REVIEW

Particulate Matter in Injectable Drug Products

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ABSTRACT: Clinicians have had concerns about particulate matter contamination of injectable drug products since the development of the earliest intravenous therapeutics. All parenteral products contain particulate matter, and particulate matter contamination still has the potential to cause harm to patients. With tens of millions of doses of injectable drug products administered in the United States each year, it is critical to understand the types and sources of particulate matter that contaminate injectable drug products, the possible effects of injected particulate matter on patients, and the current state of regulations and standards related to particulate matter in injectable drug products. Today, the goal of manufacturers, regulators, and standards-setting organizations should be to continue to minimize the risk of particle-induced sequelae, especially in high-risk patients, without trading unnecessary manufacturing burden for minimal safety gains.

KEYWORDS: Injectable, Parenteral, Particulate matter, Pharmaceutical quality, Current good manufacturing practice (cGMP).

LAY ABSTRACT: All injectable drug products are contaminated with some level of solid particulate matter, including, for example, fibers, dust, rubber, and silicone. These materials enter drug products primarily during the manufacturing process. The possible effects on patients of injectable drug products containing particulate matter depend on a number of factors. However, given the large number of patients receiving injectable drug products each year in the United States and the potential for particulate matter to cause harm to patients, it is critical to continue to minimize particulate matter contamination in injectable drug products. Manufacturing standards and regulations have helped improve manufacturing quality. Nevertheless, manufacturers, regulators, and standards-setting organizations must continue to work toward improving manufacturing quality and minimizing the risk of harm from particle contamination, especially in high-risk patients.

Introduction

One of the basic tenets of pharmaceutical quality is the manufacture of drug products that are free of microbial, chemical, and physical contaminants. Although microbial contamination of injectable drug products is fairly well understood, defined, and measureable, it remains difficult to achieve injectable drug products that are free of chemical and particulate matter contamination. This is due, in part, to the nature of contaminants, the current state of pharmaceutical manufacturing, and the availability of extremely sensitive measuring techniques.

Concerns about the clinical use of injectable drugs containing particulate matter can be traced to the earliest intravenous fluid therapies employed in the 1830s. An Edinburgh physician named John Mackintosh, while developing methods of intravenous saline infusions to treat victims of a cholera outbreak, recommended that the solutions be strained twice through leather rather than cotton or linen, which could allow "minute portions of flakey threads" to be injected into the patient (1). Although processing and filtration technologies for intravenous injections have evolved exponentially in the years since, concerns about the potential effects of injected particulate matter on pa-

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tients continue, especially given the equally exponential growth in the number of patients who could be affected.

According to the American Hospital Association, U.S. hospitals admitted 37,479,709 patients in 2009 (2). Assuming an average intravenous solution administration of 5 L per patient (3), nearly 190 million L of intravenous fluid are administered annually. Given these data, an accurate assessment is warranted of the factors causing particulate matter contamination of drug products, the patient risks associated with the administration of such contaminated drug products, and the current state of regulations and standards that provide the framework for achieving pharmaceutical quality.

This article describes some of the sources of particulate matter contamination in injectable drugs and the possible clinical effects that can result from such contamination. The article also reviews the development of standards and regulations to control contamination of injectable products and offers some preliminary next steps for manufacturers, regulators, and standards-setting organizations who are working together to ensure patient safety.

Classification and Sources of Particulate Matter

Chapter <788> of the United States Pharmacopeia (USP), Particulate Matter in Injections (4), defines *particulate matter* as "mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions". Groves (5) divided injectable drug particulate matter into two classes based on the source of the particulate matter: *intrinsic particles*, defined as those originally associated with the solution that were either not removed by filtration or precipitated out of the solution, and *extrinsic particles*, defined as those that enter the container or solution during manufacturing. USP Chapter <1788> Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions (6) provides similar, but more specific, definitions, classifying *extrinsic* particulate matter as "additive, foreign, unchanging, and not part of the formulation, package or assembly process". It classifies *intrinsic* particulate matter as "associated with the package, formulation and/or assembly process and capable of change upon aging". USP Chapter <1788> also notes that intrinsic particulate matter is not the same as *inherent* product characteristics such as the haze, coloration, or known populations of small particles common to certain high-concentration protein formulations. This inherent particle category also includes the normal particle size distribution of active pharmaceutical ingredients in suspensions and other common delivery forms (e.g., emulsions, lipids, etc.). Inherent particles or properties, when consistent and expected, may be completely acceptable.

