

Examination of Glass Particulate Contamination after Ampoule Breakage

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ABSTRACT

Background: Administering injectable medicines is an invasive procedure with potential risks, including unintentional contamination of the content by glass particles during ampoule preparation by the healthcare team. Injection of medication contaminated with microscopic particles into patients can cause serious adverse effects depending on the route of administration and particle size. This study aimed to evaluate the relationship between nurse gender, work experience, ampoule breaking method, and ampoule volume with the number and size of probable glass particles after breaking ampoules.

Methods: A total of 183 ampoules (2 ml, 5 ml, and 10 ml) were studied. Thirty male and female nurses participated, who were categorized into three groups based on work experience: 1–5 years, 5–10 years, and over 10 years. The size and number of glass particles were examined using a dynamic light scattering (DLS) system. The morphological characteristics of the particles were further studied using inverted microscopy.

Results: On average, 53.49% of the particles in the solution of the broken ampoules were greater than 10 µm in size. Additionally, 17.65% showed a size greater than 25 µm. The particle size ranged from 14.39 µm to 184 µm. The average size of glass particles was 42.65 µm in the 2 ml ampoules, 32.13 µm in the 5 ml ampoules, and 42.72 µm in the 10 ml ampoules.

Conclusion: Based on the findings, the percentage of glass particles entering the ampoule's solution upon breaking is not influenced by individual nurse characteristics. Instead, it depends on the ampoule volume, with smaller volumes associated with a higher proportion of particles larger than 10 µm and 25 µm. While the average particle size tends to decrease as nurses' work experience increases, smaller ampoules generally contain larger particles. However, the methods used by nurses to break the ampoule do not significantly affect particle size.

The authors declare no conflicts of interest.

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Introduction

Pharmaceutical packaging plays a critical role in preserving the therapeutic efficacy of medications throughout their journey from production to patient administration [1–7]. Achieving this requires careful selection of packaging materials, considering various factors such as the medication’s type and dosage form, route of administration, physical and chemical properties of both the medication and the packaging, required protection level, sterilization requirements, material compatibility, patient convenience, and cost-effectiveness [2-3,8-10]. Among available materials, glass remains the most widely used due to its long-standing history in preserving valuable substances. Its unique physicochemical properties make it highly effective in preventing medication degradation, thereby maintaining medicine stability and safety [1-3,8,11-12]. Among the various types of glass packaging, ampoules are frequently employed and are typically manufactured from two main types of glass: Type I (neutral borosilicate) and Type II (soda lime) [13-14].

While glass ampoules are generally considered appropriate for pharmaceutical use, the act of breaking them during medication preparation can introduce significant risks, primarily due to the potential release of small glass particles into the contents [15-34]. During aspiration into a syringe, these particles can contaminate the medication and be subsequently introduced into the patient’s body through various injection routes [18,22,31,35-40]. These insoluble particles have been shown to cause damage to multiple organs, including the lungs, brain, kidneys, liver, and spleen [21]. Intravenous administration of glass-contaminated medications can lead to serious complications, including pulmonary thrombosis, microembolism [41-42], infusion phlebitis, end-organ granuloma formation, and inflammatory reactions [17,25,43-45]. Similarly, intramuscular injection of solutions containing glass particles may result in pain, bleeding, or hematoma formation, acute inflammatory induration, and transient nodule formation [21,45-46].

Moreover, glass particles may carry residual metals used in the manufacturing process, which could contribute further to tissue damage. The harmful effects of these fine particles often manifest after prolonged periods. Animal studies have demonstrated that injection of small glass particles can induce pulmonary silicosis and nodular fibrosis in organs such as the liver, spleen, and small bowel, primarily through foreign body reactions and embolism [32].

Despite the well-recognized significance of glass microparticles [35] and reports on the issue dating back over 77 years [47], this problem has received limited attention from both researchers and the pharmaceutical

industry. Several studies have focused on quantitative aspects, such as the number and size of glass particles generated during ampoule breaking [26,48-49]. Others have explored preventive methods, including specific ampoule opening techniques [31], optimized needle insertion and aspiration procedures [48], the use of devices designed for safer ampoule opening [21], and filtration to minimize particle transfer into syringes. However, the lack of recent controlled human studies evaluating the clinical impact of glass particles—and the predominance of evidence coming from animal research—leaves the clinical relevance of these findings to human health still uncertain [49]. This study aimed to evaluate the relationship between nurse gender, work experience, ampoule breaking method, and ampoule volume with the number and size of probable glass contaminants introduced during ampoule breaking.

Methods

This descriptive observational study investigates the average size and percentage of glass particles unintentionally introduced into ampoule contents during nursing breaks. It examined the relationship between four variables—nurse gender, work experience, ampoule breaking method, and ampoule volume—and the number and size of potential glass contaminants.

The study utilized ampoules with volumes of 2 mL, 5 mL, and 10 mL. Based on the work by Ga Eul Joo et al. (2016) [20] and the sample size formula (provided below), the required number of ampoules was calculated:

$$n = \frac{Z_{1-\frac{\alpha}{2}}^2 \times \sigma^2}{d^2} = \left(\frac{Z_{1-\frac{\alpha}{2}} \times \sigma}{d} \right)^2$$

Accordingly, a total of 183 ampoules was required, comprising 61 ampoules each of 2 mL, 5 mL, and 10 mL volumes.

This study was approved by the Research Ethics Committee of the Faculty of Pharmacy and Pharmaceutical Sciences at Islamic Azad University and registered under the number IR.IAU.PS.REC.1402.636.

All ampoules were manufactured by the same company, with each volume sourced from a single batch to ensure consistency. Additionally, 183 syringes of 10 mL volume were procured from a single batch. (Table 1) presents the specifications of the ampoules used in this research.

