Original Article

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Microparticles for sustained release of water-soluble drug based on a containment, dry coating technology

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Summary **Controlled release microparticles in a sub-gram-scale batch were fabricated using a ball mill, dry coating technique, to coat the water-soluble core material. This process also guaranteed the maintenance of the containment's integrity during the dry coating process. Quinine (average diameter, ca. 10 μm) and carnauba wax were used as the core and coating material, respectively. We evaluated the influence of process time, milling speed, and quinine-to-carnauba wax ratio on the particle size of the coated particles and their *in vitro* drug release profiles. Scanning electron microscopic observations suggested that the small wax particles attached to the core (quinine) particles resulted in a smooth film during the dry coating process. The size distribution of the coated particles agreed with the theoretically estimated size distribution. The *in vitro* release test demonstrated that the coated particles released quinine over 2 h in a biphasic mode. These results suggest that dry coating of microparticles less than 50 μm (D_{99}) is feasible on a several-grams-batch scale. This new ball mill-coating technique also enables a guaranteed containment, a prerequisite for the manufacturing of highly bioactive or biohazard substances.**

Keywords: Microsphere, mechanofusion, ball mill coating, small-batch production, controlled release

1. Introduction

A film coating technique is often used in the pharmaceutical industry to: 1) protect active ingredients from moisture, light, or oxygen, 2) improve the product's glossy appearance for marketing, or 3) control the dissolution of drugs from pharmaceutical formulations. The coating methods used in manufacturing medications are generally based on wet coating such as a fluidized bed coating and pan coating, where the coating material solution is sprayed on the surface of the core materials in this coating method.

There is a number of technical limitations in the coating process to be solved as an unmet need in the pharmaceutical field. One such limitation is the applicable size of core materials. With respect to conventional coating machines, over 100 μm of a particle size is generally required for use as a core material. Wurster fluid-bed technique has the advantage of film-coating small particles within the micrometer magnitude. However, even under an appropriate spray liquid flow rate, 20 to 50 μm microaggregates are produced with an associated yield of 60% (*1*). Thus, applying conventional coating methods to microparticles and nanoparticles have proven difficult.

Another limitation of the coating process is the ability to coat in a small scale. In the early stage of drug development, only a milligram order of the active ingredient under investigation is often available. However, most commonly used coating machines require several hundred grams per batch, at the very least. Therefore, formulation studies on controlled release preparations cannot be executed in practice when only a limited amount of the active compound is available. This prompts the need for small-scale manufacturing of highly active pharmaceutical ingredients such as nucleic acids or biomedicines.

Maintaining the integrity of the containment during the coating process is also an unmet need. In the wet coating process, solvents are removed by blow drying,

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which may affect the containment's integrity. This inadequate containment may be associated with risks such as leakage of highly bioactive or biohazardous substances, and its exposure to these circumstances.

Mechanofusion is a surface modification method of powder (*2*). Researchers have investigated the mechanofusion method as a dry coating method to propose tentative advancements. These include improving the humidity resistance of magnesium powder (*3*), improving the aerosolization of drug powder through a reduction of the powder's intrinsic cohesion (*4*), improving the flow properties of bulk powder (*5,6*), and controlling the dissolution of a poorly water-soluble drug (*7,8*). According to a study (9), the five types of devices introduced for dry coating include mechanofusion, hybridizer, magnetically assisted impaction coater, rotating fluid bed coater and theta composer. Recently, Nobilta® and Nanocular® (Hosokawa Micron Corporation, Osaka, Japan) have become increasingly popular for dry coating on a small scale. Dry coating on a scale of approximately 10 g is possible using those machines (*4-8*).

Ordered mixing can be used for coating, where the surface of larger particles is loosely coated or covered with smaller particles (*9,10*). Micro- or nanoparticles tend to easily adhere to each other or attach to the surface of larger particles by van der Waals interaction and electrostatic force. This attachment forms aggregates or composite particles. In the field of pharmaceutical manufacturing, high-intensity mixers and grinding machines such as a ball mill, have generally been used for ordered mixing. The aggregates generated during the ordered mixing process can be broken down into primary particles using those machines (*10*). Therefore, the ordered mixing technique may have the advantage of coating microparticles to produce microcapsules below 100 μm, a current technical limitation in the applicable size of core material. However, this technique has not been applied practically, to the coating of materials prepared for controlled release. This lack of application is because of the difficulty in eliminating the gaps present between the attached particles found on the surface of core particles. In addition, exothermic effect is a known undesirable property of the machines. The exothermic heat generated by the collision of particles may affect the stability of the core active material, which may increase related compounds or change the crystalized form of the active material.

