Generation of Particulate Matter in Large-Volume Parenteral Containers

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Abstract □ Polyvinyl chloride and glass large-volume parenteral containers were examined to determine the effects of agitation, storage, and additive handling on the generation of subvisual particulate matter. It was found that particles in flexible plastic containers can be generated by continuous shaking, with the maximum number of particles recorded after 30 hr of shaking. The particles were in the range of 2.33–5.02 μm in diameter, with very few particles recorded above 5 μm. It was also established that the generation and subsequent disappearance of particles during storage after an interval of continuous shaking are not only functions of time but also of temperature.

Keyphrases □ Plastic parenteral containers—particulate contamination, simulated handling conditions □ Large-volume parenteral containers—particulate contamination, simulated handling conditions □ Parenteral containers, large volume—particulate contamination, simulated handling conditions □ Contamination—large-volume plastic and glass parenteral containers

In recent years, intravenous fluids have played an increasingly significant role as a drug delivery system in patient treatment (1). With the greater utilization of this dosage form, it is important to examine the fluids and containers employed. Parenteral solutions should be relatively free of contamination by particulate matter because particulate matter can produce harmful effects such as pulmonary microemboli, thrombi, or granulomas in the patient (1). Twenty-five cases of pulmonary arterial lesions in premature infants were characterized by macrophage reactions around foreign bodies, mainly cotton fibers (2). Platelet agglutination and the formation of thrombi were observed (3) in rabbits following injection of particles 200–500 Å in diameter; an increase in the number and size of particles increased the possibility of the side reactions.

For years, parenteral solutions have been routinely packaged in glass. Glass containers have at times contributed to contamination in intravenous fluids, and there has been substantial evidence (4) that many particles found in glass-contained intravenous fluid have been generated from the rubber closure during or after sterilization or during storage (1). It has also been shown that glass flaking or leaching of particles can occur from the walls of glass containers.

Recently, several types of plastic containers have been introduced in an attempt to prevent particulate contamination of intravenous liquids from the containers. Solutions packaged in flexible plastic polyvinyl chloride containers were reported to contain fewer particles than solutions packaged in glass containers (5). Flexible plastic intravenous solution containers have also been reported to have a lower incidence of contamination under actual use conditions (6).

A preliminary investigation (7) showed that normal saline stored in disposable plastic ampuls had fewer particles than the corresponding material in rubber-plugged glass bottles. The results were recorded as counts per milliliter for particles above 1.3 μm and were in the order of 1000–5000. The all-plastic flexible containers yielded counts of 200–600/ml. More recently, Groves (8) reported results involving particulate contamination of saline packed in polyethylene and polypropylene containers. The polypropylene containers were more heavily contaminated and the contamination increased after sterilization by autoclaving. Solutions in polyethylene ampuls were reported to have a low degree of particulate contamination (4, 7, 9).

A study of intravenous fluids contained in plastic containers was reported; in 18 samples of normal saline solution in 1000-ml plastic containers, the average number of particles over 5 μm was 137 as compared to the number of particles in glass containers that ranged from 243 for one manufacturer to 1751 for another manufacturer.

Since glass containers for intravenous fluids were reported to be a source of particulate matter contamination and since this contamination can be harmful to the patient, the development of an all-plastic container was thought to be the solution to contamination problems. Unfortunately, the plastic containers may have their own source of contamination which might be harmful to the patient (11). Plastic containers are growing in popularity because they can be stored, handled, and disposed of more easily than glass containers (10); therefore, it is important that these containers be studied closely. As yet, the research data on contamination from plastic bags are incomplete.

The objective of this study was to determine the effects of agitation, storage, and additive handling on the generation of subvisual particulate matter in polyvinyl chloride and glass liter containers.

EXPERIMENTAL

Materials and Equipment—The following were employed: polyvinyl chloride plastic containers[1] of 0.9% sodium chloride injection USP, 1000-ml units; parenteral administration sets[2], Code

[1] Viaflex containers, lot NP61X1, Travenol Laboratories, Morton Grove, Ill.

[2] Lot B103L1, Travenol Laboratories, Morton Grove, Ill.

