

*Original Article*

## Estimation of occupational exposure to drugs during tablet crushing

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**ABSTRACT** — In hospitals and pharmacies, many kinds of pharmaceutical tablets are frequently crushed to powder in order to facilitate administration. However, there is concern about the influence of this process on the health of pharmacy workers. In this study, we conducted model experiments to estimate the potential exposure of pharmacy workers to pharmaceutical particles during tablet crushing and transfer of powder. Tablets were crushed in a tablet mill. Particulates released into the air during and after milling and transfer to a mortar were counted with a dust counter, and collected on the filter of an air sampler. Amounts of pharmaceutical active ingredients collected on the filter were determined by high-performance liquid chromatography (HPLC). During tablet crushing, particulates were released into the air. We found that the particle concentration in air was highest during transfer of the powder from the tablet mill to the mortar. The amount of active ingredient collected on the filter of the air sampler was significantly higher in the case of Loxonin, as compared with Neurovitan. Although conditions under which tablets are crushed are likely to vary greatly in practice, our results and calculations at least indicate that unmasked workers might routinely inhale microgram levels of active ingredients during tablet crushing and transfer of the resulting powder. Our results should be helpful in designing appropriate protective measures and in developing professional guidelines to minimize occupational exposure of pharmacy workers to drugs.

**Key words:** Medicine exposure, Tablet crushing, Pharmaceutical pollution, Occupational exposure, Pharmaceutical particles

### INTRODUCTION

Patients may be unable to take drugs in tablet form if they have difficulty swallowing, or are being fed via a feeding tube, or for other reasons, and consequently many kinds of pharmaceutical tablets are frequently crushed to powder in hospitals and pharmacies in order to facilitate administration. However, this process involves potential exposure of pharmacy and healthcare workers to the active ingredients, and in 2004, The National Institute for Occupational Safety and Health (NIOSH) warned that “Working with or near hazardous drugs in health care settings may cause skin rashes, infertility, miscarriage, birth defects, and possibly leukemia or other cancers.” Indeed, there are many reports of adverse effects, such as wors-

ening of asthma (Asai *et al.*, 1987; Bahn *et al.*, 2006; Nakamura *et al.*, 1971), contact dermatitis (Condé-Salazar *et al.*, 2001; Swinnen *et al.*, 2013; Vander Hulst *et al.*, 2010) and rhinitis (Kataura *et al.*, 1973), due to inhalation or contact with airborne particles of drugs, especially those used to treat gastrointestinal and neuropsychiatric disorders and antibiotics. Therefore, the purpose of this study was to estimate the potential exposure of workers to drug particulates during a typical procedure of crushing tablets in a tablet mill and transferring the powder to a mortar. This information is expected to be helpful in developing countermeasures and guidelines to limit occupational exposures.

## MATERIALS AND METHODS

### Materials

LOXONIN® Tablets (Loxonin: containing loxoprofen sodium hydrate; Daiichi Sankyo Co., Ltd., Tokyo, Japan) and Neurovitan® Tablets (Neurovitan: containing octotiamine, riboflavin, pyridoxine hydrochloride and cyanocobalamin; Astellas Pharma Inc., Tokyo, Japan) were purchased. Their characteristics are summarized in Table 1. Loxoprofen sodium hydrate and riboflavin were also purchased from Sigma-Aldrich (St Louis, MI, USA). Acetonitrile and other reagents used in the analysis were laboratory-grade materials.

### Tablet crushing and air sampling

To simulate the workplace in typical pharmacies, we used a tablet mill (Takazono Corp., Tokyo, Japan) placed in a draft chamber (Shimadzu Rika Co., Tokyo, Japan). Particulates were measured with a digital dust meter LD-6N (Shibata Science Co., Ltd., Saitama, Japan) and air sampling and particulate collection were done with an air sampler equipped with a fiberglass filter and a low-volume pump LV-40 BR (Shibata Science Co., Ltd.), based on previous reports (Friedlande, 1977; Honma, 1990; Takayama *et al.*, 1999; Tomonaga *et al.*, 1983). During the experiment, the ventilation fan in the draft chamber was stopped and the glass door was kept closed as much

