Summary and conclusion
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 dissolves rapidly in the upper gastric intestinal tract and produces plasma circulation peak within 1 to 4 hour and then decline quickly. Consequently divided doses are widely used to maintain the peak plasma. The conventional formulation may be associated with the following drawbacks:

- Multiple daily dosing of the conventional Atenolol / Metoprolol formulation results in high and rapid plasma concentrations after each dose. These highly transitory plasma concentrations may be associated with undesirable beta-2 mediated side effects like fatigue and bronchospasm.
- The occurrence of myocardial ischemia (silent and symptomatic) shows circadian pattern with a definite peak in the morning a smaller peak in the late afternoon or early evening. The conventional formulation may fail to provide adequate protection against ischemic episode during such periods.
- Arterial blood pressure also exhibits a circadian rhythm. This may be a factor contributing to other serious cardiac problems that occur more frequently during early morning hours. Adequate 24-hours control of blood pressure may not be provided by the conventional formulation.
The short half life of the conventional formulation necessitates multiple dosing which may lead to blood pressure variations over 24 hour and hence may increase target organ damage.

The need for frequent drug administration is a major obstacle to compliance with drug regimens, particularly for the long-term management of life long conditions such as hypertension and angina. The short life of the standard Atenolol / Metoprolol formulation necessitates a daily dose schedule of multiple administration, thereby leading to decreased patient compliance.

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.

For the fabrication of transdermal drug delivery systems of Atenolol / Metoprolol tartarate, first the drug samples were procured from m/s Concept pharmaceuticals Ltd, Aurangabad. The procured drug(s) were identified for its purity by performing assay as per I.P. 1996, infrared, mass spectra, NMR and differential scanning colorimetry. The procured sample of Atenolol / Metoprolol tartarate of acceptable quality and purity were taken for further studies.

For the estimation of Atenolol / Metoprolol tartarate, the standard curves were prepared in saline phosphate buffer of pH 4.5 and pH 7.4 using spectrophotometric methods. The absorbance was measured at 225 nm for Atenolol and 274 nm for Metoprolol tartarate. The HPLC method was used for the estimation of Atenolol and Metoprolol tartarate in plasma. The HPLC variables for estimation of Atenolol was as follows: column: 300 X 3.9 4 µm NovaPack C18; mobile phase: MeOH: THF: buffer (65: 5: 30); column temperature: 30°; flow
rate: 0.8; injection volume: 50; detector: UV 225 and column: 100 X 3.2 10 μm μBondapak C18; mobile phase: MeCN: 100mM pH 3.0 phosphate buffer (30: 70); column temperature: 30°; flow rate: 0.5; injection volume: 94; detector: F ex 193 em (no cutoff filter).

The preformation studies are needed to ensure the development of a stable as well as therapeutically effective and safe dosage form. Preliminary evaluation of each components of transdermal drug delivery system is desirable to establish and develop an effective transdermal drug delivery system. The process variables that could affect the physical characteristics of formulation vis- à- vis in vitro release profile and in vivo drug absorption were optimized during preformation studies. The studies include solubility, partition coefficient, skin permeability, drug metabolism in skin and drug additive interaction.

Solubility studies indicate that Atenolol is sparingly soluble in both 1-octanol and water while Metoprolol tartrate is soluble in 1-octanol and very soluble in water. This indicates hydrophilic as well as hydrophobic nature of Atenolol and Metoprolol tartrate both having. The hydrophilic and hydrophobic nature of Atenolol and Metoprolol tartrate was again established by performing 1-octanol: SPB pH 7.4 partition coefficient, which was found to be 0.678 ± 0.100 for Atenolol and 0.960 ± 0.150 for Metoprolol tartrate. These partitioning values for both drugs are near to unity, which is indicative of hydrophilic and lyophilic nature of the drug and showing good candidate for transdermal drug delivery.

The drug(s) partitioning between skin and vehicle (SPB pH 7.4) was determined and noted to 1.380 ± 0.570 for Atenolol and 2.153 ± 0.650 for Metoprolol tartrate, respectively. The partition coefficient between skin and vehicle can be regarded as an index of mutual drug and vehicle affinity. The large value indicates that the vehicle has poor affinity for drug. The drug Atenolol having less affinity to skin as compared to Metoprolol tartrate.

The solubility of Atenolol in whole skin (dermatone) was noted to 0.650 ± 0.140 (mg/mL) for Atenolol and for Metoprolol tartrate 1.3857 ± 0.100 (mg/mL) which could be due to more lyophilic nature of Metoprolol tartrate as compared to Atenolol.

