

Potential stability issue of protein and peptide therapeutic with polyvinyl chloride surface materials: A review

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ABSTRACT

Polyvinyl chloride (PVC) is widely used in intravenous infusion systems due to its low cost and flexibility. Interactions between protein/peptide therapeutics and PVC surfaces pose a significant threat to drug stability and clinical efficacy. Quantitative studies show that monoclonal antibody mAb3 exhibits a 13.5% increase in protein aggregates after 1 hour of contact with PVC infusion bags. Intravenous immunoglobulin (IVIG) exposed to di(2-ethylhexyl) phthalate (DEHP)-plasticized PVC bags demonstrated a dramatic increase in particle concentration from $2,300 \pm 440$ to $96,000 \pm 28,000$ particles/ml, a change reported to correlate with increased immunogenic risk. Insulin solutions showed up to 40% initial dose loss due to surface adsorption, and IVIG monomer content dropped to 0.25 ± 0.03 mg/ml in the presence of DEHP, observed alongside a 4.69-fold increase in complement activation. Protein adsorption values on uncoated PVC reached $3.85 \mu\text{g}/\text{cm}^2$, significantly higher than coated variants. These findings highlight hydrophobic and electrostatic interactions as key contributors to protein destabilization. Mitigation strategies such as surfactant addition and advanced coatings have shown potential to reduce protein loss by up to 60%–80%, yet limitations persist. This review emphasizes the urgent need for risk-based design of delivery systems to maintain protein drug efficacy, reduce the likelihood of immune responses, and improve patient safety in clinical applications.

1. INTRODUCTION

Polyvinyl chloride (PVC) is one of the most widely used types of synthetic polymers globally [1,2]. The main characteristics of PVC include good mechanical strength, chemical resistance, and the ability to be easily molded and modified. These superior properties make PVC a top choice in the packaging industry, especially for food and beverages, pharmaceuticals, and medical devices [3].

PVC production is estimated to reach more than 25 million tons annually and accounts for 28% of medical applications. In the pharmaceutical world, PVC is often used to produce blister packs, infusion bags, and medical

tubes. This material was chosen because of its transparency, flexibility, and ability to maintain the stability of the product inside [4,5]. Despite its numerous benefits, the use of PVC also faces some significant challenges. One of the main problems is the presence of plasticizers, such as di-(2-ethylhexyl) phthalate (DEHP), which can dissolve into solutions stored in medical devices made of PVC. This can affect the stability of pharmaceutical preparations susceptible to degradation, such as peptide therapeutic preparations [6]. The molecular structures of polyvinyl chloride (PVC) and its commonly used plasticizer, di(2-ethylhexyl) phthalate (DEHP), are presented in Figure 1.

Protein-peptide therapeutic (PPTH), or known as protein and peptide-based therapy, is the drug of tomorrow as more research is dedicated to this area. PPTH is considered to have higher therapeutic effectiveness than drugs with small molecules due to its specificity and potency [7,8]. These advantages are a key driver in the development and acceptance of protein and peptide-based therapies that are increasingly widespread globally [9].

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Maintaining the structure of the PPTH has been one of the most important goals in the various studies developed by scientists in recent decades [10]. Structural instability that can arise from folding errors, opening, and alteration of covalent and noncovalent interactions can affect the properties of PPTH [11]. One of the problems that often arises is protein aggregation, which is the process by which protein molecules combine to form insoluble aggregates. This aggregation can occur during production, storage, or distribution, especially when proteins interact with packaging materials [12,13]. The impact not only lowers the efficacy of the therapy but can also trigger a harmful immune response, thereby reducing the safety and sustainability of treatment [14].

Protein-based therapy is also inevitable with packaging and medical devices made of PVC. In clinical practice, therapeutic proteins are often administered through infusions or stored using containers and tubes made of PVC [15]. The interaction between the protein and the PVC surface can lead to protein adsorption, ultimately increasing aggregation risk or even decreasing the effective protein concentration. These changes can reduce the efficacy of the therapy and increase the likelihood of side effects such as harmful immunogenic reactions [16].

Several previous studies have shown many potential interactions between PVC and PPTH. Research reported that PVC surfaces can cause adsorption and denaturation of proteins, especially in proteins with sensitive tertiary structures. PVC infusion bags can trigger conformational changes in albumin, significantly reducing its stability and biological activity [17]. In addition, the monoclonal antibodies (mAbs) that contacted with PVC infusion bags and tubes experienced increased aggregation, potentially increasing the risk of immune reactions in patients.

Several studies have demonstrated that therapeutic proteins, including mAbs, albumin, and immunoglobulins, undergo significant adsorption or aggregation when in contact

with PVC materials. For instance, one study reported a 13.5% increase in aggregate formation for mAb3 after 1 hour of stirring in a PVC infusion bag [18]. Another study observed that insulin lost up to 40% of its initial concentration due to adsorption onto untreated PVC surfaces [19]. The presence of DEHP, a plasticizer commonly found in PVC, further exacerbates this issue by inducing hydrophobic adsorption and conformational changes in protein structure, as evidenced in intravenous immunoglobulin (IVIG) solutions that generated up to 96,000 particles/ml after agitation [20]. Such alterations compromise drug potency and increase the risk of adverse immune responses, including infusion-related reactions (IRRs) and the formation of anti-drug antibodies (ADAs) [21].

Understanding the mechanism of interaction between PVC and therapeutic proteins or peptides is of great importance. This review article will discuss the effect of PVC materials on the stability of proteins and peptides in pharmaceutical formulations, the problems arising from protein aggregation, and the clinical implications of these interactions. This knowledge is expected to provide insights for developing safer and more effective packaging strategies to support the success of protein and peptide-based therapies.

2. METHODOLOGY

This article is based on a narrative literature review aimed at synthesizing current scientific evidence regarding the interactions between PVC and therapeutic proteins or peptides, particularly in the context of clinical infusion systems. The review emphasizes the mechanisms of protein instability, the impact on therapeutic efficacy, and possible mitigation strategies.

