CHAPTER V

CONCLUSIONS

Two polyamorphous forms of clopidogrel were prepared by spray drying and freeze drying methods. Many solid-state analytical techniques revealed that the samples prepared were amorphous. However, PXRD, DSC, TGA, polarized light microscope, DVS apparatus and Raman spectroscopy were not able to distinguish between these two polyamorphous forms. On the other hand, results from PCA obtained by collecting Raman spectra can be used to discriminate between the two prepared amorphous samples. Therefore, amorphous clopidogrel prepared by spray drying method and freeze drying method can be classified as different amorphous forms by only evaluating PCA obtained by Raman spectral data and termed "polyamorphous".

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The solubility studies reveal that amorphous clopidogrel prepared by spray drying method (760 g/L) and freeze drying method (877 g/L) can be classified as "freely soluble" in water according to USP 35, while, solubility of clopidogrel bisulfate can be classified as "practically insoluble" in water. These results indicate that prepared polyamorphous samples show increase in solubility compare to crystalline form of clopidogrel.

Moreover, the related substances A and C of polyamorphous clopidogrel prepared by spray drying method and freeze drying method are slightly higher than of specification of clopidogrel related compound A and clopidogrel related compound C in USP35 (Table 7) where specification of clopidogrel related compound A and C value not more than 0.2% and 1.0%, respectively.

Furthermore, surface appearances and approximate sizes of polyamorphous clopidogrel prepared by spray drying method under observation using SEM shown in Figures 63 exhibit small spherical particle with approximate particle size of 5 microns (SP^0), whereas, another amorphous sample (FZ^0) exhibit continuous flakes similar to fiber and particle size cannot be detected (Figures 64). On the contrary, clopidogrel RM are small irregular particles of approximate size of 10 microns (Figures 62). These results present that two polyamorphous prepared have clear differences in the surface appearances and approximate sizes when compared to clopidogrel RM. However, the study cannot distinguish between the two polyamorphous forms from one another.

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The present studies reveal that two polyamorphous forms of clopidogrel readily uptake moisture at higher level than its crystalline RM. All above results reveal that two prepared sample at day 0 are amorphous form. After storage at high temperature and high humidity condition (40°C 75%RH) for only 7 days, two polyamorphous forms of clopidogrel convert to crystalline form similar to clopidogrel RM. This interconversion do not occur when these amorphous form are stored at lower humidity environments of 30°C 30%RH and 40°C 30%RH. These studies indicated that humidity has higher impact on the solid-state stability and the transformation to crystalline clopidogrel structure of polyamorphous clopidogrel prepared.