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Review

Recent Development of Nanoparticle Platforms for Organophosphate Nerve Agent Detoxification

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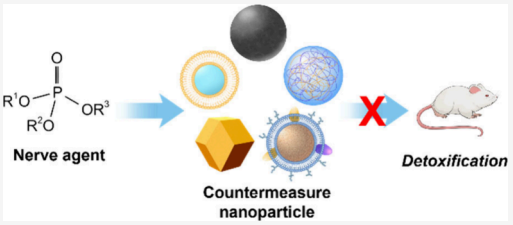
ABSTRACT: Poisoning by organophosphate (OP) nerve agents remains a pressing global threat due to their extensive use in chemical warfare agents and pesticides, potentially causing high morbidity and mortality worldwide. This urgent need for effective countermeasures has driven considerable interest in innovative detoxification approaches. Among these, nanoparticle technology stands out for its multifunctional potential and wide-ranging applications. This review highlights recent advancements in nanoparticle platforms developed for OP detoxification, focusing on five main types: inorganic nanoparticles, lipid-based nanoparticles, polymer-based nanoparticles, metal−organic framework nanoparticles, and cellular nanoparticles. For each platform, we discuss representative examples that illustrate how structural and functional properties enhance their effectiveness as nanocarriers, nanocatalysts, or nanoscavengers, ultimately enabling safe and efficient OP detoxification. This review aims to stimulate further technological innovation in OP-detoxifying nanoparticles and encourage broader development of detoxification strategies.



1. INTRODUCTION

Organophosphates (OPs) are a significant cause of poisoning worldwide, resulting in millions of cases and a substantial death rate annually.[1] OPs such as sarin, tabun, soman, and VX are among the most toxic synthetic chemicals with potential use as nerve agents in chemical warfare.[2,3] Exposure to mere milligrams of these agents can induce unconsciousness and seizures within seconds, leading to death from respiratory failure in minutes.[4] Additionally, the widespread use in pesticides has also caused high mortality arising from agricultural accidents or suicide attempts.[5,6] Given such high incidence and severe lethality, OP poisoning is a significant threat to national security and public health.

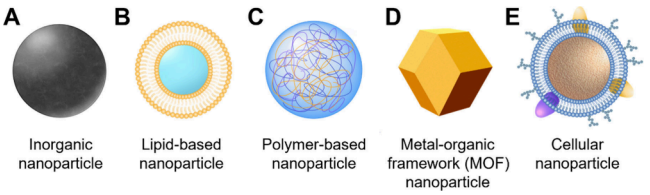


Figure 1. Major nanoparticle platforms used for OP nerve agent detoxification. These platforms include (A) inorganic nanoparticle, (B) lipid-based nanoparticle, (C) polymer-based nanoparticle, (D) metal−organic framework (MOF) nanoparticle, and (E) cellular nanoparticle.

OP poisoning occurs when individuals are exposed to OPs through inhalation, ingestion, or dermal contact.[7] Once inside the body, OPs irreversibly inactivate acetylcholinesterase (AChE) by phosphorylating its serine hydroxyl residue.[8] This inactivation leads to the accumulation of acetylcholine (ACh), which disrupts cholinergic synaptic transmission and causes various neurotoxic effects that can be fatal in severe cases.

Many strategies have been developed to combat OP toxicity. One approach relies on using personal protective equipment (PPE) to prevent contact with OPs.[9] Existing PPE systems provide a temporary barrier against OPs. However, they are not able to degrade these toxic molecules, which will continue to pose a threat.[10] Another approach focuses on developing small molecule OP antidotes.[11] For example, atropine is the most widely used antidote against OP poisoning and is

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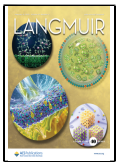

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typically used in conjunction with pralidoxime or other pyridinium oximes to reactivate AChE.[12] Despite its wide usage, studies suggest that oximes may have inconsistent efficacy and could even be harmful in some cases.[13] An overdose of atropine can result in adverse outcomes or even death in patients.[14] Although researchers are actively searching for alternative compounds, safe and effective antidotes remain lacking.[15−17]

Synthetic and biohybrid nanoparticles, including inorganic nanoparticles, lipid-based nanoparticles, polymer-based nanoparticles, metal−organic framework (MOF) nanoparticles, and cellular nanoparticles, have recently gained significant attention for their potential in detoxifying OPs (Figure 1). These tiny nanoparticles integrate multiple functionalities into one entity, offering complex functions and detoxification capabilities unattainable by small molecule drugs.[18] For example, inorganic nanoparticles offer unique functions due to their solid-state crystalline structures, which provide reactive surfaces for direct OP decomposition or easy surface modifications for OP detoxification.[19,20] Additionally, lipid-based nanoparticles such as liposomes, micelles, and emulsions, are typically composed of lipid materials known for their low toxicity. They are versatile vehicles to deliver both hydrophilic and hydrophobic payloads for OP detoxification.[21,22] Moreover, polymer-based nanoparticles present highly customizable architecture and compositions, allowing them to perform multiple functions to detoxify OPs effectively as needed.[23,24] Furthermore, MOF nanoparticles possess highly porous structures, providing extensive surface areas and a high enzyme encapsulation capacity for catalytic degradation of OPs.[25] More recently, cellular nanoparticles stand out with their unique biomimicry, allowing them to act as cell decoys to absorb and neutralize OPs for detoxification.[26]

Despite the diversity, nanoparticle platforms share a few common mechanisms for OP detoxification. For example, some nanoparticles function as nanocarriers to deliver OP-detoxifying agents. Notably, some nanoparticles can cross the blood-brain barrier (BBB), allowing them to deliver agents directly to the central nervous system for better effectiveness.[27] Additionally, some nanoparticles, especially inorganic nanoparticles, function as nanocatalysts to decompose OPs continuously.[28,29] They are highly stable in harsh environment, making them ideal for incorporation into PPE such as face masks.[20,30] Moreover, some nanoparticles function as nanoscavengers through physical partitioning or biological binding. The process avoids the byproduct from OP decomposition, making them a potentially safer choice.[26]

In this review, we explore the application of the above nanoparticle platforms for OP detoxification, focusing on elucidating the structure−function relationship in each platform that leads to effective OP detoxification. Our discussion highlights the synthesis processes, structural features, detoxification mechanisms, and therapeutic outcomes in OP neutralization applications. By investigating these aspects, this review highlights the unique roles these nanoparticle formulations play in counteracting OP toxicity, emphasizing their crucial contributions to developing more effective OP countermeasures.

2. INORGANIC NANOPARTICLES FOR OP NERVE AGENT DETOXIFICATION

Inorganic nanoparticles present promising solutions for the detoxification of nerve agents. Some function as nanocarriers, delivering agents that degrade OPs with enhanced pharmacokinetic profiles. These agents can be directly anchored onto the surfaces of inorganic nanoparticles. For example, gold nanoparticles (AuNPs) were used to load methimazole (MTZ), a small molecule that degrades OPs through thiolysis or iminolysis.[31] In this formulation, MTZ attached to AuNPs via its thiol group, while its imidazole group remained free. The AuNP substrate enhanced the ability of the imidazole group to attack the phosphorus atom in OPs, leading to more efficient detoxification.[32,33] In another example, histidine (His)-tagged phosphotriesterase (PTE) was linked to quantum dots with a cadmium selenide (CdSe) core and a zinc sulfide (ZnS) shell

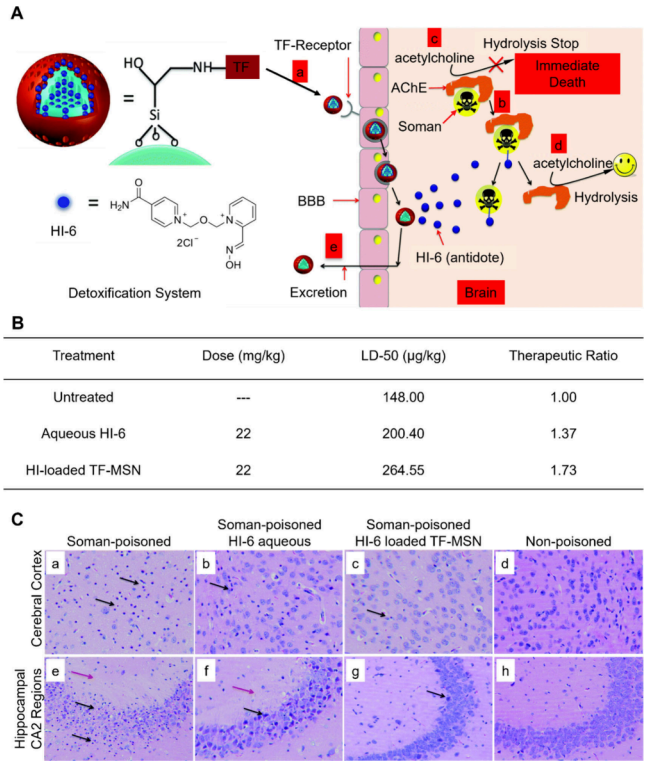

Figure 2. Rapid release of HI-6 via brain-targeted mesoporous silica nanoparticles (MSNs) for nerve agent detoxification. (A) Schematic representation of transferrin-modified MSNs loaded with HI-6 (HI-6-loaded TF-MSNs) and their detoxification process: (a) HI-6-loaded TF-MSNs cross the blood-brain barrier (BBB) via transferrin receptor-mediated endocytosis, releasing HI-6 into the brain; (b, c) Soman inhibits AChE, preventing ACh breakdown, which can lead to fatal consequences; (d) HI-6 reactivates AChE, restoring its function and counteracting the lethal effects of soman poisoning; (e) TF-MSNs are eventually excreted from the brain. (B) Therapeutic efficacy of administered agents in soman-poisoned mice. The LD_{50} represents the median lethal dose of soman required to kill 50% of the mice. The therapeutic factor is calculated as the ratio of the LD_{50} for soman in treated groups to the LD_{50} for the untreated group. A higher therapeutic ratio indicates better protection against soman poisoning. (C) Histopathological analysis of the cerebral cortex and hippocampal CA2 region in soman-poisoned mice. Images depict the cerebral cortex (a-d) and hippocampal CA2 region (e−h) after soman exposure. Black arrows: apoptotic cells, red arrows: edematous regions. Compared to untreated mice and those treated with aqueous HI-6, HI-6-loaded TF-MSNs significantly reduced soman-induced edema and cell apoptosis in both the cerebral cortex and hippocampal CA2 region, underscoring its efficacy in mitigating soman toxicity. Images shown at 200× magnification. Reproduced with permission from ref 37. Copyright 2016 Royal Society of Chemistry.

