CHAPTER I

INTRODUCTION

Pharmaceutical analysis can be regarded as the application of analytical chemistry to pharmaceutical formulations, products and substances. These samples may consist of liquids, gels, powders, tablets, aerosols etc. of various types and contents. Pharmaceutical analysis is generally of a quantitative as well as qualitative type. Examples of quantitative analyses are the determination of the content of the active compound or the content of a major impurity in a pharmaceutical formulation. Examples of qualitative analyses are the identification of an active compound, i.e. to ensure that the compound is actually the one that is wanted. An example of an analysis that is both quantitative and qualitative is of the purity of a pharmaceutical formulation, i.e. whether there are any impurities, degradation products or synthesis intermediates etc. in the sample and, if so, how many and in what concentrations.

One of the fundamental problems of the analysis of pharmaceutical preparations, which contain two or more drugs, is the simultaneous quantitative analysis without any chemical separation step. Several spectrophotometric methods such as classical derivative spectrophotometry, ratio spectra derivative spectrophotometry are frequently made on the basis of zero-crossing measurements and signals corresponding to the maximum point of wavelength for the simultaneous quantitative analysis of binary mixtures of drugs with overlapped spectra, respectively.

In view of characteristic such as: high sensibility, operational facility and low cost, the UV-VIS spectrophotometry could be one of the most useful analytical tools. Unfortunately, its chronic problems related to low selectivity usually impede the determination of analyses from complex matrices.

In recent years, the chemometric methods, involving multivariate calibration techniques, namely classical least-squares (CLS), inverse least-squares (ILS), principal

component regression (PCR) and partial least-squares (PLSR) techniques based on the computer-controlled instrumentation are playing a very important role in the spectrophotometric analysis of mixtures containing two or more compounds without preliminary separation (*1–7*). All the multivariate approaches are useful for the resolution of spectral band overlapping in quantitative determination. In the multivariate analysis, a calibration is build from spectral response values for a set of standard samples of known concentrations corresponding to the analytes of interest. The obtained calibration is used to predict the component concentrations from the sample spectrum.

Chlorzoxazone (5-Chlorobenzoxazole-2 (3H)-one), is a centrally acting muscle relaxant with sedative properties and it is used mainly as relaxation of skeletal muscle spasm. Chlorzoxazone acts primarily at the level of the spinal cord and subcortical areas of the brain where it inhibits multisynaptic reflex arcs involved in producing and maintaining skeletal muscle spasm of varied etiology. Paracetamol (N-acetyl-p-aminophenol), is a nonsteroid anti-inflammatory and antipyretic agent (*8*) useful in skeletal muscle pain. Paracetamol provides analgesic action to supplement which results secondarily from muscle relaxation. Chemical structures of chlorzoxazone and paracetamol are presented in Figure 1.

(I) (II)

Figure 1 Chemical structures of chlorzoxaxone (I) and paracetamol (II)

Chlorzoxazone, in the solid state, is stable for up to 5 years at room temperature, and up to 4 weeks without any significant degradation at temperatures up to 80 ^{0}C in artificial sunlight (1000 foot candles). Chlorzoxazone tablets have also been found to be stable for up to 5 years at room temperature. With storage condition of 60 ^{0}C, 80% relative humidity and artificial sunlight (1000 foot candles), the tablets found to be stable for up to 4 weeks with no significant degradation. An aqueous suspension of

chlorzoxazone, in distilled water or acidic media with a pH not greater than 7, is generally stable (*8*)

Dry, pure, paracetamol is very stable at temperature up to at least 45 ^{0}C. Aqueous solution of paracetamol is slightly light sensitive with the degradation appears to be both acid and base catalysis reaction. Paracetamol is relatively stable to aerial oxidation unlike its hydrolysis product p-aminophenol (*8*).

A variety of methods have been employed in quantitative determination of chlorzoxazone and paracetamol separately (*9-10*) or simultaneously in dosage forms, such as absorbance ratio (*11*), difference spectrophotometry (*11*), TLC densitometry (*12*), multi-wave length linear regression (*13*), HPLC (*14*) and orthogonal functions-ratio spectrophotometry (*15*). No official method for simultaneous determination of chlorzoxazone and paracetamol in tablets dosage form. A literature survey reveals that there are many methods reported for the determination of chlorzoxazone and/or paracetamol with different drugs in pharmaceutical formulations (*16-28*). However, no spectrophotometric methods using PCR and PLSR have been reported for the simultaneous determination of these drugs in pharmaceutical preparations.

The purpose of this study is to investigate the ability of PCR and PLSR methods for quantifying two components mixture of chlorzoxaxone and paracetamol with overlapping UV spectra, without preliminary separation, and to apply the optimized models to commercial pharmaceutical products. The proposed methods are simple, accurate, reduced the duration of the analysis, and are suitable for routine determination of such drugs in the mixture. The results obtained by the two methods are compared and discussed.