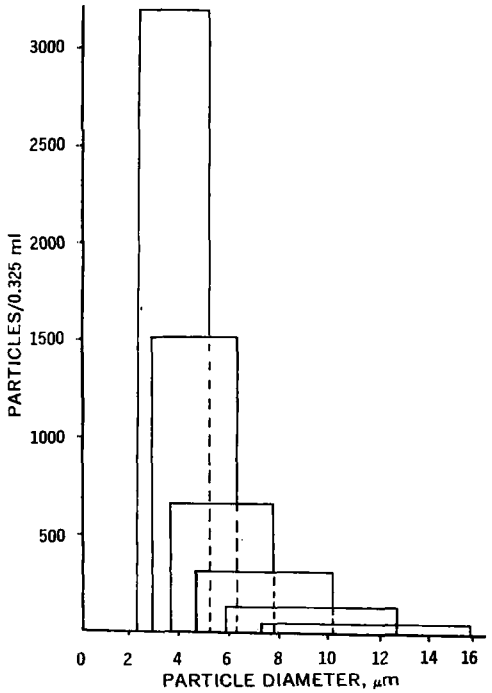

Figure 1—*Number of particles in various size ranges found in plastic bags shaken for 24 hr.*

2C0001; glass containers of 0.9% sodium chloride injection[3] USP, 1000-ml units; disposable venoclysis set[4]; laminar flow unit[4]; and gyrotory shaker[5].

An electronic particle counter in combination with a 100-channel channelyzer[6] was used to examine changes in particulate matter of the intravenous fluid. Four different size aperture tubes, 30, 50, 70, and 100 μm, were available for the experiments. The particle counter has the capability of reproducibly counting particles that are 2–40% of the size of the aperture tube (13). Since a preliminary study indicated that the greater percentage of particles was in the range of 2–6 μm, the 50-μm aperture tube was used.

Prior to counting each sample, the diluent was used to obtain the background counts; it was also used to rinse the aperture tube between samples. A detergent cleaner was used to clean and soak the aperture tube periodically and at the end of each day.

Three counts were taken for each sample, and the average was recorded. Preliminary results showed that, to obtain reproducibility, a 30-sec sampling time, equivalent to 0.325 ml, was necessary for each count.

Statistical Determination of Number of Bags per Experiment—The appropriate number of bags for each experiment was derived statistically from preliminary results. Zero counts were made on 20 control bags, and it was found that no one bag had a zero count greater than 300 particles between 2.33 and 5.02 μm/0.325 ml. The following formula was used to obtain the number of bags needed at a 95% confidence interval (14):

$$1.96(\sigma)/\sqrt{n} = L \qquad \text{(Eq. 1)}$$

where 1.96 is the representative value for a 95% confidence interval, σ is the standard deviation of the control bags, and L is the range limit of the amount of error that can be tolerated in the estimate.

With the considerations of time and expense for the study, as well as the inherent error of the instrumentation when counting 300 particles (12), it was decided to use 40 bags for each test. The values from two out of every 10 bags were plotted using the X–Y recorder integrated into the counting system to preserve and compare typical particle-size distributions.

Sampling Technique—Each plastic liter container was removed from its outer protective wrapper and was assembled with the administration set. The glass bottles were assembled with the disposable venoclysis administration sets. The tubing on the administration sets was shortened for easier sampling. All samplings were done in a laminar flow unit. Samples were collected in 20-ml plastic vials. Prior to each sampling, the administration set was flushed and the accuvette was rinsed twice with a portion of the intravenous fluid to be sampled. This procedure was followed to eliminate the possibility of particulate contamination from the tubing of the administration set and/or from the plastic vials.

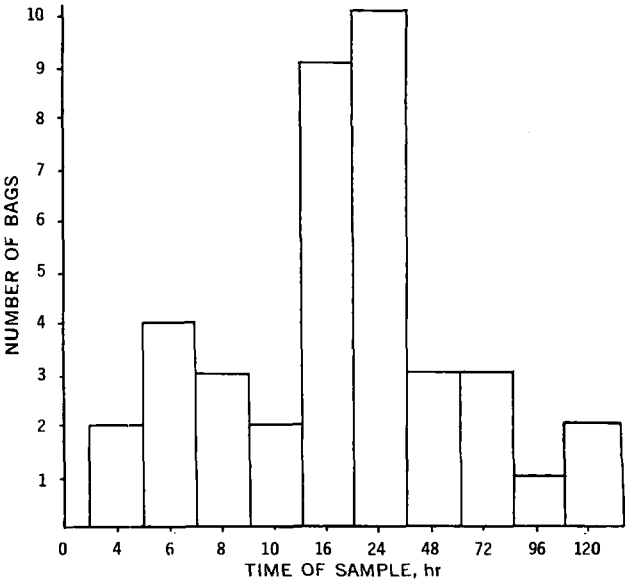

Figure 2—*Number of plastic bags exhibiting maximum particle counts at indicated time during shaking test.*