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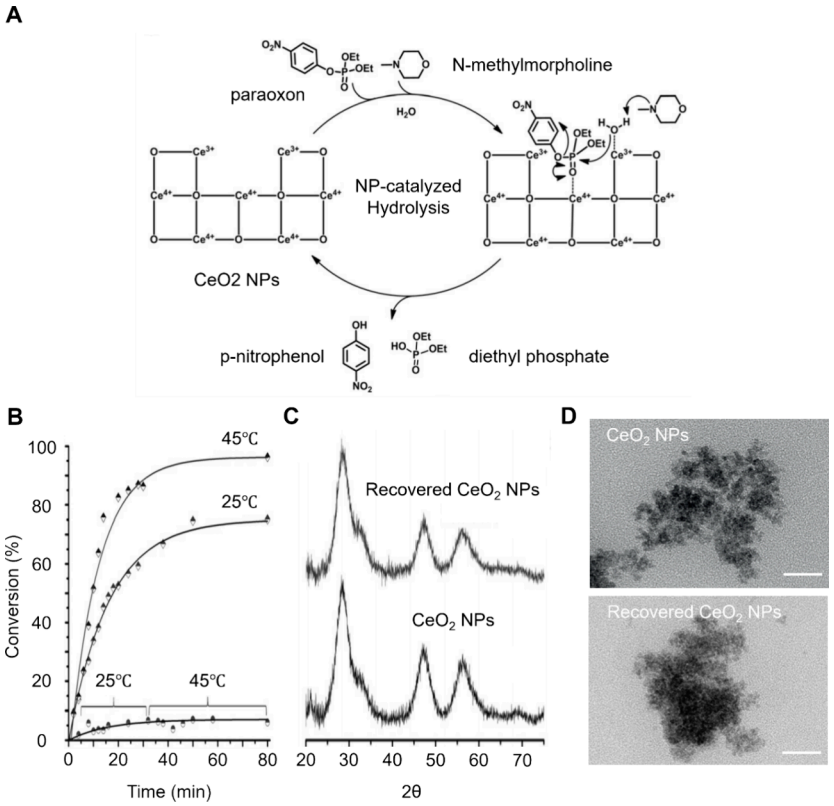

Figure 3. POX hydrolysis catalyzed by cerium dioxide nanoparticles (CeO_2 NPs). (A) Schematic illustration of the degradation process: POX initially binds to the CeO_2 NP surface via its phosphoryl oxygen. Surface hydroxyl groups on the CeO_2 NPs then react with POX, leading to its hydrolysis. *N*-methylmorpholine (NMM) acts as a general base, deprotonating water molecules on the CeO_2 NP surface, making them more reactive and accelerating the hydrolysis rate. (B) Kinetics of POX conversion catalyzed by CeO_2 NPs: the graph shows conversion rates in the presence of CeO_2 NPs at 45 °C (top) and 25 °C (middle), compared to conversion rates in the absence of CeO_2 NPs at 25 and 45 °C (bottom). CeO_2 NPs exhibit a strong catalytic ability to hydrolyze POX, with the reaction rate increasing significantly at higher temperatures. (C) X-ray diffraction (XRD) patterns of CeO_2 NPs before and after the catalytic reaction. The XRD patterns show no significant changes before (bottom) and after (top) the reaction, indicating that the structural integrity of the CeO_2 NPs remains intact throughout the hydrolysis process. This stability suggests that CeO_2 NPs can be reused for further catalytic reactions without losing their effectiveness. (D) Transmission electron microscopy (TEM) images of CeO_2 NPs before and after the catalytic reaction. The TEM images confirm that CeO_2 NPs retain their structural integrity before and after the reaction, further supporting their stability. Scale bar = 20 nm. Reproduced with permission from ref 43. Copyright 2016 John Wiley & Sons, Inc.

Table 1. Mechanisms of Inorganic Nanoparticles for OP Detoxification[a]

Mechanism		Representative example
Acting as nanocarriers for OP-degrading agents	Anchoring the agent on the surface	• AuNPs[31−33] • Quantum dots[34−36]
	Encapsulating the agent inside	• MSN[37]
Physically absorbing OPs		• MSN[38,39]
Acting as catalysts to degrade OPs	Cleaving P−OR or P−F	• Nanoparticles of TiO_2,[20,30] CeO_2,[40] CuO,[29] ZrO_2[41]
	Hydrolyzing	• Nanoparticles of ZnO,[19] CeO_2,[43] MnO_2,[44] Cu/TiO_2,[45,46] $Zr(OH)_4$[47,48]
	Oxidizing	• (MgO@C)[49]

[a]OP: organophosphate; AuNP: gold nanoparticle; MSN: mesoporous silica nanoparticle; P−OR: phosphoryl−alkyl bond; P−F: phosphoryl−fluorine bond; MgO@C: MgO−carbon hybrid nanocomposites.

via His-metal affinity coordination.[34] Anchoring PTE on the quantum dot surface accelerated product dissociation, leading to faster hydrolysis of nerve agents such as sarin, tabun, and paraoxon (POX).[35,36]

Rather than anchoring OP-degrading agents directly to nanoparticle surfaces, some inorganic nanoparticles such as mesoporous silica nanoparticles (MSNs) could encapsulate them within their porous structure. In one study, MSNs were loaded with HI-6, an AChE reactivator, through capillary absorption into the nanopores (Figure 2). The surface of the nanoparticles was further modified with transferrin, enabling the nanoparticles to cross the BBB via transferrin receptor-mediated endocytosis by brain microvascular endothelial cells. Once in the brain, these nanoparticles released HI-6 to reactivate AChE, effectively counteracting soman-induced acute neurotoxicity in zebrafish and mouse models.[37]

In another approach, MSNs were employed to scavenge OPs by physically absorbing them into their pores. For instance, MSNs absorbed OP molecules such as POX through van der Waals forces. Their high surface area and large pore volume contributed to the high capacity for entrapment.[38] When used as a topical skin protectant, MSNs effectively blocked the penetration of OPs into human skin. In addition to physical absorption, MSNs also scavenged OPs through chemical binding. For example, the silanol groups (≡Si−OH) on the MSN surface reacted with dimethyl methylphosphonate

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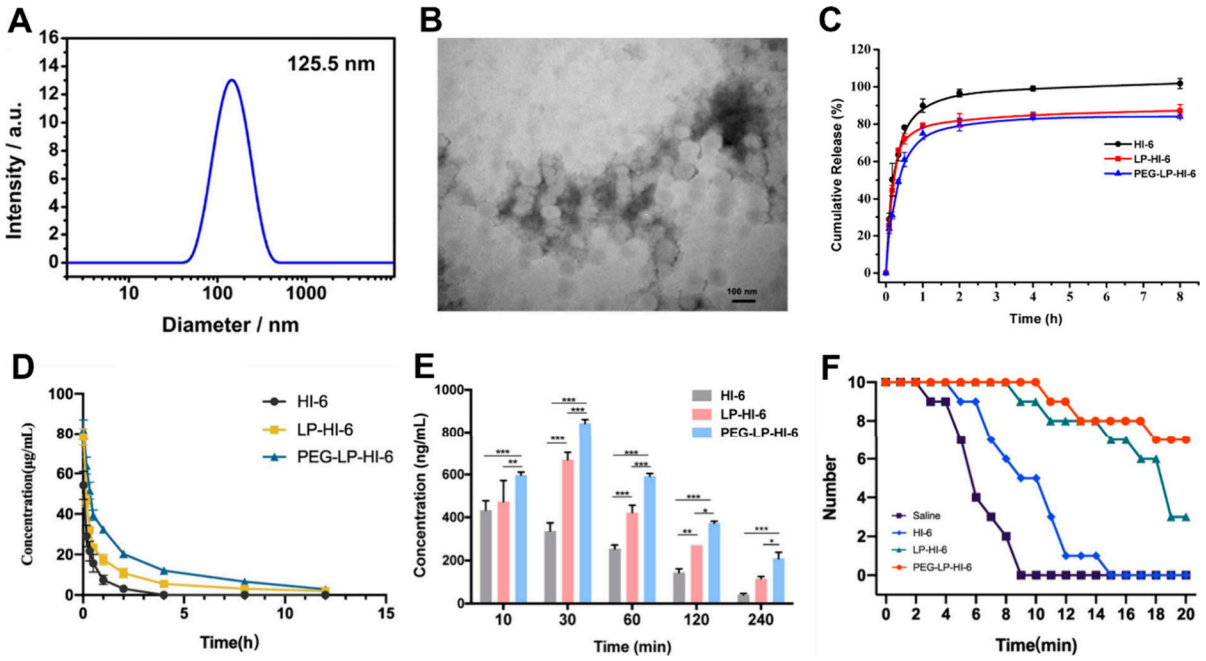

Figure 4. PEGylated liposomes loaded with HI-6 (PEG-LP-HI-6) served as on-site first-aid for acute soman poisoning. (A) Size distributions of PEG-LP-HI-6. (B) TEM image of PEG-LP-HI-6, bar = 100 nm. (C) The drug release profiles of free HI-6, LP-HI-6 and PEG-LP-HI-6 in PBS. Compared with other groups, PEG-LP-HI-6 had a slower drug release rate and showed a prolonged drug release profile. (D) The time-dependent concentrations of free HI-6, LP-HI-6, and PEG-LP-HI-6 in the plasma at various times following intravenous administration. PEG-LP-HI-6 showed delayed systematic clearance. (E) The concentration of HI-6 in cerebrospinal fluid (CSF) was evaluated. PEG-LP-HI-6 significantly reduced drug clearance. (F) In vivo treatment efficacy in a soman poisoned mice model. Intravenous administration of PEG-LP-HI-6 showed higher survival rate and prolonged survival time. Reproduced with permission from ref 56. Copyright 2023 Taylor & Francis Group.