Table 1- Specifications of ampoules used in the study

| Name | Volume (ml) | Country of manufacture |
|---------------|-------------|------------------------|
| Ondansetron | 2 | Iran |
| Lidocaine | 5 | Iran |
| Methocarbamol | 10 | Iran |
| Syringe | 10 | Iran |

In this study, 30 nurses participated and were categorized into three groups based on their years of clinical experience: 1–5 years, 5–10 years, and over 10 years. Sampling was conducted by including nurses who were present in various hospital wards on the day of data collection. The sample included an equal number of male and female nurses. Each nurse was instructed to break six glass ampoules using the routine technique they typically apply in daily clinical practice. These included two 2-mL ondansetron ampoules, two 5-mL lidocaine ampoules, and two 10-mL methocarbamol ampoules. Notably, three nurses broke seven ampoules instead of six.

The study focused on analyzing how nurses held the ampoule neck and performed the breaking procedure. This component of the research was informed by the work of Masako Hirano et al. (2019), who investigated upper limb movement patterns during ampoule breaking among nurses. According to their findings, nurses generally use three distinct techniques to hold and break ampoules. In all three methods, the ampoule is securely held with the non-dominant hand to prevent movement, while the neck is broken using the dominant hand. The specific techniques for holding the ampoule neck with the dominant hand are illustrated in (Figure 1) [13].

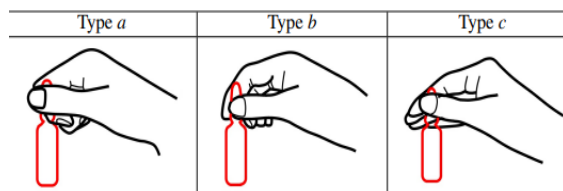


Figure 1- Ampoule-holding types [13]

After breaking the ampoule, the nurse immediately aspirated its contents into a syringe fitted with a needle. Unlike previous studies [19-20,26,31,48,50], we employed a dynamic light scattering (DLS) system (Scatteroscope1, South Korea) to determine the size of glass particles. All prepared samples were analyzed on the same day, within a few hours of collection. The contents of each syringe were transferred directly into the cuvette of the DLS device without removing the needle, to closely replicate clinical conditions—particularly the possibility of glass particles passing through the needle during the actual injection to patients.

The refractive index of water was used as the reference medium. Relevant measurement parameters, including the solvent (water) and the solute (borosilicate glass), were entered into the device before measurement. The DLS system completed each particle size analysis within 60 seconds.

Two particle size thresholds—10 μm and 25 μm —were established in accordance with the specifications outlined in the United States Pharmacopeia (USP). Specifically, USP <788> sets limits for particulate matter in injectable products, aligning with the standards of both the

European and Japanese Pharmacopoeias. This guideline describes two standard methods for particle size analysis: the Light Obscuration Particle Count Test and the Microscopic Particle Count Test.

According to the light obscuration method, for parenteral infusion solutions or injectable solutions with a volume less than 100 mL, the average number of particles present in the units tested must not exceed 6000 particles $\geq 10 \mu\text{m}$ and 600 particles $\geq 25 \mu\text{m}$ per container. Alternatively, according to the Microscopic Particle Count method, the average number of particles must not exceed 3,000 particles $\geq 10 \mu\text{m}$ and 300 particles $\geq 25 \mu\text{m}$ per container [51].

To examine particle morphology, several samples were randomly selected. A few drops of the sample content were dispensed onto a microscope slide without removing the syringe needle. While the slide was still wet, the sample was examined and photographed using an inverted microscope (Jenus NAO.30 WD72, China).

Statistical Analysis

Data were analyzed using SPSS version 27. Descriptive statistics, including mean, standard deviation, frequency percentage, and cumulative frequency percentage, were used to summarize the findings. For inferential statistics, correlation analysis was conducted to examine relationships between variables.

Additionally, independent samples t-tests and one-way analysis of variance (ANOVA) were employed to compare the mean particle size and percentage of glass particles in the prepared syringes based on nurses' work experience, ampoule volume, and ampoule breaking method.

When variables had more than two groups, the Least Significant Difference (LSD) test was applied to determine specific group differences. One-way ANOVA confirmed the presence of significant differences in the mean values across groups. The level of statistical significance was set at $p < 0.05$ and $p < 0.01$.

Results

The descriptive analysis presented in (Table 2) shows an equal gender distribution among participating nurses, with 50% female and 50% male. The nurses had an average work experience of 9.5 years, ranging from 1 to 28 years, with a standard deviation of 7.61 years.

Three types of ampoules were used in the study: Ondansetron (2 mL), Lidocaine (5 mL), and Methocarbamol (10 mL), with an equal number of 31 ampoules per type.

Participating nurses employed three distinct ampoule-breaking methods. Method A was the most common, used in 53% of cases (97 ampoules). Method B accounted for 40.4% (74 ampoules), while Method C was the least frequent, representing 6.6% (12 ampoules).

To examine the presence of glass particles in the ampoule solutions, the percentage of particles exceeding two size thresholds—10 μm and 25 μm —was calculated across 183 tested ampoules. On average, 53.49% of the particles detected in the ampoule solutions were larger than 10 μm , while 17.65% exceeded 25 μm (see (Table 3) for a detailed distribution).

The size distribution of broken glass particles in the ampoule solutions was assessed under two sampling conditions: analyzing 5% of the particles in each solution and analyzing all particles (100%). According to the data presented in (Table 4), when 5% of the particles were

analyzed, particle sizes ranged from 10 to 20 μm in 10 out of 183 cases (5.5%). In 40 cases (21.9%), sizes ranged from 20 to 30 μm ; in 63 cases (34.4%), from 30 to 40 μm ; and in the remaining 70 cases (38.2%), particle sizes ranged from 40 μm to a maximum of 134 μm .

When all particles were analyzed, particle sizes ranged from 10 to 50 μm in 6 cases (3.3%). In 91 cases (49.7%), particle sizes were between 50 and 100 μm ; in 64 cases (35%), between 100 and 150 μm ; in 17 cases (9.3%), between 150 and 200 μm ; and in the remaining 5 cases (2.7%), particle sizes ranged from 200 up to a maximum of 394 μm .

