CHAPTER I

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) has been a major public health problem since its detection in 1981. Zidovudine (3′-azido-3′-deoxythymidine, AZT), the first anti-HIV compound approved for clinical use, is still widely used for treatment of AIDS and AIDS - related complex, either alone or in combination with other antiviral agents. Since anti-HIV drugs act as metabolic antagonists against the reverse transcriptase of the virus, it is crucial for the success of AIDS therapy to maintain the systemic drug concentration consistently above their target anti-retroviral concentration throughout the course of the treatment (Chien and Wearley, 1989). In addition, because of the virustatic nature of this drug, the patients have to rely upon this drug for the whole life. Because of the short elimination half-life (about 1 h) of AZT (Matthews, Cerososimo, and Spivack, 1991), the conventional oral or IV route is inherently limited in that it cannot maintain a constant plasma level within the target therapeutic range for a prolonged duration. In addition, the oral bioavailability of AZT is small due to its rapid hepatic " first-pass" metabolism (Klecker *et al.*, 1987; Shelton *et al.*, 1992) such that the frequent high administered dose for maintaining therapeutic level is required. The result of excessive systemic concentration after IV or oral administration of AZT often exert several dose-dependent toxic side effects (Merigan and Skowron, 1990; Kieburtz *et al.*, 1992) that require dosage reduction or even cessation of treatment. Therefore, AZT has been as a noninvasive delivery for maintaining the expected anti-HIV effect and avoiding the

serious side effects attributed to the high plasma levels of these drugs immediately after conventional IV or oral administration (Chien and Wearley, 1989).

The transdermal delivery is the noninvasive delivery that maintains a suitable plasma concentration for long duration. This would enhance the efficiency of antiviral activity with high patient compliance. Therefore, transdermal drug delivery of anti HIV drugs would be an alternative dosage form to overcome the problems of conventional delivery, such as sleep interruption and a high degree of hepatic-gastrointestinal "first-pass" metabolism. It can also reduce the frequency and severity of side effects by optimizing blood concentration profiles. In contrast to these benefits, the anti HIV drugs are mostly hydrophilic that is not possible to penetrate through a dense and hydrophobic stratum corneum barrier at a rate sufficient to achieve therapeutic efficacy. One strategy to achieve adequate flux across skin is the incorporation of various skin permeation enhancers into the vehicle. Another strategy is to choose a suitable vehicle for the drug being used for transdermal administration. Especially for the hydrophilic drug, the judicious selection of solvents seems to be very important for the enhancement of transdermal delivery (Goto *et al.*, 1993; and Lee, *et al.,* 1993).

The physicochemical properties of the drug are important in transdermal drug delivery. A basic knowledge of the formulation and the transfer processes from the device into and through the skin are required. Feasibility studies of AZT transdermal delivery were performed using several solvents and penetration enhancers such as ethanol, propylene glycol, isopropyl alcohol, isopropyl myristate, *N*-methyl pyrrolidone, terpene and oleic acid. (Seki, *et al.,* 1991; Karali, *et al.,* 1995; and Kim

and Chien, 1996). However, the effect of controlling membrane on AZT permeation *in vitro* have not been reported elsewhere. Therefore it is the intention of this study to prepare transdermal delivery system for AZT and the permeation can be controlled by membranes.

The objectives of this study:

1. To prepare transdermal delivery of Zidovudine (AZT)
2. To determine the effect of controlling polymer membrane on permeation of AZT across newborn pig skin
3. To study the effect of binary vehicles and enhancers on permeation of AZT across newborn pig skin
4. To study the physicochemical properties of AZT affecting AZT permeation across newborn pig skin.