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Original Article

Occupational exposure of pharmacists to drugs during tablet crushing and its countermeasures

Tsuyoshi Murahashi, Miho Arai, Kengo Ogata, Manami Matsumoto and Toshiyuki Higuchi

Nihon Pharmaceutical University, 10281 Komuro, Ina-machi, Kita-adachi-gun, Saitama prefecture 362-0806, Japan

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ABSTRACT — To estimate the exposure of pharmacists to drugs during tablet crushing, we collected room dust in four pharmacies and a hospital and analyzed the concentrations of the drug ingredient. The ingredient concentrations in the room dust were detected in the range of 15–18000 μg/m^3, and the median concentration was 320 μg/m^3. The amount of exposure to pharmacists was estimated between 0.8–960 μg/crush, with a median of 17 μg/crush, when the respiratory volume of the pharmacist was 8 L/min. These maximum and median values were more than 10 times higher than those during the previously reported powder preparations, demonstrating that the working environment for pharmacists who crushed tablets posed more health hazards. As countermeasures, working on a bench with dust remover reduced the exposure by 99.0% compared to that on a normal bench, and wearing a medical mask reduced the exposure by 97%. The combined reduction rate of both measures was calculated to be over 99.9%. Moreover, we compared the estimated exposure by the crusher with the rotatory blade and that with two rotatory mortars and found that the estimated exposure using the latter was much less (lower than 1/1000) than that with the former. Thus, the above measures can be used to reduce the exposure of pharmacists to drugs during tablet crushing.

Key words: Occupational exposure, Pharmacist, Tablet crushing, Pharmacy, Countermeasure

INTRODUCTION

Japan's population is aging at a rapid pace. According to the Statistics Bureau of the Ministry of Internal Affairs and Communications, the population over the age of 75 in 2021 was 19 million, accounting for 15% of the total population (Ministry of Internal Affairs and Communications, 2021b). The Ministry of Health, Labor and Welfare estimated that this will increase to 24 million people in 2055 and will account for 26% of the total population (Ministry of Health, Labour and Welfare, 2021b). Elderly people may have difficulty taking tablets or capsules due to the decline in their swallowing function with age (Miura and Kariyasu, 2007). Therefore, tablet crushing and capsule opening are routinely performed in hospitals and community pharmacies (Kurata, 2011). This results in the scattering of fine particles of drugs in the air, which raises a concern about the health hazards of pharmacists due to their exposure to the drugs (Maeda *et al.*, 2016).

"Allergy in pharmacy" caused by drug exposure has been raised for about 50 years (Fueki, 1971; Kataura *et al.*, 1973). The incidence rate of this allergy was reported to be 18–45% among the hospital pharmacists, and the routes of drug invasion were mainly inhalation and contact. The major types of allergic symptoms were allergic rhinitis, contact dermatitis, pharyngeal discomfort, atopic dermatitis, asthma, and bronchitis (Fueki, 1971), which significantly increased during operations such as powder drug preparation, tablet crushing, and capsule opening using a questionnaire survey, (Inaba *et al.*, 2012, 2015).

Correspondence: Tsuyoshi Murahashi (E-mail: tmu@nichiyaku.ac.jp)

An analysis of dust in the air of hospital dispensaries revealed that the installation and proper operation of the dust remover were effective for the prevention of drug exposure (Inaba *et al.*, 2016). Recently, it has been demonstrated that the amount of exposure to a pharmacist is estimated to be 0.4–36 μg of drug ingredients per prescription in the room air of community pharmacies during powder drug preparation (Murahashi *et al.*, 2021). It is also reported that wearing a medical mask experimentally reduced drug exposure by more than 90% (Murahashi *et al.*, 2021). Regarding the tablet crushing, a large amount of drug dust was scattered in the process of transferring the crushed powder from the crushing machine to the mortar in a model experiment (Maeda *et al.*, 2016). However, there is no information regarding the concentrations of the drug in the dispensing room and the occupational exposure during tablet crushing.

Since "allergy in pharmacy" caused by tablet crushing poses a serious problem for pharmacists, it is necessary to understand the current situation and take countermeasures. Thus, in this study, we reported the concentrations of drug ingredients in the room air and drug exposure during tablet crushing based on real prescriptions at four community pharmacies and a hospital. We also verified the effect of working on a bench with dust remover and wearing a medical mask as countermeasures to prevent exposure to drugs. Furthermore, the effectiveness of using the mortar-type crusher, "SafeCrush™" developed by the Government of Canada compared with that of the general blade-type tablet crushers was evaluated from the viewpoints of drug exposure, drug loss, and pre-drug contamination. From the above experiments, we scientifically clarified the current situation and the countermeasures needed for reducing exposure.

