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Review Article

Peptide-Based Inorganic Nanoparticle – A Promising Intracellular Drug Delivery System

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ABSTRACT

Peptide-based inorganic nanoparticles (PINPs) have been a preferred system for drug delivery system. This is due to their functional and unique properties. Basically, PINPs are hybrid in nature – biomolecule and inorganic metal (like Fe, Ag) – thus they exhibit high surface area, changeable optical/magnetic properties. This leads to a better biocompatibility, responsive and more targeted. The PIPNs are used in imaging/theragnostic, tailoring targeted delivery of nanomedicines, enhancing stability of drug and improve cellular uptake. Though various advantages present there are still some drawbacks it contains such as in vivo stability, evaluation techniques and immunogenicity. In this review, formulation methods, types and characterization methods have been briefly discussed. We hope, in future PINPs will be significantly used for drug delivery and diagnostics.

INTRODUCTION

Designing, synthesising and manipulating materials to nanometer range (1 to 100 nm) is called nanotechnology. Nanoparticles exhibit high surface area, needed optical and mechanical properties. [1] This enables them to use in various fields such as biomedical, environment etc. In cancer therapy, the chemotherapeutics used has severe toxicity and side effects, it is because of attacking the healthy cells also. Here comes the targeted drug delivery for that these nanoparticles will be great in use. Especially, metal nanoparticle (MNPs) have been greatly used because of their tailorable physicochemical properties (size, surface area, functionality etc.). Widely used MNPs are gold (AuNPs), silver (AgNPs), iron oxide (Fe3O4 NPs), zinc oxide (ZnO NPs) and gadolinium (GdNPs), each having different properties. Recent studies reveals that these MNPs can be functionalised using peptides, drugs and targeting ligands for tumour targeted drug delivery. [2, 3]

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Properties Of MNPs

Size of MNPs

The size of nanoparticles typically in the range of 1 to 100 nm. Minimal change in this range results in high variations in cellular uptake, circulation time, distribution, clearance and toxicity. Thus optimization techniques are employed to achieve the desired size range. [4]

Surface Property

MNPs are greatly employed because of this easy surface modification. Changing the surface characteristics of a MNPs leads to enhanced biocompatibility, highly targetable, increased circular time. MNPs are often functionalized with desired antibodies, peptides and polymers. Silanization, click chemistry, cross-coupling, aldehyde linkers are the few chemical reactions through which the MNPs are functionalized. [5, 6]

Charge on Surface

Surface charge plays a vital role in determining the property of the nanoparticles. It prevents aggregation of nanoparticles by generating repulsive forces. This charge is obtained through the environment present. Amino or hydroxyl groups can be functionalized to surface of a naked nanoparticles to obtain positive or negative surface charge respectively. [7]

Toxicity

MNPs may have very impressive properties but some limitations are there such as toxicity, stability and environmental concerns. Unfunctinalized or poorly stabilized NPs may trigger oxidative stress and inflammatory responses thus limiting their therapeutic value. Integrating the MNPs with suitable peptide will address these issues and low immunogenicity can be achieved. [8]

Peptide In PINPs

Peptides have properties such as structural diversity, intrinsic biocompatibility and target specificity. Peptides can be selected according to the needed delivery goal and can be synthesised to interact with specific tumour cells and receptors. They acts a ligand, which recognize and binds to the targeted diseased receptor which are overexpressed. Some peptides have cell penetrating nature thus improved penetration can be achieved. [9]

Classification of Peptides

(a) Based on Structure

Table 1: Structure based peptides classification

Peptide Class	Structure Property	Application
Linear	Simple amino acid chain without branches	Modification in easy; Used as capping agents; MNPs size and functional can be modified [10]
Cyclic	Cyclization in head-to-tail/adjacently (disulphide/lactam)	Resistant against protease enzyme; Increase stability of NPs; High affinity binding [11]
Amphipathic	Spatially segregated as hydrophobic/hydrophilic residues	Enhance cellular uptakes; Stable MNPs in aqueous; Better membrane penetration [12]
Self-assembling	Form into sequences (beta-sheets)	Stimuli-responsive release can be attained; Hydrogels or Nanofibers can be formed [13]

