*REVIEW ARTICLE*

# Particulate Matter in Parenteral Products: A Review

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*ABSTRACT: Particulate matter in parenteral products is a complex subject. This article contains a discussion of several aspects of this topic including the use and limitations of the inspection and counting techniques for visible and subvisible particles, the identification of particles, and the elucidation of sources, mechanisms of formation, and particulate reduction techniques. Two significantly different approaches, human and machine inspection, have been used to detect visible particulate matter in parenteral products. A description of both methods is given along with a discussion of their typical performance characteristics. Criteria for comparison of different visual inspection systems are also presented. A variety of methods have been utilized for the measurement of subvisible particulate matter, including microscopic, electrical zone-sensing, light blockage, light scattering, and holographic techniques. Each of these particle counting methods is described. In addition, the factors that affect the measurement of subvisible particulate matter are discussed. An approach to particle identification is outlined. General comments concerning the analysis of particulate matter in parenteral products are discussed along with a description of various particle identification techniques and several examples illustrating how the methods have been applied. In particular, the techniques that are presented include light microscopy, atomic spectroscopic methods (SEM/EDXRA, electron microprobe, ESCA, and Auger electron spectroscopy), molecular spectroscopic techniques (infrared spectroscopy, Raman spectroscopy, and mass spectrometry), and chromatography. Finally, sources of particulate matter including packaging materials, manufacturing variables, formulation components, and miscellaneous factors are reviewed. The different mechanisms of particle formation, namely, direct contamination, precipitation and agglomeration are discussed. Representative examples of particulate reduction steps are presented.*

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## Introduction

Control of the key features of a product and the processes by which it is manufactured is essential to the assurance of quality for that product. With parenteral formulations there are several important variables including potency, pH, sterility, pyrogenicity, and particulate matter. Of these, control of the particulate quality can represent a significant challenge.

There are at least three reasons for focusing attention on particulate quality of parenteral products. These are

safety concerns, legal requirements, and process evaluation.

Concerns for patient safety were first addressed in the works of Garvan and Gunner (1, 2). Since their initial reports, numerous papers have been published on this topic and a few review articles have been written concerning the clinical significance of particulate matter (3–5, 234).

Although there is some controversy about this subject, it has been concluded that injectables should not contain an excessive number of particles. The primary evidence for this can be found in the literature on drug abuse (6–12). Injections of crushed tablets, capsules, and other solid dosage products have often resulted in serious consequences. For example, one drug user died after i.v. injection of Darvon capsules (8). In another report, Douglas and coworkers found that three of seven addicts who injected drugs had rontgenographic, pathologic, and functional manifestations of pulmonary foreign body emboli and granulomas; the remaining had abnormal pulmonary function (9).

The results of numerous animal experiments have also been reported (13–28). In many of these studies massive doses of particulate matter were injected into several species including dogs, rabbits, rats, mice, and hamsters. The particles consisted of glass beads, cotton fibers, polystyrene latex spheres, paper fragments, and other insoluble substances. In addition to differences in the type and shape of the particulate matter, the particle sizes ranged from a few microns to several hundred microns. Although these studies provide less direct evidence than drug abuse studies, they do indicate that excessive levels of particulate matter in i.v. solutions can be harmful.

However, the clinical ramifications are much less clear when we are concerned about the use of parenterals containing levels of particles that are typical of current products. As Turco and Davis suggested in a previous review article (3), lack of definition of these effects and, therefore, the significance of particulate matter is caused primarily by the absence of controlled studies on humans. Some studies have been reported (29–38), but their conclusions are qualitative and nonspecific. In particular, control human tissue samples are difficult to obtain because of disease, environmental pollutants, and social habits. Finally, controls are difficult since tissue samples are taken from people who may have received an undetermined number of parenteral solutions (3).

The regulations pertaining to particulate matter in parenterals vary considerably among the different compendia (39–42). For example, the specifications for the British Pharmacopeia, United States Pharmacopeia, and The Pharmacopeia of Japan are shown in Tables I–III.

