Injectable nanocarriers for biodetoxification

Hospitals routinely treat patients suffering from overdoses of drugs or other toxic chemicals as a result of illicit drug consumption, suicide attempts or accidental exposures. However, for many life-threatening situations, specific antidotes are not available and treatment is largely based on emptying the stomach, administering activated charcoal or other general measures of intoxication support. A promising strategy for managing such overdoses is to inject nanocarriers that can extract toxic agents from intoxicated tissues. To be effective, the nanocarriers must remain in the blood long enough to sequester the toxic components and/or their metabolites, and the toxin bound complex must also remain stable until it is removed from the bloodstream. Here, we discuss the principles that govern the use of injectable nanocarriers in biodetoxification and review the pharmacological performance of a number of different approaches.

JEAN-CHRISTOPHE LEROUX

Canada Research Chair in Drug Delivery, Faculty of Pharmacy, University of Montreal, P.O. Box 6128 Downtown Station, Montreal, Quebec, Canada, H3C 3J7
e-mail: Jean-Christophe.Leroux@umontreal.ca

Acute intoxications, either accidental or intentional, constitute a major public health problem worldwide[1]. Drugs account for about 40% of toxic exposures in humans, and a significant number of deaths are associated with overdoses of analgesics, antidepressants, sedatives/hypnotics/antipsychotics, stimulants and cardiovascular drugs. Unfortunately, antidotes are limited to a relatively small number of agents. For the most severe intoxications, treatments are largely based on general measures of intoxication support, such as administration of activated charcoal, gastric emptying, whole bowel irrigation, correction of electrolyte disturbances and removal of toxins through extracorporeal procedures[2]. Orally administered activated charcoal adsorbs and eliminates drugs/metabolites that are still present or being secreted in the gastrointestinal tract. Although this technique is valuable, it can only be used on conscious patients. On the other hand, whole bowel irrigation and haemodialysis are reserved for eliminating specific life-threatening toxins[3]. For instance, haemodialysis (which involves removing substances from the blood by passing the blood through a semi-permeable membrane in a bedside dialysis machine) is particularly suited for drugs or metabolites that are water soluble, have a low volume of distribution (V_d) (that is, they do not distribute to a large extent to tissues/organs), a molecular weight of less than 500 g mol^{-1} and low plasma protein binding[3].

One emerging strategy for managing overdose involves injecting nanosized particulate carriers (<1 μm) to reduce the free drug concentration in the body by acting as a sink for the toxin (Fig. 1). The injected nanocarriers that are either in the circulatory system or have diffused in the peripheral organs extract the drug from the intoxicated tissues and then exit the body via the kidneys or liver. Nanosized carriers can take the form of liposomes, nanoemulsions, nanoparticles and macromolecules. Owing to their high specific surface area and adjustable composition/surface properties, which can be manipulated to optimize uptake and circulation time, several of these carriers can function as detoxifiers. The systems used in biodetoxification usually share the same characteristics as those used in drug delivery, with the exception that the affinity of the toxic agent to the carrier should be very high to ensure rapid and efficient removal of toxins from the peripheral tissues. Here, we examine the principles and pharmacological performance of four main carrier systems currently studied as sequestering agents.

In toxicity reversal, several parameters of the toxic agent, such as its molecular weight, ionization constant, affinity for blood proteins, V_d, half-life, toxicological profile and the presence of active metabolites, must be considered. As shown in Table 1, most drugs involved in poisoning are weak bases that are characterized by a large V_d, high protein binding and the presence of active metabolites. A large V_d may complicate the detoxification procedure, especially if the transfer rate of the toxins from the tissues to the blood is slow. Similarly, when drugs bind to blood proteins, the extraction efficiency is lowered because less drug is available for capture[4]. The potential toxicity of metabolites is also an important parameter to consider. By the time an intoxicated patient is admitted to the emergency ward, a substantial amount of the drug may have been converted into active metabolites. For example, upon oral absorption, 40% of amitriptyline – an antidepressant – is metabolized by the liver into its active demethylated form, nortriptyline[5]. Finally, close attention should be paid to the delay between drug/chemical intake and administration of the antidote. In most laboratory settings, the nanocarrier is administered prior to or within minutes after exposure to the toxic agent. This almost never occurs in practice as patients are often treated hours after the onset of symptoms.