(a) Based on Function

Table 2: Function based peptides classification

Function	Description	Example
Stabilizing/ capping agents	Binds to metal surfaces and prevents aggregation; Contributes to bio functionality	Cysteine-peptides cap AuNPs by forming Au-S (thiol) bond [14]
Targeting agents	High specificity; Targets overexpressed tumour receptors	CRGDK-AuNPs shows tumour accumulation [15]
Therapeutic agents	Carry therapeutically active or responsive elements	Enzyme-cleavable linkers; AMP [16]
Reducing agents	Metal ions are reduced to NPs	Au^{3+} is reduced to AuNPs [17]

Synthesis Methods Of PINPS

Peptide-Mediated Synthesis

Peptide-mediated synthesis is an upcoming, natural based technique which depended on the structural feature of the peptide and its chemical nature. It can nucleate, reduce and stabilize the metallic nanoparticles. Controlled particle size, morphology and surface functionality can be achieved using this method. [18] Amino acid composition plays a major role in choosing the peptide. It may acts as reducing agent, capping agent or nucleating one. Some commonly used amino acids are cysteine, tyrosine, lysine, histidine and tryptophan they are preferred because of their redox activity and strong affinity. For example, cysteine used to form AuNPs, in which the cysteine plays dual role as a reducing agent, it reduces the gold ions and also it bind to the surface so that particle size and aggregation is limited. [19, 20]

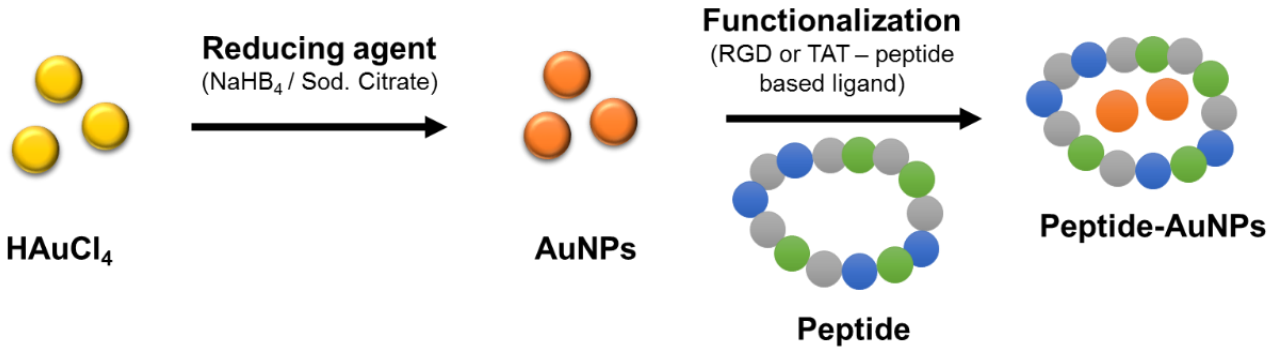

Figure 1: Schematic representation of Peptide-gold NPs synthesis

(a) Conjugation Methods

In this first the MNPs are formed and then modified using functional peptides. Because of this, we can control the orientation of peptide, bioactivity and density. This method is preferred for synthesising stimuli responsive, targeted and multifunctional PINPs. First step involves, the preparation of naked or ligand stabilizes MNPs

(e.g.: AuNPs (gold), FeO, AgNPs) cores. These have reactive surface groups such as amine, carboxyl and hydroxyl and these are conjugated with desired peptides through click chemistry, EDH coupling etc. [21, 22]

(b) One-Pot Green Synthesis

Avoiding synthetic and harsh reducing agents such as sodium borohydride, one-pot green method employs naturally obtained molecules. In this method, the complete process occurs in a single pot under optimal conditions (ambient temperature, aqueous solvent, neutral pH). The modification PINPs can be done by simply changing the conditions such as pH, temperature, concentration of metal ions and peptide. For example, increasing the concentration of peptide results in smaller sized NPs due to rapid surface passivation. Peptide mediated synthesis of PINPs can be reliable and sustainable one which is simple, green and eco-friendly. [23, 24]

Cellular Uptake Mechanisms of Peptide-INPS (PINPS)

PINPs enter the cytosol by various mechanism which can be classified into in-direct and direct way of cellular uptake. Clathrin mediated endocytosis, phagocytosis, caveolae dependent are comes under in-direct entry. Electroporation, passive diffusion, direct microinjection are come under direct entry mechanism. [25, 26] The hydrophobic and the cations plays a major role in cellular uptake mechanism. Lipid bilayer of the cell membrane is disturbed by insertion of hydrophobic molecules and loosen the lipid packing thus membrane permeation is increased. Simultaneously, the cations (e.g. arginine, lysine) makes electrostatic interaction with anionic phospholipids and boost the membrane permeation. This combined action of the two paves way for pore formation or full membrane disruption, helps the NPs to translocate into the cytosol. [27-29]