(DMMP), producing less toxic byproducts like methyl hydrogen methylphosphonate and methylphosphonic acid.[39]

Some other inorganic nanoparticles possess intrinsic catalytic properties that can degrade OPs by cleaving phosphoryl-alkyl (P−OR) or phosphoryl-fluorine (P−F) bonds, breaking OPs into less toxic products. For instance, TiO_2 nanoparticles adsorb sarin by forming bonds between the phosphoryl oxygen of sarin and the titanium atoms on the nanoparticle surface, cleaving the P−F bonds and decomposing sarin.[20,30] Similarly, CeO_2 nanoparticles decompose DMMP by binding the phosphoryl oxygen of DMMP to cerium atoms, which cleaves the P−OCH_3 bonds, producing methanol.[40] Other metal nanoparticles, such as CuO and ZrO_2 nanoparticles, have also demonstrated similar degradation abilities against various OPs.[29,41]

Some metal oxide nanoparticles degrade OPs through catalytic hydrolysis. In this process, OPs initially attach to the nanoparticle surface via their phosphoryl oxygen, then react with surface hydroxyl groups, leading to hydrolysis.[42] For example, ZnO nanoparticles adsorb DMMP by forming hydrogen bonds between the phosphoryl oxygen of DMMP and surface hydroxyl groups on ZnO, hydrolyzing DMMP into methanol.[19] Similarly, CeO_2 nanoparticles absorb POX by binding their phosphoryl oxygen (P═O) to Ce ions at catalytic hotspots on the nanoparticle surface (Figure 3).[43] The surface-bound water molecules then initiate a nucleophilic attack on POX, efficiently hydrolyzing it into *p*-nitrophenol and diethyl phosphate. Following the same principle, other metal oxide nanoparticles, such as MnO_2,[44] Cu/TiO_2,[45,46] and $Zr(OH)_4$[47,48] nanoparticles, have been shown to decompose OPs such as sarin, DMMP, and POX.

In addition to hydrolysis, some metal oxide nanoparticles catalyze OP degradation through oxidation. For example, MgO-carbon hybrid nanocomposites (MgO@C) generate superoxide ($\cdot O_2^-$) and hydroxyl (·OH) radicals on their surface via electron transfer from MgO to adsorbed oxygen.[49] These reactive oxygen species (ROS) degrade POX by cleaving phosphorus−oxygen bonds. Under near-infrared (NIR) radiation, the photothermal effect of MgO@C nanocomposites increases their temperature, accelerating electron transfer and enhancing the degradation rate of POX.

Table 1 summarizes the mechanisms of inorganic nanoparticle for OP detoxification. Overall, inorganic nanoparticles are a promising platform for nerve agent detoxification. Their cost-effective production, intrinsic stability, and multifunctionality—whether carrying OP-degrading agents, scavenging OPs, or acting as catalysts—make them an attractive solution. However, concerns about the toxicity of inorganic nanoparticles remain a significant barrier to their biomedical use. Additionally, their release into the environment poses a risk of pollution. Nonetheless, with continued development, inorganic nanoparticles are poised to play an increasingly important role in OP detoxification in health and environmental contexts.

3. LIPID-BASED NANOPARTICLES FOR OP NERVE AGENT DETOXIFICATION

OPs exert detrimental effects by phosphorylating AChE, a highly efficient enzyme crucial for neurotransmitter regulation in the central nervous system (CNS).[50] AChE inhibition leads to the accumulation of ACh in CNS synapses, resulting in neurotoxic poisoning. The BBB complicates effective drug delivery to the CNS. This selective, semipermeable barrier regulates the exchange of molecules between the bloodstream

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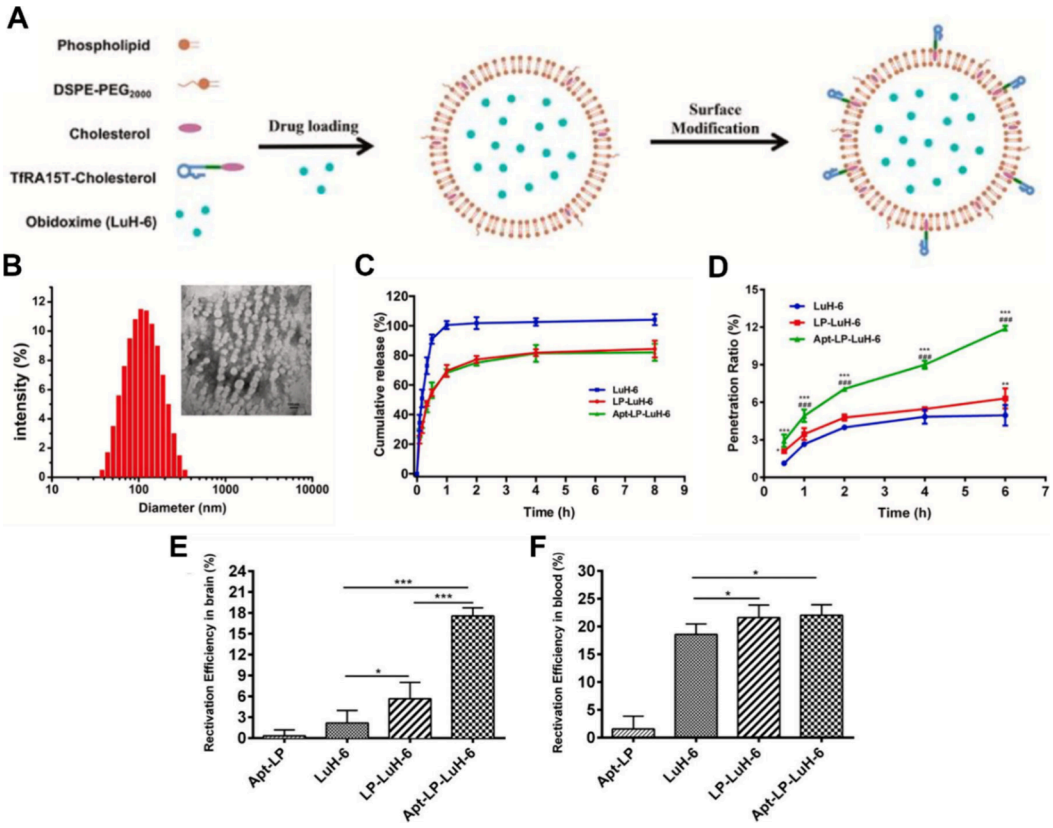

Figure 5. Aptamer-modified liposomes loaded with obidoxime (LuH-6) (named Apt-LP-LuH-6) targeted the brain to neutralize POX. (A) Schematic synthesis of Apt-LP-LuH-6. (B) Size and TEM image of Apt-LP-LuH-6, scale bar = 100 nm. (C) Release kinetics of LuH-6 under mimic physiological conditions from unmodified liposomes (LP-LuH-6) and Apt-LP-LuH-6 at pH 7.4. There were no pronounced differences in LuH-6 release profiles between the two types of liposomes at each time point. Data are presented as mean ± SD from 3 independent experiments. (D) Liposomes transported through the BBB model over a period of 6 h, corresponding to LuH-6, LP-LuH-6, and Apt-LP-LuH-6. Data are expressed as mean ± SD (n = 3), *P < 0.05, **P < 0.005, ***P < 0.0001 in comparison with LuH-6; #P < 0.05, ##P < 0.005, ###P < 0.0001 in comparison with LP-LuH-6. (E, F) Reactivation efficiency of free LuH-6, LP-LuH-6, and Apt-LP-LuH-6 in the brain (E) and blood (F). Data expressed as mean ± SD (n = 6), *P < 0.05, **P < 0.005, ***P < 0.0001 in comparison with free LuH-6 group. Reproduced with permission from ref 63. Copyright 2021 Elsevier.

and the brain. While the BBB serves to protect the brain by restricting the influx of potentially harmful substances, it also prevents over 98% of small-molecule drugs and all macromolecular therapeutics from entering the CNS.[51,52] To address this challenge, various strategies have been developed to enhance nanoparticle systems for delivering therapeutic agents to the brain.

Previous studies have shown that small, lipophilic molecules with a molecular weight below 400 Da can diffuse across the BBB endothelium, positioning lipid-based nanoparticles as potential candidates for efficient OP detoxification.[53] Solid lipid nanoparticles (SLNs), in particular, have emerged as effective drug carriers due to their enhanced drug-loading capacity, improved bioavailability, and prolonged circulation times.[18,54] For instance, intravenous administration of SLNs loaded with pralidoxime chloride (2-PAM), a small water-soluble antidote for OP poisoning, resulted in a 15% recovery of brain AChE activity and mitigated neuronal toxicity in a POX-poisoned rat model.[22] Subsequently, these nanoparticles were formulated to codeliver both 2-PAM and 6-(5-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)pentyl)-3-hydroxy picolinaldehyde oxime (3-HPA), a novel uncharged hydrophobic oxime with low water solubility.[21] The intravenous administration of this dual-oxime nanoparticle formulation enabled sequential drug release, extended the therapeutic window for oxime treatment, and achieved a 35% reactivation of brain AChE in the POX-poisoned rat model. Moreover, polyethylene glycol (PEG) has been incorporated into lipid-based nanoparticles due to its ability to increase plasma half-life and nanoparticle stability. For example, PEG-modified SLNs extended the blood circulation time of 2-PAM by more than 3-fold compared to free 2-PAM, resulting in a 36% reactivation of brain AChE in a POX-poisoned rat model.[55] Recently, PEGylated liposomes loaded with HI-6 demonstrated prolonged circulation time and reduced neuronal toxicity in a soman-poisoned mouse model, highlighting their promise as a first-aid strategy for acute neurotoxic exposure (Figure 4).[56]