Table 2- Frequency distribution of nurses' demographics and ampoule characteristics (n=183)

| Variable | Variable levels | Frequency | Valid percent | Other statistics |
|--------------------------------|-----------------|-----------|---------------|------------------|
| Nurses' gender | Male | 15 | 50 | |
| | Female | 15 | 50 | |
| | Total | 30 | 100 | |
| Work experience (years) | 0-5 | 10 | 33.33 | Mean: 9.5 |
| | 5-10 | 10 | 33.33 | SD: 7.61 |
| | ≤ 10 | 10 | 33.33 | Min: 1 |
| | Total | 30 | 100 | Max: 28 |
| Ampoule name | Ondansetron | 31 | 33.33 | |
| | Lidocaine | 31 | 33.33 | |
| | Methocarbamol | 31 | 33.33 | |
| | Total | 183 | 100 | |
| Ampoule volume (ml) | 2 | 31 | 33.33 | |
| | 5 | 31 | 33.33 | |
| | 10 | 31 | 33.33 | |
| | Total | 183 | 100 | |
| Method of breaking the ampoule | A | 97 | 53 | Min: C |
| | B | 74 | 40.4 | Max: A |
| | C | 12 | 6.6 | |
| | Total | 183 | 100 | |

Table 3- Frequency distribution of glass particles exceeding 10 μm and 25 μm in ampoule solutions

| Particle state | Percent of glass particles | Frequency | percent | cumulative percent | Other statistics | |
|----------------------|----------------------------|-----------|---------|--------------------|----------------------|--|
| Above 10 micrometers | 0.00-10 | 8 | 4.4 | 4.4 | Mean: 53.49 | |
| | 10.01-20 | 7 | 3.8 | 8.2 | SD: 22.09 | |
| | 20.01-30 | 12 | 6.6 | 14.8 | | |
| | 30.01-40 | 24 | 13.1 | 27.9 | Med: 55.26 | |
| | 40.01-50 | 19 | 10.4 | 38.3 | Mo: 76.88 | |
| | 50.01-60 | 32 | 17.5 | 55.7 | Min % of particles: | |
| | 60.01-70 | 30 | 16.4 | 72.1 | 0.00 | |
| | 70.01-80 | 34 | 18.6 | 90.7 | Max % of particles: | |
| | 80.01-90 | 13 | 7.1 | 97.8 | 99.60 | |
| | 90.01-100 | 4 | 2.2 | | | |
| | Total | 183 | 100 | 100 | | |
| Above 25 micrometers | 0.00-10 | 60 | 32.8 | 32.8 | Mean: 17.65 | |
| | 10.01-20 | 60 | 32.8 | 65.6 | SD: 13.53 Med: 14.13 | |
| | 20.01-30 | 34 | 18.6 | 84.2 | Mo: 9.61 | |
| | 30.01-40 | 14 | 7.7 | 91.8 | Min % of particles: | |
| | 40.01-50 | 11 | 6.0 | 97.8 | 0.03 | |
| | 50.01-60 | 2 | 1.1 | 98.9 | Max % of particles: | |
| | 60.01-70 | 0 | 0 | 98.9 | 71.65 | |
| | 70.01-80 | 2 | 1.1 | | | |
| | | Total | 183 | 100 | 100 | |

Table 4- Distribution of Glass Particle Sizes Based on Analysis of 5% and 100% of Particles in Solutions

| Status | Particle size (micrometers) | Frequency | Percent | Cumulative percent | Other statistics |
|--|-----------------------------|-----------|---------|--------------------|---|
| 5 %glass | 0.00-10 | 0 | 0 | 0 | Mean: 39.16 |
| particles with a size greater than the numbers in the second column | 10.01-20 | 10 | 5.5 | 5.5 | Standard deviation: 16.15 Median: 35.00 Mode: 32.3 Minimum particle size: 14.39 Maximum particle size: 134 |
| | 20.01-30 | 40 | 21.9 | 27.53 | |
| | 30.01-40 | 63 | 34.4 | 61.7 | |
| | 40.01-50 | 37 | 20.2 | 82.0 | |
| | 50.01-60 | 15 | 8.2 | 90.2 | |
| | 60.01-70 | 11 | 6.0 | 96.2 | |
| | 70.01-80 | 4 | 2.2 | 98.4 | |
| | 80.01-90 | 1 | 0.5 | 98.9 | |
| | 90.01-100 | 0 | 0 | 98.9 | |
| | 100.01-140 | 2 | 1.1 | 100 | |
| Total | | 183 | 100 | | |
| 100 %glass | 10.01-50 | 6 | 3.3 | 3.3 | Mean: 107.58 |
| particles with a size smaller than the numbers in the second column | 50.01-60 | 9 | 4.9 | 8.2 | Standard deviation: 47.3 Median: 94.9 Mode: 83.9 Minimum particle size: 18.35 Maximum particle size: 394 |
| | 60.01-70 | 12 | 6.6 | 14.8 | |
| | 70.01-80 | 16 | 8.7 | 23.5 | |
| | 80.01-90 | 37 | 20.2 | 43.7 | |
| | 90.01-100 | 17 | 9.3 | 53.0 | |
| | 100.01-110 | 12 | 6.6 | 59.6 | |
| | 110.01-120 | 19 | 10.4 | 69.9 | |
| | 120.01-130 | 14 | 7.7 | 77.6 | |
| | 130.01-140 | 16 | 8.7 | 86.3 | |
| | 140.01-150 | 3 | 1.6 | 88.0 | |
| | 150.01-200 | 17 | 9.3 | 97.3 | |
| | 200.01-400 | 5 | 2.7 | 100 | |
| | Total | | 183 | 100 | |

Correlation analysis in (Table 5) revealed no statistically significant association between nurse gender and the percentage of glass particles larger than 10 μm or 25 μm in the solution. However, a positive and statistically significant correlation was observed between nurses' work experience and the percentage of particles larger than 25 μm ($p < 0.05$). In other words, as nurses' work experience increased, the percentage of larger particles ($\geq 25 \mu\text{m}$) also increased. A significant negative correlation was found between ampoule volume and the percentage of particles larger than 10 μm and 25 μm , at the 1% significance level ($p < 0.01$), indicating that larger ampoule volumes were associated with lower percentages of particles larger than 10 μm . Analysis indicated that Method A resulted in the lowest particle counts. In contrast, Methods B and C were associated with a gradual increase in particle percentages. Correlation analysis between particle sizes in the 5% and 100% samples and the percentage of particles larger than 10 μm and 25 μm revealed a positive and statistically significant association in both cases. Further analysis using ANOVA, as shown in (Table 6), indicated no statistically significant differences in the percentage of particles larger than 10 μm and 25 μm across the three levels of work experience. This suggests that work experience did not significantly influence the proportion of glass particles in the ampoule solutions. In contrast, the analysis revealed a statistically significant difference at

the 1% level ($p < 0.01$) between ampoule volume and the percentage of particles larger than 10 μm and 25 μm , indicating that ampoule volume had a measurable effect on particle size distribution.

