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Nanodetoxification: emerging role of nanomaterials in drug intoxication treatment

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Abstract

Treatment for intoxication involves the neutralization or clearance of a toxic compound, but the current methods of treatment are limited in their ability to safely and effectively detoxify the patient. Emerging research has focused on using nanoparticles as parenteral detoxifying agents to circulate through the body and capture toxins. The variable compositions of these nanoparticles control the mechanism in which they capture and remove specific compounds. As discussed in this article, the recent methods for utilizing nanoparticles for detoxification show great potential for intoxication treatment. However, several challenges must be overcome before a universal nanoparticle detoxification method is available for clinical use.

Keywords

detoxification; drug; liposomes; nanocapsules; nanomedicine; nanoparticles; overdose treatment; silica nanotubes; toxicity; uptake

In the past few decades there has been extensive investigation into the use of nanoparticles in drug delivery, targeting, labeling and bioimaging. Numerous types of nanomaterials, such as liposomes, microemulsions, nanoparticles and nanotubes, have been developed for such applications [1–12]. The advantages of a nanoparticle-based method over conventional methods mainly results from their physiochemical properties. Nanoparticles synthesized for biological applications have been composed of fatty acids, inorganics, organics and metal oxides. The large surface area to volume ratio, tunable size distribution, ease of surface modification and specific loading capacity makes nanoparticles the optimum choice for *in vivo* applications, such as targeted delivery and controlled release of drugs [5,6,11–14]. The intrinsic versatility and multifunctionality of nanoparticles provides advancements over conventional methods by improving biocompatibility, circulation times and targeting. Most recently, a new area of study has emerged utilizing these advancements to develop nanoparticles specifically for detoxification [1,15–18].

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Current conventional treatment methods for intoxication include gastric lavage, activated charcoal and antidotes. Gastric lavage and activated charcoal are general methods of treatment in which nonadsorbed drugs are removed from the gastrointestinal system [19,20]. In order to be effective, they must be administered before the drug has been absorbed by the body. As a result, the efficacy of these methods significantly decreases as the duration between ingestion and treatment increase [20]. In addition, gastric lavage treatments carry serious risks, such as hypoxia, gastrointestinal perforations and aspiration pneumonitis [19]. Antidotes are used to neutralize the toxin and, therefore, are a more effective method of treatment than gastric lavage and activated charcoal [21]. However, antidotes cannot be utilized as a universal method of treatment because they are specific to a limited number of toxins. Due to these obstacles from current detoxification methods, it is highly desired to develop a new method of treatment that lowers the concentration of free drug in the body and combines the efficacy of antidotes with the broad applicability of activated charcoal. Nanoparticles as detoxifying agents offer a solution to achieve these requirements. Several reviews have reported the capture ability of various nanomaterials towards drugs and other toxins [22,23]. In this article, we will highlight the shortcomings of many of these nanomaterials and offer an alternative nanodetoxification method. Challenges and future outlook in this emerging nanomedicine field will also be discussed.

Nanomaterials used as detoxifying agents

Three main classes of nanomaterials have been investigated as nanodetoxifiers: micellar nanocarriers, liposomes and ligand-based nanoparticles (Table 1). These particles are to be injected into the patient, circulate through the bloodstream and capture toxic compounds by adsorption of the toxin to the surface of the material or internalization of the toxin by the material [24–33].

Micellar nanocarriers

Micellar nanocarriers of interest for detoxification are mainly composed of an amphiphilic shell and hydrophobic core. The two most studied within this class are lipid nanocapsules and microemulsions. The characteristics of these nanoparticles allow them to be circulated in a hydrophilic environment while encapsulating mainly hydrophobic compounds. Lipid nanocapsules with a phosphatidylcholine shell and triglyceride core have been shown to capture hydrophobic drugs, such as docetaxel, paclitaxel and amitriptyline (Figure 1) [34,35]. The *in vitro* uptake efficiency observed was 60% for amitriptyline and 75% for both taxanes. Microemulsions prepared from amphiphilic block copolymers were used to extract bupivacaine, a common local anesthetic, from saline solution [30]. An uptake efficiency of 60% was observed with a microemulsion composition of Pluronic[®] surfactant, oil and fatty acids. Bupivacaine was extracted from the aqueous media through adsorption at the interface between the microemulsion droplet and solution (Figure 2). Based on studies with different microemulsion compositions, extraction can also occur by the partitioning of the drug into the oil core [28,33]. However, microemulsions are prone to thermodynamic instability due to the weak interactions between hydrophobic chains. Oil droplets with a polymeric coating have been prepared to improve stability and limit aggregation [28,33]. Hexadecane microemulsions were initially formed in solution followed by the addition of octadecyltrimethoxysilane. The amphiphilic alkoxy silanes self assemble around the oil droplets with the hydrophobic chain interacting with hexadecane. The methoxysilane groups are then condensed to form a protective silica shell around the droplet.