Literature searches were conducted between January 2010 and April 2024 using databases such as PubMed, ScienceDirect, and Google Scholar. The search employed various combinations of the following keywords: "PVC", "protein adsorption", "peptide aggregation", "infusion system",

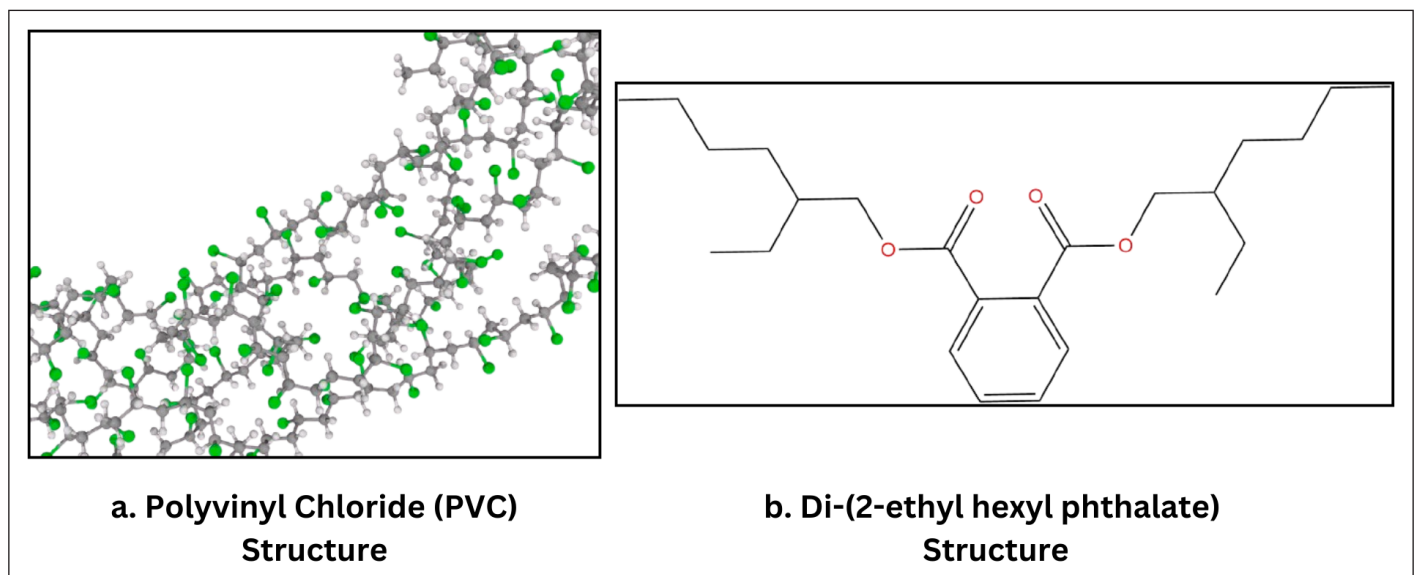


Figure 1. Chemical structure of (a) PVC, (b) DEHP.

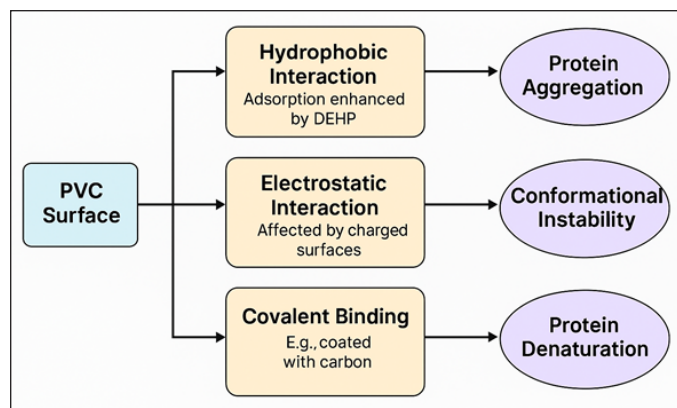


Figure 2. Flowchart of protein destabilization induced by PVC infusion surface.

“DEHP”, “biocompatibility”, “surface modification”, and “surfactant”. Boolean operators (AND, OR, and NOT) were applied to optimize the search strategy.

Articles were included in this review if they discussed original research or reviews addressing the interaction between PVC materials and protein or peptide-based therapeutics, presented quantitative data (e.g., on adsorption, aggregation, or degradation), and were published in English in peer-reviewed journals. Preference was given to studies with direct clinical relevance, such as those involving infusion systems, storage bags, or tubing materials.

Studies were excluded if they focused exclusively on non-PVC materials such as polyolefin (PO) or glass, did not involve therapeutic proteins or peptides (e.g., studies on enzymes, vaccines, or industrial proteins), or lacked primary experimental data. Nonpeer-reviewed sources, such as patents, theses, or conference abstracts, were also excluded.

3. RESULTS AND DISCUSSION

3.1. Polyvinyl chloride

PVC is a polymer produced from vinyl chloride monomers (C_2H_3Cl). Vinyl chloride monomers are strung into long polymer chains through suspension, emulsion, or bulk polymerization methods [22]. An important component in flexible PVC is plasticizers such as DEHP, which typically make up to 40%–50% of the total weight of the material [1]. Studies show that DEHP exposure can negatively affect the hormonal and reproductive systems, which makes it a major concern in medical applications [23].

The DEHP degradation process is relatively slow, raising concerns about its long-term impact on health and the environment. As an endocrine disruptor, DEHP can interfere with hormonal balance, potentially causing toxic effects on the reproductive system, growth, and metabolism. Several studies also indicate that DEHP and its metabolites contribute to neurodevelopmental disorders and increase the risk of metabolic diseases, including obesity and diabetes [24].

DEHP is toxic to the liver, kidneys, testes, lungs, and heart, with premature infants, hemodialysis patients, and individuals with prolonged PVC exposure being the most vulnerable. Rhesus monkeys that received transfusions from

PVC blood bags for 6 months to 1 year exhibited hepatocyte degeneration, necrosis, and impaired liver function for up to 26 months post-exposure. Hemodialysis patients undergoing therapy 2–3 times per week for over a year showed histological liver abnormalities, including peroxisome induction. In premature infants undergoing ECMO for 71–300 hours, DEHP exposure was significantly correlated with increased cholestasis. It also induced malignant hepatocellular carcinoma in rats and mice, with a dose-dependent increase in hepatocellular adenomas. Male rats given 750 mg/kg per day from gestational day 14 to postnatal day 3 experienced testicular atrophy, epididymal abnormalities, and hypospadias. Mice fed 12,000 ppm DEHP developed tubular degeneration and kidney atrophy within 4–8 weeks. Intravenous DEHP at 200–300 mg/kg caused respiratory distress, tracheal hemorrhage, and pulmonary edema in rats, while its metabolite Mono(2-ethylhexyl) phthalate induced bradycardia and hypotension following a 20–50 mg injection [25]. Although these systemic toxicities are not a direct measure of protein instability, they are relevant to this review because DEHP leaching from PVC surfaces can alter surface chemistry and hydrophobicity, thereby influencing protein adsorption, conformational stability, and aggregation. Such molecular-level changes may contribute indirectly to the adverse biological outcomes observed in clinical and experimental settings.