For the ampoule-breaking method, the results showed no significant difference in the percentage of particles larger than 10 μm and 25 μm across the three methods. Since the ANOVA revealed a significant effect of ampoule volume on particle size distribution ($p = 0.001$), as shown in (Table 7), a Least Significant Difference (LSD) test was conducted to identify specific group differences.

The LSD test results, presented in (Table 8), show that the percentage of particles larger than 25 μm was significantly higher in 2 mL ampoules compared to 5 mL ampoules and also higher in 5 mL than in 10 mL ampoules ($p = 0.001$). Similarly, the percentage of particles larger than 10 μm was significantly higher in 2 mL ampoules than in both 5 mL and 10 mL ampoules, with no significant difference between the latter two.

The images below (Figure 2-23) display inverted microscope micrographs of the samples at specified magnification levels, alongside their corresponding particle size measurements. The micrographs show that the diameters of the glass particles fall within the micrometer range. These microscopic observations align closely with the particle size distributions identified through dynamic light scattering (DLS) analysis.

Table 5- Statistical Correlations Between Independent Variables and Dependent Variables

| Independent variables | Dependent variable Percentage of particles above 25 micrometers | | Percentage of particles above 10 micrometers | |
|--------------------------------|--|-------------------|--|-------------------|
| | Significance level | Coefficient value | Significance level | Coefficient value |
| Nurse gender | 0.137 | -0.110 | 0.997 | 0.000 |
| Nurse's work experience | 0.028 | 0.163* | 0.132 | 0.112 |
| Ampoule volume | 0.872 | -0.012 | 0.001 | -0.264** |
| Type of ampoule breakage | 0.049 | 0.146* | 0.040 | 0.152* |
| Particle size in 5% solution | 0.001 | 0.811** | 0.001 | 0.382** |
| Particle size in 100% solution | 0.001 | 0.790** | 0.001 | 0.319** |

Table 6- Analysis of Variance (ANOVA) of Work Experience and Ampoule Volume on the Mean Percentage of Glass Particles (>10 µm and >25 µm) in Solution

| Percent of glass particles | Sig. level | F | SD | Mean | Number of ampoules | Variable levels | Statistical indicator Variable |
|--|------------|--------|--------|--------|--------------------|-----------------|--------------------------------|
| Percentage of particles above 10 micrometers | 0.323 | 1.138 | 21.893 | 50.464 | 61 | 0-5 | work experience |
| | | | 22.285 | 53.525 | 61 | 5-10 | |
| | | | 22.052 | 56.497 | 61 | ≤10 | |
| Percentage of particles above 25 micrometers | 0.082 | 2.534 | 10.767 | 14.678 | 61 | 0-5 | work experience |
| | | | 12.422 | 18.209 | 61 | 5-10 | |
| | | | 16.415 | 20.059 | 61 | ≤10 | |
| Percentage of particles above 10 micrometers | **0.001 | 10.862 | 20.184 | 63.564 | 61 | 2 ml | Ampoule volume |
| | | | 20.638 | 47.410 | 61 | 5 ml | |
| | | | 22.090 | 49.420 | 61 | 10 ml | |
| Percentage of particles above 25 micrometers | **0.001 | 13.485 | 17.714 | 21.282 | 61 | 2 ml | Ampoule volume |
| | | | 8.559 | 10.767 | 61 | 5 ml | |
| | | | 9.774 | 20.893 | 61 | 10 ml | |

Table 7- ANOVA Results for the Percentage of Glass Particles >10 µm and >25 µm Across Different Ampoule Volumes

| Percent of glass particles | Sig. level | F | Mean squares | Degree of freedom | Sum of squares | Status |
|-------------------------------------|------------|--------|--------------|-------------------|----------------|----------------|
| Percentage of particles above 10 µm | 0.001 | 10.862 | 4783.929 | 2 | 9567.859 | Between groups |
| | | | 440.427 | 180 | 79276.826 | Within groups |
| | | | | | 88844.315 | Total |
| Percentage of particles above 25 µm | 0.001 | 13.485 | 2196.158 | 2 | 6.179 | Between groups |
| | | | 160.859 | 180 | 135.22 | Within groups |
| | | | | | 141.401 | Total |

Table 8 - LSD Test Results for Pairwise Comparisons of Particle Percentages >10 µm and >25 µm Across Ampoule

| Glass particles | Significance level | Upper limit | Lower limit | Mean difference | Ampoule volume 2 | Ampoule volume 1 |
|--------------------------------|--------------------|-------------|-------------|-----------------|------------------|------------------|
| Particles above 10 micrometers | 0.001 | 23.7426 | 8.7459 | 16.2443** | 5 | 2 |
| | 0.001 | 21.7334 | 6.3767 | 14.2351** | 10 | |
| | 0.001 | -8.7459 | -23.7426 | -16.2443** | 2 | 5 |
| | 0.598 | 5.4892 | -9.5075 | -2.0092 | 10 | |
| | 0.001 | -6.7367 | -21.7334 | -14.2351** | 2 | 10 |
| | 0.598 | 9.5075 | -5.4892 | 2.0092 | 5 | |

| | | | | | | |
|--------------------------------|-------|---------|----------|------------|----|----|
| Particles above 25 micrometers | 0.001 | 15.0520 | 5.9888 | 10.5204** | 5 | 2 |
| | 0.864 | 4.9265 | -4.1366 | 0.3950 | 10 | |
| | 0.001 | -5.9888 | -15.0520 | -10.5204** | 2 | 5 |
| | 0.001 | -5.5939 | -14.6570 | -10.1255** | 10 | |
| | 0.864 | 4.1366 | -4.9265 | -0.3950 | 2 | 10 |
| | 0.001 | 14.6570 | 5.5939 | 10.1254** | 5 | |

