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Exploring the Optimized Function of Polymer Coated Nanoparticles: Applications in Drug Delivery Systems

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ABSTRACT

Nanoparticles (NPs) have gained traction throughout the recent years for their usage in many applications, including as drug delivery carriers. With their advantages - high surface area to volume ratio, surface functionalization, permeability, come with a downside of toxicity. Most of the inorganic NPs can cause ion leakage through core dissolution, leading to reactive oxygen species (ROS) production and ultimately to an extended damage to the liver and kidneys. Those side effects can be avoided by a polymer coating on the surface of the NPs. This paper aims to answer a rarely discussed question - what NPs - polymers system offers most benefits and least side effects. Throughout all the compiled findings, two strong candidates for NPs and two strong candidates for polymers stand out. Superparamagnetic iron oxide nanoparticles (SPIONs) and mesoporous silica nanoparticles (MSNs) are two of the most exceptional NPs for their unique magnetic properties and mesoporous structures, respectively, and paired with the enhanced properties of the natural polymer chitosan (Ch) and the synthetic poly(ethylene glycol) (PEG), can theoretically become the most suitable candidates for drug delivery.

Introduction

The use of nanoparticles (NPs) has brought a significant advancement of various drug delivery systems by remarkably improving the efficacy and precision of therapeutic interventions. However, the development of these systems is often hindered by the inherent toxicity of the materials used, namely metal NPs like gold and silver NPs. These NPs are known for producing reactive oxygen species (ROS), which become extremely damaging to body tissues in elevated amounts (Amora et al., 2021). In order to reduce or eliminate the side effects of the inorganic nanoparticles, both natural and synthetic polymers such as chitosan (Ch), dextran (D), and poly(ethylene glycol) (PEG) are used as surface coatings. These polymer coatings have been extensively researched for its potential in functionalizing NPs for drug delivery due to their biocompatibility and biodegradability. They have the ability of stabilizing NPs, decreasing their aggregation, and controlled drug release that can easily be modified for proper fit in various delivery systems (Wang et al., 2011). Despite these advantages, the under-researched optimization of polymer-based NPs in drug delivery systems remains an issue that limits their full potential for clinical application. Properly researching and addressing the various options of polymers and NPs systems is essential to ensuring the safety and effectiveness of these systems for use in clinical trials and eventual treatments for diseases.

With the surge in research in the past few decades, different inorganic NPs have been assessed to identify viable drug carrier candidates. One study in the *Applied Sciences* journal conducted by Siddique & Chow (2020) highlighted the application of gold nanoparticles (AuNPs) in drug delivery, stating that AuNPs have the properties such as high surface to volume ratio, small size, stability at increased temperatures, and high cellular uptake. Additionally, they have a modifiable surface for advanced functionalization. For example, AuNPs can be modified with drug moieties to deliver antibiotics into cells, or it can be capped with a cyclic peptide for better cell membrane penetration and noncovalent entrapment of the drug being administered (Siddique et al., 2020). Another study published in the *Redox Biology* journal by Li et al. (2022) found that mesoporous silica nanoparticles (MSNs) can be used

as a novel drug carrier because of their large specific surface area, mesoporous structure, pore volume, and pore size adjustability. They loaded the MSNs with a monomeric component extracted from a plant in order to improve tissue repair after a myocardial infarction, actively demonstrating that MSNs can be used as drug carriers as long as their toxicity is neutralized.

In terms of toxicology, one study by d'Amora et al. (2021) focused on the toxicity of AuNPs and AgNPs using zebrafish embryos and larvae and found prominent physicochemical causes for the toxicity of these particles. The AgNPs are mainly toxic due to the release of Ag+ ions, which can cause DNA and mitochondrial damage through the production of ROS, leading to apoptosis. For AuNPs, they found that their toxicity mainly depends on their surface chemistry and size/shape, therefore the surface coating of the AuNPs directly influences how toxic they are, while the size and shape determines their reactivity through surface area and their tendency to cause oxidative stress, with smaller NPs being more toxic (d'Amora et al., 2021). Another study published in the *Biomedicine & Pharmacotherapy* journal by Huang et al. (2022) had similar findings in regard to size influencing toxicity, in this case demonstrated for MSNs, where immune and inflammatory responses increased as the size of the MSNs decreased.

