RELAVANT LITERATURE REVIEW:

4.1 Information regarding Cardiovascular Disease:

Cardiovascular disease is a class of diseases that involve the heart, the blood vessels or both. In any of the disease if cardiac system, peripheral artery, vascular system is affected is called cardiovascular disease. Atherosclerosis and hypertension are the most common cause for cardiovascular disease. In addition, age changes the physiology and morphology of the human being, and it's a reason to alter the cardiovascular functions (229). If heart changes its cardiac function so it leads the increase the risk of cardiac disease. Cardiac problem is initiated in the age of older adults but atherosclerosis begins in the age of child. Therefore try to emphasis on preventing atherosclerosis by changing our life habit such as eating and do exercise and avoid smoking and tobacco.

Cardiac problem is mainly divided into two parts, Problem related to the pumping system of the heart and blood supply related issues. Heart attack, valvular disorder, cardiac arrhythmias, coronary artery disease and heart muscle disease is related to the pumping action of the heart. Hypertension, hypotension and atherosclerosis are related to the blood vessel related problems (230).

Hypertension, also stated to as high blood pressure, is a situation in which the arteries have persistently raised the pressure of the blood. Every time the human heart beats, it pumps blood to the whole part of the body through the arteries. Blood pressure is the power of blood pushing up against the blood vessel walls resistance. The higher the pressure the harder the heart has to pump.

Hypertension:

Hypertension can lead to damage the body organs, as well as several illnesses, such as renal failure (failure of kidney), heart failure, aneurysm, stroke, or heart attack. Researchers from UC Davis reported article in the Journal of the American Academy of Neurology that high blood pressure during middle age may increase the risk of cognitive failure later in life (231).

The normal level for blood pressure is below the 120/80, where 120 is the systolic measurement (peak pressure in the arteries) and 80 is the diastolic
measurement (minimum pressure in the arteries) (232). Blood pressure between 120/80 and 139/89 is called pre-hypertension (to denote increased risk of hypertension), and a blood pressure of 140/90 or above is painstaking hypertension.

Hypertension may be classified as secondary or essential type of the hypertension. Essential type of hypertension is the term for high blood pressure with unidentified reason. It accounts for about 95% of cases. Secondary type of hypertension is the term for high blood pressure with a known direct cause, such as kidney disease, tumors, or birth control pills. Mostly in united sate of America around 70 million adults are affected by hypertension or heart related issues. The problem related to the hypertension also affects about two million teens and children (233). As per the report published by the Centers for Disease Control and Prevention (CDC) in September 2012, over half all Americans with hypertension do not have their high blood pressure under control.

**Reasons of Hypertension:**

The exact reasons of hypertension are usually unknown; there are several factors that have been highly related with the condition. These contain:

- Diabetes
- Being obese/ overweight as a child - a research team at the Indiana University School of Medicine found that obese/overweight children are much more likely to suffer from hypertension during adulthood
- Obesity or being overweight
- . Lack of physical activity
- Smoking
- Sedentary lifestyle
- High levels of salt consumption (sodium sensitivity). As per the American Heart Association (AHA), sodium consumption should be limited to 1,500 milligrams per day, and that includes everybody, even healthy people without high blood pressure, diabetes or cardiovascular diseases. AHA's chief executive officer, Nancy Brown said "Our recommendation is simple in the
sense that it applies to the entire U.S population, not just at-risk groups (234). All ages in the Americans, regardless of individual risk factors, can recover the heart health and reduce their risk of cardiovascular disease by limiting their daily eating of sodium to less than 1,500 milligrams.” The recommendation was published in the journal Circulation (November 5th, 2012 issue)

- Insufficient calcium, potassium, and magnesium consumption
- High levels of alcohol consumption
- Vitamin D deficiency
- Aging
- Stress
- Chronic kidney disease
- Medicines such as birth control pills
- Genetics and a family history of hypertension - In May 2011, scientists from the University of Leicester, England, reported in the journal Hypertension that some genes in the kidneys may contribute to hypertension.
- Adrenal and thyroid problems or tumors

**Diagnosis of hypertension:**
Hypertension may be diagnosed by a health professional who measures blood pressure with a device called a sphygmomanometer - the device with the arm cuff, dial, pump, and valve. The systolic and diastolic numbers will be recorded and compared to a chart of values. If the pressure is greater than 140/90, you will be considered to have hypertension.

A high blood pressure measurement, however, may be spurious or the result of stress at the time of the exam. In order to perform a more thorough diagnosis, physicians usually conduct a physical exam and ask for the medical history of you and your family. Doctors will need to know if you have any of the risk factors for hypertension, such as smoking, high cholesterol, or diabetes (235).

If hypertension seems reasonable, tests such as electrocardiograms (EKG) and echocardiograms will be used in order to measure electrical activity of the heart
and to assess the physical structure of the heart. Additional blood tests will also be required to identify possible causes of secondary hypertension and to measure renal function, electrolyte levels, sugar levels, and cholesterol levels (236).

**Prevention of hypertension:**

Hypertension can best be prevented by adjusting your lifestyle so that proper diet and exercise are key components. It is important to maintain a healthy weight, reduce salt intake, reduce alcohol intake, and reduce stress. In order to prevent damage to critical organs and conditions such as stroke, heart attack, and kidney failure that may be caused by high blood pressure, it is important to screen, diagnose, treat, and control hypertension in its earliest stages. This can also be accomplished by increasing public awareness and increasing the frequency of screenings for the condition.
4.2 Treatment of Hypertension (237):

Most of the medications prescribed for high blood pressure very often:

![Hypertension Treatment algorithm](image)

Figure 18: Hypertension Treatment algorithm
**Beta-blockers:**

Beta-blocker reduces the pressure generated on heart by decrease the heart rate and minimizes the pressure on heart. High sympathetic tone, angina, and previous myocardial infarction are good reasons for using b-blockers. As a low dose minimizes the risk of fatigue (an unpleasant effect of b-blockade) addition of a diuretic or a calcium channel blocker is often beneficial. However, b-blockade therapy is associated with symptoms of depression, fatigue, and sexual dysfunction. These side-effects have to be taken into consideration in the evaluation of the benefits of treatment.

Over the past few years b-blockers have been used increasingly frequently in the management of heart failure, a known complication of arterial hypertension. They are effective but their introduction in the presence of heart failure has to be very cautious, starting with very low doses to avoid an initial worsening of heart failure.

**Water pills (diuretics):** Diuretics used in combination of other antihypertensive medicine to treat the high blood pressure by increase the sodium excretion from urine. Low-dose diuretic therapy is effective and reduces the risk of stroke, coronary heart disease, congestive heart failure, and total mortality. Whilst thiazides are most commonly used, loop diuretics are also used successfully and the association with a potassium sparing diuretic reduces the risk of both hypokalaemia and hypomagnesaemia.

Even in small doses diuretics potentiate other antihypertensive drugs. The risk of sudden death is reduced when potassium-sparing diuretics are used. In the long-term, spironolactones reduce morbidity and mortality in patients with heart failure that is a typical complication of long-standing hypertension.