Shaking Test—A zero count was made on each bag or glass bottle before it was subjected to any test. Forty bags were sequentially placed in a gyrotory shaker and shaken for 120 hr. Samples were taken and counts were made at times 0, 1, 3, 5, 10, 20, and 40 min and 1, 2, 4, 6, 8, 12, 16, 24, 48, 72, 96, and 120 hr.

The same shaking and sampling procedures were followed for the 10 glass bottles used for the test. Since preliminary results had shown that there was a smaller variation among individual glass bottles than among the plastic containers, a smaller number of glass bottles was needed per test.

Drop Test—The plastic liter containers were individually dropped once from a measured height of 1.5 m (5 ft). The containers were dropped so that each container would have a different point of impact. This test was used to simulate accidental dropping during handling. A zero count was made prior to the test, and samples were taken and counted after dropping.

Aging Test—From preliminary results it was seen that the number of particles maximized on the average at 29.64 hr of shaking. Thereafter, 30 hr was used as the $t = 0$ reference time for resting containers. Groups of 40 bags were shaken for 30 hr and then stored at room temperature, 35, 45, and 55°.

Following the shaking period, containers were sampled until the number of particles declined to the range of zero counts. For storage conditions at room temperature, samples were taken at intervals up to 5 weeks. In the case of 35, 45, and 55° storage conditions, counts were taken up to 4 weeks.

At each sampling and just prior to sampling, the container was turned "end for end" one time. This procedure was followed to assure that a representative sample was withdrawn from the container.

Simulated Addition Test—To simulate particles that might be generated during agitation and after addition of an additive, the plastic liter containers were inverted (end to end) 5 times to simulate the mixing procedure.

RESULTS AND DISCUSSION

The intent of this study was to compare the particulate contami-

[3] Lot G173A1, Baxter Laboratories, Morton Grove, Ill.
[4] Abbott Laboratories, North Chicago, Ill.
[5] Model G-25, New Brunswick Scientific Co., New Brunswick, N.J.
[6] Model ZB with P64, Coulter Electronics, Hialeah, Fla.

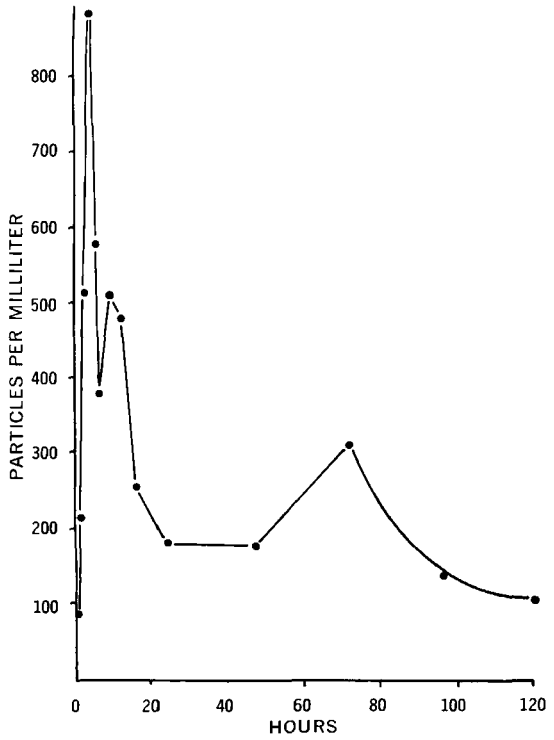

Figure 3—*Mean number of particles between 2.33 and 5.02 μm found in 10 glass containers shaken through 120 hr.*

nation emanating from flexible plastic intravenous fluid containers made from polyvinyl chloride and glass intravenous containers. The study was designed to simulate conditions that might lead to the generation of particulate matter.

