学位論文題名　Elucidation of destabilization mechanism of amorphous cyclosporin A nanoparticles prepared by wet bead milling with poloxamer 407

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【論文要約】

Poorly water-soluble drugs pose challenges to formulation scientists because poor dissolution performance results in low bioavailability. In recent years, amorphous drug nanoparticles, using a synergistic strategy of drug amorphization and nanosizing, have gained considerable interest because of the combined advantages in the improvement of dissolution performance. However, amorphous drug nanoparticles are not stable during storage because particle size increase and drug crystallization can occur. The purposes of this study are I) to characterize the amorphous drug nanoparticles obtained by a top-down approach, wet bead milling, and II) to figure out the destabilization mechanism of the product upon storage. Cyclosporin A (CyA) was used as a model of poorly water-soluble drug and poloxamer 407 (P407) was selected as the colloidal stabilizer.

In the first part of this study, an amorphous CyA nanosuspension was obtained by wet bead milling of amorphous CyA with P407. The freshly prepared and 1 month-stored products were thoroughly investigated at both microscopical and molecular levels. It turned out that the freshly prepared amorphous CyA nanoparticles (~ 370 nm) were aggregates of many primary particles (~ 50 nm) and a portion of P407 was entrapped in the nanoparticles due to the aggregation. Interestingly, the amorphous CyA nanoparticles were transformed into smaller nanocrystals (~ 200 nm) after storage.

In the second part of this study, the mechanism of the transition from amorphous to crystalline CyA nanoparticles upon storage was elucidated by monitoring the crystallization process at both the microscopical and molecular levels. It was found that the amorphous CyA nanoparticles were destabilized via a non-classical pathway cognate with oriented attachment, which is a newly discovered crystallization mechanism in the pharmaceutical field. The entrapped P407 was considered to have an important role in the destabilization of the amorphous CyA nanoparticles.