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Comparison of Two Methods for Obtaining Size Distribution Characteristics of Particulate Matter in Large-Volume Parenterals

JAMES BLANCHARD ˣ, JOHN A. SCHWARTZ, DALE M. BYRNE *, and DAVID B. MARX ‡

Received October 4, 1976, from the *Department of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, AZ 85721.* Accepted for publication June 21, 1977. *Present address: Optical Sciences Center, University of Arizona, Tucson, AZ 85721. ‡Present address: College of Agriculture, University of Arizona, Tucson, AZ 85721.

Abstract □ The size distributions of the particulate matter present in six types of large-volume parenteral solutions, as determined by an automatic particle counter and a microscopic counting technique, were compared by plotting log $N_{>D}$ *versus* log D. The resulting data were analyzed individually and also as averages. The data showed a linear relationship between log $N_{>D}$ and log D over the 1–100-μm particle-size range, indicating that both methods determine a similar particle-size distribution. The data also indicated that the particle-size distributions were largely independent of the type of solution and obeyed a power law of the form $N_{>D} = N_{>1}D^K$. These observations suggest that the major source of contamination is air-borne dust particles, which fall into a solution randomly, and that it may be possible to monitor the smaller, more abundant particles with the automatic particle counter to obtain a rapid estimate of parenteral cleanliness. The automatic particle counter thus appears to be a viable alternative to the microscopic counting technique for assessing the particulate matter content of parenterals.

Keyphrases □ Size distribution—particulate matter in six large-volume parenteral solutions, automatic particle counter and microscopic techniques compared □ Distribution, size—particulate matter in six large-volume parenteral solutions, automatic particle counter and microscopic techniques compared □ Particles—size distribution in six large-volume parenteral solutions, automatic particle counter and microscopic techniques compared □ Parenterals, large volume—six types, size distribution of particulate matter, automatic particle counter and microscopic techniques compared □ Dosage forms—large-volume parenterals, six types, size distribution of particulate matter, automatic particle counter and microscopic techniques compared

Particulate matter has been defined as "extraneous, mobile, undissolved substances, other than gas bubbles, unintentionally present in parenteral solutions" (1). The problem of particulate matter has plagued the preparers of parenterals since their introduction. Although the clinical significance of particulate matter is still somewhat controversial, it is generally accepted that the safest approach is to minimize particulate matter as much as possible (2–4).

Standards set by the USP–NF (1), based on a microscopic counting procedure, limit the allowable levels of particulate contamination. While this method is the accepted standard, it suffers from several shortcomings since it is subjective, tedious, and time consuming and requires a considerable amount of practice before the operator becomes proficient. In addition, the method is destructive and, therefore, not ideally suited for the in-line monitoring of production batches of parenterals. It is highly desirable to find an alternative method that will overcome these limitations.

In a previous study (5), the ability of several methods to monitor the levels of particulate matter in parenterals was compared. The automatic particle counter warranted further investigation since it offered some advantages over the other methods tested. This instrument was first mentioned by Draftz and Graf (6) who described its characteristics. One apparent limitation of this instrument is its inability to count accurately small numbers of particles since the minimum detectable concentration is only 1 particle/ml. This limitation could be a serious drawback when monitoring particles larger than approximately 5 μm in diameter since sufficiently high counts to obtain statistically reliable data are not normally found in the relatively clean solutions available commercially.

This limitation does not necessarily preclude the use of the automatic particle counter in monitoring the particulate matter content of these solutions provided that the number of larger, less abundant particles (upon which the present compendial standard is based) can be determined from the number of smaller, more abundant particles. The major goals of this study were to determine if such a relationship exists and, if so, to characterize its nature.

EXPERIMENTAL

Large-volume parenteral solutions[1] (1000 ml) were inspected by two methods: an instrumental technique using an automatic particle counter[2]

[1] McGaw Laboratories, Glendale, CA 91201.
[2] Prototron model ILI 1000, Spectrex Corp., Redwood City, CA 94063.