The partitioning of the drug(s) between different polymers used for the fabrication of transdermal drug delivery system and SPB pH 7.4 was studied. It was observed that the
maximum and minimum partitioning of Atenolol was found with sodium alginate and ethylcellulose (i.e. 0.0796 and 0.0124), respectively. In case of Metoprolol tartrate maximum and minimum partitioning was observed with ethylcellulose and gelatin (i.e 0.2777 and 0.1886), respectively.

The drug solubility profile and partition coefficient studies revealed that Atenolol and Metoprolol tartrate are good candidates for the transdermal drug delivery. However, it is essential to determine the maximum drug flux across the skin. Therefore, the drug skin permeation studies were performed to determine maximum drug skin permeability.

The drug skin permeability was determined using isolated pig skin in the Franz diffusion cell (1 cm², Crown Glass Co. NJ, USA). The in vitro drug skin permeability studies attributed that Atenolol permeated the skin at the rate of 969.1 mcg/hr/cm² while Metoprolol tartrate showed 1113.7 mcg/hr/cm² skin permeation rate. The difference in the skin permeation rate between Atenolol and Metoprolol tartrate could be due to difference in partition coefficient of the drug.

The skin is frequently regarded as a flexible but inert covering of the body. However, this organ has been shown to possess metabolic activity including the ability to metabolize drug and other foreign compounds. Although such activity may occur only at a relatively low level. Unlike the liver, where enzymes are concentrated within a defined region of tissue space, the cutaneous enzymes are distributed over 2 m² of skin surface of normal adult. Thus, the drug metabolism in the skin during its delivery through a limited area of the skin cannot produce such a dynamic effect as that observed in liver. In present work, the metabolic studies in skin were performed for Atenolol and Metoprolol tartrate. It is observed that both the drugs do not metabolize in the skin as no extra spot was observed in the thin layer chromatograph of drug incubated (48 hours) with skin homogenate.

The interference of the additives with the drug (Atenolol / Metoprolol tartrate) was studied for 24 hours and then the drug concentration was determined. It was thus noticed that there was no interference with the additives in the estimation of drugs.

Drug free polymeric films were prepared from ethylcellulose, polymethylmethacrylate, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, eudragit RL, eudragit RS, polyethylene glycol 4000. The best combinations of the hydrophilic and hydrophobic polymers along with
optimum concentration of the plasticizer for the preparation of clear, uniform, smooth, substantive, flexible polymeric films with desired thickness (0.034 to 0.038 mm), were selected using Three factor, three level factorial design.

It was observed that incorporation of plasticizer dibutylphthalate (5% w/w or 0.03 mL) for polymeric combinations resulted into better films of polymers. The polymeric ratio embracing PEG 4000 and PVP above 10% resulted in brittle, in substantive poor quality films. Hence, the experimental design for PEG 4000 and PVP bearing films were of compositions 10% or less than 10% along with hydrophobic polymer. The polymeric combinations bearing HPMC in concentration range at or below 60% w/w of total polymer weight resulted in desired quality film.

The polymeric films, which showed good appearance with regard to smoothness, uniformity, clarity, substantivity and flexibility, were selected for further characterization i.e. film thickness, tensile strength, hardness, % moisture content and water vapor transmission (WVT). The polymeric combinations bearing above or below 10% w/w concentration resulted in undesired thickness and such polymeric combinations were discarded for further studies.

The hardness was noted to decrease with increasing amount of hydrophilic polymer in the total polymer and tensile strength was noted to increase with increasing concentration of hydrophilic polymer. It was observed that the WVT and % moisture content increase with increasing concentration of hydrophilic polymer (PVP, HPMC, PEG 4000) in total polymer content. The polymer(s) and plasticizer combinations, which resulted in clear, uniform, smooth, substantive, flexible films with desired thickness (0.034 to 0.038 mm) were used for the preparation of transdermal drug delivery system.

The matrix diffusion controlled transdermal drug delivery systems of Atenolol / Metoprolol tartrate were prepared. These systems were comprised of different polymers i.e. ethyl cellulose, eudragit RL, eudragit RS, Polymethylmethacrylate along with hydroxypropyl methylcellulose, polyvinyl pyrrolidone, polyethylene glycol 4000 in different combinations.