Liposomes

Liposomes are composed of phospholipid bilayers, which self-assemble into spherical particles with a hydrophilic core and are nontoxic, degradable and nonimmunogenic [36].

Since liposomes can be formulated with a variety of lipid compositions and structures, they are able to encapsulate a broader range of toxins compared with micellar nanocarriers. It has been shown that ionizable drugs have been extracted with the use of several liposome compositions. Liposomes prepared with anionic phospholipids were shown to capture cationic drugs amitriptyline, bupivacaine and imipramine at a physiological pH [27,37]. The charged portion of the compound electrostatically interacts with the negatively charged phosphate group and the remaining portion with the hydrophobic tail. Leroux *et al.* prepared pH gradient spherulites, liposome-like vesicles with uniformly spaced bilayers, capable of capturing haloperidol and amitriptyline [24,25,35]. The neutral drug molecules initially cross the membrane bilayer and then become ionized in the acidic environment of the vesicle core. Once ionized, the drugs are no longer able to pass through the hydrophobic membrane (Figure 1). Liposomes with encapsulated enzymes have also been studied as detoxifiers [38,39]. Organophosphates and cyanide toxins penetrated the bilayer and were degraded by encapsulated enzymes within the core. Detoxification with enzyme-encapsulated liposomes was found to be more effective because clearance of the encapsulated enzymes from the body was significantly slower than that of the free form.

Ligand-based nanoparticles

Another class of nanoparticles currently researched for detoxification includes those which have been fabricated with capture moieties, such as proteins, chelators and antibodies, designed to scavenge specific toxins. Mertz *et al.* [32] utilized the strong protein–ligand binding interaction to demonstrate the detoxification of a simulant toxin. Magnetic nanoparticles were functionalized with streptavidin and the *in vitro* uptake of biotinylated horseradish peroxidase was studied. A 70% loading capacity of the particles was observed in blood media. In addition to the well-established streptavidin–biotin interaction, antibodies and chelating agents have also been employed to capture their highly specific targets. Magnetic nanoparticles functionalized with an ethylenediaminetetraacetic acid (EDTA)-type chelator or antibody fragments were used to extract lead and digoxin, respectively [40]. Hoshino *et al.* fabricated molecularly imprinted polymers (MIPs), often referred to as plastic antibodies, with a binding site optimized for melittin, a toxic peptide found in bee venom [31,41]. Decreased mortality was observed when the MIPs were administered immediately after the toxic peptide. By selecting the appropriate monomers, the MIP binding site can be tailored to accommodate virtually any toxin. Capture of the target compound occurs when surface functional groups from the monomers bind the target through specific molecular interactions (Figure 3). An alternative method to specific detoxification with antibodies and chelating agents focuses on less selective noncovalent capturing mechanisms between the ligand-based nanoparticle and the toxin. Derivatized oligochitosan was found to remove amitriptyline through aromatic interactions [42,43]. The electron-rich amitriptyline adsorbed to electron-deficient dinitrobenzenesulfonyl groups attached to the chitosan. Following the complexation of the derivatized chitosan, a decrease in the cardiotoxic effects of the drug was observed.

Present limitations of nanodetoxification systems

Although these nanoparticle-assisted methods of detoxification have demonstrated the ability to capture target compounds, there are several drawbacks that limit their application. As mentioned above, extraction with microemulsions and ligand-based nanoparticles occurs through the adsorption of drug molecules to the outer surface of the particle. However, the extraction efficiency is greatly reduced *in vivo* due to the presence of large amounts of serum proteins for which drugs have a high binding affinity [15,27]. In the presence of these proteins, a nanodetoxifier must aggressively compete for the binding of drug molecules. In addition, due to the low capture efficiency, a higher concentration of nanoparticles must be

administered to reach the therapeutic levels of treatment. *In vivo* experiments with modified chitosan and MIPs required dosage of 33 and 30 mg/kg, respectively [31,42].