Particle-Size Determination—Figure 1 represents a study in which six bags were shaken for 24 hr and sampled for particulate contamination over the size range of 2.33–40.12 μm in diameter. Figure 1 shows that the number of particles decreased as the diameter of the particle size increased in size, and that the greatest number of particles was in the lowest range studied. Throughout the study, the number of particles varied considerably from bag to bag. This is substantiated by previous reports (3) which showed that solutions vary, in degree of particulate contamination, among manufacturers and among different solutions from the same manufacturer. Due to instrumentation, the results were necessarily obtained by collecting data with overlapping sizes. Although samples were examined for particles up to 40.12 μm, no significant number of particles was found beyond 10 μm. It is possible that the particles measured above 10 μm may actually have been the result of agglomeration of several smaller particles. The data shown in Fig. 1 are similar to and agree with an earlier study (15) in which very few particles of greater than 5 μm were present in intravenous fluid bags of "all plastic" construction. Due to the results seen in Fig. 1, the remaining particle counts were performed in the 2.33–5.02-μm range.

Shaking Test—The purpose of the shaking test was to simulate travel or transport conditions for the intravenous fluid containers and was designed to determine if vigorous shaking contributes to particle contamination. Figure 2 shows that the maximum number of particles from plastic bags shaken for 120 hr was observed at 29.64 hr. This average peak time of particle appearance was calculated by using a weighted average of the highest particle count obtained from each bag during continued shaking for 120 hr. For ease of manipulation and calculation, bags were considered to peak at 30 hr of shaking and the results are reported as the mean number of particles per milliliter. Figure 2 represents the average of 40 bags shaken over the 120-hr test period. The peaks represent the average number of particles found at each sampling time, and there is a definite peak between 15 and 40 hr.

Since there is evidence (5–7) eluding to the fact that there are fewer particles in flexible plastic containers compared to glass containers, it was thought appropriate to establish a baseline for the glass containers under identical conditions with the plastic containers. The results from shaking glass bottles (Fig. 3) were obtained during 120 hr of shaking; highest counts for particles between 2.33 and 5.02 μm were produced after 2 hr of shaking. This is in sharp contrast to plastic containers where the number of particles was greatest at 30 hr. Figure 3 also shows that the glass bottles peaked with a particle count of 893/ml after 2 hr of shaking. Again, this finding is in contrast to plastic containers which showed an average maximum of approximately 25,000 particles/ml.

Table I—Numbers of Particles Found in Polyvinyl Chloride Containers and Glass Containers at Times Equal to Maximum Particle Generation

Time	Particles per Milliliter	
	Polyvinyl Chloride Bags	Glass Bottles
0	345	87
2 hr	16,122	893[a]
30 hr	24,308[b]	150

[a] Maximum number of particles in glass containers. [b] Maximum number of particles in plastic containers.

After approximately 2 hr of continued shaking, the glass bottles showed a decrease in particles. The total number of particles continued to decrease until 72 hr where there was an apparent increase. The number of particles continued to decrease thereafter. Although the glass bottles showed an increase in particles, the total number of particles never equaled the number found in the plastic containers. Apparently, as reported earlier (1), the particles found generated from the glass containers were a result of shedding from the rubber closures and/or leaching from the glass itself.

Table I shows a comparison of the number of particles found in both plastic and glass containers. The total number of particles in the 2.33–5.02-μm range in the glass bottles was significantly less than the total number in the plastic bags at all times. The glass bottles showed a 10-fold increase after 2 hr of shaking. The plastic bags showed an approximately 50-fold increase in 2 hr and a 70-fold increase in particle counts in 30 hr, while during the same time the glass containers showed a decrease in particles to less than a twofold increase from time zero.