It is noteworthy that the compendial requirements depend upon the size of the particulate matter and upon whether the injectable is a Large-Volume Parenteral (LVP) or a Small-Volume Parenteral (SVP). In the case of visible particles, there are regulations for both LVP and SVP products. The exact wording varies among the different compendia, but the specifications are very similar. Injectables are supposed to be clear and essentially free of particles that can be seen by the unaided eye. However, the situation is different for subvisible particulate matter. Currently, most compendia have specifications for LVP solutions, but few have requirements for SVP products. Even if one restricts a comparison of the various regulations to LVP solutions, there are significant differences in the size of particles that are measured and the methods by which they are detected. It is not possible to determine which compendial specification is more stringent without making several assumptions concerning the size distribution of particles and their shape (4).

Several rationales have been presented to justify the guidelines concerning particulate matter. Some have ar-

TABLE I. USP XXI

| Particle Size | Parenteral | Requirement |
|---|---|---|
| Visible | LVP<br>SVP | Good pharmaceutical practice requires that each final container of Injection be subjected individually to a physical inspection, whenever the nature of the container permits, and that every container whose contents show evidence of contamination with visible foreign material be rejected. |
| Subvisible | LVP | Microscopic:<br>Not more than 50 particles per ml that are equal to or larger than 10 μm and not more than 5 particles per ml that are equal to or larger than 25 μm in effective linear dimension. |
| Subvisible | SVP | Light-obscuration:<br>Not more than 10,000 particles per container that are equal to or greater than 10 μm in effective spherical diameter and/or 1000 particles per container equal to or greater than 25 μm in effective spherical diameter. |

TABLE II. British Pharmacopeia 1980

| Particle Size | Parenteral | Requirement |
|---|---|---|
| Visible | LVP<br>SVP | Injectable Preparations which are solutions, when examined under suitable conditions of visibility, are clear and practically free of particles. |
| Subvisible | LVP | Electrical zone-sensing:<br>Does not exceed 1000 per ml greater than 2.0 μm and does not exceed 100 per ml greater than 5.0 μm.<br>or<br>Light blockage:<br>Does not exceed 500 per ml greater than 2.0 μm and does not exceed 80 per ml greater than 5.0 μm. |

TABLE III. Japanese Pharmacopeia, Tenth Edition

| Particle Size | Parenteral | Requirement |
|---|---|---|
| Visible | LVP<br>SVP | When the outer surface of the container is cleaned, injectable solutions or solvents for drugs to be dissolved before use[a] must be clear and free from foreign insoluble matter that is readily noticeable when inspected with unaided eyes at a position of luminous intensity of about 1000 luxes [93 footcandles], right under an incandescent electric bulb. As for injections contained in plastic containers, the inspection is performed with unaided eyes at a position of luminous intensity of 8000 to 10000 luxes [740 to 930 footcandles] with incandescent electric bulb placed at appropriate distances above and below the container. |
| Subvisible | LVP | Microscopic:<br>The limits are not more than 50 particles per ml that are equal to or larger than 10 $\mu$m and not more than 5 particles per ml that are equal to or larger than 25 $\mu$m. |

[a] There is an analogous requirement for preparations that are to be dissolved before use.

gued that the particle standards are consistent with the capabilities of existing technology and, hence, are a measure of good manufacturing practice (4, 40, 43–45). Others have stated that they can be justified on the basis of cumulative particulate insult the patient receives (40, 46). For example, the differences in LVP and SVP regulations have been rationalized on both accounts (46, 47).

Numerous articles have been published concerning the level and sizes of particulate matter in LVP and SVP injectables (43, 48–78). These studies have utilized a variety of methods for measuring particle counts including microscopic, light blockage, light scattering, and electrical zone-sensing techniques. Furthermore, a wide variety of products, packaging types and dosage forms have been examined.

There has also been a considerable interest in particulate matter for the purpose of process evaluation. Others have suggested that a significant increase in the level of particles for a parenteral could be used as an indication that the product or the process by which it is manufactured may not be well-controlled (4, 43, 46, 49, 65, 79).