Table I—Comparison of the Particle-Size Distribution Characteristics of Large-Volume Parenteral Solutions by Two Methods

Type of Solution	Method of Measurement[a]	Average Number of Particles per Milliliter[b] >1 μm	>10 μm	>25 μm	Average Slope (K) of Log–Log Plot ± SE	Average Correlation Coefficient between Log $N_{>D}$ and Log D
Dextrose, 5% in half-strength normal saline[c]	I	255.7	0.100	0.004	−3.4070 ± 0.2052	−0.9906
	M	76.6	0.473	0.062	−2.2094 ± 0.1327	−0.9800
Normal saline[d]	I	559.1	0.205	0.009	−3.4361 ± 0.4385	−0.9900
	M	306.7	0.967	0.098	−2.5012 ± 0.2512	−0.9906
Dextrose, 5% in multiple-electrolyte solution[e]	I	425.8	2.826	0.384	−2.1781 ± 0.2843	−0.9711
	M	148.2	1.386	0.216	−2.0291 ± 0.1358	−0.9909
Dextrose, 5% in normal saline[f]	I	1414.6	2.842	0.240	−2.6970 ± 0.4357	−0.9819
	M	252.7	0.966	0.105	−2.4177 ± 0.1787	−0.9908
Dextrose, 5% in water[g]	I	1284.1	6.784	0.842	−2.2771 ± 0.1500	−0.9920
	M	12.3	0.174	0.032	−1.8490 ± 0.1769	−0.9800
Dextrose, 5% in lactated Ringer's solution[h]	I	2084.8	2.409	0.163	−2.9372 ± 0.1672	−0.9881
	M	228.2	1.302	0.167	−2.2438 ± 0.2627	−0.9862

[a] I = instrumental; M = microscopic counting. [b] Average of six bottles. [c] Lot A5D324B. [d] Lot A5J450A. [e] Dextrose, 5% in Isolyte M, Lot A5J223C. [f] Lot A5J512B. [g] Lot A5H142B. [h] Lot A5K015C.

and a membrane filtration and microscopic technique. Six types of solutions were chosen on the basis of their extensive clinical use (Table I). Prior to examination, each container was assigned a code number; labels were removed by soaking to eliminate investigator bias. Before each container was examined by either method, it was inverted 20 times to resuspend any particulate matter in accordance with USP–NF recommendations (1).

Instrumental Method—The automatic particle counter employs a revolving laser beam to measure automatically the number of particles larger than a selected threshold setting using the principle of light scattering. This instrument is capable of detecting particles as small as 1 μm in diameter. Solutions were examined using the particle counter in the manner previously described (5). The number of particles per milliliter exceeding the following diameters was determined: 1.000, 1.259, 1.585, 1.995, 2.512, 3.162, 3.981, 5.012, and 6.310 μm. These diameters were chosen to facilitate data analysis since their logarithms are equally spaced.

Starting at 1 μm, particle counts were recorded at successively increasing threshold settings until a given setting produced 10 readings whose average was less than 10 particles/ml. This value was chosen to limit the instrumental error resulting from the fact that the automatic particle counter displays the truncated, rather than the rounded, version of the number of particles counted (5).

Membrane Filtration and Microscopic Method—All cleaning, collecting, and counting procedures were performed in a laminar flow hood[3] using a modification of a reported procedure (7). Blank analyses of membrane filters were run periodically to determine the efficiency of the cleaning procedure. The blanks were negligible in relation to the total particles counted in any sample tested. This method was used to count particles in the following size ranges: 10–25, 25–50, 50–100, and greater than 100 μm. To compare these results with those obtained using the instrumental method, the particle counts per milliliter exceeding the following diameters were calculated: 10, 25, 50, and 100 μm.

The data were analyzed using a general linear model employing a weighted least-squares regression. The differences among the intercepts for solution types, methods, and bottles were examined statistically. Differences among slopes were examined similarly after adjusting for intercept differences. The results are summarized in the form of an analysis of variance (ANOVA) table (Table II).

RESULTS AND DISCUSSION

Cadle (8) noted that particulate materials present in the atmosphere exhibit a particle-size distribution that obeys a power law of the form:

$$N_{>D} = N_{>1}D^{K} \qquad \text{(Eq. 1)}$$

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 1 μm, D is the particle diameter in micrometers, and K is a constant. Equation 1 can be expressed in the following logarithmic form:

$$\log N_{>D} = K \log D + \log N_{>1} \qquad \text{(Eq. 2)}$$

which is useful for expressing the particle-size distributions in parenterals in the form of a log–log plot (9). When expressed in this manner, K is the slope and $\log N_{>1}$ is the y-intercept of a plot of $\log N_{>D}$ *versus* $\log D$.

