Original

Determination of Aerosol Particle Levels upon Ampule Opening

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Abstract

Purpose: The contamination of drugs from the containers, such as the ampules, can cause exposure and absorption in the healthcare personnel, thereby causing occupational disorders. Although the release of drugs from the ampules is presumed, there are few reports on the evaluation methods that enable the quantification of the released volume from the ampules.

Methods: We determined the levels of the aerosol particles released from the ampules in the nested clean bench, wherein the outer clean bench provides clean air through the laminar flow, and the inner bench maintains a wind-less atmosphere as the laminar flow is not operational.

Results: The levels of the aerosol particles in the inner clean bench with continuous laminar flow of the outer clean bench were negligible compared to the other conditions. The elevated levels of the small size particles were observed compared to the large ones upon ampule opening. The particles were detected both vertically and horizontally 40 cm away from the ampule cutting point, which suggested that the particles diffused in both directions. Most of the aerosol particles were observed in the first 15 s. However, they were also detected thereafter. The correlation between the years of experience as a pharmacist and the levels of the aerosol particles was not observed.

Conclusions: The established apparatus enabled us to quantitate the levels of the particles released upon the ampule opening and it will contribute in improving the skills of pharmacists and other healthcare personnel, and decreasing the exposure to the drugs in them.

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—Key words—

occupational exposure, ampule, aerosol

Background

Potential risks to the healthcare personnel associated with drug preparation have been reported previously[1)2)]. The contamination of drugs by their release from the containers, such as the ampules and vials, causes exposure and absorption in the healthcare personnel, particularly pharmacists, because they operate in an environment with relatively high concentration of drugs. Glass ampules have been used to date and their risk in exposure to healthcare personnel have been suspected[3)]. The vials containing cytarabine, an anticancer drug, have been reported to cause severe occupational disorders, although the drug is processed in a biological safety cabinet[4)].

Ampules are treated manually without aid for preventing contamination, since the variety of sizes and the operation of cutting glass would make it difficult to develop a closed system that is widely used for preparing the vials and automatic preparation using the machines. The risk of glass contamination with the drug solution has also been reported by Kawasaki et al.[5)]. Although the release of drugs from the ampules is presumed, there are no reports on the evaluation methods that enable quantitative determination of the released volume from the ampules in the best of our knowledge. Hereafter, we describe a method established for the determination

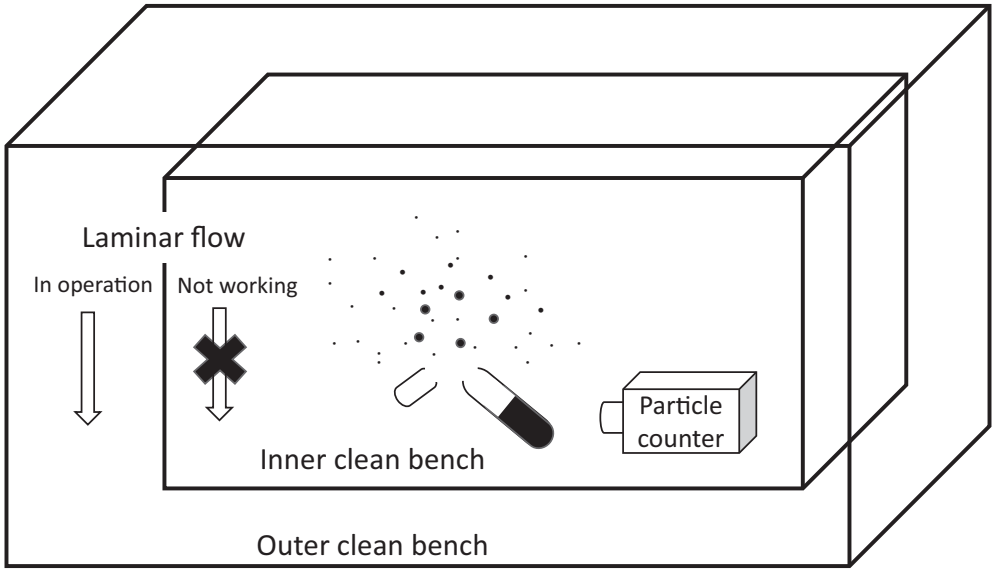

Fig. 1 Illustration of the clean benches prepared for measuring the levels of the aerosol particles released from the ampules.

of the aerosol particles released from ampules and the investigated results on the aerosol particles released in various situations.