as possible. The set-up, together with the experimental procedure and conditions, is shown in Fig. 1. The capacity of the draft chamber was approximately 1.10 m<sup>3</sup>. The distance between the drug mill and the air sampler was 50 cm. The air sampler was placed 130 cm above the floor, as this was considered to correspond approximately to the height of workers' faces. The flow rate of the air sampler was 30 L/min. Twenty-one tablets were crushed at one time, corresponding to a 7-day prescription for 1 tablet, 3 times per day. The gross weights of 21 tablets of Loxonin and Neurovitan were 5.25 g (containing 1.43 g of loxoprofen sodium hydrate) and 2.86 g (containing 52.5 mg of riboflavin), respectively. The tablets were crushed in the drug mill for 10 sec, and after standing for 5 sec, the mill was opened and the powder was transferred to a mortar with a spatula over a period of 1 min, and then left in the mortar for 5 min. Each experiment was continued for 6 min 15 sec in total and then the draft chamber was ventilated for 10 min before the next experiment. Experiments were performed 6 times for both drugs.

### Counting airborne particulates

During each experiment, airborne particulates (0.1-10 µm) were measured every 5 sec with a digital dust meter LD-6N, based on light scattering. The cumulative value of counts over the experimental period of 6 min 15 sec was calculated (total counts).

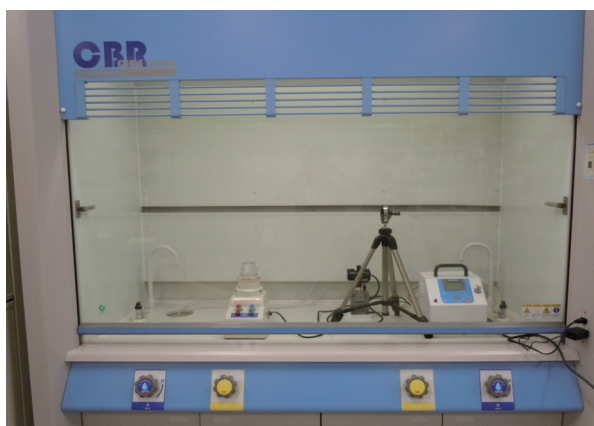
**Table 1.** Characteristics of LOXONIN® Tablets 60 mg (Loxonin) and Neurovitan® Tablets (Neurovitan).

	Active principle(s)	Additives	Dosage form	External form		
				Diameter (mm)	Thickness (mm)	Weight (mg)
LOXONIN® tablets 60 mg (Loxonin) <sup>a</sup>	Loxoprofen Sodium Hydrate 68.1 mg	Low Substituted Hydroxypropylcellulose Red Ferric Oxide Lactose hydrate Magnesium Stearate	Non-coated tablet	9.1	3.3	250
Neurovitan® tablets (Neurovitan) <sup>b</sup>	Octotiamine 25 mg Riboflavin 2.5 mg Pyridoxine Hydrochloride 40 mg Cyanocobalamin 0.25 mg	Lactose hydrate Low Substituted Hydroxypropylcellulose Hydroxypropylcellulose Magnesium Stearate Hypromellose Hypromellose phthalate Triacetin Macrogol Titanium Oxide Talc Red Ferric Oxide	Film-coated tablet	7.1	3.3	136

<sup>a</sup> Daiichi Sankyo Co., Ltd. (2013) Interview form of LOXONIN® tablets

<sup>b</sup> Astellas Pharma Inc. (2014) Interview form of Neurovitan® tablets

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**Fig. 1.** Experimental system for crushing tablets and measuring particulates in the draft chamber. Details of the set-up were: Capacity of the draft chamber, 1.10 m<sup>3</sup>; location of tablet mill, 110 cm above the floor; location of digital dust meter, 100 cm high, location of air sampler, 130 cm high; distance between tablet mill and digital dust meter, 50 cm; distance between tablet mill and air sampler, 50 cm; ventilation fan off.

### Collection of particulates

Particulates were collected on the fiberglass filter (55 mm diameter) of the air sampler, and pharmaceutical ingredients were extracted by sonication for 5 min in methanol (5 mL). The filter was extracted again with 3 mL of methanol, and the combined extract was evaporated to dryness. The residue was taken up in 200  $\mu$ L of the HPLC mobile phase (see below) and centrifuged at 5,600  $\times$  g for 5 min. The supernatant was subjected to HPLC.

