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# Nanoparticles in Drug Delivery

Jainu Ajit

## ABSTRACT

Nanoparticles are revolutionizing healthcare by offering innovative ways to achieve target-specific delivery of drugs. They range in size and chemistry and comprise various natural or artificial materials. Among these, inorganic, liposome-based, or polymer-based nanoparticles are extensively studied in generating novel therapeutics and vaccines. Each scaffold provides distinct benefits in terms of the types of cargo it can deliver and its ability to target specific sites. Notably, polymer engineering plays a crucial role in generating stimuli-responsive nanoparticles, significantly advancing tumor targeting. Nanoparticle-based drug delivery provides immense potential for generating novel medicines and vaccines and delivering them across various biological barriers. Moreover, the latest research involves integrating AI models to develop personalized drugs, further minimizing side effects and increasing the efficacy of therapeutics.

**Keywords:** Nanoparticle-based drug delivery, Polymer engineering, Stimuli-responsive nanoparticles, Personalized medicine, Artificial intelligence integration

## Introduction

### Overview of Drug Delivery Challenges

Scientific advancement has led to the generation of numerous drugs to eradicate or cure deadly diseases. The FDA has approved over 20,000 drugs following extensive mechanistic investigation, from cell-based studies to large-scale clinical trials. However, numerous small-molecule medicines that show promising results in cell-based studies fail to be effective in humans. This is mainly due to off-target effects owing to their non-specific nature, leading to decreased efficacy and unwanted side effects. Nanoparticle-based drug delivery approaches solve these problems by providing target-specific controlled delivery of small molecules.

### Advantages of Nanoparticle-Based Delivery Systems

Nanoparticles offer several advantages to drug delivery. They reside in the bloodstream longer than small-molecule drugs, prolonging their lifetime. With their adaptability through appropriate chemical functionalization, nanoparticles can be tailored to interact with specific biological membranes to enable targeted delivery. Apart from tissue-specific delivery, nanoparticles can be modified to be endocytosed by specific immune cells to achieve desired immune reactions. Nanoparticle encapsulation also improves the solubility of hydrophobic drugs, thereby lowering dosage and cost. Together, nanoparticle-based drug delivery is a cost-effective approach to ensuring targeted delivery with minimal side effects, instilling confidence in their potential.

## Types of Nanoparticles Used for Drug Delivery

Nanoparticles are typically 1–1,000 nm in diameter. Their high surface-area-to-volume ratio allows them to have a higher drug-loading capacity and interact more effectively with target cell membranes.<sup>1</sup> There are various types of nanoparticles used for drug delivery and a few are discussed in Figure 1.

### Lipid Nanoparticles (LNPs)

LNPs, a key component in the successful COVID-19 vaccines developed by Moderna and Pfizer/BioNTech, are gaining recognition for their role in mRNA delivery. Their advantages, such as controlled drug release, targeted delivery, reduced cellular degradation, and improved efficacy, have significantly contributed to the success of these vaccines. LNPs, with their cell-membrane-like properties, have played a crucial role in delivering drugs inside target cells.<sup>2</sup>

LNPs are small spherical vesicles composed of lipids. They consist of four main components: ionizable lipid, PEG-ylated lipid, phospholipids, and cholesterol. Ionizable lipids exhibit changes in their overall charge depending on the cellular environment. For example, their ionizable property and positive charge facilitate binding to negatively charged nucleic acids, ensuring higher cargo loading. These neutral constructs then bind to the cell membrane, enabling stable delivery to target cells. After endocytosis, LNPs encounter a low-pH environment in endosomes. This acidic environment allows binding to the endosomal membrane, thereby destabilizing it and releasing its contents into the cytoplasm by carefully evading lysosomal degradation.

Polyethylene glycol (PEG) lipids confer enhanced particle stability by avoiding phagocytosis by increasing hydrophilicity. PEG-ylation creates a hydrophilic shield around the nanoparticle, preventing it from being phagocytosed by immune cells or opsonized by serum proteins. Additionally, LNPs contain two helper lipids to promote stability and delivery efficiency. Phosphatidylcholine is a cylindrical-shaped phospholipid that supports the stability of the LNP bilayer. Cholesterol is another crucial component that ensures the integrity of the LNP and facilitates intracellular delivery.

While LNPs offer many advantages, they also have some limitations. For instance, their large-scale production can be challenging and may cause immune responses in some patients. However, ongoing research is addressing these issues, and LNPs continue to show promise as a drug delivery system. Besides viral infections, recent research shows promising LNPs coated with chitosan with mucoadhesive properties allowing controlled release of Rifampicin to treat tuberculosis.<sup>3</sup>

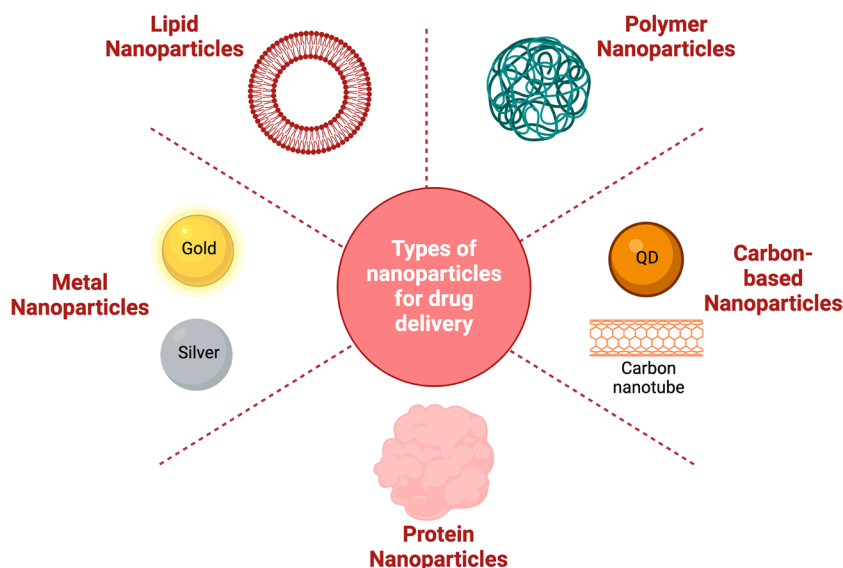


Fig 1 | Schematic showing the different types of nanoparticles including lipid nanoparticles (LNPs), polymer nanoparticles, metal (gold and silver) nanoparticles, carbon-based (quantum dots, or QDs, and carbon nanotubes), and protein nanoparticles. Created in <https://BioRender.com>