The levels of both visible and subvisible particles have been considered as useful measures for process control requirements. For example, Brownley reported on the use of process control charts for rejection rates in visual inspection (79). In addition to data for the total number of rejects, he discussed the use of charts for specific types of visible particulate matter such as lint and glass. Brownley argued that every parenteral manufacturer could benefit from this type of information in assessing the process capabilities of an operation to produce a high quality product.

As an index of quality, others have suggested that the data on the level of subvisible particles could be even more helpful than the results of visual inspection (4, 43, 46, 49). Particle size distributions have been reported for numerous parenterals (49–52, 54, 59, 63, 64, 67, 73). In the case of subvisible particles, it has been observed that there is a log–log relationship between the size and the number of particles (4, 43, 46, 49) and most workers have decided to summarize their data using the following equation

$$\ln N = \ln N_{1.0} - M \ln D$$

where $N$ is the cumulative number of particles at the threshold corresponding to diameter $D$, $N_{1.0}$ is the value of $N$ for $D = 1.0$ $\mu$m and $M$ is the slope of the log–log plot. Based on the results of these size distributions, a variety of limits have been suggested for both LVP and SVP solutions (4, 43, 46, 49, 65).

The detection and quantitation, identification and ultimate reduction of particulate matter in parenteral products represent a complex subject. This paper addresses particulate matter in parenteral products in three sections: (*1*) inspection and counting techniques—visible and subvisible particles; (*2*) identification of particulate matter; and (*3*) sources of particles, mechanisms of their formation, and particulate reduction steps.

## 1. Inspection and Counting Techniques—Visible and Subvisible Particles

Inspection for visible particulate matter and the enumeration of subvisible particles provide a quantitative assessment of product quality. This section is separated into two parts: (*A*) Visible Particles and (*B*) Subvisible Particulate Matter. Each part will contain a description of the various techniques that are utilized as well as a discussion of their performance capabilities and limitations.

**(*A*) Visible Particles:** As shown in Table I, the USP stipulates 100% inspection of injectables for visible foreign material. Not all compendia require 100% inspection of parenterals, but most state that the injectables are supposed to be practically free of particles which can be seen by the unaided eye. Two significantly different methods have been used to detect the presence of visible particles. One utilizes people and the other uses machine detection. For each method a general description will be followed by a discussion of the typical performance characteristics of the various techniques. Next, criteria that can be used to compare different inspection systems will be presented. Finally, in view of the current knowledge of visual inspection methods some general comments will be presented.

*Human Visual Inspection:* A review of the literature indicates that human inspections have been carried out in a variety of ways (80–86). General guidelines for this process were developed by a Parenteral Drug Association (PDA) Task Force (85). In particular, the normal inspection apparatus is comprised of a box containing a lamp

with sufficient light intensity and suitable lighting conditions. The lighting may be fluorescent, incandescent, spot, and/or polarized. Also, a combination of light sources may be employed and the light source(s) may be positioned above, below or behind the units to be inspected. Magnification (2X–3X) is used by some but not all manufacturers. In general, the background consists of both black and white sections, permitting inspection under both conditions. In addition, pacing methodology is often utilized in order to provide an effective rate of inspection while maintaining acceptable quality levels. Finally, those factors which can affect the human component such as training, visual acuity, and operator fatigue are usually controlled.

Besides manual inspection systems, numerous semi-automated machines have been developed which also use people for the detection of particles (80, 82–84, 87–92). These systems have a significantly higher throughput than manual processes because they perform most of the mechanical manipulations normally done by humans. These include such operations as swirling containers, inverting samples, stopping containers, and removing defects. Several people have claimed that these machines reduce eye strain for the operators and provide improved inspection quality by using significantly better imaging capabilities than exist for manual systems (80, 82–84, 87–91).