The amount of drug that is to be incorporated (4% w/w Atenolol / 5% w/w Metoprolol tartrate) into the polymeric matrix was calculated on the basis of required drug input rate (64.75 mcg/hr/cm² and 87.48 mcg/hr/cm² derived from the pharmacokinetic parameters of the drug to achieve effective plasma concentration), drug: skin partitioning and drug: polymer
partitioning.

The designed matrix diffusion controlled transdermal drug delivery systems bearing Atenolol / Metoprolol tartarate were composed of three layers i.e. backing membrane, drug bearing polymeric matrices and an adhesive layer. First of all the drug bearing polymeric matrices were constructed by casting the polymeric drug bearing film on mercury substrate as discussed by Iyer and Vasavada, using the polymers which were selected after preformulation studies. Aluminium foil was used as backing membrane, which was stucked to one of the surface of the polymeric matrix and polyisobutyrene (low molecular weight) was used as an adhesive layer, which was sprayed on another surface of the polymeric film.

The polymeric matrices bearing drug were studied under microscope and observed for distribution of drug in polymeric matrices. The prepared polymeric matrices bearing drug were elegant, good and uniform in appearance except the films of gelatin and sodium alginate (Ma GL, Ma SA, Mm GL, and Mm SA), respectively. The drug was not distributed uniformly throughout the film and crystallization of the drug (Atenolol / Metoprolol tartarate) was observed in the films comprising of gelatin and sodium alginate. The drug bearing films of gelatin and sodium alginate were discarded for further studies.

It was observed that on incorporation of drug (Atenolol / Metoprolol tartarate) into the polymeric matrices, the tensile strength, percent moisture content and water vapor transmission were found to decrease approximately 2.02 to 2.00 kg/cm², 4.52 to 4.50% and 4.22 to 4.18 gm/cm², respectively for Atenolol bearing polymeric matrices (Ma EC HPMC 3) and 2.02 to 1.98 kg/cm², 4.52 to 4.48%, and 4.22 to 4.14 gm/cm², respectively for Metoprolol tartarate bearing polymeric matrices (Mm EC HPMC 3) as compared to drug free polymeric films. This could be due to non-hygrosopic amorphous / crystalline nature of the drug that is distributed thoroughly within the polymeric matrices and reducing the tensile strength, percent moisture content and water vapor transmission. At the same time the hardness of polymeric matrices was found to increase from 335 to 338 g/cm for Atenolol and 335 to 340 g/cm for Metoprolol tartarate bearing polymeric matrices, respectively.

Finally, the drug content per square cm area of the polymeric matrices was determined for Atenolol and Metoprolol tartarate and found to be between 98.4 to 99.5% per
for Atenolol and 98.6 to 99.4% per cm² for Metoprolol tartarate, respectively.

The fabricated transdermal drug delivery systems bearing drug (Atenolol / Metoprolol tartarate) combinations which were clear, smooth, uniform, substantive, flexible, desired thickness film with promising water vapor transmission, tensile strength and uniform distribution of drug in the matrices were selected for the *in vitro* characterization.

The selected transdermal systems of Atenolol / Metoprolol tartarate were initially studied to establish the *in vitro* release kinetics of the drug from the formulations to the skin. The *in vitro* drug release studies were performed using Franz diffusion cell. The saline phosphate buffer pH 4.5 containing 20% PEG 400 was used as diffusion medium. The *in vitro* release profile data were computed to establish the release kinetics of drug from the different transdermal formulations. The release kinetics was established by determining the diffusional release exponent from the plot of log of cumulative drug release *vs* log time, inset log-log graph of Cum. Drug released and time. The slopes of the straight lines were recorded as values of diffusional release exponent (η).

The slope of diffusional release exponent (η) for matrix diffusion controlled transdermal drug delivery systems bearing Atenolol / Metoprolol tartarate with various polymeric combinations of hydroxypropyl methylcellulose was calculated to be 0.47 to 0.5 which is very near to 0.5 indicating Fickian diffusion pattern (Square root time dependent of solute release). Therefore, a linear relationship was observed with cumulative drug release *vs* square root time. The polymeric matrices comprising various combinations with either PEG 4000 or PVP exhibited nonfickian diffusion as the value of diffusional release exponent calculated from the log-log plot of cum. drug released *vs* time to be 0.7 to 0.8. A linear relationship was observed between cum. drug released *vs* (Time) ^0.8^ for polymeric matrices containing either PEG 4000 or PVP (5 to 10% w/w). The slope of the linear portion of the graph was used to calculate the release rate of the drug.