### High-performance liquid chromatography (HPLC)

Loxoprofen sodium hydrate was measured under the conditions described in The Japanese Pharmacopoeia Sixteenth Edition and riboflavin was measured according to LC Technical Note 143 (GL Sciences Inc.) and Gatautis and Naito (1981), with some modifications in each case. Loxonin was determined with a LC-10ADvp instrument (Shimadzu Co., Kyoto, Japan) equipped with an Inertsil ODS-3 column (4.6 mm I.D.  $\times$  150 mm, 3  $\mu$ m, GL Sciences Inc., Tokyo, Japan) at 20°C. The mobile phase was methanol : purified water : acetic acid : triethylamine = 600:400:1:1(v/v), at a flow rate of 0.5 mL / min, with detection at 222 nm. Phenacetin was used as an internal standard. Neurovitan was determined with a L-7485 instrument (Hitachi High-Technologies Corp.,

Tokyo, Japan) equipped with a fluorescence detector (Ex. 445 nm, Em. 530 nm). The column and column temperature were the same as for Loxonin. The mobile phase was methanol : acetic acid buffer (pH 4.5) = 35:65 (v/v), at a flow rate of 1.0 mL/min.

### Statistical analysis

Student's t test was used for inter-group comparison of particulates generation between Loxonin and Neurovitan. A P values of < 0.01 was regarded as significant. The correlation coefficient between particulates level in air and quantity of pharmaceutical ingredients collected on the air sampler filter was also determined by simple regression analysis. PASW<sup>®</sup> statistics 17.0 (SPSS Inc., Chicago, IL, USA) was used for all calculations.

## RESULTS

### Particulates concentration in air during and after tablet crushing

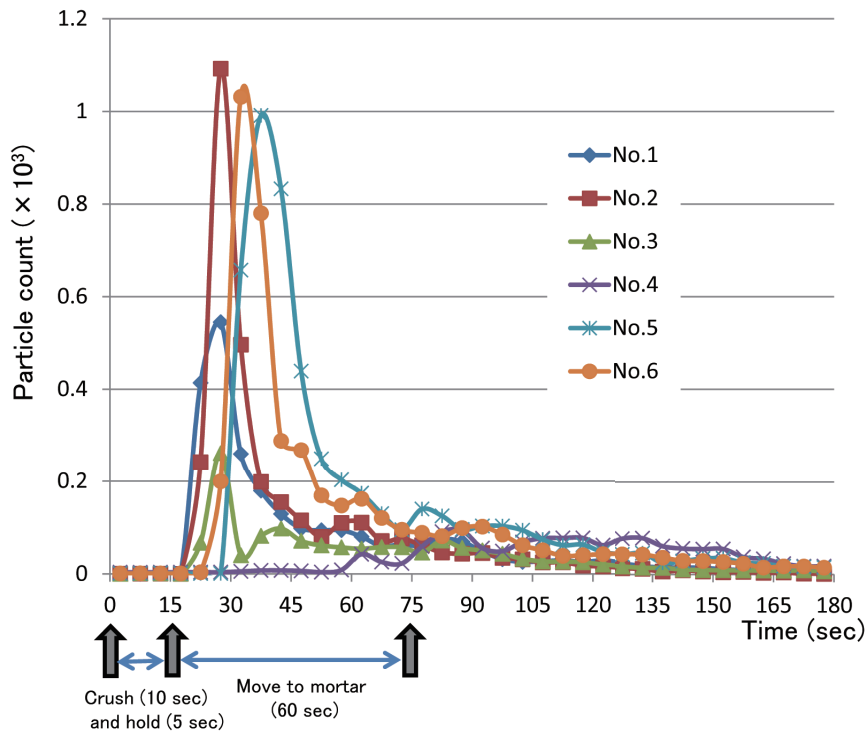
For both Loxonin and Neurovitan, the particulates concentrations in air were highest when the cover of the tablet mill was opened and the powdered drugs were transferred to the mortar after crushing, i.e., during the period of 15-75 sec. Figures 2 and 3 show the time courses (n = 6 each) of particulates concentration up to 180 sec for Loxonin and Neurovitan, respectively. There was considerable inter-experimental variability, and the highest levels were around 1,100 counts. The cumulative (total) counts up to 6 min 15 sec are shown in Table 2. The mean values were approximately 3,000 and 2,000 counts for Loxonin and Neurovitan, respectively, but the difference was not statistically significant.

