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Clinical Update

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Drugs and Filtration in Infusion Management

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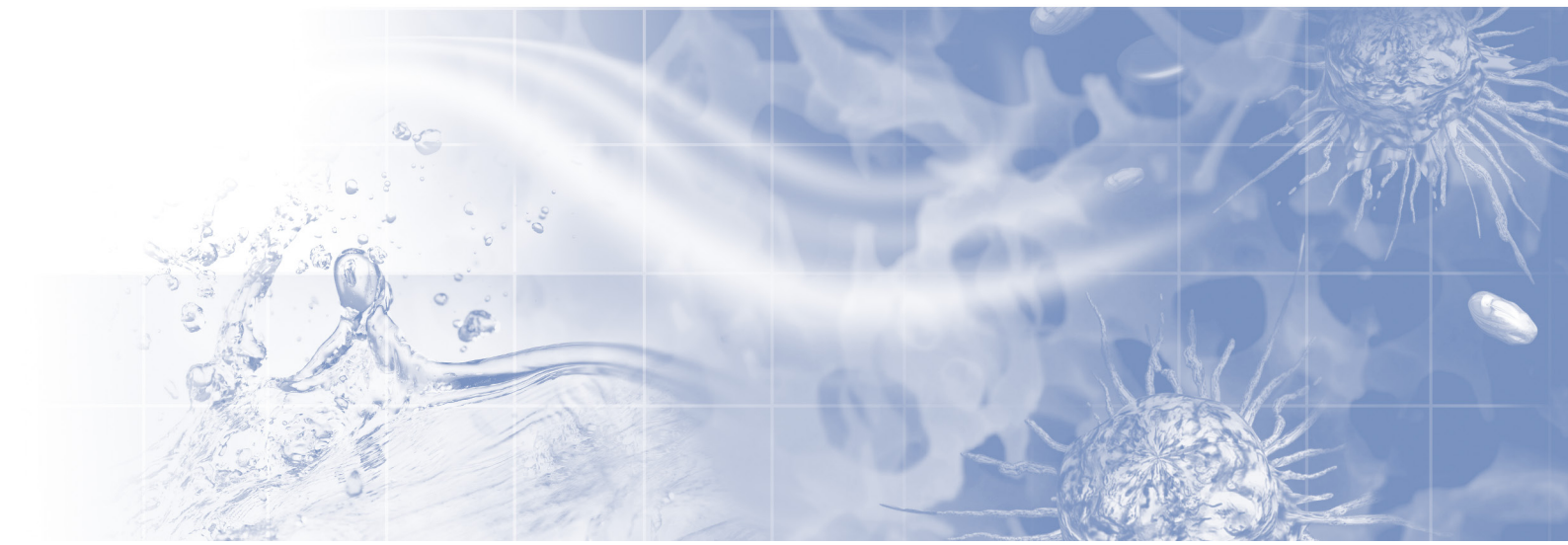


1. Introduction

In-line intravenous (IV) filters are widely used in clinical practice and play an important role in infusion therapy protecting patients against air and lipid emboli as well as potentially life-threatening inadvertent microbial and particulate contamination that may be found within drugs[1].

The benefit of in-line IV filtration in reducing the incidence of clinical complications (i.e.: phlebitis, SIRS, sepsis, thrombi and deep venous thrombosis) and preservation of vital organ function is well described in the literature[2-11].

Despite the aforementioned benefits, the primary goal in infusion management still remains to ensure that an accurate drug dosage is delivered to the patient. Therefore, for each drug formulation, a careful selection of all materials is advised since drugs may interact with the filter surface[12-27] or any other surface material in the infusion path[17,28-32] resulting in drug binding and subsequently in loss of drug concentration delivered to the patient.

The purpose of this document is to introduce the main factors and mechanisms involved in drug binding to surfaces, to identify when binding is particularly relevant in drug infusion management and to present the work carried out by Pall Corporation to investigate drug binding to its IV filter portfolio and the current available data.

