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DEVELOPMENT AND EVALUATION OF POLYAMORPHOUS STATE OF CLOPIDOGREL


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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Pharmacy Program in Industrial Pharmacy
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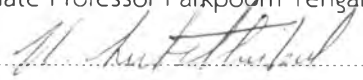
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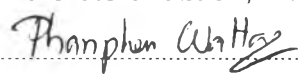
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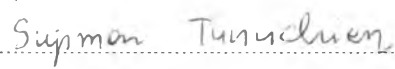
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Two polyamorphous samples of clopidogrel were generated by spray drying and freeze drying methods with water solubilities of 760 g/L and 877 g/L at 30°C, respectively. These samples were placed under 3 different storage conditions (30°C 30 %RH, 40°C 30 %RH and 40°C 75 %RH) to evaluate for their solid state stabilities. Characterization methods utilized to differentiate the two polyamorphous forms include microscopy, powder X-ray diffractometry (PXRD), Raman spectrometry (Raman), dynamic vapour sorption (DVS), thermogravimetry (TGA), differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and Principal Component Analysis (PCA). It was found that only PCA method, obtained from Raman spectrum between 3200 to 2800 cm^{-1} and 1800 to 100 cm^{-1} was able to distinguish between the two polyamorphous samples and crystalline clopidogrel with PC1 = 97.7 % and PC2 = 1.2 %.

PCA was also used to monitor the solid state transformation of polyamorphous samples during stability evaluation. The results indicated that at higher humidity condition (40°C 75 %RH), the two polyamorphous forms of clopidogrel readily convert to the crystalline form within 7 days. However, at lower humidity conditions (40°C 30 %RH and 30°C 30 %RH), the amorphous-crystalline transformation did not occur at neither temperatures used. It can be concluded from the above results that humidity have higher influence on the solid-state stability of polyamorphous clopidogrel than temperature. In addition, PCA also revealed that the transformation pathways of the two polyamorphous forms back to crystalline clopidogrel are distinctively different. These results suggest that the control of humidity during pharmaceutical manufacturing of amorphous clopidogrel products is crucial in maintaining the solid state stability of an appropriate amorphous form of the active substance.

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LIST OF ABBREVIATIONS

SP	Spray Drying Method
FZ	Freeze Drying Method
RM	Raw Material
APIs	Active Pharmaceutical Ingredients
USP	United States Pharmacopoeia
ICH	International Conference on Harmonization
DSC	Differential Scanning Calorimetry
TGA	Thermogravimetric Analysis
HPLC	High Performance Liquid Chromatography
DVS	Dynamic Vapor Sorption
SEM	Scanning Electron Microscope
PXRD	Powder X-ray Diffractometry
IR	Infrared
NIR	Near-Infrared
FT-IR	Fourier Transform Infrared
FT-Raman	Fourier Transform Raman
NMR	Nuclear Magnetic Resonance
EDA	Exploratory Data Analysis
PCA	Principal Component Analysis
PCs	Principal Components
PC1	The first Principal Component
PC2	The second Principal Component
%	Percentage



θ	Angle
min	Minute (s)
sec	Second (s)
$^{\circ}\text{C}$	Degree Celsius (centigrade)
kV	Kilovoltage (s)
\AA	Angstrom (s)
μm	Micrometer (s), Micron (s)
nm	Nanometer (s)
mm	Millimeter (s)
cm	Centimeter (s)
cm^{-1}	Centimeter-gram-second
SAS	Super Critical Antisolvent
CCD	Charge-coupled Device
Nd-YAG	Neodymium Yttrium Aluminum Garnet
He-Ne	Helium-neon
InGaAs	Indium doped with Gallium Arsenide
CSIs	Cluster Separation Indices
et al.	et alli, and others