When used as detoxifiers, injectable nanocarriers should meet a number of criteria of which innocuousness, circulation time and uptake capacity are of paramount importance. In principle, the injected carrier must remain in the blood long enough for the toxic agent to be extracted sufficiently from the peripheral

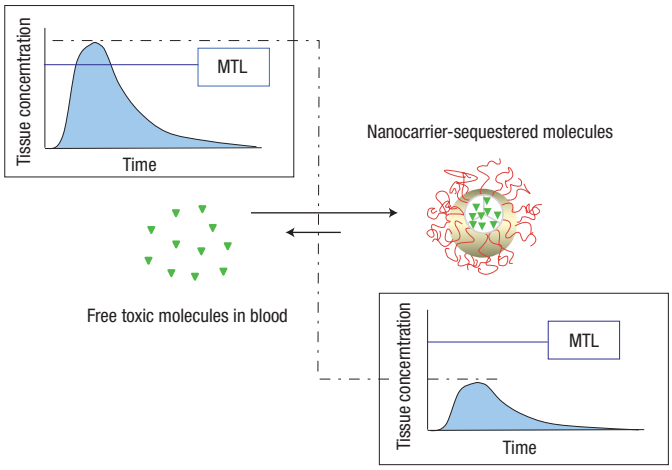

Figure 1 Treating drug overdose and chemical poisoning with nanocarriers. The ingestion of a toxic dose of a chemical results in an elevation of its tissue concentrations above the minimum toxic level (MTL; blue line). This toxic concentration is maintained until the chemical is eliminated from the tissue by diffusion and/or metabolism, resulting in a decrease of tissue levels (upper curve). The sequestration of the toxin by circulating nanocarriers allows the redistribution of the chemical from the peripheral tissues into the blood compartment. This reduces tissue exposure to the toxic compound, bringing its concentration below the MTL at a faster rate (lower curve). Note: sequestration of the toxic molecules by the nanocarrier can also take place directly in the tissues.

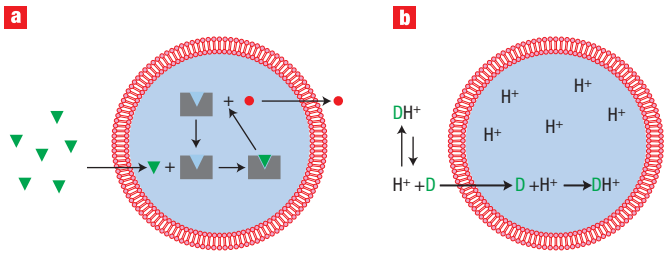

Figure 2 Schematic representation of two vesicular nanostructures used in detoxification. Nanocarriers can contain an enzyme (grey) within the vesicle (blue), which converts the toxic agent (green triangles) into an inactive product (red circles) (**a**), or they can maintain a transmembrane pH-gradient between the inside (blue) and outside of the vesicles (**b**). In the latter case, the unionized toxic agent (D) diffuses down the pH gradient into the vesicle interior where it is trapped in an ionized form (DH^+ for a weak base). Diffusion continues until the internal buffering capacity is overwhelmed.

tissues. The circulating carrier should also be stable enough to avoid rapid release of the sequestered drug back into the tissues. The circulation time of a colloid, for instance, depends on its hydrodynamic volume, shape and surface properties. Coating nanocarriers with hydrophilic, flexible polymers such as polyethylene glycol (PEG) can slow down their clearance by the immune system and improve their half-lives in the blood. For spherical colloids, maximum circulation times are obtained for those with diameters between 50–200 nm (ref. 6). Very small colloids (<8 nm) are excreted by the kidneys[7] and/or rapidly accumulate in the liver, whereas large particles (>200 nm) are subjected to major uptake by the spleen[8]. Nanocarriers (and their toxic cargos) are generally eliminated from the bloodstream within 24 h and mostly end up in the liver where the toxic compound is metabolized. Fortunately, apart from a few compounds, most drugs rarely cause liver injury upon acute poisoning[9].

To rapidly bring tissue concentrations below the toxic threshold, the overdosed agent should be extensively and rapidly sequestered. When using oil-based nanostructures as detoxifiers, the oil (that is, lipids) needs to be carefully selected to maximize compatibility with the toxin[9]. Unfortunately, because many hydrophobic and amphiphilic drugs are poorly soluble in injectable oils that are approved for human applications[10], the nanocarrier dose required to extract the toxic agent is important. Given the non-repetitive nature of the treatment, infusing high amounts of lipids may be feasible in the context of detoxification. However, injecting large doses of carrier (>1 $g\,kg^{-1}$ or >5 $ml\,kg^{-1}$ for a typical 20%-lipid emulsion) can slow down the detoxification process because this increases the time during which the antidote is given.

The partition coefficient, P — which is a measure of a compound's differing solubility in two solvents — for the oil phase is not the sole parameter governing the uptake of toxic agents by oil-based nanostructures because amphiphilic compounds that possess hydrophilic and hydrophobic properties can adsorb at the oil/water interface. Adsorption depends on specific surface area which, in turn, depends on particle size. It has been demonstrated that the extraction capacity often increases with decreasing particle size[11,12]. Furthermore, in the case of amphiphilic charged drugs, adsorption at the interface can be enhanced by adding to the nanocarrier an oppositely charged component that interacts electrostatically with the toxic agent[13]. Chemically modifying the nanocarrier with specific functional groups, such as electron-deficient aromatic rings that bind to compounds with π-electron-rich aromatic rings[14], can also increase drug uptake and improve extraction.

