***Regular Article***

# Development of Novel Bead Milling Technology with Less Metal Contamination by pH Optimization of the Suspension Medium

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**To develop novel contamination-less bead milling technology without impairing grinding efficiency, we investigated the effect of the formulation properties on the grinding efficiency and the metal contamination generated during the grinding process. Among the various formulations tested, the combination of polyvinylpyrrolidone and sodium dodecyl sulfate was found to be suitable for efficiently pulverizing phenytoin. However, this stabilization system included a relatively strong acid, which raised the concern of possible corrosion of the zirconia beads. An evaluation of the process clearly demonstrated that acidic pH promoted bead dissolution, suggesting that this could be suppressed by controlling the pH of the suspension. Among the various pH values tested, the metal contamination generated during the grinding process could be significantly reduced in the optimized pH range without significant differences in the particle size of the phenytoin suspension after pulverization. In addition, the contamination reduction by pH optimization in the presence of physical contact among the beads was approximately 10-times larger than that without bead contact, suggesting that pH optimization could suppress not only bead dissolution but also the wear caused by bead collisions during the grinding process. These findings show that pH optimization is a simple but effective approach to reducing metal contamination during the grinding process.**

**Key words** nanosized particle; bead mill; contamination; pH optimization

## Introduction

Recently, it has become possible to find a larger number of excellent drug candidate compounds in a shorter period of time thanks to the progress of various technologies, such as combinatorial chemistry and high-throughput screening technology.[1)] However, approximately 40–70% of such drug candidate compounds have been discontinued due to their poor solubility.[2,3)] Therefore, new technologies to overcome poor drug solubility have been actively investigated.[4)]

For poorly soluble drugs, pharmaceutical technologies to improve their dissolution rate and apparent solubility are essential to achieving higher bioavailability. The Noyes–Whitney equation[5)] and the Ostwald–Freundlich equation[6)] are well-known for describing the dissolution rate and apparent solubility of a drug, respectively. Based on these equations, increasing the surface area or solubility of a drug is considered to be effective for improving its dissolution rate.[7)]

Further, pulverization is one useful technology for obtaining nanosized particles to improve the dissolution rate of a drug by increasing its surface area.[8)] Nanosized particles can be prepared by bottom-up or breakdown techniques, such as pulverization, bead milling,[9–13)] high-pressure homogenizing,[14–19)] and liquid antisolvent precipitation.[20)] Among them, bead milling, a breakdown technique, offers high grinding efficiency and is superior to other technologies in terms of scalability and reproducibility.[21)] Therefore, bead milling is currently one of the most widely used wet grinding techniques.[22)]

In the bead mill grinding method, a grinding medium, such as yttria-stabilized zirconia beads, is often used to grind and disperse drugs. Therefore, the risk of metal contamination, such as from the zirconium due to collision of the grinding beads, has been a major concern.[23–26)] Although zirconium toxicity was confirmed to be moderately low by histological or cytological studies,[27)] it is essential to minimize and control undesirable contamination by impurities, particularly for pharmaceutical products. Therefore, various methods to reduce metal contamination in the grinding process have been studied, but the outcomes remain unsatisfactory.

The mainstream approach to reducing contamination by the collision of grinding beads is optimization of the grinding medium or grinding parameters of the milling equipment. As an example of the former, smaller-sized zirconia beads have been reported to reduce the amount of contamination.[28)] In addition, materials such as dry ice,[26)] sugars,[29)] and salts,[30)] which are considered safe, have been used as grinding media. As an example of the latter, the wear of the grinding media is considered to be suppressible by using a lower rotation speed and lower media filling.[31)] Although the abovementioned approaches can reduce the amount of contamination generated during the grinding process, they are known to impair the grinding efficiency. Therefore, in the present study, we attempted to find a novel approach to reduce metal contamination without impairing the grinding efficiency.

## Experimental

**Materials** Phenytoin was purchased from Shizuoka Caffeine Industries (Japan), polyvinylpyrrolidone (PVP K-25), and sodium dodecyl sulfate (SDS) from BASF Japan Ltd. (Japan), hydroxypropyl methylcellulose (HPMC TC-5E) from Shin-Etsu Chemical Co., Ltd. (Japan), hydroxypropyl cel-

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lulose (HPC-SSL) from Nippon Soda Co., Ltd. (Japan), and yttria-stabilized zirconia beads with a diameter of 500 $\mu$m (YTZ-0.5) from Nikkato Corporation (Japan). Hydrochloric acid (HCl), trisodium citrate, citric acid, sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dodecahydrate, sodium carbonate, and sodium hydrogen carbonate, used to prepare buffers of various pH, and 1 N sodium hydroxide (NaOH), used to adjust the pH, were purchased from Kanto Chemical Co., Inc (Japan). All other chemicals and solvents were of analytical reagent grade, and purified water was used throughout the study.

