CHAPTER I

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a global spread life-threatening infectious disease caused by human immunodeficiency viruses (HIV) (Fauci, 2003). The most widely used antiHIV drugs are nucleoside analogues (Wurtzer et al., 2005). Zidovudine (AZT) is a first clinically approved nucleoside analogue reverse transcriptase inhibitor for the treatment of AIDS and AIDS-related diseases that has been currently used in most antiviral combination therapies (D'Alessandro et al., 2000, Narishetty and Panchagnula, 2004, Lynx et al., 2006) and in suppression of the HIV transmission from mother to fetus (Chinis et al., 2002). Its triphosphate active form after phosphorylation exhibits antiHIV activity by binding to viral reverse transcriptase, incorporating into viral DNA consequently leading to the termination of gene synthesis (Peter and Gambertoglio, 1996, Chariot et al., 1999, Wurtzer et al., 2005, Lynx et al., 2006).

The clinical restrictions of zidovudine are short plasma half-life of approximately 1 h and dose-dependent hematological toxicities especially granulocytopenia and anemia that are found often in AZT treated patients (Thomas and Panchagnula, 2003, Flexner, 2006). Because of its short plasma half-life, frequent administrations of zidovudine at high dose are required to maintain drug level in the body. Interval administrations of the conventional pharmaceutical dosage form of zidovudine cause the fluctuation of plasma drug concentration. Initial high drug concentration increases the risk of hematological toxicities whereas subsequent low drug concentration causes non-therapeutic effect.

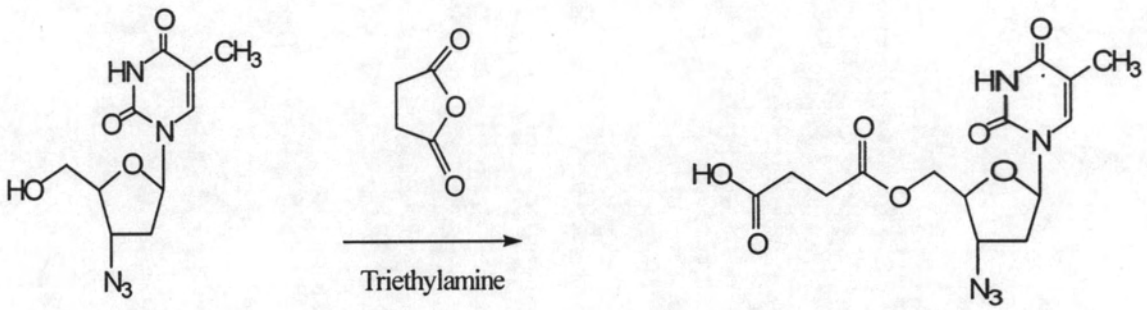
The polymeric prodrug was designed in this study to prolong the drug level in the body that provides the advantages over conventional dosage form such as reduced frequency of drug administration and decreased incidence of toxicities. Polymer-drug

conjugate is one potential type of polymeric prodrug that polymeric carrier covalently attaches the drug via a spacer that can release the drug through hydrolysis or enzymatic mechanism (Dumitriu, S. and Dumitriu, A., 1994, Lovrek et al., 2000, Zovko et al., 2001, Hoste et al., 2004). In this study, the polymeric zidovudine prodrug was prepared from dextrin (α-1,4 polyglucose) that is a natural, water soluble, linear polymeric carrier. Dextrin contains primarily α-1,4 linkages with small amount of branching α-1,6 linkages prepared by acid or enzymatic hydrolysis of starch. Dextrin is non-toxic and biodegradable that has been used in peritoneal dialysis and is degraded in the body by α-amylase found in the systemic circulation to maltose and iso-maltose (Sivakama Sundary et al., 1999, Hreczuk-Hirst et al., 2001, diZerega et al., 2002). Its structure contains many hydroxyl groups providing the reaction sites that can attach to many bioactive agents. Due to good characteristics of dextrin, it was chosen to conjugate with zidovudine. Zidovudine also bears one hydroxyl functional group that is unable to directly attach to dextrin. Therefore, the succinylation was introduced to derivatize zidovudine resulting in succinylated zidovudine containing carboxylic group that was subsequently bound to the hydroxyl groups of dextrin. In addition, the succinic cleavable ester bond serves as a spacer between the drug and the polymeric carriers that can release the drug via hydrolysis or enzymatic cleavage.