Another approach involved the formulation of cationic nanoparticles designed to penetrate the BBB by targeting anionic sites on endothelial cells.[57] In one study, liposomes modified with dihexadecylmethylhydroxyethylammonium bromide (DHDHAB), a long-chain cationic surfactant, and loaded with 2-PAM demonstrated efficient BBB penetration following intranasal administration, achieving a 35% recovery of brain AChE activity in a POX-poisoned model.[58] Additionally, liposomes modified with imidazolium, a surfactant featuring a delocalized charge, were shown to effectively deliver 2-PAM across the BBB via intravenous administration, significantly reducing neuronal death in the hippocampus compared to free

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Table 2. Mechanisms of Lipid-Based Nanoparticles for BBB Crossing and CNS OP Detoxification[a]

Mechanism	Representative examples
Relying on small sizes to directly diffuse across the BBB endothelium	• SLNs loaded with 2-PAM[21] • PEG-modified SLNs loaded with 2-PAM[55] • PEGylated liposomes loaded with HI-6[56]
Relying on the cationic charge to penetrate the BBB by targeting anionic sites on endothelial cells	• DHDHAB-modified liposomes loaded with 2-PAM[58] • Liposomes modified with imidazolium and loaded with 2-PAM[59] • Chitosan-modified liposomes[60] • Chitosan modified with L-arginine and loaded with 2-PAM[61]
Relying on conjugated ligands to target the transporters on endothelial cells	• Liposomes modified with peptides that target the integrin $\alpha v\beta 3$ receptors on BMECs[62] • Liposomes conjugated with TfR-binding aptamers[63] or with TfR-binding scFv[64]
Temporarily opening the BBB to enhance drug permeability	• Liposomes with POPS degrade to LPHS, disrupting tight junction proteins for BBB permeation[70]

[a]BBB: blood−brain barrier; SLN: solid lipid nanoparticle; 2-PAM: pralidoxime chloride; PEG: polyethylene glycol; DHDHAB: dihexadecylmethylhydroxyethylammonium bromide; BMEC: brain microvascular endothelial cell; TfR: transferrin receptor; scFV: monoclonal antibody fragment; POPS: 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoserine; LPHS: lysophosphatidylserine.

2-PAM.[59] Furthermore, chitosan, a polysaccharide known for its interaction with negatively charged sialic acid in mucous layers due to its positively charged amino groups, was incorporated into liposomes for intranasal delivery.[60,61] Chitosan modified with L-arginine and loaded with 2-PAM was found to reactivate 35% of brain AChE activity in POX-poisoned rat models.[60,61]

In an alternative strategy, lipid-based nanoparticles have been conjugated with ligands that specifically bind to transporters on endothelial cells, facilitating receptor-mediated transcytosis across the BBB. For instance, liposomes modified with c(RGDyK) cyclic peptides, which target the integrin $\alpha v\beta 3$ receptors expressed on brain microvascular endothelial cells (BMECs), were utilized to deliver HI-6 in a dichlorvos (DDVP)-poisoned rat model.[62] This approach enhanced brain targeting, extended the therapeutic window, reduced the rapid clearance of HI-6 from the bloodstream, and helped restore central toxic enzymes. Recently, liposomes functionalized with transferrin receptor (TfR)-binding aptamers were developed for the delivery of obidoxime, resulting in improved uptake by brain endothelial cells and decreased brain damage in POX-poisoned mice (Figure 5).[63] Additionally, transferrin receptor-targeting monoclonal antibody fragments (scFv) were incorporated into 2-PAM-loaded liposomes, significantly enhancing survival rates and AChE reactivation in a POX-poisoned mouse model.[64]

In addition to modifying the surface properties of nanoparticles, strategies aimed at temporarily opening the BBB to enhance drug permeability have also been investigated.[65] Various physical and chemical methods, including ultrasonic techniques and the use of mannitol, have been employed to transiently disrupt the BBB.[66−69] For example, a phospholipase A2 (PLA2)-based delivery system was developed to selectively open the BBB using liposomes containing 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoserine (POPS).[70] PLA2 hydrolyzes the sn-2 bond of POPS, generating lysophosphatidylserine (LPHS), which transiently disrupts tight junction proteins such as ZO-1 and occludin, thereby enhancing BBB permeability. This targeted approach allows only the nanoparticles to cross the BBB while larger molecules remain excluded. In a soman-poisoned mouse model, liposomes loaded with HI-6 using this system significantly improved survival rates and reduced brain damage.[70]

Table 2 summarizes the mechanisms of lipid-based nanoparticles for BBB crossing and CNS OP detoxification. Overall, advances in nanotechnology, particularly the development of lipid-based nanoparticles such as SLNs and liposomes, have shown promising results in penetrating the BBB and enhancing drug delivery. These systems, especially when functionalized with ligands, modified with surface properties, or combined with methods to transiently open the BBB, demonstrate enhanced bioavailability and efficacy in reactivating AChE in poisoned models. As research continues to evolve, these lipid-based nanoparticle systems offer a promising platform for targeting the CNS in treating OP poisoning and other neurotoxic disorders.

4. POLYMER-BASED NANOPARTICLES FOR OP NERVE AGENT DETOXIFICATION

Polymer-based nanoparticles are promising carriers for delivering small-molecule antidotes or OP-degrading enzymes, with encapsulation mechanisms varying across different formulations. For instance, with their highly branched structures, dendrimers provide versatile frameworks for payload anchoring. The anchoring can be achieved through chemical conjugation, as demonstrated in a study where small α-nucleophiles like monoisonitrosoacetamide (MINA) and hydroxamic acid (HA) were chemically attached to the branches of poly(amidoamine) (PAMAM) dendrimers.[24] In addition, PEG chains were conjugated to the dendrimer surface, protecting enzymes from catalytic degradation by α-nucleophiles, thus enhancing the specificity of OP hydrolysis. These nanoparticles successfully degraded POX-ethyl when tested on porcine skin and artificial human microtissues.

Anchoring can also be achieved through "physical trapping." For example, poly(2-alkyloxazoline) dendrimers, which feature hydrophobic cores, encapsulated OP-degrading enzymes such as organophosphorus acid anhydrolase (OPAA) or organophosphorus hydrolase (OPH), facilitating OP degradation while allowing substrates and products to diffuse freely.[71] In mice exposed to diisopropyl fluorophosphate (DFP) or POX, intravenous administration of these dendrimers effectively protected the animals by maintaining high levels of cholinesterase activity.

Unlike dendrimers, copolymers containing hydrophobic and hydrophilic chains can self-assemble into nanoparticles that encapsulate enzymes for OP degradation. For example, PEG−polypropylene sulfide (PPS) copolymers self-assembled into nanoparticles capable of encapsulating phosphotriesterase (PTE).[72] This PEG−PPS system effectively carried a high concentration of enzyme payload, facilitating efficient OP detoxification. In a mouse model of POX intoxication, these nanoparticles provided both prophylactic and postexposure protection, rescuing the animals and preventing POX-induced neuromuscular impairment.

Polymers can also be directly coated onto enzymes, forming polymer−protein nanoparticles for OP detoxification. For instance, researchers used *in situ* polymerization to coat

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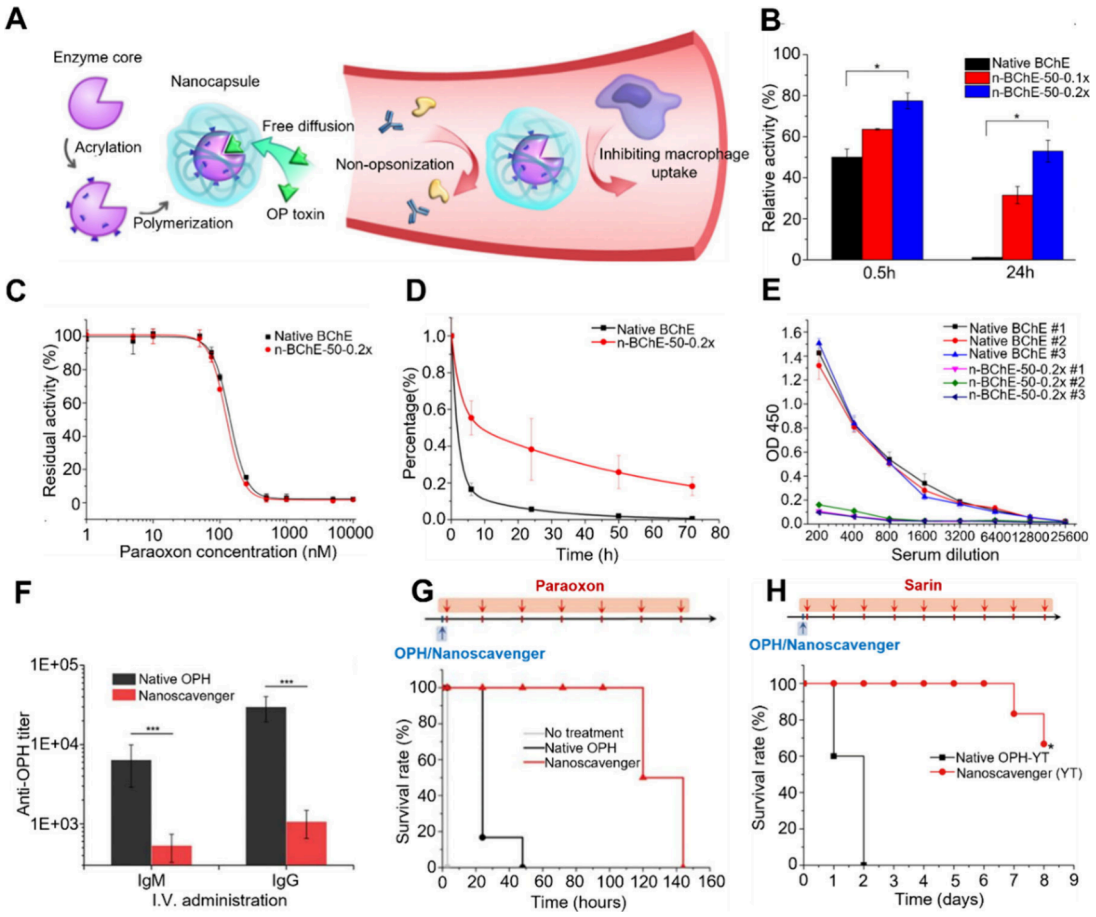

