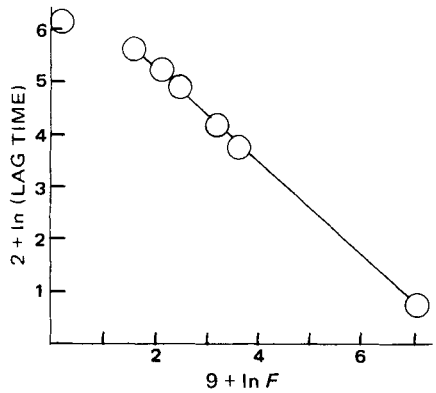

Figure 4—*Logarithm of the lag times of the lines in Fig. 3 (Table I) plotted* versus *the logarithm of the corresponding* F *values.*

log-time plots (θ') are proportional to the appropriate θ_2 values since ln (θ_2/θ') = 1.29, *i.e.*:

$$\theta_2 = 3.63\theta' \qquad \text{(Eq. 22)}$$

Although time is shown in minutes, it could be in any time unit; the important parameter is the F/q ratio. Therefore, the same curves would be generated if all time units are multiplied by ($^1/_{60}$) (to give the data in seconds) or by 15 to give the data in quarter hours, and so on.

In summary, directly compressed tablets can have sigmoid-shaped USP dissolution rate curves in which the tail is log-linear in time if sink conditions are applicable.

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Evaluation of Acceptance Criteria for Particulate Limits for Small-Volume Parenteral Products

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Abstract □ The precision of and correlation between the USP membrane filtration–microscopic method and the instrumental method for sizing and quantifying particulate matter in small-volume parenteral products were determined using simulated products. The total variance for the instrumental counts was lower than the USP method for all products in the 10–25-μm particle range and for most products in the ≥25–50-μm range. A linear relationship between the instrumental counts and the USP counts was demonstrated for the 10–25-μm particle range. However, the instrumental reading was higher than the USP method for counts of 10 or more particles/ml. The instrumental and the USP methods failed to correlate on particulate sizes greater than 25 μm. The content of particulate matter in over 100 small-volume parenteral products was sized and quantified by the USP and the instrumental methods. From the instrumental data, a statistical treatment for the analysis of particulate data is presented as an objective method of evaluating acceptance criteria on particulate matter in small-volume parenteral products.

Keyphrases □ *Particle* content determinations—small-volume parenterals, USP membrane filtration–microscopic and instrumental methods compared □ Parenterals, small volume—particle content determinations, USP membrane filtration–microscopic and instrumental methods compared □ Dosage forms—various small-volume parenterals, particle content determinations, USP membrane filtration–microscopic and instrumental methods compared

Interest in particulate matter in parenteral products was dramatically heightened by Garvan and Gunner (1, 2), who became concerned over the large number of visible particles in intravenous solutions manufactured in Australia. They presented evidence of the harmful effects of such contaminants by infusing intravenous solutions into rabbits; granulomas were produced in the lung, each containing fragments of cellulose particles. They identified the source of most particles as originating from locally produced rubber closures; other particulates were identified as cellulose fibers. They also examined numerous brands of intravenous solutions manufactured in Australia, England, Europe, the Philippines, and the United States and found particles in most products.

In 1966, Vessey and Kendall (3) published a method of determining particulate matter in large-volume parenteral solutions using an automated counter. They proposed an arbitrary limit for particulate matter in these solutions. This proposal was modified and adopted by the British Pharmacopoeia in 1973 (4); the limits are less than 1000 particles/ml equal to or larger than 2 μm and less than 100 particles/ml equal to or larger than 5 μm. Recently, Bikhazi *et al.* (5) extrapolated the BP regulation and proposed that the average counts per 1 ml of parenteral preparation should contain not more than 700 particles equal to or greater than 1 μm, 200 equal to or greater than 2 μm, 100 equal to or greater than 3 μm, and 40 equal to or greater than 5 μm.