The use of polymers to reduce toxicity of the NPs is also seen in another *in vivo* study published in the *Agronomy* journal by Candan et al. (2024). The authors analyzed the AuNPs and carbon nanotubes (CNTs) uptake and bioaccumulation in *Pisum Sativum* L. (green pea). The findings demonstrate that nanoparticles accumulate in various plant tissues, leading to chemical changes that could affect plant health and growth. The observed bioaccumulation suggests that similar mechanisms might occur in biological systems, potentially causing toxicity. However, they also agreed that this property of nanoparticles is also the main reason for their potential as vehicles for targeted drug delivery, as their ability to penetrate and accumulate in specific tissues can be harnessed for therapeutic purposes. These studies demonstrate the implication for NPs in clinical usage, as seen by their extensive properties illustrated by previous results.

Even though certain NPs possess toxic properties, the polymer coating can greatly reduce toxicity while preserving function. A study published in the *Pharmaceutics* journal by MacCuaig et al. (2022) explores the toxicity and usage of MSNs coated with either Ch or PEG when injected intravenously in mice, with important implications for drug delivery systems. The findings indicate that Ch-coated MSNs exhibit minimal toxicity, making them a safer option for drug delivery applications compared to PEG-coated MSNs, which tend to exacerbate pre-existing vascular conditions. This once again highlights the critical role of nanoparticle surface modifications in ensuring the safety and efficacy of MSNs for clinical use, illustrating the potential of chitosan-coated MSNs as a promising candidate for drug delivery due to their lower toxicity profiles.

With this demonstrated progression in the reduction of nanoparticle toxicity with polymeric coating, it is necessary to further analyze these advancements in the context of drug delivery systems to ensure their future application in safe clinical trials for the treatment of various diseases. Drug delivery systems already hold immense promise due to their ability to provide rapid and targeted therapeutic effects, but the toxicity of nanoparticles remains a significant barrier to their widespread adoption. By focusing on polymer coated nanoparticles, this study aims to provide a comprehensive understanding of how these biocompatible and biodegradable polymers can mitigate the adverse effects associated with nanoparticle-induced toxicological drawbacks as well as maintaining and even enhancing the functions of NPs. This paper brings a spotlight on the best theoretical optimization of a polymer coated NP that would enhance its application in delivery systems as well as alleviate most of the disadvantages that these NPs may have in their respective circumstances.

Methodology

The purpose of this paper is to explore and conclude the most optimized complex of natural polymers and inorganic nanoparticles for safe and efficient use in intravenous drug delivery systems. The type of research being conducted in this study is a literature review based on *in vivo* and *in vitro* trials as well as informational research articles. In order to fulfill the qualitative data analysis required for this paper, multiple studies were analyzed to accumulate and interpret

data regarding the different properties of various natural polymers and various inorganic nanoparticles that have already been extensively researched for their usage in medical applications. Data specifically about the biocompatibility, coating functionality, and synthesization of numerous polymers along with the surface properties and toxicology of inorganic nanoparticles is collected and reviewed in depth to find the best candidates for a polymer-based nanoparticle complex. Furthermore, the known applications, cost effectiveness, and the large-scale production of each polymer and nanoparticle will be studied and put into consideration for the best optimization. No physical tools or materials were used in the research besides online resources. Research biases were mitigated by analyzing various sources and international research articles and utilizing articles from varied journals for the research objectives to ensure various nuances.

Polymer Coatings

The potential of polymer coatings can range from enhancing and modifying the surface properties of inorganic NPs to mitigating their potential toxicity. The polymers themselves should have not only good biocompatibility and non-toxicity, but also controlled degradability and low immunogenicity for successful and controlled drug release, and proper blood circulation time. It is also preferred that they have favorable source material abundance and low cost large scale production. The comparison between different polymers is shown in Table 1.

Table 1. Polymer comparison. Summary of the basic properties and types of polymers discussed in the paper. Information includes the type of polymer, : biocompatibility, biodegradability, surface functionality, charge, immunogenicity, etc. The applications of these properties are discussed later in the paper.

Polymer	Natural or Synthetic	Protein or Polysaccharide	Surface functionality, biocompatibility	Other attributes (charge, degradability, immunogenicity, etc.)
Chitosan	N	PS	High functionalization & stability, biocompatible	Mucoadhesion, biodegradable, cationic, low solubility
Thiolated Chitosan	N	PS	Derivative of chitosan	Enhanced mucoadhesion, permeability, cohesion, bioavailability, targeting
Trimethyl Chitosan	N	PS	Derivative of chitosan	Enhanced mucoadhesion, permeability, cohesion, bioavailability, targeting
Carboxymethyl Chitosan	N	PS	Derivative of chitosan	Low immunogenicity, pH sensitivity
Glycol Chitosan	N	PS	Derivative of chitosan	Increased water solubility, enhanced targeting, prolonged blood circulation time (modified)
Starch	N	PS	High surface functionalization, biocompatibility, stability	Biodegradability, aggregation, swelling
Hydroxyethyl Starch	N	PS	Derivative of starch	Plasma colloid osmotic pressure & hemodynamics, anti-inflammatory effects,

