CHAPTER I

INTRODUCTION

Hypertension is one of the major public health problems in both industrial and in developing countries. The morbidity and mortality rates of hypertension are yearly increasing. From the record of public health statistics (2003), 3,402 of 100,000 populations died from hypertension. Approximately 390 of 100,000 of Thai in-patient have hypertensive state [1]. According to WHO, the definition of hypertension is taken as a level of systolic blood pressure of $\geq$140 mmHg and a level of diastolic blood pressure of $\geq$90 mmHg. Hypertension is one of risk factors for many diseases such as cardiovascular disease, kidney failure, brain vascular damage and paralysis, etc. The hypertensive patients have to take the medicine for all their life and should change life style to control the blood pressure in order to reduce the risk of related diseases.

There are many medications used for hypertension such as propranolol (β-adrenergic antagonist), enalapril (angiotensin-converting enzyme inhibitor), losartan (angiotensin II antagonist), etc. Amlodipine is one of effective drugs for mild to moderate hypertension and angina pectoris. It is well tolerated and does not cause some of undesirable effects often associated with other cardiovascular agents. Normal dose of amlodipine to control blood pressure is once a day due to its long durations [2]. However, the price of the innovative amlodipine (Norvasc®, Pfizer) is quite high. In Thailand, patients have to pay approximately 1,600 baths for the cost of 10 mg amlodipine per month. Since the patent of amlodipine will be expired in September 25, 2007, several pharmaceutical companies are preparing to launch a generic amlodipine to the market. This is an opportunity for Thai patients to pay for low cost drug. In order to assure the bioavailability of the generic amlodipine, the proof of bioequivalence must be submitted to Thai Food and Drug Administration (FDA). The Bioequivalence Guideline issued by the Thai FDA suggests that bioequivalence studies in humans can be done by comparing either pharmacokinetic, pharmacodynamic or clinical efficacy endpoints,

caused by generic and innovative drugs. However, the most appropriate method to prove bioequivalence among generic and innovative amlodipine would be pharmacokinetic studies due to its objective endpoints with the least variation compared to those obtained from both pharmacodynamic or clinical efficacy studies. In addition, pharmacokinetic study can be employed in healthy volunteers; thus there is no question of using the generic products with unclear benefit in the patients.

In future bioequivalence study, both generic and innovative amlodipine will be administered to healthy volunteers. Plasma is collected before and at various times after drug administration for the measurement of amlodipine concentration and its pharmacokinetic profile will be statistically compared according to bioequivalence criteria. The suitable method for drug analysis in plasma has to be found. As amlodipine has low concentrations in plasma, optimization of an accurate and sensitive analysis method is quite challenging.

This study was aimed at development of amlodipine determination in human plasma. The extraction and quantitation methods of amlodipine from plasma were selected and validated. The method developed in this study can be used for the future pharmacokinetic and bioequivalence study of amlodipine.