Various approaches have been developed to address this problem, one of which is by modifying PVC surfaces using cold plasma technology. This technology allows for an increase in the hydrophobic properties of PVC surfaces, which can reduce plasticizer release while lowering the risk of microorganism adhesion and biofilm formation [4]. This innovation is significant for medical devices such as endotracheal tubes that are in frequent direct contact with body fluids, where the risk of infection is a major concern [2].

DEHP migration issues have prompted the search for safer plasticizer alternatives, such as tris(2-ethylhexyl) trimellitate, which have a much lower migration rate than DEHP [1]. Another innovative approach is the use of plasticizers that are covalently bonded to PVC structures, thereby reducing the release of harmful chemicals during the use of medical devices [5].

3.2. Protein–peptide therapeutic

Therapeutic proteins are biomolecules utilized in various clinical applications to treat chronic diseases, autoimmune disorders, cancer, genetic abnormalities, and metabolic diseases [26,27]. The mechanisms of action of therapeutic proteins vary, including the replacement of dysfunctional proteins, modulation of biological activity, and regulation of the immune system to control inflammatory responses and cancer [28,29].

Various categories of therapeutic proteins have been developed for medical purposes. As of 2024, the United States Food and Drug Administration (FDA) has approved more than 350 protein and peptide-based therapies. Of the total 42 drugs approved by the FDA that year, 13 were protein or peptide-based therapies [30–32]. One of the most widely used classes is mAbs, which specifically recognize target antigens on pathological cells to inhibit particular molecular pathways or mark cells for elimination by the immune system [33]. Recombinant enzymes treat enzyme deficiencies that cause metabolic disorders and

lysosomal diseases [34]. Recombinant hormones, such as insulin for diabetes and growth hormones for growth deficiencies, have significantly improved the clinical management of endocrine diseases [35]. In addition, blood clotting factors like factor VIII and IX serve as primary therapies in hemophilia management, preventing spontaneous bleeding that could be fatal [36]. Fusion proteins, which combine two or more therapeutic proteins into a single molecule, have been developed to enhance stability, half-life, and pharmacological effectiveness [37]. Cytokines, such as interferons and interleukins, play a role in cancer immunotherapy and inflammatory diseases by either stimulating or inhibiting the immune system in a controlled manner [38].

Despite their significant clinical potential, the development of therapeutic proteins faces several major challenges [9]. Protein stability is a critical factor, as therapeutic proteins are susceptible to degradation and aggregation, which can negatively impact the efficacy and safety of the product [37,38].

3.3. Protein aggregation

Protein aggregation is a process in which proteins undergo structural changes and interact with each other, forming aggregates that can compromise their stability and biological function [9]. In the context of therapeutic proteins, aggregation can negatively impact drug efficacy and increase the risk of undesirable immune responses [41]. This process can occur at various stages, including production, storage, transportation, and administration [42]. In therapeutic applications, aggregation not only reduces the biological potency of proteins but also heightens the risk of immunogenicity, potentially triggering adverse immune reactions in patients. Therefore, understanding the factors influencing protein aggregation is crucial in the development of protein-based therapeutics [43].

Protein aggregation is influenced by intrinsic and extrinsic factors [34]. Intrinsic factors pertain to the physicochemical properties of the protein itself, such as thermal stability, propensity for misfolding, and inter-domain interactions [44]. In contrast, extrinsic factors include environmental conditions such as temperature, pH, ionic strength, mechanical stress (e.g., agitation or pumping), and interactions with container surfaces or excipients in the formulation [45]. A comprehensive understanding of these factors enables drug developers to identify optimal conditions that minimize protein aggregation throughout the product's lifecycle [9].

The aggregation process is multifaceted and involves three primary mechanisms, depending on the types of components involved: native monomers, denatured proteins, or pre-existing aggregates [9]. Under folded conditions, native monomers can form oligomers through noncovalent interactions between hydrophilic and hydrophobic residues on the protein surface or through complementary charge interactions between monomers. If these interactions persist, larger aggregates can develop, which are often immunogenic [4,46]. Over time, these aggregates grow in size, reducing the protein's ability to revert to its native conformation [47]. Pharmaceutical protein formulations typically contain a small fraction of denatured proteins, which are more prone to forming permanent aggregates [48]. However, some partially folded proteins may regain their native structure under specific conditions [35]. In addition,

aggregation can occur through interactions between native protein monomers and pre-existing oligomers, contaminants, or container surfaces, initiating nucleation and promoting aggregate growth [44,49].

Various analytical techniques are employed to study protein aggregation. Spectroscopic methods, such as intrinsic and extrinsic fluorescence, are used to detect conformational changes before aggregation occurs [50]. Microscopy techniques, including light and electron microscopy, allow for direct visualization of protein aggregates [42,51]. In addition, biochemical methods such as ultrafiltration, chromatography, and SDS-PAGE facilitate the characterization of aggregate size and properties. The integration of these approaches provides a more comprehensive understanding of the mechanisms and kinetics of protein aggregation [30].

Strategies to prevent protein aggregation include formulation optimization, such as the use of appropriate buffers, stabilizers, and excipients that mitigate protein-protein interactions [9]. Protein engineering can also enhance structural stability by modifying amino acid sequences to reduce aggregation susceptibility [40]. Furthermore, stabilizing additives such as surfactants or hydrophilic polymers help maintain the native protein structure and minimize aggregation risk [39].

3.4. Interaction between PVC and PPT_h

PVC is a material that is often used in medical devices such as infusion bags and medical tubes because of its flexibility, durability, and affordability. However, the release of plasticizers such as DEHP into the solution can affect the stability of therapeutic proteins stored in these devices [Figure 2](#) [20]. Studies show that DEHP detached from PVC bags into an infusion solution can trigger the aggregation of proteins such as intravenous immunoglobulins (IVIG) through hydrophobic interactions between the surface of DEHP and the proteins. This aggregation not only reduces protein stability but also increases the activation of the complement system, which can trigger an excessive immune response and reduce the effectiveness of therapy [52].