MATERIALS AND METHODS

Chemicals

Acetaminophen, amlodipine besilate, aspirin, L-carbocisteine, famotidine, loxoprofen sodium hydrate, magnesium oxide, naproxen, rebamipide, tadalafil, and verapamil hydrochloride were purchased from FUJIFILM Wako Pure Chemical Corporation (Tokyo, Japan). Camostat mesilate, cilostazol, metformin hydrochloride, and paroxetine hydrochloride were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Water was purified by Elix-3 (Millipore-Merck KGaA, Darmstadt, Germany). All other reagents were from FUJIFILM.

Collection of drug dust in the dispensing rooms during tablet crushing

Samplings were done in four community pharmacies and a hospital in Tochigi and Saitama Prefectures. An open-face filter holder was clipped to the collar of the lab coat. The filter holder was connected to a portable air sampler (MP-∑500N, SIBATA Scientific Technology Ltd., Saitama, Japan) at a suction rate of 3 L/min. Drug dust was collected on a pre-washed glass fiber filter (AP2002500, pore size 2.0 μm, diameter 25 mm, Millipore-Merck), and ingredients on the filter were analyzed.

Analysis of drug ingredients

For the analysis of magnesium oxide, the filter was placed in a 10 mL glass beaker with the collection side facing up, 2 mL of 1% hydrochloric acid solution was added, and ultrasonic waves were applied for 10 min using a Branson 3510 ultrasonic cleaner (Yamato Scientific Co., Ltd., Tokyo, Japan). The extract solution (20 μL) was injected into an ion chromatograph system. The system consisted of a DGU-20A3 degasser, LC-20AD pump, CTO-20A column oven, CDD-10Avp conductivity detector, and Chromatopac C-R8A data processor (Shimadzu Corporation, Kyoto, Japan) with a 7725i sample injector (Rheodyne, Cotati, CA, USA). The separation column was Shodex IC YS-50 (4.6 × 150 mm, Showa Denko K.K., Tokyo, Japan) and it was used at a temperature of 40°C. The mobile phase was 4 mmol/L methanesulfonic acid solution, pumped at a flow rate of 1 mL/min. Magnesium ion was detected, and the concentration of magnesium oxide was calculated.

For the other agents, the analyte of interest collected on the filter was ultrasonically extracted with 1 mL of the HPLC mobile phase for 10 min and then introduced to the HPLC system. The HPLC system was constructed by changing the conductivity detector of the above ion chromatograph system to an ultraviolet absorption detector (SPD-20A, Shimadzu). The mobile phases (flow rate, 1 mL/min) used were as follows: acetonitrile/0.5% acetic acid solution (2:8, v/v) for the analysis of acetaminophen and paroxetine; 3:7 for aspirin; 1:1 for amlodipine, loxoprofen, and rebamipide; 0.1% trifluoroacetic acid for L-carbocisteine; methanol/0.2% 1-heptanesulfonate solution/0.1% sodium lauryl sulfate solution/acetic acid (200:100:50:1) for camostat and famotidine; acetonitrile/methanol/water (7:3:10) for cilostazol; acetonitrile/0.13% sodium lauryl sulfate solution/phosphoric acid (380:616:4) for metformin; methanol/0.01 mol/L potassium dihydrogen phosphate solution (75:25) for naproxen; methanol/water (7:3) for tadalafil; and methanol/water/perchloric acid (550:450:1) for verapamil. The

separation columns (temperature, 40°C) Inertsil ODS-3 (4.6 mm i.d. × 250 mm, GL Science Inc., Tokyo, Japan) or Cosmosil 5C_{18}MSII (4.6 mm i.d. × 250 mm, Nacalai Tesque Inc., Kyoto, Japan) were used. Analytes were detected at wavelengths of 220 nm for loxoprofen, 225 nm for aspirin, 235 nm for metformin, 238 nm for amlodipine, 240 nm for L-carbocisteine and naproxen, 245 nm for acetaminophen, 254 nm for cilostazol, rebamipide and camostat, 265 nm for famotidine, 280 nm for verapamil, 290 nm for tadalafil, and 295 nm for paroxetine.