### Polymer-Based Nanoparticles

Particles composed of polymers ranging from 1 to 1,000 nm in size are called polymer nanoparticles. These nanoparticles, with their distinct physical properties like size, charge, and degradation rate, are designed with a key focus on biocompatibility. The use of biocompatible polymers ensures minimal immune response, preserving the lifetime of the encapsulated or conjugated drugs. Additionally, polymer engineering enables fine-tuning of the degradation rate. For example, increasing the length and hydrophobicity of the monomeric components can extend the lifespan of a nanoparticle and achieve controlled release of the encapsulated nanoparticle. Stimuli responsiveness can also be achieved using monomers sensitive to physical parameters such as light, temperature, and pH.<sup>4</sup>

There are different types of polymeric nanoparticles based on their shape.<sup>5</sup> Micelles consist of a hydrophobic core and hydrophilic shell. The hydrophobic core facilitates drug encapsulation. Dendrimers are branched and three-dimensional polymeric nanoparticles. Drugs can be attached either to the core of the dendrimer or on the surface. Bigger aggregates formed by the self-assembly of block copolymers are called polymersomes. They are similar to liposomes and can carry both hydrophilic and hydrophobic drugs. Hydrogels also form large networks and contain hydrophilic polymers that can be cross-linked. Nanocapsules and nanospheres are other types of polymeric nanoparticles with varying architectures.

Although polymer nanoparticles can be engineered for target-specific and controlled release of drugs, they also suffer from some limitations. There are currently very few FDA-approved polymer nanoparticles due to toxicity induced by the aggregation of nanoparticles.<sup>6</sup>

To prevent aggregation and promote tumor targeting, Lim et al. performed a comprehensive review and identified key particle parameters. They reported that smaller and cationic nanoparticles aggregate less and are more efficiently endocytosed at the tumor micro-environment. Additionally, surface coatings that exert steric hindrance prevent aggregation.<sup>7</sup>

### Metal Nanoparticles

Nanoparticles made of pure metals like gold, silver, or iron or their compounds make metal nanoparticles. Their unique optical properties allow them to be used in photothermal therapy for cancer. A larger surface area allows conjugation with drugs through various molecular interactions, including electrostatic forces. However, at high concentrations, some metal nanoparticles are toxic and elicit inflammation.<sup>8</sup> Gonzalez et al. recently demonstrated the PEG and silica coating of gold nanoparticles significantly increased stability, reduced toxicity, and improved loading of drugs.<sup>9</sup> Metal nanoparticles also suffer poor solubility, limiting their use in clinical applications.

### Carbon-Based Nanoparticles

The high stability, electrical and thermal conductivity, and ease of functionalization make carbon-based nanoparticles a versatile and inspiring strategy for enhancing drug delivery. They can be of different types, including nanotubes, nanodiamonds, quantum dots, or fullerenes. Carbon nanotubes have garnered much attention in quickly detecting viral pathogens like the coronavirus causing COVID-19.<sup>6</sup> Carbon dots doped with nitrogen and conjugated with paclitaxel through an ester bond induced apoptosis in cancer cells with minimal effects on healthy cells.<sup>10</sup> Carbon nanostructures have also shown promising applications in targeting the brain owing to their small size.<sup>11</sup> However, carbon nanomaterials suffer from a significant drawback, mainly cell toxicity. They damage mitochondria and DNA and generate reactive oxygen species (ROS), leading to apoptosis or programmed cell death.<sup>12</sup> As a result, there are no FDA-approved carbon-based nanomaterials for drug delivery currently.

### Protein Nanoparticles

Nanoparticles composed of proteins such as albumin, fibroin, gelatin, and ferritin are protein nanoparticles (PNPs). Proteins offer unique benefits such as high biocompatibility, less toxicity and immunogenicity, and a longer half-life. PNPs can be surface-modified by incorporating appropriate amino acid monomers with functional groups. This enables control over antigen conformation and spacing and has been recently explored to generate vaccines.<sup>13,14</sup> Wang and colleagues developed a multifunctional peptide nanoparticle for atherosclerosis treatment. Specifically, collagen targeting created steric hindrance preventing platelet adhesion. Simultaneous delivery of rapamycin to the plaques directly showed significant improvement in mice models of atherosclerosis.<sup>15</sup> PNPs offer the unique advantage of directly activating

the immune system structurally and functionally as opposed to synthetic nanoparticles that exert their effects after endocytosis.<sup>16</sup>

Below is Table 1 outlining various types of nanoparticles, their applications, and associated disadvantages to provide a comprehensive overview of current clinical applications.

### Mechanisms of Drug Delivery Using Nanoparticles

Once nanoparticles enter the bloodstream, they form a protein corona by adsorbing various plasma proteins like albumin, fibrinogen, and apolipoprotein. The characteristics of this protein corona can significantly influence nanoparticle lifetime and stability. The nature of the protein corona depends on the surface properties of the nanoparticle, such as the shape, size, and charge.<sup>58</sup>

From the blood, nanoparticles can either reach the target organ or be cleared by different mechanisms like the kidneys, liver, or lymphatic system. Typically,

the kidneys clear nanoparticles smaller than 10 nm in diameter. Phagocytic cells like macrophages clear up nanoparticles around 50 nm in diameter. A diameter of 100 nm is now recognized as optimal for prolonged blood circulation. Besides diameter, various other strategies can be employed to evade clearance mechanisms by enzymatic proteins in the blood. One such mechanism involves coating with polyethylene glycol or PEG-ylation.<sup>6</sup>

For targeted delivery, nanoparticles must evade clearance mechanisms, exit the bloodstream, and bind to specific receptors on the cell surface. In certain cases, blood vessel fenestrations and gaps allow small nanoparticles to extravasate and passively diffuse into nearby organs. Larger nanoparticles decorated with ligands conjugated on their surface undergo transcytosis by binding to specific receptors on the endothelium. They are transported inside endosomes and undergo efferocytosis on the other end, thereby entering target tissues.<sup>59</sup>