[Table 1](#) summarizes the interactions between various proteins and PVC surfaces under different medical conditions. The data indicate that PVC has a strong tendency to adsorb proteins, which can impact their stability and therapeutic effectiveness. For example, mAbs mAb3 exhibited significant aggregation, increasing by 13.5% after 1 hour of stirring in a PVC infusion bag, while human serum albumin (HSA) underwent secondary structural changes, with its α -helix content decreasing from 57.6% to 45.9% due to interactions with PVC micro plastics [16]. This suggests that PVC can alter the structure and function of plasma proteins, potentially disrupting their biological activity. Furthermore, the use of PVC containing the plasticizer DEHP in NaCl infusion bags increased the adsorption of mAbs and antibody-drug conjugates, which may lead to a reduction in effective drug dosage and a higher risk of immunogenicity [53].

In addition to direct interactions with therapeutic proteins, the table highlights differences in protein adsorption levels across various types of PVC. Uncoated PVC exhibited

Table 1. Interaction between PVC and PPTth.

Name of protein	Types of protein	Surface type	Observed outcome	Types of interactions	Clinical implications	Reversibility
mAb1, mAb2 and mAb3 [18]	mAbs IgG1	Infusion bag made from PVC 250 ml	<p>A. mAbs and antibody – drug conjugate</p> <p>mAb1: Does not show any change in turbidity or particle formation after stirring.</p> <p>mAb2 (2.4 mg/ml): Slightly increases the amount of aggregate of solution after stirring in an infusion bag, with an increase of approximately 0.1% aggregate after 1 hour of stirring.</p> <p>mAb3 (5 mg/ml): Shows a significant increase in solution aggregate (13.5%) after 1 hour of stirring, and particle formation is obvious.</p>	Plastic surfaces (PVC) can cause protein aggregation, especially after dilution and stirring, which can be related to hydrophobic interactions and bonding that occur at the water–air interface.	It leads to dehydration or aggregation of proteins, reduces therapeutic effectiveness and even elicits adverse immune responses, such as the formation of anti therapeutic antibodies (ATAs) that can reduce the effectiveness of treatment or cause adverse reactions in patients.	Reversible
Monoclonal antibody A (mAbA), Monoclonal Antibody N (mAbN), and Antibody-Drug Conjugate (ADC) [53]	mAbs, IgG1 and antibody-drug conjugate	PVC plate (surface model) and PVC bag NaCl/G5% (medical surfaces). Its surface composition includes PVC with DEHP as a <i>plasticizer</i>	<p>Surfactant-free mAb adsorption in PVC Bag NaCl was recorded at 12.8 ± 1.4 ng/cm² for mAbA, 6.3 ± 1.4 ng/cm² for ADC, and 4.6 ± 0.9 ng/cm² for mAbN.</p> <p>The efficacy of PS80 surfactant in PVC NaCl bags is lower than that of other materials, with protection of about 60%–80% at high concentrations (200–8,000 ppm)</p>	The interactions that occur are hydrophobic interactions, especially between the hydrophobic regions of proteins (such as ADCs) and PVC surfaces that are hydrophobic.	Protein adsorption on medical surfaces can lead to loss of active doses of drugs and the formation of protein aggregates, potentially increasing the risk of immunogenicity in patients.	Reversible
Rituximab and IVIG. [52]	mAbs and immunoglobulins	PVC tube free DEHP	In IVIG infusion using a peristaltic pump with saline, sub visible particles reached 26.456 P/ml (size 1–10 µm) at a flow rate of 250 ml/hour.	Surface adsorption: Proteins adhere to the surface of PVC tubing.	Increases the risk of immunogenicity, causing IRRs.	Irreversible
IVIG and mAb [60]	mAbs	Infusion bags made of PVC with a solution of 250 ml sodium chloride (saline) 0.9% or 5% dextrose solution	<p>In Rituximab infusion with peristaltic pumps, sub visible particles were less than 1,800 P/ml (1–10 µm in size) at a concentration of 1 mg/ml, but increased significantly at a concentration of 4 mg/ml.</p> <p>IVIG: Transport using a PTS (pneumatic tube system) significantly increases the concentration of protein particles, especially in saline solution compared to dextrose.</p> <p>mAb: In saline solution, an increase in protein particles occurs in PO bags but not in PVC bags. There was no significant increase in dextrose solutions for PVC or PO bags.</p>	Hydrophobic interactions: Antibodies (e.g. Rituximab) are maintained by surfactants such as polysorbate which reduces surface adsorption.	Risk of forming ADAs, which can reduce the efficacy of therapy.	Reversible
HSA [16]	Plasma protein	Microplastics PVC (MPs)	<p>B. Plasma – derived therapeutic proteins</p> <p>HSA fluorescence is subjected to static quenching by PVC MPs, with binding constants (Ka) of 4.97×10^6 M⁻¹ at 298 K, respectively.</p> <p>The secondary structure of HSA showed a decrease in α-helix content from 57.6% to 45.9%, indicating the potential loss of biological activity</p>	The interactions that occur are mainly electrostatic interactions. Thermodynamic data showed that the change in enthalpy ($\Delta H = -59.27$ kJ/mol) and the change in entropy ($\Delta S = 70.76$ J/mol·K) supports the dominance of electrostatic force	PVC MPs can cause changes in the secondary structure of HSA, potentially impairing the physiological function of proteins.	Irreversible

