Investigation and control of the uniformity of drug nanoparticles directly deposited on the particulate surfaces of excipient by PLD

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Abstract
Pulsed laser deposition (PLD) of drug nanoparticles for pharmaceutical preparation was investigated. Indomethacin (IM) was preliminary mixed with magnesium stearate (StMg) to prepare a target for PLD. By using the composite targets, the percentage of deposited nanoparticles in the collected powder increased compared to when only IM was ablated. The percentage of IM nanoparticles was the highest when IM and StMg were mixed at 1:1 ratio. Nanoparticles of the composite target were deposited on the micron sized particulate excipient, i.e., SiO₂, potato starch, and lactose. The excipient powders were mixed by rotation. Their surface coverage was evaluated by FE-SEM observation and diffuse reflectance (DR) UV-Vis spectroscopy. The surface coverage was estimated to be around 50 % for 20 min deposition time. Simple rotation of the excipient powders was found to be one of the effective methods for uniform deposition of nanoparticles.

1. Introduction
Increasing the dissolution rate of poorly water-soluble drugs is extremely desired in the pharmaceutical field, in order to improve the bioavailability of these drugs. Preparing nanoparticles of these drugs is one of the attractive methods for increasing the dissolution rate due to the increasing surface area, but is difficult to obtain by conventional methods such as mechanical grinding [1,2]. In our previous work [3,4], we have deposited phenytoin (PT) and indomethacin (IM) nanoparticles, both a poorly water-soluble drug, without photodecomposition by using an infrared laser (1064nm). The average particle sizes were 16.4±8.2 nm and 10.4±5.7 nm for PT and IM, respectively. However, formation of large amount of particulate debris, a photomechanical product, was a problem.

We have also deposited nanoparticles of IM directly on the excipient powder, i.e., potato starch (PS) by fluidizing the powder by vibration [4]. Pulsed laser deposition (PLD) on particulate systems is attractive for surface coating of micron-sized particles with nanoparticles as contamination-free and completely dry process, but only a few studies have been reported [5,6]. In all the cases, vibration was used for powder fluidization. However, fluidization only by vibration may have limitation depending on the property of the excipient powders, especially when the powders form agglomerates as a consequence of vibration.
In this work, we have prepared mixed targets by addition of magnesium stearate (StMg), to give mechanical strength to the target, for suppression of particulate debris. We also devised uniform deposition on particulate systems by mixing of the excipient powders by rotation, an alternative method for powder fluidization.

2. Experimental
IM and StMg were coground by a planetary ball mill (Fritsch, Pulverisette-5) for 60 min, with the amount of StMg varying between 0-90 wt %. The coground powders were, then, compressed at 55.5 MPa for 3 min at room temperature to prepare targets for PLD. PLD was carried out by the Laser Ablation System (Nara Machinery Co., Ltd.), equipped with a 1064nm Nd:YAG laser. The pulse width, the repetition rate, and the laser fluence were all fixed at 5 ns, 10 Hz, and 20 J/cm², respectively. Helium was used as the background gas and its pressure was set to 100Pa.

Before deposition on excipient powders, percentage of IM nanoparticles out of all the powdery products including debris was determined. The ratio of the absorption intensity at 320 nm before and after filtering with a 200 nm membrane was measured by transmission mode of UV-Vis spectrometer (V-550, JASCO). The powder samples were dispersed in water with ultrasonication for 10 min and then filtered. The filtrate was diluted in methanol and the absorption intensity of the solution was measured.

For the uniform deposition of nanoparticles on the excipient particles, powders were mixed by rotation using the unit shown in Figure 1. As the model excipients, SiO₂, potato starch (PS), and lactose (LT) with the average particle size around 10-20 μm were used. During the laser deposition, 0.5 g of the excipient powders were mixed by rotation. The surface morphology of the excipient powders after deposition was observed by an FE-SEM (S-4700, Hitachi). Surface coverage was estimated by diffuse reflectance (DR) UV-Vis spectrometer used above, a method similar to that of Igarashi et al [7]. MgO was used as the standard and the intensity of the spectra was shown by Kubelka-Munk (KM) factor, \((1-R)^2/2R\), where R is the intensity of DR relative to the standard.