2. How drugs bind to surfaces

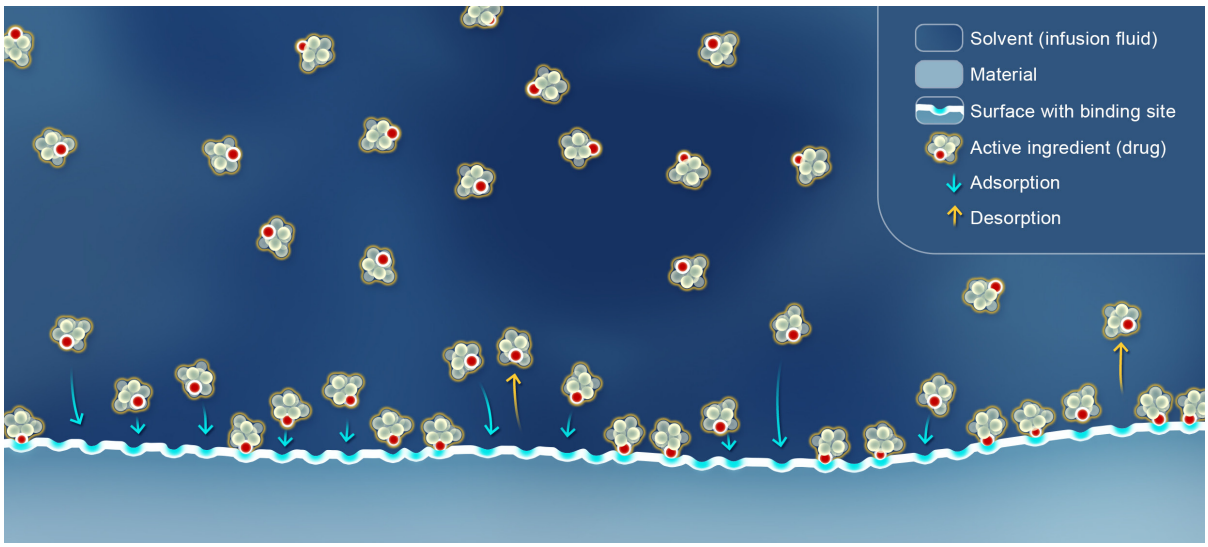
Drug binding to surface materials is a multifactorial process influenced by a wide range of different factors such as, drug nature, drug concentration, dosing regimen, temperature, pH, ionic strength, surfactants, infusion pressure, infusion flow rate, material surface properties and the number and type of active binding sites of the exposed surface area, amongst others[12,17,22,23,28,32-35].

While contact time during infusion is predominantly short, drug reaction with exposed surfaces is intimate resulting in high potential for both physical and chemical interactions. Surface drug binding is governed at the liquid-solid interface by sorption (adsorption and absorption) processes, adsorption being the predominant and most relevant interaction taking place[33].

Adsorption in IV therapy is the process by which drugs (ions or molecules) bind to the available active surface sites as they progress throughout the infusion pathway whereas desorption is the opposite process (Figure 1). Once binding sites are exhausted (saturated) rates of adsorption and desorption are equal[66] and no further effective drug loss takes place, consequently a constant drug delivery (equilibrium or plateau concentration) is achieved[17,26,35-37].

Figure 1

Drug binding adsorption and desorption processes.



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The effect caused by adsorption takes place early during passage of the IV solution but under certain infusion conditions the loss may be close to 100%[32,33,38,39] which may affect proper drug dosing and its therapeutic effectiveness[40]. The extent and length of the adsorption effect will vary for each drug and infusion regime from within minutes to several hours[17,20,26,28,31,32,35].

3. When drug binding is particularly relevant?

From an adsorption perspective, the internal surface area of an infusion line may be perceived as the number of active sites which are to be neutralized as the administration of drug molecules progresses. As previously mentioned, drug binding occurs until the available binding surface sites are saturated leading to initial drug loss, delayed infusion and subsequently, to potentially inaccurate therapeutic drug monitoring specially for those medications with a narrow therapeutic range (i.e. dopamine, aminoglycoside antibiotics and insulin) or short half-lives[22,41,42].

