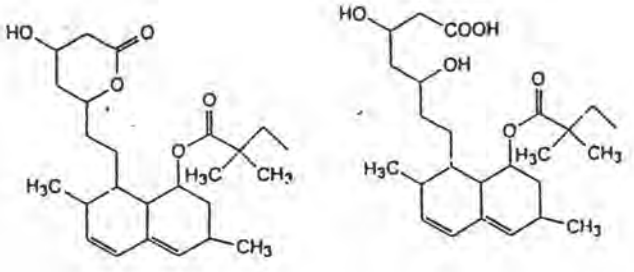
CHAPTER I

INTRODUCTION

Simvastatin is a number of a new class of drugs used in the treatment of hypercholesterolemia. Simvastatin, containing a lactone moity as shown in Figure 1, is a prodrug of an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Although simvastatin itself is pharmacologically inactive, the lactone is hydrolysed to form the carboxylic acid as a major metabolite that acts as a potent, reversible, competitive inhibitor of HMG-CoA reductase which catalyzes the conversion of hydroxymethyl glutarate to mevalonate. This conversion is an early and rate-limiting step in the biosynthesis of cholesterol.



Lactone form Hydroxy acid form

Figure 1 Structures of lactone and hydroxy acid form of simvastatin.

There is the only one originally commercial simvastatin preparation available in Thailand which imported and have quite expensive prices. Because of the budgetary and economical reasons, it is necessary to develop locally made simvastatin preparation. Eventhough, a new locally made product

must be approved in safty and efficacy prior to market for human use. One of clinical evaluation for a new drug dosage form is to conduct an *in vivo* bioavailability study in human or suitable animal model.

Comparative efficacy of the same drug from each manufacturer can be performed both *in vitro* and *in vivo*. For *in vitro*, simvastatin has a low water solubility of only 0.03 mg/ml at room temperature (Ellison, Moore and Petts, 1993). This low solubility will affect its delivery from the dosage form. Since, dissolution test method for simvastatin tablet is not available in any pharmacopoeias, thus it is interesting to develop dissolution conditions which are appropriate for routine testing and for discriminating between different formulations.

For *in vivo*, such as pharmacokinetic study, there are many analytical methods available for determinating simvastatin in plasma such as enzymatic inhibition assay, gas chromatography/ mass spectrometry (GC/MS), liquid chromatography/ mass spectrometry (LC/MS) and high performance liquid chromatography (HPLC). An enzymatic inhibition assay is farely sensitive. However, it is not specific because it measures all of the inhibitor present (Takano, Abe and Hata, 1990). The methods based on GC/MS measurement of either ferroceneboronate or pentafluorobenzyl bromide derivative of simvastatin hydroxy acid as well as the LC/MS technique were reported to have good sensitivity and selectivity. However, their sensitivity highly depends on the type and efficiency of MS that cause a great deal of technical problems (Takano, Abe and Hata, 1990; Morris, 1993; Iwabuchi et al.,1994). An HPLC method was developed, since it was reported that the method has good selectivity and sensitive enough to determine simvastatin and its hydroxy acid level in dog plasma. In this study, simvastatin was converted its hydroxy acid form, to eliminate possible variation in the extent of prodrug hydrolysis during

storage and analysis, and the total plasma simvastatin hydroxy acid level was determined.

It has been reported previously that the dog is an appropriate paradigm for man in the disposition and quantitation study of simvastatin. Both dog and man seemingly have similar material balance profiles, metabolic profiles and low level of plasma "lactonase" activity (Vickers et al., 1990a; Duggan and Vickers, 1990). In addition, simvastatin did not accumulate in dog hepatic tissue during 2 weeks of 5 mg/kg/day dosing and there was a low incidence of cataracts in dogs that underwent chronic dosing with simvastatin at 50 mg/kg/day (Cheng et al., 1993).

At present, there are four different brands of simvastatin tablets. One is an innovator's product with expensive retail price and others are locally manufactured brands. Therefore, it is interesting to investigate the bioavailabilities and pharmocokinetics profiles after single oral dose administration of simvastatin tablets in dogs for pilot animal bioequivalent studies, and, to develop dissolution test method to obtain the suitable conditions that can distinguish the dissolution rate of each brand. In addition, acute pharmacological effect of simvastatin was also assessed by determinating the percentage change from baseline in total plasma cholesterol at 2 hour after drug administration.

Objectives

Therefore, the objectives of this study were as follows:

1. To evaluate the *in vivo* bioavailabilities between locally - manufactured and innovator's simvastatin tablets after single oral dose using

dogs as an animal model.

2. To develop the *in vitro* dissolution test method for simvastatin tablets to obtain conditions suitable for routine testing and formulation screening.

3. To assesses the acute pharmacological effect (plasma cholesterol-lowering effect) among four different brands of simvastatin tablets after single oral dose in dogs.