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Preparation of silymarin nanocrystals using a novel high pressure crystallization technique and evaluation of its dissolution and absorption properties

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Oral bioavailability of drug is limited by the factors such as the membrane permeability, the solubility, the dissolution rate and so on [1]. In case of a poorly water-soluble drug, its solubility and dissolution rate is a critical factor for its oral bioavailability. Among various techniques for enhancing solubility or dissolution properties, physical modification of drug products such as reducing the particle size is one of common approaches [2]. In previous studies, we have succeeded in preparation of nanocrystal suspensions of poorly water-soluble drugs by using a high pressure crystallizer (PureNano®).

Cyclodextrins (CyDs) are cyclic oligosaccharides consisting of six to eight glucose units linked by α-1,4-glycosidic linkage. The potential use of natural CyDs and their synthetic derivatives have been extensively studied to improve certain properties of the drugs, such as solubility, stability, and/or bioavailability. One of the most useful applications of CyDs in dosage form design is enhancing the solubility of poorly water-soluble drugs by complex formation.

In the present study, we tried to prepare drug nanoparticles of a poorly water-soluble drug by high pressure crystallization method using CyDs or erythritol as additives in freeze-drying process. Silymarin (SLM) is a functional food ingredient that has very low aqueous solubility (solubility in water: 50 μg/mL). In the present method, the model drug was dissolved in organic solvent, which was mixed with the aqueous phase under a high pressure. The obtained dispersions were freeze-dried for further physicochemical characterization of the obtained powdered nanoparticles.

The nanocrystal of SLM produced with this high pressure crystallization process exhibited a narrow size distribution. The particle size of SLM crystals powdered with erythritol or hydroxypropyl-β-CyD (HP-β-CyD) was observed about 230 nm

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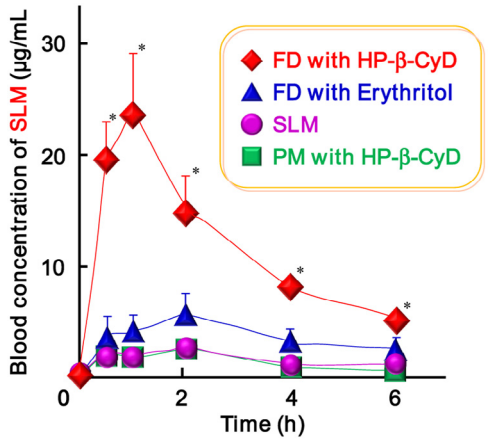

Fig. 1 – Blood concentration profile after oral administration of various SLM nanoparticles in rats.

after hydration. When measuring the concentration of SLM in the dissolution test, SLM/HP-β-CyD showed the maximum supersaturated concentration of SLM (100 μg/mL). The plasma concentration profiles in absorption test in rats with various SLM nanoparticles samples prepared with this high pressure crystallization process were shown in Fig. 1. The SLM/HP-β-CyD nanoparticles exhibited significantly increased $AUC_{0\text{-}6\,h}$ and *Cmax* compared with other SLM nanoparticles. Such a high AUC value was not observed with SLM/erythritol nanoparticle, where erythritol was used as a stabilizer instead of HP-β-CyD, and with physical mixture of SLM and HP-β-CyD. From these results, a combination of the high pressure crystallization method and use of HP-β-CyD is useful for the effective production of drug nanoparticles of SLM showing enhanced dissolution rate and absorbability.

REFERENCES

[1] Langguth P, Hanafy A, Frenzel D, et al. Nanosuspension formulations for low soluble drugs: pharmacokinetic evaluation using spironolactone as model compound. Drug Dev Ind Pharm 2005;31:319–329.

[2] Liversidge G, Cundy K. Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. Int J Pharm 1995;125:91–97.