Although not limited to, the following have been identified in the literature as clinical scenarios where drug binding is particularly relevant:

3.1 Low Drug Dose/Flow Rates

While drug binding complications are usually under control when drugs are administered in relatively high doses[23,27,33,39,42], they may become real infusion management challenges when drugs are delivered at low concentrations and flow rates[13,14,20-23,26,31,33,39,41,42]. This situation is often observed in pediatric, neonatal and extremely low birth weight (< 1000 g) patients due to the exceptionally low dose concentrations (between ng and µg/Kg body mass), low flow rates (1-10 mL/h) and fluid allowance restrictions (i.e. limitations of flushing volume for drug binding desorption)[12,40,41].

3.2 Protein-Based Drugs

Besides the infusion regime, certain drugs are more prone to bind to surface materials than others. Proteins are highly complex biomolecules made of 20 naturally occurring amino acids in addition to potential side chains like phosphates, oligosaccharides or lipids[43]. Their inherent complexity makes it difficult to predict their adsorption behavior however, the fact that charged amino acid side chains may bind to surfaces and their known propensity to form aggregates[33,43-46] illustrate the relevance of an appropriate selection of the infusion line materials when administering protein-based active ingredients.

Examples of this are insulin, which has been extensively investigated with different infusion materials[14,17,20,26,28-31,35,36,61] and the more recently-developed monoclonal antibodies with explicit instructions for bolus or continuous administration with low protein-binding devices (i.e. syringe or in-line filters respectively) from drug manufacturers[47-60].

4. How does Pall investigate drug binding?

Although drug binding may occur to any surface material (i.e. administration set, three-way valves, catheters, etc), filters add to the potential adsorptive surface area of the infusion system[20].

Marked variations in binding properties of many drugs to different types of membrane filters are well described in the literature[12,15,18,20,22,26,35-40], therefore it is essential the most appropriate filter material is selected prior to drug administration[12,33].

Given the increasing role of filtration in infusion management, the following Pall filtration products (Table 1) have been the subject of investigation to assess their potential impact on drug dosage delivery.

Table 1

Pall filtration products subject to drug binding studies.

Product Family*	Membrane	Surface Area	Other Construction Materials	Application	Main Features
Pall AEF1	0.2 µm PES (Supor®)	4.5 cm^2	Housing: Acrylic Vent: PTFE	• Drug administration	• Low protein binding • Extensive drug compatibility
Pall HP (PharmAssure®)	0.2 µm; 0.45 µm; 0.8 µm; 1.2 µm; 5 µm PES (Supor)	2.8 cm^2	Housing: Acrylic	• Drug preparation • Intravenous or subcutaneous syringe bolus drug administration	• Low protein binding • Extensive drug compatibility
Pall ELD96	0.2 µm Nylon 6,6 (Posidyne®)	11 cm^2	Housing: Acrylic Vent: PTFE	• Drug administration	• Extended 96 h use • Endotoxin-retentive
Pall NE096	0.2 µm Nylon 6,6 (Posidyne)	1.65 cm^2	Housing: Acrylic Vent: PTFE	• Drug administration	• Extended 96 h use • Endotoxin-retentive • Small volume
Pall Lipipor™TNA1	1.2 µm Nylon	11 cm^2	Housing: Acrylic Vent: PTFE	• Drug administration	• Suitable for-lipid containing solutions for parenteral nutrition • Suitable for drugs requiring ≥ 1.2 µm filtration

**Please contact your local Pall representative for filter variant details.*

Binding compatibility of each type and drug concentration with in-line filters must be determined under clinically relevant conditions. However, due to the wide range of medications and variables involved in IV drug delivery and the subsequent cost, it is not possible to perform adsorption studies for every clinical infusion regime.

The following Technical Reports[61-65] describe the extensive work carried out by Pall to investigate and produce relevant filter drug binding data as part of an ongoing response to concerns raised by healthcare practitioners. For full details regarding Materials and Methods or access to these technical references, please contact your local Pall representative.

4.1 Compatibility of Various Pharmaceutical Agents with Pall Supor™ Intravenous Filter Devices[61]

Summary

Binding compatibility of more than 50 drugs was assayed via HPLC, direct UV/VIS spectrophotometry, or indirect methodologies before and after passage through filter devices containing polyethersulphone Supor membrane.