An alternative strategy to optimize extraction is to create an elevated concentration gradient between the inside and outside of the nanocarrier. This can be achieved by encapsulating an enzyme that degrades the toxic agent into water-filled vesicular structures (Fig. 2a)[15]. As the toxin diffuses into the carrier and is metabolized by the enzymes, more toxic compounds can be pumped into the carrier. This detoxification measure requires the toxic agent to freely permeate the vesicle membranes and the entrapped enzyme to remain active for at least a few hours while circulating in the blood.

Another approach, which is simpler but only applicable to ionizable drugs (this includes weak bases or acids, Table 1), involves sequestering the toxic agent into nanosized vesicles by creating a transmembrane pH gradient. This concept is similar to the urinary pH manipulation technique used by clinicians to accelerate excretion of ionizable drugs from the kidneys. The neutral form of low-molecular-weight weak acids and bases can permeate vesicle membranes at much faster rates than their ionized forms. If a vesicle exhibits a pH gradient (acidic or basic for weak bases or acids, respectively), the unionized compound diffuses down its concentration gradient into the vesicle interior where it is subsequently ionized and trapped (Fig. 2b)[16]. The diffusion of the toxic agent's neutral form will continue until the interior buffering capacity is overwhelmed. This extraction process is very efficient, even for molecules that are highly protein-bound[4].

Several colloidal carriers have been investigated for detoxification applications over the past two decades (Table 2). These systems have sizes ranging from a few nanometres (polymers) to half a micrometre (emulsions in parenteral nutrition). The following section provides an overview of their pharmacological performance as sequestering agents.

Table 1 Pharmaceutical agents commonly involved in overdoses. Most drugs do not have specific antidotes. They are generally ionizable, possess a large volume of distribution (*Vd*), bind avidly to blood proteins and are often degraded into pharmacologically active metabolites. Compiled from refs 1,9,48.

Drug	Class	Base/acid	Half-life (h)	Protein binding (%)	V_d (l kg^{-1})	Active metabolites	Specific antidote
Acetaminophen	Analgesic	-	1–3	8–43	0.8–1	No	Acetylcysteine
Aspirin	Analgesic	Acid	2–4.5	50–80	0.1–0.3	Yes	No
Fentanyl	Analgesic, narcotic	Base	2–7	80	4	No	Naloxone
Methadone	Analgesic, narcotic	Base	15–59	80–85	1–8	No	Naloxone
Amitriptyline	Antidepressant	Base	9–25	95	8	Yes	No
Bupropion	Antidepressant	Base	14	82–88	19–21	Yes	No
Doxepine	Antidepressant	Base	8–15	80	6–8	Yes	No
Venlafaxine	Antidepressant	Base	3–7	27	7.5	Yes	No
Diltiazem	Cardiovascular drug	Base	4–6	77–85	3–7	Yes	No
Verapamil	Cardiovascular drug	Base	2–8	90	4.7	Yes	No
Metformin	Antidiabetic drug	Base	2–6	Negligible	650	No	No
Valproic acid	Anticonvulsant	Acid	5–20	80–95	0.1–0.5	Yes	No
Phenobarbital	Anticonvulsant	Acid	80–120	20–50	0.5–0.9	No	No
Alprazolam	Anti-anxiety drug	-	12–15	80	0.9–1.2	No	Flumazenil
Haloperidol	Antipsychotic	Base	20	90	18–30	Yes	No
Quetiapine	Antipsychotic	Base	6	83	10	No	No
Diphenhydramine	Antihistamine	Base	2–8	78	5	No	No

Table 2 Non-immune nanocarriers under investigation for biodetoxification. These carriers have sizes ranging from a few to several hundred nanometres. With the exception of polymers, most of the systems described so far in the literature to treat drug overdose have been prepared from natural or synthetic lipids.

System	Composition	Diameter (nm)	Mechanism*	Model toxin/drug	Reference
Liposomes	POPC/Chol/ DPPE-PEG	100	Enzymatic degradation	Paraoxon	19
	POPC/Chol/DPPE-PEG	100	Enzymatic degradation	Diisopropylfluoro-phosphate	21
	DOPC/Chol ± DSPE-PEG	1600	Chelation	^{239}Pu-phytate ^{238}Pu-citrate	49
	DOPC/Chol/DSPE-PEG	100–1,600	Chelation	^{238}Pu-phytate	28
	DMPC/DOPG	40–45	Partition/electrostatic interactions	Amitriptyline	50
	SPC/Chol	200	pH gradient	Haloperidol	4
	SPC/Chol	180	pH gradient	Amitriptyline	23
Nanoemulsions	Soybean oil/egg PC	430	Partition	Bupivacaine	29,30
	Ethyl butyrate/fatty acid/poloxamer	15–40	Partition/electrostatic interactions	Bupivacaine	13
	SPC/MCT/HSA-EO	118	Partition	Bupivacaine	11
	PC/MCT/HSA-PEG ± lauric acid ± DSPE-PEG	60–90	Partition/electrostatic interactions	Haloperidol Docetaxel Paclitaxel	33
	SPC/MCT/HSA-PEG ± lauric acid	60–90	Partition/electrostatic interactions	Amitriptyline	23
Nanocapsules	Hexadecane/polysiloxane-silicate	98	Partition	Quinoline Bupivacaine	35
	PS-80/ethyl butyrate/PC/polysiloxane-silicate	30–300	Partition	Quinoline	12
Nanospheres	Magnetite	8	Chelation	Uranyl(2+) cation	51
Polymers	γ-cyclodextrin derivative	~1	Hydrophobic/electrostatic interactions	Rocuronium Vecuronium	41 52
	Dinitrobenzesulfonyl chitosan	n.a.	π–π interactions	Amitriptyline	14,43