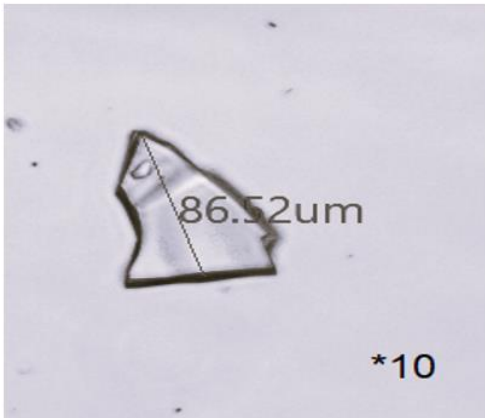


Figure 2- Male nurse – 1 year of experience

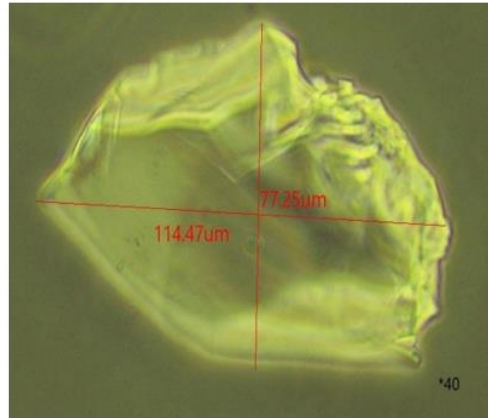


Figure 3- Male nurse – 1 year of experience

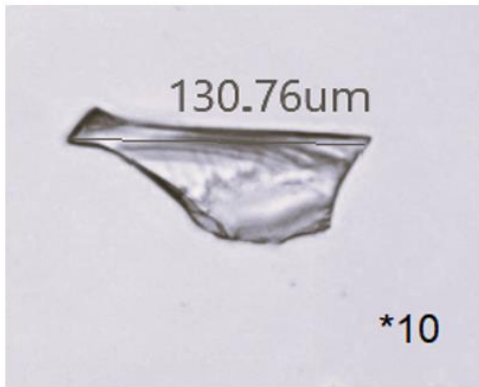


Figure 4- Female nurse – 2 years of experience

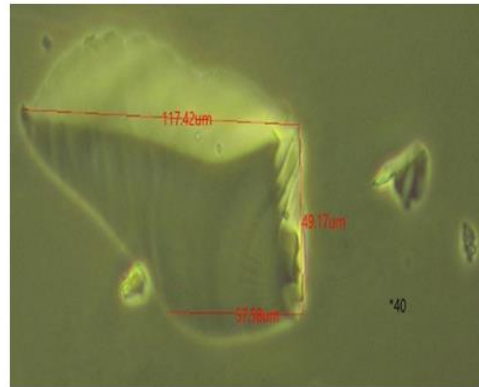


Figure 5- Female nurse – 2 years of experience



Figure 6- Female nurse – 4 years of experience

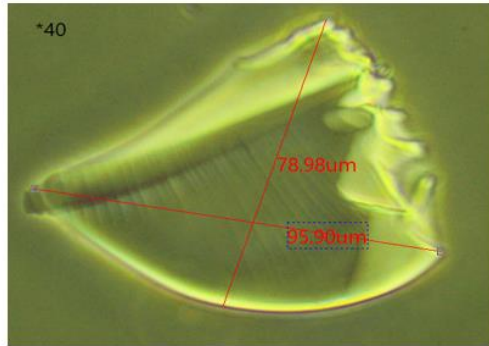


Figure 7- Female nurse – 5 years of experience

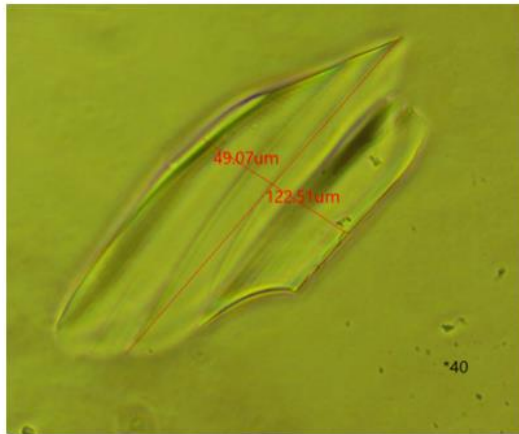


Figure 8- Male nurse – 6 years of experience

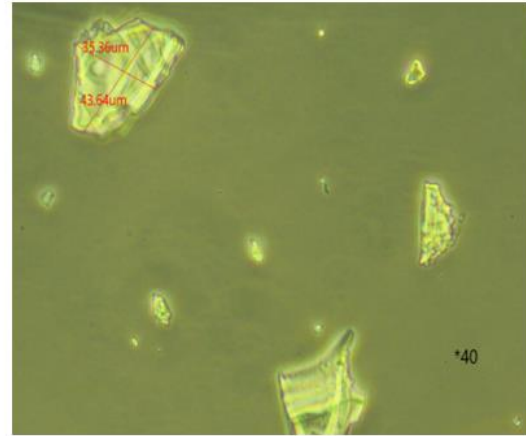


Figure 9- Female nurse – 7 years of experience

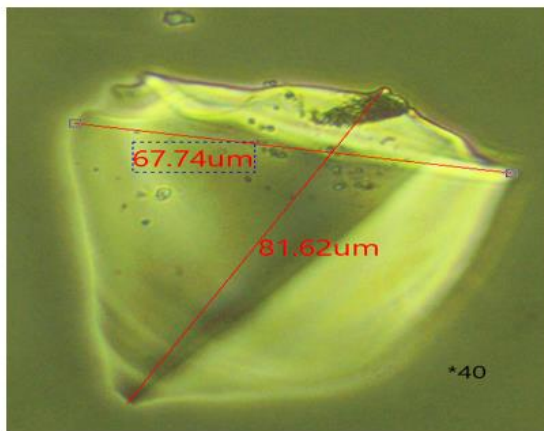


Figure 10- Male nurse – 7 years of experience



Figure 11- Female nurse – 8 years of experience

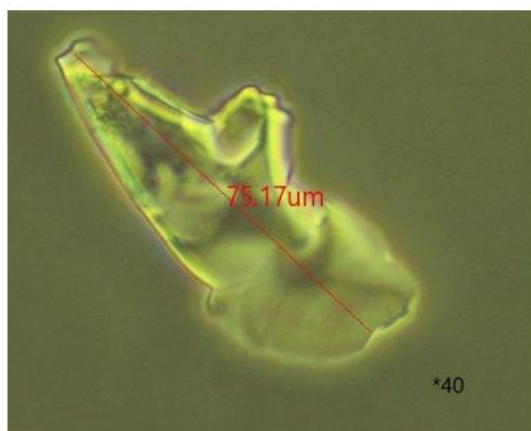


Figure 12- Female nurse – 9 years of experience

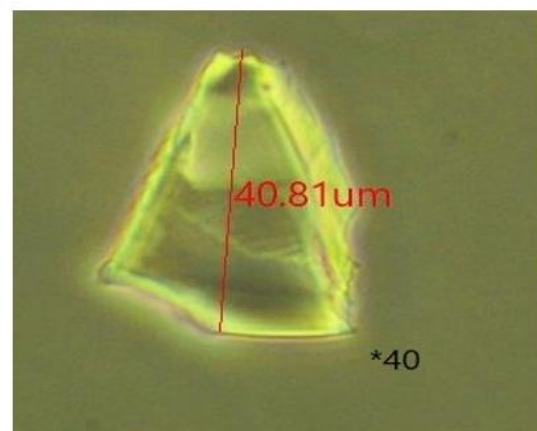


Figure 13- Female nurse – 9 years of experience

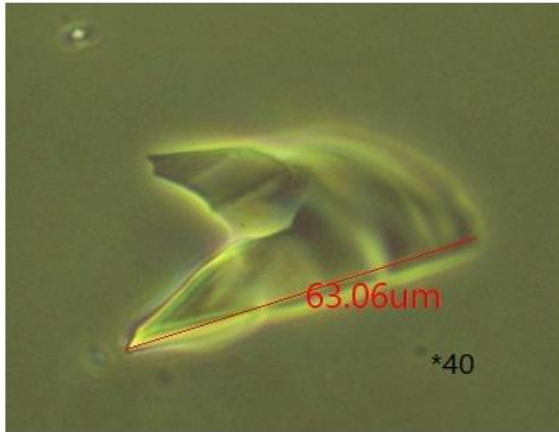


Figure 14- Male nurse – 10 years of experience

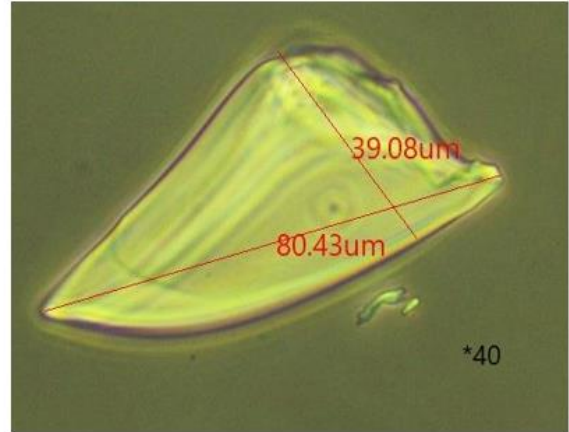


Figure 15- Male nurse – 12 years of experience

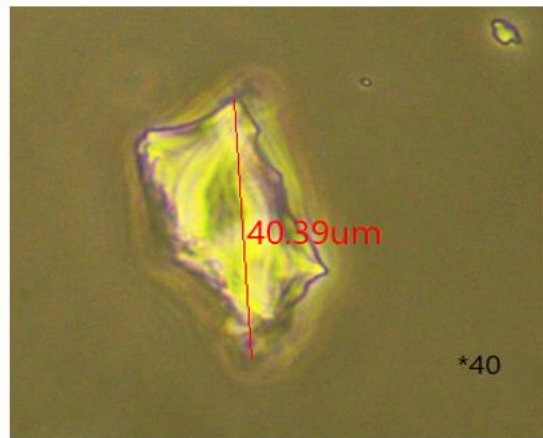


Figure 16- Female nurse – 15 years of experience

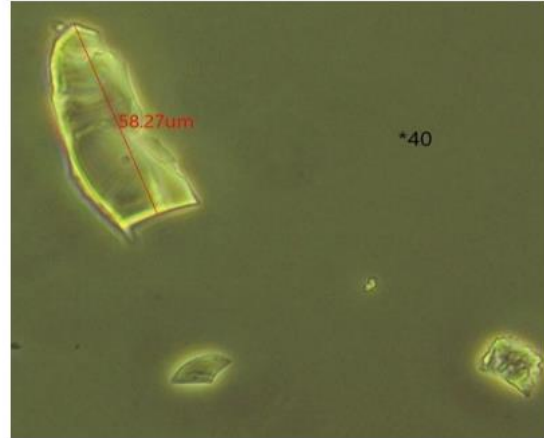


Figure 17- Male nurse – 16 years of experience

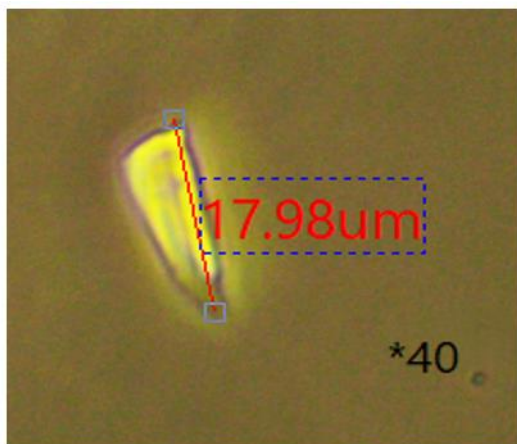


Figure 18- Male nurse – 19 years of experience

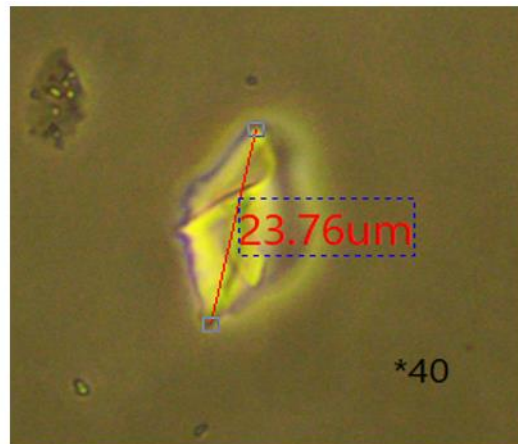


Figure 19- Female nurse – 21 years of experience

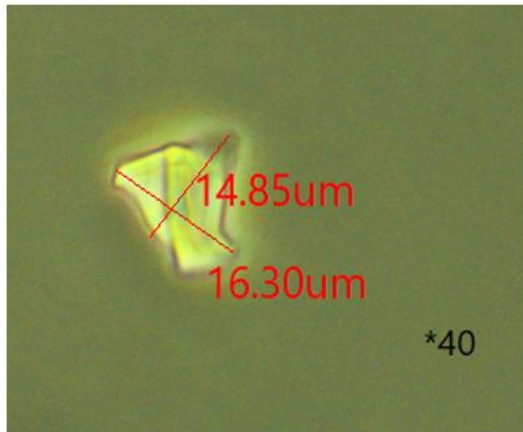


Figure 20- Male nurse – 23 years of experience

