Characterization and Formulation Optimization of Grinding-Induced Drug Nanoparticle Using Solid-State NMR Relaxometry
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Purpose
Drug nanoparticle formulations are one of the useful ways to improve dissolution and subsequent absorption through small intestinal membrane for the poorly water-soluble drugs. In this study, nifedipine (NIF) nanoparticles were prepared by co-grinding with polymers, hypromellose (HPMC) or polyvinylpyrrolidone (PVP), and sodium dodecyl sulfate (SDS). The molecular states of NIF in the ground mixture were investigated using solid-state NMR techniques including NMR relaxation time measurements. The correlation between the elucidated molecular state of the solid formulations and the aqueous dispersion behavior of NIF nanoparticles was analyzed to determine the most suitable process for formulating the nanoparticle dispersions.

Methods
HPMC and PVP were used as polymer excipients. A physical mixture of NIF, polymer, and SDS at a weight ratio of 1:2:1 were ground for 15, 40, and 100 min using a vibration rod mill to prepare the ground mixture [GM (grinding time)]. The $^{13}$C NMR spectra of GM were obtained using cross polarization (CP) and magic-angle spinning (MAS) at 15 kHz. The laboratory frame spin-lattice relaxation time ($T_1$) and rotating frame spin-lattice relaxation time ($T_{1ρ}$) of the proton were measured using an inversion-recovery and a spin-lock sequence, respectively, at MAS rate of 5 kHz. The nanoparticle formation of NIF was evaluated by determining the NIF concentration in centrifuged GM dispersions into distilled water.

Results
The solid-state NMR measurements revealed that the co-grinding of NIF crystal with the polymer reduce $T_1$ and $T_{1ρ}$ value of NIF crystal. NIF crystalline size was reduced by the co-grinding with polymers. The $T_1$ value of NIF crystal was accorded with that of polymers in GM (100 min) of NIF/HPMC/SDS and GM (40 min) of NIF/PVP/SDS, indicating homogeneous mixing of NIF crystal with polymers in the domain size of 80–90 nm or less. HPMC required more grinding time to attain similar homogeneity with the NIF crystal compared with PVP. These homogeneous mixing of NIF crystals with polymers indicated that the NIF crystalline size was reduced to several tens nm. The GM (100 min) of NIF/HPMC/SDS and GM (40 min) of NIF/PVP/SDS formed a large amount of NIF nanoparticles during aqueous dispersions followed by the polymer dissolutions, reflecting the nano-sizing of the NIF crystal in the polymer matrix. Further grinding of NIF with PVP resulted in the amorphization of most of the NIF followed by nano-sizing of the NIF crystals. The excess amorphization of NIF in the GM worked negatively for the NIF nanoparticles formation during aqueous dispersion. The effective size reduction of the NIF crystal in the solid state without excess amorphization achieved the NIF nanoparticle formation.

Conclusion
The molecular state of drug in polymer matrix, including the crystallinity and domain size of the dispersed drug crystals, directly correlated with the nanoparticle-formation efficiency during aqueous dispersion. The direct monitoring of the molecular state of a solid drug based on solid-state NMR techniques including relaxometry could be a powerful tool for the optimization of drug nanoparticle formulations.