Measurement of particle size distribution

The particle size distribution of drug powder was measured as described in the previous report (Murahashi *et al.*, 2021). Briefly, four Calonal® tablets (200 mg acetaminophen, Ayumi Pharmaceutical Corporation, Tokyo, Japan) were crushed by an HST-160 tablet crusher (Fig. 1, Takazono Corporation, Tokyo, Japan) and drug powder was fractionated by particle size with ten sieves (pore sizes, 20, 40, 53, 75, 106, 150, 212, 300, 425, and 600 μm), and the weight of powder in each sieve was measured using an electric balance.

Protective effects of working on a bench with dust remover and wearing a medical mask on drug exposure

The effect of working on a bench with dust remover was investigated. Ten Calonal® tablets were crushed using an HST-160 crusher and drug powder was transferred to a plastic tray on a lab bench, or on a bench for powder drug mixing with dust remover (G-1100, Takazono). After crushing, the inside parts of the crusher cell were dry-cleaned with five sheets of Kim Wipes (Nippon Paper CRECIA Co., Ltd., Tokyo, Japan). Collection of drug dust and analysis of ingredients are described above. The reduction rate (%) was calculated using the formula 100 × (A–B)/A; where A is the mean exposure during tablet crushing on the lab bench, and B is that on the bench with dust remover.

The effect of wearing medical masks was investigated as described in our previous report (Murahashi *et al.*, 2021). Briefly, the drug powder from crushing ten Calonal® tablets was suspended in the air, and the powders were collected on two filters; one was covered with a medical mask and the other was not. Two types of medical masks were investigated in this study. Brand A mask was "Face mask" no. 1-9698-01 (AS ONE, Osaka, Japan) and Brand B mask was "Fit mask" (BMC, Tokyo, Japan). Both masks consisted of three sheets of non-woven polypropylene fabric. Then, the acetaminophen levels on the two filters were analyzed by HPLC as described above.

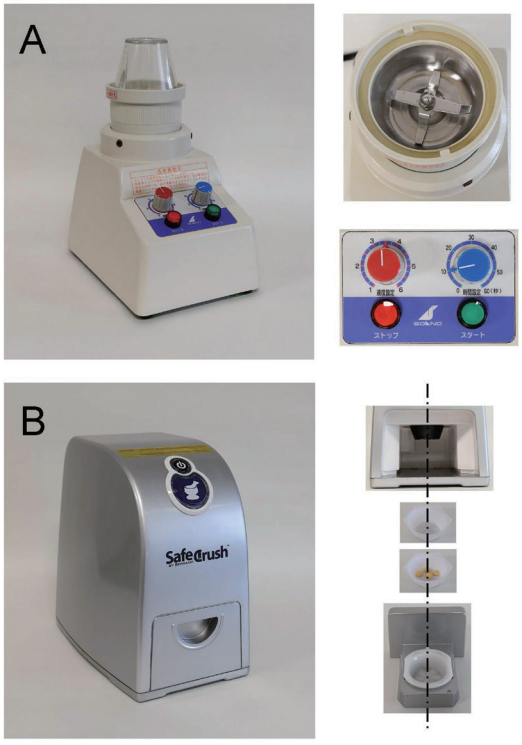

Fig. 1. Blade-type tablet crusher (HST-160, A) and mortar-type tablet crusher (SafeCrush™, B).

The removal rate (%) was calculated using the formula 100 × (C–D)/C; where C is the amount of acetaminophen on the filter without a covering mask, and D is that with the mask.

Time course of ingredient concentration in room air during tablet crushing

Ten Calonal® tablets were removed from the PTP sheet and placed in the cell of an HST-160 crusher for 30 sec (0 min 0 sec–0 min 30 sec). Simultaneously, room dust was collected. After changing the filter holder (0 min 30 sec–1 min 0 sec), tablets were crushed using the crusher at a speed of 3.5 for 10 sec, and room dust was collected in this term (1 min 0 sec–1 min 30 sec). After changing the filter holder (1 min 30 sec–2 min 0 sec), drug powder was transferred to a plastic tray (2 min 0 sec–3 min 30 sec), then the filter holder was changed (3 min 30 sec–4 min 0 sec). Finally, the cell of the crusher was cleaned with five sheets of Kim Wipes (4 min 0 sec–7 min 30 sec). The ingredient on each filter was analyzed as described above.