**Calcium channel blockers:** Calcium channel blockers can be separated into dihydropyridines (e.g. nifedipine, nimodipine, amlodipine) and non-dihydropyridines (verapamil, diltiazem). Both groups reduced the peripheral vascular resistance but verapamil and diltiazem have negative inotropic and
chronotropic effects. It is worked by relaxing muscles of the wall of arteries. Short-acting dihydropyridines, such as nifedipine cause reflex sympathetic beginning and tachycardia, while long-acting drugs such as amlodipine and slow-release arrangements of nifedipine cause less sympathetic beginning. Short-acting dihydropyridines appear to raise the risk of sudden death.

Calcium channel blockers are active in the elderly and may be selected as mono therapy for patients with Raynaud’s phenomenon, peripheral vascular disease, or asthma; as such patients do not tolerate b-blockers. Diltiazem and verapamil are contraindicated in heart failure. Nifedipine is actual in severe hypertension and can be used sublingually; there is need for caution because of the risk of excessive hypotension. Calcium channel blockers are often associated with b-blockers, diuretics and/or ACE inhibitors.

**Angiotensin-converting enzyme (ACE) inhibitors:** Angiotensin II is compulsory to agreement the blood vessels and angiotensin-converting enzymes stop the production of ACE II. ACE inhibitors are increasingly being used as first line therapy. They have relatively few side-effects and contraindications except bilateral renal artery stenosis. Though ACE inhibitors are actually in unilateral Reno vascular hypertension, there is risk of ischemic atrophy. Therefore, angioplasty or surgical renal artery reconstruction are preferable to long-term purely medical therapy. ACE inhibitors are first option agents in diabetic hypertensive patients as they slow down the progression of renal dysfunction. In hypertension with heart failure, ACE inhibitors are also first choice drugs.

**Angiotensin receptor blockers:** Angiotensin II uptake by the receptor and contract the blood arteries, losartan and valsartan works on receptors to prevent uptake of angiotensin II, and therefore inhibit the vasoconstrictor effect of angiotensin II.

**Alpha-blockers:** Free from metabolic side-effects, these drugs reduce blood cholesterol and reduce peripheral vascular resistance. Alpha-blockers block the
massages from nervous system and relax the blood vessel. Prazosin is shorter acting than doxazosin, indoramin and terazosin. These drugs are highly selective for \(\alpha_1\)-adrenoceptors. Drowsiness, postural hypotension, and occasionally tachycardia, can be troublesome. Fluid retention may require the addition of a diuretic. Phenoxy benzamine is a non-competitive \(\alpha\)-adrenoceptor agonist used (in association with a \(\beta\)-blocker) in the management of patients with phaeochromocytoma, though recently doxazosin has been used successfully. Blockers of central sympathetic (autonomic nervous) system these agents block messages out of the brain from the autonomic nervous system that contract blood vessels. The autonomic nervous system is the part of the nervous system that is automatic and controls heart rate, breathing rate, and other basic functions. The effect of these drugs is to relax blood vessels, thus lowering blood pressure. E.g. Clonidine

**Direct vasodilators:** Direct vasodilators relax (dilate) the blood vessels to allow blood to flow under lower pressure. These medications are often given through an IV line in an emergency (that is, in malignant hypertension). E.g., Nitroprusside Diazoxide Oral medications are hydralazine and minoxidil.

**Review of the drug:**
Captopril is given by free sample from Torrent Pharmaceuticals. Captopril is a white to off-white crystalline powder that may have a slight sulfurous odor. It is soluble in water, ethanol and methanol and sparingly soluble in ethyl acetate and chloroform. It was well known that the rate of solubility is directly related to particle size of API.

Micro size particles give faster solubilization and uniform solution compared to macro particle size which has low and variable surface area of API. The formulation requires soluble API in a suitable polymer matrix, hence micronized grade of captopril was preferred over non-micronized grade, to get uniform drug distribution in the dry matrix. The captopril, micronized used in the development studies was tested for compliance with critical USP specifications. Thus
micronized captopril (149) was used during formulation development and stability study.

Captopril is an angiotensin-converting enzyme (ACE) inhibitor. Captopril is used for the treatment of hypertension and some types of congestive heart failure. Captopril is well known drug to treat the hypertension because of its novel mechanism of action to treat the hypertension and innovative development process. Captopril is commonly marketed by Bristol-Myers Squibb under the trade name Capoten.

Table 5: Physical properties of the captopril (143, 1444, 145, 150):

<table>
<thead>
<tr>
<th>Name</th>
<th>captopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>White to of white crystalline powder</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td></td>
</tr>
<tr>
<td>Chemical IUPAC Name</td>
<td>(2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl]pyrrolidine-2-carboxylic acid</td>
</tr>
<tr>
<td>Average Molecular Weight</td>
<td>217.2850 (&lt;500 DA)</td>
</tr>
<tr>
<td>Drug Category</td>
<td>Angiotensin-converting Enzyme Inhibitors.</td>
</tr>
<tr>
<td></td>
<td>Antihypertensive Agents.</td>
</tr>
<tr>
<td>Melting Point</td>
<td>106°C (&lt;200°C)</td>
</tr>
<tr>
<td>Assay (% w/w)</td>
<td>97.0-103.0</td>
</tr>
<tr>
<td>pH of solution</td>
<td>2.0-2.6</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤ 1.0%</td>
</tr>
<tr>
<td>Experimental Water Solubility</td>
<td>Freely soluble,</td>
</tr>
<tr>
<td></td>
<td>Source: PhysProp</td>
</tr>
<tr>
<td>Experimental LogP</td>
<td>0.6</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>An angiotensin-converting enzyme (ACE) inhibitor</td>
</tr>
</tbody>
</table>
| Absorption                | 75% without food (the presence of food in the gastrointestinal tract reduces absorption by about 40
Mechanism of action of captopril (146):
The mechanism of action of captopril has not yet been fully elucidated. Its beneficial effects in hypertension and heart failure appear to result primarily from suppression of the rennin angiotensin-aldosterone system. However, there is no consistent correlation between renin levels and response to the drug. Renin, an enzyme synthesized by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin-I, a relatively inactive decapeptide. Angiotensin-I is then converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent endogenous vasoconstrictor substance. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention.
Figure 19: Mechanism of action of Renin angiotensin-aldosterone system
Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidylldipeptide carboxy hydrolase (147). This inhibition has been demonstrated in both healthy human subjects and in animals by showing that the elevation of blood pressure caused by exogenously administered angiotensin I was attenuated or abolished by captopril. In animal studies, captopril did not alter the presser responses to a number of other agents, including angiotensin II and norepinephrine, indicating specificity of action.

ACE is identical to "bradykininase", and Captopril may also interfere with the degradation of the vasodepressor peptide, bradykinin. Increased concentrations of bradykinin or prostaglandin E 2 may also have a role in the therapeutic effect of Capoten.

Inhibition of ACE results in decreased plasma angiotensin II and increased plasma renin activity (PRA), the latter resulting from loss of negative feedback on renin release caused by reduction in angiotensin II. The reduction of angiotensin II leads to decreased aldosterone secretion, and, as a result, small increases in serum potassium may occur along with sodium and fluid loss.

The antihypertensive effects persist for a longer period of time than doe’s demonstrable inhibition of circulating ACE. It is not known whether the ACE present in vascular endothelium is inhibited longer than the ACE in circulating blood.