**Table 1 | Table showing various recent applications of nanoparticles and their disadvantages**

| Type of Nanoparticle        | Applications                                                                                                             | Disadvantages                                                                                         |
|-----------------------------|--------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Lipid Nanoparticles         | COVID-19 vaccine <sup>17</sup>                                                                                           | Non-specific uptake, causing cytotoxicity <sup>18</sup>                                               |
|                             | Generating in vivo CAR T-cells <sup>19</sup>                                                                             | Pro-inflammatory symptoms <sup>20</sup>                                                               |
|                             | Sustained drug release (aztreonam) for cystic-fibrosis-associated <i>Pseudomonas aeruginosa</i> infections <sup>21</sup> | Instability, leading to degradation and release of RNA <sup>22</sup>                                  |
|                             | Decreasing metastasis in head and neck squamous cell carcinoma <sup>23</sup>                                             |                                                                                                       |
|                             | Remodeling macrophages for treatment of atherosclerosis <sup>24</sup>                                                    |                                                                                                       |
|                             | Increased potency of mRNA vaccine using manganese oxide encapsulated LNPs <sup>25</sup>                                  |                                                                                                       |
|                             | Treatment of hepatitis B infection <sup>26</sup>                                                                         |                                                                                                       |
|                             | Ultrasound-responsive LNPs for treatment of non-small-cell lung cancer <sup>27</sup>                                     |                                                                                                       |
| Polymer-based nanoparticles | Treating bacterial infections using controlled release of erythromycin <sup>28</sup>                                     | Variability among batches <sup>29</sup>                                                               |
|                             | Alleviating established pulmonary fibrosis <sup>30</sup>                                                                 | Lack of standardized in vitro release assays <sup>31</sup>                                            |
|                             | Targeted ovarian cancer therapy <sup>32</sup>                                                                            | Faster drug release than predicted rate <sup>33</sup>                                                 |
|                             | Atherosclerosis treatment <sup>34</sup>                                                                                  | Low translatability between in vitro and in vivo studies <sup>35</sup>                                |
|                             | Dual drug loading for treatment of pancreatic ductal adenocarcinoma <sup>36</sup>                                        |                                                                                                       |
|                             | Enzyme-responsive drug delivery for cancer treatment <sup>37</sup>                                                       |                                                                                                       |
|                             | Multi-branched polymer NPs with antibacterial effects <sup>38</sup>                                                      |                                                                                                       |
| Metal Nanoparticles         | Skin permeable gold NPs for the treatment of inflammatory skin disease <sup>39</sup>                                     | Induces liver toxicity <sup>40</sup>                                                                  |
|                             | Iron oxide nanoparticles against anti-viral infections <sup>41</sup>                                                     | Generating reactive oxygen species (ROS) <sup>42</sup>                                                |
|                             | Treating multi-drug resistant bacteria <sup>43</sup>                                                                     | Damages DNA <sup>44</sup>                                                                             |
|                             | Gold and silver NPs for cancer treatment <sup>45</sup>                                                                   |                                                                                                       |
| Carbon Nanoparticles        | Targeted delivery of tamoxifen for breast cancer treatment <sup>46</sup>                                                 | Initiate inflammatory reactions <sup>47</sup>                                                         |
|                             | Nanorods with near IR responsiveness for cancer treatment <sup>48</sup>                                                  | Batch variations due to size, chirality, and so on <sup>49</sup>                                      |
|                             | Carbon quantum dots with pH sensitivity for anti-cancer effects <sup>50</sup>                                            |                                                                                                       |
|                             | Antibacterial effects when conjugated with levofloxacin <sup>51</sup>                                                    |                                                                                                       |
| Protein Nanoparticles       | pH-sensitive mussel-inspired protein NPs target cancer cells <sup>52</sup>                                               | Heterogeneity in nanoparticle structure and their interactions with cellular components <sup>53</sup> |
|                             | Human serum albumin-based protein NP for brain targeting in glioblastoma <sup>54</sup>                                   | Immunogenicity to proteins <sup>55</sup>                                                              |
|                             | Ferritin NPs for brain targeting <sup>56</sup>                                                                           | Increased manufacturing costs <sup>13</sup>                                                           |
|                             | Apotransferrin and lactoferrin NPs encapsulating doxorubicin in cancer targeting <sup>57</sup>                           |                                                                                                       |

Once nanoparticles reach the target tissue or cell, their degradation is critical in releasing the encapsulated drug. The process of nanoparticle degradation is influenced by factors such as the molecular weight and composition of its components. For instance, the degradation of polymeric nanoparticles made of PLGA is dependent on the molecular weight and functionalization of the polymer components.<sup>60</sup> Understanding and modulating these parameters can confer controlled-release properties and kinetic control of drug delivery.

### Targeted Drug Delivery Mechanisms

#### *Contact-Facilitated Drug Delivery*

Liposome interaction with a target cell membrane enables contact-facilitated drug delivery (CFDD). The interaction is facilitated by electrostatic forces or receptor-ligand binding and is a slow second-order reaction. As a result of persistent interaction, CFDD allows for the efflux of drugs across the nanoparticle membrane to the lipid bilayer of the target cell.<sup>61</sup> Such liposome-based nanoparticles serve as drug depots, allowing slow release of encapsulated drugs. Nanoparticles exhibiting CFDD have been successfully developed for animal models of multiple myeloma, asthma, and cancer.<sup>62</sup>

#### *Passive Targeting*

This targeting strategy involves modulating nanoparticle properties to passively reach target organs, primarily tumors. Small-diameter nanoparticles, between 20 and 200 nm, exhibit the enhanced permeability and retention (EPR) effect and diffuse through blood vessel walls. Tumor vasculature is often defective and contains numerous pores compared to healthy vasculature, allowing targeted delivery. However, passive targeting requires longer half-lives of nanoparticles, evading opsonization, and renal clearance. PEGylation is often used as a stealth coating to avoid immune reactions and clearance.<sup>63</sup>

#### *Active Targeting*

Active targeting involves conjugating drug-loaded nanoparticles with targeting moieties like ligands, antibodies, polysaccharides, or aptamers to recognize specific receptors on target cells. This strategy minimizes off-target effects and decreases cytotoxicity. After binding to the target receptor, nanoparticles undergo endocytosis to enter the cells and undergo lysis to release drugs.<sup>64</sup>

#### *Controlled Drug Release*

Controlled or sustained drug delivery ensures the release of drugs over a defined time to elicit desired immune effects. It is highly beneficial to avoid the need for repeated dosing, such as those needed for vaccinations, thereby improving patient compliance. The controlled release also maintains low dosing levels, ensuring effectiveness while minimizing toxicity due to high concentrations. Drug release rates can be modulated by factors such as the choice of polymer, thickness of coating, and functional groups.