Application Of PINPs in Drug Delivery

Targeted Delivery

Many delivery agents or carriers have been developed for targeted drug delivery but PINPs has their own benefits to get into the top. Easy modification of the physicochemical properties, high biocompatibility compared to others and dual action of peptide-metal ion NPs. For example, doxorubicin-loaded AuNPs functionalized with RGD peptides have great tumour accumulation and decreased toxicity compared to free drug formulations. AuNPs has photothermal conversion efficiency and high drug loading capacity thus it acts as a great tool for chemo-photothermal therapy. [30, 31] PINPs provide us a reliable and robust platform for targeted drug delivery by combining the benefits of peptides and metal nanocores. Thes hybrid systems helps to reduce side effects, increase therapeutic precision, to develop personalized and image-guided medicine.

Stimuli-Responsive

The diseased site is always differ from the normal condition site in a body, it's because of biological chemical released at the site, when a stimuli-resposive drug delivery system comes into contact with the diseased site, in response to the change (trigger) the drug gets released. Two types of stimuli are present internal (pH, enzymes) and external (light, temperature). [32]

(a) pH-responsive systems

The microenvironment condition of tumour has acidic pH (~ 6.5). Peptides, which are sensitive to acidic environment undergo conformational changes then the drug is released. Histidine

combined AuNPs undergone conformational changes and releases drug at the site. [33]

(b) Redox-responsive systems

High concentration of glutathione (GSH) is present intracellular in cancer cells. This is aa reductive condition thus disulphide-bridged peptides will break in this area which results in intracellular drug release. Paclitaxel loaded AgNPs modified with disulphide bonds showed drug release within tumour cells. [34, 35]

(c) Enzyme-responsive systems

Proteolytic enzymes such as cathepsins, matric metalloproteinases (MMPs) are present highly in the cancer cells. Simply, linking the MNPs with these proteolytic enzyme cleavable molecules will result in site specific drug release upon exposure to these enzymes. [36]

(d) Light and Heat responsive systems

Silver and gold NPs have high surface plasmon resonance (SPR), converts light into heat when exposed to near-IR irradiation. Through photothermal disruption, AuNPs or AgNPs modified using this peptides and drug can release the drug at targeted site. [37]

Limitation of PINPs

Stability

Degradation, opsonisation and aggregation are the common problems arises immediately after introduction of PINPs in the plasma. Even though peptides are biocompatible, they are vulnerable to enzymatic action. Metal core (Au, Ag, Fe) may get oxidised or undergo surface changes, especially on salt (Na^+, K^+) and physiological pH conditions. These interaction results in reduced circulation time, premature drug release, decreased target action and therapeutic efficacy. [38]

Immunogenicity and Toxicity

Peptide alone, biodegradable and less immunogenic but when combined with MNPs they obtain immunogenic properties. Silver and gadolinium metals may release toxic ions or reactive oxygen species, results in cytotoxicity and inflammatory responses. Of all PINPs, AuNPs is the most inert. [39]

Scalability

Industry-scale production of peptides is cost and time consuming. A slight changes in the conditions or quality of material used, results in peptide functionalization capacity reduction. Nanoparticle formation also tedious process, maintaining optimal temperature, pH and reactant ratios is crucial one, to confirm the uniform size, drug loading capacity are achieved. More pilot scale-up study should be done to get a standard process, quality control test and to reduce variations and to conform product reproducibility. [40]

CONCLUSION

PINPs, a fast-growing delivery system in nanomedicine, which is a great fusion of biological peptides and inorganic metals. Peptides help us to increase the biocompatibility, target specific area and also sometimes carry a biological therapeutic action. While, metals such gold, iron oxide, silver act a carrier, a physicochemical property modifier and helps us to diagnose. Addressing the problems such as stability in *in-vivo,* immunogenicity, toxicity of metals and scalability will make PINPs a promising delivery system for cancer treatment. PINPs taking place in theragnostic integration, peptide engineering and AI driven design which results in patient-tailored nanomedicines.

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