"The First Supplement to the USP XIX and NF XIV" (6) established the limit for particulate matter in large-volume parenteral products as not more than 50 parti-

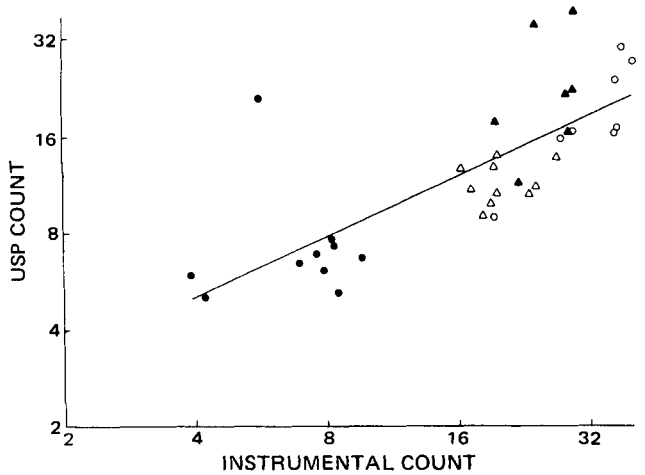

Figure 1—*Correlation between the USP method and the instrumental counts by day for particles of the 10–25-μm range in simulated products. Key: ○, Product I; △, Product II; ●, Product III; and ▲, Product IV.*

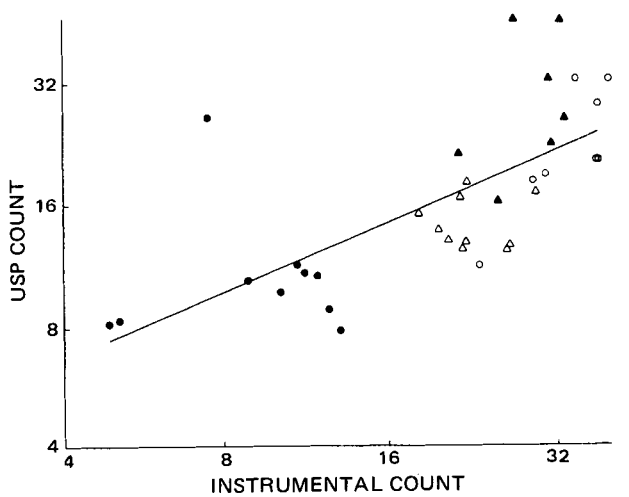

Figure 2—*Correlation between the USP method and the instrumental counts by day for particles of the ≥10-μm range in simulated products. Key: same as Fig. 1.*

cles/ml equal to or larger than 10 μm and not more than 5 particles/ml equal to or larger than 25 μm. The USP also recognized the membrane filtration–microscopic method as the official method for particulate determination. These methods and limits became effective July 1, 1975.

This report provides data on the precision of and correlation between the USP and the instrumental methods. It also presents data on particulate matter in over 100 small-volume parenteral products and suggests an approach for evaluating acceptance criteria on particulate matter in small-volume parenteral products.

EXPERIMENTAL

The membrane filtration–microscopic method used to size and quantitate particulate matter was described in "The Second Supplement to the USP XIX and NF XIV" (7). The sample preparation procedure includes opening of ampuls by the melt-open technique. This technique involves placing the upper widest part, above the breakline, of an ampul into the oxygen–gas torch flame. As the glass softens, the internal pressure forces the glass to pop out, forming a hole. As soon as the hole appears, a glass rod is used to melt away and remove the upper portion of the ampul. Thus, the particulate matter in an ampul can be counted without interference by the broken glass formed during an ampul-opening operation. The superiority of the melt-open technique over the break-open technique was amply demonstrated (8).

The particle-size analyzer[1] used was equipped with a small-volume sampler and a six-channel line printer. This instrument, which operates by the principle of light blockage, was used at a flow rate of 20 ml/min with 1-ml sample size. The small-volume sampler worked well at 20 ml/min but not at 60 ml/min.

The six channels were set to operate in the delta mode to record the following particle-size ranges: 5–10, 10–25, 50–100, 100–125, and over 125 μm. Due to extreme difficulty in obtaining reproducible results on particulate counts in the 5–10-μm range, this size range was not used in the statistical evaluation. Any proposal limiting particulate matter in this or a smaller size range (4.5) would be beyond the capability of the current particulate monitoring technology.

To minimize container-to-container variations, four simulated bulk product solutions (I–IV) were prepared. These solutions were aseptically dispensed into particle-free 50-ml vials and capped with clean butyl rubber stoppers. The vials, after machine washing, were manually cleaned by rinsing several times with particulate-free distilled water through a 0.22-μm membrane filter. Vials were then dry heat sterilized at 280° for 1 hr.

To establish the precision of the particle-size analyzer readings, a calibration solution[2] containing latex spheres of various sizes was used. The solution was aseptically dispensed into particle-free 50-ml vials. These bulk solutions were examined by the USP and the instrumental methods for up to 10 consecutive days. Instrumental drift was checked each day by examining the calibration solution three times a day.