3. Results and Discussion
Figure 2 shows the percentage of IM particles with sizes below 200 nm, calculated from the ratio of the absorption intensity at 320nm before and after filtering with a membrane filter of 200 nm. By adding StMg in the target, this percentage increased reaching the maximum value of 15 % when StMg was added by 50 wt%. The increase in the IM nanoparticles by addition of StMg is presumably due to the decrease in the amount of debris, particles mechanically removed from the target, by the improvement of the mechanical strength of the target. When the addition of StMg exceeds 50 wt%, the percentage of IM nanoparticles decreases simply because the amount of IM in the target is low.

Walsh et al. have ablated several tissue targets with different tensile strengths by CO₂ laser, and found that tissue with high tensile strengths have a low deposition rate [8]. They have concluded that the mechanical strength of the tissue can affect explosive mass removal by pulsed laser ablation. Detailed mechanisms, including the chemical interactions between IM and StMg, are yet to be elucidated.
The IM-StMg composite target with 50 wt% of StMg was used as the target and the drug nanoparticles were directly deposited on the particulate excipients. Figure 3 shows the FE-SEM picture of SiO$_2$ particles, with the average particle size of 15 μm after a 20 min deposition. Nanoparticles of the target drug uniformly cover the surface of SiO$_2$ particles.

To estimate the surface coverage of the excipient powders, their diffuse reflectance (DR) UV-Vis spectra was measured. Figure 4 shows the DR spectra of intact SiO$_2$, intact IM-StMg, and samples prepared by varying the deposition time. The fractional amount of IM-StMg on the host excipient particle is linearly related to the absorbance according to Lambert-Beer’s equation. Therefore, curve fitting on the spectra of the coated excipient was carried out using the spectra for the non-coated excipients and the coating material, IM-StMg. The dotted curve represents the fitted spectra. The fraction of IM-StMg after 20 min deposition on SiO$_2$ was estimated to be 0.56. According to Figure 3, the surface of SiO$_2$ particles was uniformly coated with nanoparticles of IM-StMg, and the fraction obtained from the DR spectra can be regarded as the fractional coverage of the excipient. In the same way, the DR spectra of the drug deposited on PS and LT was measured and the surface coverage was estimated by curve fitting (Figure 5). The fractional coverage of PS and LT after 20 min deposition was 0.52 and 0.43, respectively.
4. Conclusion

PLD of poorly water-soluble drug, indomethacin, was performed to prepare nanoparticles of the drug which cannot be achieved by conventional methods such as mechanical grinding. Suppression of particulate debris, a major hurdle to overcome, was examined by addition of StMg to the target. The key technology of PLD on particulate systems for uniform deposition of nanoparticles was studied by rotational powder mixing, and the surface coverage was estimated by DR UV-Vis spectroscopy.

The percentage of IM nanoparticles under 200 nm increased by addition of StMg in the target, due to the increase in the mechanical strength of the target, and thus decreasing the amount of mechanical removal of particles debris. Detailed mechanisms, including the chemical interactions between IM and StMg, are yet to be elucidated.

Uniform deposition of IM nanoparticles was achieved by mixing the excipient powders by rotation, as confirmed by FE-SEM observations and DR UV-Vis spectroscopy. The fractional surface coverage of the excipient powders after 20 min deposition was estimated to be 0.56, 0.52, and 0.43, for SiO₂, PS, and LT, respectively. Mixing the powders by rotation is a promising technology for uniform deposition on particulate systems.

References
[1] A.A. Date and V.B. Patravale, 2004, *Current Opinion Colloid Interface Sci.*, 9, 222
[2] R.H. Muller, C. Jacobs, and O. Kayser, 2001, *Advanced Drug Deliv. Rev.*, 47, 3
[3] S. Nagare and M. Senna, 2004, *Solid State Ionics*, 172, 243
[4] S. Nagare and M. Senna, 2004, *J. Nanopart. Res.*, 6, 589
[5] J.M. Fitz-Gerald, T.A. Trottier, R.K. Singh, and P.H. Holloway, 1998, *Appl. Phys. Lett.*, 72, 1838
[6] J.M. Fitz-Gerald, P.D. Rack, T.A. Trottier, M. Ollinger, S.J. Pennycook, H. Gao, and R.K. Singh, 1999, *J. Appl. Phys.*, 86, 1759
[7] T. Igarashi, T. Kusunoki, K. Ohno, T. Isobe, and M. Senna, 2001, *J. Electrochem. Soc.*, 148, J59
[8] J.T. Walsh and T.F. Deutsch, 1989, *IEEE Trans. Biomed. Eng.*, 36, 1195