Linearity of Log–Log Plots—The data shown in Fig. 1 indicate that the particle-size distributions obtained in both the <10-μm region (using the automatic particle counter) and the >10-μm region (using the microscope) appear to be linear when plotted on a log–log scale. A weighted least-squares program executed on a digital computer[4] was used to fit the automatic particle counter data. The weighting factor was the reciprocal of the variance (10) since each data point represented the average of 10 readings.

This weighting procedure was used because the variances of the 10 readings recorded at each threshold setting were not equal since the numbers of particles exceeding the given threshold setting were not uniformly distributed in the volume of fluid examined. This phenomenon has been referred to as "schooling," analogous to the schooling of fish. Data obtained using the microscopic counting technique were fitted using an unweighted least-squares program because no precise statistical

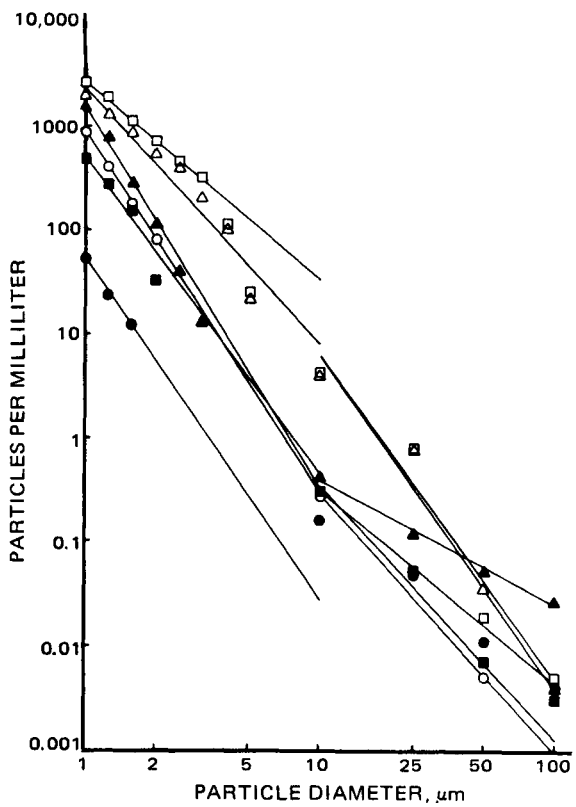

Figure 1—*Particle-size distributions for individual samples of three types of large-volume parenteral solutions. The two samples denoted by the open and closed symbols represent extremes of the slope* (K) *within a given solution type. Key:* ○ *and* ●, *dextrose, 5% in half-strength normal saline;* □ *and* ■, *dextrose, 5% in normal saline; and* △ *and* ▲, *dextrose, 5% in lactated Ringer's solution.*

[3] Model B-D 048, Envirco, Albuquerque, NM 87107.

[4] CDC 6400.

Table II—ANOVA to Test the Effects of Bottles, Methods, and Solution Types on the Slopes and Intercepts of the Log–Log Plots

Source of Variation[a]	*df*	*SS*	*MS*	*F*
S_α	5	15.026	3.005	4.03[b]
B/S_α	27	20.126	0.745	27.90[b]
M_α	1	7.600	7.600	13.35[b]
MS_α	5	13.032	2.606	4.58[b]
BM/S_α	27	15.364	0.569	21.30[b]
S_β	5	0.962	0.192	1.70
B/S_β	27	3.056	0.113	4.24[b]
M_β	1	0.077	0.077	3.50
MS_β	5	0.053	0.011	0.48
BM/S_β	27	0.596	0.022	0.83
Residual	191	5.103	0.027	—

[a] α = intercept, β = slope, S = solution type, B = bottle, and M = method. [b] Significant at the 0.05 level.

weighting factor was calculated since each filter was only counted once.

The correlation coefficients varied from −0.9561 to −0.9991 for the weighted instrumental data and from −0.9431 to −0.9998 for the unweighted microscopic data. These values justify the use of Eq. 2 to describe the particle-size distributions observed. The linear nature of this relationship is further exemplified in Fig. 1.

Intercepts of Log–Log Plots (log $N_{>1}$)—As previously indicated, the intercept of the log–log plot described by Eq. 2 equals the logarithm of the number of particles per milliliter exceeding 1 μm in diameter. As derived from data obtained using the automatic particle counter, the intercepts imply a variation of 53.20–2853 particles/ml among the individual bottles tested. The statistical analyses demonstrated that the intercepts for data obtained from individual bottles of a given solution type differed significantly ($F_{27,191}$ = 27.90) and also exhibited a significant method by bottle interaction ($F_{27,191}$ = 21.30). This variation in the intercept values (Fig. 1) is merely indicative of the different levels of contamination (>1 μm) in each individual bottle of a given solution type.

