HYPERTENSION IS the term used to describe the persistent elevation of systolic and/or diastolic blood pressure. Hypertension because it is so common is perhaps the most important risk factor underlying cardiovascular morbidity and mortality in industrialized countries. It is a major factor underlying the 500,000 strokes and the 175,000 deaths from strokes that occurs annually in the USA. In addition it is a significant contribution factor in the 1,500,000-heart attack and 567,000 heart attack deaths per year in the USA.

Treating hypertension reduces the incidence of cardiovascular morbidity and mortality. In general, the treatment should be effective and well tolerated so that the patient’s quality of life remains satisfactory. The therapeutic efficacy of beta-blockers and in particular Atenolol / Metoprolol tartrate are widely recognized and extensively prescribed as the first choices drug in the treatment of the majority of the hypertensive population. The conventional formulation associated with many drawbacks.

These drawbacks necessitated the development of an even and effective beta blockade throughout 24 hours in order to achieve maximal cardio protection, improved patient compliance and enhanced bioavailability.

Large area and easy accessibility of skin makes the transdermal drug delivery a promising route for administration of beta-blockers of systemic circulation. The delivery of drug by this route has distinct advantage of protecting the drug from first hepatic pass degradation and to control the systemic availability of the drugs in addition improved bioavailability and better patient compliance.

The present work is an insight of fabrication of transdermal drug delivery systems of Atenolol / Metoprolol tartrate. The thesis comprises of eight chapters.

The introduction chapter is an insight of brief account of transdermal drug delivery systems. Their necessity, conditions, merits, demerits, system design, kinetics and evaluation of transdermal system. The transdermal delivery of Atenolol and Metoprolol tartrate is desired since the drugs are biological short half-life drugs as they are metabolised by first hepatic
pass. The long acting formulations are demanded for the treatment of hypertension. The drugs Atenolol and Metoprolol tartrate are reported to be significantly absorbed through skin on topical application. Therefore, the designing of TDDS of these drugs are realized in order to exclude first hepatic pass effect and control the systemic availability of the drugs.

The chapter drug profile provides detailed information of drug profile including Pharmacology and pharmacokinetics parameter of Atenolol and Metoprolol tartrate.

The chapter three is an analytical approach of Atenolol and Metoprolol tartrate and deals with purification, identification and estimation of drugs in SPB pH 4.5 and pH 7.4 using spectrophotometric method. The estimation of Atenolol at 225 nm and Metoprolol tartrate at 274 nm using linearly regressed calibration curves were carried out. Similarly, Atenolol and Metoprolol tartrate was estimated in plasma using HPLC method.

Preformation studies, which is desired to ensure the development of a stable as well as therapeutically effective and safe dosage form. Preliminary evaluation of each component of transdermal drug delivery system is desirable to establish and develop an effective transdermal drug delivery system. The process variable, which could affect the physical characteristics of formulations vis-a-vis in vitro release profile and in vivo drug absorption were optimized during the preformulation studies. The studies include solubility, partition coefficient, drug metabolism in skin and drug polymer interaction.

The successful designing of transdermal drug delivery system requires selection of independent variables i.e. hydrophilic, hydrophobic polymers and plasticizer. The present work is focused on optimizing the combination of polymer blend and plasticizer to produce uniform, smooth, clear, substantive, flexible and desired thickness (0.034 to 0.038 mm) films. Since three independent variables are to be studied at three levels, Three-factor, three-level factorial design is selected. The free polymeric films were casted using the method reported by Iyer and Vasavada. The prepared films were characterized for film thickness, tensile strength, water vapour transmission (WVT), hardness, %moisture content. The polymer(s) and plasticizer combinations that yielded clear, uniform, smooth, substantive, flexible and desired thickness (0.034 to 0.038 mm) were used for the preparation of transdermal drug delivery system.

The fabrication matrix diffusion controlled transdermal drug delivery system consisted of different polymers (selected on the basis of preformulation studies) i.e. Ethylcellulose,
Eudragit RL, Eudragit RS, Polymethylmethacrylate, Hydroxypropyl methylcellulose, PEG 4000 and PVP singly or in different combinations.