Drug exposure, drug loss, and pre-drug contamination using two types of crushers

Four Loxonin® tablets (68.1 mg loxoprofen sodium hydrate, Daiichi Sankyo Healthcare Co., Ltd., Tokyo, Japan), four Calonal® tablets, and four Bufferin® A tablets (660 mg aspirin, Lion Corporation, Tokyo, Japan) were crushed in sequence using a blade-type crusher (HST-160) or a mortar-type crusher (SafeCrush™, Fig. 1, Serrano Medical Solutions, Surrey, BC, Canada). Drug powder was transferred to a plastic tray and the cell of the HST-160 crusher was cleaned using five sheets of Kim Wipes. SafeCrush™ grinds tablets between two plastic trays, eliminating the need to transfer the powder and clean. Collection of drug dust and analysis of ingredients were performed as described above. The reduction rate (%) was calculated using the formula 100 × (E–F)/E; where E is the mean exposure using the blade-type crusher, and F is that using the mortar-type crusher.

For the analysis of drug loss, four tablets before crushing and drug powder after crushing were weighed using an electric balance (TE124S, Sartorius, Goettingen, Germany), and drug loss rate was calculated using the formula 100 × (G–H)/G; where G is the weight of tablets before crushing, and H is that of powder after crushing.

For the analysis of pre-drug contamination in the following crushed powder, the ingredients of the pre-crushed tablets in the generated powder from the following crush were analyzed as described above. The pre-drug contamination rate (%) was calculated using the formula 100 × J/K; where J is the amount of the ingredient in the generated powder from the following crush, and K is that from the pre-crushed tablets.

Aggregation of drug prescription amount

The amounts of drugs prescribed for patients over the age of 75 were calculated as follows. The fifth NDB open data of the Ministry of Health, Labor and Welfare were downloaded from the website (Ministry of Health, Labour and Welfare, 2021a). Data on "prescriptions for hospital inpatient" and "prescriptions for outpatient" were combined and sorted by drug code, and tablets with the same ingredients were totaled.

Data analyses and statistics

All data are expressed as mean ± standard deviation (SD). We analyzed the results by Student's *t*-test using Microsoft Excel version 2202 (Seattle, WA, USA). A P value < 0.05 was considered statistically significant.

Ethics

This study was approved by the ethical review board of Nihon Pharmaceutical University (Approval No. NPE3-15).

RESULTS AND DISCUSSION

Drug concentration in the room air and estimated exposure of pharmacists to drug dust during tablet crushing

In dispensing rooms of community pharmacies and hospitals, there are concerns about health hazards caused by tablet crushing. According to the NDB open data (Ministry of Health, Labour and Welfare, 2021a), amlodipine was the most commonly prescribed drug for the patients over the age of 75 (1.0×10^9 tablets), followed by mecobalamin (8.2×10^8 tablets), rebamipide (7.2×10^8 tablets), limaprost alfadex (5.7×10^8 tablets), sennoside (5.6×10^8 tablets), ursodeoxycholic acid (4.7×10^8 tablets), aspirin (4.7×10^8 tablets), L-carbocisteine (4.2×10^8 tablets), lansoprazole (4.0×10^8 tablets), acetaminophen (3.6×10^8 tablets), rosuvastatin (3.5×10^8 tablets), atorvastatin (3.5×10^8 tablets), mosapride (3.5×10^8 tablets), nifedipine (3.4×10^8 tablets), magnesium oxide (3.4×10^8 tablets), metformin (3.1×10^8 tablets), etizolam (3.1×10^8 tablets), loxoprofen (3.1×10^8 tablets), celecoxib (2.9×10^8 tablets), and furosemide (2.9×10^8 tablets). Many of these are drugs that are indicated for treating lifestyle-related diseases. These tablet medications are routinely crushed in the dispensing room.

To examine the drug contamination in the room air during tablet crushing, we collected drug dust during tablet crushing in four community pharmacies and a hospital and analyzed the concentrations of the active ingredients in the drug dust. As listed in Table 1, the ingredient concentrations in the room air were detected in the range of 15–18000 μg/m^3 with a median of 320 μg/m^3. Assuming that the pharmacist's respiratory volume is 8 L/min, the amount of drug exposure to the pharmacist was calculated by multiplying the amount of drug collected on the filter by 8/3, because the suction volume rate of the air sampler was 3 L/min. The calculated results are listed in Table 1. The estimated exposures were in the range of 0.80–960 μg/crush with a median of 17 μg/crush. A pharmacist in one hospital crushed the tablets with a mortar and pestle, while pharmacists at four community pharmacies crushed with tablet crushers. Median exposures with a mortar and pestle (33 μg/crush) were higher than that with crushers (17 μg/crush), suggesting that the crushing with a mortar and pestle may cause health hazard. We have previously reported that the expected amount of drug exposure to a pharmacist during powder drug preparation in pharmacies was up to 36 μg/prescription with a median of 1.3 μg/prescription (Murahashi *et al.*, 2021). The maxi-

Table 1. Drug concentration in the room air and estimated exposure during tablet crushing in four pharmacies and a hospital.

