CHAPTER - XII

SUMMARY AND FUTURE PROSPECTIVE
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Recently, there has been explosion in the research on drug delivery via the skin, due to the success of several transdermal devices in sustaining the drug delivery to the systemic circulation.

Skin is the most extensive and readily accessible organ in the body. Such a large and easily accessible organ apparently offers ideal and multiple sites to administer therapeutic agents for both local and systemic actions. The permeation of drug molecule can be enhanced by physical approach, chemical approach and biochemical approach. Many recent techniques are developed to enhance the permeation of drug through the skin. The transdermal delivery devices can be developed by using four approaches, membrane - moderated, adhesive dispersion, matrix diffusion- controlled and micro reservoir dissolution- controlled TDDS. 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.

The physiochemical, pharmacokinetic and pharmacological properties of Glipizide makes it a good candidate for formulation and development of transdermal delivery system. 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. Literature survey reveals that, transdermal route can serve as a better alternative for the treatment of Diabetes mellitus with better patient compliance.

The present study was pursued with the major objective to develop and evaluate TDDS of Glipizide.
Summary and future prospective

Development of analytical method is important part of any research work. A new RP-HPLC method was developed with intention to reduce retention time, requiring less mobile phase and time. The analytical performance parameters of the method such as linearity, precision, and accuracy, limit of detection and limit of quantification were validated according to International Conference on Harmonization (ICH Q2B) guidelines.

Preformulation studies conforms various physiochemical properties of Glipizide. DSC studies conforms the identification of the received sample. The IR spectrum of sample reflects all the reported major peaks of Glipizide and also matches with the various functional groups present in the chemical structure. The UV spectrum of Glipizide revealed two absorption maxima at 230 nm and 276 nm (λ max.).

In-vitro permeation studies revealed that the required flux of Glipizide could be achieved with the help of penetration enhancers. Amongst various penetration enhancers tried, Eugenol, a natural terpene derivative demonstrated highest enhancement in permeation. The mechanism of penetration enhancement by Eugenol was evaluated by FTIR studies.

To fabricate matrix diffusion controlled transdermal drug delivery system, various polymeric combinations were evaluated for optimum film forming properties. The best possible drug free formulations were selected from each combination of polymers depending upon the physicochemical and other properties. The formulation code M-58 (EC-PVP, 1:4), M-66 (ERS- ERL, 3:2), M-67(ERS- ERL, 2:3), M-70 (ERL-PVP, 1:1) and M-79 (HPMC- ERS, 1:4) were found to be best amongst all the developed drug free polymeric film formulations and used for further development of matrix diffusion controlled transdermal patches of Glipizide.
Matrix diffusion controlled transdermal patches of Glipizide were designed using various optimized combinations of hydrophilic and lipophilic polymers, penetration enhancers and plasticizer. The results of physicochemical evaluation, *in-vitro* permeation studies and stability studies of various developed formulations revealed that matrix diffusion controlled transdermal patch (formulation code M-19) of Glipizide containing ERS-ERL (2:3) as polymer matrix, Eugenol 1% w/w as penetration enhancer, DBT 20% w/w as pasticizer and Glipizide 15% w/w, was the optimized and most stable formulation. Considering the required flux and steady state flux obtained from the matrix patch formulation M-19, the application area of transdermal patch was found to be 8.24 cm² (approx: 3×3 cm²), which is very much convenient for the patient from skin application point of view.

In the second approach to develop reservoir gel formulation, Glipizide was complexed with β-cyclodextrin. The complexation of Glipizide and β-CD was carried out by kneading and other methods with various molar ratios. Aqueous solubility of Glipizide was significantly increased after complexation with β-CD. The DSC studies clearly demonstrated that the enthalpy of fusion and height of endothermic peak of Glipizide was reduced as the complex formation increases. The Gli-β-CD complex i.e Gli-β-CD (1:2 T-20) was found to be most stable complex with desired properties. The permeation studies showed that the complexation of Glipizide with β-CD increases the flux significantly (P< 0.01). The required flux of Glipizide (184.5 μg/cm²/h) could be achieved by using Eugenol as a penetration enhancers. Eugenol further increases the flux synergistically with optimized vehicle. The result of the study revealed that formulation CG-12, containing 1% w/w carbopol 934-P as gelling agent, 0.5% w/w TEA as neutralizing agent, 5% w/w Eugenol as penetration enhancer and Glipizide 5mg/gm (equivalent amount of Gli-β-CD (1:2 T-20) complex) in the
optimized vehicle of NMP: Water (20:80) was found to be most stable, non irritating and safer. The maximum steady state flux obtained from formulation CG-12 was 32.6 ± 2.4 μg/cm²/h and hence minimum application area of 5.66cm² (approx: 3×2 cm²) was calculated to achieve required flux (184.5μg/h). This formulation was further subjected to in-vivo pharmacokinetic evaluation studies. In order to restrict the area of application of the developed gel formulation and to hold the gel at the applied site a device was fabricated with circular ‘O’ ring shaped spacer, backing membrane (3M Scotchpak backing-1006), fluropolymer coated films (3M Scotchpak backing-1022) as release liner and PSA (DuroTak 387-2287) as an adhesive.

The in-vivo performance studies of the optimized formulations were carried out using guinea pigs. The study was performed to evaluate pharmacokinetic and pharmacodynamic performance of the developed formulations. A new RP-HPLC method was developed and validated for the analysis of Glipizide in guinea pig plasma. The developed method was found to be selective, simple, sensitive, accurate and linear for the analysis of Glipizide in guinea pig plasma. The retention time and in-turn run time was very short for the method making it more economical and rapid.

Comparative pharmacokinetic evaluation of the developed formulations was carried out with guinea pigs in three groups. The pharmacokinetic parameters obtained with transdermal patches were significantly (p<0.01) different from those obtained with oral administration. The studies revealed that absorption of Glipizide after oral administration was rapid as compared to transdermal formulations and was indicated by high Cmax and low Tmax values.

The result of glucose tolerance test clearly indicated that, transdermal formulations could eliminate the initial rapid reduction in blood glucose level, which is a major limitation of Glipizide as an oral hypoglycemic agent.
Thus *in-vitro* and *in-vivo* evaluation of both the optimized transdermal formulations showed that these formulations can served as better alternative to the oral therapy of Glipizide in NIDDM patient.

**Future prospective**

The optimized formulations showed very encouraging results in animal studies. These formulations can overcome the limitations of oral therapy of Glipizide. The *in-vitro* and *in-vivo* evaluation of the optimized formulations was carried out with guinea pigs, but the permeability of human skin is varying significantly than the animal skin. All such attributes warrants for further investigation of these formulations of Glipizide in patient volunteers to assess their ability in providing an effective and safe anti-diabetic therapy. The clinical studies in human volunteers will prove the clinical effectiveness of the developed transdermal formulations, which may be required further modifications.