POPC = palmitoyloleoylphosphatidylcholine, Chol = cholesterol, DPPE = dipalmitoylphosphatidylethanolamine, DSPE = distearoylphosphatidylethanolamine, DOPC = dioleoylphosphatidylcholine, PG = phosphatidylglycerol, DMPC = dimyristoylphosphatidylcholine, DOPG = dioleoylphosphatidylglycerol, PC = phosphatidylcholine, MCT = medium chain triglycerides, SPC = soybean phosphatidylcholine, HSA-PEG = poly(ethylene glycol)(660)-12-hydroxystearate, PS-80 = polysorbate 80, n.a. = not available.

*In this table, all reported electrostatic interactions occur between a negatively-charged colloid and a positively charged drug.

LIPOSOMES

Liposomes are spherical vesicles that possess one or more concentric phospholipid bilayer membrane that delimit aqueous compartments. They have been extensively studied for the treatment of intoxications due to organophosphorus agents (OPs), which are toxic agents commonly found in agriculture pesticides. The first use of liposomes as antidotes for OPs was a follow-up to the work of Way and co-workers wherein resealed red blood cells served as vesicles to encapsulate the enzymes rhodanese and organophosphorus acid anhydrolase (OPAA) which degrade cyanide[17] and OPs[18], respectively (Fig. 2a). The approach was later refined by entrapping OPAA in neutral long-circulating PEGylated liposomes[19–21]. Compared with red blood cells, liposomes are advantageous because they are built from non-human-derived material, can undergo large-scale production and exhibit a greater shelf-life. In mice, liposomal OPAA was found be quite efficient in detoxifying OPs, but only when administered in prevention (that is, prior to intoxication)[19]. Unfortunately, a substantial loss of protection against OP-induced mortality was observed when the antidote was given after the injection of the OP — a situation more likely to happen under real conditions of intoxication[20]. Although these data confirmed the therapeutic value of liposomal OPAA, they also revealed how important timing is in reversing intoxications.

As pointed out previously, transmembrane pH gradients can help take up low-molecular-weight weak acids or bases from physiological media. In an elegant study, Mayer *et al.*[22] demonstrated

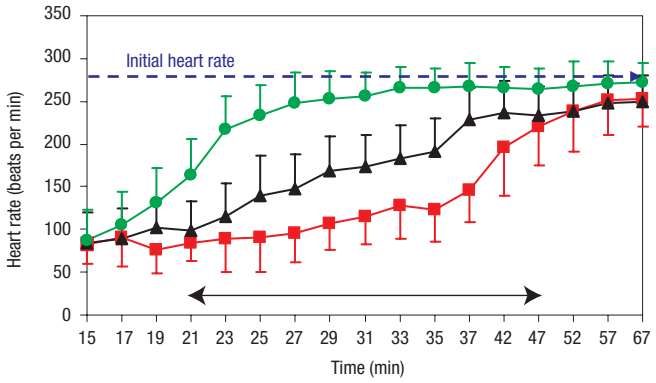

Figure 3 Heart-rate recovery after intoxication and addition of a nanocarrier. Overdose of amitriptyline — an antidepressant — elevates heart rates and brings about deleterious effects on the heart (cardiotoxicity). Isolated rat hearts were infused for 12 min with amitriptyline (17 μM) to cause intoxication and subsequently perfused with pH 7.4 buffer (red squares), pH 7.4 spherulites (black triangles), or pH 3.0 gradient spherulites (green circles) from 15 to 37 min. Perfusion of pH 3.0 gradient spherulites resulted in swift recovery of heart rate to its initial value because the nanocarrier extracted amitriptyline from the heart tissue and the protonated drug was sequestered within the vesicle aqueous core. The black arrows indicate the time during which the difference in heart beats between the pH 3.0 spherulite and pH 7.4 buffer group was statistically significant ($p<0.01$). Reproduced with permission from ref. 23. Copyright (2007) Elsevier.