Crushed tablets, number of tablets	Drug ingredient, total weight	Concentration (μg/m^3)	Exposure (μg/crush)
Pharmacy A (Utsunomiya, Tochigi)			
Amlodipine Besilate, 14T	Amlodipine Besilate, 0.07 g	15	0.80
Amlodipine Besilate, 14T	Amlodipine Besilate, 0.07 g	21	1.2
Amlodipine Besilate, 35T	Amlodipine Besilate, 0.175 g	36	1.9
*Camostat Mesilate, 105T	Camostat Mesilate, 10.5 g	63	3.4
*Camostat Mesilate, 105T	Camostat Mesilate, 10.5 g	270	15
*Rebamipide, 42T	Rebamipide, 4.2 g	1600	88
Famotidine, 140T	Famotidine, 1.4 g	49	2.7
*Bayaspirin®, 14T	Aspirin, 1.4 g	40	2.1
Pharmacy B (Misato, Saitama)			
*Zenaspirin, 14T	Aspirin, 1.4 g	1100	59
Cilostazol, 35T	Cilostazol, 3.5 g	320	18
Magmitt®, 42T	Magnesium Oxide, 13.8 g	980	52
Magmitt®, 14T	Magnesium Oxide, 4.62 g	3200	170
*Metgluco®, 14T	Metformin HCl, 7 g	13000	690
*L-Carbocisteine, 28T	L-Carbocisteine, 14 g	18000	960
Pharmacy C (Fukaya, Saitama)			
*Adcirca® 14T	Tadalafil, 0.28 g	56	4.2
Pharmacy D (Okegawa, Saitama)			
Naixan®, 84T	Naproxen, 8.4 g	440	35
Hospital E (Saitama City)			
Vasolan®, 14T	Verapamil HCl, 0.84 g	910	58
*Paxil, 10 T	Paroxetine HCl, 0.1 g	225	7.3

*: Film-coated tablets. Tablets were crushed using a blade-type crusher in the pharmacies A–D and mortar and pestle in hospital E.

mum and median expected drug exposures to a pharmacist during tablet crushing were more than 10 times higher than those during powder drug preparation, demonstrating that the working environment for pharmacists who crush tablets poses more hazards.

Next, the factors affecting the exposure amount will be discussed from the viewpoint of exposure of each active ingredient in the dust during drug crushing. In pharmacy A, there were two samplings during crushing of 14 amlodipine tablets or 105 camostat tablets. In the case of amlodipine, the amounts of exposure to a pharmacist were 0.80 μg/crush at the first time and 1.2 μg/crush at the second time, which were within a 2-fold difference. Whereas, in the case of camostat, the amounts of exposure were 3.4 μg/crush and 15 μg/crush, which were over a 4-fold increase. In pharmacy B, 14 and 42 Magmitt® tablets were crushed. Exposure amounts during the crushing of 14 tablets (170 μg/crush) were about three times higher than that during the crushing of 42 tablets (52 μg/crush). From these results, there is no proportional relationship between the number of crushed tablets and the amount of exposure to drug dust during crushing, suggesting that factors other than the characteristics of the tablet affect drug exposure. We have previously reported that the difference in drug exposure was attributed to individual handling differences during powder drug preparation (Murahashi *et al.*, 2021). Individual differences in the handling of drug crushing could be one of the major factors of drug exposure.