The following test scheme and order were used each day.

1. The calibration solution was analyzed by the instrumental method (10 1-ml readings).
2. Product I was analyzed in the following order: USP method (one 5-ml sample), instrumental method (10 1-ml readings), USP method, instrumental method, USP method, and instrumental method.
3. Product II was analyzed in the same order as Product I.
4. The calibration solution was analyzed by the instrumental method.
5. Product III was analyzed in the same order as Product I.
6. Product IV was analyzed in the same order as Product I.
7. The calibration solution was analyzed by the instrumental method.

Thus, each product solution was examined consecutively by both the USP and the instrumental methods, repeating the sequence three times. The actual sequence of the product examination was randomized after the 1st day.

RESULTS AND DISCUSSION

The first experiment was designed to determine the correlation and precision of the USP and the instrumental methods. The experiment was then followed by the application of these two methods to obtain particulate levels in over 100 small-volume parenteral products.

Correlation Study—Each of the four bulk product samples yielded three USP counts and 30 instrumental counts per day. Preliminary analysis indicated that there was no short time trend in either the USP or the instrumental method. Since these within-day variations appeared to be random, daily averages were used in the correlation study. Additionally, the distribution of the counts appeared to be log-normal. Thus, the statistical evaluation of the data was performed using the number formed by the natural log of the sum of the observed count plus 0.5.

The transformed data of the USP and the instrumental counts were plotted against each other (Figs. 1–4), and the linear regression analyses were run. Since regression analysis assumes that the independent variable (the instrumental count) is known without error, the regression lines in Figs. 1–4 should be regarded as approximate. The results of these regression analyses for 35 daily average USP counts against 35 daily average instrumental counts fell into two groups (Groups 1 and 2, Table I) depending on the particle size. Thus, there appears to be a rough linear relationship between the USP and the instrumental counts for the 10–25-μm particle range. The effect of one outlier point (Product III) in Figs. 1 and 2 on the correlation coefficient is minimal.

In the 10–25-μm particle range, the instrumental method gave higher counts than the USP method for counts of 10 or more. This discrepancy may result from the use of the membrane filter required in the USP method; *i.e.*, silicone stopcock grease is used to hold the membrane filter on a plastic petri slide for microscopic counting, and any particles soluble

[1] HIAC model PC-320 with an E5-150 sensor, Pacific Scientific Co., Montclair, Calif.

[2] Lot 292, Pacific Scientific Co.

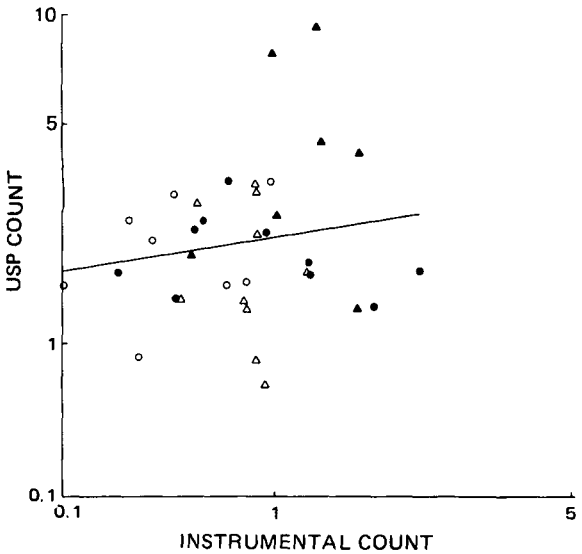

Figure 3—*Comparison of the USP method and the instrumental counts by day for particles of the 25–50-μm range in simulated products. Key: same as Fig. 1.*

in the grease may not be counted. Also, as the count becomes larger, the chance of clumping increases, thus giving falsely lower counts in the subvisual range (<20 μm).

It was not totally unexpected that the USP and the instrumental methods failed to correlate on particle sizes greater than 25 μm (9). This difficulty was most likely due to one or both of the following physical properties of the four simulated bulk products. The first property was the similarity of the particle densities (counts per milliliter) in the ≥ 25-μm size range. This similarity of densities, relative to the variation in densities within each product, would mask any correlation between the methods. The correlations reported above the 10–25- and ≥10-μm ranges were observable because there were distinct differences between the particle densities of the bulk products. The within-product correlation was largely masked by measurement error.