The nonfickian type of drug release in matrix diffusion controlled transdermal drug delivery system may be due to the fact that the system mainly consisted of high concentration of hydrophobic polymers with a small concentration of hydrophilic polymers. The hydrophilic
polymers form a gelaneous channels in the polymeric matrix due to dissolution of hydrophilic polymers in diffusion media.

The formation of such gelaneous channels lead to a decrease in the mean diffusional path length of the drug molecule to leach out into diffusion medium which results higher drug release from these matrices and probably a reason for nonfickian diffusion.

An initial rapid release was observed in matrix diffusion controlled transdermal drug delivery systems, which could be accounted for direct exposure of system to diffusion media and quick release of drug present at the surface. The drug release was least with Ma EC (62.63 mcg / hr$^{0.5}$/ cm$^2$) for Atenolol and Mm EC (89.36 mcg / hr$^{0.5}$/ cm$^2$) for Metoprolol tartarate. Minimum drug release from these formulations could be ascribed to absence of hydrophilic polymer in these systems, which rendered the matrix absolutely hydrophobic in nature. The formulation Ma HPMC of Atenolol and Mm HPMC of Metoprolol tartarate showed maximum release (98.81 mcg / hr$^{0.5}$/ cm$^2$) and (110.81 mcg/hr$^{0.5}$/ cm$^2$), respectively.

The drug release was observed to increase with increasing in hydrophilic polymer concentration in total polymer content of transdermal formulations of Atenolol and Metoprolol tartarate. The release rate of Atenolol increased from 84.00 to 132.09 mcg / hr$^{0.5}$/ cm$^2$ on increasing concentration of hydroxypropyl methylcellulose (20-60% w/w) in ethylcellulose hydroxypropyl methylcellulose matrix type transdermal system. Similarly, incorporation of increased amount of PEG 4000 and PVP (5 to 10% w/w) in the ethylcellulose matrix, the release of Atenolol increased from 122.00 to 128.00 mcg / hr$^{0.8}$/ cm$^2$ and 106.18 to 111.36 mcg / hr$^{0.8}$/ cm$^2$, respectively.

Similar increase in release rate was observed with Polymethylmethacrylate, eudragit RL and eudragit RS formulations. The eudragit RL formulations were more permeable than those of eudragit RS due to its higher concentration of hydrophilic quaternary groups.

The in vitro drug skin permeation from the prepared transdermal drug delivery system bearing Atenolol / Metoprolol tartarate was studied on Franz-diffusion cell (1 cm$^2$, Crown Glass Co., NJ, USA) using pig skin. The histological characteristics of pig and human skin have been reported to be comparable, with similarities existing for epidermal thickness and composition. The saline phosphate buffer of pH 7.4 containing 20% PEG 400 was used as the receptor
medium in the diffusion cell. The kinetics of drug permeation across the skin was established by determining the value of diffusional release exponent ($\eta$) from the slope of graph between log of cumulative drug permeated vs log time. The value of ($\eta$) was calculated to be one, which is an indicative of zero order release kinetics. Hence, a linear relationship was obtained between the cumulative amount of drug (Atenolol / Metoprolol tartrate) permeated through skin and time. A linear relationship was obtained after a lag time of 30-60 minutes, which could be accounted for time taken by the drug to diffuse across the skin. The slope of the linear portion of the graph was used to calculate skin permeability rate.

The drug skin permeation was observed to increase with increase in the hydrophilic polymer concentration in total polymer content of transdermal formulations of Atenolol / Metoprolol tartrate. The eudragit RL formulations were more permeable than those of Eudragit RS due to its higher concentration of hydrophilic quaternary groups. The skin permeation rate of Atenolol increased from 25.00 to 66.65 mcg / hr / cm$^2$ with increase in concentration of hydroxypropyl methylcellulose (20-60% w/w) in ethylcellulose matrix, while the Atenolol skin permeation increased from 73.73 mcg / hr / cm$^2$ to 80.17 and 54.78 mcg / hr / cm$^2$ 60.86 mcg / hr / cm$^2$ with increase in concentration 5 to 10% w/w of PEG 4000 and PVP respectively in ethylcellulose matrix.

In case of polymethylmethacrylate formulation with hydroxypropyl methylcellulose (20 to 60% w/w) the Atenolol permeation enhanced from 34.00 to 69.17 mcg / hr / cm$^2$. On increasing the concentration of PEG 4000 and PVP (5-10 % w/w) in polymethylmethacrylate matrix the skin permeation enhanced from 51.91 to 56.13 mcg /hr/ cm$^2$ and 42.00 to 49.21 mcg / hr / cm$^2$ respectively.

