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EVALUATION OF PACKAGING MATERIAL INTERACTION IN PHARMACEUTICAL PREPRATION

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ABSTRACT

Plastic materials are widely used in medical items, such as solution containers, transfusion sets, transfer tubing and devices. While an important performance characteristic of plastics used in medical application is chemical inertness, interactions between a plastic material and a contacted pharmaceutical Products are well documented. In the case of leaching, both the identity of the leached substances and their accumulation levels may impact the ultimate utility of the product. In this article Summarizes the packaging material interaction with; product material affects the product quality. A review is provided related to the accumulation of organic and inorganic leachable substances from DEHP plasticized PVC, polyolefin and various other related pharmaceutical plastic packaging materials.

KEYWORD: Plastic Material, Extractable, leachable, PVC, DEHP.

INTRODUCTION

In the context of pharmaceutical and medical products, a container/closure system is the sum of packaging components that together contain and protect the dosage form. The ideal container/closure system would be inert in the sense that it would have no ability to interact with the dosage form it contacts. Available container/closure systems typically fall short of this ideal and have an ability to interact with the dosage form so as to modify its composition. In general the compositional change can be reductive, in which case the amount of a component of the dosage form is reduced as a result of contact, or additive, in which case the dosage form is supplemented to contain a new component whose genesis can ultimately be linked to the container/closure system.[2]

Plastic materials are widely used in medical items, such as solution containers, transfusion sets, transfer tubing, and devices. The physiochemical nature of these materials provides medical products with their necessary, desirable performance characteristics. While an important performance characteristics of plastics used in medical application is chemical inertness, interactions between a plastic material and the pharmaceutical product it contacts are well documented. Such interactions may include sorption, the uptake of product components by the plastic material, or leaching, and the release of plastic material components to the product. In the case of leaching, both the identity of the leached substances and their accumulation levels may impact the material's ultimate compatibility with the product. The assessment of the impact of the accumulation of leached substances in pharmaceutical products contacted by a plastic material during their manufacture, storage, or use is a multi-faceted undertaking involving several disciplines within the applied physical, chemical and biological sciences. While numerous strategies can be envisioned and have been utilized to perform such an assessment, they all share two fundamental components, the identification of the leached substances and the measurement of the actual or probable accumulation levels of the identified substances. These substances may be extractable, which are inherently present in the material, or may be secondarily derived from the material as a result of its processing, utilization and/or sterilization.[1]

Polyvinyl chloride (PVC) is one of the most widely used plastics in medical applications. While "pure" PVC is a hard and brittle material, when plasticized with esters of phallic, citric, maleic, sebacic, adipic, and other acids, it becomes soft and flexible. Medical grade flexible PVC. Most often contains di (2-ethylhexyl) phthalate (DEHP) as the primary plasticizer as well as secondary additives. Many investigations have been published regarding the migration of these additives and other material-related compounds from PVC-containing products into intravenous solutions. An important utilization of plasticized PVC is as storage bags for primary IV diluents and parenteral solutions. Diethylhexylphthalate (DEHP) is one of the main phthalates used as plasticizer in production of PVC and other polymers including rubber, cellulose and styrene. Because of this, DEHP is distributed ubiquitously in the environment and also in laboratory materials such as tubes, caps and gas chromatography septa.The US Environmental Protection Agency (EPA) has classified DEHP as a B2 substance, which is a possible human carcinogen substance. The most probable route of human exposure toDEHP is through food, with an average intake of 0.25 mg/d, being migration from plastics during processing and storage the main source exposure DEHP can also occur due to the use of certain medical devices for blood transfusions, kidney dialysis and the use of respirators. On the other, DEHP is present at high concentrations in PVC products used as basic materials in doll manufacturing; therefore children are exposed to DEHP due to the high migration ability of DEHP in PVC derivatives. Several studies have shown that DEHP is embryo toxic and teratogenic in rodents; in addition, adverse effects. Most Containers for intravenous solutions are made with plasticized polyvinyl chloride (PVC). The most common form of plasticizer used is di-2-ethylhexylphthalate (DEHP), a phthalate ester of PVC. There have been reports of extract DEHP from plastic intravenous infusion sets or containers into certain infuse. 1 - 3 Patients undergoing hemodialysis are exposed to DEHP via the contact of blood with this type of plastic. 4 Consequently, the possibility of harmful effects from DEHP to the human body has recently been raised. 5 In addition, DEHP has been reported as an environmental contaminant.