Polymers consisting of polyesters, polyamides, polysaccharides, and poly(amino acids) undergo enzymatic or hydrolytic degradation.<sup>65</sup> Apart from polymer nanoparticles, liposomes complexed with polymers can also be engineered to exhibit sustained release.<sup>66</sup> PLGA is the most commonly used and FDA-approved polymer used for drug delivery. The degradation rate of PLGA nanoparticles depends on the monomers, lactic-acid-to-glycolic-acid ratio, molecular weight, crystallinity, drug encapsulation process, and drug hydrophilicity.<sup>67</sup>

#### *Stimuli-Responsive Release*

External or internal stimuli like temperature, pH, sound, light, electric, and magnetic fields can be harnessed to trigger drug release from responsive nanoparticles. The adaptability of these stimuli makes them versatile tools for drug delivery. Localized application of external stimuli like light, heat, and sound enables precision in targeting, thereby minimizing adverse effects. Internal stimuli like pH are extensively used to develop nanoparticles targeting acidic tumor microenvironments (Figure 2).<sup>65</sup>

### Applications in Medicine

#### *Cancer Therapy*

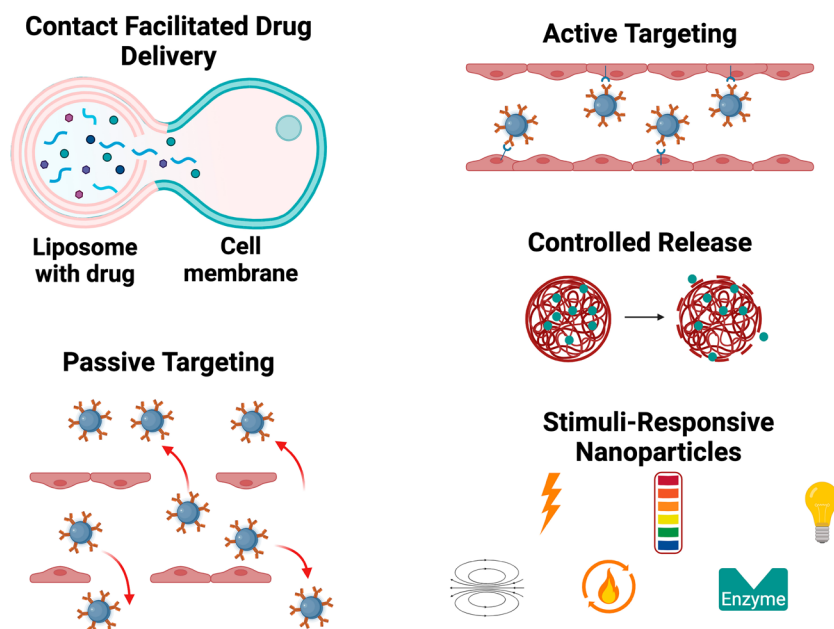
Nanoparticles, particularly pH-sensitive polymers, play a crucial role in cancer therapy. Their ability to target tumors, which have an acidic environment, is well-established. The increased vascular pores and the EPR effect also make tumors accessible through passive targeting. Several FDA-approved nanomedicines, such as Doxil and Onivyde, are PEG-functionalized liposomal nanoparticles designed for various cancer treatments. Abraxane, an albumin-bound nanoparticle formulation, and NBTXR3, composed of hafnium oxide nanoparticles, also target tumors through active or passive targeting.<sup>19–21</sup>

#### *Vaccination*

Vaccination involves administering antigenic material into the human body to generate an antibody response to tackle an infection. Although immunization has successfully eradicated and controlled various deadly diseases, the emergence of new diseases calls for improved engineering efforts to develop efficient vaccines.<sup>68</sup> Antigens can be conjugated or encapsulated within nanoparticles to introduce low amounts to activate the immune system more efficiently. Increased coating and optimizing monomer properties can facilitate sustained release to enhance the duration of immune response and optimal B-cell and antibody generation. Nanoparticle size and functionalization enable phagocytosis by antigen-presenting cells like dendritic cells (DCs). The most recent success with liposomal nanoparticles was the Pfizer/BioNTech and Moderna COVID-19 vaccine.<sup>69</sup>

#### *Gene Therapy*

Gene therapy is widely used to treat or prevent genetic and acquired diseases like cancer, cystic fibrosis, and



**Fig 2 | Different routes of nanoparticle-based drug delivery.** Contact-facilitated drug delivery through liposomes to cell membranes by fusion. Passive targeting is mediated through a disrupted vasculature through which nanoparticles pass through the endothelial membrane into the target tissue. Active targeting follows receptor binding, followed by endocytosis. Controlled-release formulations allow delivery of drugs over time by various routes such as polymer degradation. Stimuli-responsive nanoparticles degrade after applying an appropriate stimulus, such as magnetic field, electric field, temperature, pH, enzymes, or light. Created in <https://BioRender.com>

diabetes. Gene therapy offers long-lasting treatment as it directly targets genes instead of downstream proteins. Recently, the FDA approved Casgevy, a cell-based gene therapy that treats patients with sickle cell anemia. Cationic polymers that bind negatively charged nucleic acids are extensively explored to develop novel gene delivery systems. Chitosan and cyclodextrins can form water-soluble and biodegradable polymers with siRNA molecules. Lipid-based nanoparticles closely resemble cell membrane structures and allow the encapsulation and delivery of mRNA molecules. LNPs encapsulating mRNA was the most recent FDA-approved vaccine for the COVID-19 pandemic.<sup>70-72</sup>

### Chronic Diseases

Nanomedicines offer several advantages over conventional therapies in the treatment of chronic diseases such as cancer, diabetes, and heart disease. These advantages include controlled release, better pharmacokinetics, and limited toxicity. For example, liposomes are employed to deliver insulin due to their unique structure. Similarly, anti-hypertensive drugs can be released over time using lipid and polymeric nanoparticles. Sustained effects are higher for nanoparticles encapsulating steroids to treat airway inflammation. Various nanoparticle formulations have been explored for cancer treatments, prioritizing site-specific, cell-targeting, and sustained-release approaches.<sup>73,74</sup>