Figure 6. Zwitterionic nanocapsules provide long-term prophylactic protection against nerve agents in rodents. (A) Schematic structure of zwitterionic poly(carboxybetaine) (PCB) nanocapsules. (B) Relative activities of native butyrylcholinesterase (BChE) and nanocapsules incubated at 55 °C with trypsin (*P < 0.05). (C) BChE inhibition by POX-ethyl. (D) Blood circulation profiles of native BChE and nanocapsule after intravenenous administration. (E) Detection of anti-BChE IgM by direct ELISA. (F) Detection of anti-OPH antibodies by direct ELISA after intravenenous injection. (G) Survival rate of rats after repetitive POX exposure. (H) Survival rate of guinea pigs after repetitive sarin exposure. (A–E) Reproduced with permission from ref 75. Copyright 2016 Elsevier. (F, G) Reproduced with permission from ref 76. Copyright 2019 American Association for the Advancement of Science.

nonhuman butyrylcholinesterase (BChE) with a layer of poly(4-acryloylmorpholine) (PAcM).[73] This resulting "nanodepot" significantly enhanced the enzyme's stability, extended its circulation time in plasma, reduced antigenicity, and minimized accumulation in nontarget tissues. In a mouse model of POX intoxication, the nanodepot enabled continuous degradation of POX, providing sustained prophylactic protection and dramatically increasing the survival rate of the treated mice.

Most OP-degrading enzymes are exogenous and exhibit high immunogenicity with short circulation half-lives. Traditionally, PEGylation has been the gold-standard approach to extending enzyme stability and circulation time. However, the emergence of anti-PEG antibodies has been shown to reduce its efficacy.[74] To address this challenge, researchers have turned to zwitterionic polymers like poly(carboxybetaine) (PCB) as an alternative. Compared to PEG, PCB forms a more robust hydration layer, leading to reduced nonspecific protein adsorption and improved biocompatibility. For example, nonhuman BChE was coated with PCB using free radical polymerization (Figure 6 A-E).[75] The PCB polymer shell significantly reduced immune recognition, extending the circulation half-life of BChE to 45 h —three times longer than that of unmodified BChE. Similarly, PCB was coated onto OPH for the degradation of sarin and POX (Figure 6 F-G).[76] This zwitterionic shell extended OPH's circulation half-life to 26.2 h, an impressive 60-fold increase compared to the native OPH. This dramatic enhancement in circulation time enabled continuous in vivo OP detoxification, protecting rats from POX or sarin poisoning for up to a week.[77] When administered via intubation-assisted intratracheal instillation (IAIS) in rats, these nanoparticles delivered significantly higher concentrations of OPH into circulation compared to free OPH inhalation, effectively preventing POX-induced death.

Polymeric nanoparticles have also demonstrated the ability to cross the BBB, offering the potential for OP detoxification within the CNS. For instance, cationic poly(L-lysine)-*graft*-poly(ethylene oxide) (PLL-*g*-PEO) copolymers were used to form nanoparticles with a BChE protein-polyion complex core, surrounded by a water-soluble, nonionic shell. These nanoparticles successfully delivered BChE into the CNS of mice.[78] When administered intramuscularly or intravenously, the nanoparticles led to significantly higher levels of BChE accumulation in the brain compared to free BChE, demonstrating their effectiveness in overcoming the BBB and enhancing enzyme delivery.

Polymers can also complex with inert proteins to form nanocomposites, which create nanoscale spaces on the protein

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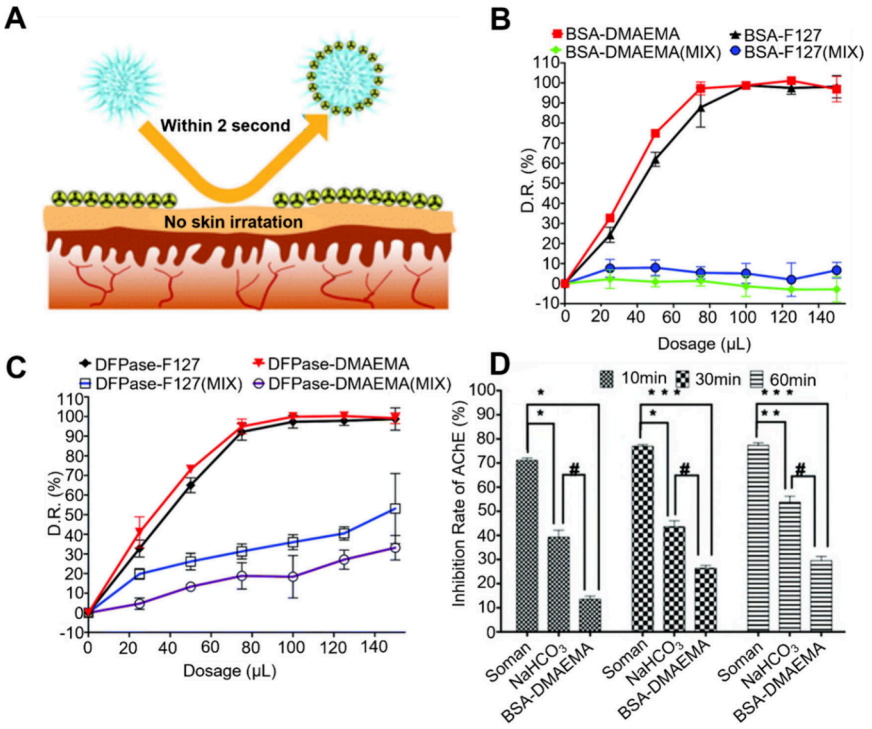

Figure 7. A protein nanocomposite for ultrafast, efficient and nonirritating skin decontamination of nerve agents. (A) Schematic of the protein nanocomposite decontaminate OP on skin. (B) Decontamination ratio (D. R.) of different nanocomposites including BSA-DMAEME, BSA mixed with DMAEMA, BSA-F127, and BSA mixed with F127. (C) Decontamination ratio of different nanocomposites including DFPase-F127, DFPase mixed with F127, DFPase-DMAEMA, and DFPase mixed with DMAEMA. (D) Inhibition ratio of AChE in blood treated with $NaHCO_3$ and BSA-DMAEMA after Soman poisoning of different durations. Reproduced with permission from ref 79. Copyright 2020 Royal Society of Chemistry.

Table 3. Mechanisms of Polymer-Based Nanoparticles for OP Detoxification[a]

Mechanism		Representative example
Acting as nanocarriers	Chemical conjugation of OP-binding agent	• Dendrimers attached with small α-nucleophiles[24] • BChE coated with PCB for long circulation[75]
	Physical encapsulation of OP-binding agent	• Dendrimers encapsulating OP-degrading enzymes[71] • Polymeric nanoparticles encapsulating PTE[72]
Acting as nanoscavenger		• Polymer–protein nanocomposites attract and trap OPs[79]
Compensating for the activity loss of enzymes inhibited by OPs		• MIP nanoparticles that bind to a tryptic peptide epitope of AChE restore ACh hydrolysis and counteract OP poisoning[80]

[a]BChE: butyrylcholinesterase; PTE: phosphotriesterase; AChE: acetylcholinesterase; ACh: acetylcholine.

surface to attract and trap OP molecules for effective detoxification. For example, bovine serum albumin (BSA) was linked to 2-(dimethylamino)ethyl methacrylate (DMAEMA) or Pluronic F127 to create protein–polymer nanocomposites designed for soman detoxification (Figure 7).[79] In a rat model of soman skin exposure, these nanocomposites protected the animals by absorbing soman from the skin and sustaining high levels of AChE activity in the bloodstream.

Polymeric nanoparticles can mitigate OP intoxication by compensating for the activity loss of enzymes inhibited by these compounds. For instance, Polymeric nanoparticles can mitigate OP intoxication by compensating for the activity loss of enzymes inhibited by these compounds.[80] The MIP nanoparticles were specifically designed to bind a tryptic peptide epitope, a precursor of AChE, thus facilitating increased cholinesterase activity. Consequently, these MIP nanoparticles effectively restored sufficient ACh hydrolysis, helping to counteract malathion poisoning by boosting the activity of uninhibited cholinesterase enzymes.

We have summarized the mechanisms of polymer-based nanoparticles for OP detoxification in Table 3. Overall, polymer-based nanoparticles exhibit significant potential for OP detoxification. As carriers, these nanoparticles offer robust protection for their payloads, enhancing their pharmacokinetic profiles and therapeutic potency. Furthermore, polymer-based nanoparticles can be engineered to detoxify OPs through mechanisms such as direct absorption or by facilitating compensatory effects. With advantages like high biocompatibility and tunability, these nanoparticles are poised to play an increasingly vital role in developing effective countermeasures against OP intoxication.