				low immunogenicity, influence on coagulation function, biodegradability
Carboxymethyl Starch	N	PS	Derivative of starch	Negatively charged, stabilized drug conjugation and cellular uptake, increased water solubility, pH sensitivity
Cellulose	N	PS	Surface functionalization and stability, biocompatible	Biodegradable, environmentally friendly, low solubility, high stability drug loading, dispersibility, absorbance capacity
Hairy Cellulose Nanocrystals	N	PS	Derivative of cellulose	High density, efficient stress transfer, large hydrodynamic size, pH & ion-responsive behavior
Dextran	N	PS	Surface functionalization, biocompatible	High solubility and hydrophilicity, immunomodulatory effects, immunostimulant
Carboxymethyl Dextran	N	PS	Derivative of dextran	Chemical conjugation and ion complexation, high thermodynamic stability, prolonged circulation, and have the enhanced permeation and retention (EPR) effect
Thiolated/aldehyde Dextran	N	PS	Derivative of dextran	Cationic, good transfection efficiency, interaction with negative charges
Hyaluronic Acid	N	PS	Surface functionalization, biocompatible	Non-immunogenetic, biodegradable, intrinsic negative charge, active & passive targeting, enzymatic and oxidative degradation properties
Albumin	N	PR	Surface functionalization, biocompatible	Negative charge, active and passive delivery, EPR effect, hydrophobic interior, covalent conjugation, bond functionalization
Gelatin	N	PR	Surface functionalization, biocompatible	Biodegradability, low cost preparation, abundant reactive functional groups

Silk Fibroin	N	PR	Surface functionalization, biocompatible	Low immunogenicity, high stability, theoretical control & resistance to degradation
Poly(ethylene glycol)	S	-	Surface functionalization, biocompatible	High solubility in water & organic substances, thermal & physical stability, modification potential, low immunogenicity, "stealth" property

Refs: Daraee et al. (2014), D'souza & Shegokar (2016), Endes et al. (2016), Fernández-Serra et al. (2024), Hao et al. (2021), Kaltbeitzel & Wich (2023), Mehdi-Sefani et al. (2024), Pooresmail & Namazi (2021), Quan et al. (2022), Rehman et al. (2020), Thambi et al. (2014), Wang et al. (2011), Wu et al. (2024), Yasmin et al. (2016).

Natural Polymers

Polysaccharides

Biopolymers such as chitosan, hyaluronic acid, starch, cellulose, and dextran are some of the most commonly used options for nanoparticle coatings because they have a wide range of sources, availability, and functionality. Not only are they inherently non-toxic because of their biocompatibility and biodegradability, (Quan et al., 2022) but also have low cost, easy availability, targeting abilities, antioxidant properties, and antiproliferative effects, making them excellent candidates for coating nanoparticles in purpose of drug delivery (Rehman et al., 2020). Wu et al. (2024) details the functions and properties of the natural polymers as well as their derivatives being discussed in this paper in the context of targeted cancer treatments.

Chitosan (Ch)

Wang et al. (2011) explored the characteristics and properties of Ch in the context of drug carrier candidates. The study covered that the molecule has great mucoadhesion due to the molecular structure as well as the biodegradability and the extent of its toxicity, stating that it is inherently prone to being cleared by the body, but can become increasingly toxic with the scaling of charge density. Wu et al. (2024) discussed that Ch at its base molecular structure is a cationic biopolymer that has low water solubility and only dissolves in acidic conditions; however, it can be modified and has many derivatives that induce greater functionality. Thiolated chitosan (TSCh) and trimethyl chitosan (TMCh) are derivatives that illustrate high levels of permeability, cohesion, bioavailability, drug delivery capabilities, targeting, and enhanced mucoadhesive properties. Carboxymethyl chitosan (CMCh) is another derivative that exhibits properties of pH sensitivity and low immunogenicity, making it appropriate for drug delivery shown by its utilization towards creating pH-responsive nanomicelles that can perform controlled drug release in acidic environments. Glycol chitosan (GCh) is another Ch derivative that displays increased water solubility over an increased range of pH, as well as enhancing targeting capabilities and prolonged blood circulation time when modified with PEG. The most notable disadvantage is that the safety properties of Ch *in vivo* have not been studied thoroughly enough to gain approval for clinical applications, as it can trigger dendritic cells and macrophage activation (Wu et al., 2024).