that stealth (long-circulating) liposomes with an internal pH of 4, when administered prior to injection of the anticancer drug doxorubicin, captured the drug *in vivo* and decreased its toxicity while maintaining the drug's anti-tumour potency. The pH gradient was relatively stable with a decrease of only 1.5 units over 20 h following injection and this allowed doxorubicin to be sequestered *in situ* at clinically relevant doses of liposomes. Although the aim of this study was to show that pre-treatment with empty liposomes could improve the pharmacokinetic profiles of drugs, it revealed their potential as detoxifying agents. Along those lines, pH-gradient spherulites — a type of multilamellar liposome made from uniformly spaced concentric bilayers — were investigated to counteract an overdose of amitriptyline[23], a potentially cardiotoxic antidepressant. Isolated hearts were first perfused with amitriptyline at a concentration causing cardiotoxicity. Subsequent infusion of pH-gradient spherulites resulted in swift recoveries of heart functions (Fig. 3). These preliminary data are promising because the spherulite concentration in this investigation could be readily achieved *in vivo*[24].

The chelating agent diethylene triamine pentaacetic acid (DTPA) — a molecule that binds cations — is used to decontaminate individuals who have been exposed to toxic heavy metals such as ytterbium[25] and plutonium[26]. DTPA-Pu/Yb complexes are stable, soluble and readily eliminated in the urine. Incorporating DTPA into liposomes was shown to increase its half-life and promote its deposition into tissues such as the liver and bone where heavy metals tend to accumulate and exert their toxicity. Fattal and co-workers[27,28] prepared uncoated and PEGylated liposomes containing DTPA ranging from 100 to 1,600 nm and assessed their Pu decorporation capacities. The encapsulated DTPA exhibited a 3- to 90-fold decrease in clearance with the longest circulation time achieved with small stealth liposomes. This was accompanied by substantial DTPA deposition in the liver regardless of the liposome formulation and comparatively higher levels in the bone compared to the free chelator. Liposomal DTPA improved the Pu excretion, thereby reducing the total Pu burden 30 days after toxic exposure[28].

NANOEMULSIONS

Liposomes have proven to be effective antidotes for amphiphilic compounds that can be inactivated by encapsulated enzymes or actively trapped within their aqueous compartments, but they may not be ideal for highly hydrophobic and poorly or non-ionizable molecules. Under these circumstances, colloidal systems such as nanoemulsions (that is, nanosized droplets of oil dispersed in an aqueous phase), where drug uptake mostly relies on a favourable partition coefficient for oil droplets, may be more appropriate. In some cases, ionizable drugs may exhibit a high affinity for oils or oil/water interfaces and can therefore be extracted by nanoemulsions.

Intralipid — a nutritional supplement — is a soybean oil-in-water emulsion (430 nm) that is stabilized with egg phosphatidylcholine lipid and is commonly injected as a source of triglycerides for individuals who cannot ingest fats orally. This emulsion was evaluated as a detoxifier for hydrophobic drugs such as bupivacaine, a local anaesthetic associated with occasional but severe and potentially lethal cardiotoxicity. In animals, it was found that the infusion of Intralipid immediately after the injection of lethal bupivacaine doses increased survival[29,30]. Case reports documenting the efficacy of Intralipid in humans experiencing anaesthetic-induced cardiotoxicity have also been published[31,32]. Considering the low affinity of bupivacaine for Intralipid ($\log P_{\text{emulsion/plasma}}<10$), the positive effect of the treatment could be partially attributed to the large dose of lipids injected (several grams of triglycerides per kilogram), which favoured drug partition to the oil phase.

Recently, the effect of pre- and post-dosing of PEGylated tricaprylin emulsions (another triglyceride based emulsion) on the pharmacokinetics and biodistribution of docetaxel (a model non-ionisable anticancer drug) was addressed[33]. The injection of the emulsion (500 mg kg^{-1}) 20 min after docetaxel administration produced a rapid drug sequestration in the blood pool. Furthermore, after uptake by the emulsion, the drug was mainly redirected to the liver and spleen, which are the main organs of colloid deposition. These findings clearly illustrate that nanoemulsions can extract drugs that have already been distributed to peripheral tissues.

NANOPARTICLES

Emulsions are particularly attractive in the biomedical field because they can be prepared from generally recognized-as-safe excipients. However, they often face inherent formulation issues arising from thermodynamic instability, which can lead to the coalescence of oil droplets over time or their disassembly in the bloodstream. Moreover, their long-term stability is also limited by difficulties in obtaining dry formulations for prolonged storage. This is particularly relevant in the context of detoxification because turnover is expected to be low. To enhance stability, nanoemulsions can be coated with a hard polymeric shell, leading to the formation of nanocapsules. The shell renders the carrier more robust and controls drug uptake kinetics[34]. Underhill *et al.*[35] prepared hexadecane-filled polysiloxane/silicate nanocapsules and assessed their ability to sequester bupivacaine and quinoline. *In vitro*, the nanocapsules rapidly removed these two drugs from a normal saline solution. Nonetheless, the low biodegradability of their polymeric shell and their interaction with blood components — rupturing red blood cells and delaying clotting time — would hamper their use in the clinic.