5. MOF NANOPARTICLES FOR OP NERVE AGENT DETOXIFICATION

MOF nanoparticles have recently garnered significant attention for OP detoxification due to their unique advantages.[81] Certain MOFs exhibit an intrinsic ability to decompose OPs directly.[82,83] MOF nanoparticles can be precisely engineered with specific compositions and pore sizes, enabling targeted

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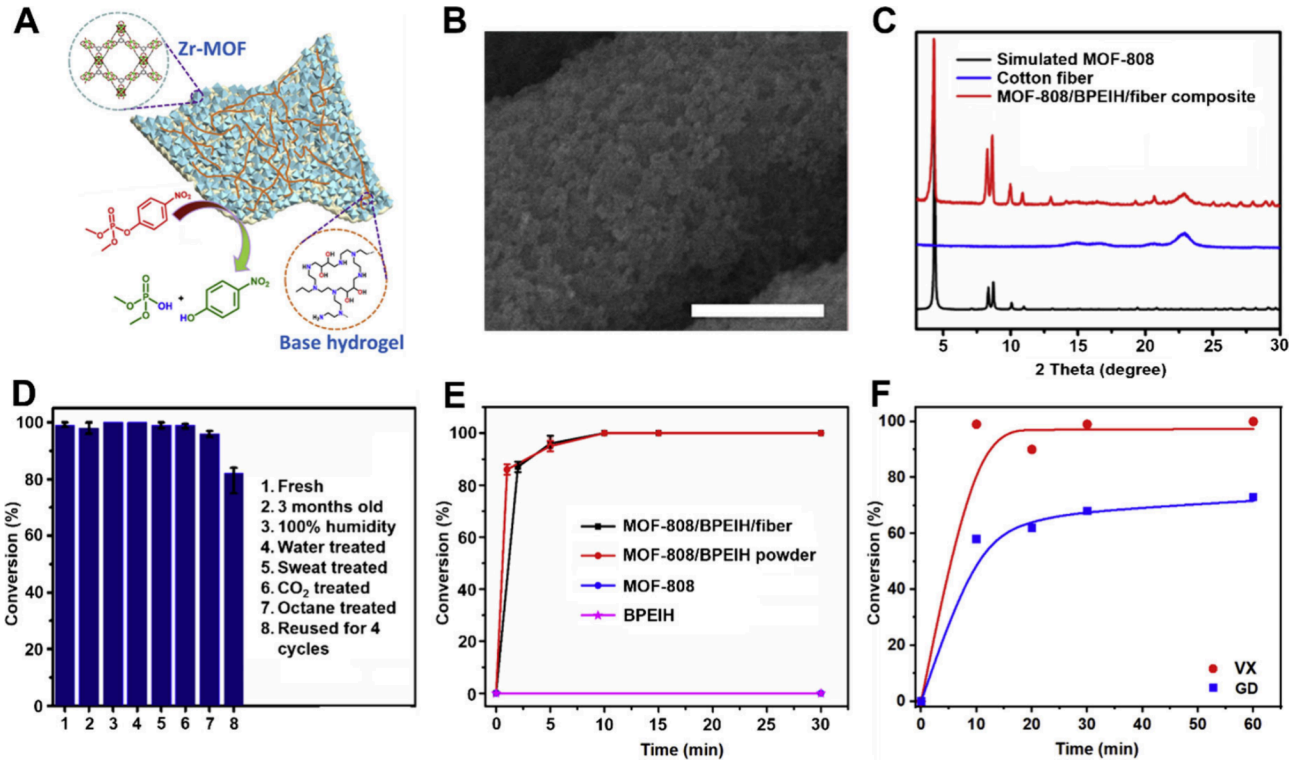

Figure 8. Rapid catalytic hydrolysis of OP nerve agents using zirconium-based MOF/hydrogel composites. (A) Schematic of the MOF-808/BPEIH composite, engineered for efficient solid-state OP detoxification under ambient conditions. (B) SEM image showing the fibrous structure of MOF-808/BPEIH/fiber, prepared via a dip-coating technique that forms a dense, continuous coating on cotton fibers. Scale bar: 4 μm. (C) Powder X-ray diffraction (XRD) patterns of various formulations, indicating that the MOF-808 crystallinity was retained during composite formation. (D) Catalytic performance of MOF-808/BPEIH/fiber in degrading dimethyl 4-nitrophenyl phosphonate after stability tests. MOF-808/BPEIH/fiber demonstrated functionality after 3 months of storage, environmental resilience, and reusability through simple water washing. (E) Conversion profile of the VX simulant, O, S-diethyl methylphosphonothioate, to the nontoxic product ethyl methyl phosphonic acid (EMPA), via selective P−S bond cleavage by MOF-808/BPEIH. High EMPA conversion indicates the composite's high specificity for OP detoxification. (F) Hydrolysis of VX and GD (O-pinacolyl methylphosphonofluoridate or Soman) by MOF-808/BPEIH/fiber. Error bars indicate standard deviation. Reproduced with permission from ref 95. Copyright 2021 Elsevier.

binding of OPs and promoting efficient catalytic degradation.[84] Additionally, their porous structures allow for the encapsulation and delivery of degradation enzymes.[85] MOF nanoparticles can also be incorporated into composite materials without losing their catalytic activity, broadening their potential applications for versatile OP detoxification.[86]

Among various types of MOF nanoparticles, zirconium-based MOF nanoparticles (Zr-MOF-NPs) have attracted much attention due to the unique structure of their Zr nodes, which possess an intrinsic ability to catalyze OP hydrolysis, particularly under alkaline aqueous conditions. For example, several Zr-MOF-NPs, such as NU-1000, UiO-66, UiO-66-NH2, and MOF-808, have been shown to effectively degrade OPs like soman and VX by breaking the P−F or P−S bonds, respectively.[87,88] The catalytic efficiency of these MOF nanoparticles can be further enhanced by modifying their lattice composition. For instance, doping magnesium into Zr-MOF-NPs created bimetallic nodes, such as MgZr5O2(OH)6, which introduced additional catalytic sites, thereby improving OP detoxification efficiency.[89]

Researchers have further enhanced OP detoxification of Zr-MOF-NPs by incorporating additional catalysts into the MOF lattice. For instance, Pd nanoparticles (Pd-NPs) were loaded into PCN-224, a Zr-MOF-NP known for its enriched Zr nodes. In this system, the Zr nodes hydrolyzed POX into the mildly toxic *p*-nitrophenol. At the same time, the Pd-NPs facilitated the further breakdown of *p*-nitrophenol into the much less poisonous *p*-aminophenol.[90] Another study encapsulated iron-doped carbon dots (Fe-CDs) within MOF-808 nanoparticles, where the host lattice hydrolyzed parathion, and the Fe-CDs provided an alternative pathway by cleaving the P═S bond, significantly enhancing detoxification efficiency.[91] Additionally, MOF-808 nanoparticles were loaded with imidazole derivatives, such as imidazole and 2-methylimidazole, which acted as proximal bases to accelerate the regeneration of Zr nodes after OP degradation, further boosting detoxification performance.[92]

Zr-MOF-NPs have also been incorporated into nanocomposites with other materials to enhance OP degradation. For instance, UiO-66-NH2 nanoparticles were coated onto photothermal microparticles, where the UiO-66-NH2 facilitated the degradation of dimethyl nitrophenyl phosphate (DMNP).[93] The photothermal cores accelerated this process, significantly improving detoxification efficiency. In another study, UiO-66-NH2 nanoparticles were applied to an ultrafiltration membrane substrate, catalytically degrading OP while enabling the physical removal of OPs through membrane filtration.[94] Moreover, a MOF/hydrogel composite was developed by cross-linking polyethylene imine (PEI) with an epoxide in the presence of MOF-808 nanoparticles (Figure 8).[95,96] The hydrogel retained water, facilitating OP hydrolysis, and the amine groups in PEI supported the regeneration of Zr

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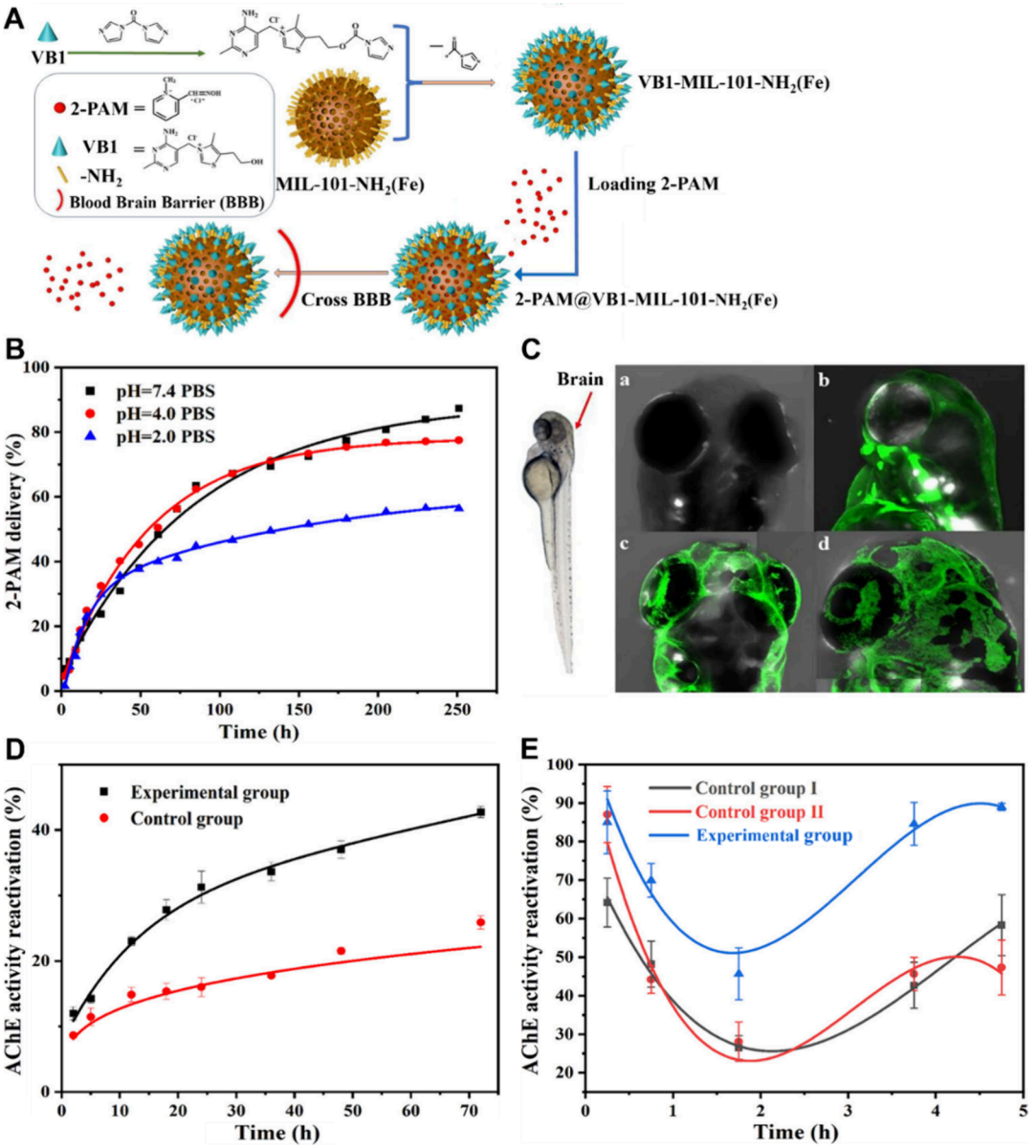

