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SIZE DISTRIBUTION CHARACTERISTICS OF PARTICULATES FROM GLASS AND PLASTIC LVP'S

James W. Warren, Jr., Pablo U. Alvarez*, and Joseph D. Benmaman
Medical University of South Carolina College of Pharmacy
Charleston, South Carolina 29401

ABSTRACT

An automated microscopic system was used to detect particulates from four different large-volume parenteral solutions in glass and plastic containers. Solutions from glass containers were found to contain a significantly greater number of particles; however, the mean diameter of particles from plastic containers was greater. Characteristics of the size distribution of particles from glass and plastic containers were also different. An overall (particle size 5-50μ) cleanliness factor was calculated. Cleanliness factors for glass containers were larger by 55.5% to 264.1% than those for plastic.

INTRODUCTION

Since about 1964, the interest of pharmaceutical investigators concerning particulates in large-volume parenterals has been reflected by numerous publications. While the presence of particulates in

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*Visiting Professor, School of Pharmacy, University of Guayaquil, Ecuador

parenterals is well documented, the clinical significance of introducing particulates into the body is inconclusive.

Turco and Davis (1) have reviewed the literature relative to the clinical significance of particulate matter until 1973. This review, as well as other reports (2-5) reveals a number of adverse effects resulting from introduction of particulates into general circulation. Some of the physiological problems reported include embolus formation in venous tissue, lungs, and kidneys; allergenic responses; blockage of blood vessels; and inflammatory conditions resulting from embedded particles.

Large-volume parenteral solutions in plastic containers have been available since 1971. Since that time, several reports have appeared which compare the level of particulate contamination in plastic and glass containers. Turco and Davis (6) found that the average number of particles greater than 5μm from plastic containers was 76 particles per liter, while glass containers averaged 204 to 488 particles per liter. Using scanning electron microscopy, Levinson et.al.(7) showed that particles found in glass and in plastic containers have distinctive differences in size and gross morphology. Davis et. al. (8) in a comparative study, reported that plastic bags contain fewer particles than solutions in glass bottles.

These reports show that there are in general fewer particles in large-volume parenteral solutions from plastic containers as compared to glass. The present report compares the number of particles detected in solutions from glass and plastic containers over a broad particle size range; characterizes the particles relative to mean

particle size and particle-size distribution; and quantitates the difference in the level of particulates using cleanliness factors.

EXPERIMENTAL

Materials: Four commerically prepared large-volume parenteral solutions (1000 ml), in both glass and plastic, were evaluated. The solutions studied were 5% dextrose[1], 5% dextrose in normal saline[1], lactated ringers[1], and 0.9% sodium chloride[1].

Membrane Filtration: All containers were inverted 20 times prior to filtration. The content of each large-volume parenteral (1000 ml) was filtered under laminar flow through a 0.45μ cellulosic membrane filter[2]. A detailed description of the filtration procedure was described previously (9).

Microscopic Counting: Microscopic counting of particles on transparent filter membranes was performed using a microscopic particle-measurement computer system[3] (9). Particles in a given field having a maximum horizontal chord greater than 5μ, 10μ, 15μ, 20μ, 25μ, 35μ and 50μ, respectively, were counted with the computer set in the oversize count mode. For each membrane filter, 60 fields were scanned with the 10X objective. A cumulative count from the 60 fields was recorded. The microscopic particle-measurement system was internally calibrated with National Bureau of Standards traceable check slides.

Control counts, particles in 100ml of 0.45μ filtered water, were subtracted from the sample counts.

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1. Travenol Laboratories, Inc., Deerfield, IL.
2. Millipore Corporation, Bedford, MA.
3. πMC, Millipore Corporation, Bedford, MA.

RESULTS AND DISCUSSION

Particle Counts and Mean Particle Diameter: The number of particles detected in each size group for solutions from glass and plastic containers is given in Table I. For each solution, the total number of particles from glass containers was significantly ($p=0.05$) greater. With the exception of 5% dextrose solution, the total counts agree closely with those reported by Dodd (10). He reported the particle count for intravenous fluids in plastic containers is approximately one-tenth of that of glass containers.