The second property was the shape of the ≥25-μm particles in relation to the difference in the mode of sizing used by the USP and instrumental methods. The particle-size analyzer is operated on the concept of light blockage or geometric shadowing. A beam of light is focused through the window of a flowcell onto a photocell. As particles, in a fluid flow, individually pass the window, a fraction of the light beam is interrupted, thus generating a series of pulses. These pulses are fed into six counting channels to record the particle size as a sphere corresponding to its equivalent geometric mean diameter.

The USP method, on the other hand, measures the longest axis or effective linear dimension (6, 7). Therefore, differences in the numerical results of the two methods become greater when the particle shape deviates further from the spherical shape. For example, a fiber 50 μm long, 2 μm wide, and 2 μm thick will be sized as a 50-μm particle by the USP method. The particle-size analyzer will recognize the fiber as a spherical particle having a geometric mean diameter of 11.3 μm.

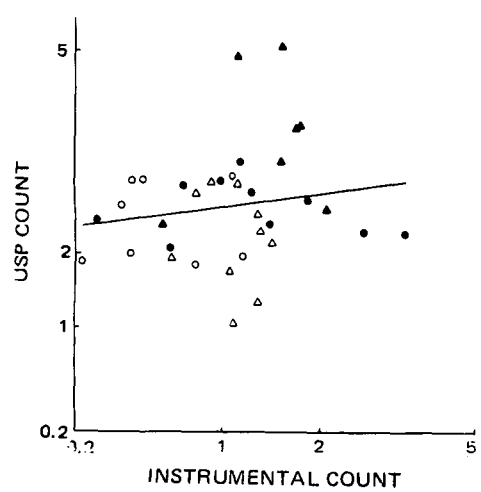

Figure 4—*Comparison of the USP method and the instrumental counts by day for particles of the ≥25-μm range in simulated products. Key: same as Fig. 1.*

Table I—Correlation Results for Bulk Product Samples

Group 1, 10–25- and ≥10-μm Particle-Size Range	Group 2, 25–50- and ≥25-μm Particle-Size Range
1. Data form a distinct cluster for each product. Center of cluster is near regression line[a].	1. A large amount of scatter is in the data; product clusters overlap.
2. Instrumental counts greater than 10 generally exceed corresponding USP count (Figs. 1 and 2).	2. Instrumental counts are usually lower than USP counts (Figs. 3 and 4).
3. Linear regression is statistically significant. Correlation coefficients were 0.75 and 0.68 for 10–25- and ≥10-μm ranges, respectively.	3. Linear regression is not significant. Correlation coefficients were less than 0.20.

[a] Linear regression equations were $\ln(USP + \frac{1}{2}) = 0.80 + 0.63 \ln(\text{instrumental} + \frac{1}{2})$ for the 10–25-μm range and $\ln(USP + \frac{1}{2}) = 1.13 + 0.57 \ln(\text{instrumental} + \frac{1}{2})$ for the ≥10-μm range.

Need for a Particulate Standard—The instrumental counter can be calibrated to compensate for the difference in shape of particles once the shape is defined. The National Fluid Power Association recognized the problems and established an acceptance criterion (AC) fine test dust standard for particles normally encountered in hydraulic fluids. The instrument calibrated with this standard correlates extremely well with the data gathered by the microscopic method (10).

It is unlikely that the particulate matter in pharmaceutical preparations is in spherical form; therefore, establishment of a standard with well-characterized and defined particles normally encountered in parenterals is highly desirable. The pharmaceutical industry may not have recognized this need. Pollen (spherical) was used in two of four collaborative studies conducted by the Pharmaceutical Manufacturers Association to simulate particulate matter in injectables.

An interim report on physical attributes of parenteral preparations by two Australian committees (11) stated that a quantitative method for particle-size determination should be based on the counter[1] used in this study. They considered that a method based on membrane filtration, such as the USP method, would be inappropriate in view of the difficulty in visualizing particles of less than 20 μm in diameter. Therefore, it would be appropriate to use the instrument and to supplement the data with the USP method to investigate particulate matter in injectable products.

Among the various instrumental particle-size analyzers, many investigators have chosen the instrument based on the light blockage principle since it operates independent of the presence of electrolyte and the color, shape, or composition of particles have a minimum effect on size measurement. Light-scattering and electrolyte instruments would be influenced greatly by these factors.

Precision of Instrumental and USP Methods—The data on the four simulated bulk product samples were used to estimate the within- and between-day variances for both methods. The within-day variance of the instrumental method has been divided by 5 to correct for the larger sample volume used in the USP method (the USP method used 5 ml; the instrumental used 1 ml of sample). The resultant variance is equivalent to averaging five 1-ml sample counts from the instrument.