### Neurological Diseases

Nanoparticles are used to treat neurological diseases such as brain tumors, Parkinson's disease, Alzheimer's disease, and stroke, despite the significant restrictions imposed by the blood-brain barrier (BBB). One method to bypass the BBB is receptor-mediated transcytosis, a process where nanoparticles are designed to target receptors such as the transferrin receptor specific to the brain vasculature. Upon ligand binding, these nanoparticles enable transcytosis, a process where they are transported across the endothelial cells of the BBB. Using positively charged nanoparticles to adsorb to the negatively charged brain endothelium is another way of surpassing the BBB through adsorptive transcytosis. Small-diameter (15 nm) gold nanoparticles undergo passive diffusion to enter the blood-brain barrier. Brain tumors cause disruptions to the brain vasculature, facilitating nanoparticle transport. While intranasal delivery allows direct access to the brain via the olfactory nerve, sound and light-based transient opening of the BBB provides access to intravenously administered nanoparticles. However, brain delivery suffers from a significant limitation of non-specific delivery, with nanoparticle uptake occurring in the kidneys and liver, causing adverse effects. Research is ongoing to generate multifunctional nanoparticles that improve targeting effects and minimize cytotoxicity.<sup>75</sup>

Table 2 highlights various types of nanoparticles, along with FDA-approved drugs and their respective applications, showcasing their versatility in therapeutic advancements.

### Challenges in Nanoparticle-Based Drug Delivery

Nanoparticles offer numerous advantages over conventional drug delivery, increasing the stability and lifetime of drugs and allowing better targeting, thereby minimizing toxicity. They can also be tailored to achieve a desirable size, charge, and 3D structure suitable for the application. However, several challenges associated with nanoparticle-based delivery need to be addressed.<sup>78</sup>

A new field of study called nanotoxicology is dedicated to examining the occurrence of adverse effects of nanomaterials in humans.<sup>79</sup> Due to their larger surface area, nanomaterials readily adsorb to cellular components, including enzymes, affecting their biological activity. For example, a study performed in BALB/c mice with intraperitoneally administered silver nanoparticles of varying diameters reported increased toxicity associated with the smallest-sized nanoparticles tested (10 nm).<sup>80</sup> Chen et al. reported the systemic biodistribution of polystyrene nanoparticles of different diameters in an inflammatory setting. They reported that the size of nanoparticles affects leukocyte uptake amid the polarization of splenic macrophages.<sup>81</sup> In another study testing the in vivo biodistribution of fluorescent mesoporous silica nanoparticles, the authors showed that short-rod structures accumulated in the liver, whereas long-rod particles distributed in the spleen.<sup>82</sup>

The shape of nanoparticles also alters cytotoxicity. Zhou et al. observed that gold nanoparticles induce

**Table 2 | A list of FDA-approved nanomaterials in medicine**<sup>6,76,77</sup>

| Nanoparticle type           | Drug name  | Disease                                                                            |
|-----------------------------|------------|------------------------------------------------------------------------------------|
| Lipid-based nanoparticles   | Doxil      | Kaposi's sarcoma, ovarian cancer, multiple myeloma                                 |
|                             | DaunoXome  | Kaposi's sarcoma                                                                   |
|                             | AmBisome   | Fungal/protozoal infections                                                        |
|                             | Epaxal     | Hepatitis A                                                                        |
|                             | Amphotec   | Severe fungal infections                                                           |
|                             | Visudyne   | Wet age-related macular degeneration, myopia, ocular histoplasmosis                |
|                             | Onivyde    | Metastatic pancreatic cancer                                                       |
|                             | Vyxeos     | Acute myeloid leukemia                                                             |
|                             | Onpattro   | Transthyretin-mediated amyloidosis                                                 |
|                             | Inflexal   | Influenza                                                                          |
|                             | Myocet     | Combination therapy with cyclophosphamide in metastatic breast cancer              |
|                             | Lipusu     | Ovarian cancer                                                                     |
|                             | Shingrix   | Shingles and post-herpetic neuralgia                                               |
|                             | Onpattro   | Polyneuropathy caused by hATTR                                                     |
|                             | Mosquirix  | Malaria                                                                            |
|                             | Comirnaty  | COVID-19                                                                           |
|                             | mRNA-1273  | COVID-19                                                                           |
| Polymer-based nanoparticles | PegIntron  | Hepatitis C infection                                                              |
|                             | Eligard    | Prostate cancer                                                                    |
|                             | Neulasta   | Neutropenia, chemotherapy induced                                                  |
|                             | Abraxane   | Lung cancer, metastatic breast cancer, metastatic pancreatic cancer                |
|                             | Cimzia     | Crohn's disease, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis |
|                             | Plegridy   | Multiple sclerosis                                                                 |
|                             | ADYNOVATE  | Hemophilia                                                                         |
|                             | Paclical   | Ovarian cancer                                                                     |
|                             | Nanoxel    | MBC, NSCLC, and ovarian cancer                                                     |
|                             | Genexol    | MBC, NSCLC, and ovarian cancer                                                     |
| Metal nanoparticles         | Feraheme   | Anemia related to chronic kidney disease                                           |
|                             | Injectafer | Iron deficiency anemia                                                             |
|                             | Monofer    | Iron deficiency anemia                                                             |
|                             | NanoTherm  | Prostate cancer and glioblastoma multiforme                                        |
|                             | INFeD      | Iron deficiency anemia                                                             |
|                             | DexFerrum  | Iron deficiency anemia                                                             |
|                             | Ferlecit   | Iron deficiency in chronic kidney disease                                          |
|                             | Venofer    | Iron deficiency in chronic kidney disease                                          |
| Protein nanoparticles       | Oncaspar   | Acute lymphoblastic leukemia                                                       |
|                             | Ontak      | T-cell lymphoma                                                                    |
|                             | Eligard    | Prostate cancer                                                                    |
|                             | Abraxane   | Breast cancer                                                                      |
|                             | Kadcyla    | Breast cancer                                                                      |
|                             | Pazenir    | Breast cancer                                                                      |
| Hybrid nanoparticles        | Mircera    | CKD-associated anemia                                                              |
|                             | ADYNOVATE  | Hemophilia A                                                                       |
|                             | Neulasta   | Febrile neutropenia                                                                |
| Carbon-based nanoparticles  | NONE       |                                                                                    |

autophagy in a shape-dependent manner. Autophagosomes were higher when exposed to nanospheres than nanorods.<sup>83</sup> In another study performed in HeLa cells, Gratton et al. observed that nanorods were internalized faster than nanospheres through endocytosis.<sup>84</sup> In another study, Li et al. observed the benefits of using nanorods in exerting superior anti-cancer properties in both in vitro and in vivo studies when compared to other shapes tested.<sup>85</sup>