The intercepts for each type of solution were then averaged to minimize this sample-to-sample variation. The resulting average values for the intercepts, as determined by the automatic particle counter, imply a range of 255.7–2084.8 particles/ml (Fig. 2). The values indicate that the number of particles exceeding 1 μm based on an average of six samples varies with the type of solution examined. The statistical analyses demonstrated that the intercepts for data pertaining to the six solution types differed significantly ($F_{5,27}$ = 4.03) as determined by both methods. In addition, the differences in the intercepts from method to method were not constant (*i.e.*, varied in magnitude) between solution types ($F_{5,27}$ = 4.58). These differences are not surprising in view of the temporal variations in air quality likely to exist during the filling operation. All solutions appeared relatively clean in relation to the USP–NF standard (1), which implies an intercept of 16,280 particles/ml >1 μm.

Slopes of Log–Log Plots (K)—The slopes of the least-squares-fitted lines of the individual samples, as determined using either instrumental data or microscopic counting data, varied from −1.6616 to −4.8293 and from −1.1595 to −3.7303, respectively. These ranges are consistent with those previously reported (9, 11). These observations, together with Fig. 1, indicate that the value of K in Eqs. 1 and 2 varies from bottle to bottle. This result implies that the particle-size distributions differ among individual bottles and that the log–log plots of these distributions may not be parallel to one another.

The statistical analyses demonstrated that the slopes for data obtained from individual bottles of a given solution type were significantly different ($F_{27,191}$ = 4.24). However, for an individual bottle of a given solution type, the slopes were not significantly different from method to method ($F_{27,191}$ = 0.83). The data presented in Fig. 1 were chosen to illustrate the wide variability between particle-size distributions that is possible and represent extreme cases of the individual samples tested. The range of slopes observed also seems to indicate that the variation in the particle-size distributions determined by the automatic particle counter (in the 1–10-μm range) is greater than that determined microscopically (in the 10–100-μm range).

A possible explanation for the wider particle-size distribution observed using the automatic particle counter may result from the fact that, for the relatively clean solutions utilized, most of the usable instrumental readings (*i.e.*, those with sufficiently high counts to ensure accuracy) fell in the 1–3-μm range; therefore, only about 50% of the 1–10-μm logarithmic

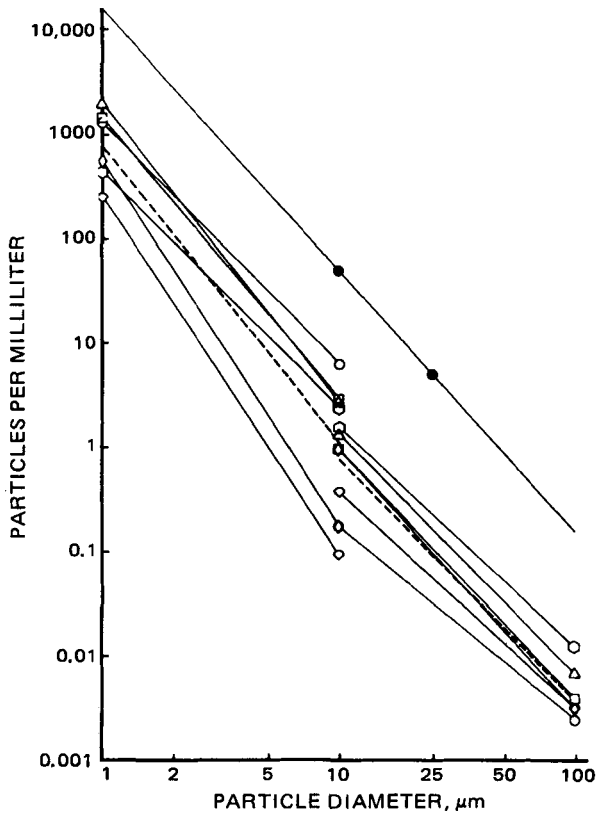

Figure 2—*Average particle-size distributions of six types of large-volume parenteral solutions as determined by the automatic particle counter (1–10-μm region) and the microscope (10–100-μm region). Key:* ▽, *dextrose, 5% in half-strength normal saline;* ◇, *normal saline;* ○, *dextrose, 5% in multiple electrolyte solution;* □, *dextrose, 5% in normal saline;* ○, *dextrose, 5% in water;* △, *dextrose, 5% in lactated Ringer's solution; - - -, overall average; and* ●, *USP–NF standard.*

interval was used. Thus, when determining the least-squares fit of such data, a greater degree of variability was possible.