Such exothermic property of milling, however, may have the advantage of tight coating. Namely, the exothermic effect should promote the melting of guest particles to form a seamless film on the surface of a host particle (*11*). This indicates that the guest particles consisting of a material with a lower melting point can tightly bind or fuse with each other. This fusion may then be applied to the coating for a controlled drug release particle. In addition, among the high-intensity mixers and grinding machines, only ball milling machines can be operated under a closed condition. Thus, coating with a ball mill, if feasible, may guarantee the integrity of the containment when contained during the coating process.

In the present study, we assessed the feasibility of dry coating microcapsules that are less than 100 μm, used for controlled drug release and created using the ball mill technique. Quinine hydrochloride (m.p., ca. 115ºC) was used as the water-soluble core particle, and was pulverized to microcrystals with an average diameter of approximately 10 μm (the host particle). Carnauba wax (m.p., ca. 85ºC), a common inactive pharmaceutical ingredient, was used as the hydrophobic coating material (the guest particle).

2. Materials and Methods

2.1. *Materials*

Carnauba wax (density, 0.99 g/cm^3) was purchased from Alfa Aesar (Lancashire, UK) while quinine hydrochloride 2-hydrate (quinine) (density, 1.27 g/cm^3) was purchased from Nakarai tesque (Kyoto, Japan). All other chemicals used were of reagent grade.

2.2. *Pulverizing quinine*

Three-hundred milligrams of quinine was pulverized by a planetary mill (pulverisette6, FRITSCH GmbH, Germany) using the ball mill pot (ϕ 40 mm; H 40 mm) with 4 balls (ϕ 10 mm). The ball milling rotated at 250 rpm for 2 h to prepare the pulverized quinine particles.

2.3. *Dry coating by the ball milling method*

The 250-300 mg mixture of pulverized quinine particles (ca. 10 μm) and carnauba wax (ca. 40 μm) was applied to an agate ball mill pot (ϕ 40 mm; H 40 mm) with 4 balls (ϕ 10 mm). The ball mill was then rotated at 22-23ºC using the planetary mill (pulverisette6, FRITSCH GmbH, Germany).

2.4. *Microscopic observations*

The coated samples obtained were observed using a scanning electron microscope (SEM) (JSM-5500LV, JOEL Ltd., Tokyo, Japan). To evaluate aggregation, the coated particles were dispersed in 0.05% Tween 80 aqueous solution, filtrated by 0.22-μm membrane filter and dried on the filter for 2 h at 22-23ºC. The collected particles on the filter were used as samples. Cross sections of the samples were obtained by cutting using a razor. Samples for SEM observation were prepared by depositing gold-palladium at 15 mA for 3 min (Quick Auto Coater JFC-1500, JOEL Ltd.).

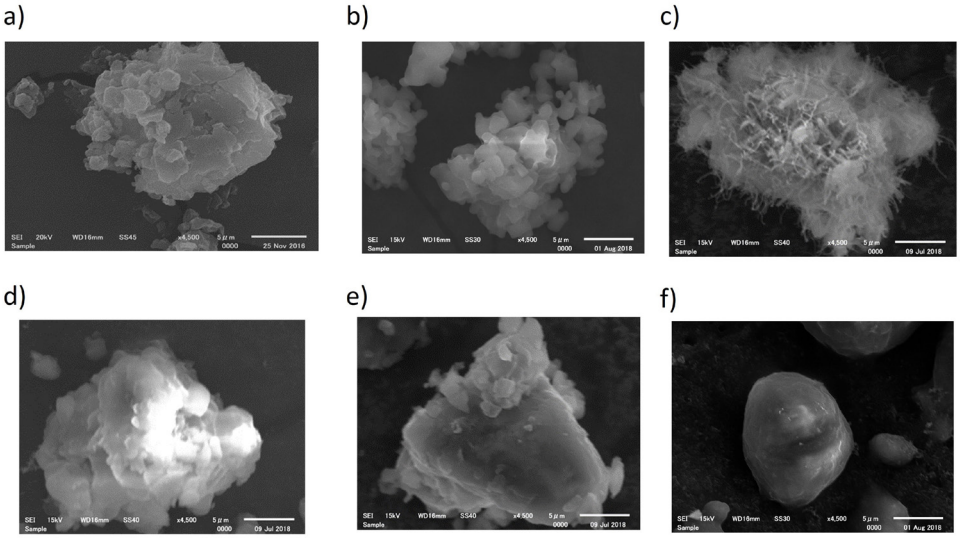

Figure 1. Scanning electron micrographs of the pulverized quinine and the coated particles. a) 2 h-pulverized quinine particles, **b)** 8 h-pulverized quinine particles, and the quinine and carnauba wax (1:1) coated particles prepared at 250 rpm for **c)** 0.5 h, **d)** 3 h, e) 6 h, and **f)** 12 h. Morphology changed during the dry coating process was demonstrated.