In order to attach zidovudine to dextrin, the chemistry of both substances is considered. The general reactive functional groups that can be linked are amino, hydroxyl, or carboxylic, etc. Here, the conjugation of dextrin with zidovudine will be performed via succinic spacer. The spacer has the influence on the release of the drug from the polymer backbone. Firstly, zidovudine containing hydroxyl group will be modified to be 5'-O-succinylzidovudine containing carboxylic end group (Giammona et al., 1998). Secondly, 5'-O-succinylzidovudine will be conjugated with hydroxyl group of dextrin to yield the final product. The reaction conditions for this synthesis will be adjusted to achieve final product.

Synthetic steps of conjugation

1) Zidovudine is modified by succinylation that is the reaction to introducing succinyl groups. The product will be succinylated zidovudine containing free carboxylic groups.



Zidovudine

Succinylated zidovudine

Figure 1 Succinylation of zidovudine.

2) The succinylated zidovudine is conjugated with dextrin. The final product will be dextrin-zidovudine conjugate.

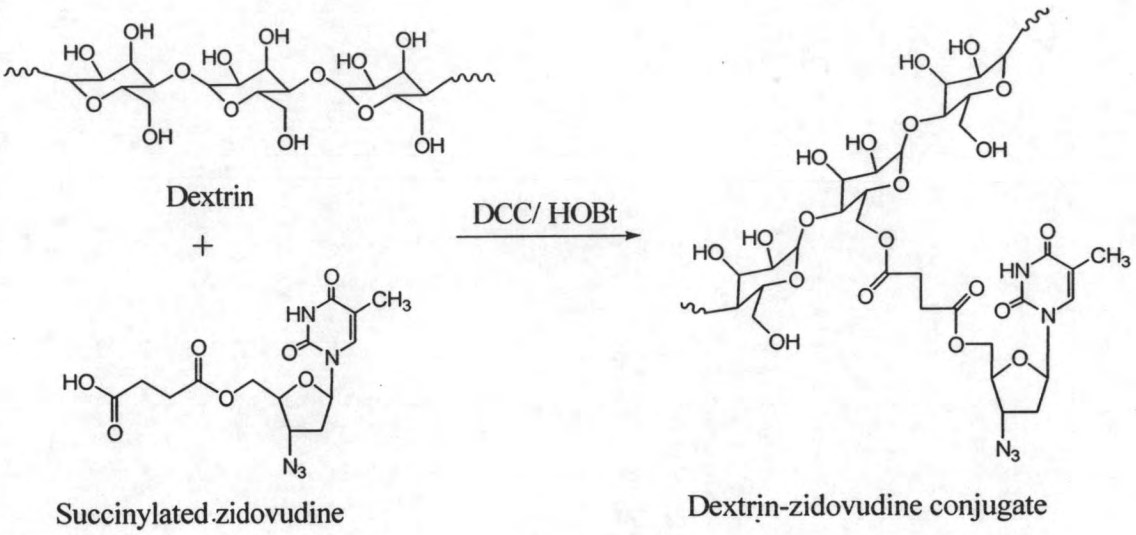


Figure 2 Conjugation of succinylated zidovudine and dextrin.

This research scope included synthesis and characterization of dextrin-zidovudine conjugate as a potential zidovudine prodrug. The *in vitro* drug release from the dextrin-zidovudine conjugate in buffer solutions was determined in buffers at pH 5.5, 7.4 and in human plasma. The safety issue was examined using hemolysis assay and cytotoxicity assay. Intravenous administration of the dextrin-zidovudine conjugate in rats allowed comparison of pharmacokinetics of the conjugate and free drug.

Objectives of the study are:

1. To synthesize the dextrin-zidovudine conjugate
2. To investigate the drug released from the dextrin-zidovudine conjugate *in vitro*
3. To examine hemolytic effect and cytotoxic effect of the dextrin-zidovudine conjugate
4. To determine drug release and pharmacokinetic properties of the dextrin-zidovudine conjugate *in vivo*

Significant of the study:

This study will provide the dextrin-zidovudine conjugate as a new prodrug of zidovudine. The conjugate could solve the problem of short plasma half-life of zidovudine that will be beneficial for the HIV-infected patients who are not resistant to zidovudine. The dextrin-zidovudine conjugate should have better pharmacokinetic properties than zidovudine. In addition, the dextrin-zidovudine conjugate may also provide the convenience to patients because of less frequent drug administration, resulting in an increase of the patient's compliance.