Long-term toxicity is another drawback arising from biomedical applications of nanoparticles. A study by Coccini et al. evaluated the safety of magnetic iron oxide nanoparticles. These nanoparticles disrupt iron metabolism, inducing toxicity in the central nervous system. Long-term exposure to iron oxide nanoparticles resulted in toxic effects in astrocytes but did not affect neurons. Such studies underline the significance of long-term exposure studies in accessing the safety profiles of newly developed nanoparticles.<sup>86</sup> Another study evaluated the toxicity of clinically relevant concentrations of cobalt, chromium, and titanium nanoparticles in the RAW264.7 macrophage cell line. Only cobalt nanoparticles showed dose-dependent cell toxicity among the samples tested, as assessed by Live/Dead assay and Alamar Blue assay.<sup>87</sup>

Nanoparticles offer versatility in the type of drugs that can be conjugated or encapsulated. However, the physical properties of the final construct made of the same component but encapsulating a different drug vary substantially. The chemical and physical properties of the resulting nanoparticles vary vastly and need to be extensively evaluated before use in humans. For example, the interaction of chemicals with a polymer backbone is very different from that of nucleic acids. These differences influence polymer degradation rate and drug delivery kinetics. Similarly, increasing ligand density to improve targeting might result in complement activation and phagocytosis, initiating an unwanted immune response.

Nanoparticles induce complement activation through various pathways. These include classical pathways (antibody-mediated IgG/IgM), mannose-binding lectin, and alternative pathways.<sup>88</sup> As the nanoparticle size increases, the opsonization probability increases, resulting in greater complement activation. Chonn et al. studied the effects of nanoparticle surface charge on complement activation. They observed increased activation in liposomes with charged phospholipids.<sup>89</sup> Other factors that affect complement activation include topography and drug loading.<sup>88</sup> Hamad et al. recently explored a detailed structure-activity-relationship of nanoparticles with surface-conjugated polyethylene oxide in two conformations—mushroom brush and brush. They reported that changes to polymer architecture regulate the type of complement activation pathway triggered. For example, brush configurations elicit a lectin pathway-based activation, whereas mushroom brush conjugation induces a C1q-dependent classical pathway.<sup>90</sup> Therefore, it is crucial to evaluate every chemical, physical, and biological parameter to ensure

the use of a nanoparticle delivery system relevant to the disease in question.

Another area for improvement of nanoparticle research is better translatability between in vitro cell-based results and in vivo conditions. For example, drug release rates or polymer degradation kinetics performed in PBS differ significantly from those in vivo due to multiple enzymes and other immune and clearance mechanisms. In vitro studies usually use cells maintained in a culture flask with optimum nutrients at 37 °C in a CO<sub>2</sub> incubator. Uptake assays and quantitate analysis are performed using advanced microscopic and flow cytometry methods.<sup>91</sup> However, in vivo uptake of nanoparticles is influenced by various factors such as immune activation, temperature, diffusion, and blood flow. Therefore, in vitro cell-based models studying the uptake efficiency of nanoparticles by a desired cell type will not translate in vivo. Simplified tissue models aid in quantitatively studying the impact of various nanoparticle parameters in drug release and are more advantageous than cell-based models.<sup>92</sup>

Nanoparticle formulation involves complex chemical procedures, such as sonication, homogenization, emulsification, cross-linking, and centrifugation. Precise ratios of monomers and order of addition are crucial to replicating results; therefore, even slight changes in methods can generate very different nanoparticles. The risk of introducing impurities during the manufacturing process that can result in adverse effects further highlights the need for caution. Moreover, the potential antigenicity of certain nanoparticles or their ability to initiate immune responses after binding to the target necessitates careful analysis to ensure the safety of novel nanoparticle formulations. A study conducted across 14 different European laboratories found that different batches of nanoparticles induce variable levels of ROS. This work calls for the use of multiple assays to access free radical formation to eliminate any potential adverse effects.<sup>93</sup>

Poor tissue targeting is another major concern of nanoparticles. During the course of the disease, receptor expression changes, leading to ineffective targeting. Moreover, as nanoparticle engineering continues to alter their shape, size, surface coatings, charge, and so on, they also tend to aggregate, affecting biodistribution.<sup>94</sup> Poor biodistribution and pharmacokinetic profiles further limit targeting efficiency. Additionally, enzymatic degradation and phagocytosis decrease the effective concentration of the nanoparticles reaching the target organ.<sup>95</sup> Zhu et al. studied the enzymatic degradation of polymeric shells around inorganic nanoparticles by chemically conjugating dyes. They observed that degradation depends on various factors such as the type of enzymes encountered, conjugation chemistry, and ligand density. Since the degradation of shell coatings can determine the functionality of the nanoparticle, careful analysis is necessary during the testing phase.<sup>96</sup> Overcoming these challenges could lead to significant advancements in drug delivery, potentially revolutionizing the treatment of various diseases.

## Future Perspectives

### *Nano-Vaccines*

Nano-vaccines consist of nanoparticles that contain components that stimulate the host immune response. Nanoparticle delivery enables targeted delivery, antigen presentation, and sustained immune reaction, generating adequate T-cell and B-cell responses. For the same reasons, nano-vaccines often elicit higher protective responses than soluble proteins.