Materials and Methods

Reagent

Flavitan injection (20 mg, 2 mL) including flavin adenine dinucleotide sodium was obtained from Toa Eiyo (Tokyo, Japan).

Clean bench

The apparatus used for evaluating the aerosol particles released from the ampules is illustrated in Fig. 1. The inner clean bench (CT-900AD, As One, Osaka, Japan) was nested in an outer clean bench (NCF-W, Nikka Micron, Saitama, Japan). The laminar flow of the inner and outer clean benches was independently controlled during the experiments. The laminar flow of the inner clean bench was operated until the levels of the aerosol particles were constant otherwise described.

Counting levels of particles

The regions of an ampule were named from top to bottom as "head", "neck" and "body". The ampules were turned upside down to fill the liquid in the head, then reversed to an ordinary position, and the liquid was moved to the body through the neck by tapping. The ampules were opened 30 s after the liquid was cleared from the top. The hands holding the ampule were drawn back immediately after opening the ampule. The laminar flow of the outer clean bench was operated until the levels of the aerosol particles in inner clean bench were constant otherwise described. Both of the outer and inner clean benches were lightened with the attached fluorescent lamp. The operators of the experiments wore white coat with rolled up sleeves and nitrile gloves. The experiment was repeated five times under ambient temperature and fluorescent lamp in the room. The particle counter KC-52 (Rion, Tokyo, Japan), which was used to evaluate the levels of the aerosol particles with size ranging from $>$ 0.3, 0.5, 1.0, 2.0, and 5.0 μm, was placed nearby the ampule cutting point, and vertically/horizontally 40 cm away from the point in the inner clean bench. The levels of aerosol particles were determined every 15 seconds until 120 s after cutting the ampules and summed up. Four pharmacists with 1, 7, 12, and 20 years of experience and a pharmacy student participated in the experiment for age influence. The number of particles was measured. The data are representative of the three independent experiments. The statistical significance was determined by Dunn's test.

Results

The background levels of the aerosol particles are shown as the sum of all sizes of the particles (Fig. 2). The mean level outside the outer clean bench was 276,952. The level of the particles in the outer clean bench where the laminar flow of the outer clean bench was ceased was 311,209. The level of the particles in the inner clean bench where the laminar flow of the outer clean bench was stopped was 235,920. The level of the inner clean bench where the laminar flow of the outer clean bench was operational was 2.6.

The particles were detected for all size ranges upon ampule opening irrespective of the counter position (Table 1). The levels of the aerosol particles were almost equal to the background level in sham operation, in which all operations were same as the ordinary method except breaking the glass of the ampules (data not shown). The level of the small size particles (> 0.3 μm) was found to be elevated, and it decreased as the size of the particles increased. The mean level of small size particles (> 0.3 μm) was 51 and SD were 45 when the counter was placed nearby the cutting point. The total levels of the particles at the point horizontally 40 cm away from the ampule cutting point were determined, and the mean level of the small size particles (> 0.3 μm) was 142. The total levels of the particles at the point vertically 40 cm away from the cutting point were also assessed. The mean level of the small size particles (> 0.3 μm) was 33. The levels of the particles were significantly higher horizontally than vertically, regardless of the difference in the particles size except > 0.3 μm. The levels of the particles were assessed every 15 seconds (Fig. 3). The maximum level was detected at 15 seconds and it decreased until 120 seconds, regardless of the particle size.

The levels of the particles were investigated by the pharmacists with different years of experience and the pharmacy student (Table 2). The total levels of the small size particles (>0.3 μm) varied from 41 to 199, and the correlation factors between the years of the experience and levels of the particles were between 0.0005 and 0.0666.

Discussion

The contaminations of the drug from ampules and vials has been reported by wipe method, in which the drug on the surface of the equipment was wiped and the contamination of the summation for certain period was determined[7]. The method established here estimated the contamination of single operation of ampule opening, which enable the evaluation of the skill of the single operation. The skill of preparation of the injection was also studied by fluorescein as a dummy of drug[8]. The method evaluate the contamination as the levels of the settled drops without the information on the sizes by fluorescence, however it disappeared as dried[9]. Our method estimated the intact floating particles for each size. There are few reports on the aerosol particles that are released from the ampules upon opening, although the release of drugs from them is speculated[3]. To accurately assess the levels of aerosol particles released from the ampules, the operation of cutting the ampules should be conducted in a clean (i.e., particle-less) and wind-less environment, which seemed to be conflicting because the clean air was obtained upon passing through the high-efficiency particulate air (HEPA) filter at high speed. We resolved this problem through developing an apparatus for counting the particles released from the ampules using a nested clean bench. The outer clean bench provided the clean air from the laminar flow, while the inner bench maintained a wind-less atmosphere where the laminar flow was not operational. The combined levels of the aerosol particles of all ranges in the inner clean bench with continuous laminar flow of the outer clean bench were negligible compared to the other conditions. The use of the clean bench also has an advantage over other equipment such as cardboard