There are five general sources of particulate matter in injectable drug products: the environment, packaging materials, solution and formulation components, product packaging interactions, and process-generated particles. Proper product development and appropriate manufacturing and packaging process design can successfully exclude particulate matter sourced from four of the five categories. The fifth category, particulate matter sourced from the environment, can be excluded only by use of highly controlled filling areas, rather than by an intimate understanding of the product, process, and container closure system. A list of potential particle contaminants, their sources, and intrinsic/extrinsic natures as defined by USP Chapter <1788> is presented in Table I.

Note that certain types of particulate matter, including metal and glass, may be either intrinsic or extrinsic depending on the point at which they enter the container. For example, glass particles can enter the manufacturing process from the outside (extrinsic, e.g., through the use of broken or poorly washed incoming vials) or come from inside the container through degradative change during product storage or from process-related glass breakage events (intrinsic, e.g., lamellae, tunnel/oven, or during filling). Likewise, metal particles can come from the containers, the manufacturing environment (extrinsic, e.g., building materials), or the manufacturing process (intrinsic, e.g., blending equipment). Even particle levels that meet compendial or company target limits can be of concern. For example, so-called *point-source contamination,* which is the predomination of one particle type (7), may indicate the presence of process contribution or package instability that requires investigation and remediation. An overall understanding of the product and processes and the establishment of methods that can control particulate matter contamination during development, manufacture, and packaging are essential to be able to design systems capable of preventing particulate matter contamination problems before they start (8, 9).

TABLE I
Types and Sources of Injectable Particulate Matter

Source	Particulate Material	Intrinsic/Extrinsic
Environment (including personnel)	Dust Fibers Biologics—insect parts, microorganisms, pollens Fibers of anthropogenic origin Hair Skin Paint/coating chips Rust Metal (non-product contact types) Minerals Polymers (unknown source) Glass (e.g., carry over from components) Extraneous Material (e.g., carry over from rubber stopper components)	Extrinsic
Packaging material	Rubber Glass Polymers Silicone	Intrinsic
Solution and formulation components	Precipitates Oligomers Degradants Agglomerates Undissolved material	Intrinsic
Product–package interactions	Glass lamellae Silica Rubber Plastic	Intrinsic
Process-generated particulate matter	Metal (e.g., stainless steel from processing equipment) Filter and Consumables fibers Glass (from breakage events)	Intrinsic

Clinical Effects of Injected Particulate Matter

Many clinical effects have been documented in subjects who have received injections containing particulate matter contamination. Examples include phlebitis (3, 10–13), pulmonary emboli (14–16), pulmonary granulomas (3, 11, 17), immune system dysfunction (3, 18), pulmonary dysfunction (13, 15), infarction (15, 19), and death (14, 20–22). The patient risk associated with the injection of drugs containing particulate matter depends on a number of factors, including the route of administration used, the particle size and shape, the number of particles injected, the particle composition, and the patient population.

Route of Administration

The route of pharmaceutical product administration can influence the deposition of the injected particles, the total particle load administered to the patient, and the overall risk to the patient. Immunologically inert particles, such as glass or cellulosic fibers, delivered via intramuscular and subcutaneous routes have received little attention with regard to their potential for causing adverse events due to the fact that the delivered volumes (and the overall particle load) are relatively small, the risk of a systemic reaction is low, and the ability of these particles to migrate far from the injection site is negligible (23). However, vascular

injections make possible the delivery of greater volumes of fluids and the broader dissemination and deposition of particulate matter throughout the body.