PEGylation of these nanocapsules was, however, found to improve blood compatibility[36].

An interesting concept based on injectable magnetic nanospheres was recently introduced to remove deleterious compounds. Magnetic nanospheres were functionalized with ligands that recognize a particular toxin[37]. Once bound to the ligand on the carrier, the toxin is removed using a magnetic filter unit. Such a system is still in the early development stage, and no data other than *in vitro* extraction results are available so far.

MACROMOLECULAR CARRIERS

Water-soluble macromolecules have been investigated as nanomedicines for more than three decades to increase the circulation time of bound drugs and improve their site-specific delivery[38]. Whole antibodies and antibody fragments represent one of the most studied classes of macromolecular carriers. Their first documented therapeutic human application dates back to the 1970's and concerned the treatment of digitalis (a cardiovascular drug) intoxication[39]. Since then, the concept has been applied with some success to several drugs (for example, amitriptyline) and toxins (for example, colchicine). This detoxification procedure, which is potentially very powerful owing to the high specificity and affinity of the antibody–antigen interaction, nonetheless, faces important limitations. In order to produce specific high affinity antibodies directed towards the toxic compound, the latter should have an immunogenic character, which is not always the case. Moreover, each antibody or antibody fragment can neutralize a limited number of toxic molecules, making this approach appropriate mostly for compounds that are toxic at very low doses.

Non-immune macromolecules such as cyclodextrins (cyclic oligosaccharides), can also reverse the pharmacological effect of drugs. For example, Sugammadex is a novel γ-cyclodextrin based molecule that forms an exceptionally stable 1:1 complex with the neuromuscular blocking agent, rocuronium (association constant ~10^7 M^{-1})[40]. Neuromuscular blocking drugs are used to relax muscles during surgery. After completion of the surgery, these drugs are often neutralized with a pharmacological agent to accelerate recovery from neuromuscular blockade. In Sugammadex, the dextrose units of cyclodextrin were modified to better accommodate the rocuronium and enhance the electrostatic interactions between them. The intravenous injection of Sugammadex was shown to deplete the free rocuronium in plasma and enhance its urinary excretion[41]. Several clinical studies have clearly established the remarkable efficacy of Sugammadex at quickly reversing the neuromuscular block without inducing serious adverse events[42].

Recently, oligochitosan, a linear biodegradable copolymer of *N*-acetyl-D-glucosamine and D-glucosamine (1150 g mol^{-1}), was studied as a detoxifier for amitriptyline. The polymer was modified with dinitrobenzenesulfonyl groups to selectively bind amitriptyline via π–π interactions. The functionalized polymer alone seemed inert because it did not affect blood clotting *in vitro*[14]. Perfusion of the amitriptyline-polymer complex in isolated hearts reduced the drug's cardiotoxicity, whereas the unmodified polymer had no effect[43]. This study proves that the amitriptyline binding to the chitosan derivative prevents the drug from diffusing into the heart tissue. However, the potential liver toxicity of the dinitrobenzylsulfonide moiety, which could arise at the high doses that are required for biodetoxification, remains to be investigated.

CONCLUSION AND PERSPECTIVES

Since liposomes were first proposed as a means of treating poisoning almost 35 years ago[26], tremendous progress has been made in perfecting nanocarriers for biodetoxification applications. Yet, only a single system developed so far has reached the clinical stage, partly because combining properties such as biocompatibility, long circulation time, stability and high extraction efficacy is not trivial. Recent advances in the field of nanotechnology may be exploited to successfully attain this goal. For instance, instability problems commonly encountered with liposomes can be circumvented by engineering nanosized vesicles from biodegradable multiblock polymers[44] or shell crosslinked nanocages[45]. On the other hand, the affinity between the drug and nanocarrier can be enhanced by using molecular imprinting techniques[46]. Polymeric matrices are imprinted with a template (which could, for example, be made from a drug) and are then washed away. This leaves vacant sites that can rebind the imprinted molecule with high specificity and affinity. In the future, nanocarriers may also be used to sequester high-molecular-weight hydrophilic toxins. Indeed, reverse polymeric micelles from hyperbranched and star-shape polymers can be tailored to take up macromolecules in their hydrophilic inner core[47].

