CHAPTER V

CONCLUSION

Zidovudine has short plasma half-life and dose dependent toxicities that limit the clinical uses of zidovudine. Therefore, the aim of this study was to prepare the sustained release of zidovudine in the form of polymeric prodrug using dextrin as drug carrier. The scope of this study included synthesis, characterization, *in vitro* drug release study, hemolysis study, cytotoxicity study and *in vivo* pharmacokinetic study in animals.

A polymeric prodrug of zidovudine was successfully synthesized by linking dextrin, polysaccharide polymer to succinylated zidovudine using DCC and HOBt as coupling agents. Zidovudine was covalently attached to dextrin backbone via ester bonds through succinic spacer by succinylation. The structure of the conjugate was confirmed by FT-IR and ^{1}H-NMR spectroscopy. The dextrin-zidovudine conjugate contained 18.92 % w of zidovudine.

The *in vitro* drug release study showed that the dextrin-zidovudine conjugate was stable at pH 5.5 and could release drug at pH 7.4 and in human plasma resulting in prolonged release of zidovudine. The release of zidovuduine in buffer pH 7.4 and in human plasma followed zero order release. The hemolytic activity and cytotoxicity of the conjugate were performed to evaluate the safety of this zidovudine prodrug for systemic administration. The results showed that the conjugate had low hemolytic activity similar to parent polymer. The cytotoxicity study on BEAS-2B cells showed that the conjugate had a little higher cytotoxicity compared to parent polymer. However, it showed significantly lower cytotoxicity than free zidovudine indicating that the conjugation could reduce the cytotoxicity of zidovudine.

The *in vivo* investigation in rats showed that the dextrin-zidovudine conjugate provided improved pharmacokinetic properties of zidovudine and sustained the

release of zidovudine in blood circulation for at least 30 h. Maintenance release and improved pharmacokinetic properties were achieved that is likely to be helpful for the treatment of HIV infection that requires constant drug levels to successfully suppress viral replication. The more stable of zidovudine concentrations obtained from the dextrin-zidovudine conjugate may result in a decrease in the fluctuation of drug levels.

From this study, the dextrin-zidovudine conjugate provided promising properties especially an increased plasma half-life of zidovudine. The dextrin-zidovudine conjugate could be further developed for clinical uses as a new zidovudine prodrug. For examples, the drug release pattern can be tailor-made by designing different linkers. Changing the molecular weight of the polymer, varying drug loading in the polymer backbone or using co-polymers would affect the release profile of drug and alter biodistribution. In addition, dextrin-zidovudine conjugate could be served as a model for synthesizing other polymer-drug conjugate.