The automatic particle counter may underestimate the number of particles counted at the larger particle diameters, *i.e.*, where the counts become relatively low and the error due to the truncated display becomes larger. This error could increase the slope of the least-squares fit of the instrumental data. For two out of every three individual solutions examined, the slope of the instrumental data exceeded the slope of the microscopic data.

The automatic particle counter requires a calibration (12) and is, therefore, a relative measuring technique whereas the microscope provides an absolute measurement. An error may arise because the particle counter is calibrated using a monodisperse set of latex spheres that have uniform, well-defined optical properties and are suspended in a halomethane–alcohol mixture. In contrast, the particles in parenterals are primarily quartz in composition (*i.e.*, dust), nonuniform in their optical properties, irregular in shape, and suspended in water. The microscopic counting technique is not subject to this potential source of variation. Possibly a calibration standard consisting of quartz particles suspended in water (not presently available) would permit a better correlation between the two techniques.

In addition to these possible explanations for the variability between the two measuring techniques is the fundamental difference that the automatic particle counter utilizes a nondestructive technique whereas the microscopic counting procedure is destructive. The ramifications of this difference are that the counts obtained using the particle counter are dependent on the combined properties of the countainer, the contaminants, and the solution itself and how they mutually interact. In other words, the laser beam of the instrument must penetrate the glass container and then detect and count particles in the environment of the solution. In the destructive microscopic counting technique, the solution is removed from the bottle and then filtered. Thus, only the particulates to be counted remain on the collecting filter, thereby eliminating any variations in counts due to differences in the properties or position of the container (13).

In contrast to Fig. 1, which shows data for individual samples, Fig. 2 displays averaged data. From Fig. 2, it appears that the log–log plots for each type of solution are essentially parallel to one another in both the 1–10- and 10–100-μm size ranges. In fact, the statistical analyses demonstrated that the slopes for data pertaining to the six solution types were not significantly different ($F_{5,27} = 1.70$) as determined by both methods. In addition, as expected, there was no significant method by solution-type interaction ($F_{5,27} = 0.48$). This parallelism of the log–log plots indicates that each measurement method produces a similar value for K in Eq. 2. This result means that each method determines approximately the same relative number of particles exceeding a given size. However, as indicated by the different intercepts of the log–log plots, the absolute number of particles counted may vary.

Alignment of Log–Log Plots—Austin (14) noted that air-borne dust present in a clean room exhibits a particle-size distribution that obeys a power law identical in form to Eq. 2. Since air-borne dust is believed to be one primary source of parenteral contamination, it has been suggested (15) that a similar power law relationship might be observed in parenterals. If, indeed, there is a single particle-size distribution extending over the 1–100-μm range that can be described by Eqs. 1 and 2, then both counting methods theoretically should produce linear log–log plots with equal slopes and equal intercepts, subject to the limitations previously discussed.

The extreme examples shown in Fig. 1 indicate that there may be a rather poor alignment between the size distributions in the 1–10- and 10–100-μm regions in individual bottles. However, the averaged data in Fig. 2 indicate a much improved agreement between the distributions measured by the two methods. This apparent misalignment can be resolved partially by noting that the two measuring techniques size and count particles differently. The microscopic counting technique sizes particles according to their "longest dimension"; the automatic particle counter sizes particles in terms of their "equivalent spherical diameter." Therefore, it was not surprising that a perfect alignment of the two particle-size distributions was not observed since they were obtained by two methods utilizing different types of size estimation (16).

This problem probably would be magnified when comparing a destructive technique with a nondestructive technique as in this study. The destructive microscopic counting technique requires that the parenteral solution be removed from the container and collected on a filter. During this filtration procedure, the solution was passed through an infusion set, thereby exerting an additional shear force on the particles, which could alter the observed particle-size distribution (17). In contrast, the instrumental measurements were obtained from solutions not subjected to this additional shear force. The effects of different degrees of shear force on the particle-size distributions of parenterals recently were observed (11, 18).