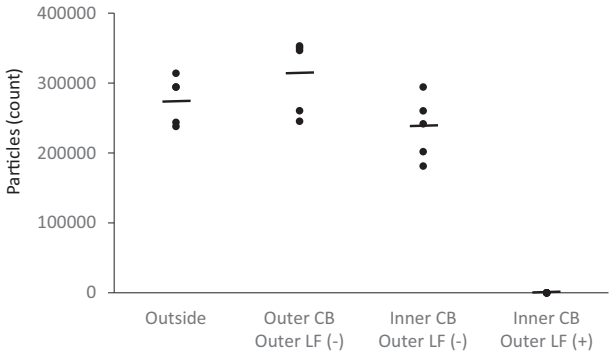

Fig. 2 The background levels of the aerosol particles present in the clean benches.
CB and LF indicates clean bench and laminar flow, respectively.

Table 1 The effect of the distance from the point where the ampules were cut on the aerosol particle levels

A) Determined value

Determined value		>0.3 um	>0.5 um	>1.0 um	>2.0 um	>5.0 um
Nearby	Mean	51	34	22	14	4
	SD	45	28	17	10	3
Horizontal	Mean	142	101	67	49	14
	SD	75	68	52	42	15
Vertical	Mean	33	22	11	6	1
	SD	23	18	8	6	1

B) Dunn's test

p-value	>0.3 um	>0.5 um	>1.0 um	>2.0 um	>5.0 um
Nearby-Horizontal	0.182	0.441	0.357	0.381	0.436
Nearby-Vertical	1.000	1.000	0.771	0.467	0.354
Horizontal-Vertical	0.077	0.044	0.017	0.008	0.006

The particle counter was placed nearby, horizontally or vertically 40 cm away from the point where the ampules were cut in the inner clean bench. The number of aerosol particles were counted every 15 s and summed up to 120 seconds. The experiments were repeated five times by the single operator and the mean and SD were estimated. The statistical significance was determined by Dunn's test.

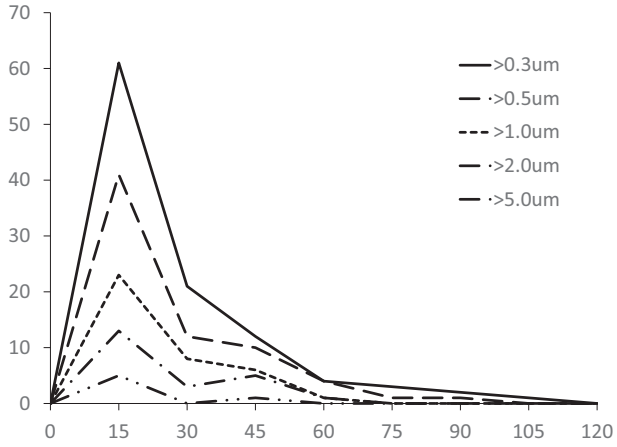

Fig. 3 Variation in the levels of the aerosol particles released from the ampules.
The particle counter was placed nearby the point where the ampules were cut. The number of aerosol particles were counted every 15 seconds and summed up to 120 seconds. The experiments were repeated five times.

boxes in not providing the dust.

The nested clean bench enabled us to quantitate the levels of the particles released upon the ampule opening. The levels of the particles varied greatly among the experiments, wherein the SDs were comparable with the mean levels of the particles. These results suggested that unknown factors influenced the release of particles from the ampules, although we could not identify such factors during the experiments. The levels of smaller particles were observed to be higher than those of the larger ones, although the statistical significance was not detected. The deposition of inhaled particles in the respiratory tract was estimated using the human respiratory tract model, which is intended for radiological protection. According to the model, the small size particles (> 0.3 μm) reached the alveolar interstitium, which is the deepest region in the lung, better than the particles of other sizes[6]. The most abundant size of the aerosol particles detected in our experiment corresponded to the size most suitable for inhalation, which suggest risk of inhalation of the drug through lung upon ampule opening.