2.5. *Differential scanning calorimetry (DSC) analysis*

The particles (2 mg) were analyzed using DSC (DSC-60; Shimadzu Co., Ltd.) under N_2 gas (50 mL/min). The temperature rising speed was 20ºC/min.

2.6. *Determination of particle size*

The size of the pulverized quinine particles and coated particles was determined as a volume-based diameter using a laser diffraction particle size analyzer (SALD-2200, Shimadzu Co. Ltd., Kyoto, Japan). For the dispersion medium, soybean oil-hexane (1:2) and 0.05% Tween 80 aqueous solution were used as the dispersion media for the pulverized quinine and the coated particles, respectively. The size was measured within 1 min after the addition of the dispersion medium. To determine the volume-based diameter of carnauba wax in the coated particles, quinine was washed out of the coated particles through a 3 h incubation in the dispersion medium at 37ºC. The theoretical size of the coated particles was calculated using the following equation that is based on the hypothesis that the quinine particle were coated as the primary particle:

$$\text{Theoretical size } (D_x) = d_x \left[(W_1/\rho_1 + W_2/\rho_2)\right]^{1/3}$$

where D_x and d_x is diameter of coated particles and pulverized quinine microcrystals at the X% of cumulative distribution, respectively. W_1 and W_2 is weight of pulverized quinine and carnauba wax, respectively. ρ_1 and ρ_2 is the density of pulverized quinine and carnauba wax, respectively.

2.7. *In vitro dissolution test*

The dissolution test was performed in triplicate for each batch using the paddle method of the JP dissolution test. Briefly, 0.05% Tween 80 aqueous solution (900 mL), which was degassed at 41ºC for 2 h prior to use, was stirred using a paddle at 50 rpm and 37 ± 0.5ºC, with 20-75 mg (5 mg as quinine hydrochloride 2-hydrate) of particles added to the medium. 1 mL of the medium was periodically collected at predetermined time intervals, followed by the addition of 1 mL of fresh medium during the dissolution test. For the assay of quinine concentration, 100 µL of 0.1 M HCl was added to 400 µL of each collected sample, and the concentration determined by the fluorescent method (Ex., 350 nm; Em., 450 nm) using a hybrid multimode microplate reader (Synergy H4; BioTek Instruments, Winooski, VT, USA).

3. Results

3.1. *Observed morphological changes in the coated particles during dry coating process*

To evaluate the influence of process time, the particles were observed with the SEM at different process times. The typical scanning electron micrographs are shown in Figure 1. For the pulverized quinine crystals, the surface changed from a scale-like shape (2 h, Figure 1a) to aggregates of small particles (8 h, Figure 1b) as the milling process progressed at 250 rpm. For the coated particles, the surface changed from an aggregate with small particles, to one with a smooth surface as the dry coating with quinine and carnauba wax (1:1) at a speed of 250 rpm (Figures 1c, 1d, 1e, 1f) progressed. Interestingly, the coated particles obtained when dry coating was performed once for 30 min with the wax, had a brush surface or a fibrous surface standing upright (Figure 1c). However, the particles became spherical with a rather smooth surface at 12 h (Figure 1f). The

SEM observation of the cross-section of the sample obtained by 12 h of dry coating (Figure 2), revealed that a layer existed around the core section, although the core or quinine crystal was not clear. Through the observation of the well-dispersed particles, the coated particles prepared at 250 rpm in a 1:1 ratio of quinine and carnauba wax were observed as primary particles despite the 6 h or 12 h process time (Figures 3a and 3b). However, the particles prepared at 500 rpm were aggregates of several coated particles (Figure 3c). The particles fabricated in a 1:4 ratio of quinine to carnauba wax at 250 rpm for 6 h, also resulted in aggregates (Figure 3d).

