CHAPTER I

INTRODUCTION

The solid state characterization of active pharmaceutical ingredients (APIs) plays an important role in drug development due to its implications in terms of the physicochemical and biopharmaceutical properties such as solubility, dissolution rate, bioavailability and stability (1).

Solid materials can exist in different polymorphic (crystalline) forms and amorphous forms. It is not surprising that the use of different approaches to prepare amorphous solids may influence thermal properties, structural and physical stability of amorphous materials derived from it (2). Polymorphism is defined as the different arrangements and conformation of molecules in crystal lattices. Many drugs exhibit polymorphisms leading to differences in the physical and chemical properties between the different forms of a drug such as melting point, chemical reactivity, solubility, dissolution rate, optical or electric parameters, vapor pressure and density. Pseudo-polymorphism is a kind of polymorphism that is characterized by the regular pattern for the incorporation of solvents within the crystal lattices, including water hydrates. Polymorphisms and pseudo-polymorphisms exist in many APIs in drug products. Recently, because of the effects of polymorphisms and pseudo-polymorphisms on the stability and solubility of drugs, crystal form analysis of drug products has become very important. The US-FDA and International Conference on Harmonization (ICH) recommend monitoring and controlling the polymorphs in drug substances and drug products since early stages of drug development and throughout the lifecycle. For these reasons, pharmaceutical industries have a keen

interest in the quantitative solid-state characterization and evaluation of APIs and drug products (3).

Clopidogrel bisulfate is chosen as the model drug for this study because it exists in 2 polymorphic forms (Form I and Form II). In addition, several methods were used to prepare amorphous state, such as, freeze drying, spray drying, melting and quench-cooling, anti-solvent crystallization, melt extrusion and mechanical activation (milling) (4). The amorphous state is characterized by the absence of long range positional orientation of molecules leading to improved solubility. However, the amorphous state is thermodynamically unstable and can readily convert to more stable crystalline form upon storage, especially when exposed to heat and humidity (5). Due to the fact that many methods were used to prepare amorphous samples, it is interesting to note that these amorphous solids were shown to exhibit noticeable differences in the physiochemical, biological and mechanical properties. Thus, the term "polyamorphous" was proposed. However, analytical techniques to differentiate between these polyamorphous solids are currently being developed and remained highly controversial. Due to diverse solid morphology of drug can show differences in its pharmaceutical properties, therefore, it is important to characterize and control the solid-state forms as early in product development process as possible (6).

There are many conventional solid-state techniques used alone or in combination to characterize and control amorphous form prepared by spray drying, freeze drying methods and to evaluate for their stability, such as, polarized light microscopy, powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), dynamic vapor sorption (DVS), infrared (IR)

and Raman spectroscopy. However, these analytical techniques alone without further data treatment were unable to differentiate the two suspected "polyamorphous" sample effectively. Thus, multivariate statistical analysis tool called Principal component analysis (PCA), are used on preprocessed Raman spectroscopic data to increase the power of polyamorphous differentiation and acceptance. The Principal Component Analysis (PCA) is mathematical manipulation of data matrix to represent the variation present in many variables using a smaller number of "factors" called principal components (PCs). Therefore, the results from all Raman spectral data are analyzed using PCA in order to distinguish between groups of data.

The aims of this study are to differentiate the polyamorphous samples prepared by two different methods. Furthermore, this study investigates the solid-state conversion of amorphous clopidogrel bisulfate samples prepared by spray drying and freeze drying and after stored in 3 different environmental conditions (30°C 30%RH, 40°C 30%RH and 40°C 75%RH). Moreover, this study will evaluate the physicochemical characteristics of polyamorphous samples and understand the effect of humidity and temperature on phase conversion.

Objectives

1. To develop reliable solid-state analytical technique to confirm and differentiate the polyamorphous state of clopidogrel
2. To evaluate the differences in physicochemical properties of polyamorphous state of clopidogrel prepared
3. To study the effects of temperature and humidity on the conversion of polyamorphous state of clopidogrel prepared