Starch (S)

S being a main energy source for many plants makes it a very abundant and easily accessible resource as well as FDA approved for pharmaceutical applications (Wu et al., 2024). Similar to Ch, it exhibits properties like biocompatibility, biodegradability, and stability. The limitations of unmodified S are that it has the tendency of rapid enzymatic

degradation, aggregation, as well as swelling properties, but it can be chemically modified in order to enhance its performance (Pooresmaeil & Namazi, 2021). Hydroxyethyl starch (HES) is one of the most common modifications of S, and possesses improved plasma colloid osmotic pressure & hemodynamics, anti-inflammatory effects, low immunogenicity, influence on coagulation function, as well as even superior degradation performance and biocompatibility as Wu et al. (2024) compared it to PEG for anti-tumor drug delivery. Carboxymethylated starch (CMS) is another derivative , which is negatively charged allowing for stabilized drug conjugation and cellular uptake, and has an increased water solubility and pH sensitivity (Pooresmaeil & Namazi., (2021). Wu et al. (2024) elaborated that in low pH environments, the drug release is inhibited through protonation, while under high pH drug release is facilitated by ionization.

Cellulose

Cellulose is the most abundant polysaccharide in nature, inherently non-toxic, biodegradable, and environmentally friendly. It is insoluble in common solvents, yet its high functionality enables it to sustain surface modifications to allow high stability drug loading (Wu et al., 2024). Its base structure and its derivatives have mainly shown its potential in biosensors, with excellent dispersibility and high absorbance capacity. One derivative, cellulose nanocrystals (CNCs), have been used as drug carriers in many studies with high density, efficient stress transfer, high surface area, and abundance of hydroxyl groups for surface modification, making it very useful for many applications including drug loading (Endes et al., 2016). Another functionalized amorphous derivative, hairy nanocrystalline cellulose (HCNCs), contains a larger hydrodynamic size and significant pH & ion-responsive behavior, as well as increased adsorption efficiency.

Dextran

Dextran is a biocompatible and biodegradable polysaccharide that is found in bacteria and fungi, and contrary to many of the previously discussed polymers, is highly water soluble, allowing for excellent properties for restricting cell adhesion and diffusion. β-Dextran has immunomodulatory attributes, with it being selectively recognized by receptors on certain immune cells and being able to activate the immune system through signaling pathways, making it presentable for an effective immunostimulant. Carboxymethyl dextran (CMD) is a polyanionic derivative of dextran that facilitates chemical conjugation and ion complexation with drugs, has high thermodynamic stability, prolonged circulation in the bloodstream, and have the enhanced permeation and retention (EPR) effect (Thambi et al., 2014). Cationic derivatives of dextran such as thiolated dextran (TD) or aldehyde-modified dextran (AD) offer good transfection efficiency while avoiding major cytotoxicity and can interact with negative charges for certain applications (Wu et al., 2024). One downside of dextran that was noted is that its molecular modification can lead to cytotoxicity, as well as different sources of dextran having different structures and activities, meaning the conformations need to be studied further.

Hyaluronic Acid (HA)

Wu et al. (2024) discussed that HA is a biopolymer that is found in the human body, unlike the polymers discussed so far, making it excellently non-immunogenetic, biodegradable, and biocompatible. They also discussed that it has an abundance of functional groups on its surface to aid in targeting with substances like ramified glyphosate, as well as intrinsic negative charge, enabling it to act as a carrier for various substances such as proteins and other polymers through electrostatic interaction, which further aids in targeting. HA can also achieve both active and passive targeting, and the enzymatic and oxidative degradation properties allow for responsive activation of drug release dependent on space and time. It was also clarified that researchers modify HA itself is unstable and amenable to enzyme degradation, so it is often modified by introducing functional groups to increase its performance in terms of viscoelasticity and prolonged accumulation in the body (Song et al., 2021). However, Wu et al (2024) states some of the main flaws of HA in the context of drug delivery. The biggest disadvantage of HA is that it can form a protein corona which can affect degradation and behavior. HA modification can lead to altered ability to bind with receptors and hinder its

targeting, and that industrial-scale production of HA has various limitations, therefore impeding its widespread applications.

Proteins

Protein polymers, such as albumin (Alb), gelatin (Gel), and silk fibroin (SF), similar to natural polysaccharides, are some of the most commonly used polymer coatings for nanoparticles in many contexts because of their availability, low toxicity, and modification potential. They are intrinsically biodegradable, biocompatible, have low immunogenicity, and high specificity for receptors and substrates that allow for good targeting (Kaltbeitzel & Wich, 2023).