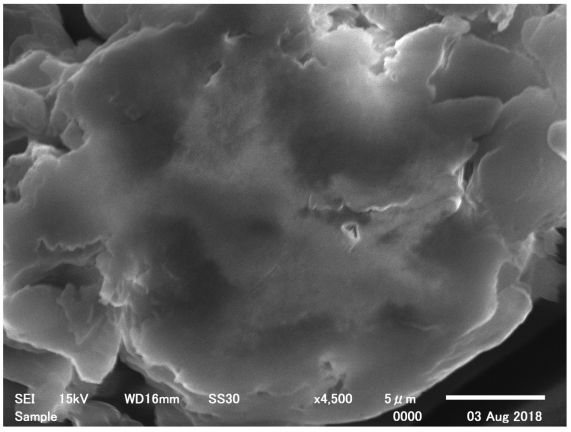

Figure 2. Scanning electron micrograph of the cross section of the coated particles. The coated particle of the quinine and carnauba wax (1:1) were prepared at 250 rpm for 12 h.

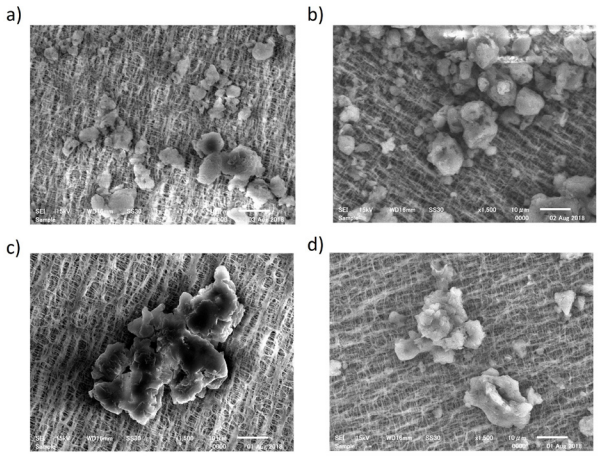

Figure 3. Scanning electron micrographs of the coated particles. The particles prepared by **a)** standard conditions, **b)** process time of 12h, **c)** milling speed of 500rpm, **d)** quinine-to-carnauba wax ratio of 1:4. The conditions of 1:1, 250 rpm, and 6 h for quinine/carnauba wax ratio, milling speed, and process time, respectively, were selected as the standard.

3.2. *Particle size of the coated particles*

The volume-based diameters of the coated particles prepared by the dry coating technique were evaluated using the laser diffraction particle size analyzer. Comparisons between the actual and theoretical diameters were made as shown in Table 1. The average diameter increased as the additive amount of the guest particles increased. For the dry coating process at 250 rpm, the actual average diameters were well in agreement with the theoretical average diameters for the 1:2 and 2:1 ratios of quinine to carnauba wax: this was not observed for the 1:4 ratio. In particular, the coated particles in the 1:1 ratio of quinine to carnauba wax showed that the actual cumulative size distribution was almost identical to the theoretical value (Table 1, Figure 4). With respect to the milling speed in the 1:1 mixture of quinine and carnauba wax, the actual average diameter of the particles prepared at 250 rpm was close to that of the theoretical value when processed for 6 h. Thus, the actual and theoretical average diameters observed were well in agreement after 3 h of processing (data not shown). However, the actual diameter of the coated particles prepared using the 6 h processing time at 100 rpm and 500 rpm was found to be larger than the theoretical values for the identical time. In the later study, the dry coating speed of 250 rpm, process time of 6 h, and the 1:1 ratio of quinine and carnauba wax were selected as the standard conditions.

Quinine as the core material was removed from the coated particles to evaluate the change in size of carnauba wax during the dry coating process. The mean

Table 1. Comparisons between actual and theoretical particle sizes of the coated particles

Quinine/ carbauna wax	Dry-coating condition	Particles size (μm)							
		Mean		D_{25}		D_{50}		D_{75}	
		actual	theoretical	actual	theoretical	actual	theoretical	actual	theoretical
1/1	250 rpm, 6hr	11.8 ± 2.5	12.3	6.7 ± 1.5	7.8	14.6 ± 2.9	15.0	25.0 ± 4.9	23.7
	100 rpm, 6hr	12.3 ± 1.2	12.3	5.0 ± 0.5	7.8	16.9 ± 1.8	15.0	33.0 ± 4.5	23.7
	500 rpm, 6hr	18.4 ± 4.8	12.3	12.8 ± 4.3	7.8	21.3 ± 4.5	15.0	31.6 ± 5.9	23.7
	250 rpm, 12hr	11.6 ± 1.3	12.3	6.9 ± 1.1	7.8	14.5 ± 1.6	15.0	23.8 ± 1.5	23.7
2/1	250 rpm, 6hr	10.9 ± 1.3	11.0	4.6 ± 0.6	7.0	11.0 ± 1.6	13.4	30.3 ± 7.2	21.2
1/2	250 rpm, 6hr	19.4 ± 2.0	14.2	12.1 ± 1.2	9.0	22.9 ± 1.5	17.4	37.8 ± 2.8	27.5
1/4	250 rpm, 6hr	26.1 ± 3.1	17.1	16.5 ± 1.8	10.8	29.4 ± 3.0	20.8	48.9 ± 5.4	33.0
Pulverized quinine		10.1 ± 1.9	-	6.4 ± 1.5	-	12.3 ± 2.8	-	19.5 ± 3.4	-