### HPLC determination of active ingredients collected by the air sampler

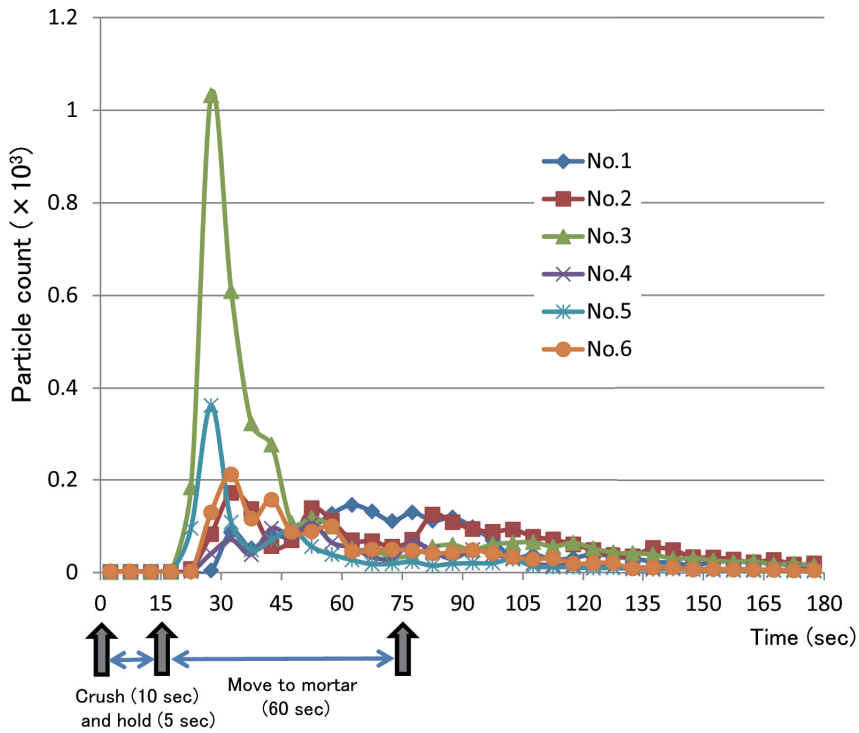
The results of HPLC measurement of active ingredients in particulates collected on the fiberglass filter over the 6 min 15 sec experimental period are summarized in Table 3 as total amounts, together with the calculated equivalent weight of tablet for each experiment. The mean weight of Loxonin collected on the filter as tablet-equivalent was 93.6  $\mu$ g (0.0178 % of the gross weight of crushed tablets), and the corresponding value for Neurovitan was 49.4  $\mu$ g (0.0173 % of gross weight). The difference between the two types of tablet is significant (P < 0.01).

### Prediction of the quantity of drugs inhaled by pharmacy workers

If pharmacy workers conducted tablet crushing without



**Fig. 2.** Particulate count number during and after crushing of Loxonin. Particulates count number was measured during and after crushing of 21 tablets of Loxonin (experimental duration 6 min 15 sec). The experiment was repeated 6 times. For details, see MATERIALS AND METHODS.



**Fig. 3.** Particulate count number during and after crushing of Neurovitan. Particulates count number was measured during and after crushing of 21 tablets of Neurovitan (experimental duration 6 min 15 sec). The experiment was repeated 6 times. For details, see MATERIALS AND METHODS.

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a mask, we can calculate the amount of drugs that would be inhaled by using the results in Table 3. We assume that the inspiration volume is 0.5 (L/time) and the respiratory rate is 15 (times /min) in healthy men (Marieb, EN 2014).

Total inspiration volume over the experimental period (L) = 0.5 (L / time)  $\times$  15 (times / min)  $\times$  6.25 (min)

Total intake volume of air sampler (L) = Flow rate (L / min) of the air sampler  $\times$  6.25 (min) = 30 (L / min)  $\times$  6.25 (min)

Calculated inhalation of drug particulates by worker ( $\mu\text{g}$ ) = Total inspiration volume (L) of worker  $\times$  quantity of pharmaceutical ingredients collected by air sampler / Total intake volume (L) of the air sampler

The results indicate that 23.4  $\mu\text{g}$  and 12.4  $\mu\text{g}$  of Loxonin and Neurovitan, respectively, would be inhaled. These values correspond to 6.38 and 0.227  $\mu\text{g}$  of active ingredient (loxoprofen sodium hydrate for Loxonin and riboflavin for Neurovitan).