Table 1. Plastic Polymer Applications in Injectable Drug Delivery.

Type of plastic device	Typical type of polymer used
Plastic vials	Polycyclopentane, cyclic olefin copolymer
Containers for blood products	Polyvinyl chloride, polyolefin, others
Disposable syringes	Polycarbonate, polyethylene, polypropylene
Irrigating solution container	Polyethylene, polypropylene, polyolefin
Intravenous infusion container	Polyvinyl chloride, polyester, polyolefin
Administration set	Acrylonitrile butadiene
Administration set spike	Nylon
Administration tubing	Polyvinylchloride, other
Needle adapter	Polymethylmethacrylate
Clamp	Polypropylene
Catheter	Teflon, polypropylene

DEHP is nearly insoluble in water or in an aqueous solution of electrolytes or carbohydrates. Stability studies on several different parenteral solutions, completed by the manufacturer under a variety of controlled environmental conditions, indicated that the concentration of DEHP ranged from 0.01-0.02 ppm and, thus, did not exceed 0.1 ppm or 0.1 mg/L. Addition of alcohol or surfactant10 may enhance extraction of DEHP into aqueous solutions. There have been a number of observations on the metabolism and clearance of DEHP. Shaffer et al. noted that phthalates appear in urine after oral administration to human subjects and to several animal species. In mice, after intravenous administration, radiolabeled DEHP was rapidly taken up by the liver and excreted in the urine and feces. Auto radiographic studies showed nearly total elimination from the body within 24 hours after injection. In rats, Rubin and Miller found that the major metabolism of intravenously administered DEHP occurred in the liver. Mon esterase hydrolyzed DEHP to mono-2-ethylhexylphthalate (MEHP), and a nicotinamide-adenine-dinucleotide (NAD)-dependent oxidizing system catalyzed oxidation of the remaining side chain via and oxidation. Both enzymatic activities occur in the microsomal fraction of the liver. Recent reviews provide more extensive data on metabolism of DEHP. Published reports of experiences with human adults as well as results from experiments with healthy, intact animals indicate that acute toxicity with DEHP is uncommon and may very well be negligible. However, the data are not as clear and conclusive in two important areas: the use of DEHP-containing products in infants and in pregnant women. Hillman et al. demonstrated accumulation of DEHP in critically ill infants. DEHP was found in the heart tissue of patients in the study group at concentrations nine times higher than those in controls. Levels of plasticizer in the gastrointestinal tissues of infants who died from necrotizing enter colitis were significantly higher than those in gastrointestinal tissue from infants without the disease. Although no causative correlation was proven, the authors provide some evidence that clearance of DEHP may be altered in prematurity, in the early neonatal period, and ongoing illnees.[4]

DEHP Toxicity- Following case studies are reported in under DEHP toxicology.

1) Mixed Connective Tissue Disease-An Apparently Distinct Rheumatic Disease Syndrome Associated with a Specific Antibody to an Extractable Nuclear Antigen (ENA).[6]
2) Case Studies on Nitrate Leaching 1n Arable Fields of Organic Farms.[7]
3) Effects of Surfaces and Leachables on the Stability of Biopharmaceuticals.[9]

4) A Cytotoxic Leachable Compound from Single-Use Bioprocess Equipment that Causes Poor Cell Growth Performance .[10]
5) Lack of genotoxic activity of di(Ibex Phthalate) (DEHP) in rat and human hepatocytes.[5]
6) Di (2 -ethylhexyl) pthalaten supreeses Estradiol and Ovulation in cycling rats.[8]
7) Evaluation and analysis of exposure levels of di (2-ethylhexyl) phthalate from blood bags.[12]
8) Di(2-ethylhexyl) Phthalate Metabolites May Alter Thyroid Hormone Levels in Men.[11]
9) Evaluation of the Di(2-ethylhexyl)phthalate released from polyvinyl chloride medical devices that contact blood.[12]
10) Subchronic Oral Toxicity of Di-n-Octyl Phthalate and Di(2-Ethylhexyl) Phthalate in the Rat.[14]
11) Developmental Toxicity Evaluation of Dietary Di(2-ethylhexyl)phthalate in Fischer 344 Rats and CD-Mice1.[13]

Table 2. Concentration of DEHP in IV Soluation.