Mechanism of action of nano-vaccines: Nanoparticles first activate the innate immune system, such as macrophages, neutrophils, monocytes, and DCs. This can be modulated by conjugating appropriate pathogen-associated molecular patterns (PAMPs) on the surface of the nanoparticles. PAMPs are readily recognized by pattern recognition receptors (PRRs) on innate immune cells and are activated, leading to cytokine release. Activated macrophages endocytose larger nanoparticles with a diameter greater than 500 nm, whereas activated DCs uptake smaller-sized particles. Together, these processes initiate an adaptive immune response initiating T-cell and B-cell responses.<sup>16</sup>

A nano-vaccine conjugating a Dectin-1 agonist b-glucan with capsular polysaccharide (CPS) led to an eightfold higher IgG titer than CPS alone.<sup>97</sup> PAMP conjugation also increases immunogenicity, innate immune activation, and lymph node draining. Guo and colleagues observed that b-glucan-conjugated mesoporous silica nanoparticles effectively targeted lymph nodes and stimulated the maturation of DCs without additional adjuvants.<sup>98</sup> Another study by Ramirez et al., also exploited the functionalization of nanoparticles with ligands targeting PRRs to elicit higher responses against HIV-1. Carbohydrate functionalization of polyanhydride nanoparticles encapsulating an HIV-1 antigen upregulated CD40 and CD206 and increased secretion of IL-6 and TNF- $\alpha$  compared to non-functionalized particles.<sup>99</sup> Moreover, multiple studies have identified single-dose nano-vaccines delivering antigens within lipid and silica nanoparticle constructs against plague bacteria and Zika virus.<sup>100,101</sup>

While traditional vaccines are delivered through syringes to transport contents through the dermis, recent research is directed toward developing needle-free vaccines. Nanotechnology enables engineering novel needle-free techniques to increase patient compliance, delivering vaccines through inhalation, oral, and transdermal routes.<sup>102</sup> Needle-free vaccines simplify vaccine delivery, not necessitating the presence of medical professionals, which is very useful in rural areas and military zones. They also decrease pain and fear associated with traditional syringe-based methods. Additionally, reducing the use of needles decreases the spread of blood-borne diseases.<sup>103</sup>

### *Integration with Artificial Intelligence (AI)*

Integration of AI with nanoparticle-based drug delivery has the potential to make significant impacts in the fast development of novel therapeutics. Harnessing features such as predictive modeling, data-driven

analysis, and high-throughput screening accelerates drug discovery. Theoretical predictions by AI expedite the synthesis and testing of novel nanoparticle constructs to develop precise and targeted therapies. AI-controlled robots facilitate the manufacturing process with minimal resources, providing a cost-effective strategy. Additionally, the advent of quantum computation and the capability to predict material behavior from the atomic level significantly improve nanoparticle design.<sup>104</sup>

Recently, Kumari and colleagues utilized an AI-driven design of experiments to optimize lipid nanoparticle formulations for anti-*Helicobacter pylori* activity by improving amoxicillin delivery. This study showed that AI-based methodology improved cost efficiency in determining how factors like lipid and surfactant concentration and sonication parameters modulated particle properties like size, encapsulation efficiency, zeta potential, and polydispersity index.<sup>105</sup> AI and machine learning algorithms can also improve nanoparticle targeting. Chou et al. developed a novel screening tool to improve tumor targeting by integrating an AI-based structure-activity-relationship model with a physiologically based pharmacokinetic model. They validated their model by correlating the results obtained to existing literature reports, demonstrating a cheaper method of screening and testing evading complex animal models.<sup>106</sup> Another study used an AI-generated model to predict experimental conditions to obtain smaller-sized zinc oxide nanoparticles with excellent photocatalytic properties, yet again demonstrating the cost and time benefits.<sup>107</sup>

Automation of the manufacturing process using robots is another emerging field in nanotechnology. Using robots for manufacturing improves accuracy, decreases variability, and is cost-effective. Jiang et al. recently developed an autonomous chemical synthesis robot to discover and synthesize novel nanomaterials with unique properties. They used a fully digitized approach to synthesize nanostructures with desired optical properties.<sup>108</sup> Another study by Dembski and colleagues describes developing a dual-arm robot-based system for the reproducible production of silica nanoparticles. The authors demonstrated a striking 75% reduction in personnel time and cost compared to manual synthesis and increased accuracy and reproducibility.<sup>109</sup> Similarly, Zhao et al. also used a robotic platform to achieve morphological control of gold and double-perovskite nanocrystals with tunable properties.<sup>110</sup>

Besides improving the efficiency of synthesis, AI and machine learning models can help predict nanoparticle toxicity. Liu et al. performed structure-activity-relationships on a dataset of 44 iron oxide nanoparticles in four cell types, which reported high accuracy.<sup>111</sup> Ahmadi et al. recently developed machine learning models to predict nanoparticle toxicity. The model used parameters such as nanoparticle properties, cell responses, and exposure conditions. One of the five tested models could predict nanoparticle toxicity with high efficiency.<sup>112</sup>

Despite significant advances in AI integration, this field also faces major roadblocks. Most machine learning methods need large databases for training and validation. Unfortunately, most reported manuscripts use small databases, lowering prediction capabilities. More research is required to address these shortcomings and effectively utilize existing information for efficient nanomaterial synthesis.<sup>113</sup>

### **Personalized Medicine**

Personalized therapy with nanoparticles is an effective strategy to generate effective patient-tailored treatment. Nanoparticles improve the effect of already existing drugs by conferring targeting and minimal side effects. Factors such as genetic information, comorbidities, and environmental factors influence the pharmacokinetics and pharmacodynamics of drugs. Personalized medicines take such factors into consideration, and nanoparticle engineering allows for more efficient drug delivery than conventional methods. However, this strategy poses serious challenges, mainly due to the need for standard safety parameters to assess potential toxicity.<sup>114</sup> AI integration can further accelerate personalized medicine by rapidly assessing genetic and omics data and identifying novel, patient-specific biomarkers.<sup>104</sup>

There are several avenues where nanoparticles can benefit personalized treatment approaches. One avenue eliminates the need for repeated dosing by incorporating controlled-release platforms in nanoparticle design, thereby increasing the bioavailability of the drug. For instance, Bagheri et al. developed mesoporous silica nanoparticles capable of targeted delivery of doxorubicin. They observed better biodistribution and anti-cancer efficacy using nanoparticles than free doxorubicin in C26 tumor-bearing mice due to enhanced tumor accumulation.<sup>115</sup> Additionally, transdermal patches are an alternative to patients who struggle with oral consumption of drugs. Personalized treatments may also involve the simultaneous delivery of multiple drugs, which can be easily achieved by nanoparticles. Shuhendler and colleagues demonstrated a synergistic effect of delivering both mitomycin C and doxorubicin in polymer lipid hybrid nanoparticles. The new construct significantly lowered multi-drug resistance at lower dosages, thereby improving anti-cancer effects.<sup>116</sup>