**PHARMACOKINETICS:** After oral administration of therapeutic doses of Captopril, rapid absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 50 percent (148); captopril therefore should be given one hour before meals. Based on carbon-14 labeling, average minimal absorption is approximately 75 percent. In a 24-hour period, over 95 percent of the absorbed dose is eliminated in the urine; 40 to 50 percent is unchanged drug; most of the remainder is the disulfide dimer of captopril and captopril-cysteine disulfide. Due to problem in delivery through oral drug delivery, transdermal drug delivery is suitable delivery system for captopril.

**Table 6: Pharmacokinetic data of captopril (147):**
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$ (H)</td>
<td>0.98 ± 0.13</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mcg/ml)</td>
<td>1.31 ± 0.20</td>
</tr>
<tr>
<td>Elimination half-life (H)</td>
<td>2.00 ± 0.25</td>
</tr>
<tr>
<td>Volume of distribution (per kg)</td>
<td>0.614 ± 0.104</td>
</tr>
<tr>
<td>Total clearance (per hour per kg)</td>
<td>0.690 ± 0.082</td>
</tr>
<tr>
<td>Absorption</td>
<td>60-70% Without food</td>
</tr>
<tr>
<td></td>
<td>25-40% with food</td>
</tr>
<tr>
<td>Protein binding</td>
<td>25-30%</td>
</tr>
</tbody>
</table>

**Pharmacodynamics:** Administration of Captopril results in a reduction of peripheral arterial resistance in hypertensive patients with either no change, or an increase, in cardiac output. There is an increase in renal blood flow following administration of Capoten and glomerular filtration rate is usually unchanged. Reductions of blood pressure are usually maximal 60 to 90 minutes after oral administration of an individual dose of Captopril. The duration of effect is dose related. The reduction in blood pressure may be progressive, so to achieve maximal therapeutic effects, several weeks of therapy may be required. The blood pressure lowering effects of thiazide-type diuretics are additive (149). In contrast, captopril and beta-blockers have a less than additive effect.

**Adverse Effects and Toxicity:** In hypovolemic patients, severe hypotension may occur after initial doses. ACE inhibitors should not be used in pregnant women. Other adverse effects: Angioedema (rare), dry cough, rashes, altered taste, and proteinuria, hyperkalemia.

**Contraindication:** Captopril tablets are contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).
### Table 7: Marketed product of captopril:

<table>
<thead>
<tr>
<th>Active Ingredients</th>
<th>Dosage Form/Route</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPTOPRIL</td>
<td>TABLET;ORAL</td>
<td>PAR PHARM</td>
</tr>
<tr>
<td>CAPTOPRIL</td>
<td>TABLET;ORAL</td>
<td>APOTEX</td>
</tr>
<tr>
<td>CAPTOPRIL</td>
<td>TABLET;ORAL</td>
<td>HIKMA PHARMS LLC</td>
</tr>
<tr>
<td>CAPTOPRIL</td>
<td>TABLET;ORAL</td>
<td>MYLAN</td>
</tr>
<tr>
<td>CAPTOPRIL</td>
<td>TABLET;ORAL</td>
<td>SANDOZ</td>
</tr>
<tr>
<td>CAPTOPRIL</td>
<td>TABLET;ORAL</td>
<td>STASON</td>
</tr>
<tr>
<td>CAPTOPRIL</td>
<td>TABLET;ORAL</td>
<td>TEVA</td>
</tr>
<tr>
<td>CAPTOPRIL</td>
<td>TABLET;ORAL</td>
<td>WATSON LABS</td>
</tr>
<tr>
<td>CAPTOPRIL</td>
<td>TABLET;ORAL</td>
<td>WOCKHARDT</td>
</tr>
</tbody>
</table>

#### 4.3 Literature Review of Transdermal Formulation:

1.0/ Sameer Singh (2012), *Pre-formulation studies of captopril for novel oral drug delivery system* (143), The aim of the present work was to study the pre-formulation for novel oral drug delivery system of gastro retentive dosage forms. It is difficult to develop the formulation of controlled release for improve the bioavailability and better absorption. Drug absorption in gastrointestinal tract involves very complicated steps and also involves the lots of variability in absorption. Captopril is selected as model drug due to interaction with food in stomach, lower half life, and first pass metabolism. Variability in gastrointestinal tract needs to be considered before development of the gastro retentive formulation. Due to complication in development of dosage form, many of the pre-formulation parameter needs to be considered. They considered melting point, physical appearance, IR for purity, solubility in solvent and buffer, partition coefficient for hydrophilic and lipophilic nature, UV absorption spectra for identification. As per pre-formulation report captopril is soluble in water, ethanol and 0.01N HCL, partition coefficient value was 0.95 and as per UV spectrophotometric study, captopril follows the beer’s low of absorption. After getting all the pre-formulation information, they concluded that, captopril could serve as a suitable candidate for gastro retentive type of novel oral drug delivery system to improve the bioavailability of the drug.
2.0/ Mohd Amjad(2011), Formulation and evaluation of transdermal patches of Atenolol (164). In novel drug delivery system, Drug delivery through skin are becoming more popular compared to oral drug delivery system. The aim of the present investigation was to develop the mono layer matrix type transdermal drug delivery system containing Atenolol as a model drug with different ratios of hydrophilic and hydrophobic polymer by solvent casting method. They used HPMC (hydroxypropyl methylcellulose) & EC (ethyl cellulose) as a polymer for transdermal patches, propylene glycol as plasticizer, span 80 as permeation enhancer. FTIR were studied for the compatibility of the different excipients with atenolol. They prepared different formulation with different ratio of polymer with 10mg of atenolol 3mg of propylene glycol. All seven formulations of atenolol were evaluated for in-vitro drug delivery, physicochemical characteristics and stability study. All seven formulations had the good physical stability. Out of seven formulations two formulations deliver the desired delivery of atenolol for 24 hrs. So out of total seven, two formulations were selected as a better formulation of atenolol transdermal patch.

3.0/ Rakesh P. Patel (2009), Formulation and evaluation of transdermal patch of Aceclofenac (152). The aim of the present research work was to develop a monolithic matrix type transdermal drug delivery system containing Aceclofenac as a model drug with different ratios of hydrophilic and hydrophobic polymer by solvent casting method. They used HPC (hydroxypropyl cellulose) & EC (ethyl cellulose) as a polymer for transdermal patches. They used different ratios of hydrophilic (hydroxypropyl cellulose) and hydrophobic (ethyl cellulose) polymeric systems by the solvent evaporation technique. They used 15 % w/w of dry polymer matrix dibutyl phthalate as a plasticizer. They used oleic acid and isopropyl myristate as a penetration enhancer of model drug Aceclofenac. FTIR and different scanning calorimetry were studied for physicochemical compatibility of drug with different type of excipients. As per compatibility study, both the polymers were compatible with Aceclofenac. Developed transdermal system were evaluated for weight variation, tensile strength, regard to thickness, folding endurance, drug content, flatness, percentage of moisture content and water vapour transmission rate. They used Franz type diffusion cell for evaluation of in-vitro drug delivery. All
prepared formulation had good physicochemical stability as per the results and formulation prepared with hydrophilic polymer showed desired drug delivery through rat skin as compared to other formulation. They prepared total nine formulations and out of nine F9 formulation gives highest drug delivery. Formulation with 15% oleic acid and 10% IPM is the best Aceclofenac transdermal formulation.

