ABSTRACT

The thesis describes biopharmaceutical studies carried out on cyclodextrin complexation of aceclofenac and glipizide for enhancing their dissolution rate, bioavailability and therapeutic efficacy. The objective of the research work is to study complexation of aceclofenac and glipizide, two BCS class II drugs with two cyclodextrins, β-cyclodextrin and hydroxypropyl-β-cyclodextrin to evaluate the feasibility of enhancing their solubility, dissolution rate, bioavailability and therapeutic efficacy. The feasibility of formulating the CD complexes into tablets with enhanced dissolution rate characteristics was also investigated.

Complexation of aceclofenac and glipizide with β-cyclodextrin and hydroxypropyl-β-cyclodextrin was investigated by phase solubility, DSC, XRD, TLC and FTIR studies. Solid inclusion complexes of drug-CD were prepared by kneading method employing different ratios of drug and CD in each case and were evaluated. Selected drug-CD complexes in each case were formulated in to tablets by wet granulation and direct compression methods and the resulting tables were evaluated. Drug-CD (1: 3) complexes of aceclofenac and glipizide were subjected to pharmacokinetic evaluation in rabbits in comparison to pure drugs. The anti inflammatory activities of selected aceclofenac-CD complexes and anti diabetic activity of glipizide-CD complexes were also evaluated to assess the therapeutic activity of drug-CD complexes. Drug-CD tablets were also subjected to stability evaluation as per ICH guidelines.
The phase solubility studies indicated the formation of aceclofenac-CD and glipizide-CD inclusion complexes at a 1:1 M ratio in solution with both β-CD and HP β-CD. The complexes formed were quite stable. The aqueous solubility of aceclofenac and glipizide were increased linearly as a function of concentration of the β-CD and HP β-CD. HP β-CD exhibited higher solubilizing efficiency when compared with β-CD with both the drugs. DSC and XRD indicated better drug inclusion in CDs, and good drug amorphization and entrapment in CDs. IR spectral and TLC studies indicated no chemical interaction between the drug and CDs.

CD complexes of aceclofenac and glipizide exhibited higher rates of dissolution and dissolution efficiency values than the pure drugs. Drug-CD complexes could be formulated in compressed tablets by wet granulation and direct compression methods. All the drug-CD tablets prepared fulfilled the official specifications of hardness, friability and disintegration time and gave rapid dissolution of the contained drug.

All pharmacokinetic parameters estimated (\(C_{\text{max}}\), \(T_{\text{max}}\), \(K_a\) and \((\text{AUC})_0^\infty\) ) indicated rapid and higher absorption and bioavailability of aceclofenac and glipizide when administered as CD complexes. A 2-3 fold increase in the \(K_a\) was observed with β-CD and HP-β-CD complexes when compared to pure drug with both aceclofenac and glipizide. \((\text{AUC})_0^\infty\) was increased by 1.5-2.0 folds with the complexes. CD complexes also exhibited a rapid onset and a greater extent of
therapeutic activity when compared to pure drug with both aceclofenac and glipizide.

Thus, the results of the investigation clearly indicated that the solubility, dissolution rate, bioavailability (both rate and extent of absorption) and anti-inflammatory activity of aceclofenac and anti-diabetic activity of glipizide could be enhanced markedly by complexation with β-CD and HP-β-CD. As the bioavailability and therapeutic activity of these drugs were markedly enhanced by CD complexation, the dose needed can be markedly reduced by using their CD complexes in formulations.