Developing hybrid nanoparticles is another route to achieving targeted delivery, multifunctional capability, and patient-specific treatment. Hybrid nanoparticles are derived from at least two different nanoparticles, overcoming individual limitations, and conferring unique advantages. Tiriyaki and colleagues developed an enzyme-responsive hybrid nanoparticle composed of organic polymers, dextran, and dextran aldehyde, to coat inorganic silica aerogels. This biocompatible construct was further coated with targeting ligands to deliver 5-fluorouracil to the colon, successfully evading upper gastrointestinal regions.<sup>117</sup> Hybrid nanoparticles can also be engineered to deliver multiple drugs. For example, Chen and colleagues successfully

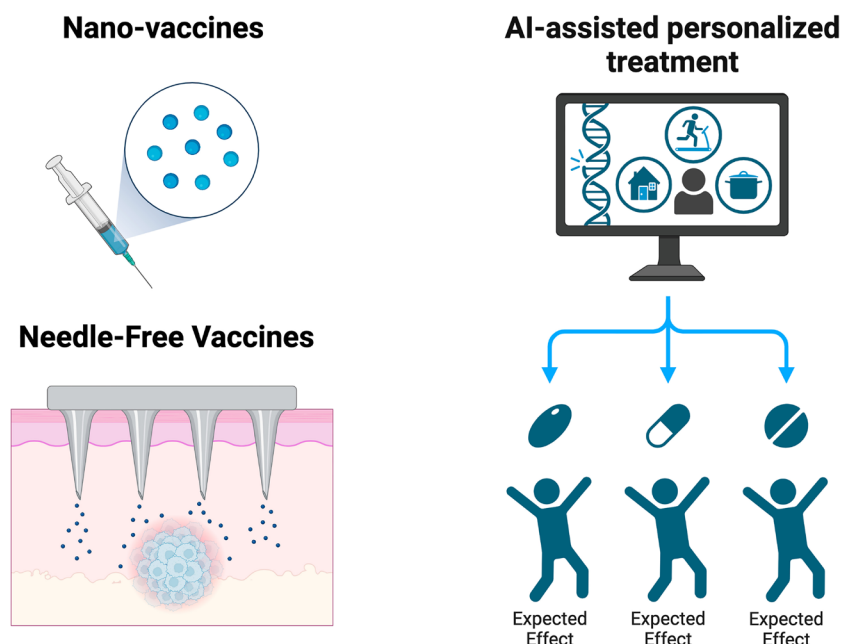


Fig 3 | Future of nanoparticles—development of novel nano-vaccines including needle-free vaccines. AI-based integrative models accelerate the generation of personalized medicines. Created in <https://BioRender.com>

developed a lipid-polymer hybrid nanoparticle to treat prostate cancer and simultaneously delivered curcumin and cabazitaxel to achieve synergistic effects in tumor growth inhibition.<sup>118</sup>

The use of in vitro engineered tissue models enhances the development of personalized medicine by enabling precise evaluation and optimization of nanoparticle transport and performance, ensuring that treatments are tailored to individual patient needs.<sup>119</sup> Analysis of nanoparticle behavior using advanced models enables high-throughput and cost-effective alternatives over conventional cell-based methods. Sun et al. review the testing of nanoparticle efficacy in multi-cellular spheroids, hydrogels, and composite tissue models.<sup>92</sup> Such innovative approaches bridge the gap between preclinical studies and clinical applications, enabling patient-specific nanoparticle-based therapies (Figure 3).

### Conclusion

Nanoparticle-based drug delivery is an exciting avenue of research that has the potential to revolutionize vaccinations and treatment options. This review provides an overview of the different types of nanoparticles used for drug design and their various applications. It also elaborates on the current challenges and future directions for nanoparticle engineering for drug delivery.

The significant advantage of using nanoparticles to deliver drugs is their increased stability and half-life, evading clearance. With nanoparticles, it is possible to deliver drugs at a much lower concentration to minimize side effects, such as those of the anti-cancer drug doxorubicin. Although strategies such as PEG-ylation minimize the immune clearance of nanoparticles, the effects are not universal. For example, nanoparticles

can cause adverse effects or be cleared during the defense mechanisms against an ongoing disease, reducing effectiveness.<sup>120</sup>

Nanoparticle properties, such as size, shape, charge, and lipophilicity, determine its cell-penetrating properties. Such features determine when and where nanoparticles leave the bloodstream, recognize target proteins on cells of interest, and subsequent endocytosis and lysis to release encapsulated drugs. Therefore, a clearer understanding of the correlation between the physiochemical properties of nanomaterials and their interaction mechanisms within the body is crucial for advancing therapeutic applications.<sup>121</sup>

The regulatory landscape for nanomedicines is shaped by organizations like the FDA and EMA, but nanoparticles pose a unique challenge for evaluation due to their variability in size, shape, function, and other physical and chemical properties. A change in one parameter can significantly impact drug release and biodistribution patterns. As manufacturing ramps up, regulatory agencies struggle with a lack of standardized nomenclature, analytical methods, and safety testing protocols. Although the FDA approved the use of LNP-based COVID-19 vaccines, the long-term effects of delivering genetic material through nanoparticles remain poorly understood.<sup>122</sup> Ensuring safety testing at clinically relevant dosages is another important consideration.<sup>123</sup> Despite these challenges and the lack of fixed guidelines, over 50 nanomaterials have been approved for drug delivery to treat various diseases.<sup>124</sup>

Additionally, as we continue improving nanoparticle design, genetic and environmental differences make it difficult to generalize effects across populations. This is where precision medicine and AI tools come into focus, leveraging information from large-scale databases and predicting newer designs that are tailored to generate patient-specific responses. Therefore, the future of nanoparticle-based drug delivery will depend on interdisciplinary collaboration between materials chemists, physicians, AI experts, nanotechnology specialists, and so on to generate next-generation therapeutics.<sup>104</sup>

Lastly, bringing down the cost of discovering and manufacturing nanoparticle-based drugs is paramount to positively impact global healthcare. Tools such as needle-free vaccines using nanoparticles offer one alternative that benefits underprivileged communities. Such strategies will also improve patient compliance, ensure adequate immune protection across communities, and reduce financial burdens. The disposal of nanoparticles or side products during their manufacturing and their potential environmental contamination is another important issue. The high manufacturing costs associated with developing novel nanoparticle delivery platforms could potentially limit access to developing nations and create health disparities.<sup>124</sup>

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