

Biophysicochemical Characteristics & Applications of Nanoparticles: Mini Review

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Abstract

In order to successfully prepare and biofunctionalise nanoparticles for a given biomedical application, a wide range of physical, chemical, biological and physiological factors and conditions must be taken into account. However, by tuning the nature of the core, shell and ligands, these factors can be taken advantage of to provide the desired, biocompatibility and biofunctionality, making nanocrystals suitable for a very wide range of applications in diagnostics and therapy for numerous medications. By utilizing carbohydrate ligand –receptors binding can also be beneficial for the future prospects of the many therapeutic applications.

Keywords- Biophysicochemical, Nanoparticles, Nanocrystals.



Pubicon

The Biophysicochemical Characteristics of Nanoparticles

The physicochemical properties of nanoparticles, such as size, geometry/shape, surface charge, surface chemistry, hydrophobicity, roughness, rigidity, and degree of composition, can affect in the differential uptake and/or targeting to certain organs, tissues or cells.⁵⁷

Influence of Nanoparticles size

One of the parameters affecting the cellular uptake rate of nanoparticles is its size as it influences their internalization mechanism, and thus affects the *in vivo* circulation half-life. The two major endocytic mechanisms by which cells take up particles and macromolecules, and these are referred to as phagocytosis and pinocytosis (or fluid-phase uptake)⁵⁸. The phagocytosis mechanisms are responsible for internalization of large particles (41mm), which are present only on phagocytic cells, such as macrophages, neutrophils, or dendritic cells. Therefore, pinocytosis is more relevant to nanoparticle cellular uptake and can occur either via adsorptive pinocytosis (non-specific adsorption of nanoparticle or macromolecules to the cell membrane followed by internalization) or via receptor-mediated endocytosis (RME, which describes the interaction of nanoparticles and macromolecules with receptors, followed by their internalization).^{59,60} Pinocytic mechanisms of uptake can be further divided into caveolae mediated endocytosis or clathrin-mediated endocytosis, as well as clathrin-independent or caveolin-independent endocytosis (smaller nanoparticles can be internalized through a number of these pathways).⁶¹⁻⁶³ Cellular internalization of nanoparticles is majorly dependent on the size of the nanoparticles, and in general, particles in the 40–50 nm range exhibit maximal uptake *in vitro*.⁶²

The accepted size range for the development of nanoparticles is 10–100 nm for *in vivo* applications which relates to their *in vivo* clearance and biodistribution patterns. The main problem with the large nanoparticles is their interactions with the opsonins. The nanoparticles, smaller than approximately 5.5 nm have been shown to be rapidly cleared by glomerular filtration in the kidneys.

Influence of nanoparticles shape

The majority of nanoparticles developed for drug delivery have a spherical shape. In some cases, it was found that spherical nanoparticles had a higher and faster rate of endocytosis compared to rods or disks shaped nanoparticles.⁶⁴

Recent studies have shown that particle shape may be an important factor in the rate of nanoparticle cellular internalization. This is mainly due to the fact that nanoparticle shapes that can accommodate cellular membrane wrapping processes become more effective at cellular uptake.⁶⁴

Nanoparticles, shape are also an important factor for the biodistribution and circulation of nanoparticles, *in vivo*. Geng and Decuzzi *et al.* have reported that non-spherical particles with longitudinal lengths reaching cellular diameters and discoidal shapes can exhibit long circulation times than spherical particles.⁶⁵

Influence of Nanoparticles surface charge

Surface charges of nanoparticles also have an important influence on their interaction with cells and on their uptake. Positively charged nanoparticles have higher extent of internalization, apparently as a result of the ionic interactions established between positively charged particles and negatively charged cell membranes.⁵⁸ Moreover, positively charged nanoparticles seem to be able to escape from lysosomes after being internalized and exhibit perinuclear localization, whereas the negatively and neutrally charged nanoparticles prefer to colocalize with lysosomes⁶⁶

