CHAPTER 5

CONCLUSION

This research was conducted to examine the solid state properties of N (2-propylpentanoyl) urea (VPU), a newly synthesized compound which exerted anticonvulsant activity. Solid state chemical characterization of VPU include solid phase identification, solid state stability and solubility measurement.

Solid phase screening was investigated by treating the reference VPU by various methods as following;

Method I – Recrystallization by rapid solvent evaporation
Method II – Recrystallization by temperature change
Method III – Recrystallization by slow evaporation
Method IV – Recrystallization from binary mixture of solvents
Method V – Evaporation crystallization
Method VI – Immediate solidification of the melt
Method VII – Thermal treatment

All of the products obtained presents the same chemical identity and purity as the reference VPU identified by TLC and FTIR analysis. Morphology of the samples obtained by SEM (1000X) is needle-like (acicular) form. The crystals obtained are different in their size which result from the solvent and method used to obtain the solids.

By XRPD analysis, almost all of the products exhibited same XRPD patterns as the reference VPU, except the products obtained from hexane and heptane by method I which a peak at $2\theta = 19.2°$ was absent. This difference was not the result of preferred orientation but may occurred from internal structure variation. However, it is possible that internal structure variation may have little effect on the thermoanalytical behavior of the product because the difference in DSC and TGA thermograms between those two groups are not observable. These results was not conclusive and cannot implied that polymorph does not exist. Single crystal XRPD analysis is required to confirm the internal structure of molecules.

The DSC and TGA analysis have been conducted. Also, The DSC and TGA thermograms of all products selected are similar to that of the reference VPU.

From solid phase screening studies, no evidence supports the existence of polymorph, solvate and hydrate form of VPU. In addition, the pure amorphous form cannot be achieved by any methods used in this study, which may be the result of rapidly recrystallized behavior of VPU.

Solid state stability of VPU was studied. The objective of this investigation was to examine solid phase transformation of VPU over a range of temperatures as a function of time. The preliminary study by thermal treatment suggested that, when expose to heat, the crystal form of VPU transformed to amorphous form. The samples were determined for its amorphous content by quantitative XRPD analysis with sodium chloride used as internal standard. To investigate the kinetics of transformation, a plot of ralative amount of crystalline phase ($x_c = I_C/I_{NaCl}$), versus time t, using the kinetic equations based on reaction orders and the reactions controlled by contracting geometries were constructed. More than one equation fits the data indicates that solid-state kinetic data cannot be used to prove the only mechanism of solid-state reaction. Thus, the mechanism of the transformation from crystal form to amorphous of VPU cannot be described by only one model. The rate constants obtained by the equations suggested that the higher temperature, the greater rate of transformation.

Using Arrhenius equation, activation energies obtained from all correlated equations was not significantly different. Therefore, the major transformation pathway occurred was not observable. Thus, the transformation may include various mechanisms all together making it more complex.

The solubility of reference VPU was measured compared with the solubility of sample obtained from stability study at 80°C for four weeks. This sample exhibited the highest transition to amorphous form. The highest solubility of the sample presents 1.4 times greater solubility than that of the reference VPU.

The future study using single crystal x-ray powder diffraction should be conducted to reveal the internal structure of VPU and to provide more insight into the nature of the solid.

Although polymorph, solvate, hydrate and complete amorphous forms of VPU cannot be prepared using all the methods used in this study, other methods might be tried such as recrystallization in mixed solvent by varying its proportion and type of solvents, rapid cooling of the melted product over an oil bath to control the temperature or heating the solid at the boiling point of a solvent and then pouring the hotsolution over dried ice. In addition, if the large scale synthesis of VPU can be developed, spray drying and grinding should be examined. Lyophilization is also attractive to obtained pure amorphous form if the instrument for organic solvents is available.

However, one of the advantages of being only one crystalline phase substance is its physicochemical properties will not be altered easily. Thus, its bioavailability will remain unchange. In addition, although the poor aqueous solubility is not a crucial problem for oral absorbtion and bioavailability in rats, the importance of the amorphous state should still be considered since amorphous form may exhibit distinctive physicochemical properties from its crystalline form. Therefore, understanding of the transformation of crystalline to amorphous phase should be clarified.