The alignment of the particle-size distributions recorded in the 1–10- and 10–100-μm regions is obviously dependent on the linearity, slopes, and intercepts of the log–log plots. Therefore, all previously mentioned differences existing between the two measuring techniques also could be cited here to account for the imperfect alignment.

As previously noted, the average slopes for the six types of solutions shown in Fig. 2 are essentially parallel to one another, both within each size range examined and between the two size ranges. These results indicate that the relative distribution of particles was largely independent of the solution composition. This observation recently was made by other investigators (17, 19). Thus, it seemed appropriate to average the data over all solutions examined, without regard to solution type.

The dashed line in Fig. 2 shows the overall average particle-size distribution for all bottles tested as determined by the two methods. The alignment, parallelism, and slopes of the overall average data are in better agreement than the data for any of the individual solutions or the six solution types previously averaged. This result would be anticipated solely on the basis that a larger number of readings was averaged; any differences would likely be minimized when averaged over a greater number of readings provided that there was no true difference between the two techniques. If a true difference existed, it would have been magnified by averaging a greater number of readings. The statistical analyses obtained by pooling the data from all bottles tested indicated that the intercepts were significantly different from method to method ($F_{1,27} = 13.35$) whereas the slopes did not differ from method to method ($F_{1,27} = 3.50$).

The solid circles shown in Fig. 2 represent the levels of particulate matter allowed under the recently proposed USP–NF standard (1). The log–log plots representing the averages for the six types of solutions, as determined by either method, were well below the levels represented by the linear extrapolation of this standard. Thus, the solutions tested were relatively clean in relation to this standard.

SUMMARY AND CONCLUSIONS

The results of this study indicate a linear relationship between log $N_{>D}$ and log D over the 1–100-μm size range using averaged data. The data not only substantiate previous work (9) concerning particle-size distributions of parenterals but also extend the range of 1–30 μm over which this relationship had previously been observed using a particle counter[5] operating on the light-blockage principle (20). These previous studies used destructive counting techniques that can reportedly alter particle-size distributions. In this study, both a destructive and a nondestructive technique were utilized to determine the particle-size distributions over the 1–100-μm range. The observed linearity of this relationship over this extended range indicates that the two methods are broadly comparable in their ability to determine the particle-size distribution.

The apparent adherence of the particle-size distribution to a single power law (Eq. 1) indicates that it may be possible, at least with averaged data, to extrapolate particle counts obtained in the 1–10-μm region with the automatic particle counter to particle counts obtained in the 10–100-μm region using the microscopic counting technique. The significance of this observation is that one could monitor the smaller, more abundant particles with the automatic particle counter (or other suitable instrumental techniques) and thereby obtain a rapid estimate of the quality of the solution. Furthermore, since the method is nondestructive, the actual bottle tested can be administered to the patient.

Since the average slopes for the various types of solutions examined were essentially parallel, it can be concluded that the average particle-size distributions of the contaminants were independent of the contents of the solution. This conclusion implies that each solution contained contaminants of similar origin. If, in fact, different solutions do contain similar contaminants, then the use of averaged data appears to be both valid and highly desirable when examining the levels of particulate contamination in parenterals for quality control purposes. Since the particle-size distributions appear to be independent of solution type, the major source of contamination normally found in parenterals probably is air-borne dust particles, which contaminate the parenterals according to a power law similar to one used by Cadle (8) to describe air-borne dust particles.

In spite of the previously listed potential differences between the two methods of measurement, the automatic particle counter and the microscopic counting technique apparently are broadly comparable in their ability to characterize the particle-size distributions of large-volume parenterals. Therefore, the automatic particle counter, when used in the manner described, is a reasonably accurate device for determining particle-size distributions and appears to be a viable alternative to the microscopic counting technique for assessing the cleanliness of large-volume parenterals. More elaborate studies involving samples of various lots of parenterals from different manufacturers are needed to establish unequivocally the utility of the automatic particle counter in assessing parenteral cleanliness.

