CHAPTER 4

Conclusion

The enhancement of solubility of piroxicam by complex formation with BCD has been described. This study demonstrates that inclusion complexation is also a promising means for improving the solubility and the dissolution behaviors of meloxicam.

The solubility of meloxicam substantially increases in the presence of CDs. The CD types and methods of preparation have significant effect on the dissolution rate improvement. The CD derivatives show better solubilizing efficiency than the parent CDs. Due to the marked solubility enhancement, MeBCD is recommended for substituting BCD in those piroxicam-BCD complex based products.

GCD shows higher potential than BCD for increasing the solubility of meloxicam. In addition to CD derivatives, it is suggested as a solubilizing agent for meloxicam. On the dissolution improvement point of view, lyophilization has been shown as a perfect method for preparing the inclusion complexes. However, it is impracticable especially for scaling up. The weak point of co-evaporation method is due to the re-crystallization of drug which occasionally occurs during the process. This retards the maximum dissolution enhancement by CDs. The conventional kneading method is suggested as an alternative method for preparing piroxicam or meloxicam and CDs inclusion complexes.

The information obtained from DSC, XPD, FTIR and NIR spectroscopy confirmed the existence of the interaction between the drugs and CDs. The inclusion complex formation was also evidenced in some cases. Nevertheless, whether or not

the true inclusion complex was formed, the dissolution behavior of the drug is improved in all cases.

The thermodynamic studies substantiate that the inclusion complex formation between piroxicam or meloxicam and CDs is an exothermic, enthalpically-driven process. The negative enthalpy changes also signify that van der Waals interaction plays an important role for the association of the drug into CDs cavity. The enthalpy-entropy compensation phenomenon is observed for meloxicam and CDs interaction. The stability constant of the drugs and CDs depends primarily on temperature and the pH value of the medium. The zwitterionic drugs form stronger complexes with CDs than the ionic species which is exhibited by higher K values.

A good QSPR model for predicting the stability constants of the complexes between guests and HPBCD was obtained. The high quality of the model was reflected by high linear correlation coefficient value (0.95). The model moreover exhibits high internal predictive ability shown by high cross-validated r^2 value (0.87). Nevertheless, the model shows low predictive ability for piroxicam and meloxicam inclusion complex with HPBCD due to the limited number of the compounds in the training set. Additionally, their molecular structures were utmost diverse from those of these drugs. The useful aspect of the model is to signify the involvement of van der Waals forces and hydrophobic interaction in the inclusion complexation.

The conformational studies of piroxicam using semi-empirical by PM3 and AM1 methods and ab initio method using B3LYP/6-31G** basis sets reveals that the drug exists in several conformations, which the stability is greatly influenced by the orientation of side chain as well as the prototropic species of the drug.

PM3 calculations indicated that the stable conformation of piroxicam and BCD inclusion complexes can be obtained by either mode of inclusion, by which the benzene ring or pyridyl ring oriented towards the narrow end of the BCD cavity.