4.0/ Ashish A. Heda (2010), Development and In vitro Evaluation of Betahistine Adhesive-Type Transdermal Delivery System (90), The aim of the present research work is to develop a transdermal formulation of beta histine using silicone, acrylate and polyisobutylene pressure sensitive adhesives. Transdermal patches were prepared by solvent casting and adhesive transfer method. They used vinyl acrylate, hydrophilic acrylate, non-cured acrylate, polyisobutylene rubber polymer and styrene rubber polymer as a tackifier. They select polymer based on drug loading, adhesion properties, miscibility and in vitro drug delivery through guinea pig skin. Formulations with vinyl acrylate and hydrophilic acrylate were only stable but delivery of drug from hydrophilic acrylate formulation was higher. 2.0% oleic acid given good adhesion and delivery also. Based on the all transdermal formulation evaluation, hydrophilic acrylate pressure sensitive adhesive with 2.0% oleic acid was showed best stable transdermal formulation to deliver the beta histine.

5.0/ Dandigi M Panchaxari, Design and characterization of diclofenac diethylamine transdermal patch using silicone and acrylic adhesives combination (163). The aim of the present investigation is to develop the transdermal formulation of the diclofenac diethylamine with combination of silicone and acrylate polymer combination to get the combined properties of the dry polymer matrix. Formation of monolithic transdermal matrix type of system by solvent evaporation method for casting of film on fluoropolymer coated polyester release liner. They used the different type of drug solubilizers to solubilize the drug in matrix. They also evaluate the penetration enhancers to improve the delivery of the drug from pig ear skin. After optimization of the formulation, transdermal patches were evaluated for dissolution, adhesion and stability studies. All the optimized formulation was tested for rabbit skin irritation test. As per the
investigation results, solubility of diclofenac diethyl amine was lower in silicone polymer compared to acrylate polymer but delivery in silicone polymer was higher. Fabrication of transdermal system alone with silicone polymer was not possible. The combination of acrylate and silicone polymer showed desired characteristic of the matrix like delivery and adhesion of the patch. Also the acute skin irritation testing study supported the non-irritation adhesives used. Based on the research study, they concluded that an ideal ratio of acrylate to silicone polymer would serve the best desired characteristics and robustness of the transdermal formulation.

6.0/ Shashikant D. Barhate (2011), Formulation of transdermal patch of carvedilol by using novel polymers (236), The aim of the present investigation is to develop and optimize the transdermal system of carvedilol by using combination of different type of novel polymer. In transdermal system they used HPMC E5, PVA, HPMC K100M and Eudragit RL100 as a polymer and oleic acid and propylene glycol used as penetration enhancers. They used full factorial design to optimize the formulation of carvedilol transdermal system. After finalization of the formulation, transdermal system of carvedilol was evaluated for tensile strength, folding endurance, thickness, drug content, moisture vapor transmission and moisture content. Final formulation is evaluated for permeation study and in-vitro permeation studies showed that carvedilol was deliver in the range from 0.964 to 1.616 mg/cm2/hr. As per study, transdermal formulation follows the zero order kinetic. Final formulation is also charged for stability study in accelerated and critical room temperature and it showed no significant change in drug content.

7.0/ Kunal N Patel (2012), Formulation and characterization of drug in adhesive transdermal patches of diclofenac acid (161), The aim of the present investigation is to develop a monolithic matrix type of transdermal drug delivery system containing Diclofenac acid as a model drug and acrylate adhesive as a pressure sensitive adhesive. Transdermal formulation was manufactured by solvent evaporation method by casting technique. Different type of penetration enhancer like Labrasol, oleic acid and triacetin were also used to improve the penetration of the diclofenac acid. Silicone
coated polyester film used as liner and polyethylene monolayer film used as a backing film. Final formulations were physically evaluated with regard to drug content, percentage moisture absorption, % elongation thickness, tensile strength, folding endurance and weight variation in dry matrix. Formulation containing 5.0% diclofenac acid with 10.0% triacetin delivered the desired amount of diclofenac from human cadaver skin using Franz diffusion cell. Delivery of the drug from the system followed the zero order kinetic. Final formulation was also stable in all physical parameters. Out of twelve formulations, F3 has shown optimum formulation for delivery and stability. They also conduct stability and irritation study and final formulation was stable in six month and no irritation.

**8.0/ Shailesh T. Prajapati (2011), Formulation and Evaluation of Transdermal Patch of Repaglinide (237),** the aim of the present investigation is to develop repaglinide transdermal formulation. Final formulation was also evaluated for different type of parameters. As per physicochemical characterization, repaglinide is the suitable candidate for transdermal drug delivery system. They used different grade of HPMC and PVP-K30 for preparation of transdermal patch of repaglinide by solvent casting method. They conduct the different scanning calorimetry and FTIR for compatibility study of different excipient and purity of drug. They applied design expert software for selection of excipients and also for optimize the formulation. Final formulations were physically evaluated with regard to drug content, percentage moisture absorption, and % elongation thickness, tensile strength, folding endurance and weight variation in dry matrix. They used 32 full factorial designs to optimize the formulation and to see the effect of different grade of HPMC and PVP. Out of nine formulations F6 formulation delivered 92.343% of drug up to 12hr and it was considered as optimized batch. After finalization of the formulation, moderate level of HPMC and PVP useful for the sustained release transdermal formulation of repaglinide.

**9.0/ Francesco Cilurzo (2011), Design and Characterization of an Adhesive Matrix Based on a Poly (Ethyl Acrylate, Methyl Methacrylate) (2),** the aim of the present investigation is too prepared and evaluate the adhesive matrix. Main problem of
hydrogel formulation when matrix made up of poly (ethyl acrylate, methyl methacrylate) (Eudragit® NE 40D, PMM) is adhesive matrix shrinkage during coating and drying of blend on release liner. To resolve the issue of shrinkage they used two methods, one is freeze dried and then dissolves in organic solvent and other one is to addition of commercial PMM latex as a plasticizer like triacetine and tributyl citrate and additives like anti-shrinkage agents. As per there research some of the active ingredients also work as a anti-shrinkage agents like potassium diclofenac and nicotine. Prepared transdermal patches were evaluated for peel, tack and shear study for in-vitro adhesion evaluation. Interaction study of plasticizer was evaluated by FTIR-AIR spectroscopy. They also evaluated drug delivery from skin by help of the Franz diffusion cell. Based on drug delivery PMM latex can be used in the transdermal drug development patches.