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Autoradiographic Distribution Studies of 2-^{14}C-Fluorouracil following Oral or Intravenous Administration in Mice Bearing Solid Sarcoma-180

JASHOVAM SHANI, JEFFREY A. BERMAN, and WALTER WOLF ˣ

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Abstract □ 2-^{14}C-Fluorouracil was injected or fed to mice bearing sarcoma-180, a tumor sensitive to fluorouracil, and the fate and localization of the label were followed for 2 hr. The disappearance of the label from the blood and its localization in the tumor and organs of these mice were studied by autoradiography as a model for scintigraphic localization. In tumor-bearing mice, the tumor, kidney, liver, and bladder were visualized 10 min after intravenous injection of 2-^{14}C-fluorouracil; 2 hr after the injection, the activity in the tumor and bone marrow was still noticeable. The localization in the tumor and the liver appeared visually to be rapid, and the retention of the label in the liver of the tumor-bearing animals was noticeably greater than in the control mice by visual observation. There seemed to be no difference in the distribution of 2-^{14}C-fluorouracil when the drug was administered orally to starved or to fed mice. The tumor was visualized equally after oral administration as well as after intravenous injection, except for a somewhat faster clearance from most organs in the intravenous group. There was no difference in uptake and excretion if additional carrier was added, which doubled the administered dose of fluorouracil per mouse. Inasmuch as most of the activity viewed in the sarcoma-180 bearing mice is known to be due to the metabolite floxuridine monophosphate, a correlation between the tissue localization of the drug and its clinical efficacy may lead to a method for predicting the chemotherapeutic regimen in patients. The present work attempted to determine animal data relevant to a nuclear medicine observation.

Keyphrases □ 2-^{14}C-Fluorouracil—tissue distribution in mice after oral or intravenous administration, autoradiographic determination □ Autoradiography—determination, 2-^{14}C-fluorouracil, tissue distribution in mice after oral or intravenous administration □ Distribution, tissue—2-^{14}C-fluorouracil in mice after oral or intravenous administration, autoradiographic determination □ Antineoplastic agents—2-^{14}C-fluorouracil, tissue distribution in mice after oral or intravenous administration, autoradiographic determination

Fluorouracil[1] has been indicated since 1958 for treatment of patients with primary carcinoma of the breast, stomach, or colon with metastases to the liver (1). However, there are different views on its optimal chemotherapeutic regimens, *i.e.*, acute loading *versus* weekly therapy, rapid *versus* slow infusion, oral *versus* intra-arterial administration, and regional infusion *versus* radiological adjunct therapy (2).

BACKGROUND

Due to the inconsistency and variability of the clinical response to fluorouracil, the regimen of its systemic administration is controversial. For the past 12 years, the following regimens have been tested. Oral daily administration proved effective in patients with liver metastases due to the high concentration in the portal system (3–5). In cases of rectal carcinoma, oral administration was replaced by rectal instillation (6). Intravenous weekly administration (without a loading dose) maintained antitumor effectiveness and reduced toxicity in studies with 437 patients (7–9) and in a cumulative study of 548 patients with disseminated cancer (10). Intra-arterial infusion, through a catheter into the external carotid artery, the hepatic artery, or the bronchial artery, exhibited improvement in over 50% of patients (11, 12). Intralymphatic injection was tested for lymphoreticulosarcoma and lymph node metastases (13). Intralumenal infusion into sequestered intestinal lumen prior to surgery (14) and intramuscular and intraperitoneal (15) injections also were evaluated.

In the first comprehensive study of a regimen of choice in cancer patients, Mukherjee *et al.* (15) administered 2-^{14}C-fluorouracil by oral, intravenous, intramuscular, and intraperitoneal routes. They measured the radioactivity in the plasma, respiratory carbon dioxide, and urine and observed that the unchanged drug was detected in the urine following intravenous administration longer than after administration by any other route.

Since the intravenous and oral routes remained the preferred methods for administering fluorouracil, most recent studies compared those two routes. Bateman *et al.* (16) found a clinically useful response rate in 21% of the intravenous group and in 40% of the oral group. Although the response duration for both groups was not significantly different, great variability in peak plasma level and decay was observed after oral administration, while the range of peak levels and plasma decay in the intravenously administered patients was relatively uniform (17). Cohen *et al.* (18) reported that patients receiving intravenous doses showed consistent and rapid plasma clearance, while patients demonstrated widely varying peak plasma concentrations after oral ingestion.

Comparison of therapy regimens after intraperitoneal administration of fluorouracil to mice bearing L-1210 solid lymphocytic leukemia demonstrated essentially no schedule dependency; this finding is consistent with the effectiveness of weekly doses (19). It was suggested that the optimal treatment might be injections of fluorouracil every 2 days

[1] 5-Fluorouracil.