CHAPTER - III

OBJECTIVE AND PLAN OF WORK
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3.1 Objective of work

At present many therapeutic agents are available to control diabetes mellitus, which includes Insulin, Sulfonylureas, Biguanides etc. Second generation Sulfonylureas are the most popular and inexpensive drug treatment for NIDDM patients, which include namely Glibenclamide, Glipizide, Glyclazide, Glyburide and Glimipride.

Literature survey revealed that the conventional oral therapy with Sulfonylureas has been associated with severe and sometime fatal hypoglycemia, gastric disturbances like nausea, vomiting, heartburn and anorexia. As these drugs are taken for a very long duration patient compliance is also very important parameter. One of the novel and recent approaches to eliminate some problems associated with traditional dosage forms is development of transdermal delivery system of the drugs.

After going through the physicochemical and pharmacokinetic properties of all the second generation Sulfonylureas, Glipizide was found to be one of the most suitable candidates for the development of transdermal drug delivery system.

Glipizide is an oral hypoglycemic agent, which is second-generation Sulfonylurea derivative. It stimulates insulin secretion from beta cells of pancreatic islet tissues. It increases the concentration of insulin in pancreatic vein and may increase the number of insulin receptor. It stimulates insulin release similar to natural insulin secretion pattern. The half life of Glipizide is 2 to 4 h and oral absorption is delayed by food. The rate and extent of absorption is significantly reduced in presence of food. It has to be taken at least 30-40 mins before meals. The maximum daily dose is 5 to 20 mg, as single or divided doses as per the requirement. It is required to be administered 2 to 3 times daily in more than 45% of the patients. It is extensively (90%) metabolized in liver to inactive metabolite. The common side effect includes GI disturbances, nausea.
and vomiting. The solubility of Glipizide is minimal at very low pH which causes large variation in oral bioavailability. The oral therapy with Glipizide also associated with increase in body weight.

Glipizide has been formulated and tried as microcapsules, as control released tablets and sustained released microcapsules. When the efficacy of once daily controlled release formulation of Glipizide was compared with immediate release formulation in NIDDM patients, it was found that fasting plasma glucose had been significantly lowered with controlled release than immediate release formulation. Transdermal route is found to be one of the best alternatives to deliver the drug at controlled rate with better patient compliance.

Transdermal drug delivery system of Glipizide can offer following advantages over the oral therapy.

1) It will prevent severe and sometime fatal hypoglycemia.
2) It can reduce gastric disturbances like nausea, vomiting, heartburn and anorexia.
3) Frequent dosing will be reduced due to transdermal delivery system.
4) Increased patient compliance.
5) Increased bioavailability through the transdermal route.

Attempts have already been made to develop many anti-diabetic drugs into transdermal dosage forms. (Details are given in literature review section)

Literature reveals that, the physiochemical, pharmacokinetic and pharmacological properties of Glipizide makes it a good candidate for formulation and development of transdermal delivery system.

It is also revealed that Glipizide has been successfully tried as candidate for development of transdermal drug delivery system (Chapter-II). Out of several
approaches available for development of TDDS. Glipizide was studied by various researchers for;

1) Membrane moderated gel reservoir system.
2) Effect of Iontophoresis on its transdermal permeation in its solution form.
3) Effect of complexation with Cyclodextrin on its in-vitro permeation.

Hence in the present study attempts are being made;

i) To formulate and develop matrix type of TDDS for Glipizide using patch approach.

ii) To formulate and develop reservoir transdermal gel of Glipizide by complexation with β-Cyclodextrin.

The study was designed to achieve the following objectives -

- To formulate and develop suitable transdermal drug delivery system for Glipizide
- To optimize the formulation variables on the basis of in-vitro performance of the drug delivery system.
- To check the skin irritation potential of developed formulation.
- To study stability of developed formulations.
- To perform in-vivo (Pharmacokinetic and pharmacodynamic) studies of the optimized formulations.

3.2 Plan of work

The development of transdermal drug delivery system for Glipizide was done as per following plan of work-

3.2.1 Phase-I

1) Physicochemical evaluation of Glipizide, as a part of pre-formulation study.
2) Development and validation of UV Spectrophotometric and RP- HPLC Methods for analysis of Glipizide
3) Determination of partition coefficient value in Octanol – Water and Octanol – phosphate buffer (pH 7.4) system.

4) Determination of saturation solubility studies in different solvents like distilled water, phosphate buffer (pH 7.4), NMP, ethanol, methanol and their various combinations.

3.2.2 Phase-II

1) Design of permeation studies using modified Keshary - Chien diffusion cell.

2) Selection of recipient medium.

3) Permeation studies of Glipizide through Guinea pig skin.

4) Effect of various chemical penetration enhancers on permeation of Glipizide to achieve the required flux.

3.2.3 Phase-III

1) Preparation of the drug free films using various combinations of polymers like HPMC, ERL 100, EC, PVP and ERS100.

2) Evaluation of drug free films by the tests like percent moisture absorption, percent moisture loss, water vapor transmission rate, thickness, folding endurance, tensile strength and elongation, weight variation and flatness test.

3) Effect of plasticizer on film properties.

3.2.4 Phase-IV

1) Development of matrix type of transdermal drug delivery system of Glipizide using optimized polymeric combination, plasticizer and penetration enhancer.

2) In-vitro permeation studies of Glipizide from the developed formulations through guinea pig skin.

3) Enhancement of permeation by using the penetration enhancer.

4) Physicochemical evaluation of drug loaded films.
5) Study of drug-polymer interaction.

6) Stability studies.

7) Selection of optimized matrix type patch formulation.

3.2.5 Phase V

1) Complexation of Glipizide with β-Cyclodextrin (Glip-β-CD) using different ratios.

2) Evaluation of the complexes using UV absorption spectra, IR and DSC studies.


4) In-vitro permeation studies of Glip-β-CD complex through guinea pig skin

6) Development and evaluation reservoir gel formulations.

5) Permeation studies of Glip-β-CD complex from various gel formulations.

6) Effect of various penetration enhancers on permeation of Glip-β-CD from the gel formulation.

7) Stability studies of gel formulations.

3.2.6 Phase VI

In-vivo evaluation of the optimized formulation:

1) Skin irritation studies.


3) Pharmacokinetic evaluation of optimized formulations in guinea pigs.

4) Pharmacodynamic studies of optimized formulations in guinea pigs.