Data represents mean ± S.D. (n = 3 batchs).

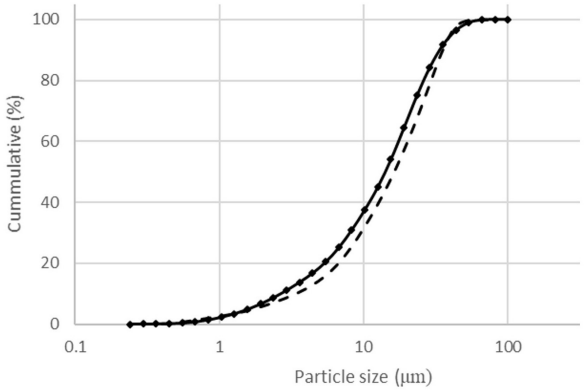

Figure 4. Cumulative particle size distribution of the typical coated particles. The solid and dot lines express the actual size and theoretical size distribution, respectively. The coated particles were prepared by the condition: quinine/carnauba wax ratio 1:1, milling speed 250 rpm, process time 12 h.

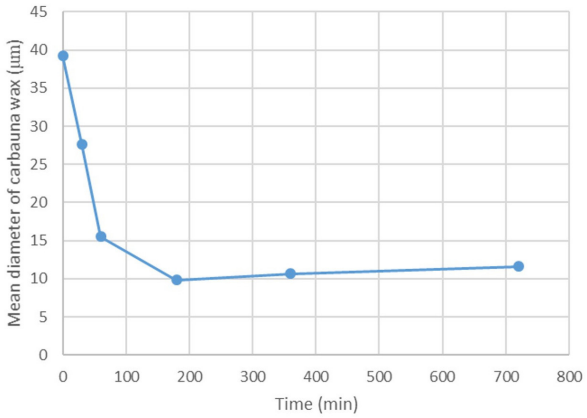

Figure 5. Change in size of carnauba wax particles during the dry coating process. Quinine-to-carnauba wax ratio and milling speed were 1:1 and 250 rpm, respectively.

particle size of the carnauba wax particles decreased while the dry coating process progressed and plateaued at 3 h (Figure 5).

3.3. *DSC analysis of coated particles*

DSC analysis was used to examine the influence of the dry coating process on the thermodynamic properties of carnauba wax and quinine. For the coated particles, the melting point derived from carnauba wax shifted higher while that of quinine experienced a lower shift than that of carnauba wax (Figure 6).

3.4. *In vitro drug release from the coated particles*

The release of quinine from the coated particles is shown in Figure 7. As the process advanced, the initial release at 10 min decreased and the duration of release extended from 10 min to 2 h (Figure 7a). Although up to 95% of the pulverized quinine was dissolved within 5 min, the quinine released from the coated particles obtained by the 12 h processing time, lasted over 2 h.

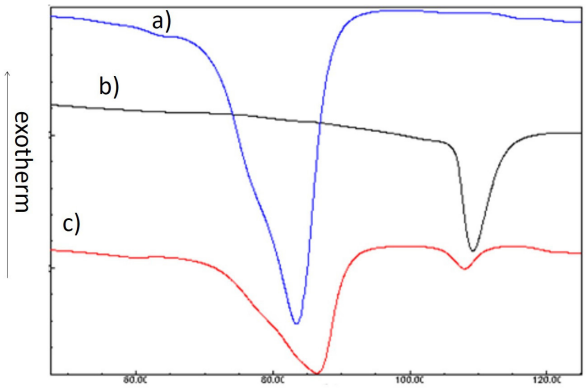

Figure 6. DSC charts. a) carnauba wax, **b)** quinine, **c)** the coated particles perepared by the standard condition: quinine/carnauba wax ratio 1:1, milling speed 250 rpm, process time 6 h.