**Formulation Study Using a Rotation–Revolution Mixer** Phenytoin at 5% (w/w) in purified water was stabilized with 1% (w/w) polymer and 0.1% (w/w) SDS. Phenytoin was dispersed in a dispersion medium with a stirrer and then sonicated to form a suspension. An amount of 2 mL of suspension and 4 g of zirconia beads, 500 $\mu$m in diameter, were placed into a zirconia vessel, followed by milling at 2000 rpm for 4 min with a chamber temperature of 5 °C using a rotation–revolution mixer (NP-100, Thinky Corp., Japan). The same cycle was repeated 9 times, for a total of 36 min of milling. The temperature of the milling chamber was maintained at 4–7 °C during grinding. Particle size distributions as Z-averages were measured using dynamic light scattering (DLS; Zetasizer Nano, Malvern Panalytical Ltd., Japan). The Z-average was determined by taking the refractive index value of 1.61 for phenytoin particles and 1.33 for the measurement medium (water). To measure the particle size, water was used to dilute the drug to maintain the drug concentration of 0.4 mg/mL.

**Evaluation of the pH-Dependent Dissolution of Zirconia Beads** A pH 1 buffer was prepared using 0.1 N HCl. The pH 3–5 buffer was prepared using 100 mM citrate buffer, pH 6–8 buffer using 100 mM phosphate buffer, and pH 9 and 10 buffers using 100 mM carbonate buffer. An amount of 9.25 g of yttria-stabilized zirconia beads of 500-$\mu$m diameter was placed into a metal-free container. The sample was inverted 5 times for homogenization with 5 mL of each pH buffer. These samples were incubated at 25 °C for 24 h, and the supernatant was obtained after 5 repeats of inversion at predetermined times. The obtained sample was evaluated for metal contamination using inductively coupled plasma-mass spectrometry (ICP-MS, iCAPQ, Thermo Fisher Scientific, U.S.A.).

**Procedure for Wet Milling with Dyno-Mill** Phenytoin at 5% (w/w) in purified water was stabilized with 3% (w/w) PVP K-25 and 0.25% (w/w) SDS. Phenytoin was dispersed in a dispersion medium with a stirrer and then sonicated to form a suspension. For pH adjustment, 1 N of NaOH was added until the target pH was reached. After adjusting the pH, stirring was conducted with a stirring bar for 90 min, then 150 g of suspension was prepared, and 100 g was used. Wet milling was performed using a Dyno-mill Research Lab apparatus (Willy A. Bachofen AG, Germany). For all experiments, the milling chamber was filled with beads at a ratio of 70% (v/v). The rotation speed of the accelerator was set to 4 m/s for 90 min for the grinding process. Yttria-stabilized zirconia beads with a diameter of 500 $\mu$m were used as the grinding medium. The process was performed in the recirculation mode. The grinding chamber was connected to an external cooling device BH-302 (Yamato Scientific Co., Ltd., Japan) to dissipate the heat generated during milling. Samples were taken from the outlet of the grinding chamber for particle size measurement and metal contamination determination at different time intervals. Particle size distributions as D50 were measured using DLS (UPA150, Nikkiso Corp., Japan) after milling times of from 5 to 90 min. The volumetric median particle size D50 was determined by taking a refractive index value of 1.61 for the phenytoin particles and 1.33 for the measurement medium (water). To measure the particle size, water was used to dilute the drug to maintain the drug concentration of 0.4 mg/mL.

**Determination of Metal Contamination in the Nanosized Particle Suspension** The metal contamination in the nanosized particle suspension was determined by elemental analysis. Both the solid and dissolved components in the suspension were quantified by ICP-MS. An amount of 0.5 g of the sample was placed into a metal-free chamber, and an internal standard substance (Co) and the NMP/HCl/$HNO_3$ mixture (90 : 5 : 5) were added. The samples were completely dissolved by ultrasonic irradiation. Elemental analysis was performed with four different calibration solutions and an internal standard. The range of the calibration was 0.5–2.0 ppm.