Day-to-day differences (Table II) were statistically significant for Products I, III, and IV; however, these differences appeared to be random. The day-to-day differences were small and sometimes nonexistent for Product II.

The total variance (sum of between and within variances) for the instrument was lower than for the USP method for all four products in the 10–25- and ≥10-μm ranges and for three of the four products in the 25–50- and ≥25-μm ranges. Thus, overall the instrument was more precise than the USP method.

The latex sphere calibration suspensions run consecutively with the four product samples were used to determine the absolute precision of the instrument. The variance estimates (Table III) indicate that most variation is between samples in one container within days. The overall variation (expressed as a relative standard deviation, *RSD*) varied from 3.1 to 7.8%, depending upon the particle-size range. The average for the 50–100-μm size quoted by the manufacturer on the latex sphere calibration suspension (860/ml) differed slightly from the average count

Table II—Estimated Variance Components for the Instrumental and the USP Methods

Range of Particulate Matter, μm	Product		Variance, ln[(counts/ml + 0.5)²] Instrumental	USP
≥10	I	Between day	0.031	0.098
		Within day	0.038	0.048
		Total	0.068	0.146
	II	Between day	0.002	0.000
		Within day	0.019	0.128
		Total	0.021	0.128
	III	Between day	0.100	0.056
		Within day	0.037	0.173
		Total	0.137	0.229
	IV	Between day	0.019	0.103
		Within day	0.013	0.094
		Total	0.032	0.197
≥25	I	Between day	0.056	0.045
		Within day	0.127	0.109
		Total	0.183	0.154
	II	Between day	0.000	0.088
		Within day	0.102	0.096
		Total	0.102	0.185
	III	Between day	0.106	0.000
		Within day	0.147	0.146
		Total	0.253	0.146
	IV	Between day	0.050	0.188
		Within day	0.116	0.122
		Total	0.166	0.310
10–25	I	Between day	0.044	0.108
		Within day	0.050	0.059
		Total	0.094	0.167
	II	Between day	0.004	0.000
		Within day	0.019	0.171
		Total	0.023	0.171
	III	Between day	0.075	0.075
		Within day	0.043	0.203
		Total	0.117	0.283
	IV	Between day	0.016	0.114
		Within day	0.014	0.118
		Total	0.031	0.232
25–50	I	Between day	0.059	0.069
		Within day	0.119	0.135
		Total	0.178	0.204
	II	Between day	0.000	0.131
		Within day	0.106	0.116
		Total	0.106	0.247
	III	Between day	0.073	0.006
		Within day	0.134	0.138
		Total	0.208	0.144
	IV	Between day	0.044	0.305
		Within day	0.127	0.164
		Total	0.171	0.469

obtained (744/ml).

Small-Volume Parenteral Products—Samples from over 100 small-volume parenteral products on the market were examined by both the USP and the instrumental methods. For the USP method, four containers/lot were tested and the total content of each container was filtered through a membrane filter. The results were expressed per milliliter of solution tested. For the instrumental method, 10 containers/lot were examined. The vials were sampled by taking as many 1-ml samples as possible up to a maximum of 10/vial, and the results were expressed on a per milliliter basis.

In general, the variation in particle count between the containers within a given lot was extremely large. The results of the USP and instrumental counts indicated a similar trend. The variation in these products was from

Table III—Variance Components of the Instrumental Method by Latex Sphere Samples

Particle-Size Range, μm	Arithmetic Average Count	Estimated Variance, ln[(counts/ml)²] Between Days	Within Days	Total	*RSD*, %
10–25	698	0.0	0.044	0.044	3.2
25–50	44.9	0.008	0.079	0.086	7.8
50–100	1.20	0	0.574	0.574	294
≥10	744	0	0.042	0.042	3.1
≥25	46.2	0.007	0.077	0.084	7.6