The analysis conducted by liner fitting indicated that the release of quinine from the coated particles was biphasic (Figure 7b). The particles prepared at 100 and 250 rpm showed similar drug release profiles in the release of approximately 80% of quinine within the initial 30 min. However, the particles prepared at 500 rpm showed a slower drug release, where 80% of quinine was released in 1.5 h (Figure 7c). The influence of the ratio of quinine and carnauba wax on drug release, was evaluated on the coated particles fabricated at the 6 h processing time at 250 rpm. Initial release at 10 min decreased as the amount of carnauba wax increased. However, the initial release plateaued around 50-60% release of the prepared coated particles when the amount of carnauba wax was more than that of quinine (Figure 7d).

4. Discussion

Before we performed the dry coating of quinine by carnauba wax, we selected quinine microcrystals as core particles that were pulverized to a mean diameter of approximate 10 μm, as this size is considered the lower critical limit of pulverization. Dry grinding with a ball mill is a popular technique used in the pharmaceutical industry; however, a lower critical particle size can be achieved through pulverization. In general, it is difficult to reduce particle size below 10 μm by dry milling. This is explained by several theories in terms of the energy for pulverization. For example, according to the theory by Bond (*12*), the energy for pulverizing powder is calculated using the following equation:

$$E = C_B\,(1/\sqrt{x2} - 1/\sqrt{x1})$$

where E is the net specific energy, C_B is a constant, and $x1$ and $x2$ are the feed and pulverized size (D_{80}), respectively. This equation indicates that more energy is required when the particle size gets smaller. Moreover, the lower critical size in pulverizing is explained by

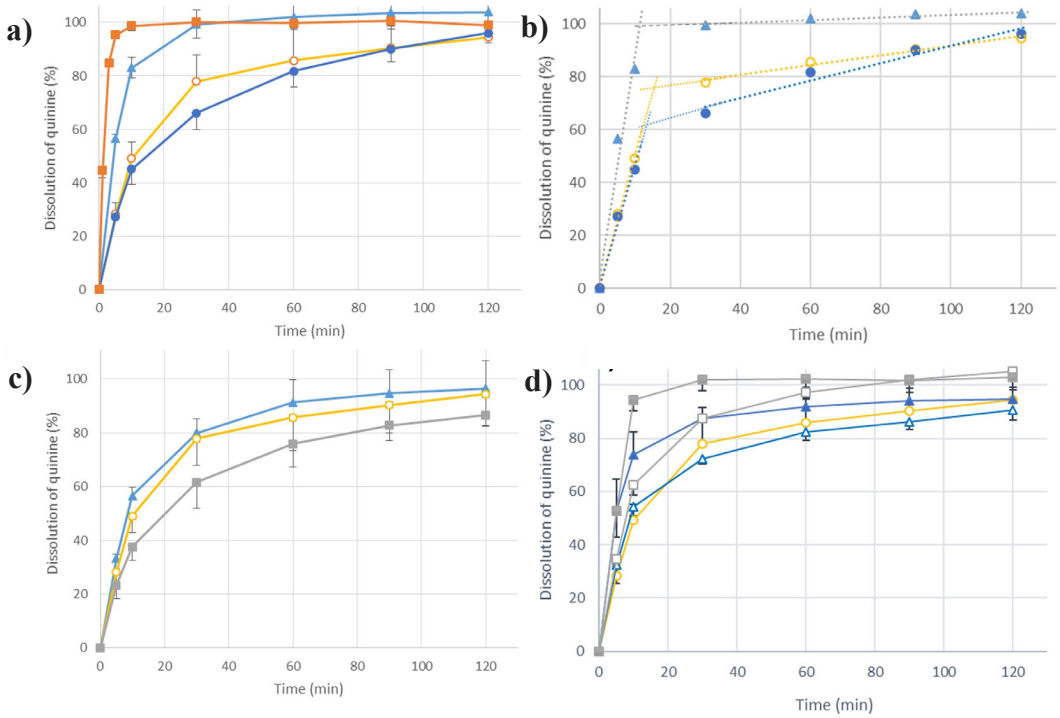

Figure 7. ***In vitro*** **dissolution of quinine from the coated particles.** Effect of the process time on **a)** *in vitro* dissolution profiles and **b)** liner fitting: ■ 0 h (pulverized quinine), ▲ 0.5 h, ○ 6 h, and ● 12 h. **c)** Effect of milling speed on in vitro dissolution profiles: ▲100 rpm, ○ 250 rpm, and ■ 500 rpm. **d)** Effect of quinine-to-carnauba wax ratio on *in vitro* dissolution profiles: ▲4:1, ■ 2:1, ○ 1:1, □ 1:2, and Δ 1:4. The standard conditions were 1:1, 250 rpm, and 6 h for quinine/carnauba wax ratio, milling speed, and process time, respectively. Data represents the means ± S.E. for 3 batches.