Results

Adsorptive losses were negligible for all drugs studied, with the exception of insulin, which displayed moderate initial adsorptive characteristics to Supor membrane in the first aliquot (4 mL) but 100% was recovered after 5 aliquots (20 mL).

4.2 Binding of Monoclonal Antibodies to Pall Supor AEF Intravenous Filters[62]

Summary

Binding compatibility of Pall Supor AEF1 intravenous filters containing a 0.2 µm Supor membrane with a monoclonal antibody was assessed and compared against a protein binding filter reference. Simulation of two typical administration scenarios (high and low dosing regimes) was performed by infusion of radiolabelled immunoglobulin G (IgG) in saline.

Results

Binding of Supor membrane to IgG was negligible (< 0.3%) for both dosing regimes whereas high drug retention (> 30%) was observed in the protein binding filter reference at low dose regime.

4.3 Effects of Using Pall ELD Filters for Administering Short Drug Infusions[63]

Summary

Binding compatibility of short drug infusions of 23 drugs with Pall ELD96 intravenous filters containing a 0.2 µm nylon Posidyne membrane was investigated by UV spectrophotometry before and after passage through the filter.

Results

Adsorptive losses due to the filter were negligible for all drugs. A minor delay in delivery time of 15-20 seconds was observed when using a filter compared to no filter.

4.4 Filterability of Drugs Through Pall ELD Filters[64]

Summary

Binding compatibility of 17 pharmaceutical drugs with Pall ELD96 intravenous filters containing a 0.2 µm nylon Posidyne membrane was analyzed either by UV spectrophotometry, High Performance Liquid Chromatography (HPLC) or by Enzyme Immunoassay (EIA)

Results

No significant binding losses were found for 14 of the 17 drugs tested. Isosorbide dinitrate, Actinomycin D, and Ramosetron showed binding losses between 9 and 30.6%.

4.5 Filterability of Paclitaxel, Methotrexate and Phenytoin Through Pall ELD Filters[65]

Summary

Binding compatibility of 3 commonly used pharmaceutical drugs with Pall ELD96 intravenous filters containing a 0.2 µm nylon Posidyne membrane was examined using UV spectrophotometry before and after the filter.

Results

Negligible binding of all three drugs to the ELD96 filters was detected.

Table 2 provides details of currently available drug recovery data for Pall filtration devices.

Table 2

Pall filtration devices and available drug recovery data

Drug Name	Filter Family	Reference
Acetazolamide sodium	AEF1, HP	61
Actinomycin D	ELD96, NEO96	64
Acyclovir sodium	ELD96, NEO96	63
Albumin	AEF1, HP	61
Aminophylline	AEF1, HP	61
Ampicillin sodium	AEF1, HP, ELD96, NEO96	61,63
Azasetron hydrochloride	ELD96, NEO96	64
Azlocillin sodium	ELD96, NEO96	63
Benzylpenicillin sodium	ELD96, NEO96	63
Bevacizumab	ELD96, NEO96	64
Bupivacaine HCl	AEF1, HP	61
Calcium folinate	ELD96, NEO96	64
Cefazolin sodium	AEF1, HP	61
Cefoxitin sodium	AEF1, HP	61
Ceftazidime	AEF1, HP, ELD96, NEO96	61,63
Ceftriaxon disodium	ELD96, NEO96	63
Ceftriaxone sodium	AEF1, HP	61
Cimetidine HCl	AEF1, HP	61
Ciprofloxacin	ELD96, NEO96	63
Cisplatin	AEF1, HP	61
Clindamycin dihydrogen phosphate	ELD96, NEO96	63
Cyclosporin	ELD96, NEO96	63
Cytarabine	ELD96, NEO96	64
Daunorubicin	ELD96, NEO96	24
Dexamethasome	AEF1, HP	61
Digitoxin	AEF1, HP	61
Digoxin	AEF1, HP	61
Dobutamine HCl	AEF1, HP	61
Dopamine HCl	AEF1, HP	61
Doxorubicin HCl	AEF1, HP, ELD96, NEO96	24,61
Enocitabine	ELD96, NEO96	64
Ephedrine hemisulfate	AEF1, HP	61
Epinephrine HCl	AEF1, HP	61
Erythromycin	ELD96, NEO96	63
Etoposide	AEF1, HP	61
Filgrastim	AEF1, HP	61
Flucloxacillin sodium	ELD96, NEO96	63
Fluconazole	ELD96, NEO96	63
Fluorouracil	AEF1, HP	61