Continued

Name of protein	Types of protein	Surface type	Observed outcome	Types of interactions	Clinical implications	Reversibility
Albumin, $\alpha 1$ -globulin, $\alpha 2$ -globulin, and β -globulin, and γ -globulin [54]	Plasma protein	Uncoated PVC (Brand A and Brand B) PVC with phosphorylcholine coating PVC with triblock copolymer coating (polycaprolactone-polydimethylsiloxane-polycaprolactone) PVC with PME A coating.	The results showed protein adsorption in all types of PVC tubing. The total protein adsorption rate is as follows: Uncoated PVC Brand A: 2.28 $\mu\text{g}/\text{cm}^2$ Uncoated PVC Brand B: 3.85 $\mu\text{g}/\text{cm}^2$ PME A: 4.71 $\mu\text{g}/\text{cm}^2$ Phosphorylcholine: 2.94 $\mu\text{g}/\text{cm}^2$ Triblock copolymer: 2.62 $\mu\text{g}/\text{cm}^2$. There were no statistical differences in protein adsorption between the triblock-copolymer-treated tubing, the phosphorylcholine-coated tubing and the uncoated PVC tubing of brand A PVC with carbon coating shows higher adsorption of protein (albumin) than PVC without treatment. Proteins remain firmly bound to the surface of carbon-coated PVC even when washed with a detergent solution (SDS), while proteins in untreated PVC are easily detached. The study also showed an increase in cell proliferation in PVC with carbon coating compared to PVC without treatment.	The main interactions that occur are hydrophobic interactions and electrostatic interactions. More hydrophobic surfaces (e.g. PVC without coating) show higher protein adsorption than more hydrophilic surfaces (e.g. phosphorylcholine).	Triggers a systemic inflammatory response, including activation of the immune system through the adsorption of proteins such as γ -globulin and C3 (complement). It can improve the adhesion and activation of immune cells and platelets, potentially leading to clinical complications during extracorporeal circuit procedures.	Reversible
Bovine Serum Albumin [55]	Albumin	PVC without treatment (control). PVC that has been treated with carbon coating through ion-plasma treatment with an ion energy of 20 keV and a fluxion of 10^{16} ions/ cm^2 .	After agitation, the concentration of micro particles in PVC bags increased drastically from 2,300 \pm 440 particles/ml to 96,000 \pm 28,000 particles/ml, while PO bags showed minimal increase from 720 \pm 450 particles/ml to 640 \pm 110 particles/ml. DEHP accelerated IVIG aggregation, which was reflected by a decrease in IVIG monomer concentrations to 0.25 \pm 0.03 mg/ml after 24 hours of agitation at the highest concentration of DEHP droplets (2 mg/ml). Complement activation (C5a protein) increased to 4.69 \pm 0.14-fold in IVIG solution with DEHP droplets compared to control solution without droplets.	The interaction that occurs between the protein and the surface of carbon-coated PVC is a covalent bond. Carbon layer with aromatic structure and free radicals strengthens the covalent adsorption of proteins	Causes adhesion of leukocytes to the surface of blood bags	Irreversible
IVIG [20]	Antibody polyclonal	The PVC surface comes from an infusion bag made of plasticized PVC with a DEHP plasticizer		This type of interaction involves hydrophobic adsorption between DEHP and IVIG droplets, resulting in a monolayer with a saturation of 2.65 \pm 0.50 mg IVIG/ m^2 of DEHP surface. The addition of IVIG also increases the fluorescence intensity of bis-ANS, which indicates disruption of protein structure due to hydrophobic interactions.	Triggers an inflammatory reaction or even anaphylaxis during infusion. Reduces therapeutic efficacy and increases the risk of adverse immune responses.	Irreversible

Continued

Name of protein	Types of protein	Surface type	Observed outcome	Types of interactions	Clinical implications	Reversibility
HSA [22]	Plasma protein	The PVC surface used is a 35-mer PVC chain model representing an amorphous PVC surface with a density of about 1.24 g/cm ³ , which is modeled using molecular dynamics simulation.	The interaction energy between HSA and PVC has a Gibbs free energy value of -507 kJ/mol at 300 K, indicating a spontaneous and stable thermodynamic adsorption process. The analysis showed dominant hydrophobic interactions with the additional contribution of hydrogen bonds mediated by water. Amino acids that interact with PVC surfaces include aliphatic residues (22.9%), aromatics (68.9%), uncharged polar (21.1%), acids (15.3%), and bases (11.8%).	Hydrophobic interactions are the main mechanism, which facilitates the stability of proteins on PVC surfaces. Water-mediated hydrogen bonds are also observed. Quantitative contribution is not fully defined for each type of interaction other than an analysis of the contribution of the amino group of interacting acids.	The adsorption of proteins such as HSA on PVC surfaces can initiate biofouling, which is the process of forming protein layers that facilitate the adhesion of cells and microorganisms. Biofouling in medical devices can reduce biocompatibility and increase the risk of infection or malfunction of the device.	Irreversible
C. Peptide hormones and small proteins						
Vasopressin [17]	Peptide synthesis	PVC bags for infusion solution storage	Vasopressin 0.4 units/mL remains stable (>90% initial potential) for up to 90 days at room temperature and in refrigeration. Vasopressin 1.0 units/ml is stable for up to 90 days only at cold temperatures.	Unexplained	Unexplained	-
Dulanermin[58]	Recombinant therapeutic proteins	The PVC surface comes from a 100 ml infusion bag containing a 0.9% saline solution. This bag uses a plasticizer, as well as a rubber stopper made from natural rubber.	Stability in PVC: Dulanermin is stable in PVC bags, without significant loss of monomers. The monomer percentage remains at 99% after 18 hours at 30°C. Zinc and UV Absorption: Solutions from PO bags have a UV peak at 320 nm (not found in PVC). The zinc level in the saline solution from PO bags reaches 729 ppb, compared to less than 20 ppb in PVC. Effect of PO stoppers: Stoppers from PO bags contain zinc-2-mercaptobenzothiazole, which causes protein instability of up to 5% loss of monomers within 16 hours at 30°C.	The main interactions identified involve surface adsorption between proteins and zinc-based leachables compounds.	Immunogenicity Risk: Leachables compounds such as zinc-2-mercaptobenzothiazole can trigger an immune response, potentially harming patients. Drug Stability: Protein instability such as loss of monomers can reduce therapeutic efficacy, increase the risk of ineffective treatment, or cause side effects.	Reversible
Regular human insulin [19]	Regular human insulin	The PVC surface is derived from a standard PVC infusion bag with a total volume of 100 ml, used to mix a solution of insulin and 0.9% sodium chloride.	Insulin concentrations were stable at all measurement times, except at the 120th hour, when the concentration dropped below the stability threshold (0.46 ± 0.05 units/ml, lower than the stability limit of 0.52 units/ml). At 168 hours, insulin concentrations returned to 0.63 ± 0.07 units/ml, higher than the specified stability limit (90% of the equilibrium concentration). The graph shows the stability of insulin concentrations in general over 168 hours with a slight decrease at any given time.	The main interaction is the adsorption of insulin on the surface of the PVC, which causes an initial loss of up to 40% of insulin due to adsorption. Most of the losses occur at the beginning of the time of contact with the PVC surface.	Adsorption of insulin onto the surface of the PVC can lead to a reduction in the effective dose of insulin received by the patient, thus affecting the efficacy of the therapy	Reversible

the highest protein adsorption, whereas phosphorylcholine-coated and triblock copolymer-coated PVC showed reduced protein adsorption, although interactions with plasma proteins such as albumin and globulins still occurred [54]. The findings confirm that more hydrophobic PVC surfaces tend to exhibit higher protein adsorption rates, which can trigger systemic inflammatory responses, immune system activation, and platelet adhesion during extracorporeal circuit procedures. In addition, studies show that carbon-coated PVC surfaces display increased protein adsorption compared to untreated PVC due to covalent bonding, potentially leading to leukocyte adhesion on blood bags [55]. Therefore, understanding the characteristics of PVC–protein interactions is crucial for developing safer and more biocompatible medical materials.