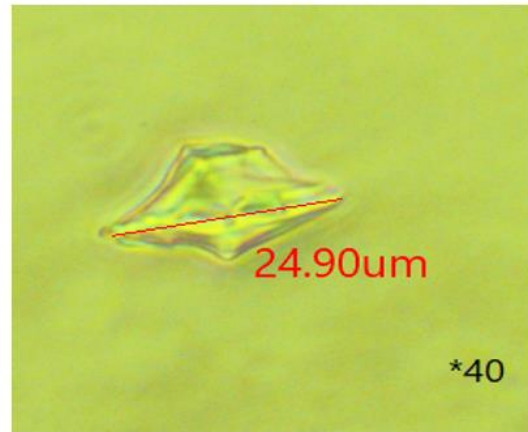


Figure 21- Female nurse – 26 years of experience

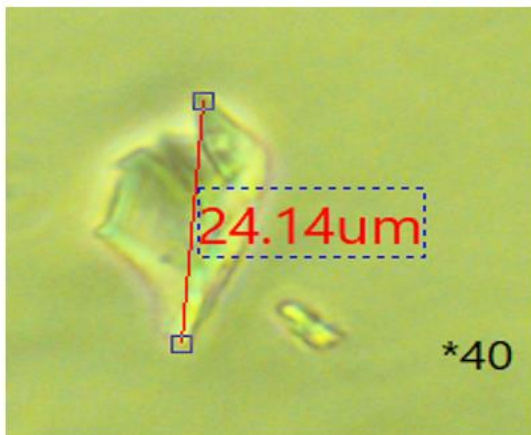


Figure 22- Female nurse – 26 years of experience

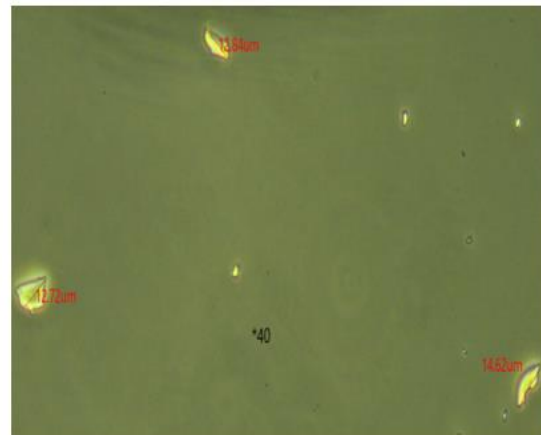


Figure 23- Male nurse – 28 years of experience

Discussion

In this study, glass particle contamination was analyzed using a dynamic light scattering (DLS) device. In contrast to previous investigations, which utilized a range of equipment such as optical and electron microscopes, slide scanners, computer microscopes, light-blockage counters, and KL-04 particle counters, the present study collected samples without removing the syringe needle to closely replicate clinical conditions, particularly the potential for glass particles to pass through the needle during actual injection into patients [19-20,26,31,48,50].

In some previous studies, particle analysis was conducted using only one or two drops of solution extracted from the ampoule samples, which may not accurately represent the uniform distribution of glass particles within the entire volume [19,40]. In contrast, the present study analyzed the full contents of each ampoule after breakage. The entire volume of the medicine solution, potentially contaminated during the breaking

process, was transferred into the cuvette of the DLS device for analysis. Consequently, the findings of this study are more representative of real-world clinical scenarios compared to those based on partial sampling.

