ABSTRACT

Many types of therapeutic agents are being used to control diabetes mellitus. The age-old molecules such as sulfonylureas and biguanides are still considered as drugs of choice because of their well-studied mode of action, safety, better tolerability and ideal pharmacodynamic effects. Until an ideal drug for Type II diabetes is available, there is much scope and interest for pharmaceutical companies to modify the pharmacokinetics of these older molecules by developing different drug delivery systems, for better compliance.

Glipizide is a very potent and safe second generation sulfonylurea derivative commonly used for the treatment of NIDDM patents. Administration of Glipizide, by conventional oral route is having many limitations like short duration of action, hepatic first pass metabolism, hypoglycemic episodes, gastrointestinal disturbances etc.

Present study was pursued with the objective to develop delivery system for Glipizide using skin as the port of administration and to evaluate its in-vitro and in-vivo performance.

The study included i) pre-formulation studies ii) development of RP-HPLC methods for analysis of Glipizide in receptor medium and guinea pig plasma iii) in-vitro permeation studies iv) enhancement of permeation with different penetration enhancers v) development and evaluation of matrix diffusion controlled transdermal patch of Glipizide vi) development and evaluation reservoir gel formulation of Glipizide by complexation with β-cyclodextrin vii) pharmacokinetic and pharmacodynamic evaluation of the optimized formulations.

In the preformulation studies, various physicochemical properties of Glipizide were evaluated. New RP-HPLC methods were developed and validated for analysis of
Glipizide in receptor medium and guinea pig plasma with high degree of accuracy, precision and specificity. The *in-vitro* permeation studies across guinea pig skin demonstrated that the required permeation rate (flux) could be achieved by incorporating Eugenol as a penetration enhancer in the drug solution.

Matrix type transdermal patch formulations were developed using various combinations of hydrophilic and lipophilic polymers with di-Butyl phthalate (DBT) as a plasticizer and Eugenol as penetration enhancer. The formulations were optimized for drug loading, ratio of polymers, plasticizer and penetration enhancers. The formulations were further optimized on the basis of various physiochemical evaluation tests and stability studies as per ICH guidelines. Considering the required flux of Glipizide and steady state flux obtained from the optimized matrix patch formulation (M-19), the required application area of patch was calculated to be 8.24 cm².

Reservoir type transdermal gel formulations were developed by complexation of Glipizide with β-cyclodextrin. The complexes were characterized by DSC, IR and UV. Amongst the various polymers evaluated as gelling agents for the optimized vehicle system (Water: NMP, 95:5), Carbolpol 934P was found to produce consistent gels. To further enhance permeation from gel formulations, Eugenol (5% w/w) was added as a chemical penetration enhancer. Addition of Eugenol synergistically enhanced the permeation of Glipizide across the guinea pig skin. The results of skin irritation studies of optimized formulation (CG-12) indicated its suitability for transdermal application. CG-12 was also found to be stable when studied as per ICH guidelines.

Pharmacokinetic studies of optimized formulations (M-19 and CG-12) indicated that drug would remain in the body for longer duration and thus exert a sustained action.
when administered by transdermal route. Transdermal delivery of Glipizide produced improvement in all the pharmacokinetic parameters as compared to oral administration.

The pharmacodynamic (PD) studies of optimized formulations (M-19 and CG-12) in guinea pigs demonstrated that severe hypoglycemic episodes associated with oral Glipizide therapy could be overcome by transdermal administration. *In-vivo* studies revealed a close pharmacokinetic and pharmacodynamic relationship.

In the view of encouraging results obtained in animal studies it can be predicted that required minimum effective concentration could be achieved within an appreciable range of application area in humans. The development, optimization and evaluation of transdermal formulations indicated that the transdermal route can serve as a better alternative to deliver Glipizide for the treatment of NIDDM patients.
CHAPTER - I

INTRODUCTION