Similarly increased permeation effect was observed with eudragit RL formulations and eudragit RS formulations. On increasing the concentration of HPMC (20% to 60% w/w) or PEG 4000 and PVP (5 to 10% w/w) in eudragit RL matrix the skin permeation of Atenolol was increased from 45.43 to 64.22 mcg / hr / cm$^2$, 60.17 to 66.13 mcg / hr / cm$^2$ and PVP 47.13 to 53.00 mcg / hr / cm$^2$ respectively.
The Atenolol skin permeation was enhanced from 50.17 to 70.82 mcg / hr / cm² on incorporating HPMC (20-60% w/w), 70.00 to 73.95 mcg / hr / cm² on incorporating PEG 4000 (5-10% w/w) and 62.17 to 67.04 mcg / hr / cm² on incorporating PVP (5-10% w/w) in eudragit RS matrix.

Similar enhancement in Metoprolol tartrate skin permeation rate from matrix type transdermal formulations was recorded on increasing the concentration of hydrophilic polymer HPMC (20-60% w/w), PEG 4000 and PVP (5-10% w/w) for ethylcellulose matrix i.e. 67.00 to 79.08 mcg / hr / cm², 81.65 to 88.26 mcg / hr / cm², and 71.78 to 78.04 mcg / hr / cm² respectively. In polymethylmethacrylate combination with similar increase in concentration of HPMC, PEG 4000 and PVP the skin permeation rate increased from 72.21 to 89.34 mcg / hr / cm² for HPMC, 82.00 to 88.91 mcg / hr / cm² for PEG 4000 75.00 to 80.00 mcg / hr / cm² for PVP, respectively.

The Metoprolol tartrate skin permeation was found to increase from 77.91 to 87.95 mcg / hr / cm², 79.00 to 85.82 mcg / hr / cm² and 75.83 to 82.00 mcg / hr / cm² on increasing the concentration of HPMC (20-60% w/w), PEG 4000 and PVP (5-10% w/w) in eudragit RL matrix, respectively. Similar pattern in Metoprolol tartrate skin permeation rate was observed on increasing the concentration of hydrophilic polymers i.e. HPMC (20-60% w/w), PEG 4000 and PVP (5-10% w/w) in eudragit RS matrix.

The formulations which exhibited *in vitro* drug skin permeation nearly equal to the calculated skin permeation rate for Atenolol / Metoprolol tartrate required to achieve an effective plasma concentration were selected for stability studies.

The stability studies were performed as per ICH guidelines. The parameters selected for evaluation were tensile strength, percent moisture content, drug content and skin permeation rate. The formulations Ma EC HPMC 7, Ma RL PEG 5, Mm RL HPMC 7 and Mm RS PVP 3 of Atenolol / Metoprolol tartrate respectively were physically stable with regard to their physical characteristics. The physical stability of the formulations could be accounted because of flexural rigidity, which resulted in minimum variation in materialistic properties of polymers. Moreover, these formulations exhibited very little change in drug content.
The overall performance of transdermal drug delivery system was tested through *in vitro* drug skin permeation studies. The studies showed significant increase in drug skin permeation rate for physically unstable formulations of Atenolol and Metoprolol tartrate. The increase in skin permeation rate may be due to increase in moisture content in the formulation, which ultimately causes the hydration of skin.

The change in skin permeation rate for Atenolol formulations Ma EC HPMC 7, Ma RL PEG 5 and Metoprolol tartrate formulations Mm RL HPMC 7, and Mm RS PVP 3 was negligible. Hence, these formulations were selected for *in vivo* performance evaluation.

The *in vivo* studies were performed by measuring drug plasma concentration and the results were compared with the performance of orally administered conventional tablets of Atenolol and Metoprolol tartrate, respectively.

