

Design of poorly-water soluble drug nanocrystals by spherical crystallization method with Microfluidizer®

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To improve the water solubility of drugs, nanocrystallization is one of relevant solution. There are two methods to prepare the nanocrystal. One is break down method (wet milling) and another is build-up method. We have key technology that is the emulsion solvent diffusion method for preparation of spherical crystal with build-up method. This technique can be adopted to prepare nanocrystals. In the present study, microfluidizer® which is high shear fluid processors, was applied to the emulsion solvent diffusion method to establish the efficiently nanocrystal preparation process.

Probutol (PC) and nimodipine (NP) was used as model poorly water soluble drug. Poly vinyl alcohol (PVA) and hydroxyl propyl cellulose (HPC) were used as hydrophilic dispersing agents. Break-down (BD) method: 40mg of drug were dispersed in 40mL of the aqueous dispersing agent solution. This suspension was wet milled by MF (Microfluidics LV1, Powrex corp.) Build-up (BU) method: 120mg of model drug were dissolved in 6mL of good solvent (ethanol). This drug solution was injected into 9mL of the poor solvent (aqueous dispersing agent solution) by using MF at 10,000~15,000 psi. Particle size and dissolution behavior were evaluated. Particle shape was observed by scanning electron microscope.

Nanocrystallization by BD method: Particle size of milled crystal became smaller with increase pass number. After 30 pass, particle size of PC and NP were ca. 400nm and ca. 500nm, respectively. Type of dispersing agent affects the particle size. The smallest particle sizes were obtained in 0.5% PVA solution for NP and in distilled water for PC. Nanocrystallization by BU method: In BU method, nanocrystal with <400nm could be obtained by only single process. Especially, particle size of PC nanocrystal was around 250nm with narrow distribution. Crystal growth was observed in NP nanocrystal suspension. This phenomenon depends on the type of dispersing agent.

Conclusion: Nanocrystal can be obtained by using microfluidizer® based on high shear fluid processors. Especially, by fusion of technologies microfluidizer and emulsion solvent diffusion method, it is possible to prepare nanocrystals more efficiently. In these processes, it was suggested that the optimum combination exists between the drug and the dispersing agent to stabilize the dispersion.