Although competitive binding is not a limitation of lipid nanocapsules and liposomes, the captured toxins must still pass through the phospholipid membrane before partitioning into the core. In order for this to occur, the toxin must have an affinity for the membrane components. As a result, lipid nanocapsules and liposomes are typically effective at removing mostly amphiphilic and hydrophobic compounds. Another limitation is due to the fact that anionic liposomes can capture molecules within the membrane bilayer, which can disrupt the ordering of phospholipids and result in leakage of the core components [37].

Ligand-based nanoparticles are limited by the same constraint as conventional antidotal treatment. At present, every known toxin does not have a corresponding ligand; therefore, the method is only applicable to a small class of drugs. As stated before, MIPs can be synthesized with a wide range of monomers in order to tailor the binding sites to capture any compound. They can be fabricated to capture a specific target by optimizing the types and ratios of specific monomers. However, this process is time consuming and costly.

The overarching problem to the proposed methods is their inability to accommodate the diversity of available drugs and other toxins. Ideally, a successful detoxification method should focus on the inactivation of toxins, rather than the removal of them. In this view, studying the human xenobiotic metabolism can offer insight into achieving this method of detoxification.

Detoxification system that mimics biotransformation

The body is equipped with a highly evolved system of metabolic pathways that perform detoxifying biotransformations on foreign drugs and other toxins. Biotransformations alter the chemical nature of a toxin, which reduce its activity and allow for easier excretion from the body [44]. The systematic mechanisms of the body's biotransformations can be used as a model in designing the ideal nanodetoxifier. The detoxification process is divided into two main phases based on the type of biotransformation performed. In phase I, the substrate, or toxin, is modified through the addition of a chemically active functional group, which can occur by a number of reactions, including oxidation, reduction, hydroxylation and demethylation [45,46]. In general, the purpose of the modification is not to detoxify the compound but quite the opposite. Modification to the parent substrate can often result in the production of a metabolite with increased toxicological activity compared with the parent compound. The most common reaction of the phase I metabolism, oxidation by the cytochrome P450 enzyme system, converts relatively innocuous compounds, such as polyaromatic hydrocarbons and paracetamol, into reactive electrophilic metabolites [45,47]. The primary function of phase I is to prepare the parent compound for the phase II metabolism, which is considered the 'true detoxification' step [45]. During phase II, the metabolite is conjugated with an endogenous compound, most notably glutathione and glucuronic acid. The conjugation causes a significant modification of the chemical structure and, as a result, virtually all compounds become inactivated and are easily excreted from the body [44].

It is important to note the existence of an interrelationship between phase I and II pathways. The multitude of pathways are interconnected through overlapping substrate specificity, which allows numerous drugs to be metabolized through many different pathways [45,48]. Furthermore, a critical factor in the regulation of toxicity is the balance between these various pathways [44]. The overlapping specificity results in a competition between substrates for an enzyme and between enzymes for a substrate. Therefore, concentration of toxin and endogenous compound and enzyme activity are the main factors in determining

the major pathway for detoxification. An activated phase I metabolite can immediately be conjugated under normal conditions. In the case of an overdose, however, the phase II pathways are challenged by an excessive concentration of the toxin. The conjugative enzyme activity increases to accommodate the influx of toxic compounds; however, the rate of enzyme activity is limited by the availability of the endogenous compound being conjugated [44]. As the toxin concentration exceeds the capacity of the conjugation pathway, the activity of alternative phase I pathways are increased. However, the accumulation of active metabolites produced by these pathways results in systemic toxicity. In order to completely eliminate toxins from the system, the balance between activating and deactivating reactions must be restored. By mimicking the biotransformations performed by the body, suitable nanoparticles can be designed to effectively restore this balance.