In this study, tablet-type medications with or without film coating were investigated. Since it is necessary to sift the debris of the films after crushing the tablets, film coating of tablets may affect the drug exposure to a pharmacist. Generally, the debris after crushing the film-coated tablets is removed by sifting the drug powder. This operation can cause higher drug exposure because extra high exposures (960 and 690 μg/crush) were observed for film-coated tablets such as Metgluco® and L-carbocisteine, respectively. It was hypothesized that the diameter of drug particulates from tablet crushing also affects the exposure amount because particles smaller than 106 μm were less likely to fall in our previous study (Murahashi *et al.*, 2021). In this study, we compared the distribution of particle diameter generated from crushing two types of tablets using the blade-type tablet crusher (HST-160), L-carbocisteine (Mucodyne® tablets 500 mg,

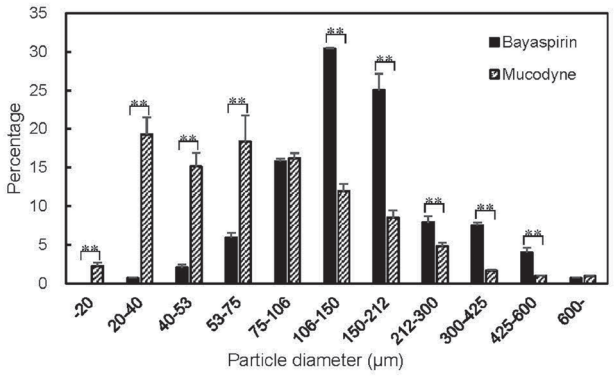

Fig. 2. Size distributions of particles from crushed Bayaspirin® and Mucodyne® tablets. **, significant difference ($P < 0.01$).

KYORIN Pharmaceutical Co. Ltd., Tokyo, Japan) which showed the highest exposure amount, and Bayaspirin® (Bayer AG, Leverkusen, Germany) which showed a relatively low exposure amount. Particles larger than 600 μm from both types of tablets were mainly debris of film coating. By comparing the particle size distribution below 600 μm, the percentages of coarse particulates (106–150, 150–212, 212–300, 300–425, and 425–600 μm) from Mucodyne® were significantly lower than those from Bayaspirin® ($P < 0.01$), whereas the percentages of fine particulates (below 20, 20–40, 40–53, and 53–75 μm) from Mucodyne® were significantly higher than those from Bayaspirin® ($P < 0.01$) (Fig. 2). These results indicate that particles of Mucodyne® were much smaller than those of Bayaspirin®, were easily dispersed, and were more difficult to settle down from the room air, resulting in the observed high exposure to L-carbocisteine particulates.

Prevention of drug exposure by working on a bench with dust remover and wearing a medical mask

Installation of a dust remover is a common measure to reduce drug exposure (Hayashi *et al.,* 1980; Takayama *et al.,* 1999). Dust Hazard Prevention Regulations based on the Industrial Safety and Health Act (Ministry of Internal Affairs and Communications, 2021a) require companies to take necessary measures such as improving equipment, work processes, work methods, and the work environment to prevent health hazards for workers exposed to dust. Following these regulations, a local exhaust system or a push-pull type ventilation system is required. It has been reported that the installation and proper operation of dust removers had a great influence on the dust concentration in the room air (Inaba *et al.*, 2016). In this study, we evaluated reduction efficiency using dust remover by the simulation survey.

Concentrations of drug ingredients in the room air and estimated exposure of drug ingredients during tablet crushing on the lab bench and the dispensing bench with dust remover are listed in Table 2. When tablets were crushed on the lab bench, the active ingredient, acetaminophen, was detected at a mean value of 1280 μg/m^3, and its exposure was estimated to be 51 μg/crush. On the other hand, when tablets were crushed on the bench with a dust remover, the active ingredient concentration was reduced to 12 μg/m^3, and the estimated exposure was reduced to 0.5 μg/crush. The reduction rate by working on the bench with a dust remover was calculated to be 99.0%, suggesting that the proper operation of a dust remover was very effective in reducing the drug exposure.

We also evaluated the effect of wearing a medical mask on the prevention of drug exposure. Our previous report demonstrated that wearing a medical mask reduced over 90% of drug exposure during powder drug preparation (Murahashi *et al.*, 2021). In this study, the reduction effect of wearing the mask during tablet crushing was tested (Table 3). In the case of brand A's mask, the mean amount of the active ingredient, acetaminophen, on the filter covered with the mask (1.36 μg/filter) was much lower (less than 40 times) than that without the mask (57.7 μg/filter). Brand B's mask showed similar results. The calculated removal rates were 98% and 96% for brands A's and B's masks, respectively. These results suggested that wearing a medical mask could reduce about 97% drug exposure during tablet crushing.

In this study, we revealed that working on a bench with a dust remover reduced exposure by 99.0%, and wearing a medical mask while working reduced exposure by 97%.

Table 2. Concentration in room air and estimated exposure of acetaminophen during simulation tablet crushing on a lab bench and a dispensing bench with dust remover.