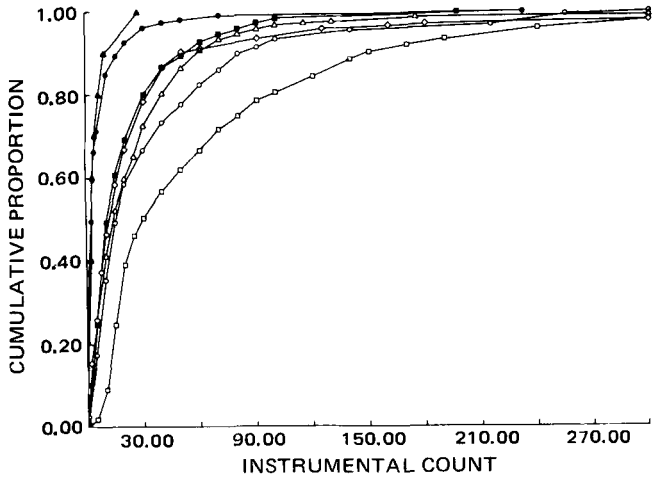

Figure 5—*Cumulative relative frequency distribution plots of the instrumental counts by product type for the ≥10-μm particle range. Key: △, aqueous solution, vials; ●, aqueous solution, ampuls; ▲, aqueous solution, syringes; ○, aqueous solutions; □, freeze-dried products; ■, oil solutions; and ◇, sterile powders.*

two to 10 times larger than the variation found in the four simulated bulk product samples tested earlier. This large variation would make a correlation study between the instrumental and the USP methods based on actual product samples extremely difficult.

The balance of the statistical analysis was conducted using the instrumental data, since the USP test requires the entire contents of each container, resulting in the complete confounding of measurement as well as container-to-container variations and in a high frequency of "too numerous to count" results that made statistical treatment of these data impossible.

Summarization of the instrumental data by product type, *i.e.*, aqueous solutions, oil, *etc.*, is given in Table IV. For the same raw data, cumulative particle frequency distribution curves (by product type) were constructed (Figs. 5 and 6). The difference between the arithmetic mean and the median (50th percentile) demonstrates the skewness in these raw count distributions.

Effects of Varying Acceptance Criteria—The effects of various acceptance criteria were demonstrated by computing lot rejection rates for the product samples for various acceptance criteria. The accept/reject decisions were based on the following statistical decision rule: accept a lot whose estimated proportion of container average particle counts exceeding the maximum allowable particulate count (MAPC) was greater than the unacceptable quality level (UQL). Since the distribution of counts was approximately log-normal, the calculations required to apply this rule were performed on the number formed by the natural log of the sum of the observed count plus 0.5.

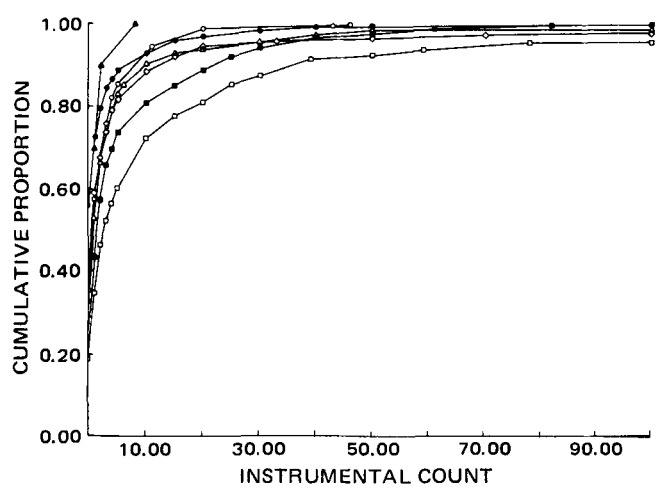

Figure 6—*Cumulative relative frequency distribution plots of the instrumental counts by product type for the ≥25-μm particle range. Key: same as Fig. 5.*