Influence of Nanoparticles hydrophobicity

Hydrophobic surfaces of nanoparticles can be easily binds with opsonins so in order to avoid this interaction by surface modification with hydrophilic polymers. In addition, surface effects such as smooth versus rough surfaces also influence the degree of nanoparticles, surface binding to cells.⁶⁷

Influence of nanoparticles PEGylation

The body recognizes hydrophobic particles as foreign. The reticulo-endothelial system (RES) eliminates these from the blood stream and takes them up in the liver or the spleen. This process is one of the most important biological barriers to nanoparticles-based controlled drug delivery¹⁰. The binding of opsonin proteins present in the blood serum to inject nanoparticles leads to the attachment of opsonized particles to macrophages and subsequently to their internalization by phagocytosis²⁵

In order to avoid these problems, several methods of surface modifications have been developed to produce nanoparticles not recognized by the RES. Nanoparticles can be coated with molecules that hide the hydrophobicity by providing a hydrophilic layer at the surface. The most common moiety for surface modification is the hydrophilic and non-ionic polymer polyethylene glycol (PEG). It has been largely demonstrated that the “PEGylation” increases their blood circulation half-life by several orders of magnitude.²⁵ Moreover, PEG exhibits an excellent biocompatibility. PEG is a highly hydrophilic polymer that ensures prolonged *in vivo* half-lives.

Indeed, uncoated NPs have been observed to be rapidly cleared by the macrophages. The density and thickness of this PEG masking layer have also been found to affect opsonization and distribution of injected nanoparticles, and should be studied with more high-throughput and combinatorial approaches that can reproduce in a reproducible manner, together with a comprehensive

study that combinatorially investigates the interrelation of nanoparticles, PEG lengths and densities leading to reduced clearance.

Another application of surface modification is the targeting of tumors or organs to increase selective cellular binding and internalization through receptor-mediated endocytosis. Targeting ligands are often grafted at the nanoparticles surface via a linkage on PEG chains²⁶ Ligands need to be optimally conjugated on nanoparticles to maintain their affinity for receptors binding. As a sufficient PEG coating is essential for avoiding recognition by the RES, ligands should be extended away from the nanoparticle surfaces to avoid shielding by the PEG chains.

APPLICATIONS OF NANOPARTICULATE DELIVERY SYSTEMS

a. Tumor targeting using nanoparticulate delivery systems

The rationale of using nanoparticles for tumor targeting is based on:

1. Nanoparticles will be able to deliver a concentrate dose of drug in the vicinity of the tumor targets via the enhanced permeability and retention effect or active targeting by ligands on the surface of nanoparticles;
2. Nanoparticles will reduce the drug exposure of health tissues by limiting drug distribution to target organ.⁸¹

Long circulating Nanoparticles

To be successful as a drug delivery system, nanoparticles must be able to target tumors which are localized outside mononuclear phagocytic system - rich organs. In the past decade, a great deal of work has been devoted to developing so-called “stealth particles or PEGylated nanoparticles, which are invisible to macrophages or phagocytes. A major breakthrough in the field came when the use of hydrophilic polymers (such as polyethylene glycol, poloxamines, poloxamers, and polysaccharides) to efficiently coat conventional nanoparticle surface produced an opposing effect to the uptake by the MPS. These coatings provide a dynamic “cloud” of hydrophilic and neutral chains at the particle surface which repel plasma proteins. As a result, those coated nanoparticles become invisible to MPS, therefore, remained in the circulation for a longer period of time. Extensive efforts have been devoted to achieving “active targeting” of nanoparticles in order to deliver drugs to the right targets, based on molecular recognition processes such as ligand-receptor or antigen-antibody interaction. Considering that fact that folate receptors are over expressed on the surface of some human malignant cells and the cell adhesion molecules such as selectins and integrins are involved in metastatic events, nanoparticles bearing specific ligands such as folate may be used to target ovarian carcinoma while specific peptides or carbohydrates may be used to target integrins and selectins.^{82,83}