Future perspective: new platform for nanodetoxification

The development of a universal method that can imitate, or in some cases reverse, the body's own biotransformations has the potential to be successful at detoxifying xenobiotics. Porous nanoparticles, such as mesoporous silica nanoparticles and silica nanotubes (SNTs) with open gates, have primarily been researched for drug delivery systems and not for use in detoxification [1,5,6,11,12]. It is known that the porous structure of these nanoparticles creates a larger surface area and thus allows greater uptake of molecules compared with their solid counterparts [49]. It is expected that the ability to introduce multifunctionality into the nanoparticles will make porous nanoparticles an ideal platform for detoxification. SNTs offer ideal physical and chemical properties that make them a good representation of this type of nanomaterial. One main advantage of using SNTs is the well-established, controlled fabrication and straightforward surface modification. Fabrication of monodisperse nanotubes of nearly any size is performed in the pores of a nanoporous alumina template film via the 'surface sol-gel' method [2,3,5,6,49–53]. The pore size of the SNT, which acts as an open gate, can be precisely controlled within 1 nm, which permits selective targeting of specific molecules based on size [5]. The surfaces of the SNT can easily be modified with various silane derivatives using well-known silane chemistry [3,5,6,53,54]. Additional functionalization to the silane chains can be performed using the nanotube surface as a solid support. As a result, almost any type of surface chemistry can be desired. Another virtue of the template synthesis method is the ability to differentially functionalize the inner and outer surfaces of the SNT in a straightforward manner [3,5,53,54]. The first surface modification is performed on the inner surface while the nanotubes are still embedded in the template film. In this step, the external surfaces of the SNT remain unexposed and protected by the template walls. The second functionalization occurs after the template has been removed, leaving free nanotubes with outer surfaces freely exposed for modification. Differential functionalization between the inner and outer surfaces of the SNT provides a facile and effective way to integrate the multifunctionality necessary for a universal detoxification method.

Several proof-of-concept studies demonstrate the diversity and selectivity of functionalized SNTs. Lee *et al.* attached antibovine IgG to one set of nanotubes and antihuman IgG to another set using an aldehyde silane and Schiff base chemistry [6]. The outer surfaces of all nanotubes were functionalized with polyethylene glycol (PEG) to limit nonspecific adsorption. When placed in a solution containing human IgG, only the nanotubes functionalized with antihuman IgG were able to capture the antigen. More importantly, Mitchell *et al.* showed that enzymes remained active and functioned properly when attached to the nanotube surface [3]. The enzyme functionalized nanotubes in solution were used to measure glucose oxidase activity. In addition to specific targeting and controlled enzymatic activity, the selective uptake and release rate of 4-nitrophenol, fluorouracil and ibuprofen by SNTs was also studied by the Lee group [6]. The inner nanotube surface was first

functionalized with amino silane then the SNTs were added to a hexane or ethanol solution containing one of the drugs. The drugs accumulated in the nanotubes through ionic interactions between the molecules and surface amines of the SNT.

Based on the principles highlighted above, a detoxification system based on SNTs can be envisioned. The inner surface of the SNTs can be functionalized with specific chemistry modeled after the natural detoxification mechanisms found in the body. Phase II detoxification pathways can be mimicked inside the SNT by modifying the inner pores with terminal chains similar in chemistry to glutathione and glucuronic acid. Glutathione and glucuronic acid conjugation can be performed on a number of functional groups and, therefore, are the most versatile pathways in phase II [45]. A wide variety of toxins can be targeted and captured by functionalizing SNTs with compounds capable of forming similar thiol and glycosidic bonds. Another approach to perform biotransformations within SNTs is the inactivation of metabolites formed during oxidation in phase I. As previously mentioned, the P450 cytochrome system performs a variety of oxidation reactions, which often results in a highly reactive metabolite. SNTs can be used to develop a nanotube reactor that converts the metabolites back to their original, nontoxic form. A reducing agent can be attached to the inner surface of the nanotube and act as a reaction site for the reduction of the oxidized metabolite. Toxic compounds can diffuse into the open pore of the nanotubes, approach reaction sites anchored to the inner nanotube wall and become reduced and inactivated. Once reduced, the detoxified molecules can diffuse out of the nanotube and follow the normal excretion pathway without causing harmful effects. A general schematic of the detoxification mechanism of the nanotube reactor is shown in Figure 4. Recently, a similar nanotube reactor demonstrated successful catalytic polymerization using catalyst-anchored SNTs [55]. Other types of reducing agents, such as ascorbic acid, vitamin E and other antioxidants, are naturally found in the body and can also function as reaction sites inside the nanotubes [56]. Research aimed to improve the methodologies of nanoparticle-assisted detoxification should lead to many different and exciting developments where they can progress towards reducing not only toxins but harmful free radicals and reactive oxygen species in the body as well.