Table IV—Particle Counts in Small-Volume Parenterals by Instrumental Method

Product Type	Level	Particle-Size Range, μm					
		10–25	25–50	50–100	≥100	≥10	≥25
Aqueous solution: vial (n = 990)	Minimum	0	0	0	0	0	0
	Maximum	161	430	241	17	796	635
	Average	19.9	5.0	2.9	0.3	28.1	8.2
	50th percentile	11	1	0	0	15	1
	90th percentile	52	6	4	0	59	10
	95th percentile	66	13	9	1	84	26
	99th percentile	99	70	71	6	223	174
Aqueous solution: ampul (n = 610)	Minimum	0	0	0	0	0	0
	Maximum	144	110	55	13	232	168
	Average	4.2	1.5	1.1	0.3	7.0	2.8
	50th percentile	2	0	0	0	3	0
	90th percentile	10	3	3	1	16	7
	95th percentile	15	6	5	2	26	14
	99th percentile	40	20	18	6	68	40
Aqueous solution: syringe (n = 10)	Minimum	0	0	0	0	0	0
	Maximum	19	6	2	0	27	8
	Average	4.3	0.9	0.6	0	5.8	1.5
	50th percentile	2	0	0	0	3	1
	90th percentile	9	1	2	0	9	2
	95th percentile	19	6	2	0	27	8
	99th percentile	19	6	2	0	27	8
Oil solution (n = 630)	Minimum	0	0	0	0	0	0
	Maximum	176	36	69	28	197	105
	Average	13.3	1.9	3.6	1.5	20.3	7.0
	50th percentile	6	1	0	0	11	2
	90th percentile	30	4	12	5	51	22
	95th percentile	55	7	19	8	72	34
	99th percentile	110	18	38	22	130	63
Sterile powder (n = 719)	Minimum	0	0	0	0	0	0
	Maximum	1067	403	362	12	1306	727
	Average	28.8	6.6	3.8	0.2	39.4	10.6
	50th percentile	9	1	0	0	12	1
	90th percentile	41	9	4	0	49	13
	95th percentile	86	18	8	1	112	23
	99th percentile	403	140	99	6	1002	233
Sterile freeze-dried product (n = 350)	Minimum	2	0	0	0	2	0
	Maximum	362	177	148	13	589	299
	Average	46.9	10.2	5.9	0.3	63.3	16.4
	50th percentile	23	2	1	0	30	3
	90th percentile	107	25	10	1	149	37
	95th percentile	139	51	29	2	226	78
	99th percentile	288	129	108	5	415	227

The proportion of a given lot exceeding the limit was estimated in the following way:

1. The within- and between-container variances (σ_w^2 and σ_b^2, respectively) are estimated by analysis of variance.
2. The variance of the container average ($\sigma_{\bar{x}}^2$) is given by:

$$\sigma_{\bar{x}}^2 = \sigma_b^2 + \frac{\sigma_w^2}{NS} \qquad \text{(Eq. 1)}$$

where NS is the number of samples per container examined. The value of NS must be greater than 1 or separate estimates of σ_w^2 and σ_b^2 are not obtainable.

3. The proportion of the lot above the MAPC is the area under the standard normal curve to the right of z, where:

$$z = \frac{\text{MAPC} - \bar{\bar{x}}}{\sigma_{\bar{\bar{x}}}} \qquad \text{(Eq. 2)}$$

and $\bar{\bar{x}}$ is the average particulate count over all containers and samples in the lot.

This accept/reject procedure was applied to the product sample data for nine acceptance criteria consisting of all combinations of three UQL's and three MAPC's. The UQL's were arbitrarily set at 5, 10, and 25%. The first MAPC was set equal to the USP limit for large-volume parenterals, and the remaining two were equated to the 95th and 99th percentiles of the cumulative relative particle count frequency distribution for freeze-dried products (Table IV and Figs. 5 and 6). The cumulative relative frequency plotted in Figs. 5 and 6 is the proportion of the counts in a product group less than or equal to a given count. For example, 0.5 (or 50%) of the particle counts in the ≥10-μm range (Fig. 5) for sterile powder are less than or equal to 30.

The number of lots rejected by each criterion was tabulated and converted to percentages. These percentages are given in Tables V and VI

Table V—Percent of Lots Tested that Fail Acceptance Criteria for ≥10-μm Particle Range

Product Type	UQL, %	Maximum Allowable Particle Count[a]		
		LVP	A_1	A_2
Aqueous solution	5	39	8	4
	10	29	4	4
	25	17	2	2
Freeze-dried product	5	55	23	13
	10	48	10	10
	25	32	7	3
Oil solution	5	47	7	7
	10	33	0	0
	25	27	0	0
Average	5	45	12	13
	10	36	5	5
	25	24	3	2

[a] LVP = NMT 50 ≥10-μm particles, A_1 = NMT 200 ≥10-μm particles, and A_2 = NMT 420 ≥10-μm particles.

Table VI—Percent of Lots Tested that Fail Acceptance Criteria for ≥25-μm Particle Range

Product Type	UQL, %	Maximum Allowable Particle Count[a]		
		LVP	B_1	B_2
Aqueous solution	5	46	6	2
	10	44	6	2
	25	31	4	0
Freeze-dried product	5	65	19	3
	10	52	19	3
	25	36	7	3
Oil solution	5	100	7	0
	10	87	0	0
	25	53	0	0
Average	5	60	10	2
	10	53	9	2
	25	36	4	1

[a] LVP = NMT 5 ≥25-μm particles, B_1 = NMT 50 ≥25-μm particles, and B_2 = NMT 230 ≥25-μm particles.