b. Nanoparticles for oral delivery of peptides and proteins

Significant advances in biotechnology and biochemistry have led to the discovery of a large number of bioactive molecules and vaccines based on peptides and proteins. Development of suitable carriers remains a challenge due to the fact that bioavailability of these molecules is limited by the epithelial barriers of the gastrointestinal tract and their susceptibility to gastrointestinal degradation by digestive enzymes. Polymeric nanoparticles allow encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation. For instance, it has been found that insulin-loaded nanoparticles have preserved insulin activity and produced blood glucose reduction in diabetic rats for up to 14 days following the oral administration.

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c. Targeting of nanoparticles to epithelial cells in the GI tract using ligands

Targeting strategies to improve the interaction of nanoparticles with adsorptive enterocytes and M-cells of Peyer's patches in the GI tract can be classified into those utilizing specific binding to ligands or receptors and those based on nonspecific adsorptive mechanism. The surface of enterocytes and M cells display cell-specific carbohydrates, which may serve as binding sites to colloidal drug carriers containing appropriate ligands. Certain glycoproteins and lectins bind selectively to this type of surface structure by specific receptor-mediated mechanism. Different lectins, such as bean lectin and tomato lectin, have been studied to enhance oral peptide adsorption. Vitamin B₁₂ absorption from the gut under physiological conditions occurs via receptor-mediated endocytosis. The ability to increase oral bioavailability of various peptides (e.g., granulocyte colony stimulating factor, erythropoietin) and particles by covalent coupling to vitamin B-12 has been studied.⁸⁵

d. Nanoparticles for gene delivery

Nanoparticles loaded with plasmid DNA could also serve as an efficient sustained release gene delivery system due to their rapid escape from the degradative endo-lysosomal compartment to the cytoplasmic compartment. Hedley *et al.* reported that following their intracellular uptake and endolysosomal escape, nanoparticles could release DNA at a sustained rate resulting in sustained gene expression. This gene delivery strategy could be applied to facilitate bone healing by using PLGA nanoparticles containing therapeutic genes such as bone morphogenic protein.⁸⁶

e. Nanoparticles for drug delivery into the brain

Strategies for nanoparticle targeting to the brain rely on the presence of nanoparticle interaction with specific receptor-mediated transport systems in the BBB (blood brain barrier). For example polysorbate 80/LDL, transferrin receptor binding antibody (such as OX26), lactoferrin, cell penetrating peptides and melanotransferrin have been shown capable of delivery of a self

non transportable drug into the brain via the chimeric construct that can undergo receptor-mediated transcytosis. It has been reported poly (butylcyanoacrylate) nanoparticles was able to deliver hexapeptide dalargin, doxorubicin and other agents into the brain which is significant because of the great difficulty for drugs to cross the BBB . Despite some reported success with polysorbate 80 coated NPs, this system does have many shortcomings including desorption of polysorbate coating, rapid NP degradation and toxicity caused by presence of high concentration of polysorbate 80.⁸⁷

CONCLUSION

Polymeric nanoparticles have therapeutic potential at both research and clinical levels. In order to successfully prepare and biofunctionalise nanoparticles for a given biomedical application, a wide range of physical, chemical, biological and physiological factors and conditions must be taken into account. However, by tuning the nature of the core, shell and ligands, these factors can be taken advantage of to provide the desired, biocompatibility and biofunctionality, making nanocrystals suitable for a very wide range of applications in diagnostics and therapy for numerous medications. By utilizing carbohydrate ligand –receptors binding can also be beneficial for thefor the future prospects of the many therapeutic applications. We have confidence that with a well characterized system including: safe, effective, and specific targeting ligands, biocompatible, biodegradable and bioeliminable materials, and appropriate choice of therapeutics and disease models, targeted polymeric nanoparticles could yield more effective treatments of important human diseases.

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