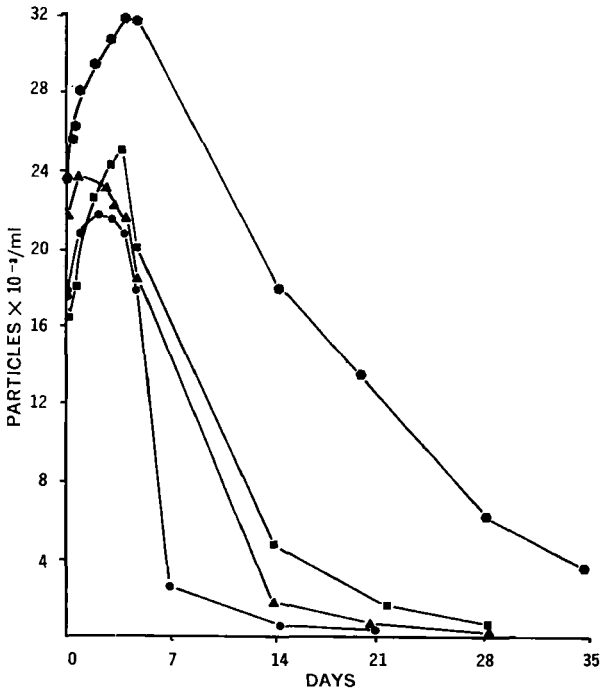

Figure 4—*Number of particles between 2.33 and 5.02 μm found in resting plastic bags after shaking for 30 hr as a function of time and temperature. Key: ■, 35°; ●, 45°; ▲, 55°; and ●, room temperature.*

Drop Test—Initial dropping tests, when carried out as previously described, showed no significant change in the number of particles. Additional tests were made on bags tossed and handled roughly for 1–2 min. These results also failed to establish an appreciable change in number of particles.

Aging Test—For the aging test, it was desirable that the bags contain a maximum number of particles due to shaking to establish what effects storage may have on the appearance and disappearance of particles. Therefore, prior to storage the plastic bags were shaken for 30 hr to generate particles.

To obtain significant results, 160 plastic containers were shaken for 30 hr each. These containers were divided into four batches to be stored at room temperature, 35, 45, and 55°. In each case, base counts were established at the start of the rest or storage periods and are shown as time equal zero in Fig. 4. For all cases and at all storage conditions, each container showed an initial increase in particles. In Fig. 4, particles per milliliter are plotted *versus* time. The resting bags stored at room temperature showed an increase in particles from time zero to 120 hr, and the resting bags stored at 35° showed an increase in particles from time zero to 96 hr. For the bags stored at 45°, an increase in particles from time zero to 48 hr was recorded, and an increase in particles to 24 hr was found for bags stored at 55°. From Fig. 4 it may also be seen that bags stored at the lower temperatures showed a longer period of sustained increase in particles while this was not as apparent in bags stored at 45 and 55°.

It is apparent from Fig. 4 that there was a general increase in the number of particles at all temperatures, with the degree of increase and the time over which the increases was recorded varying directly with temperature. A general decrease in particles, at what appears to be an essentially uniform rate, takes place after 120 hr of resting. At this time there is no clear explanation for these phenomena.

Since the number of particles generated in the bottles after 30 hr of shaking was so small and was almost identical to the number of particles observed before shaking, any changes in the average number of particles on aging would be within the interbottle variation and, therefore, not significant. In addition, it was found that with no shaking and after resting for 30 days in the original container, approximately 90 particles/ml in the 2.33–5.02-μm range were found in the glass containers.

Simulated Addition Test—The simulated addition test was performed to examine the potential particulate generation that might occur after the addition of an additive to the intravenous fluid containers. The turning end to end of both the bags and bottles failed to show any significant increase in particle contamination.

In summary, it may be seen that particles in polyvinyl chloride plastic containers can be generated by continuous shaking. It was established that plastic bags, even of the same lot number, varied considerably in the number of particles generated and that very few particles were found to be larger than 5 μm in diameter, with the greater number of particles in the lower range of 2.33–5.02 μm.

In all cases, glass bottles produced fewer particles than did plastic bags under similar conditions.

The results indicate that the storage conditions of the container after agitation can contribute to the time span involved in additional generation and the subsequent reduction in the number of particles.

During this study, it was established that significant numbers of particles could not be generated by mere handling of the containers such as turning end for end, nor was there a significant generation of particles by dropping the plastic containers from a height of 1.5 m (5 ft).

Therefore, from this study it may be concluded that by continuous shaking, particles can be generated in polyvinyl chloride plastic containers. These results are important because the travel or transport and storage conditions of the plastic containers must be considered to play a significant role in particle contamination of intravenous fluids.

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