Table VII—Percent of Lots Tested that Fail Acceptance Criteria for ≥10- and ≥25-μm Particle Ranges Simultaneously

Product Type	UQL, %	Maximum Allowable Particle Count[a] LVP	C_1	C_2
Aqueous solution	5	62	8	4
	10	58	6	4
	25	37	4	2
Freeze-dried product	5	71	29	13
	10	61	23	10
	25	42	6	3
Oil solution	5	100	13	7
	10	93	0	0
	25	67	0	0
Average	5	70	15	7
	10	64	10	7
	25	43	4	2

[a] LVP = NMT 50 ≥10-μm and NMT 5 ≥25-μm particles, C_1 = NMR 200 ≥10-μm and NMT 50 ≥25-μm particles, and C_2 = NMT 420 ≥10-μm and NMT 230 ≥25-μm particles.

for the ≥10- and ≥25-μm ranges, respectively. Table VII presents the overall rejection rate when both particulate ranges are considered simultaneously. The overall reject rates for product samples at or beyond their expiration date are not significantly different from those reported in Table VII. Thus, the direct application of the USP large-volume parenteral limits to the present data resulted in an overall rejection rate of 43–70%, depending upon the UQL. If the present data are indeed representative of the current industrial technology, adoption of the large-volume parenteral limits for small-volume parenterals would cause extreme difficulty.

Guidelines in Establishing Small-Volume Parenterals—The medical consequences of subvisual-size particulate matter in parenteral formulations are believed to be dependent on the total number and nature of particles that a patient receives from injectables. The standard criteria for particulate matter in a small-volume parenteral could be established based on the concept of the maximum injectable dose.

The USP requirement for particulate matter in large-volume parenterals allows up to 50 and 5 particles for the ≥10- and ≥25-μm size ranges, respectively. Therefore, a patient could receive up to 5000 particles ≥10 μm and 500 particles ≥25 μm from a dose of a 100-ml large-volume parenteral (the minimum size for large-volume parenterals). Infusion from 1 liter of parenteral solution could subject a patient with as many as 50,000 and 5000 particles in the respective size ranges. Therefore, any proposal limiting the particulate matter in small-volume parenteral products could be established based on the concept of the maximum injectable dose and on the statistical acceptance criteria.

This paper represents only the beginning of an evaluation of the quantitative aspects of particulate level methodology. More quantitative data together with the investigation of large numbers of lots and wide varieties of products are needed prior to the establishment of particulate limits in small-volume parenterals. In view of the inevitability that particles of various sizes will be generated by manipulations necessary prior to injection, *e.g.*, breaking a glass ampul and piercing a rubber septum, an in-line final filter is recommended as an efficient means of eliminating particulate introduction into a patient.

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Chemical Constituents of Gentianaceae XXIII: Tetraoxygenated and Pentaoxygenated Xanthones and Xanthone *O*-Glucosides of *Swertia angustifolia* Buch.-Ham.

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Abstract □ The whole plant extract of *Swertia angustifolia* Buch.-Ham., collected at different stages of growth, contained 14 tetraoxygenated and five pentaoxygenated xanthones and xanthone 1-*O*-glucosides. Of the eight xanthone 1-*O*-glucosides isolated, five were previously unreported in nature. The xanthones are broadly based on 1,3,5,8- and 1,3,7,8-oxygenated systems, with an added oxygen function at C-4 in some compounds, and represent a number of methoxylated patterns. The content and relative abundance of the free xanthones and their 1-*O*-glucosides changed with plant growth. These results are the first demonstration of the variation in chemical characters in the different parts of a *Swertia* species during its ontogeny. The biological significance of these results is appraised.

Keyphrases □ Xanthones and *O*-glucosides—isolated and identified in *Swertia angustifolia*, whole plant extract, various growth stages compared □ *Swertia angustifolia*—whole plant extract, various xanthones and *O*-glucosides isolated and identified, various growth stages compared

Swertia angustifolia (var. *angustifolia*) Buch.-Ham., native to the subtropical Himalayas from the Chenub to Bhutan, 304.8–1828.8 m (1000–6000 ft), is a small flowering species. It is used as a substitute for the Indian pharmacopeial drug *S. chirata* Buch.-Ham. Extracts of this plant are used as a bitter tonic, as a febrifuge, in epilepsy, and