doi:10.1038/nnano.2007.339

References

1. Watson, W. A. *et al.* 2004 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am. J. Emerg. Med.* **23,** 589–666 (2005).
2. Mokhlesi, B., Leiken, J. B., Murray, P. & Corbridge, T. C. Adult toxicology in critical care - Part I: general approach to the intoxicated patient. *Chest* **123,** 577–592 (2003).
3. Zimmerman, J. L. Poisonings and overdoses in the intensive care unit: general and specific management issues. *Crit. Care Med.* **31,** 2794–2801 (2003).
4. Babu Dhanikula, A., Lafleur, M. & Leroux, J. C. Characterization and in vitro evaluation of spherulites as sequestering vesicles with potential application in drug detoxification. *Biochim. Biophys. Acta* **1758,** 1787–1796 (2006).
5. Breyer-Pfaff, U. The metabolic fate of amitriptyline, nortiptyline and amitriptylinoxide in man. *Drug Metab. Rev.* **36,** 723–746 (2004).
6. Allen, T. M. & Cullis, P. R. Drug delivery systems: entering the mainstream. *Science* **303,** 1818–1822 (2004).
7. Yamaoka, T., Tabata, Y. & Ikada, Y. Distribution and tissue uptake of poly(ethylene glycol) with different molecular weights after intravenous administration to mice. *J. Pharm. Sci.* **83,** 601–606 (1994).
8. Moghimi, S. M., Hunt, A. C. & Murray, J. C. Long-circulating and target-specific nanoparticles: theory to practice. *Pharmacol. Rev.* **53,** 283–318 (2001).
9. Olson, K. R. Poisoning and drug overdose. (Lange Medical Books / McGraw-Hill, New York, 2007).
10. Rossi, J. & Leroux, J. C. in *Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery* (ed. K. M. Wasan) 88–123 (John Wiley & Sons, Hoboken, 2006).
11. Morey, T. E. *et al.* Treatment of local anesthetic-induced cardiotoxicity using drug scavenging nanoparticles. *Nano Lett.* **4,** 757–759 (2004).
12. Jovanovic, A. V., Underhill, R. S., Bucholz, T. L. & Duran, R. S. Oil core and silica shell nanocapsules: toward controlling the size and the ability to sequester hydrophobic compounds. *Chem. Mater.* **17,** 3375–3383 (2005).
13. Varshney, M. *et al.* Pluronic microemulsions as nanoreservoirs for extraction of bupivacaine from normal saline. *J. Am. Chem. Soc.* **126,** 5108–5112 (2004).
14. Lee, D. W. & Baney, R. H. Oligochitosan derivatives bearing electron-deficient aromatic rings for adsorption of amitryptiline: implications for drug detoxification. *Biomacromolecules* **5,** 1310–1315 (2004).
15. Walde, P. & Ichikawa, S. Enzymes inside lipid vesicles: preparation, reactivity and applications. *Biomol. Eng.* **18,** 143–177 (2001).
16. Cullis, P. R. *et al.* Influence of pH gradients on the transbilayer transport of drugs, lipids, peptides and metal ions into large unilamellar vesicles. *Biochim. Biophys. Acta* **1331,** 187–211 (1997).
17. Leung, P. *et al.* Encapsulation of thiosulfate:cyanide sulfurtransferase by mouse erythrocytes. *Toxicol. Appl. Pharmacol.* **83,** 101–107 (1986).
18. Pei, L., Petrikovics, I. & Way, J. L. Antagonism of the lethal effects of paraoxon by carrier erythrocytes containing phosphotriesterase. *Fundam. Appl. Toxicol.* **28,** 209–214 (1995).
19. Petrikovics, I. *et al.* Antagonism of paraoxon intoxication by recombinant phosphotriesterase encapsulated within sterically stabilized liposomes. *Toxicol. Appl. Pharmacol.* **156,** 56–63 (1999).
20. Petrikovics, I. *et al.* Comparing therapeutic and prophylactic protection against the lethal effect of paraoxon. *Toxicol. Sci.* **77,** 258–262 (2004).
21. Petrikovics, I. *et al.* Long circulating liposomes encapsulating organophosphorus acid anhydrolase in diisopropylfluorophosphate antagonism. *Toxicol. Sci.* **57,** 16–21 (2000).
22. Mayer, L. D., Reamer, J. & Bally, M. B. Intravenous pretreatment with empty pH gradient liposomes alters the pharmacokinetics and toxicity of doxorubicin through in vivo active drug encapsulation. *J. Pharm. Sci.* **88,** 96–102 (1999).
23. Babu Dhanikula, A., Lamontagne, D. & Leroux, J. C. Rescue of amitriptyline-intoxicated hearts with nanosized vesicles. *Cardiovasc. Res.* **74,** 480–486 (2007).
24. Simard, P., Hoarau, D., Khalid, M. N., Roux, E. & Leroux, J. C. Preparation and in vivo evaluation of PEGylated spherulite formulations. *Biochim. Biophys. Acta* **1715,** 37–48 (2005).
25. Blank, M. L., Cress, E. A., Byrd, B. L., Washburn, L. C. & Snyder, F. Liposomal encapsulated Zn-DTPA for removing intracellular ^{169}Yb. *Health Phys.* **39,** 913–920 (1980).
26. Rahman, Y. E., Rosenthal, M. W. & Cerny, E. A. Intracellular plutonium: removal by liposome-encapsulated chelating agents. *Science* **180,** 300–302 (1973).

