

Liquid-Assisted Grinding to Prepare Cocrystals of Adefovir Dipivoxil and Dicarboxylic Acids

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1. Introduction – Crystal structures directly affect the physical properties of active pharmaceutical ingredients (APIs), such as solubility and stability, which in turn determine the pharmaceutical performances of the APIs. Cocrystallization is one of the more versatile methods to control the physicochemical properties of APIs especially because of the diverse possibilities of coformers (usually non-active building blocks that strongly interact with API molecules) [1,2]. However, the exact compositions of the cocrystal phases are difficult to predict until the full characterization of the crystal structures, which is often time-consuming and sometimes elusive. Liquid-assisted grinding has been utilized as a simple method to discover the viable pairs of API-coformer, and it is also environmentally more sustainable with a smaller amount of solvent usage compared to conventional solution crystallization.

2. Results and Discussion - In the present study, we tested the possibility of semi-quantitatively establishing the API-coformer compositions through the grinding method. Adefovir dipivoxil (AD) and dicarboxylic acids, a system long studied in our research group, were used as model molecules [3-5]. Specifically, AD was ground with succinic or suberic acids (SUC or SUB) in the presence of a minute amount of methanol or ethanol. The molar ratios of AD/dicarboxylic acid as well as grinding time were varied. The ground powders were characterized with X-ray diffraction and differential scanning calorimetry. The results of the characterization were enough to lead us to conclude the correct cocrystal compositions of AD/SUC = 2:1 and AD/SUB = 1:1.

3. Conclusions - The liquid-assisted grinding followed by careful powder characterization can be useful to semi-quantitatively assess the cocrystal phases, especially when the full characterization of the crystal structures is not immediately available.

4. References

- [1] W. Jones, W.D.S. Motherwell, A.V. Trask, *MRS Bull.*, **31** (2006) 875-879.
- [2] N. Shan, M.J. Zaworotko, *Drug Discov. Today*, **13** (2008) 440-446.
- [3] S. Jung, J. Lee, and I. W. Kim, *J. Cryst. Growth*, **373** (2013) 59-63.
- [4] S. Jung, J.-M. Ha, and I. W. Kim, *Polymers*, **6** (2014) 1-11.
- [5] S. Jung, I. Choi, and I. W. Kim, *Crystals*, **5** (2015) 583-591.