Albumin (Alb)

Wu et al. (2024) covered the functions of Alb, as it is the most common protein found in human blood, making it innately easy to obtain. Alb is a water soluble protein due to its net negative charge, which also allows it to avoid clearance by the kidneys while possessing inherent binding sites that make it a valid candidate for a drug delivery carrier. It also possesses the mechanisms for active and passive delivery through the EPR effect in the context of drug-loaded tumor targeting. Alb has the intrinsic ability to encapsulate drugs on its own with its hydrophobic interior, with some researchers also using covalent conjugation and bond functionalization to load polar drugs (Hao et al., 2021). The most significant drawbacks of Alb that Wu et al. (2024) noted are that despite its innate selective binding to receptors and substrates, it has limitations to its specificity and targeting, and is also prone to enzyme degradation, which could lead to unstable or complete failure of drug release.

Gelatin (Gel)

Gel is another protein that is easily available as it derives from the degradation of collagen (Wu et al., 2024). Due to this, it possesses excellent biocompatibility, biodegradability, easy preparation at low cost, and abundant reactive functional groups, making it a viable candidate for a drug carrier. Furthermore, it displays stable physical properties and can suffice as an adaptable matrix for loading various substances, which researchers were able to use for many different applications; Yasmin et al. (2016) performed a review and discussed its application in its NP form as a DNA carrier, in tissue engineering, vaccines, and more due to its properties as a drug carrier. According to a study conducted by Mehdi-Sefiani et al., (2024), Gel can be modified with other polymers to improve its mechanical and thermodynamic stability, which were the mainly noticeable drawbacks of this polymer.

Silk Fibroin (SF)

Fernández-Serra et al. (2024) detailed that SF is another protein that can be used for drug delivery applications because of its low immunogenicity and high stability. Wu et al. (2024) noted that it has already been approved by the FDA for medical use as suture material. Fernández-Serra et al. (2024) highlighted that it has *in vivo* resistance to degradation and could theoretically be controlled for shorter or extended drug delivery time requirements. SF can also deliver four fluorescent molecules of differing sizes, hydrophobicity, and charge, and possess reduced stability and proper delivery in a phosphate-buffered saline environment, making it a promising drug delivery candidate. The study concluded that most applications of SF would be in the form of nanospheres/fibers and that the most significant drawbacks are that SF lacks good mechanical properties, is prone to sudden drug release, and lacks targeting properties.

Others

PEG, unlike the polymers previously discussed, is a synthetic hydrophilic polymer, yet it possesses some of the key functions that the other polymers possess. Knop et al. (2010) and D'souza et al. (2016) found that the notable advantages of PEG were its biocompatibility, its solubility in water and many organic substances, thermal and physical

stability, modification potential low immunogenicity and "stealth" property, and its inherent low toxicity that renders it a viable polymer for biological applications. Shi et al. (2021) conducted a review in which they also covered the functions and effects of PEG on NPs in drug delivery systems. They detailed that PEGylated NPs have increased stability through steric repulsion, which is more evident for PEG with higher molecular weight, because the distance between the NPs increases with the length of PEG chains, thus enhancing steric repulsion and evading aggregation of NPs. However, Knop et al. (2010) also noted some of the drawbacks, such as adverse effects on the body including rare hypersensitivity reactions, and unexpected changes in pharmacokinetic behavior.

Inorganic Nanoparticles

Inorganic NPs are suitable drug delivery carriers due to their modifiable surface, permeability, high surface area to volume ratio, degradability, low immunogenicity, and biocompatibility. All inorganic NPs researched in this paper exhibit excellent stability, high surface to volume ratio, and surface functionalization. Furthermore, each one also possesses unique properties which makes them suitable as drug carriers–discussed later. Most metal NPs are known for having toxic effects when releasing ions from their cores which causes ROS production and cellular damage/apoptosis. However, not all NPs leach toxic ions, yet can still lead to ROS production from other factors. Daraee et al. (2014) noted that citrate-capped NP surfaces led to increased cellular uptake due to the negative charge allowing for scaffolding of positively charged proteins like transferrin that make it possible to get better entry to cells, which could define a good guideline for what to look for when coming up with a proper NP complex. The comparison between different inorganic nanoparticles is shown in Table 2.

Table 2. Inorganic nanoparticles comparison**.** Summary of the properties of the nanoparticles (NPs) discussed in the paper. Information includes: Physicochemical properties such as surface area, surface stability, and any other additional properties, toxicity, and the mechanism of toxicity.

