compared to spheres as a result of a higher surface-to-volume ratio but a decrease in cellular uptake due to sharp edges (Iqbal et al., 2024). In magnetic hyperthermia—magnetic NP-mediated generation of localized heat via alternating magnetic field, the same sharp edges

have proven helpful by enhancing the specific absorption rate (SAR) value of Iron oxide NPs (Mai et al., 2019). However, in PTT using AuNPs, the LSPR of cubes is incomparable to prisms, ellipsoids, and especially rods, neither in absorption wavelength nor in intensity (Khajegi & Rashidi-Huyeh, 2021).

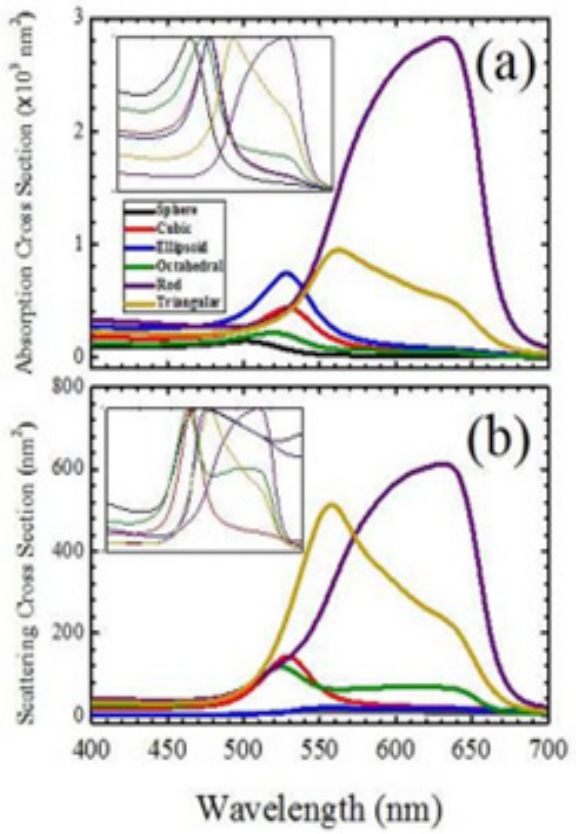

Fig 4. NIR-I absorption and scattering profile of differently shaped gold NPs at different wavelengths. Adapted from (Khajegi & Rashidi-Huyeh, 2021).

In drug deliver, dendrimers appear in various therapeutic and diagnostic studies (Pérez-Ferreiro et al., 2023). Their intense branching sets them apart from conventional tangled bulbs of linear polymers creating well-organized extending space for compartmentalization of various cargo (WOLINSKY & GRINSTAFF, 2008). They are named based on their constituent monomer and the number of branch rings extending outwards, called generation (G), starting with G0 for the core branch. Size grows with generation, thus impacting NP internalization kinetics (Avila et al., 2025).

Dendrimers are hydrophilic, which makes them suitable carriers for hydrophobic agents. However, the ratio of loaded hydrophobic material impacts carriers over all water affinity and decreases uptake in a cell-dependent fashion (Vaidyanathan et al., 2016). Ultimately, the motivation behind the development of the mentioned shapes and many more remains the heterogeneous nature of cancer research, a multiplication of variety in cancer cell lines and treatment/diagnostic methods. The goal is to find essential properties that give rise to the favored quality in different practices. Sharp edges in AuNPs, for example, are correlated with LSPR thus, studies focus on going beyond rods, creating prisms (Carnovale et al., 2019), stars (Su et al., 2023), and bipyramids (Campu et al., 2020) of AuNPs for PTT and photoacoustic (PA) imaging.

Conclusion

In oncology, modern nanodrugs provide remarkable tunability, enabling unprecedented control over their effects compared to conventional agents. As demonstrated, the 3 parameters of shape, surface chemistry, and morphology govern NPs' fate at the biological interface at physiological and cellular levels. Altered size and shape, in particular, also define NPs' reaction to physical triggers like NIR, yielding on-command activation of agents while surface engineering localized them at designated sites. The importance of the nature of constituent atoms of NPs is also self-evident; however, detailed examination of this factor would exhaust this current work and beckon future investigations. In the final analysis, modifying these characteristics enables targeted but interdependent design of smarter and safer drugs, paving the way for more potent treatments with least side effects.

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