## Results and Discussion

**Suspension Formulation Design for Bead Milling** Prior to this study, the suspension formulation was optimized to stabilize the dispersion of phenytoin. It has been reported that the formulation of a polymer and surfactant is useful for stabilizing the dispersion of a drug.[32] In this study, we selected HPMC, HPC, and PVP as the polymer candidates. In addition, SDS was used as a surfactant to prepare a combination formulation with a polymer. Subsequently, phenytoin was dispersed in water with these additives and then subjected to grinding with zirconia beads using a rotation–revolution mixer. The effects of the dispersion medium on the phenytoin particle size are shown in Fig. 1. The grinding process was continued until the particle size reduction transition reached equilibrium. The grinding efficiency was evaluated by measuring the particle size reduction of phenytoin in the suspension at each grinding time. The particle size at the pulverization equilibrium differed depending on the type of polymer used, with the smallest being in the suspension with PVP and SDS. This result was similar to that of a previous study in which the size reduction of phenytoin was successfully promoted through the combinatorial use of 0.5% PVP and 0.1% SDS.[33] Furthermore, earlier reports have suggested that a PVP-based layering

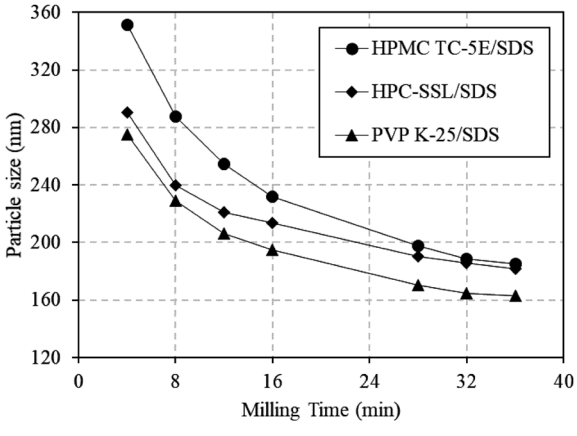


Fig. 1. Effect of Polymer and Surfactant on Particle Size of Phenytoin

structure with SDS would surround drug particles with static barriers and effectively suppress their aggregation.[34,35] Therefore, PVP and SDS were selected to stabilize the dispersion of phenytoin to maintain high grinding efficiency throughout this study.

**Effect of Additives on the Suspension pH** Zirconia beads, which are commonly used in the bead milling method, are partially stabilized by yttrium oxide and aluminum oxide, which are added to aid sintering.[36] However, in zirconia ceramics, the phase transition from tetragonal to monoclinic, which is considered to be the cause of microcracks, has been reported to progress more vigorously in water than in air.[37] It has also been suggested that these oxides can corrode depending on temperature and pH,[38,39] and the dissolution of yttrium from yttria-stabilized zirconium oxide powders has been observed at low pH.[40] Therefore, we focused on the effect of the suspension pH on the metal contamination generated during the grinding process.

The effects of various additives on the pH of the dispersion medium are shown in Table 1. The pH of the dispersion medium was found to be affected by the addition of the polymer. Most importantly, the addition of PVP, a polymer that is effective for grinding phenytoin, shifted the pH of the dispersion medium to 3.81, which is relatively strongly acidic. PVP has an aldehyde group at the end of its molecular structure.[41] Some of the aldehyde group react with water to form a carboxylic acid, which could result in the aqueous solution becoming acidic. Meanwhile, when HPMC or HPC were added, the pH of the dispersion medium shifted slightly from pH 6.15 to either more alkaline or acidic, respectively (Table 1). The addition of SDS did not significantly affect the pH of the dispersion medium with or without the presence of polymers.

Table 1. Effect of Additives on pH of the Dispersion Medium

| Stabilizer | Additive | pH | |
|---|---|---|---|
| Surfactant | SDS | (−) | (+) |
| Polymer | (−) | 6.15 | 6.05 |
| | PVP K-25 | 3.81 | 3.89 |
| | HPMC TC-5E | 6.72 | 6.94 |
| | HPC-SSL | 5.41 | 5.48 |

**Evaluation of the pH-Dependent Dissolution of Zirconia Beads** The dissolution of the zirconia beads themselves at various pH values was evaluated without other additives, and the dissolution amounts of zirconium, yttrium, and aluminum from the beads at each pH are shown in Fig. 2. The largest dissolution was observed for zirconium, which is the main component of zirconia beads. The dissolution amounts of yttrium and aluminum were also confirmed. Interestingly, the dissolved amount of all metallic elements was minimized in the pH range of 6–8. Zirconium oxide, which accounts for 95% of zirconia beads, has been reported to have increased solubility under acidic or alkaline conditions.[39] Therefore, zirconia beads were suggested to dissolve depending on pH and at least partly contribute to metal contamination in the grinding process. Moreover, this result strongly indicates that corrosion due to the dissolution of zirconia beads could be