Because the size of veins increases in the direction of blood flow, most particles injected intravenously will travel through the venous system to the heart on their way to the lungs via the pulmonary artery. The diameter of capillaries is approximately 6–8 um. As a result, most particles larger than 6–8 um will remain in the pulmonary capillaries, with smaller particles passing through the lungs and depositing in organs such as the liver and spleen, where they are processed by phagocytic cells of the reticuloendothelial system (16). Phagocytic overload of the reticuloendothelial system by large numbers of particles has the potential to block the system and lead to secondary infections in a debilitated host (3). There is little information in the literature regarding the ability of the immune system to clear relatively large (>10 um) inorganic particles (e.g., rubber, glass, and metal) lodged in organs such as the lung or what effect, if any, the accumulation of such particles in vital organs may have over time.

Because arteries decrease in size with the direction of blood flow, the inadvertent administration of intra-arterially injected particles that are too large to pass through arterioles and capillaries may cause occlusions that could affect blood flow to tissues downstream of the injection site. The physiological effects of any such occlusion will depend upon the size of the particle and the collateral circulation available to the affected area (23). Ironically, smaller particles capable of blocking terminal arterial vessels—and causing infarctions—may be more detrimental than larger particles capable of arteriole occlusion due to the reduced collateral blood supply available to the affected tissue (24). The inadvertent intravascular injection of corticosteroid formulations containing particles has been linked to adverse central nervous system sequelae in humans not observed with non-particulate steroid formulations (24). A study involving pigs injected in the vertebral artery with particulate- or non-particulate-based steroids yielded similar results, with pigs receiving the particulate-containing steroids displaying brain stem edema and significant tissue damage (25).

Other routes of administration, such as the intrathecal, epidural, intraocular, and intracranial routes, may carry different risks due to the direct delivery of the particulate matter to specific areas of the body. The risks of particulate matter delivered via these routes of administration should be considered during product development when assessing the critical quality attributes for a given product (26).

Size and Shape

The size and shape of an injected particle can affect both its deposition within the body and its clinical effects on the subject. Rabbits injected with radiolabeled polystyrene particles of different sizes showed rapid deposition of 15.8 um particles in the lungs while 1.27 um particles were deposited mainly in the liver (16). Similar results were obtained when dogs were injected intravenously with radiolabeled microspheres of 3, 5, 7, and 12 um in diameter. The 7 and 12 um particles were deposited primarily in the lungs, while the 3 and 5 um particles migrated mainly to the spleen and liver. As expected, clearance from the bloodstream was size-dependent, with the larger particles clearing first (27). Rabbits injected with 5 um diethylaminoethyl (DEAE) cellulose fibers demonstrated deposition primarily in the lungs, but also in the liver and kidneys (16). Rabbits injected intravenously with 30 um DEAE cellulose fibers died within 4 minutes of administration due to an acute toxic response (tachycardia, dyspnoea, dystaxia) caused by pulmonary emboli (16). In contrast, 40 to 60 um DEAE cellulose microspheres, although entrapped by the lung, caused no adverse reactions and each of the rabbits injected survived until the completion of the study (16). These studies suggest that the shape of a particle may be just as important as its size when determining its potential for harm. Certainly the total particle load must be considered as well.

Due to the obvious challenges associated with controlled clinical studies to investigate the effects of injected particles in humans, little is known about the risk to diverse patient populations posed by particles of various sizes, shapes, and composition injected via different routes of administration. Adverse event reports and autopsy results are the only sources of information about the effects of larger particles on patient populations. Visible particulate matter composed of calcium salt precipitates in drug admixtures has caused a number of serious clinical events (21). In 1994, two young female patients undergoing treatment for pelvic infections died of pulmonary emboli following intravenous administration of total nutrient admixtures containing FreAmine III as an amino acid source (14, 20). Analysis of the precipitate isolated from the admixtures administered to each patient revealed the