## DISCUSSION

Our findings indicate that, during tablet crushing in a mill and subsequent transfer of the powder to a mortar, quite high levels of drug particulates become airborne. Approximate calculations suggest that a worker engaged in tablet crushing without a mask might inhale particulates corresponding to microgram levels of exposure to the active ingredients. Of course, there are many variables that might affect this, including temperature, humidity, care taken in opening the cover of the tablet mill, and the position of the worker relative to the mill. The variability is emphasized by the low correlations found between the quantity of particulates in the air and the amount of material collected on the filter of the air sampler ( $R^2 = 0.22$  for Loxonin and  $R^2 = 0.64$  for Neurovitan). This correlation may be greatly affected by differences in the relative position and height of the various items of experimental equipment.

Although the putative exposure levels are very low, the possibility that chronic, long-term, low-level exposures to powerful drugs may have adverse health effects cannot be ruled out. There are many reports concerning drug

**Table 2.** Total particle counts measured during crushing of Loxonin (a) and Neurovitan (b) tablets.

(a) Loxonin		(b) Neurovitan	
	Total counts (6 min 15 sec)		Total counts (6 min 15 sec)
No.1	2649	No.1	2066
No.2	3182	No.2	2414
No.3	1459	No.3	3992
No.4	1948	No.4	1153
No.5	5161	No.5	1293
No.6	4398	No.6	1600
Mean $\pm$ S.D.	3133 $\pm$ 1452	Mean $\pm$ S.D.	2086 $\pm$ 1047

Relative concentration of 0.1-10  $\mu\text{m}$  particles in the air was measured with a digital dust meter. The counts were recorded every 5 sec and total counts were accumulated for 6 min 15 sec.

**Table 3.** Amount of active ingredients collected on the air sampler.

(a) Loxonin			(b) Neurovitan		
	Loxoprofen sodium hydrate ( $\mu\text{g}$ )	Loxonin ( $\mu\text{g}$ )		riboflavin ( $\mu\text{g}$ )	Neurovitan ( $\mu\text{g}$ )
No.1	25.0	91.8	No.1	1.09	59.1
No.2	34.0	125	No.2	0.493	26.8
No.3	18.3	67.2	No.3	1.82	98.8
No.4	23.9	87.7	No.4	0.829	45.1
No.5	28.1	103	No.5	0.495	26.9
No.6	23.7	87.1	No.6	0.725	39.4
Mean $\pm$ S.D.	25.5 $\pm$ 5.23	93.6 $\pm$ 19.2	Mean $\pm$ S.D.	0.908 $\pm$ 0.498	49.4 $\pm$ 27.1

Loxoprofen sodium hydrate and riboflavin were extracted from the filters of the air sampler and quantitated by means of HPLC. From these results, we calculated the quantities of Loxonin (a) and Neurovitan (b) collected on the filters. Values are mean  $\pm$  S.D. from 6 experiments.



exposure of healthcare workers, especially in connection with the preparation of antineoplastic drug injections. Antineoplastic drugs have been detected in workers' urine (Burgaz *et al.*, 1999; Sessink *et al.*, 1992; Sessink *et al.*, 1997), and pharmacists have complained of headache and dizziness after preparing antineoplastic drugs (Ladik *et al.*, 1980). Symptoms such as hair loss, skin rash and light-headedness have been reported in nurses (Krstev *et al.*, 2003). Surface contamination with antineoplastic drugs is also a problem in hospitals (Connor *et al.*, 1999; Ramphal *et al.*, 2014; Sessink *et al.*, 1992; Sugiura *et al.*, 2011). Consequently, closed systems for preparing antineoplastic drugs have been introduced in many hospitals (Nygren *et al.*, 2002; Sessink *et al.*, 2011; Wick *et al.*, 2003). However, little is known about actual levels of exposure.

Our results and calculations indicate that exposure levels to active ingredients as a result of tablet crushing or powder dispensing are likely to be low in practice, but nevertheless the exposures may be chronic, and the above reports indicate that they may have serious consequences. Therefore, it is important for hospital managers and healthcare workers to ensure that suitable facilities are available to minimize exposure. As interim measures, it would at least be desirable to ensure that suitable masks are worn, and that tablet mills are not opened immediately after completion of crushing. But, in the longer run, it will be important to develop proper, evidence-based guidelines for pharmacists and other workers. Further work is in progress to measure actual contamination levels in pharmacies, in the light of the present results.

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**Conflict of interest----** The authors declare that there is no conflict of interest.

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