10.0/ Updesh B. Lade (2011), Design, Formulation and Evaluation of Transdermal Drug Delivery System of Budesonide (239). The aim of the present investigation is to design and formulate and evaluate the budesonide transdermal drug delivery system. As per physicochemical properties, Budesonide is suitable candidate for transdermal drug delivery system. Budeasone is highly potent steroids. Due to first pass metabolisam and lower systemic availability, Budeasone is not suitable candidate for oral drug delivery system. In development, they used Eudragit RL 100, RS, ethyl cellulose and povidone as a polymer with different ration of drug. They used mercury substrate for coating of blend and PEG-400 as a plasticizer. They also evaluate the different penetration enhancers like urea, DMSO on delivery of the budesonide. Final formulations were physically evaluated with regard to drug content, percentage moisture absorption, % elongation thickness, tensile strength, folding endurance and weight variation in dry matrix. Thay also evaluate the skin irritation study. They prepared the patch and evaluate the % of permeation on different moisture contents. As per the investigation, PVP and Eudragit protect the loss of the water from skin, so it’s provided the more occlusion and increase the penetration of drug.

11.0/ Wang Hao (2000), Improvement of transdermal permeation of captopril by iontophoresis (239), the aim of the present investigation is to improve the permeation
of captopril from transdermal delivery by preparation of iontophoresis formulation. Iontophoresis was used to enhance the in-vitro and in-vivo delivery of captopril through rat skin. Targeted drug delivery from iontophoresis was 60-90 mcg/cm²/hr. As per physicochemical properties, captopril is the suitable candidate for transdermal drug delivery. They prepared captopril hydrogel formulation with help of PVP and glycerol and adjust the pH of the patch with HCL solution. Final formulation was evaluated for in vitro drug release from Franz diffusion cell. In the in vitro drug delivery, they evaluate the effect of drug concentration and pH of the film. They evaluate the comparative delivery of captopril from hydro gel patch and iontophoresis and as per investigation, iontophoresis gives 10 fold higher drug delivery compare to hydrogel patch formulation.

12.0/ Vandana Mohabe (2011), preparation and evaluation of captopril transdermal patches (240), the aim of the present investigation is to develop the transdermal patch of anti-hypertensive drug of captopril. Transdermal systems were prepared by solvent casting method and also used different type of polymer in different ratio. They used polyvinyl alcohol, hydroxypropyl methylcellulose, polyvinyl pyrrolidone and polyvinyl pyrrolidone as a polymer. They also conduct the DSC of different excipients and drug for compatibility of individual. The prepared 22 transdermal system and all formulation were evaluated for physicochemical characteristics like weight variation, drug content, and thickness, folding endurance, percent moisture content, in vitro drug permeation and water vapor transmission. Some of the formulation was discarded due to higher level of solvent and turbidity or precipitation. Out of all permeation enhancer 5.0% PBT with span-80 and EC was work as a good penetration enhancer and plasticizer. After final formulation development, it can be concluded that span 80 with n-dibutyl phthalate were better penetration enhancer and plasticizer for captopril transdermal system. After finalization in laboratory scale transdermal system, however other pharmacodynamics and pharmacokinetic study need to be carried out before stable usefulness of the captopril transdermal product.

13.0/ Yuveraj Singh Tanwar (2007), Development and evaluation of carvedilol transdermal patches (241), the aim of the present investigation is to develop and
evaluate the transdermal patch of carvedilol. Carvedilol transdermal drug delivery system was prepared using solvent evaporation method. They used HPMC as a polymer to prepare the reservoir type of transdermal system. Membrane of Eudragit RL100 and Eudragit RS100 were used to control the drug delivery. Transdermal formulation of carvedilol was prepared with hydrophilic polymer. Organic solvent based pressure sensitive adhesive was not used to develop the carvedilol transdermal. They used polyvinyl alcohol as a backing layer, HPMC as a drug reservoir system, eudragit act as a rate controlling membrane and tween 80 and span 80 acts as penetration enhancers. After preparation of transdermal patches, prepared patches was evaluated for physicochemical characteristics like weight variation, drug content, thickness, folding endurance, percent moisture content, in vitro drug permeation and water vapor transmission and all formulation possessed satisfactory physicochemical properties. Final formulation was evaluated for in vitro permeation study using K-C diffusion cell in hairless guinea pig skin and super case two mechanism of transportation. As per investigation, non-ionic surfactants like tween 80 and span 80 increased the penetration of drug from skin. Over all conclusion of the present work is to HPMC, tween and eudragit demonstrate to control the release of carvedilol from guinea pig skin.

14.0/ Gajanan Darwhekar(2011), Formulation and Evaluation of Transdermal Drug Delivery System of Clopidogrel Bisulfate (243), the aim of the present study is to formulate and evaluate the transdermal patch formulation of bisulfate salt of clopidogrel. A bisulfate salt of clopidogrel is suitable candidate for transdermal drug delivery system as per physicochemical properties like shorter half-life, lower bioavailability, extensive first pass metabolism and lower bioavailability. HPMC, PVP and EC had been used as polymer in transdermal formulation of clopidogrel by solvent casting method. After preparation of transdermal patches, prepared patches was evaluated for physicochemical characteristics like weight variation, drug content, thickness, folding endurance, percent moisture content, in vitro drug permeation and water vapor transmission and all formulation possessed satisfactory physicochemical properties. The in-vitro diffusion study was performed using Franz type diffusion cell. They prepared total six formulations and out of six formulation, formulation F2 showed
maximum and F5 showed minimum release up to 24hrs of drug from the formulation. As per the aim of the present study, final formulation increases the efficacy and reduced the toxicity.

15.0/ Ting Li (2007), Optimized preparation and evaluation of indomethacin transdermal patch (243). The aim of the present study is to develop and evaluate the transdermal formulation of indomethacin. MASCOS 10 used as an acrylate polymer in drug in adhesive matrix formulation. To determine the formulation composition of a transdermal drug delivery system of indomethacin, MASCOS 10 (polyacrylic acid type) pressure sensitive adhesive and azone, L-menthol, M-HEP, IPM and oleic acid were used as a penetration enhancer to prepare a drug-in-adhesive type transdermal patch. DSC was used to evaluate the reactivity and purity of the drug and polymer. Penetration enhancers were evaluated in Franz type side by side diffusion cell using rat skin. Adhesion properties of the patch were evaluated based on peel, tack and shear strength. Adhesion and drug delivery of the final formulation is critical quality attributes for transdermal patch. After investigation, azone and L-menthol were increase the delivery of indomethacin compared to IPM, oleic acid and Tween 80. 5.0% penetration enhancer was suitable to improve the delivery and to get the optimum adhesion properties. In conclusion, indomethacin is suitable candidate for transdermal patch development.

16.0/ Somasundaram Jayaprakash(2010), Design and evaluation of monolithic drug-in-adhesive transdermal patches of meloxicam (244). The aim of the present study is to develop and evaluate the monolithic transdermal formulation of meloxicam. They used ethyl cellulose (EC), hydroxy propyl methyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP) as a polymer and different type of plasticizers in preparation of patch by solvent casting method. The interaction between polymer and drug were investigated by help of FTIR. After preparation of transdermal patches, prepared patches was evaluated for physicochemical characteristics like weight variation, drug content, thickness, folding endurance, percent moisture content, in vitro drug permeation and water vapor transmission and all formulation possessed satisfactory physicochemical
properties. In vitro drug delivery from patch was evaluated for 24hrs from porcine ear skin and it follows the zero order kinetic. Irritation of the patch was evaluated and final formulation exhibits no irritation and best pharmacodynamics activity with respect to commercially available transdermal patch of diclofenac. Transdermal patch of meloxicam is suitable for 24 hr drug delivery with patient comfortless.