presence of calcium and phosphorous salts matching those found in the pulmonary microvasculature of the autopsy specimens. Co-administration of the antibiotic ceftriaxone and calcium-containing intravenous solutions to neonates resulted in eight adverse event reports and seven deaths. One patient experienced cardiopulmonary arrest after a white precipitate in the patient's intravenous tubing was pushed into the infant in an effort to clear the tubing (28). Pulmonary emboli were reported in multiple cases, and autopsies revealed the presence of white crystalline precipitates in the lungs, heart, kidney, and liver (21, 28). Both the ceftriaxone and FreAmine III incidents resulted in the issuance of U.S. Food and Drug Administration (FDA) drug safety warnings regarding the potential for calcium precipitation in these drug products (28, 29). Cant et al. (22) reported the case of a premature neonate who was treated with an umbilical artery catheter shortly after birth. Injections were made into the catheter using polypropylene syringes. The catheter was removed on day 4, but the patient soon developed abdominal distension and died at 52 days of age. An autopsy revealed acute infarction of the small bowel and the presence of polypropylene fragments of 50 to 200 um in size. Although this may be the only documented case of a fatality resulting from injection of material derived from a pharmaceutical container closure system, the case underscores the vulnerability of neonates to sequelae resulting from the infusion of particles and suggests that the intra-arterial route of administration may carry additional risks.

Number

Estimates are that patients in intensive care receive more than a million injected particles >2 microns in size daily (18, 30, 31). One method for controlling the particle load administered to critically ill patients has been through the use of final filters. A controlled clinical study of 88 infants receiving either filtered or unfiltered infusions via a central line revealed significant reductions in the incidence of complications such as thrombi and necrotizing enterocolitis (32). Studies on adult patients using 0.22 and 0.45 um intravenous in-line filters seem to indicate that the use of in-line filters reduced the incidence and time of onset of particle-induced phlebitis (3). In vitro studies also showed that human macrophages and epithelial cells displayed decreased cytokine production following exposure to silicone particles mimicking those obtained from intravenous line filters obtained from pediatric intensive care units (18). However, the use of final filters may present other problems, such as the possibility of drug product reaction with or absorption by the filter material or impaired fluid flow through the filter. Opinions vary regarding the economic benefit of in-line filtration to remove microorganisms and particulate matter during drug product infusion (32–36). Nevertheless, a review of clinical case reports involving calcium phosphate precipitation in intravenous admixtures revealed that the use of in-line filtration made the difference between non-fatal and fatal cases (37). Thus, the use of in-line filtration for extemporaneously prepared, multi-component intravenous admixtures may be prudent.

Composition

Barber (23) provides an excellent review of several pre-1980 animal studies involving different types of particulate matter (filter paper, glass, rubber, hair, polystyrene, plastic, and insoluble drug residues) in various animal models (rabbits, dogs, rats, mice, guinea pigs, and hedgehogs). The clinical effects seen in these studies range from relatively minor tissue damage associated with the administration of silicone and polystyrene particles to rabbits and dogs, to more serious reactions such as local inflammation, the formation of pulmonary granulomas, and death in rabbits, dogs, and rats injected with plastics, ground filter paper, or large numbers of polystyrene particles >40 um in size.

One of the most common contaminants of injectable drug products is glass derived from the manufacturing process, reaction of the drug with the container closure system, or that produced by opening glass ampoules (36, 38, 39, 40). Recent glass delamination issues involving multiple drug products have increased concern about the risk posed by glass particles and interest in developing methods to control the formation of glass lamellae over the product shelf life (40, 41). Sequelae attributed directly to glass particles include phlebitis (3), pulmonary granulomas (31), systemic inflammatory response syndrome (18), and adult respiratory distress syndrome (34). Studies have also suggested that glass particle–induced sequelae may require considerable time to develop and, as a consequence, may often be overlooked (38, 39, 42).

Another common pharmaceutical contaminant is metal particles (43, 44). Although the most common source of metal particles is processing equipment, they have also been found to contaminate the raw materials used

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