Most of the aerosol particles were observed in the first 15 s, regardless of the particle size; however, they were also detected thereafter. The particles were also detected vertically and horizontally 40 cm away from the ampule cutting point, which suggested that the particles diffused in both directions. However, the levels of horizontal dispersion significantly increased compared to the levels of vertical dispersion.

We predicted that the years of experience as pharmacists influenced the release of the particles from the ampules, since a skilled pharmacist can generally prepare the injection mixture smoothly and rapidly. However, contrary to our expectation, the correlation factor between the levels of the released aerosol particles and the years of experience as a pharmacist was low level which suggested that the relationship was not observed in this experiment.

The number of the commercially available ampule injection has gradually decreased to date. The contami-

Table 2 The relationship between the years of the experience as a pharmacist and the aerosol particles levels released from the ampules

Years		>0.3 um	>0.5 um	>1.0 um	>2.0 um	>5.0 um
0	Mean	145	86	48	29	6
	SD	133	72	33	19	4
1	Mean	78	52	34	21	5
	SD	44	38	21	12	3
8	Mean	145	113	79	51	10
	SD	94	72	55	37	11
12	Mean	199	156	108	65	13
	SD	131	100	68	46	12
20	Mean	41	34	26	17	5
	SD	36	88	24	15	5
Correlation factor		0.0666	0.0005	0.0022	0.0065	0.0145

The particle counter was placed nearby the point where the ampules were cut. The number of aerosol particles were counted every 15 s and summed up to 120 seconds. The experiments were repeated five times and the mean and SD were estimated for each individual. The correlation coefficient was estimated between the years of the experience as the pharmacist and the aerosol particles levels.

nation of the glass from ampule in injection solution has been reported[5]. Although we showed here the method which evaluate the contamination on ampule opening, our study has also limitations. The results were obtained using a limited number of operators. It is possible that the particle counter can detected the particles originated from glass, since it detected the particles by optical scattering. Nevertheless, the method for determining the levels of the aerosol particles has not been established previously and there has been no possibility to assess their own skills in the best of our knowledge. The method established here will contribute in improving the skills of pharmacists and other healthcare personnel, and decreasing the exposure to the drugs in them.

Conclusion

There are few reports on the contamination of the drug from ampule, although it is speculated as the reason for the contamination, which also means that the improvement of handling technique for the ampule is impossible. The established method enabled us to determine the aerosol particle levels upon ampule opening. The method will contribute in improving the skills of pharmacists and other healthcare personnel and decreasing the occupational exposure of the drugs.

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アンプル開栓時のエアロゾル飛散量の測定

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―キーワード―
職業曝露，アンプル，エアロゾル

背景：アンプルのような容器からの医薬品の汚染は，医療従事者の曝露や吸収をひき起こし，これにより職業病を引き起こす可能性がある．アンプルからの医薬品の飛散は想定されてきたが，アンプルからの飛散量を定量的に測定できる方法に関する報告はなかった．

方法：私達は，入れ子にしたクリーンベンチを用いて，アンプルから放出されるエアロゾル量を測定した．この入れ子にしたクリーンベンチの外側のクリーンベンチは層流によって清浄な空気を供給し，内側のクリーンベンチでは層流が止められているために無風の状態を維持する構造となっている．

結果：外側のクリーンベンチの層流を維持しながら，内側のクリーンベンチ内のエアロゾルを測定したところ，他の条件と比較してほぼ無視できるエアロゾル量であった．アンプル開栓時には，小さいサイズのエアロゾルが大きいものより多く測定された．アンプルを開栓した位置から垂直および水平方向に 40cm 離れた位置においてもエアロゾルは確認された．このことはエアロゾルが両方向に飛散することを示唆している．ほとんどのエアロゾルははじめの 15 秒間に計測された．薬剤師としての経験年数と飛散するエアロゾル量との間に相関は認められなかった．

結論：確立した方法によってアンプル開栓時に放出されるエアロゾルを定量することが可能になり，薬剤師や他の医療従事者の技術の向上や曝露防止に寄与できるものと考えられる．

［COI 開示］本論文に関して開示すべき COI 状態はない

（日職災医誌，70：102―107，2022）