the relationship between hardness and size of particles. The hardness of a particle is related to the magnitude of the crack in the particle (*13*), which is considered to be decreased when the particle size is reduced. Thus, more energy is required for pulverization along with a smaller size of particles. Besides the selection of the core particle size, we also chose a moderate milling speed (250 rpm as the standard speed) for the dry coating process so that the reduction in particle size of the core particles would not proceed during the dry coating process. To confirm no reduction of the core particle size, we examined the influence of the pulverization time on the quinine particle size at 250 rpm. When only the quinine particles were pulverized for 8 h, the particles were larger in size than those obtained through 2 h of pulverization (10.1 ± 1.9 µm and 20.8 ± 6.4 µm for the 2 h and 8 h process, respectively; the mean particle size ± S.D. for 3 batches). Considering the SEM image shown in Figure 1b, the increase in the particle size of quinine by the 8 h pulverization may be due to the formation of aggregates. Consequently, the size of cores particle was considered not to reduce during the dry coating process. So, when the dry coating with the pulverized quinine and carnauba wax was performed, it was suggested that the carnauba wax may be dominantly pulverized in the 6 h dry coating process, which had in advance, a 2 h pulverization process.

Under the condition that the size of the core particles (10 µm quinine) would not reduce, we performed the dry coating by 40 µm carnauba wax. The dry coating technology used in the present study is related to mechanofusion, which is mainly used for modifying the surface of particles. For the conventional mechanofusion and dry coating procedures reported, smaller particles were used as guest particles and larger particles as host particles (*3,7,9,14*). In this study, quinine particles used as host particles were smaller than the carnauba wax particles that were used as guest particles to result in the achievement of dry coating. The possible explanation for the conflict is related to the size reduction in carnauba wax during the dry coating process. Since the host quinine particles had a mean particle size similar to the minimum critical particle size obtainable by pulverization, carnauba wax particles may dominantly be milled to become finer particles during the coating process as indicated above. This selected pulverization provides a high surface energy to carnauba wax particles by engendering new surfaces and showing the tendency to attach to other particles. The generated small particles of carnauba wax were gathered with quinine particles and melted to incorporate the quinine particles. This is supported by the electron microscopic observation, where most of the particles changed in morphology from a composite with small particles, to a particle with a smooth surface as the process of dry coating proceeded. The echinoid-shaped particles were produced by the initial 30 min coating, which may have been formed when the

carnauba wax particles were teared off by milling. The production of echinoid-shaped particles may enhance further aggregation of particles by increasing the surface area. Particles forming a composite could not be clearly identified in the microscopic observation (neither carnauba wax nor quinine), although the observation of the cross section suggested this recognition.

To prove the coating of a quinine particle with carnauba wax, we evaluated the particle size distribution and drug release profiles of the coated particles. In the dry coating process, the coated particles decreased in particle size down to the theoretical diameter in the 3 h required to reach a plateau. Similar tendency was observed on the guests obtained when quinine was washed out of the coated particles. Therefore, the observed size reduction is considered to be of carnauba wax. This observation supports that the coating process may proceed with the progress of pulverization of the carnauba wax as mentioned above. Therefore, by the inadequate pulverization of carnauba wax, the actual particle size of all particles including coated particle, quinine and carnauba wax was therefore larger than that of the theoretical size in the early period of the process. This is seen to hold true for other coated particles prepared at a low milling speed. Indeed, the dry coating at 100 rpm produced coated particles with relatively larger sizes, especially in D_{75}. On the other hand, the average diameter of the particles obtained at 500 rpm was found to have a value twice that of the theoretical value. This is not due to inadequate pulverization. This is explained by assuming that the milling at 500 rpm gave rise to excess energy for coating the particles, which may be used to aggregate the coated particles as shown in Figure 3. Thus, it was indicated that 250 rpm is the optimal milling speed to obtain primary coated particles. The volume-based particle sizes, D_{25}, D_{50}, and D_{75}, of the coated particles prepared by 6 or 12 h of dry coating with quinine and carnauba wax (1:1) at 250 rpm, were close to the theoretical values estimated by assuming that the particles were primary particles. In addition, the size distribution of the particles obtained by the 12 h dry coating period coincided with the theoretical size distribution. On the other hand, when the ratio of quinine to carnauba wax was 1:4, the average diameter of the obtained coated particles was larger than the average theoretical diameter. This is probably due to the production of aggregates, judging from the observation of the dispersed particles (Figure 3). This indicates that there are optimum conditions in terms of the host-to-guest ratio and milling speed, to obtain primary particles. For quinine and carnauba wax, the optimum ratio at 250 rpm was found to exist between 2:1 and 1:2.

