CHAPTER V

CONCLUSION

As the previous studies demonstrated that TMZ-HE possesses a good balance of skin permeation and retention through rat and human skin by means of flux (J_{ss}) and permeability coefficiency (K_p) (Suppasansatorn *et al.,* 2006). Therefore, TMZ-HE was considered worth to pursue further studies to evaluate whether or not it could be a candidate for development into an anti skin cancer drug through skin delivery.

In this project, TMZ-HE was synthesized using Pybrop® and DMAP as coupling agents and fully characterized in comparison with the authentic sample. The solubility of TMZ-HE was re-evaluated and log p of TMZ-HE was measured. In collaboration with partners, the antitumor activity of TMZ-HE was assessed *in vitro* and *in vivo*. *In vitro*, TMZ-HE demonstrated as equal activity as TMZA and TMZ against the panel of cancer cell lines. *In vivo* TMZ-HE significantly inhibited tumour growth on BALB/c nude mice, which were inoculated with human MV3 skin cancer cells. These results indicated TMZ-HE was a promising candidate for development of a skin deliverable product for treatment of skin tumours.

It was well known the challenges in formulation of imidazotetrazinone compounds, such as TMZ, TMZA and TMZ-HE, are their insolubility in both organic and aqueous solvents and instability with a media which contains a nucleophilic group, such as water, alcohol, amine etc. The relative high concentration of the compounds needed for inhibition of cancer growth renders the task of development of clinically acceptable formulation of TMZ-HE being more challenging.

The ME formulations using vitamin E-TPGS as a surfactant demonstrated superior ability in increase of transdermal skin delivery of TMZ-HE (up to 7-fold) in comparison with aqueous solution or neat oil as a control. IPM introduced as an oil phase in microemulsion seems to enhance the permeation of TMZ-HE greater than the use of OA. The combination of co-surfactant (IPA) and surfactant (VE TPGS) greatly improve TMZ-HE permeability when compare to the use of surfactant alone. The incorporation of OA was the promising for topical formulation while IPM promoted transdermal absorption. Therefore, ME is a good vehicle for delivery of TMZ-HE topically. Further studies are needed for development of a clinically acceptable formulation of TMZ-HE.