From the data given in Table I, the mean particle diameter over the size range 5-50μ was calculated using the method of Parrott (11). Mean particle diameters were as follows: 5% Dextrose, 14.31μ for glass and 12.89μ for plastic; 5% Dextrose in Normal Saline, 12.51μ for glass and 13.52μ for plastic; Lactated Ringers, 13.73μ for glass and 16.64μ for plastic; and 0.9% Sodium Chloride, 12.13μ for glass and 15.06μ for plastic.

Blanchard et.al. (12) have shown that the relative distribution of particles from intravenous solutions is largely independent of the composition of the solution. Therefore, to further compare the mean particle diameters, they were calculated without regard to solution type. This involved the particulate counts from 40 glass bottles and 40 plastic bags. The mean diameter of particles from glass containers was 12.96μ. The mean diameter was 14.44μ for particles from plastic containers.

Size Distribution Characteristics and Cleanliness Factors: The particle-size distributions of parenteral solutions can be described by

TABLE I - Particulate Counts: Solutions from Glass and Plastic LVPs

Size Group (μ)	Number [a] of Particles Per 1000 ml in Each Size Group							
	Solution 1[b]		Solution 2[b]		Solution 3[b]		Solution 4[b]	
	Glass	Plastic	Glass	Plastic	Glass	Plastic	Glass	Plastic
5-10	2178	815	8936	445	5616	304	5762	495
10-15	1511	382	4388	113	2722	267	2547	383
15-20	867	185	2732	113	2198	111	1393	215
20-25	400	122	1477	145	1129	269	755	178
25-35	511	47	683	60	751	142	360	169
35-50	124	58	153	2	275	11	132	13
TOTALS	5591	1609	18369	878	12691	1104	10949	1453
		S[†]		S[†]		S[†]		S[†]

[a] Average of 10 solutions [b] 1 , 5% Dextrose; 2, 5% Dextrose in NS; 3, Lactated Ringers; 4,0.9% NaCl

[†] Statistical analysis for significantly fewer particles in plastic versus glass by signed - rank Sum test. NS is $p > 0.05$.

a straight-line equation (13): $\log N_{>D} = K \log D + \log N_{>1}$ (Eq.1) where $N_{>D}$ is the number of particles per milliliter with a diameter larger than D, $N_{>1}$ is the number of particles per milliliter with a diameter larger than 1μ, D is the particle diameter in microns, and K is equal to the slope of a plot of $\log N_{>D}$ versus $\log D$.

Using this treatment, values for K, $N_{>1}$, and correlation coefficients were determined for the four solutions from glass and plastic containers. A typical plot of $\log N_{>D}$ versus $\log D$ is shown in Figure 1. The particle counts per milliliter for each size setting and values for K and $\log N_{>1}$ are given in Table II.

The data in Table II indicate the particle-size distribution characteristics are different for solutions from glass and plastic

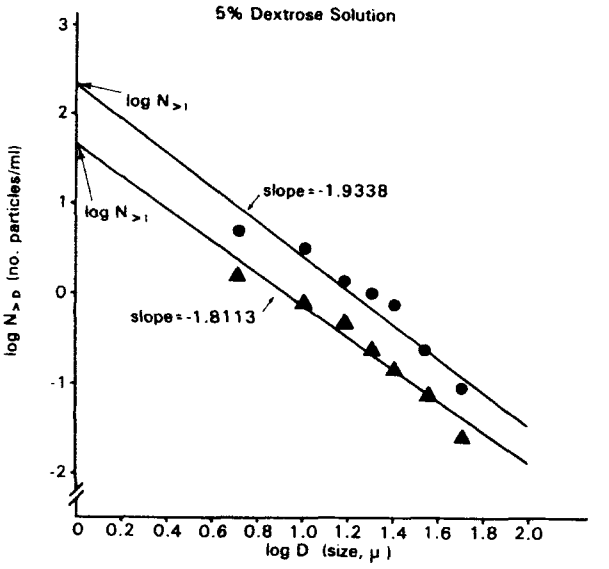

Figure 1: Particle-Size Distributions of 5% Dextrose Solution in Glass (●) and Plastic (▲).