REFERENCE	SOLUTIONS TESTED	CONCENTRATION OF DEHP	
Rubin[6]	sodium chloride 0.9%, dextrose 5.0%, protein hydro-lysates 5.0%	none with concentration > blank for assay system used (~ 0.24 ppm)	
Needham and Luzzi[7]*	sodium chloride 0.9%	0.1 mg/L	
Needham and Corley[8]	sodium chloride 0.9%	0.126-0.588 mg/L	
		NONAGITATED	AGITATED
Corley et al.[8]†	sodium chloride 0.9%	0.172 mg/L	0.635 mg/L
	dextrose 5.0%	0.142 mg/L	2.869 mg/L
	Ringer's solution	0.168 mg/L	0.551 mg/L
	M/6 sodium lactate	0.087 mg/L	0.848 mg/L
	sterile water for irrigation	0.096 mg/L	1.592 mg/L

Table 3: Chart of Vulnerability of a Packaging System to a dosage form.

Degree of concern associated wit route of administration	Likelihood of packaging component-dosage form interaction		
	High	**Medium**	**Low**
High	Inhalations: aerosols, sprays	Injections and injectable suspensions, inhalational solutions Powders	Powders: sterile, injectable inhalation
Highest	Transdermal ointments and patches	Ophthalmic solutions and suspensions, nasal aerosols and sprays	-
Low	Topical: solutions and suspensions, powders, Topical: powders Testing Aerosols oral : solutions and suspension	-	Oral: tablets, capsules,

- **Regulation Of FDA**

Table 4. Guidance of FDA and Chapters of US.

Guidance Published	Year
FDA guidance for industry: container closure systems for packaging human drugs and biologics. Chemistry, manufacturing, and controls documentation	1999
FDA draft guidance for industry. Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) drug Products. chemistry manufacturing and controls documentation	1998
FDA guidance for industry nasal spray and inhalation solution, suspension, and spray drug products chemistry, manufacturing, and controls documentation	2005
FDA reviewer guidance for nebulizers, metered dose inhalers, spacers, and actuators	1998
FDA guidance for industry and FDA staff: technical considerations for pen, jet, and related injectors Intended for use with drugs and biological products	2013
Chapters in USP	Number
Assessment of extractables associated with pharmaceutical packaging/delivery systems	USP 1663
Assessment of drug product leachables associated with Pharmaceutical Packaging/Delivery Systems	USP 1664

- **Regulations and chapters from the FDA on leachable and extractable -**

1. USP 661 (Plastic Packaging Systems and their materials of construction), USP 1663 (Assessment of extractable associated with pharmaceutical packaging/delivery systems), USP 1664 (Assessment of drug product leachable related to pharmaceutical packaging/delivery systems) mentioned earlier.
2. USP 661.1 Plastic Materials of Construction.
3. USP 661.2 Plastic Packaging systems for pharmaceutical use.
4. USP 1664.1 Orally Inhaled and Nasal Drug Products.
5. USP 1665 Toxicological Assessment.
6. USP 661.3 Plastic Systems used for manufacturing pharmaceutical products.
7. USP 661.4 Plastic Medical Devices used to deliver or administer pharmaceuti.

Table 5. Guidelines and standards relevant to extractables and leachables evaluation for drug products and devices.

Regulatory Guidance, Guidelines, and Legislative Directives	Standards
FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics. Chemistry, Manufacturing, and Controls Documentation (1999)	ISO 10993 Biological Evaluation of Medical Devices
FDA Draft Guidance for Industry. Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products. Chemistry Manufacturing and Controls Documentation (1998	ISO 11040 Prefilled syringes
FDA Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing, and Controls Documentation (2005)	ISO 11979 Ophthalmic implants
FDA Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators (1998	ISO 14971 Application of Risk Management to Medical Devices
FDA Guidance for Industry and FDA staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (2013)	ISO 15747 Plastic containers for intravenous injections
EMA Guideline on Plastic Immediate Packaging Materials (2005)	ISO 20072 Aerosol drug delivery device design verification—Requirements and test methods
EMA/Health Canada Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (2006	ISO 27427 Anaesthetic and respiratory equipment — Nebulizing systems and componen
COMMISSION REGULATION (EU) 2015/174 amending and correcting Regulation (EU) No 10/2011on plastic materials and articles intended to come into contact with foodJournal of the European Union. 6 February 2015	USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
Directive 2007/47 / EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 93/42/EEC concerning medical	USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery

CONCLUSION

The evaluation parameter of packaging material interaction between pharmaceutical preparation and their toxic effects can be studied. The following guidelines and standard useful for the safety and efficacy of the pharmaceutical product and useful for the pharmaceutical container and closures system.

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