17.0/ Bing Cai(2012), A New Drug Release method in Early Development of Transdermal Drug Delivery Systems (245). The aim of the present study is to develop the drug release method for transdermal formulation. In vitro drug delivery from formulation with help of Franz diffusion cell is acceptable for many of the authorities but to correlate with in vivo drug delivery is not possible. Sometimes in vitro result cannot match with in vivo drug release. Durogesic transdermal patch of fentanyl was used as model patch for evaluation and USP apparatus 2 and 5 used as a model instrument for evaluation. Transdermal patches were placed on artificial membrane with three moisture level and withdraw the sample on six time points and evaluate by reverse phase high pressure liquid chromatography method. Synthetic skin simulator method used to compare with conventional drug delivery system and SSS was delivered the drug similar to label claim given of duragesic patch. Drug delivery from patch was increase with increase the moisture level on the synthetic skin. New method of the drug delivery with artificial drug will be used for initial development of formulation differentiate.

18.0/ Ankur Gupta (2007), Design and Development of a proniosomal Transdermal Drug Delivery System for Captopril (148), the aim of the present study is to develop and evaluate the captopril gel using pronisomal gel. Pronosomal gel is using the carrier for transdermal drug delivery of the captopril. As per physicochemical properties of captopril, it is the suitable candidate for transdermal drug delivery. Captopril is entrapped encapsulated into different formulation of the pronisomal gel. Pronisomal gel composed of different ratio of cholesterol, sorbitan fatty acid esters, lecithin by coacervation phase separation method. After formation of the captopril gel, formulation was evaluated for drug entrapment, drug release, vesicle count and size of the vesicle.
After finalization of the formulation, final formulation was evaluated in stability at different storage condition. Only 66.7-78.7% of captopril was loaded on pronisomal gel encapsulation method. Different formulations of pronisomes gel were characterized by transmission method of electron microscopy. Results indicate that captopril was release from entrapped vesicles and at refrigerator higher drug retention was observed. After finalization of the formulation, final formulation was evaluated in stability at different storage condition. After all investigation, it will be concluded that pronisomal gel formulation of captopril are providing promising prolonged drug delivery of captopril. After finalization of the formulation, final formulation was evaluated in stability at different storage condition.

19.0/ Sandhu Premjeet (2011), Transdermal drug delivery system (patches), applications in present scenario (34), this review article are based on the application of transdermal formulation in current time. Even after common dosage form, conventional dosage form have many of the drawbacks like poor bioavailability, hepatic metabolism, GIT disturbance, uneven distribution of drug in blood stream. To avoid problem related to the conventional dosage form, there was a need to develop the novel drug delivery system; which can be improve the patient comfort and safety and efficacy of the dosage form thereby decease the size and number of doses. In novel drug delivery system, transdermal formulation or drug delivery through skin is the most interesting dosage form, due to delivery for systemic and delivery by predetermined rate. Delivery of drug from transdermal formulation is more controllable compared conventional dosage form. Transdermal drug delivery may be active or passive type delivery through skin which can provide an alternative route for parenteral application. Delivery of drug from transdermal formulation depend upon the size, amount of drug, excipients composition and application site. Many of the transdermal dosage form are available in the market. Mainly matrix type of the dosage form is available.

20.0/ Sonia Dhiman (2011), Transdermal patches: a recent approach to new drug delivery system (137). This review article is based on the application of transdermal formulation in current time. Even after common dosage form, conventional dosage form
have many of the drawbacks like poor bioavailability, hepatic metabolism, GIT disturbance, uneven distribution of drug in blood stream. To avoid problem related to the conventional dosage form, there was a need to develop the novel drug delivery system; which can be improve the patient comfort and safety and efficacy of the dosage form thereby decease the size and number of doses. In novel drug delivery system, transdermal formulation or drug delivery through skin is the most interesting dosage form, due to delivery for systemic and delivery by predetermined rate. Delivery of drug from transdermal formulation is more controllable compared conventional dosage form.

Transdermal drug delivery may be active or passive type delivery through skin which can provide an alternative route for parenteral application. Delivery of drug from transdermal formulation depend upon the size, amount of drug, excipients composition and application site. Many of the transdermal dosage form are available in the market. Mainly matrix type of the dosage form is available.

21.0/ R. Panner Selvam (2010), Transdermal drug delivery systems for antihypertensive drugs - A review (127). This review article is based on the transdermal formulation of anti-hypertensive drug delivery system. Hypertension is the most common disease in worldwide due to drastic change in life style. Even after common dosage form, conventional dosage form have many of the drawbacks like poor bioavailability, hepatic metabolism, GIT disturbance, uneven distribution of drug in blood stream. To avoid problem related to the conventional dosage form, there was a need to develop the novel drug delivery system; which can be improve the patient comfort and safety and efficacy of the dosage form thereby decease the size and number of doses.

This review article is considering the improvement of the bio availability of antihypertensive drug from transdermal drug delivery route. In novel drug delivery system, transdermal formulation or drug delivery through skin is the most interesting dosage form, due to delivery for systemic and delivery by predetermined rate. Delivery of drug from transdermal formulation is more controllable compared conventional dosage form. Transdermal drug delivery may be active or passive type delivery through skin which can provide an alternative route for parenteral application. List of antihypertensive drug that can be used in transdermal drug delivery is timolol maleate,
nicardipine hydrochloride, captopril, atenolol, metoprolol tartrate, clonidine, indapamide, labetolol, pinacidil, verapamil hydrochloride, nitrendipine, nifedipine, nicorandil, propranolol hydrochloride, diltiazem hydrochloride, amlodipine besilate, carvedilol and lisinopril.

22.0/ Nikhil Sharma (2010), a review: Transdermal drug delivery system: a tool for novel drug delivery system (246). This review article is related to the transdermal formulation as a novel drug delivery system. Even after common dosage form, conventional dosage form have many of the drawbacks like poor bioavailability, hepatic metabolism, GIT disturbance, uneven distribution of drug in blood stream. To avoid problem related to the conventional dosage form, there was a need to develop the novel drug delivery system; which can be improve the patient comfort and safety and efficacy of the dosage form thereby decease the size and number of doses. Human skin is the largest organ of the body and that can be used for the delivery of the drug. In every square centimeter on an average 10-70 no of hair follicles and 200-250 no of sweet ducts are present. Due to encouraging characteristic, human skin is the most attracting site of the application for novel pharmaceutical dosage form. Delivery of drug from transdermal formulation is more controllable compared conventional dosage form. Transdermal drug delivery may be active or passive type delivery through skin which can provide an alternative route for parenteral application. Outermost layer of the skin is stratum corneum, main obstacles for the delivery of the drug from skin. Now days many of the technics are available to improve the delivery of the drug.