We then evaluated the influence of process time, coating speed and ratio of host and guest materials on *in vitro* quinine release from the coated particles. With increased processing time, a longer drug release was sustained with a suppressed initial release. The influence of the process time on the drug release can also be explained by the morphological changes of particles shown in Figures 1c-1f. It was indicated that the attachment of only intact, small guest particles (Figure 1c) cannot control drug release as there are gaps between the adhered wax particles; even as close-packed spherical particles provide approximately 0.26% of porosity. The attachment of guest particles on the host particles may be based on the steric repulsive force among the guest particles, besides the attractive force between the host and guest particles. This steric repulsive force prevents close-packing. Changing the shape of the attached particles for controlled drug release is also essential. It was reported that heating melts the adhered particles resulting in the formation of a smooth layer (*15*). For the dry coating process using an electric mortar and a powder surface reforming system, it was reported that a change in shape of the adhering particles is observed as a relaxation process takes place during process progression (*16*). In this study, we observed the changing of the adhered particles (Figure 1c) to the smooth layer (Figures 1d-1f) with process progression. One of the important factors in morphological changes during the process is the melting points of the guest and host particles. Melting points of the guest and host particles used in this study were approximately 85ºC and 115ºC, respectively. Considering that the original quinine particles were not clearly observed in the cross section of the coated particles (Figure 2), carnauba wax and quinine are considered to melt during the dry coating process. The DSC analysis attributed the thermal peaks of the coated particles, to the melting of carnauba wax and quinine. This indicates that quinine exists as a crystallized structure, but may interact with carnauba wax during the dry coating process.

The coated particle obtained at 500 rpm showed a slower release than those obtained at 100 and 250 rpm. Although the dry coating at 500 rpm gave rise to aggregates, the coated particles consisted of quinine and carnauba wax in the ratio, 1:4 at 250 rpm also gave rise to aggregates. These aggregates showed a similar release of quinine particles to those in the 1:1 ratio at 250 rpm, which were suggested to exist as primary particles. The aggregation of the coated particles cannot completely account for the slower release of the coated particles at the 500 rpm. Considering the degree of compaction in a coating layer, the magnitude of the milling speed may affect the coating layer more than the amount of coating material.

It is well-known that drug release through a water-insoluble membrane shows the zero-order pattern. A model proposed by Chien (*17*) has been commonly accepted as a mechanism of drug release by hydrophobic polymer coating particles. Drug molecules underlying the shell of a capsule, left the crystal to penetrate the

polymer wall by a partitioning phenomenon, diffuse through the wall using a driving force that differs in concentration across the wall, dissolve in the solution surrounding the capsule to form saturated and diffusion phases, prior to dispersal in the bulk solution. A modified model proposed by Ito *et al*. (*18*) takes it into consideration the medium penetrating through the coating layer to the core compartment of a capsule, followed by dissolving of the crystallized drug in the core prior to drug release. Drug release from the matrix formulation is proportional to the square of time. In this study, the drug release from the coated particles did not fit a matrix-type kinetic, as it was not proportional to the square of time. This suggests that the particles obtained were not of the matrix type. Although the release did not show zero-order kinetics, biphasic kinetics which involves a zero-order pattern was observed. A decrease in the release in the early phase was observed while the latter phase increased along with the extension period of the dry coating process. This suggests that the coating layer may have two regions of diffusion: a leaky and rigid region, and that a leaky region may be present within the gaps between the guest particles. The leaky region reduces as guest particles bind tighter to each other during the progression of dry coating.

In conclusion, controlled release coating of quinine microcrystals less than 50 μm with carnauba wax was achieved by the ball mill dry coating method. The method selected may avoid the lower size limitation of coating, in the pharmaceutical manufacturing. In addition, the ball milling technique guaranteed that the integrity of the containment is maintained when contained during the dry coating process. Thus, our method may be useful in coating highly bioactive substances that may present a variety of risks when exposed to the environment. Through the use of a dry coating technology with a ball mill, we are proposing that this method may provide a breakthrough solution in the manufacture of controlled release microparticles that undergo contained conditions. Application of nano-order particles should be investigated in a future study.

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