Several previous studies have reported particle size measurements. One study identified particle sizes ranging from 8 to 172 μm [52], while another observed glass particles measuring between 1.92 and 504.67 μm [20]. Research by a different group reported sizes ranging from 62.5 to 250 μm [50]. Similarly, in the present study, all detected particles were within the micrometer range, starting from 14.39 μm . Although the largest precisely measured was 134 μm , the data suggest the presence of larger particles as well, certainly exceeding 134 μm but remaining below 394 μm , based on the measurement limits and observed scattering patterns.

Several studies have quantified both the size and number of glass particles introduced into ampoule contents during breakage. For example, Yorioka et al. (2009) reported particle concentrations of 252.9

particles/mL for sizes ranging from 1.3 μm to less than 5 μm , 12.5 particles/mL for 5–10 μm , 3.2 particles/mL for 10 to less than 50 μm , and 0.09 particles/mL for 50 to less than 100 μm [48]. In another study, Lee et al. (2011) observed that manual breaking of ampoules generated 84.1 ± 16.6 particles in 1 mL ampoules and 24.9 ± 6.27 particles in 2 mL ampoules [31]. Similarly, Joo et al. (2016) reported a range of 15 to 419 glass particles per ampoule, with a mean count of 108.18 ± 79.45 particles [20]. In the present study, however, the total number of particles was not directly measured due to the use of a dynamic light scattering (DLS) device. Instead, the focus was placed on assessing the proportion of particles exceeding two specific size thresholds: 10 μm and 25 μm . The results indicated that, on average, 53.49% of particles were greater than 10 μm , while 17.65% exceeded 25 μm .