23.0/ Hiren Patel (2013), Formulation and Evaluation of Transdermal Gel of Sildenafil Citrate (247). The aim of the present investigation is to develop and evaluate the transdermal formulation of the sildenafil citrate. As per physicochemical properties of model drug, sildenafil citrate is suitable candidate for transdermal drug delivery. Sildenafil citrate is used for the disorder related to the premature ejaculation. Transdermal gel based formulation has more importance compared to cream and ointment bases. Carbopol 934P and PEG 400 were used as polymer and penetration enhancer at different proportions. Drug content, FTIR spectra, drug content,
Spreadability, viscosity and pH determination were the testing parameter for sildenafil citrate gel formulation. Out of 8 formulations, F2 is the best formulation with concern of Spreadability and drug release from formulation. Goat skin was used as a barrier layer for flux study and evaluate for 4 hrs. Final formulation is also charged in stability at room temperature and accelerated condition and as per results, final formulation is stable in both the storage condition. Based on the evaluation and stability study, it was concluded that, sildenafil citrate gel formulation showed good Spreadability, consistency, stability and homogeneity. So, transdermal formulation of sildenafil had broad vision for transdermal formulation.

24.0/ Kalpana S. Paudel (2010), Challenges and opportunities in dermal/transdermal delivery (8), This review article is related to the problem to develop and scope of the transdermal formulation. Transdermal formulation development is the most exciting field for novel drug delivery system. Many of the transdermal formulations are available in the pharmaceutical market. However, constrain related to the drug selection and barrier of skin. Many of the investigation related to the permeation of the drug and irritation of the drug molecules is carry out in novel system. Novel techniques are related to the permeation of the hydrophilic and lipophilic molecules from skin and decrease the irritation of drug molecules and excipients during and after application. Many of the new drug molecules are in the investigation at the stage of the clinical study. Due to increase the market requirement and many of the pharmaceutical company involving in the development, Transdermal formulation has the great future in pharmacy.

25.0/ G. D. Gupta (2013), Formulation and evaluation of transdermal gel of ketorolac tromethamine along with Neem oil, Tulsi oil and Oleic acid as penetration enhancers (148). The present investigation is relaed to the transdermal formulation of the ketorolac trimethamine with evaluating the effect of the penetration enhancers like neem oil, tulsi oil and oleic acid. K etorolac is non-steroidal anti-inflammatory drug and used for the treatment of nociceptive somatic pain. Carbopol 940 and carbopol Ultrez 10NF polymer were used in polymer with three penetration enhancers. Evaluate the delivery of drug with help of three concentrations 2.0%, 3.0%
and 4.0% of penetration enhancer and as per the delivery profile, oleic acid is found the best enhancer for tromethamine. After finalization of the formulation polymer, Carbopol 940 and Carbopol Ultrez 10NF is the best polymer used with natural penetration enhancer for preparation of transdermal gel formulation. All formulation was evaluated for the spreadability, drug content, viscosity, pH, and release of drug from the formulation. All prepared formulation had the good spreadability, homogeneity and absence of lumps. Compared with other penetration enhancer, oleic acid deliver the higher tromethamine with compared to other penetration enhancers. Drug delivery from the formulation was evaluated using the Keshary-Chien type diffusion cell. They evaluate the release of tromethamine with respect to the zero order, first order and higuchi release kinetic.

26.0/ K. P. Sampath Kumar (2010), Transdermal drug delivery system-a novel drug delivery system and its market scope and opportunities (133), This review article is related to the transdermal formulation scope and opportunities. Even after common dosage form, conventional dosage form have many of the drawbacks like poor bioavailability, hepatic metabolism, GIT disturbance, uneven distribution of drug in blood stream. To avoid problem related to the conventional dosage form, there was a need to develop the novel drug delivery system; which can be improve the patient comfort and safety and efficacy of the dosage form thereby decease the size and number of doses. In novel drug delivery system, transdermal formulation or drug delivery through skin is the most interesting dosage form, due to delivery for systemic and delivery by predetermined rate. Delivery of drug from transdermal formulation is more controllable compared conventional dosage form. Transdermal drug delivery may be active or passive type delivery through skin which can provide an alternative route for parenteral application. Decrease the dosing due to lower metabolization pathway for transdermal drug delivery. Every year 12% increase in revenues in transdermal market and total market of transdermal in 2010 is increase up to $21.5 billion and $31.5 billion expectation in the year of 2015.
27.0/ Dipen Patel (2012), the Pharma Innovation, Transdermal Drug Delivery System: A Review (17), this article is related to the transdermal formulation, the novel innovation in pharma industry. Transdermal drug delivery system, patch is the type of dosage for that delivers the drug from skin to systemic blood stream. Patches are available to deliver the drug for local as well as systemic application. Patches are mainly used for the controlled deliver of the drug and predetermine rate delivery. Human skin is the largest organ of the body and that can be used for the delivery of the drug. In every square centimeter on an average 10-70 no of hair follicles and 200-250 no of sweet ducts are present. Due to encouraging characteristic, human skin is the most attracting site of the application for novel pharmaceutical dosage form. Delivery of drug from transdermal formulation is more controllable compared conventional dosage form. Transdermal drug delivery may be active or passive type delivery through skin which can provide an alternative route for parenteral application. Outermost layer of the skin is stratum corneum, main obstacles for the delivery of the drug from skin. Now days many of the technics are available to improve the delivery of the drug. A very wide variety of active pharmaceutical ingredients are now available to deliver through transdermal patch form.

28.0/ Umesh Ramchandani (2012), Development and Evaluation of Transdermal Drug Delivery System of Ketoprofen Drug with Chitosan for Treatment of Arthritis (174), The present investigation is related to the development and evaluation of the ketoprofen transdermal drug delivery system. Transdermal formulation has the many of the superiority compared to conventional type of the dosage form like avoid first pass metabolism, higher bioavailability, zero order drug delivery, study state drug delivery, non-invasive technique. Transdermal formulation is the adhesive bandage having dry matrix with drug and apply on skin to get the systemic or local availability. Present investigation concentrated on the development and evaluation of the ketoprofen transdermal patch with chitosan as a polymer for treatment of arthritis. Arthritis is related to the inflammation of the joint of the any part of the body. Osteoarthritis is the common form of the joint inflammation. Osteoarthritis is result of joint infection or trauma of the body joints. Ketoprofen is medically prescribed drug as a non-steroidal anti-
inflammatory class. It has also analgesic and antipyretic application. Chitosan is used as a polymer in ketoprofen transdermal patch. Chitisan is nontoxic, hydrophilic, biocompatible polymer. Solvent casting method is used for preparation of transdermal patch.

29.0/ Alpana Ram (2012), Proniosomal provesicular system for transdermal delivery of hydralazine for hypertension (113), Aim of the present investigation is to prepare the transdermal formulation of the hydralazine pronisomal provesicular system for hypertension. Hydralazine is used for the prophylaxis treatment of hypertension. Pronisomal provesicular system is efficient to deliver the drug from system for extended time period. Pronisomal gel composed of the different ratio of the sorbitan ester, lecithin and cholesterol. Coacervation phase separation method used to prepare the pronisomal gel. Total 14 formulations were prepared and evaluate for the different evaluation parameters. Evaluation parameters are vesicle count, size of the vesicular, entrapped drug, release of the drug from matrix and stability study for 6 week of the vesicular. After evaluation, thermodynamic law of release applies to characterize the delivery profile. Size of the vesicle of pronisomal gel was evaluated by the electron microscopy and drug release from the vesicle is evaluated by the help of diffusion cell through artificial cellophane membrane. At refrigerated condition, hydralazine deliver the higher amount of drug, It is proof that pronosomal vesicle are the deliver the drug from prolong period of time and have good stability. As per evaluation of drug delivery from cellophane membrane, pronisome gel is suitable for drug deliver for extended period of time.