Figure 9. Penetrating the BBB for targeted treatment of sarin poisoning by nanosustained-released 2-PAM@VB1-MIL-101-NH_2(Fe). (A) Schematic synthesis of 2-PAM@VB1-MIL-101-NH_2(Fe), in which an Fe-MOF nanoparticle, MIL-101-NH_2(Fe), was applied to load 2-PAM and then modified with Vitamin B1 (VB1) through a nucleophilic substitution reaction. (B) Release profile of 2-PAM from 2-PAM@VB1-MIL-101-NH_2(Fe) in 1X PBS solution with different pH values within 0−250 h in 37 °C. (n = 3) (C) In vivo brain targeting of different regimens. The images showed fluorescence distribution in the brain sections of (a) zebrafish without any administration, (b) zebrafish injected with FITC, (c) zebrafish treated with FITC-labeled MIL-101-NH_2(Fe), and (d) zebrafish treated with FITC-labeled VB1-MIL-101-NH2(Fe). The fluorescence images were taken after 3 h of administrations on zebrafish under a confocal microscope at an excitation wavelength of 470 nm. (D) In vivo blood AChE activity reactivation over time. Male Kunming mice were first gavage administered sarin above LD50. In the control group, there was no further treatment for sarin-poisoned mice. In the experimental group, mice were given atropine and 2-PAM@VB1-MIL-101-NH2(Fe) via gavage immediately after sarin exposure. AChE was measured within 72 h (n = 6). (E) In vivo brain AChE activity reactivation over time. Male Kunming mice were first gavage administered sarin in nonlethal dosage (1.472 mg/kg). Mice in control group I did not receive any treatment after intoxication. Mice in control group II were gavaged with atropine and intravenously injected with 2-PAM@MIL-101-NH_2(Fe) immediately after intoxication. Mice in experimental group were gavaged with atropine and intravenously injected with 2-PAM@VB1-MIL-101-NH_2(Fe) immediately after intoxication. Error bars represent the standard deviation. Reproduced with permission from ref 99. Copyright 2023 American Chemical Society.

nodes within the embedded MOF-808 nanoparticles, enhancing the degradation process. When coated onto fibrous cotton, this composite achieved effective soman and VX detoxification under ambient conditions.

Zinc-based MOF nanoparticles, particularly zeolitic imidazolate frameworks (ZIFs), have been extensively studied for their potential in OP detoxification. ZIFs are formed through the coordination of zinc ions with imidazole derivatives, and these coordination bonds facilitate the hydrolysis of OPs by breaking P−F or P−Cl bonds. Additionally, the imidazolate linkers released from decomposed ZIFs can further interact with OP-AChE adducts, restoring AChE activity. One study explored the OP-degrading capacity of ZIFs constructed with various imidazolate linkers and framework topologies,

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Table 4. Mechanisms of MOF Nanoparticles for OP Detoxification[a]

Mechanism	Representative example
Providing intrinsic catalytic activity	• Zr-MOF-NPs (such as NU-1000, UiO-66, UiO-66-NH2, and MOF-808)[87,88] • Mg-doped Zr-MOF-NPs[89] • ZIF[97]
Loading additional catalysts for enhanced activity	• Pd-NP-loaded PCN-224[90] • MOF-808 nanoparticles encapsulated with Fe-CDs[91] • MOF-808 nanoparticles loaded with imidazole derivatives[92]
Forming nanocomposites with other materials to enhance OP degradation	• Photothermal microparticles coated with UiO-66-NH_2[93] • UiO-66-NH_2-modified ultrafiltration membrane[94] • MOF-hydrogel composite[95,96]
Acting as nanocarriers	• Fe-MOF-NPs with pH-responsive delivery[98] or BBB-crossing capability for CNS targeting[99]

[a]MOF: metal−organic framework; ZIF: zeolitic imidazolate framework; Pd-NP: Pd nanoparticle; Fe-CD: iron-doped carbon dot; Fe-MOF-NP: Fe-based MOF nanoparticle; CNS: central nervous system.

demonstrating their effectiveness in neutralizing DFP and restoring AChE function.[97]

Researchers have also explored other MOF nanoparticles for OP detoxification, with iron-based MOF nanoparticles (Fe-MOF-NPs) standing out due to their pH-responsive and swellable properties. In polar solvents like water and ethanol, Fe-MOF-NPs expand, increasing their volume and pore size, making them highly efficient for molecule loading with pH-dependent release. In one study, MIL-88B(Fe), a type of Fe-MOF-NP that expands its lattice in high-polarity solvents like water, was used to absorb 2-PAM, an OP antidote that reactivates AChE, enabling sustained release. The combination of these nanoparticles with atropine, a muscarinic receptor antagonist commonly used as an antidote for nerve agent toxicity, provided significant survival benefits to sarin-poisoned mice.[98] Another study modified MIL-101-NH2(Fe), another Fe-MOF-NP, by attaching Vitamin B1 (VB1) through a nucleophilic substitution reaction.[99] VB1 enables brain targeting due to its binding specificity to thiamine transporters on the BBB. These nanoparticles, loaded with 2-PAM, were injected into zebrafish, where they successfully targeted deeper brain regions. When coadministered with atropine in sarin-poisoned mice, these nanoparticles helped maintain higher AChE activity levels in the brain (Figure 9).

Table 4 summarizes the mechanisms of MOF nanoparticles for OP detoxification. In summary, MOF nanoparticles represent an intriguing platform for OP detoxification due to their inherent ability to degrade OPs. Researchers have advanced this potential by tailoring MOF compositions, encapsulating catalytic agents, and integrating MOFs with other materials to create composite systems that enhance detoxification efficiency. Ongoing research and development are expected to further expand the capabilities of MOF nanoparticles, unlocking even more significant potential for OP detoxification.

6. CELLULAR NANOPARTICLES FOR OP NERVE AGENT DETOXIFICATION

Cellular nanoparticles, created by coating natural cell membranes onto synthetic cores, have recently emerged as a unique biomimetic platform for OP detoxification. These nanoparticles retain essential cell membrane components such as proteins, lipids, and carbohydrates. This membrane coating process enables cellular nanoparticles to mimic the functions of host cells.[100] Early designs utilized these cell-mimicking nanoparticles as decoys to sequester toxins and prevent them from attacking target cells, a mechanism that is independent of toxin structure, thus enabling broad-spectrum detoxification. Recent advancements have enhanced the efficacy of cellular nanoparticles by modifying membrane compositions, engineering core properties, and fine-tuning cell membrane functions, leading to increasingly effective OP detoxification formulations.[26]

Among various cellular nanoparticle formulations, those made from poly(lactic-*co*-glycolic acid) (PLGA) and coated with red blood cell (RBC) membrane (RBC-NPs) were first developed for detoxifying OPs.[101] The study showed that these nanoparticles inherited active AChE enzymes from the source cells and scavenged DDVP in a concentration-dependent manner. In vivo studies showed that RBC-NPs improved the survival of mice challenged with lethal doses of DDVP, intravenously or orally. Similarly, RBC-NPs effectively scavenged chlorpyrifos (CPS) and retained endogenous

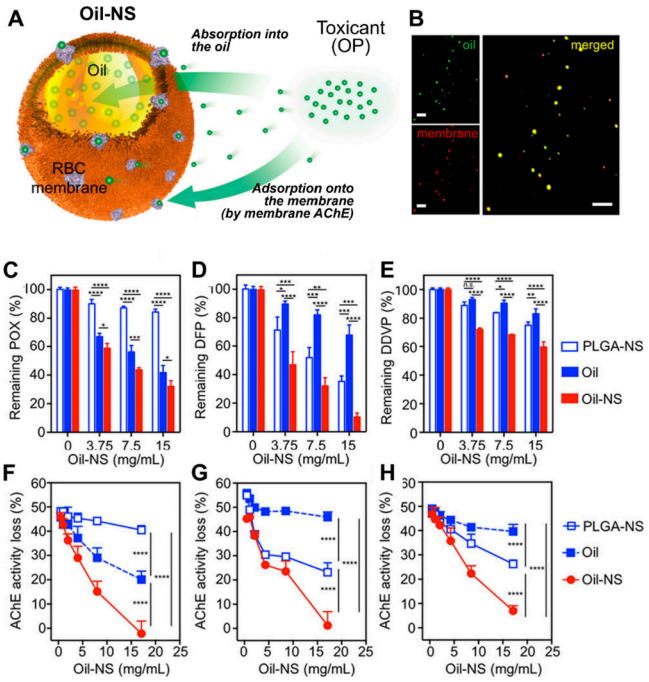

Figure 10. Cell membrane-cloaked oil nanosponges (Oil-NS) enable dual-modal detoxification. (A) Schematic representation of Oil-NS, consisting of an oil droplet surrounded and stabilized by a naturally derived RBC membrane. (B) Confocal fluorescence images of dual-dye-labeled Oil-NS (oil, green; membrane, red). Scale bar = 500 nm. (C−E) Removal efficiencies of three representative OPs, including POX (C), DFP (D), and DDVP (E) when incubated with various concentrations of Oil-NS. PLGA-NS and oil droplets without RBC membrane coating were used as controls. (F−H) Loss of AChE activities was measured for the three scenarios. Statistical analysis was performed using one-way ANOVA followed by Tukey's posthoc analysis based on IC_{50} values. Data presented as mean ± SD (n = 3, ns: not significant, *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001). Reproduced with permission from ref 103. Copyright 2019 American Chemical Society.