Nanoparticle	Physicochemical Properties	Toxicity	Mechanism of Toxicity
Gold	SPR, high absorption	Cytotoxicity	Size, surface, concentration, and charge dependent
Silver	Localized SPR and electronic absorption, antibacterial, fungicidal	Cytotoxicity and genotoxicity	Ion leakage, dissolution
Iron Oxide	Magnetic targeting, low solubility, thermal stability	Cytotoxicity, genotoxicity	Ion leakage, dissolution, high agglomeration, size and concentration dependent
Silica	Mesoporous, large and adjustable pore size, high specific surface area	Cytotoxicity and hepatotoxicity	Size, surface, concentration, and charge dependent
Zinc Oxide	Antibacterial, antimicrobial	Cytotoxicity, genotoxicity, neuronal toxicity	Ion leakage, dissolution, size and concentration dependent

Refs: Chandran et al. (2017), Czyżowska & Barbasz (2022), d'Amora et al. (2021), Daraee et al. (2014), Gupta & Gupta (2005), Li et al. (2022), Lopez-Chaves et al. (2018), MacCuaig et al. (2022), Malhotra et al. (2020),

Niżnik et al. (2024), Pissuwan et al. (2011), Rasmussen et al. (2010), Rosenholm et al. (2010), Siddique & Chow (2020), Singh et al. (2010), Talarska et al. (2021), Tang et al. (2012), Truong et al. (2019), Wei et al. (2015), Zhou et al. (2018).

Gold

Gold NPs (AuNPs) are known for their stability, excellent surface functionalization, strong optical absorption , (Pissuwan et al., 2011), high surface area to volume ratio, stability at increased temperatures, high reactivity to living cells (Siddique et al., 2021), and even for their photothermal and photodynamic properties through surface plasmon resonance (SPR) (Yang et al., 2022). Talarska et al. (2021) mentioned that AuNPs had shown significant absorption in biological systems, with the NPs spreading throughout the organs and ending up in the liver for excretion shown by multiple experiments with rats and humans.

Previous studies have mentioned that AuNPs are biocompatible and have low toxicity, (Pissuwan et al., 2011) (Yeh et al., 2012), but newer studies have observed the effects of ROS production of AuNPs more thoroughly, and found that AuNPs can be toxic. One *in vivo* study conducted by Lopez-Chaves et al. (2018) found that antioxidant enzymes were said to be overworked after ROS overproduction caused by AuNPs, and confirmed it by showing a presence of ROS after 16 hours of treatment of AuNPs in mice, and revealed a growing cell mortality as ROS increased. They also showed that DNA damage happened in all samples that were treated with AuNPs, with smaller sizes of the NPs resulting in more damage observed.

Truong et al. (2019) conducted a study in which they mentioned that even though AuNPs don't leach toxic gold ions, they believe that core size had a correlation with the toxicity of the NP. After their experiments, they concluded that the core size isn't the main driving factor and instead correlated well with surface area, where higher surface area meant more exposure of catalytically active sites and surface ligands. For the metric of exposure, it was found instead that the highest diameter of AuNPs were the most toxic. One review discussed that the majority of *in vivo* and *in vitro* studies show that AuNPs demonstrate cytotoxic and genotoxic effects in mammalian cells and can activate the immune system when interacting with organs, but it is dependent on a range of factors including concentration, size, shape, and surface chemistry (Chandran et al. 2017), exhibiting a wide spectrum from minimal to substantial toxicity (Niżnik et al., 2024).

Silver

Talarska et al. (2021) discussed that silver NPs (AgNPs), similar to AuNPs, are known for their surface stability to allow for modification, optical and electronic absorption, high surface area to volume ratio, and easily assimilated by cells. Another study verified the optical properties of AgNPs and emphasized the use of localized SPR, meaning it has similar photothermal properties to AuNPs, even being used in thermolytic laser therapies (Wei et al., 2015). Talarska et al. (2021) also discussed properties unique to AgNPs such as antibacterial, antiviral, and fungicidal properties.

They also noted that AgNPs have similar exceptional absorption properties to those of AuNPs. However the main difference that AgNPs are known for is their mechanism towards cytotoxicity, which is the release of toxic ions from the core of the NP through dissolution, which makes it a less preferable candidate for drug delivery compared to the other NPs. They elaborated that the AgNPs degrade after cellular uptake, releasing Ag+ ions that impair mitochondrial function. Due to the disrupting the electron transport chain by inhibition of ATPase, ROS accumulates as a byproduct, and causes DNA and mtDNA (mitochondrial DNA) damage on top of peroxidation of lipids and protein elements, finally leading to cellular apoptosis. Wei et al. (2015) also discussed that the toxicity of AgNPs remains unclear, as its toxicological properties may differ depending on a variety of factors such as sizes, presence of capping agents, and different cultures/cells, coming with a similar conclusion to AuNPs and additionally suggesting that the risks need to be assessed by a case-by-case basis.