Drug Name	Filter Family	Reference
Foscarnet sodium	AEF1, HP	61
Furosemide	AEF1, HP	61
Ganciclovir sodium	AEF1, HP	61
Gentamicin sulfate	AEF1, HP, ELD96, NEO96	61,63
Granisetron chloride	ELD96, NEO96	64
Heparin sodium	AEF1, HP	61
Human serum albumin	ELD96, NEO96	64
Immunoglobulin G	AEF1, HP	62
Insulin (Human and Porcine)	AEF1, HP	61
Isosorbide dinitrate	ELD96, NEO96	64
Lidocaine HCl	AEF1, HP	61
Mannitol	AEF1, HP	61
Meropenem	ELD96, NEO96	63
Methotrexate	AEF1, HP, ELD96, NEO96	24,61,65
Methyl prednisolone	AEF1, HP	61
Methyldopate HCl	AEF1, HP	61
Metronidazole	AEF1, HP, ELD96, NEO96	61,63
Mezlocillin sodium	ELD96, NEO96	63
Mithromycin	AEF1, HP	61
Mitozantrone	ELD96, NEO96	24
Morphine sulfate	AEF1, HP	61
Nafcillin sodium	AEF1, HP	61
Nedaplatin	ELD96, NEO96	64
Nitroglycerin	AEF1, HP	61
Nogitecan/Topotecan	ELD96, NEO96	64
Paclitaxel	AEF1, HP, ELD96, NEO96	61,65
Penicillin G potassium	AEF1, HP	61
Phenytoin	AEF1, HP, ELD96, NEO96	61,65
Piperacillin sodium	AEF1, HP, ELD96, NEO96	61,63
Procaine HCl	AEF1, HP	61
Propacetamol HCl	ELD96, NEO96	63
Propofol	TNA1	27
Prostaglandin	ELD96, NEO96	64
Ramosetron	ELD96, NEO96	64
Rituximab	ELD96, NEO96	64
Sodium bicarbonate	AEF, HP	61
Sodium citrate	AEF1, HP	61
Sodium nitroprusside	AEF1, HP	61
Streptokinase	AEF1, HP	61
Sulbactam sodium	ELD96, NEO96	63
Sulfamethoxazole	AEF1, HP	61
Tazobactum + Piperacillin	ELD96, NEO96	63
Teicoplanin	ELD96, NEO96	63
Tobramycin sulphate	AEF1, HP, ELD96, NEO96	61,63
Trastuzumab	ELD96, NEO96	64

Drug Name	Filter Family	Reference
Trimethoprim + Sulphamethoxazole	ELD96, NEO96	63
Trimethroprim	AEF1, HP	61
Vancomycin HCl	AEF1, HP, ELD96, NEO96	61,64
Vidarabine	AEF1, HP	61
Vinblastine sulfate	AEF1, HP	61
Vincristine sulfate	AEF1, HP, ELD96, NEO96	61,64

5. Conclusion

Drugs may potentially bind to any surface material within the infusion line, this is mainly governed by adsorption-desorption processes and may result in effective drug loss and subsequent therapeutic problems. Although such complications are generally under control at relatively high-dose infusion regimes, drug binding is particularly relevant at low concentrations and flow rates and it may become a real infusion management challenge during the administration of certain types of drugs (i.e. protein-based, with narrow therapeutic range, with short half-lives).

While IV filters play an increasingly important role in clinical practice, their use adds to the potential adsorptive surface area of the administration set and consequently may significantly increase drug binding losses. The selection of the appropriate filter material is therefore essential for drug infusion management and, despite limitations to perform adsorption studies for every drug and infusion regime, this is the subject of a continual area of research within Pall with the aim to answer current or future drug binding concerns raised by healthcare practitioners.

This Clinical Update compiles the extensive work carried out by Pall Corporation in a list of drugs with the currently available binding data to the corresponding Pall filter families.

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