Whether one uses a completely manual system or one of the semi-automated processes, the decision to accept or reject a container is still made by a person. Therefore, it is important to review what is known about the human visual inspection process. From the broad range of literature on the subject (80–106), the articles published by Knapp and coworkers (80, 93–97) stand out as key references.

The USP specifications for visible particles suggest that human visual inspection is a deterministic process. For a deterministic process, if the same set of containers is examined under the same inspection conditions several times, then the same containers will always be rejected. The rejection probability can be only one of two values, 0 for good and 1 for bad containers. In contrast, for a probabilistic process, each container has a rejection probability associated with it, and the rejection probability can be any value between 0 and 1.

Knapp and Kushner carried out some experiments to determine if human visual inspection is deterministic or probabilistic (80). In their studies a set of 1000 uninspected vials was examined by each of five inspectors ten times each for a total of fifty inspections. Rejection records were maintained for each vial; any rejection score from 0 to 50 was possible. A summary of these results, shown in Table IV, indicates that containers were found in every rejection probability group. Only 2 samples were rejected all the time and approximately 20% of the containers were rejected at least 10% of the time. These experiments confirmed that the inspection process is probabilistic.

In addition, Knapp and coworkers found there is a relationship between rejection probability and the size of the particle (80, 96–97). They observed that the vials with the smallest particulate matter were in the lowest rejection probability groups and the samples with the largest particles were in the highest rejection probability groups. They concluded that the larger the particle (all else constant) the more certain its detection. Therefore, it is no longer adequate to state that particles have been observed in a parenteral, but the probability with which they can be detected is also essential information (80, 93–97).

TABLE IV. Results of Knapp and Kushner Experiments (Data Taken from Ref. 80)

| Rejection Probability | Number of Vials |
|---|---|
| 0.0 | 805 |
| 0.1 | 98 |
| 0.2 | 33 |
| 0.3 | 17 |
| 0.4 | 11 |
| 0.5 | 10 |
| 0.6 | 8 |
| 0.7 | 6 |
| 0.8 | 5 |
| 0.9 | 5 |
| 1.0 | 2 |

The findings summarized above are consistent with the biophysical literature on human vision (96, 107–109). An objective description of visual inspection contains several essential elements, including the capability of the viewer, the size of the target, the total background illumination, and the contrast of the target against its background.

The concept of rejection probability zones, introduced by Knapp and coworkers, is very useful for assessing visual inspection systems (80, 93–97). The range of the rejection probability, $p$, can be conveniently divided into three regions:

$0.0 \leq p < 0.3$ Accept Zone
$0.3 \leq p < 0.7$ Gray Zone
$0.7 \leq p \leq 1.0$ Reject Zone

The region of low rejection probability, to which most containers in a well-controlled process will belong, is termed the "Accept Zone." The region of moderate rejection probability, the "Gray Zone," is most sensitive to any changes in the visual inspection process. This zone is a buffer region between the truly bad containers, which should be rejected, and good containers that should be accepted. The remaining region of high rejection probability is termed the "Reject Zone." This group of samples is especially interesting from a quality assurance standpoint and the inspection process should be very efficient in rejecting these containers.

A more thorough understanding of this subject can be obtained by reviewing the references cited above. However, for the purposes of this article it will be sufficient to discuss several general observations concerning human visual inspection.

First, one of the most important characteristics of any visual inspection system is its detection limit. Several workers have reported that particles larger than 50 μm are usually detected by the naked eye (87, 110–113). Although these claims are not necessarily inaccurate, they

can be very misleading if they are applied without qualification to human visual inspection processes.

In any analytical measurement there are several factors (sample matrix, experimental conditions, signal/noise, etc.) which must be specified in order to determine the detection limit (114). For example, it is usually significantly more difficult to measure low levels of a species in a solution containing many components than it is in a medium with only a few species. The actual experimental conditions are defined because methods of concentrating samples, time-averaging, and other procedures can dramatically affect the detection limit. Finally, the ratio of the measured signal to the response in the absence of the species of interest is specified at the limit of detection.