Work environment	Concentration (μg/m^3)	Exposure (μg/crush)	Reduction rate (%) 100 × (A–B)/A
On a lab bench	1280 ± 35	51 ± 1 (A)	—
On a dispensing bench with dust remover	12 ± 4	0.5 ± 0.1 (B)	99.0

Each value represents mean ± SD ($n = 3$).

Table 3. Effect of covering a medical mask on the drug exposure.

Brand of mask	Amount of ingredient (μg/filter)		Removal rate (%) 100 × (C–D)/C
	without mask (C)	with mask (D)	
A	57.7 ± 12.7	1.36 ± 0.55	98
B	54.6 ± 29.8	1.99 ± 0.40	96

Each value represents mean ± SD (n = 3).

Table 4. Time course of acetaminophen concentration in room air and estimated exposure in each process of Calonal® tablet crushing.

Time (min:sec)	Process	concentration in room air (μg/m^3)	Exposure (μg/process)
0:00–0:30	Placing of tablets in the cell of crusher	< 1	< 0.005
0:30–1:00	(Change the filter holder)	—	—
1:00–1:30	Crushing of tablets	< 1	< 0.005
1:30–2:00	(Change the filter holder)	—	—
2:00–3:30	Transfer drug powder to the tray	56 ± 1	0.67 ± 0.01
3:30–4:00	(Change the filter holder)	—	—
4:00–7:30	Clean the cell of the crusher	2460 ± 1570	69 ± 44
7:30–8:00	(Change the filter holder)	—	—

Each value represents mean ± SD (n = 3).

It was estimated that the exposure could be reduced by over 99.9% by taking both measures. A synergistic effect of exposure reduction can be expected by combining multiple measures, estimating that a reduction of over 99.9% can be achieved by taking both measures.

Utilization of mortar-type tablet crusher, SafeCrush™

General tablet crushers have a rotary blade like a household coffee mill to crush tablets. Pharmacists are exposed to the drug dust scattered in the room air when they are transferring the drug powder after crushing it to an inlet of automatic dividing and packaging machines (Maeda *et al.*, 2016). In addition, drug dust also scatter during the cleaning of the crusher. Therefore, to know the exposure amount in each process from putting the tablets into the cell of the crusher to transferring the crushed powder to an automatic dividing and packaging machine, we analyzed the concentration of the active ingredient, acetaminophen, in the room air in each process of crushing Calonal® tablet and estimated its exposure (Table 4).

In the processes of placing the Calonal® tablets into the cell of the crusher and the crushing of the tablets, the levels of acetaminophen on the filters of the processes were hardly detected. This result suggested that the exposure amount during placing and crushing in the machine would be extremely small because the drug dust did not scatter in the air in these processes. On the other hand, large amounts of acetaminophen in the air were detected during both processes of transferring the crushed powder to the tray and cleaning the crusher. This high exposure of the drug dust to pharmacists in these processes would be unavoidable using the crusher with the rotary blade.

SafeCrush™ was developed by the Government of Canada. The machine does not have a rotating blade but rather crushes tablets by sandwiching them between two plastic trays and rotating them while applying force from above and below like a stone mortar. In Canada, nurses crush tablets immediately before administration by the patients, thus this machine was developed to ensure the safety of nurses. In Japan, pharmacists crush the tablets in community pharmacies and dispensing rooms in hospitals according to the law. We compared the drug exposure, drug loss, and pre-drug contamination during the crushing of Loxonin® and Calonal® tablets by pharmacists using the general blade-type crusher HST-160 and Canada's mortar-type crusher SafeCrush™.

When four tablets of Loxonin® were crushed, the exposure of the active ingredient, loxoprofen, in the room air using the mortar-type crusher (0.007 μg/crush) was much lower than that using the blade-type crusher (8.1 μg/crush) as listed in Table 5, because transferring the crushed powder to the tray and cleaning the crusher are not necessary when using the mortar-type crusher. Due to the little scattering into the atmosphere, the mortar-type crusher can reduce 99.9% of loxoprofen exposure to pharmacists. Similar results were obtained by crushing Calonal® tab-

Table 5. Comparison of reduction rate of exposure by blade-type and mortar-type tablet crushers.