The drug Atenolol / Metoprolol tartrate required to achieve an effective plasma concentration for 24 hours was calculated on the basis of Pharmacokinetic parameters of the drug. Atenolol 4% w/w and Metoprolol tartrate 5% w/w was therefore incorporated into the transdermal formulations. The incorporated quantity of drug takes care of loss due to drug: skin and drug: polymer partitioning. The prepared transdermal drug delivery system of Atenolol and Metoprolol tartrate were characterized for film thickness, tensile strength, WVT, hardness, % moisture content, drug content and microscopic studies.

The chapter in vitro characterization focuses on in vitro characterization of the prepared transdermal drug delivery system. The transdermal drug delivery system bearing Atenolol and Metoprolol tartrate was first studied to establish the release kinetics of the drug from the product. The release studies were performed on Franz-diffusion cell. The diffusion medium was SPB of pH 4.5 containing 20% PEG 400 as the pH of the stratum corneum side is relatively acidic (pH 4.5 - 5.5).

The release kinetics were established by determining the diffusion exponent (η) which reveals that the drug release from the matrix diffusion controlled transdermal drug delivery system with polymeric combinations is fickian or nonfickian type diffusion. The slope of the straight line was used to calculate the release rate of the drug(s). A rapid initial release of drug was observed in matrix diffusion controlled transdermal drug delivery system because the system was directly exposed to diffusion media. The increase in vitro release from transdermal system was recorded where the concentration of hydrophilic polymer in total polymer content was increased.

The in vitro drug skin permeation studies of all the transdermal drug delivery system of Atenolol and Metoprolol tartrate were performed using Franz diffusion cell and pigskin. The SPB of pH 7.4 with 20% PEG 400 was used as diffusion medium. These studies reveals that the drug penetrated through skin by zero order kinetics with a lag time of 30-60 minutes. This lag time could be accounted for the time taken by the drug to diffuse across the skin. The drug
skin permeation rate was increased on increased concentration of hydrophilic polymer in total polymer content of transdermal systems.

The products that exhibited in vitro drug skin permeation nearly equal to the calculated skin permeation rate for Atenolol and Metoprolol tartarate (required to achieve an effective drug plasma concentration) were selected for stability studies as per ICH guidelines.

The stability of different transdermal system at 40 ± 2° / 75% RH ± 5% was determined by measuring physical parameters i.e. tensile strength, % moisture content for matrix diffusion controlled transdermal drug delivery system.

The products, which were found to be physically stable and exhibited little change in in vitro drug skin permeation characteristics were selected for in vivo studies performed on Albino rabbits. The in vivo studies were performed on selected products by measuring the drug plasma concentration in Albino rabbits and results were compared with the performance of orally administered conventional tablets of respective drugs. The plasma concentration of drug Atenolol and Metoprolol tartarate gradually increased and reached a steady state level constant for 24 hours, then declined gradually on removal of the transdermal system after 24 hours.

However, the oral administration of drug by conventional tablets exhibited the peak plasma concentration within 3 hours for Atenolol and 1 hour for Metoprolol tartarate, but declined gradually. In order to obtain smooth drug plasma profile following oral administration the tablets were given every 6 hours for Metoprolol tartarate and every 12 hours for Atenolol. The oral multiple dosing by conventional tablets of respective drug resulted in usual trough and peaks in drug plasma profile. The improved performance of the designed transdermal drug delivery system of Atenolol and Metoprolol tartarate is reflected by Area under the curve as compared to oral administered conventional doses.

The enhanced bioavailability of drugs following transdermal application may be due to protection of drug from first hepatic pass in conjunction with protection of drug loss via entero-hepatic circulation of short biological half-life drugs.

It is thus established that transdermal route has great potential for safe effective administration of Atenolol and Metoprolol tartarate. The transdermal drug delivery was devoid of contraindicative manifestation associated with oral route and eliminated the therapy-genic
stress commonly associated with drug plasma profile (through and peak shape). The polymeric combinations i.e. hydrophobic to hydrophilic weight ratio, could control the drug release vis-á-vis delivery to the dermis for permeation.

The outstanding benefits and great potential of transdermal drug delivery system of Atenolol and Metoprolol tartrate demands the further exploration for clinical trials. It may lead a path towards the development of transdermal drug delivery system for ready or commercial viability. Such a development will bring a remarkable change in existing treatment of hypertensive patient, which will be a boon to humanity.