TABLE II - Particle-Size Distribution Characteristics of LVP Solutions in Glass and Plastic

Solution[b]	Number[a] of Particles per Milliliter >5μ	>10μ	>15μ	>20μ	>25μ	>35μ	>50μ	Slope (K) of log - log plot	log $N_{>1}$	Correlation Coefficient between log $N_{>D}$ and log D
No. 1										
Glass	5.642	3.449	1.960	1.084	0.688	0.191	0.069	-1.9338	2.3757	-0.9533
Plastic	1.633	0.818	0.436	0.251	0.129	0.082	0.024	-1.8113	1.6494	-0.9783
No. 2										
Glass	18.444	9.508	5.120	2.388	0.911	0.228	0.075	-2.4753	3.3366	-0.9572
Plastic	0.911	0.466	0.353	0.240	0.095	0.035	0.033	-1.5898	1.2312	-0.9547
No. 3										
Glass	12.813	7.198	4.476	2.278	1.149	0.398	0.122	-2.0364	2.8116	-0.9562
Plastic	1.227	0.922	0.656	0.544	0.276	0.133	0.122	-1.1186	1.0177	-0.9463
No. 4										
Glass	10.977	5.215	2.668	1.275	0.520	0.160	0.028	-2.5617	3.1793	-0.9553
Plastic	1.466	0.971	0.588	0.373	0.195	0.026	0.013	-2.1467	2.0357	-0.9207

[a]Average of 10 solutions [b]1,5% Dextrose; 2,5% Dextrose in NS; 3, Lactated Ringers; 4,0.9% NaCl

containers. The slopes (K) and log $N_{>1}$ (y intercept) values for glass were greater than those for plastic. The correlation coefficients for the four solutions, glass and plastic, were high ranging from - 0.9207 to - 0.9783. This high degree of correlation indicates linearity of the particle-size distribution when plotted as log $N_{>D}$ versus log D. Variation of these parameters indicates a distinct difference in the particle-size distributions.

A cleanliness factor based on particle-size distribution has also been developed for assessing parenteral cleanliness (14). The cleanliness factor was derived from the USP standard for particulate contamination levels (not more than 50 particles/ml greater than 10μ and not more than 5 particles/ml greater than 25μ) and the particle-size distribution parameters, log $N_{>1}$ and K. Accordingly if the values listed in the USP standard exhibit a linear relationship as described by Eq. 1, then the slope (K) and the y intercept (log $N_{>1}$) of this line are - 2.5126 and 16,280 (log $N_{>1}$ = 4.2116), respectively. From the USP standard, plotted as log $N_{>D}$ versus log D, an equation was derived as follows (14):

$$C_i = \frac{\log N_{>1} - 0.6990}{-K} \quad \text{(Eq. 2)}$$

where C_i is the cleanliness factor, log N>1 is the y intercept, and K is the slope.

Using Eq. 2 and the data from Table II, the cleanliness factors for solutions from glass and plastic containers were calculated. Cleanliness factors are given in Table III. The cleanliness factor for solutions from plastic containers was always smaller. The percent difference in cleanliness factors for solutions from glass and plastic

TABLE III - Cleanliness Factors [a] for Large - Volume Parenteral Solutions in Glass and Plastic Containers

Solution[b]	Cleanliness Factors		Difference in Cleanliness Factor, %[c]
	Glass C_i	Plastic C_i	
No. 1	0.8670	0.5247	65.2
No. 2	1.0656	0.3348	218.3
No. 3	1.0374	0.2849	264.1
No. 4	0.9682	0.6227	55.5

[a] Measurements from 10 solutions

[b] 1,5% Dextrose; 2,5% Dextrose in NS; 3, Lactated Ringers; 4, 0.9% Na Cl

[c] $\% \text{ Difference} = \frac{Ci \text{ (glass)} - Ci \text{ (plastic)}}{Ci \text{ (plastic)}} \times 100$

containers is also shown in Table III. Cleanliness factors for glass containers, ranged from 55.5% to 264.1% greater than those for plastic containers.

SUMMARY

Results of the present study indicated:

1. The number of particles detected in solutions from glass containers was significantly ($p = 0.05$) greater as compared to plastic containers.

2. Mean diameter of particles from 40 plastic containers was 14.44μ, while the mean diameter of particles from 40 glass containers was 12.96μ.

3. The size distribution of particles from glass and plastic containers was different relative to parameters K, $N_{>1}$ and D.

4. Cleanliness factors were calculated for solutions from glass and plastic containers. The cleanliness factor for solutions from plastic containers was always smaller. The difference in cleanliness factors ranged from 55.5% to 264.1%.

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