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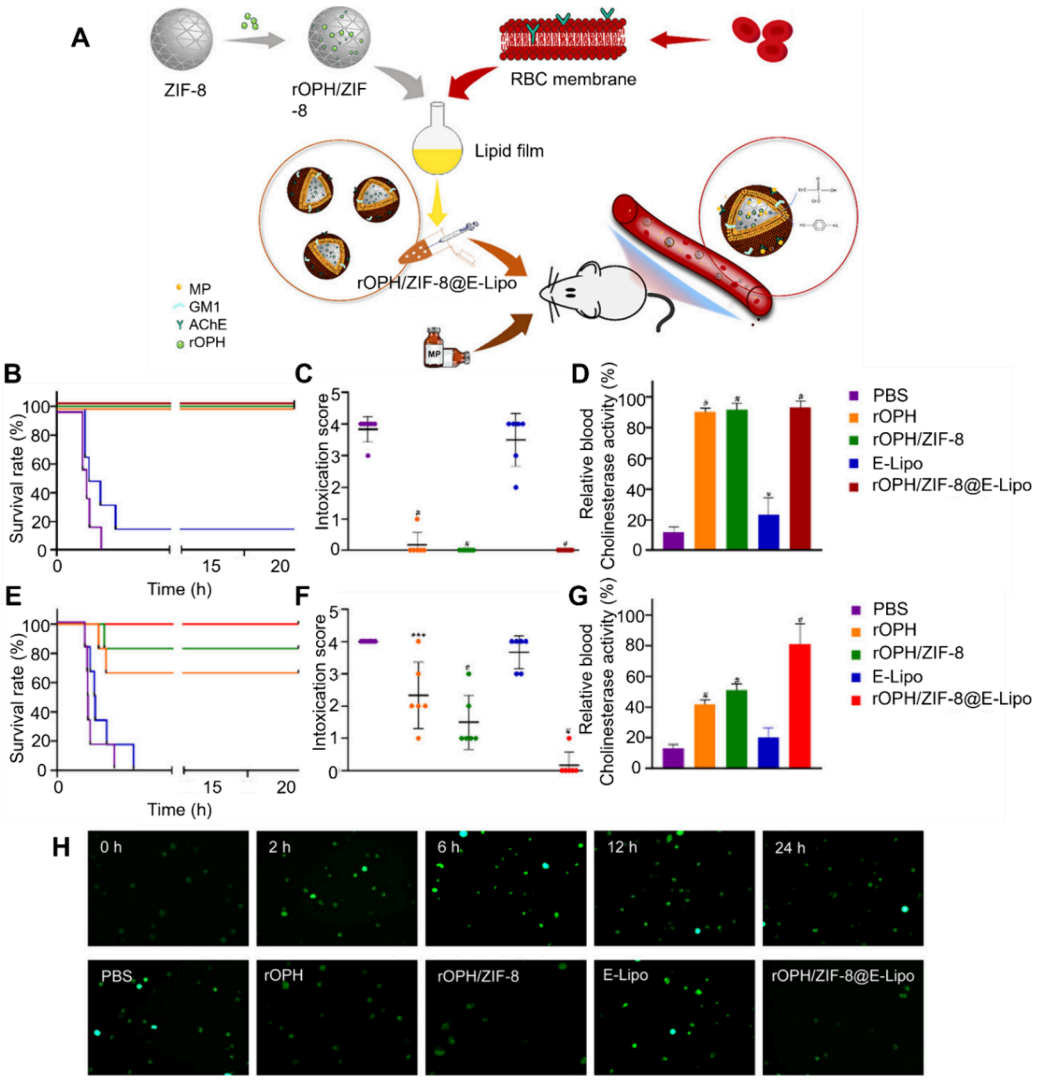

Figure 11. A dual-modal nanoscavenger using hybrid cell membrane for OP detoxification. (A) Schematic representation of rOPH/ZIF-8@E-Lipo and its application in a mouse model. (B–D) Therapeutic effects of nanoscavengers on lethal MP intoxication. (B) Survival rate, (C) intoxication score, and (D) blood cholinesterase activity of mice exposed to lethal MP (1.38 mg/kg) with remedial administration of rOPH/ZIF-8@E-Lipo, rOPH, rOPH/ZIF-8, or E-Lipo. Data are shown as the means ± SE $n = 6$, $^{*}P < 0.05$, $^{**}P < 0.01$, $\#P < 0.0001$. (E–G) Prophylactic efficacy of the nanoscavengers against MP challenges. (E) Survival rate, (F) intoxication signs, and (G) blood cholinesterase activity of lethal MP-challenged mice pretreated with rOPH/ZIF-8@E-Lipo, rOPH, rOPH/ZIF-8, or E-Lipo. Data are shown as the means ± SE $n = 6$, $^{***}P < 0.001$, $\#P < 0.0001$. (H) ROS production (green) in EL4 cells exposed to MP (660 μM) with different time points (upper); effects of various detoxification regimens on MP (660 μM, 6 h)-induced ROS production (lower) (original magnification ×200). Reproduced with permission from ref 104. Copyright 2022 American Chemical Society.

Table 5. Mechanisms of Cellular Nanoparticles for OP Detoxification[a]

Mechanism	Representative example
Scavenging by cell membrane receptors	• RBC-NPs[101,102]
Scavenging concurrently by cell membrane receptors and physical absorption of the core	• Oil-NS[103]
Degrading OPs continuously through encapsulated enzymes	• Cell membrane-coated ZIF-8 core that encapsulates OP-degrading enzymes[105−107]

[a]RBC-NP: poly(lactic-*co*-glycolic acid) core coated with red blood cell membrane; Oil-NS: cell membrane-coated oil nanosponge; ZIF-8: zeolitic imidazolate framework-8.

AChE activity, enhancing survival in a rabbit model of CPS intoxication.[102]

Building on this approach, researchers replaced the PLGA cores with oil nanodroplets, creating cell membrane-coated oil nanosponges (Oil-NS) (Figure 10).[103] The oil core non-specifically absorbed OPs through physical partitioning, while the cell membrane shell provided biological binding for toxin absorption, enabling a dual-mode detoxification system. When tested against three model OPs—POX, DFP, and DDVP—Oil-NS consistently outperformed RBC-NPs (which had solid PLGA cores) and plain oil nanodroplets in OP-binding and AChE protection, highlighting the advantages of its dual detoxification mechanism. Additionally, Oil-NS effectively protected mice from POX-induced lethality in both preventive and therapeutic regimens.[103]

Recently, more structurally complex cellular nanoparticles have been developed to enhance dual-modal detoxification. One study focused on integrating RBC membrane-anchored

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AChEs with catalytic bioscavengers, which acted as enzymes to hydrolyze OPs rapidly (Figure 11).[104] The researchers encapsulated recombinant organophosphorus hydrolase (rOPH) within a ZIF-8 core, forming rOPH/ZIF-8 nanoparticles.[105] These cores were then cloaked with a hybrid membrane composed of monosialoganglioside (GM1)-modified RBC membrane and liposome components (E-Lipo). The RBC membrane retained AChE activity, while the liposomes facilitated BBB penetration, improving the ability to prevent cholinergic crises and address brain-targeted toxic effects. The resulting rOPH/ZIF-8@E-Lipo nanoscavengers demonstrated excellent stability, biocompatibility, and BBB permeability. In a mouse model of OP poisoning, these nanoparticles provided prophylactic protection against OP exposure and therapeutic benefits, preventing AChE inactivation, oxidative stress, and cytotoxicity. Subsequent research explored their brain-targeting abilities, attributed to the GM1, which enabled specific recognition by BBB-associated neurons. As a result, the nanoscavengers effectively neutralized intracerebral OP and delayed cognitive deficits and psychiatric disorders.[106]

Cellular nanoparticles designed for OP detoxification also have valuable environmental applications. In one example, researchers encapsulated PTE within bacterial outer membrane vesicles (OMVs) by fusing PTE with a SpyCatcher protein domain, which bound to the SpyTag peptide on OMV membrane proteins, forming OMV-PTEs.[107] This design protected PTE from harsh conditions, such as lyophilization and extended heat exposure, making the nanoparticles suitable for transport and use in field conditions. These nanoparticles were tested for detoxifying water samples and solid surfaces, including glass, painted metal, and fabric contaminated with the chemical warfare agent POX. The results demonstrated effective detoxification of both water and solid surfaces, with sustained enzyme activity even under challenging conditions.

We have summarized the mechanisms of cellular nanoparticles for OP detoxification in Table 5. Overall, these studies underscore the versatility of cellular nanoparticles for OP neutralization, consistently demonstrating high efficacy, biocompatibility, and biodegradability.[101,103,104,107] These attributes position cellular nanoparticles as promising candidates for future OP detoxification applications.

7. SUMMARY

This review has outlined recent advancements in inorganic nanoparticles, lipid-based nanoparticles, polymer-based nanoparticles, MOF nanoparticles, and cellular nanoparticles for the detoxification of OP nerve agents. These nanoparticle platforms showcase three key mechanisms that distinguish them from traditional countermeasure technologies: as carriers that deliver OP-detoxifying agents with optimized pharmacokinetics, as nanocatalysts that decompose OPs efficiently and continuously, and as nanoscavengers that mimic host cell functions for broad-spectrum OP detoxification.

In the review, we have highlighted promising results of nanoparticle platforms for OP detoxification. However, significant challenges exist in developing therapeutic nanoparticles for future translation. For example, most nanoparticle formulations are complex. Therefore, large-scale and cost-effective nanoparticle manufacturing remains challenging in meeting clinical and commercial needs.[108,109] Another challenge is to ensure long-term storage stability and biocompatibility to prevent adverse immune responses or toxicity.[110] Furthermore, the environmental impact of nanoparticle production and disposal raises sustainability concerns, highlighting the need for eco-friendly materials and green synthesis methods, especially for metallic nanoparticles.[111] Addressing these obstacles is crucial for successfully translating nanoparticle-based therapies into clinical applications. As the field evolves, these nanoparticle platforms are expected to drive innovations in biointerfacing, enhance detoxification potency, and enable adaptable field applications, ultimately advancing OP detoxification approaches and saving lives.

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Notes

The authors declare no competing financial interest.

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