Chiannilkulchai and Kejkornkaew (2021) investigated the relationship between nurses' work experience, ampoule-breaking methods, and the resulting glass particle size and count. Their study assessed six breaking techniques applied to 2 mL and 10 mL ampoules, using gauze (Methods 1 and 2), a cotton ball (Methods 3 and 4), or a syringe wrapper (Methods 5 and 6). Each technique involved breaking the ampoule either outward (Methods 1, 3, 5) or inward (Methods 2, 4, 6).

The lowest number of particles was observed when using a cotton ball in an outward-breaking motion. However, particle size did not significantly vary across methods. [53]. In the present study, we similarly evaluated the effects of the ampoule-breaking technique and nurses' clinical experience on particle size and distribution. The results showed no statistically significant impact of either variable on the proportion of particles larger than 10 μm or 25 μm . Additionally, no significant differences were observed among the three breaking methods with respect to average particle size. However, a significant negative correlation was identified between the group with 0–5 years of experience and the group with more than 10 years ($p = 0.001$), indicating that average particle size decreased with greater clinical experience.

Studies conducted by Carbone-Traber and Shanks (1986), Preston and Hegadoren (2004), and Lye and Hwang (2003) demonstrated that the level of glass particle contamination was higher in larger ampoules compared to smaller ones [18-19,23]. In contrast to these findings, the present study showed a higher level of contamination with particles $> 10 \mu\text{m}$ in 2 mL ampoules compared to 5 mL and 10 mL ampoules. Similarly, contamination with particles $> 25 \mu\text{m}$ was also greater in 2 mL ampoules than in 5 mL ampoules.

Contrary to the findings of Carbone-Traber and Shanks (1986) and Chiannilkulchai and Kejkornkaew (2021), who reported no relationship between ampoule volume and particle size [18,53], our results indicated otherwise.

The average particle size in 2 mL ampoules (42.65 μm) was significantly greater than in 5 mL ampoules (32.13 μm), a difference confirmed by the LSD testing.

Implications for practice and research

Although ampoules typically contain sufficient medication, it is generally recommended to keep them upright during aspiration to minimize the risk of contamination. Nevertheless, in real-world practice, healthcare professionals often tilt or angle the ampoule to ensure complete withdrawal of the contents and avoid medication loss [54]. This practice highlights the need for further research to determine the optimal aspiration technique and volume, balancing efficiency with safety, particularly to prevent drawing up glass particles that may settle at the bottom of the ampoule.

Previous studies have demonstrated that glass particles smaller than 7 μm can reach vital organs such as the brain, lungs, liver, kidneys, spleen, and small intestine, potentially causing inflammation and tissue damage. Particles measuring between 7 and 12 μm may obstruct capillaries, increasing the risk of embolism and thrombosis. Furthermore, glass particles have been implicated in pathological conditions including phlebitis, granuloma, pulmonary hypertension, and granulomatous pulmonary arteritis [19-20,55-60]. The particles detected in our study, which originated from syringes equipped with needles and included some exceeding 12 μm in size, pose a serious clinical concern for patient safety.

Millions of particulate contaminants are inadvertently injected into patients each day during hospitalization, particularly in intensive care units (ICUs), where patients are highly vulnerable to adverse effects. Most of these particles range in size from 1 μm to over 100 μm , with some exceeding 500 μm , and the majority measuring approximately 2 μm in diameter [61]. The injection of such particles presents a potentially significant risk to patient safety. Increasing reliance on medications packaged in glass ampoules is likely to amplify these risks. Therefore, the development and implementation of effective strategies to reduce particulate contamination remain a critical priority for ensuring patient safety.

The risk of particulate matter injection may vary across all age groups, as physiological differences between pediatric and adult populations can influence the severity of potential adverse effects. Postnatal developmental changes, particularly in the cardiovascular system, may account for this variability [62]. Although the size of pulmonary capillaries in neonates is similar to that in adults, infants have fewer and narrower blood vessels. These anatomical and physiological characteristics may heighten their susceptibility to vascular obstruction and inflammatory responses following exposure to particulate contaminants [63]. Thus, further investigation is essential to clarify the potential health consequences of

inadvertent particle injection in both pediatric and adult patients.

Several strategies have been proposed to minimize glass particle contamination during the use of glass ampoules. Among them, filter needle syringes, already in limited clinical use, are recommended in specific settings, particularly in neonatal care, to enhance patient safety [15]. The American Society of Health-System Pharmacists (ASHP) guidelines recommend the use of 5 µm filter straws or filter needles when withdrawing medication from ampoules to reduce particulate contamination [64]. However, cost constraints and workflow challenges across institutions and countries hinder the widespread implementation of such devices.

researchers have proposed the use of prefilled syringes as an effective strategy to eliminate the risk of glass particle contamination [65]. Nevertheless, given the widespread and continued reliance on glass ampoules in many healthcare systems, their complete replacement remains impractical. Accordingly, further research is necessary to develop more effective strategies for reducing particulate contamination.

Conclusion

The average percentage of detected glass particles was 63.56%, 47.41%, and 49.42% in the 2-, 5-, and 10-mL ampoules, respectively. In all ampoule sizes, the mean particle size exceeded pharmacopeial specifications, measuring 42.65 µm, 32.13 µm, and 42.72 µm for the 2-, 5-, and 10-mL ampoules, respectively.

The proportion of glass particles introduced into the ampoule contents following breakage was not significantly affected by the nurse's gender, years of experience, or the technique used to break the ampoule. However, ampoule volume demonstrated a significant impact on both particle count and size distribution. Smaller ampoules were associated with a higher proportion of particles larger than 10 µm and 25 µm, as well as greater average particle sizes.

Furthermore, increased clinical experience was associated with the production of smaller glass particles, while the ampoule-breaking technique had no significant effect on average particle size.

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