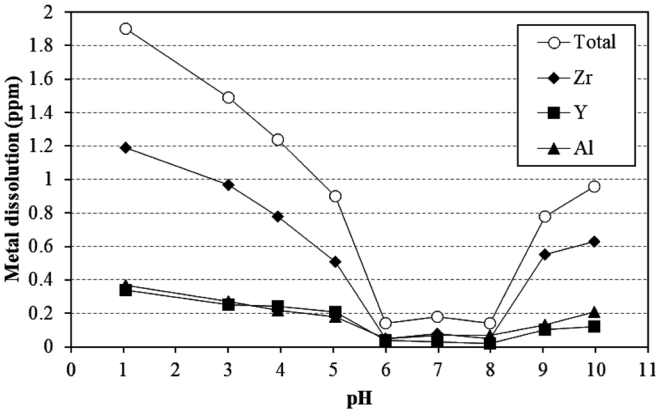


Fig. 2. pH-Dependent Dissolution of Zirconia Beads

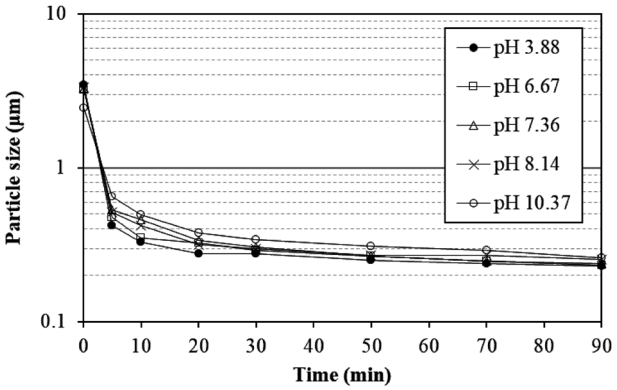


Fig. 3. Effect of pH on Grinding Efficiency of Phenytoin

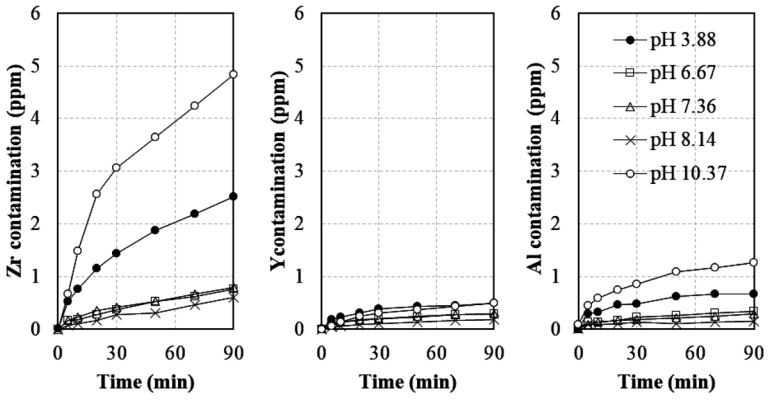


Fig. 4. Effect of pH Optimization on the Metal Contamination in the Grinding Process

suppressed by controlling the pH of the suspension.

**Effects of pH on Grinding Efficiency** Next, we evaluated the effect of pH on the particle size of phenytoin in the grinding process (Fig. 3). A previous study found that the rotation speed was the most important parameter affecting metal contamination due to bead collision among the various process parameters of bead milling.[42] To minimize the metal contamination generated during the grinding process, the rotation speed of the accelerator of the Dyno-mill was set to 4 m/s, which is the lowest value that can be set. The pH of the phenytoin suspension was adjusted to 6.67, 7.36, or 8.14 before pulverization of the phenytoin suspension, and the resulting particle sizes of phenytoin were measured over time. The results are summarized in Fig. 3. For comparison, the same evaluation was conducted for unadjusted pH (pH 3.88) and alkali pH (pH 10.37). The particle sizes of phenytoin decreased over time, and the size after 90 min of pulverization was approximately 0.23–0.26 $\mu$m at all pH values. Although there was a slight difference in the particle size of phenytoin after pulverization for 0–30 min, the particle sizes considered to have reached equilibrium after 90 min of pulverization were similar among the various pH values tested.

**Effects of pH Optimization on Metal Contamination during the Grinding Process** Among the various metal elements involved, we focused on the materials of the zirconia beads and the grinding chamber of the Dyno-mill as possible sources of metal contamination and measured the amounts of contaminating zirconium, yttrium, and aluminum after the grinding process (Fig. 4). As expected, the metal contamination in the suspension tended to increase depending on the grinding time. The highest contamination was observed with zirconium followed by aluminum and then yttrium. It is worth noting that when the pH was adjusted in the range of pH 6.0–8.0, where the dissolution amounts of metallic elements were found to be minimized (Fig. 2), the metal contamination generated during the grinding process was also significantly reduced. Whereas, at pH 3.88 and 10.37, which are out of the optimized pH range, metal contamination was larger, particularly for zirconium. Therefore, pH optimization of the phenytoin suspension would be a simple but effective approach to reducing the metal contamination generated during the grinding process (Figs. 2, 4) without impairing the grinding efficiency (Fig. 3).