Iron Oxide

Superparamagnetic Iron Oxide nanoparticles (SPIONs) are one of the most used NPs in medical applications, and similar to previously mentioned NPs, have high surface area and stability, which allows for the functionalization of the NP for many uses. The main difference is the presence of magnetic properties, which can play a big role in applications such as MRI and targeted drug delivery, although heavily reliant on the size of the NPs being administered (Gupta & Gupta, 2005). It was also noted that the size, charge, and surface chemistry, and blood circulation time, just like the other NPs, are important for their viability as drug carriers. Singh et al. (2010) described that uncoated SPIONs have very low solubility and high agglomeration that may impede blood vessels in a clinical setting, and may be coated to increase their biocompatibility and biodistribution.

Singh et al. (2010) also covered the potential toxicity of SPIONs, detailing that the cytotoxicity and genotoxicity of the NPs mainly depends on concentration, size, and the magnetic properties, as it could cause high agglomeration that can potentially cause oxidative stress, DNA damage, and may even initiate carcinogenesis. A more recent study conducted by Malhorta et al. (2020) compiled *in vivo* and *in vitro* studies, majority of which confirmed that uncoated SPIONs showed cytotoxicity through ion leakage, and that coated SPIONs exhibited lower toxicity of bare SPIONs, but still exhibited levels of toxicity in cells due to high concentration and/or surface charge. With those factors in mind, the notion is given that the polymer coating must not induce great surface charge or increased cellular uptake, as it can potentially lead to increased cytotoxicity.

Silica

Mesoporous silica NPs (MSNs) have gained popularity by showing their excellent properties regarding their enhanced structure, allowing for a plethora of the characteristics that are favorable for drug delivery and many other applications. Tang et al. (2012) elaborated that they have a tailorable mesoporous structure, high specific surface area leading to better adsorption, and large pore volume for potential therapeutic applications like drug loading. They also elaborated that it has a scalable and cost effective fabrication, as well as good biocompatibility due to its many properties, recognized as safe by the FDA, on top of being abundant in nature.

Tang et al. (2012) also found evidence that MSNs could be potentially toxic, again depending on their size, dose, and concentration. They found *in vivo* studies where MSNs were administered to rats at different sizes, and that generally the smaller sizes correlated to higher cytotoxicity and hepatotoxicity due to higher cellular uptake. They also noted that functionalizing the surface with chemical groups with high zeta potential could modify the cellular uptake and agglomeration, and therefore lower the toxicity to some extent. Rosenholm et al. (2010) also elaborated on the main causes of toxicity, where small concentrations and cationically modified MSNs were deemed to be less toxic than their bare counterparts.

Zinc Oxide

Zinc Oxide NPs (ZnNPs) are another NP with promising attributes for drug delivery. They contain similar characteristics to NPs formerly discussed, such as high surface area - volume ratio, superior catalytic activity, antibacterial and antimicrobial properties (Czyżowska & Barbasz, 2022), as well as an inherent positive charge (Rasmussen et al., 2010). However, studies recommend that ZnNPs be coated with a polymer to increase its biocompatibility and make it a more suitable candidate to be used for drug delivery.

Rasmussen et al. (2010) elaborated on the various toxicity mechanisms that ZnNPs have shown *in vivo* and *in vitro* studies previously. They detailed how ZnNPs can cause toxicity in the same way that previous NPs mentioned can potentially cause toxicity, with the generation of ROS and apoptosis. They stated that some studies correlate their toxicity to ion leakage, while others don't, and concluded that this difference in data could stem from differences in

synthesis conditions and procedures. Under normal conditions, the levels of free Zn2+ ions remain low and regulated, but excess zinc could cause neuronal toxicity and brain injury. Similar to previously mentioned NPs, charge and size correlated with increased toxicity, as smaller size and positive charges causes increased uptake and cytotoxicity. Czyżowska & Barbasz. (2022) further elaborated on this toxicity, as they noted it can cause significant liver, kidney, and other biological systemic damage through oral and inhalation administration, which they concluded poses threats at both the consumer and professional level.

Discussion

Optimized Complex

The compiled data on both natural/synthetic polymers and inorganic NPs show an abundance of potential candidates for a functional and safe drug carrier. The biggest disadvantage of inorganic NPs is their potential toxicity, whether through ion leakage or through oxidative stress. Most of the polymers discussed in this work have the potential to subside these effects while still maintaining the core functions of NPs and possibly even enhancing them. Most of the NPs discussed possess the desired drug carrier properties and surface functionalization ability. The best bare NPs in terms of physicochemical properties are SPIONs and MSNs, particularly for their unique paramagnetic properties and mesoporous structure, respectively.