Conclusion

From the analysis of the literature, it is apparent that the advancements in nanotechnology can extend treatment of intoxications beyond the limitations of gastric clearing and antidotes. Several types of nanoparticles were found to address specific problems with conventional detoxification methods. Nanocapsules, microemulsions and nanoparticles have all been used to demonstrate the potential of nanodetoxifiers by adsorbing, encapsulating and binding specific toxins based on surface chemistry and capture moieties. The characteristics of those nanoparticles can be further optimized to improve their performance by using the body's biotransformation processes as a model. SNTs offer the ideal structure for offering several advantages over these methods, including differential surface functionalization and the uptake of any type of molecule. The incorporation of a nonspecific reduction catalyst inside SNTs can lead to the inactivation of a broad range of compounds. By optimizing the internal surface modification, SNTs can be an ideal platform for a nanodetoxification system.

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Executive summary

- Nanoparticles were introduced as potential parenteral detoxifying agents designed to circulate the bloodstream and capture toxic compounds, with the ultimate goal of reducing the concentration of free drug in the body.
- Microemulsions, lipid nanocapsules, liposomes and polymer nanoparticles have the capability to capture various drugs, either through adsorption to the surface or internalization by the material.
- Versatility and multifunctionality of inorganic, hollow nanoparticles offer an ideal platform for the uptake of toxic compounds.
- Biotransformations performed by the human xenobiotic metabolism offer insight into the mechanisms that can be used to improve the efficacy of detoxification systems.
- Methods that combine inorganic, hollow nanoparticles and biotransformation mechanisms have tremendous potential to treat drug intoxications.
- Further investigation of suitable inner surface modifications of the hollow nanoparticles is required to develop a general nanodetoxification system.

Figure 1. Amitriptyline uptake by pH gradient spherulite and lipid nanocapsule
Adapted with permission from [35].

Figure 2. Removal of drug molecules by microemulsion droplet
Adapted with permission from [30].

Figure 3. Molecularly imprinted polymer fabrication

MIPNP: Molecularly imprinted polymer nanoparticle.

Adapted with permission from [55].

Figure 4. Nanodetoxification by silica nanoreactor
PEG: Polyethylene glycol.

Table 1

Nanomaterials under investigation as nanodetoxifiers.

Type of nanomaterial	Composition	Mechanism of uptake	Ref.
Microemulsion	Poloxamer/ethyl butyrate/fatty acids	Adsorption	[30]
	Brij 97/hexadecane/octadecyltrimethoxysilane Tween-80/ethyl butyrate/fatty acids/octadecyltrimethoxysilane	Partition	[28,33]
Lipid nanocapsule	Phosphatidylcholine/triglyceride	Partition	[34]
Liposomes	Dimyristoylphosphatidylglycerol/dioleoylglycerophosphoglycerol	Electrostatic interactions	[27,37]
	Phosphatidylcholine/distearoylphosphatidylethanolamine-PEG	pH gradient	[24,25,35]
	Palmitoylcholine/dioleoylglycerophosphocholine/ dioleoylglycerophosphocholine/dipalmitoylglycerophosphocholine/ dipalmitoylglycerophosphoethanolamine-PEG/Rhodanese	Enzymatic degradation	[38]
	Oligochitosan/dinitrobenzenesulfonyl	π - π interactions	[42,43]
Polymers	<i>N</i> -isopropylacrylamide/ <i>N,N'</i> -methylenebisacrylamide/ butylacrylamide/acrylic acid	Hydrophobic/hydrogen bonding/ electrostatic interactions	[31]
	Carbon-coated iron carbide magnetic nanoparticles, digoxin anti-immune FAB	Antibody-antigen interactions	[40]
	Carbon-coated iron carbide/diethylenetriaminepentaacetic acid	Chelation	[40]
	Magnetic latex nanoparticles, streptavidin	Protein-ligand interaction	[32]

FAB: Antigen-binding fragment; PEG: Polyethylene glycol.