Chapter I

INTRODUCTION

The important considerations for development of a solid oral pharmaceutical dosage form are organoleptic properties that can influence patient compliance and preference. Bitter taste plays as one of the most important parameters relating to patient compliance. Oral administration of bitter tasting drug is of great concern especially in pediatric and geriatric drug products.

Procedures in taste masking depend on the bitterness of the drug on a pharmaceutical dosage form. Granule preparation is an inexpensive taste masking technology and is easy to prepare. This granulation technique can improve the taste of drugs with slightly bitter taste by reducing the substance's surface area when it comes in contact with the tongue upon oral administration. Polymer coating is another method to mask the bitter taste by coating the drug particles. The polymer most often used for taste masking is Eudragit® E PO, a cationic copolymer of butyl methacrylate, methyl methacrylate and dimethylaminoethyl methacrylate.

Azithromycin is an azalide, a subclass of macrolide antibacterial. It is synthesized from erythromycin, with a CH_3-substituted nitrogen atom in the lactone ring, thus making the 15-membered lactone ring. Azithromycin is used for treating various types of bacterial infections, such as sexually transmitted diseases, ear infections, respiratory infections and skin infections. Further deployment of azithromycin oral preparations and their clinical applications are limited by its bitter taste. Reducing adherence of patient, especially when pediatric and geriatric are concerned. Being a highly bitter drug, azithromycin poses a challenge in the formulation of a pediatric dosage forms.

The definition of Process Analytical Technology (PAT) by The United States Food and Drug Administration (USFDA) is "a system for designing, analyzing and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality". In addition to, the USFDA requires a new real-time monitoring and process control in PAT applications. The International Conference on Harmonization (ICH) recommends the Quality-by-Design (QbD) guidelines for real-time monitoring and control. The goal of this application is to obtain clearer insight in the pharmaceutical production processes through knowledge management. Thus, PAT is based on the process understanding to identify key parameters and control strategy based on the selected multivariate real-time analysis.

Near-Infrared spectroscopy (NIRs) is the most utilize PAT process analyzer. It is a rapid and non-destructive sample analysis tool and suitable for the timely measurement of blending process during taste masking. Moreover, NIRs can be used in pharmaceutical development, process monitoring, or an off-line analysis. The analyses by NIRs can be qualitative or quantitative. Qualitative analysis refers to classification of the samples regarding to their NIRs spectra in Principal Component Analysis (PCA). Quantitative analysis as Partial Least Square (PLS) regression can be chosen to learn more precisely in what extent samples are different.

The chemometric is a branch of sciences that obtains data by the application of chemical, statistical and mathematical methods, for the extraction of useful information from physical and chemical phenomena involving in a manufacturing process. The chemometric approaches can be used to analyze the data derived from

NIRs. The integration of chemometric and NIRs is a potential analyzer for the pharmaceutical processes.

Objectives of the present study were:

1. To apply Process Analytical Technology (PAT) using NIR spectroscopy for process monitoring of masking unpleasant taste of azithromycin powder in order to evaluate the homogeneity end-point of the final product.
2. To develop the qualitative model for optimal solid ratio between Eudragit® E PO and AZD, mixing time and to develop quantitative model on homogeneity state by chemometric.