In addition to adsorption, plasticizers such as DEHP in PVC can interact with proteins through diffusion and leaching mechanisms. DEHP that is not chemically bonded to the PVC matrix can migrate to the surrounding solution and interact with proteins through hydrophobic forces [52]. These interactions often trigger protein aggregation, as seen in IVIGs, where DEHP creates hydrophobic contact surfaces that trigger the formation of protein aggregates. This aggregation not only reduces protein stability but also increases the risk of immunogenicity due to immune system activation [20].

Aromatic amino acids such as tyrosine, tryptophan, and phenylalanine are commonly involved in protein degradation processes. These residues are particularly susceptible to oxidation and conformational changes, especially during physical stress such as agitation, exposure to light, or contact with synthetic infusion materials. Their structural sensitivity makes them important indicators of protein instability, including in HSA formulations [56,57].

The interaction between proteins and PVC surfaces is another challenge in ensuring protein stability. The surface of materials used in the storage and administration of therapeutic proteins plays a crucial role in determining protein stability [16]. One of the key factors influencing protein-surface interactions is the roughness of the surface itself. Rougher surfaces tend to have a larger contact area, which can increase the likelihood of interactions between proteins and the material [53]. Consequently, protein adsorption to the surface becomes more significant, which, in the long run, can lead to conformational changes, aggregation, and even degradation. In the context of pharmaceutical formulations, increased protein adsorption due to surface roughness not only reduces therapeutic efficacy but also raises the risk of immunogenicity [54]. However, certain DEHP-free PVC grades have demonstrated significantly lower protein adsorption levels [51], likely due to differences in surface chemistry and hydrophilicity introduced by alternative plasticizers or manufacturing processes. These variations highlight the importance of PVC formulation in modulating protein-surface interactions.

HSA is one example of a protein that interacts with PVC microplastics through electrostatic bonding that causes changes in the secondary structure of proteins [16]. Multispectroscopic studies show that this interaction reduces the number of α -helix in the structure of the HSA protein, which in turn can affect the stability of the protein and its potential in

therapeutic applications. In addition, the rougher PVC surface was found to increase protein adsorption, thereby accelerating the process of aggregation and degradation of proteins in the infusion solution [54].

In clinical applications, the use of PVC bags for intravenous fluids such as insulin and immunoglobulins often leads to protein instability due to interactions with PVC surfaces or microenvironment changes, such as pH induced by leachables [58]. For example, insulin in PVC bags shows significant adsorption on the surface of the bags with a loss of activity of up to 40% in a short period of time. This phenomenon necessitates increasing the dose to achieve the desired therapeutic effect, which ultimately increases the risk of dosage errors and treatment costs [19]. Furthermore, the transport or stirring of PVC bags during the process of distribution and clinical use increases the formation of sub visible particles, which contribute to further protein aggregation and the possibility of increased risk of immunogenicity [18].

The use of PVC in medical devices also has implications for the stability of other therapeutic drugs, such as vasopressin and insulin [19]. Research shows that PVC bags can cause a decrease in drug concentration due to interactions with PVC surfaces and protein adsorption. Vasopressin shows significant degradation when stored in PVC bags at room temperature, while insulin undergoes high adsorption, which affects its pharmacological efficacy. This challenge highlights the importance of a thorough evaluation of the interaction between PVC devices and the proteins or drugs used in them [59].

The mechanism of plasma protein adsorption on PVC surfaces has been discussed in recent studies using molecular dynamics (MD) simulations. In this work, these insights are integrated with clinical observations to provide a unified mechanistic framework. The study showed that HSA had the highest binding energy on PVC surfaces, with interactions dominated by water-mediated hydrogen bonding and van der Waals forces. This adsorption occurs spontaneously, as indicated by Gibbs' very negative free energy value, and without major disruption of HSA's secondary structure. Importantly, these molecular events parallel clinical evidence showing that DEHP-containing PVC can promote complement activation via protein aggregate formation, highlighting a direct link between nanoscale interactions and pro-inflammatory responses *in vivo* [17].

The interaction between PVC and proteins occurs through various physical and chemical mechanisms involving the PVC surface, plasticizer molecules, and the surrounding environment. One of the main mechanisms is the adsorption of proteins on PVC surfaces driven by electrostatic, hydrophobic interactions, as well as hydrogen bonding. PVC surfaces have strong hydrophobic properties that can attract hydrophobic residues on proteins, especially on the surfaces of HSA and IVIG. Structural analyses reveal that, despite retention of global secondary structure, extensive PVC–protein contact can modulate surface residue accessibility, potentially facilitating subsequent cell adhesion and biofouling. Literature comparisons show that previous reviews have treated MD results and clinical findings as separate discussions, whereas here they are explicitly connected [16,17].

This work uniquely integrates atomistic MD simulations with clinical evidence to provide a cross-scale understanding of PVC–protein interactions. The MD simulations elucidate residue-specific binding patterns and thermodynamic signatures, while clinical findings associate these interactions with complement activation and inflammation in DEHP-containing PVC devices. By linking nanoscale interaction mechanisms to clinically observed biofouling phenomena, this study offers a perspective not previously presented in the literature. Furthermore, the molecular determinants identified here can directly inform the design of surface modification strategies or alternative polymer chemistries aimed at reducing high-affinity protein binding and improving the blood compatibility of PVC-based medical devices.

Transportation and mechanical conditions also play a crucial role in facilitating the interaction between PVC and proteins. In pneumatic tube systems commonly used in hospitals, PVC bags experience mechanical shocks that induce cavitation within the infusion solution. This cavitation generates air bubbles and additional liquid–air interfaces, which serve as sites for protein adsorption. Furthermore, interactions with PVC surfaces can be exacerbated by mechanical movement, leading to the formation of sub visible particles and protein aggregation. Studies have shown that IVIG in saline solution is more prone to forming sub visible particles compared to dextrose solution. This indicates that different ionic strengths of solutions also influence the intensity of protein–PVC interactions [60].

