Development of nanocrystal formulation of mebendazole with improved dissolution and pharmacokinetic behaviors

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Nanosizing by wet beads milling is a method to improve the solubility of poorly water soluble compounds [1,2]. Mebendazole (MBZ) is a well-known anthelmintic drug in wide clinical use. There were some reports that MBZ had the anticancer effect in preclinical study. However, the bioavailability of MEB is low (<10%) due to the poor solubility in water (0.5 μg/mL). The present study aimed to develop the nanocrystal formulations of MEB to improve dissolution behavior and enhance oral absorption.

The MBZ nano-suspension was prepared by milling with zirconia beads (milling media) in polymer aqueous solution (dispersion stabilizer) by the rotation/revolution pulverizer [3]. Then, milled MBZ powder was prepared by freeze-drying the MBZ nano-suspension. Four polymers (polyvinyl alcohol (PVA), hydroxypropylcellulose-SSL (HPC), methylcellulose (MC), and copolymer of PVA, acrylic acid and methyl methacrylate (POVA)) were used to evaluate the dispersion stabilities of the MBZ nano-suspension and the re-dispersion stability of the milled MBZ powder. Dispersion stability, re-dispersion stability, and crystallinity of the MBZ nano-suspensions and the milled MBZ powders were evaluated by particle size analyzer and powder X-ray diffraction (PXRD), respectively. In addition, the dissolution behavior and the oral absorption of the milled MBZ powder were evaluated. The MBZ nano-suspensions with PVA and HPC had better dispersion stability [the diameters at 90% of the population distribution (D90) = ca. 0.210 μm] than the MBZ nano-suspensions with MC and POVA (D90 > 1 μm). The milled powder with PVA showed the good re-dispersion stability when the mass ratio of PVA to MEB was more than three (Fig. 1a). On the other hand, five of the mass ratio of HPC to MEB was necessary to re-disperse the milled MBZ powder in water. Therefore, the milled MBZ powder with PVA (MBZ: PVA = 1:3) was used to evaluate the crystallinity, the dissolution behavior and the oral absorption. The PXRD patterns of the milled MBZ were similar to that of the original MBZ, which showed that the milled MBZ maintained its crystallinity. In comparison of the...
original MBZ with the milled MBZ powder, the dissolution behavior of MBZ in aqueous solutions adjusted pH 1.2 and pH 6.8 were improved by milling to nanoparticles. After oral administration of the milled MBZ powder (10 mg MBZ/kg) in rats, the enhanced oral absorption of MBZ was observed with increases of C_{max} and AUC_{0–8} by 4- and 3-fold, respectively, compared with those of the original MBZ (Fig. 1b). The nanosizing approach was effective to enhance the bioavailability of MBZ. From the improvement of oral absorption, the nano-sized MBZ could increase the probability of application for the cancer treatment.

REFERENCES