The mean drug (Atenolol / Metoprolol tartrate) plasma concentration as function of time for matrix diffusion transdermal drug delivery systems was compared to orally administered tablets. The plasma concentration of Atenolol gradually increased and reached steady state level of 100.2 ± 0.50 and 115.4 ± 0.54 ng/mL for formulation Ma EC HPMC 7 and Ma RL PEG 5, respectively within 7 hours. In case of Metoprolol tartrate the plasma concentration gradually increased and reached steady state level of 29.0 ± 0.14 ng/mL and 24.5 ± 0.14 ng/mL for formulation Mm RL HPMC 7 and Mm RS PVP 3, respectively within 6 hours. The average plasma concentration of drug remained nearly constant for 24 hours then declined on removal of the transdermal system (after 24 hours). However, oral administration of conventional tablets resulted in peak plasma concentration 98 ± 0.46 ng/mL for Atenolol within three hours and 22.5 ± 0.11 ng/mL for Metoprolol tartrate within one hours. Twelve hourly dose of Atenolol and six hourly dose of Metoprolol tartrate were administered for this purpose.

The delayed $t_{\text{max}}$, the time taken to reach peak plasma concentration of drug on transdermal application, may be accounted for the time required for penetration of the drug through the skin and to reach the blood circulation. Once the peak plasma concentration of the drug is attained, it remained constant for 24 hours. On multiple oral dosing with conventional
tablets of Atenolol (12 hours interval) and for Metoprolol tartarate (6 hours interval) the drug profile assumed the usual shape of troughs and peaks.

The *in vivo* performance studies revealed improved performance of Atenolol / Metoprolol tartarate matrix diffusion controlled transdermal drug delivery system which is evident from the area under the curve determination for various formulations. The most effective *in vivo* performance was recorded for the Ma RL PEG 5 for Atenolol matrix diffusion controlled transdermal drug delivery system AUC<sub>0-28</sub> 2478 ng.hr/mL. Similarly, *in vivo* performance for Metoprolol tartarate for Mm RL HPMC 7 matrix diffusion controlled transdermal drug delivery system AUC<sub>0-28</sub> 723 ng.hr/mL exhibited best *in vivo* performance as compared to other formulation.

The enhanced bioavailability of transdermal drug delivery system of Atenolol and Metoprolol tartarate may be due to protection of drug from first hepatic pass or mucosal metabolism probably in conjunction with entero-hepatic recirculation of drug. Controlled delivery of the drug from the transdermal system to the blood circulation is evident from the absence of troughs and peaks, which are characteristic of oral dosing. The AUC for transdermal drug delivery system are obtained after the application of 20 mg of Atenolol and 25 mg Metoprolol tartarate, whereas oral administration of 100 mg of Atenolol (50 mg administered every 12 hours) and 100 mg of Metoprolol tartarate (25 mg administered every six hours) respectively are required to obtain the desired AUC values. The formulation of transdermal drug delivery system of Atenolol and Metoprolol tartarate resulted in significant dose reduction viz. 1/5<sup>th</sup> for Atenolol and 1/4<sup>th</sup> for Metoprolol tartarate as compared to oral administration, thus avoiding high peak drug concentration (which are often associated with more severe adverse effects), loss of selectivity or induction of counter-regulative mechanisms by the body. It would also ensure the continuance of its cardio vascular protective properties, even during the circadian “problem period” such as the early morning hours.

The skin irritation studies was attempted to observe any visual skin irritation after the application of the patch to the Albino rabbits. The results indicated that neither the adhesive nor the drug Atenolol / Metoprolol tartarate caused any noticeable irritation on the Albino rabbit skin throughout the 7-day study period.
The outstanding benefits and great potentials of the transdermal drug delivery systems of Atenolol and Metoprolol tartrate, demands the further exploration in clinic, an insight vision towards the development of transdermal drug delivery systems for commercial use. Such a development will be a boon to humanity.
Appendices
# List of Chemicals

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<th>S. No.</th>
<th>Chemical</th>
<th>Supplier</th>
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<tr>
<td>1</td>
<td>Acetone</td>
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<td>Polyethylene glycol 400</td>
<td>Loba Chemie Indoausatranol Co., Bombay</td>
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<td>31</td>
<td>Potassium dihydrogen ortho-phosphate</td>
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<td>32</td>
<td>Potassium hydroxide</td>
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<tr>
<td>33</td>
<td>Sodium alginate</td>
<td>Qualigens Fine Chemicals, Bombay</td>
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<tr>
<td>34</td>
<td>Sodium hydroxide</td>
<td>Ranbaxy fine Chemicals Ltd, New Delhi</td>
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<td>35</td>
<td>Triethylamine</td>
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<td>36</td>
<td>Trifluoroacetic acid</td>
<td>Loba Chemie Indoausatranol Co., Bombay</td>
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4. Effective and Controlled transdermal delivery of Atenolol - Drug Development and Industrial Pharmacy.