3.5. Modification to prevent protein adsorption on PVC materials

PVC is a very useful material in medical devices, but the challenges related to protein stability caused by leachables, adsorption, and surface interactions remain issues that need to be addressed [58]. The material has physical advantages and low cost, making it a top choice for medical devices, but various factors, including plasticizer migration, protein adsorption on PVC surfaces, as well as mechanical dynamics such as transport using pneumatic tubes, can affect the stability and efficacy of therapeutic proteins [52]. Under static conditions, hydrogen bonding and van der Waals forces can stabilize the adsorbed proteins on PVC surfaces [17]. Conversely, under mechanical conditions such as transport, the stability of proteins can be compromised [60].

Table 2 presents various mitigation strategies and surface modifications designed to reduce protein adsorption on PVC, thereby enhancing the stability and safety of protein-based therapies. One approach detailed in the table involves the addition of surfactants such as polysorbate 80 and polysorbate 20 to minimize protein–PVC interactions. Studies have shown that adding 0.01% polysorbate 80 to IVIG infusions significantly reduces sub visible particle formation compared to samples without polysorbate 80, indicating that surfactants can help prevent protein aggregation during infusion [52]. In addition, polysorbate 20 was found to be more effective than polysorbate 80 and poloxamer 188 in reducing adsorption in polypropylene (PP)-based NaCl bags, while polysorbate 80 was most effective

Table 2. Mitigation or modification to prevent protein adsorption.

Name of protein	Type of protein	Surface type	Mitigation/Modification	Result	Mechanism
Rituximab and IVIG [52]	mAbs and immunoglobulins	Tubing PVC non DEHP	The addition of Polysorbate 80 0,1% (PS80) as surfactant	Infusion of 100 mg/ml IVIG without PS80 results in a higher particle concentration compared to samples containing 0.01% PS80	Surfactant creates barrier to prevent adsorption
mAbA, mAbN, and ADC [53]	mAbs IgG1 and antibody-drug conjugate	PVC plate (surface model) and PVC bag NaCl/G5% (medical surfaces). Its surface composition includes PVC with DEHP as a plasticizer	The addition of Polysorbate 80 (PS80) or Polysorbate 20 (PS20) or Poloxamer 188 (P188) as surfactant	Polysorbate is more effective or at least equivalent to P188 in preventing adsorption. PS20 provides better protection than PS80 and P188 on certain surfaces, particularly for mAbA and mAbN in PP NaCl bags. PS80 is the most effective for ADC, but only at high concentrations (1,000–8,000 ppm).	Surfactant – mediated surface shielding
Bovine Serum Albumin [55]	Albumin	PVC without treatment (control). PVC that has been treated with carbon coating through ion-plasma treatment with an ion energy of 20 keV and a fluence of 10^{16} ions/cm ² .	Carbon coating using the ion – plasma method	Blood bags processed with carbon coating using the ion-plasma method are more effective in preserving leukocytes compared to untreated bags.	Surface passivation via covalent carbon layer
HSA [17]	Plasma protein	The PVC surface used is a 35-mer PVC chain model representing an amorphous PVC surface with a density of about 1.24 g/cm ³ , which is modeled using MD simulation.	<i>In silico</i> method	HSA exhibits the highest affinity for PVC, with a binding energy of –25.9 kJ/mol. This interaction is primarily driven by water-mediated hydrogen bonds and van der Waals forces.	Hydrophobic and electrostatic interaction modeling

for antibody-drug conjugates at high concentrations ranging from 1,000 to 8,000 ppm [53].

Beyond surfactant use, another method highlighted in the table is surface modification through carbon coating using the ion-plasma method, which has been shown to be more effective in preserving leukocytes in blood bags compared to untreated PVC [55]. An *in silico* approach was also used to analyze protein–PVC interactions at the molecular level, revealing that HSA exhibits the highest affinity for PVC, with a binding energy of -25.9 kJ/mol, primarily driven by water-mediated hydrogen bonds and van der Waals forces [17]. Collectively, the research findings outlined in this table provide insights into potential strategies for mitigating the negative effects of protein adsorption on PVC, which is essential for the development of safer and more efficient medical materials.

Mitigation strategies, such as modifying PVC surfaces to reduce their hydrophobic properties and using more effective surfactants to prevent protein adsorption, have shown promising results. Combination studies *in silico* and experimental provide valuable insights for designing more biologically compatible PVC materials in medical applications. In addition, the evaluation of transportation conditions and the development of more inert alternative materials can help mitigate these challenges, thereby ensuring better clinical safety and effectiveness [20,52,53].

Studies have shown that the interaction of proteins with PVC surfaces can be affected by the presence of nonionic surfactants such as polysorbate (PS80 or PS20). These surfactants are able to compete with proteins for adsorption sites on PVC surfaces, thereby reducing the possibility of protein aggregation. However, the effectiveness of surfactants depends on the type of protein, the concentration of surfactants, and the surface properties of PVC. For example, PS80 is effective in preventing the adsorption of monoclonal proteins on some PVC surfaces, but its effectiveness is reduced on other surfaces that are coarser or have a different composition. More research is needed to optimize this compatibility and ensure better protein protection during storage and clinical administration [53].

Modification of PVC surfaces through special coatings, such as carbon, has been proposed as a solution to reduce protein adsorption. Carbon coating on infusion tubing in the pharmaceutical field refers to the process of applying a thin carbon layer to the inner or outer surface of the tubing to enhance the stability of drug formulations delivered via infusion. These modifications aim to create a more chemically inert surface and reduce electrostatic interactions with proteins. Preliminary studies suggest that carbon coating may improve the compatibility of PVC with biological fluids, although more research is needed to confirm its effectiveness in large-scale applications [55].

Surfactants and surface modifications are widely used in pharmaceutical and biomedical applications to enhance protein and peptide stability, yet they pose potential risks related to toxicity and long-term effects. Surfactants like polysorbate 20 and 80, while commonly employed as stabilizers, can undergo oxidative degradation, forming reactive peroxides and aldehydes that promote protein aggregation and increase immunogenicity [21]. Sodium lauryl sulfate, although effective as a solubilizing agent, is known to cause irritation to mucosal

membranes and has cytotoxic potential at high concentrations [61]. Pluronic F-68, considered relatively safe, can still lead to hemolysis or neurotoxic effects when used in excess [62]. Over time, residual surfactants may accumulate in tissues, leading to hypersensitivity reactions and disruption of membrane integrity [63]. Similarly, surface modifications such as PEGylation, though beneficial in reducing protein adsorption and immune detection, have been associated with renal and hepatic accumulation and delayed clearance [64]. Coatings like silicone oil can generate micro droplets that trigger protein aggregation and immune activation, especially in pre-filled syringes [65]. Furthermore, plasma-treated or heparin-coated surfaces may degrade or lose their functional stability, releasing potentially cytotoxic fragments over extended use [33]. These findings underscore the necessity of evaluating not only the short-term efficacy but also the long-term biocompatibility and systemic effects of these mitigation strategies.

