Preparation and evaluation of novel sustained-release formulations based on the crystal polymorphism of clarithromycin

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Considering a polymorphism of active ingredients is crucially important to prepare the pharmaceutical formulations because different polymorphs exhibit different stability, solubility and/or bioavailability. As for clarithromycin (CAM), 14-membered macrolide antibiotic, two anhydrous crystal forms are known to exist; metastable form I and stable form II. CAM form I rapidly transits to form IV when exposed to external solution. In this study, the effect of the crystalline transition of CAM on the dissolution behavior from tablets was examined.

CAM tablets were prepared by compressing the mixtures consisting of CAM form I or II, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, colloidal silica and magnesium stearate. The dissolution test and the disintegration test were performed according to the Japanese Pharmacopoeia 16th edition. In addition, using the CAM form I tablets which were withdrawn from disintegration test at 15 min after the start of disintegration test, the changes of crystal form of CAM and morphology of the tablets were determined by powder X-ray diffraction (PXRD) and scanning electron microscope (SEM).

More than 90% of CAM was dissolved from CAM form II tablets at 30 min after the start of dissolution test, whereas only 5.7% of CAM was dissolved from CAM form I tablets. In addition, although CAM form II tablets were disintegrated within 2 min, CAM form I tablets were not disintegrated even after 2 hr. Furthermore, from the results of PXRD and SEM, the appearance of needle microcrystals of CAM form IV was abundantly observed on the surface of CAM form I tablets. Taken together, the microcrystalline coating of form IV on the surface of CAM form I tablets might prevent external solution from penetrating into the tablet, and consequently CAM form I tablets showed sustained-release for long-term. In conclusion, our study demonstrated for the first time that the crystalline transition from CAM form I to IV may be applied to design novel sustained-release formulations.