Table 2. Contamination Reduction by pH Optimization with or without Physical Contact among Zirconia Beads

| Rotation speed (m/s) | pH | Contamination (ppm) | | | |
|---|---|---|---|---|---|
| | | Zr | Y | Al | Total |
| 4 | 3.88 | 2.52 | 0.49 | 0.66 | 3.67 |
| | 7.36 | 0.79 | 0.29 | 0.29 | 1.37 |
| 0 | 3.88 | 0.03 | 0.13 | 0.08 | 0.24 |
| | 7.36 | 0.00 | 0.01 | 0.03 | 0.04 |

**Elucidation of the Mechanisms of the Contamination Reduction by pH Optimization** The possible sources of metal contamination can be roughly categorized into the following: (i) dissolution of metals from metallic elements or (ii) wear generated by the collision of beads due to physical contact among beads. Based on these considerations, we tried to estimate the contamination reduction by pH optimization with and without physical contact among the beads (Table 2). By setting the rotation speed of the Dyno-mill to 0 m/s, there is no physical contact among beads, allowing evaluation of only the dissolution process of the beads. Whereas, by setting the rotation speed of the Dyno-mill to 4 m/s, not only the dissolution of the beads but also the wear caused by the physical contact among the beads could be evaluated. The contamination reduction by pH optimization was only 0.2 (0.24–0.04) ppm with respect to the total amount of metal contamination without physical contact among the beads. Meanwhile, the contamination reduction by pH optimization with physical contact among the beads was approximately 2.3 (3.67–1.37) ppm, which was approximately 10-times larger than that without bead contact. These results suggest that pH optimization not only suppressed the dissolution amount of the beads, but also prevented the wear caused by bead collisions during the grinding process.

**Proposed Mechanisms of Reduced Metal Contamination by pH Optimization** The binding strength of zirconium oxide has been reported to dramatically change when the content of yttrium oxide changes, and microcracks can occur on the surface of the sintered body due to crystal transition from tetragonal to monoclinic.[43] In addition, pre-damaged zirconia beads were found to generate an increased amount of wear.[44] These findings together with the results obtained in the present study led us to propose the following mechanism for reduced metal contamination by pH optimization (Fig. 5).

First, the metal components of the zirconia beads dissolve from the surface. This generates microcracks on the surface of the zirconia beads, making the surface unstable. Finally, wear due to collision of the beads occurs from the unstable surface of the zirconia beads. We consider that pH optimization reduces the dissolution of metal components and helps maintain stable and smooth surfaces of zirconia beads, leading to a reduced amount of wear from bead collisions.

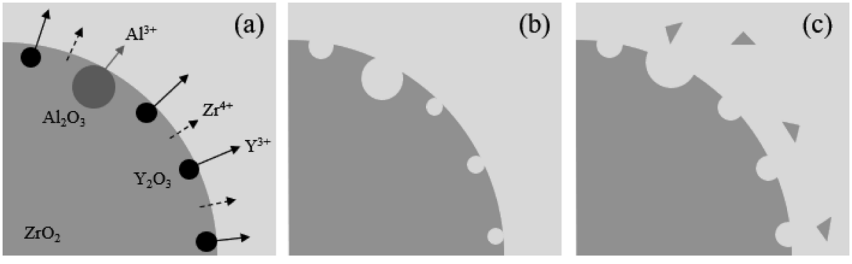


Fig. 5. Schematic of the Proposed Mechanism of Metal Contamination from Zirconia Beads during the Bead Milling Process

(a) Dissolution of metal components of zirconia bead from the surface; (b) Microcracks generated on the surface, making the surface unstable; (c) Wear due to bead collision easily occurs as a result of the unstable surface of the zirconia bead.

## Conclusion

To reduce metal contamination in the bead milling process, we focused on the pH-dependent dissolution of zirconia beads in addition to the wear generated by bead collision. Based on our findings, pH optimization appears to be a simple but effective approach to reduce the metal contamination generated during the grinding process without impairing the grinding efficiency. This approach should be applicable to the pulverization of other drugs using bead milling technology. Although further studies are necessary, the results reported herein should provide valuable information to further optimize contamination-less bead milling technology.

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**Conflict of Interest** The authors declare no conflict of interest.

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