The magnetic properties of SPIONs aid the targeting of certain tissues or organs for maximum therapeutic effects and proper drug delivery. It has also been shown that they have proper NP characteristics for optimal surface functionalization and cellular uptake. However, as previously discussed, SPIONs have been known for causing some level of toxicity in the body, and therefore need to be coated by a polymer in order to subside these effects.

The physicochemical properties of MSNs also have incredible potential for drug delivery, as the special mesoporous structure not only serves as a great surface for drug loading, but also has adjustable pore sizes for even more loading or functionalization. MSNs retain much of the important properties of other NPs, with optimal surface area and cellular uptake. Although, similar to SPIONs, they are still toxic and either need to be studied more to reduce those toxicological properties or be coated with a polymer to subside these effects and enhance their properties to make it a potential drug carrier.

As for polymers, the “best” polymer is difficult to determine, as most of them have similar characteristics that make them all adequately good candidates as coatings for drug delivery. However, two polymers stand out: Ch and PEG. Ch stands out as a strong and well researched biopolymer, as it has a lot of derivatives - TMCh, TSCh, CMCh, and GCh, suitable for many different applications. PEG, on the other hand, is a synthetic polymer, with a unique “stealth” property, which lowers blood opsonization, and enhanced circulation time . PEG also has high modification potential, even being used as a modification with some derivatives of Ch to make a more enhanced version of them. The known disadvantage of PEG is the rare hypersensitivity and anaphylactic shocks. Based on the data we suggest that the best polymer coated NP for use in drug delivery system would have to involve SPIONs or MSNs as the core NP component, with either modified Ch derivatives or PEG as a polymer coating.

In one study performed by Feng et al. (2018), they coated SPIONs with both PEG and polyethyleneimine (PEI) and investigated the *in vitro* uptake in tumor and macrophages and toxicity of these NPs. They found that SPIONs coated with PEI exhibited extreme cellular uptake, resulting in cytotoxicity through mechanisms like ROS production and apoptosis, and also exhibited dose-dependent lethal toxicity. On the contrary, 10 nm PEGylated SPIONs showed high cellular uptake, but only expressed little cytotoxicity at high concentrations. They reached the conclusion that even though the biodegradation was relatively slow, no obvious toxicity was found for PEGylated SPIONs in mice, even though 10 nm PEGylated SPIONs achieved the highest cellular uptake among tumor cells. Another study done by Shevtsov et al. (2018), however, did not follow the same toxicological profile with Ch as a coating to SPIONs,

with moderate toxicity shown as charge increased, mainly due to the increased cellular uptake and therefore increased cytotoxicity.

Another study done by Zhou et al. (2018) detailed that MSNs coated with PEG were found to be able to "escape" endosomal entrapment, and were internalized into cells and partially located in acidic environments. They also cited how one experiment was done where PEG-folic acid-functionalized polydopamine-modified MSNs were synthesized and used to perform a pH sensitive controlled delivery of doxorubicin, a common chemical used for drug delivery experiments. It was found that the film coating covering the MSNs would dissolve and release the loaded drug rapidly, successfully exhibiting controlled drug delivery.

Conclusion

This paper discusses the complex properties, toxicity, and many other factors that come into play when advancing towards better polymer coated nanoparticles for drug delivery agents. Based on the data we suggest that the most optimal complex for drug delivery systems would have to be based around SPIONs and MSNs as the core NP. In order to reduce the toxicity and enhance the properties of the system, we recommend to use either chitosan (Ch) or Polyethylene glycol (PEG) as a polymer coating. With these findings, it's important to note that the adverse effects of such NPs and polymers are heavily reliant on the system they're used in and in the fashion that they are administered, as it was generally discovered that small size and concentration might lead to adverse effects, or might reduce them. Many articles, including this paper, conclude that any use of NPs and polymers should be confirmed on a case by case basis to confirm the proper conditions and administration methods before being utilized for drug delivery or any other application.

Limitations

As a secondary literature review, this paper mainly intends to provide deeper insight into the combination of two components of nanotechnology for a theoretical advanced treatment method in the field of drug delivery and pharmaceutics. Numerous primary articles and reviews were interpreted to properly examine and summarize the key components of these two factors, and majority of research reviewed established a common list of properties that were all comprised in this paper. Ultimately, the use of NPs and polymers will continue to grow, and the toxicity and side effects mentioned in this paper will nigh in comparison to the truly exceptional mechanical and medicinal properties of these substances, more evidently shown when these two factors are merged together in this method. Therefore, this paper mainly aims to provide information on the current state of a few examples of these two components and provide a proposition as to what might be the best composition of said components.

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