Current clinical practices have increasingly acknowledged the risks posed by interactions between PVC and therapeutic proteins or peptides, particularly in intravenous infusion systems. To mitigate these effects, healthcare providers frequently utilize nonionic surfactants, such as polysorbate 20 or 80, within the formulation or as part of a pre-conditioning process [63]. In some settings, clinicians pre-rinse infusion bags with surfactant-containing solutions prior to drug administration to reduce the number of active binding sites on PVC surfaces [65]. In addition, several institutions—particularly oncology and pediatric units—have adopted alternative materials such as PO, ethylene-vinyl acetate, or PP to avoid DEHP-associated risks and minimize protein adsorption [66]. While surfactants can be effective in mitigating protein loss, their use at suboptimal concentrations may paradoxically accelerate aggregation [64], underscoring the importance of optimized formulation parameters.

Technological strategies to overcome the limitations of PVC include both material substitution and surface modification. For instance, phosphorylcholine-coated and poly-2-methoxyethyl acrylate (PMEA)-modified PVC have shown promise in reducing protein adsorption and immune activation due to their hydrophilic and cell-mimetic properties. Phosphorylcholine-coating is a biomaterial coating that mimics the outer cell membrane and is used to improve the biocompatibility of medical devices, particularly those used in contact with blood. PMEAC modified refers to a polymer that is often used for surface modification to improve biocompatibility and reduce thrombogenicity (the tendency to cause blood clots) in medical devices [33,67]. Moreover, carbon-coated PVC, while providing strong adsorption resistance, may cause excessive leukocyte adhesion due to covalent interactions, potentially limiting its clinical use [68]. Triblock copolymers and PEGylated coatings also serve as potential surface barriers to reduce biofouling and protein denaturation. A triblock copolymer is a polymer composed of three different polymer chains linked together. A PEGylated coating is a surface modification using polyethylene glycol (PEG), a hydrophilic polymer, often to improve biocompatibility and prevent protein adhesion. When a triblock copolymer is PEGylated, it means that at least one of its blocks is PEG, or that PEG is grafted onto its surface, resulting in a material with enhanced properties for biomedical or other applications [69].

From a regulatory perspective, several agencies have addressed the risks of using PVC materials with biologics. The U.S. FDA has issued safety alerts discouraging the use of DEHP-containing PVC in critical patient populations, such as neonates and immunocompromised individuals, and recommends assessing container closure compatibility as part of current good manufacturing process compliance [70]. Similarly, the European Medicines Agency requires rigorous compatibility testing of container systems with protein-based therapeutics and emphasizes the need to avoid extractables and leachables that may impact product stability [71]. Guidelines from WHO and International Council for Harmonisation Q3D further reinforce the importance of evaluating material safety in parenteral drug delivery, particularly for biologics susceptible to structural and functional degradation [72].

These practices and guidelines collectively underscore the urgent need for a risk-based approach in the selection of infusion materials, especially when administering protein or peptide drugs. Integration of clinical precautions, engineered mitigation strategies, and adherence to regulatory standards can significantly improve therapeutic outcomes and patient safety.

Although this review primarily addresses the physicochemical and clinical aspects of PVC–protein interactions, it is essential to also consider the ethical implications, particularly in the context of patient safety. Vulnerable populations such as oncology patients, neonates, and individuals with autoimmune diseases are at greater risk of adverse outcomes due to impaired immune tolerance and higher exposure to biologics. The use of infusion systems that induce protein aggregation or degradation—and thereby increase immunogenicity—can compromise therapeutic effectiveness and lead to severe IRRs. From an ethical standpoint, continued use of materials like DEHP-containing PVC, despite available safer alternatives, raises concerns regarding nonmaleficence and informed risk communication in clinical settings [63,66].

Furthermore, there remains a significant gap in long-term safety data concerning the impact of PVC-derived microplastics and chronic protein denaturation caused by repeated exposure to medical device surfaces. The chronic accumulation of protein aggregates, potential biofouling, and immune sensitization could lead to cumulative physiological effects that are currently underreported or insufficiently studied [21,68]. In light of the increasing global attention to microplastic exposure and material safety in medicine, future research should aim to evaluate these risks using long-term *in vivo* studies and post-marketing surveillance data. Addressing these ethical and safety concerns is critical to ensuring equitable and responsible patient care, especially when treating fragile or immunologically compromised individuals.

4. CONCLUSION

The interaction between PVC and proteins is greatly influenced by a combination of material, environmental, and mechanical dynamics. An in-depth understanding of these mechanisms is important for developing more effective and innovative mitigation strategies. By using approaches such as surface modification, surfactants, and alternative materials, PVC-based medical devices can continue to be used without

sacrificing the stability and efficacy of therapeutic proteins. Further studies are needed to strengthen the understanding of these interactions, so that medical devices can be designed to support increasingly complex clinical needs while ensuring patient safety.

5. LIMITATION

This review has several limitations that should be acknowledged. First, there is considerable variability across the included studies, particularly in experimental parameters such as protein concentration, surface area of contact, infusion duration, and agitation intensity. These differences make it challenging to directly compare results or draw quantitative conclusions about the degree of protein loss or aggregation across systems. Second, the majority of data discussed in this review are derived from *in vitro* experiments, which may not fully replicate the complexity of *in vivo* infusion conditions, including blood flow dynamics, presence of serum components, or patient-specific physiological factors. Third, there is a lack of standardized methodologies for evaluating the performance of surface coatings and mitigation strategies. Differences in coating materials, application techniques, and testing environments limit reproducibility and hinder consensus on the most effective clinical solutions. Finally, the long-term effects of repeated exposure to PVC-derived leachables or microplastics remain underexplored, further emphasizing the need for longitudinal *in vivo* studies and regulatory harmonization in medical material testing.

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7. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

8. CONFLICT OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

9. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

10. DATA AVAILABILITY

All data generated and analyzed are included in this research article.

11. PUBLISHER'S NOTE

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13. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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