Crushed tablet	Ingredient	Tablet crusher	Concentration ($\mu g/m^3$)	Exposure (μg/crush)	Reduction Rate (%) 100 × (E–F)/E
Loxonin®, 4T	Loxoprofen	Blade type	264 ± 15	8.1 ± 1.0 (E)	—
		Mortar type	0.4 ± 0.3	0.007 ± 0.006 (F)	99.91
Calonal®, 4T	Acetaminophen	Blade type	1830 ± 70	70 ± 3 (E)	—
		Mortar type	0.6 ± 0.2	0.012 ± 0.004 (F)	99.98

Each value represents mean ± SD (n = 3).

Table 6. Comparison of drug loss rate by blade-type and mortar-type tablet crushers.

Crushed tablet	Crusher type	Weight (g)		Drug loss rate (%) 100 × (E–F)/E
		Before crush (tablets, E)	After crush (powder, F)	
Loxonin®, 4T	Blade type	1.041 ± 0.006	0.780 ± 0.030	25.1
	Mortar type	1.029 ± 0.015	1.029 ± 0.015	0.0
Calonal®, 4T	Blade type	1.205 ± 0.004	0.913 ± 0.027	24.2
	Mortar type	1.194 ± 0.006	1.194 ± 0.006	0.0

Each value represents mean ± SD (n = 3).

Table 7. Comparison of pre-drug contamination rate by blade-type and mortar-type tablet crushers.

Pre-crushed tablet	Active Ingredient	Next crushed tablet	Crusher type	Amount of ingredient (mg)		Contamination rate (%) 100 × H/G
				in the pre-crushed tablets (G)	in the next crushed powder (H)	
Loxonin®, 4T	Loxoprofen	Calonal®, 4T	Blade type	272.4	0.071 ± 0.021	0.026
			Mortar type	272.4	0.0026 ± 0.0017	0.001
Calonal®, 4T	Acetaminophen	Bufferin®, 4T	Blade type	800	1.57 ± 0.97	0.20
			Mortar type	800	0.037 ± 0.014	0.005

Each value represents mean ± SD (n = 3).

lets using the mortar-type crusher.

Next, the drug loss while crushing using the two machines was investigated. In the case of the mortar-type crusher, since the drug powder did not scatter in the air, drug loss was too low to be measured (Table 6). When four tablets of Loxonin® or Calonal® were crushed with the blade-type crusher, a loss of approximately 25%, equivalent to one tablet, was observed due to scattering and sticking to the inside of the cell and blade.

Finally, we compared the contamination by pre-drugs (drugs pre-crushed with blade- or mortal-type crushers) using the two types of crushers. Table 7 lists the pre-drug contamination when three types of drugs are crushed in sequence. When four tablets of Caronal® were crushed with the mortar-type crusher after Loxonin® pre-crushing, trace levels of loxoprofen from pre-crushing were detected and the contamination rate of the pre-crushed drug was calculated to be 0.001%. On the other hand, the contamination rate of the pre-drug, loxoprofen, with the blade-type crusher (0.026%) was much higher than that with the mortar-type crusher, because the drug stuck to the backside of the rotary blade. A similar result was obtained for the contamination rate of the pre-drug, acetaminophen, to Bufferin® after the Calonal® tablets crushing. This poses a problem of contamination with even small amounts of pre-crushed anti-cancer drugs or allergens; however, this does not pose a problem for general drugs.

This study showed that the mortar-type crusher SafeCrush™ was superior to the current crushers widely used in terms of release of ingredients into the air, drug loss, and pre-drug contamination. SafeCrush™ cannot be used instead of the general blade-type crusher, because SafeCrush™ can only crush up to several tablets. It was reported a "simple suspension method" in which tablets are disintegrated and suspended in warm water at 55°C without being crushed in the case of administration to patients through a gastric fistula, intestinal fistula, or nasal tube (Kurata *et al.*, 2001). However, tablets for oral administration are generally still crushed.

In this study, we scientifically reported the concentra-

tion of drug ingredients in the air and the estimated exposure of pharmacists to drugs during crushing tablets. Furthermore, we suggested wearing a medical mask and working on the dispensing bench with dust remover as exposure prevention measures, and that performing both measures could result in more than a 99.9% reduction in the exposure.

Since occupational exposure of pharmacists to drugs is a serious problem, it is necessary to set a standard value for the drug concentration in the room air and prepare a guideline for countermeasures. To determine the threshold value required for setting the standard value, we are developing a study examining the relationship between the exposure of drugs to pharmacists and the appearance of symptoms.

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Conflict of interest---- SafeCrush™ was provided by Medicalpine Corporation (Tokyo, Japan).

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