27. Phan, G. *et al.* Pharmacokinetics of DTPA entrapped in conventional and long-circulating liposomes of different size for plutonium decorporation. *J. Controlled Release* **110,** 177–188 (2005).
28. Phan, G. *et al.* Enhanced decorporation of plutonium by DTPA encapsulated in small PEG-coated liposomes. *Biochimie* **88,** 1843–1849 (2006).
29. Weinberg, G. L., VadeBoncouer, T., Ramaraju, G. A., Garcia-Amaro, M. F. & Cwik, M. J. Pretreatment of resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesthesiology* **88,** 1071–1075 (1998).
30. Weinberg, G. L., Ripper, R., Feinstein, D. L. & Hoffman, W. Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. *Reg. Anesth. Pain Med.* **28,** 198–202 (2003).
31. Rosenblatt, M. A., Abel, M., Fischer, G. W., Itzkovich, C. J. & Eisenkraft, J. B. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. *Anesthesiology* **105,** 217–221 (2007).
32. Foxall, G., McCahon, R., Lamb, J., Hardman, J. G. & Bedforth, N. M. Levobupivacaine-induced seizures and cardiovascular collapse treated with Intralipid. *Anesthesia* **62,** 516–518 (2007).
33. Babu Dhanikula, A. *et al.* Long circulating lipid nanocapsules for drug detoxification. *Biomaterials* **28,** 1248–1257 (2007).
34. Joncheray, T. J. *et al.* Electrochemical and spectroscopic characterization of organic compound uptake in silica core-shell nanocapsules. *Langmuir* **22,** 8684–8689 (2006).
35. Underhill, R. S. *et al.* Oil-filled silica nanocapsules for lipophilic drug uptake: implications for drug detoxification therapy. *Chem. Mater.* **14,** 4919–4925 (2002).
36. Jovanovic, A. V. *et al.* Surface modification of silica core-shell nanocapsules: biomedical implications. *Biomacromolecules* **7,** 945–949 (2006).
37. Mertz, C. J. *et al.* In vitro studies of functionalized magnetic nanospheres for selective removal of a simulant biotoxin. *J. Magn. Magn. Mater.* **293,** 572–577 (2005).
38. Duncan, R. Polymer conjugates as anticancer nanomedicines. *Nat. Rev. Cancer* **6,** 688–701 (2006).
39. Bateman, D. N. Digoxin-specific antibody fragments. *Toxicol. Rev.* **23,** 135–143 (2004).
40. Bom, A. *et al.* A novel concept of reversing neuromuscular blok: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. *Angew. Chem. Int. Edn* **41,** 266–270 (2002).
41. Sorgenfrei, I. F. *et al.* Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex. *Anesthesiology* **104,** 667–674 (2006).
42. Naguib, M. Sugammadex: another milestone in clinical neuromuscular pharmacology. *Anesth. Analg.* **104,** 575–581 (2007).
43. Lee, D. W. *et al.* Aromatic-aromatic interaction of amitriptyline: implication of overdosed drug detoxification. *J. Pharm. Sci.* **94,** 373–381 (2005).
44. Discher, D. E. & Eisenberg, A. Polymer vesicles. *Science* **297,** 967–973 (2002).
45. O'Reilly, R. K., Hawker, C. J. & Wooley, K. L. Cross-linked block copolymer micelles: functional nanostructures of great potential and versatility. *Chem. Soc. Rev.* **35,** 1068–1083 (2006).
46. Mayes, A. G. & Whitecombe, M. J. Synthetic strategies for the generation of molecularly imprinted organic polymers. *Adv. Drug Deliv. Rev.* **57,** 1742–1778 (2005).
47. Jones, M. C. *et al.* Self-assembled nanocages for hydrophilic guest molecules. *J. Am. Chem. Soc.* **128,** 14599–14605 (2006).
48. Lacy, C. F., Armstrong, L. L., Goldman, M. P. & Lance, L. L. *Drug Information Handbook* edn 14 (Lexi-Comp, Hudson, 2006).
49. Phan, G. *et al.* Targeting of diethylene triamine pentaacetic acid encapsulated in liposomes to rat liver: an effective strategy to prevent bone deposition and increase urine elimination of plutonium in rats. *Int. J. Radiat. Biol.* **80,** 413–422 (2004).
50. Fallon, M. S. & Chauhan, A. Sequestration of amitriptyline by liposomes. *J. Colloid Interface Sci.* **300,** 7–19 (2006).
51. Wang, L. *et al.* A biocompatible method of decorporation: bisphosphonate-modified magnetite nanoparticles to remove uranyl ions from blood. *J. Am. Chem. Soc.* **128,** 13358–13359 (2006).
52. Suy, K. *et al.* Effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block with sugammadex, a selective relaxant binding agent. *Anesthesiology* **106,** 283–288 (2007).

Acknowledgements

The Canada Research Chair program and the Natural Sciences and Engineering Research Council of Canada (NanoIP program) are acknowledged for their financial support.
Correspondence should be addressed to J.-C. Leroux.