An analogous situation exists for a human visual inspection process. The set of samples used to determine the detection limit should be well-characterized. In particular, one needs to specify the fraction of that set which is defective, the solution volume, and the nature of the defects, including the number of particles per container, their size, their shape, and their reflectivity. Also, the conditions under which the inspections are carried out should be described. The inspection rate, the amount of magnification, the visual acuity of the inspectors, and the type of illumination and background that are used can have a significant effect on the detection of particulate matter. Finally, the rejection probability at the detection limit should be defined.

The work of Knapp and coworkers provides useful information concerning detection limits for human visual inspection (97). The ampoules that were inspected were thoroughly characterized using a nondestructive technique, transmission holography. The inspection conditions were also well-defined. The Schering standard 10-sec paced inspection (two ampoules) with a 3× magnifying lens, a diffuse light source, and a white/black background were utilized. The light intensity at the position of the samples was approximately 225 foot-candles. In addition, the inspectors chosen for the study were selected on the basis of measurements of their visual acuity, and the results of 70 inspections provided an accurate estimate of the rejection probability for each of the ampoules. In these studies a 70% detection probability was obtained for a spherical particle with a diameter of 65 μm. The equivalent rejection probability using the same conditions without magnification would be seen for a spherical particle approximately 100 μm in diameter.

Using a slightly different protocol than that reported by Knapp et al. (97), we have also studied the visual inspection process. In our experiments a set of 1000 ten-ml ampoules having the composition shown in Table V was used. The defectives were randomly distributed and all the ampoules had been thoroughly characterized by nondestructive techniques. The particles were fluorescent-dyed polystyrene divinylbenzene spheres and the sizes of these beads were measured in-situ using an inverted microscope procedure. Each inspector examined the entire group without magnification in an inspection booth with typical lighting and background conditions. Paced inspection was utilized with a clip of 10 ampoules being examined every 38 sec. The people chosen for the studies included both quality assurance and production inspectors at a few of our manufacturing sites. The results of one study with 14 inspectors at one facility is shown in Table VI. Based on these data, the 70% rejection probability would occur for a spherical particle with a diameter between 100 and 165 μm. In view of the differences in inspection rates, magnification and other conditions, these results are comparable with the findings of Knapp and coworkers (97).

TABLE V. Ampoule Particulate Set

| Number of Ampoules | Number of Particles/Ampoule | Size of Particles (μm) |
|---|---|---|
| 50 | 1 | 165 |
| 75 | 1 | 100 |
| 875 | — | — |

TABLE VI. Average Results for 14 Inspectors at One Facility

| Category | Mean Rejection Probability (%) |
|---|---|
| Good | 1.1 |
| One 100-μm particle per 10-ml ampoule | 59 |
| One 165-μm particle per 10-ml ampoule | 82 |

Most of the above discussion has assumed that there is one visible nonreflecting particle per container. As expected, for the same type and size of particle the detection probability increases as the number of particles increases. Also, the human rejection probability is strongly affected by the optical characteristics of the particulate matter (97).

A second important characteristic of a visual inspection system is its reproducibility (84, 93, 94, 97, 106). If the same set of samples is examined several times by several people under identical inspection conditions, one would like to know the consistency of both the rejection rate and the defectives for an individual inspector as well as for the entire group of inspectors. Moreover, it would be desirable to have this information as a function of time. Although a number of articles have been published on this subject (84, 93, 94, 97, 106), it is difficult to summarize the observations. In particular, this topic is similar to the previous subject since an informative discussion cannot be given without defining the specific range of rejection probabilities for the samples of interest.

In general, the performance of a human visual inspection system is only moderately reproducible. There is a wide variability in the capabilities of individual inspectors and the performance of each inspector can change significantly over the course of time. For example, when the set of ampoules described in Table V was examined by inspectors at one facility, the results in Table VII were observed. Among these inspectors the rejection probability varied from 19 to 84% for a 100-μm sized particle and from 64 to 96% for a 165-μm sized particle. Similar results

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