30.0/ Abid Hussain (2012), Development of a novel ketoprofen transdermal patch: Effect of almond oil as penetration enhancers on in-vitro and ex-vivo penetration of ketoprofen through rabbit skin (148). The aim of the present investigation is to prepare the transdermal patch of the ketoprofen and use the almond oil as a natural penetration enhancer and evaluate the delivery of the ketoprofen from rabbit skin. Delivery of the drug is depend upon the particle size of the drug, so before formulation particle size of the ketoprofen was evaluated by particle size analyzer. Formulations of ketoprofen with different concentration of almond oil were prepared and evaluated for
the homogeneity, pH, skin irritation, consistency, spreadibility and drug content. Franz diffusion cell was used to evaluate the delivery of ketoprofen from formulation with help of artificial membrane and rabbit skin. Also from drug delivery, kinetic model was prepared to evaluate the release patterns of the ketoprofen. Release profile of the different formulations was evaluated by the ANOVA. Final formulation was also evaluated for the stability study. It was concluded that almond oil used as a penetration enhancer for ketoprofen transdermal gel formulation.

31.0/ Anisree G S (2012), Fabrication and evaluation of domperidone transdermal films (249), the aim of the present investigation is to formulation and evaluation of the domperidone transdermal patch formulation. Domperidone is suitable candidate for transdermal drug delivery through skin due to first pass metabolism and finally having the poor bioavailability. HPMC, EC and eudragit RS-100 polymer used to prepare the transdermal formulation of the domperidone. HPM was used as a main polymer with the ratio of the EC and eudragit RS-100. PEG was used as a plasticizer in final formulation. Final formulation was evaluated for the different evaluation parameter like, in vitro permeation studies, physico chemical parameters and stability studies. FTIR had been used to evaluate the compatibility study of drug and excipients. In-vitro drug delivery was performed by Franz type diffusion cell with help of cellophane membrane. After finalization of formulation, final formulation was evaluated for the 24 hours delivery and that was showed the 99.13% drug release from film. Film had the ratio of 7:3 of HPMC and EC was showed good delivery and stability with compared to other formulations.

32.0/ Kooriyattil Naseera (2012), Formulation, optimization and evaluation of matrix type of transdermal system of simvastatin using permeation enhancers, The aim of the present investigation is to prepare the transdermal formulation of the simvastatin. Optimizes the delivery and evaluate the different evaluation parameters after finalization of the formulation. Simvastatin transdermal formulation is the matrix type single layer formulation. Different ratio of hydrophilic and hydrophobic polymer used to prepare the patch by solvent evaporation method. FTIR was used to evaluate the compatibility of the excipients and simvastatin. Different ratio of HPMC, EC and
eudragit RL-100 was used to prepare the transdermal patch. After formulation, all formulation were evaluated for thickness, tensile strength, folding endurance, percent flatness, surface pH, swelling index, weight variation, water vapor transmission etc. Franz type of diffusion cell was used to evaluate the delivery of drug from patch with use of dialysis membrane and goat skin. Final formulation was evaluated for delivery by using different penetration enhancers like DMSO, Oleic acid, eugenol and menthol. Out of total 16 formulation, F12D4 with menthol as penetration enhancer was showed the best formulation as delivery related and considered the optimized formulation.

33.0/ Kunal N Patel (2012), **Formulation and characterization of drug in adhesive transdermal patches of diclofenac acid** (161), the aim of the present investigation is to prepare the transdermal patch of diclofenac acid. Pressure sensitive adhesive like acrylate and silicone was used to prepare the patch by solvent evaporation technique. Labrasol, oleic acid, and triacetin were used in different concentration as penetration enhancers for diclofenac acid transdermal formulation. Polyethylene used as backing film and silicone coated polyester film used as release liner to prepared transdermal formulation. Formulation prepared by diclofenac acid were evaluated for thickness, percentage moisture absorption, drug content, tensile strength, weight variation, folding endurance and % elongation. All formulation was also charged in stability study and all prepared formulation had the good physical stability. Drug delivery through skin was evaluated by Franz type diffusion cell. Formulation containing 85% adhesive, 5% drug and 10% triacetin showed good drug delivery compared to other formulation. Final formulations follow the zero order release kinetic. Out of total 12 formulations, F3 formulation had shown the optimum release and all had the stable formulation in stability study. All stability data and physic chemical result of the diclofenac transdermal system indicate that diclofenac acid is suitable for formulation development of transdermal patch.

34.0/ Rajan Rajabalaya (2008), **Design of a matrix patch formulation for long-acting permeation of diclofenac potassium**, the aim of the present investigation is to prepare the transdermal patch of diclofenac potassium. Pressure sensitive adhesive like
acrylate and silicone was used to prepare the patch by solvent evaporation technique. Labrasol, oleic acid, and triacetin were used in different concentration as penetration enhancers for diclofenac potassium transdermal formulation. Polyethylene used as backing film and silicone coated polyester film used as release liner to prepared transdermal formulation. Formulation prepared by diclofenac potassium were evaluated for thickness, percentage moisture absorption, drug content, tensile strength, weight variation, folding endurance and % elongation. All formulation was also charged in stability study and all prepared formulation had the good physical stability. Drug delivery through skin was evaluated by Franz type diffusion cell. Total 10 formulations were prepared and out of that formulation, it was found that all the formulation followed the fickian diffusion for release of the drug from formulation but except two formulations that follow the higuch release profile. Permeation profile of the drug was depended upon the concentration of the drug in the formulation. Final conclusion for diclofenac delivery was, DBT were better choice compared to other polymer.

35.0/ Angelo Antonini (2010), Rotigotine transdermal patch in the management of Parkinson’s disease (PD) and its night-time use for PD-related sleep disorders, This review article is based on the application of transdermal formulation in current time. Even after common dosage form, conventional dosage form have many of the drawbacks like poor bioavailability, hepatic metabolism, GIT disturbance, uneven distribution of drug in blood stream. To avoid problem related to the conventional dosage form, there was a need to develop the novel drug delivery system; which can be improve the patient comfort and safety and efficacy of the dosage form thereby decease the size and number of doses. In novel drug delivery system, transdermal formulation or drug delivery through skin is the most interesting dosage form, due to delivery for systemic and delivery by predetermined rate. Delivery of drug from transdermal formulation is more controllable compared conventional dosage form. Transdermal drug delivery may be active or passive type delivery through skin which can provide an alternative route for parenteral application. Delivery of drug from transdermal formulation depend upon the size, amount of drug, excipients composition and
application site. Many of the transdermal dosage form are available in the market. Mainly matrix type of the dosage form is available.

36.0/ Sonia Dhiman (2011), Transdermal patches: a recent approach to new drug delivery system (18), this review article is based on the application of transdermal formulation in current time. Even after common dosage form, conventional dosage form have many of the drawbacks like poor bioavailability, hepatic metabolism, GIT disturbance, uneven distribution of drug in blood stream. To avoid problem related to the conventional dosage form, there was a need to develop the novel drug delivery system; which can be improve the patient comfort and safety and efficacy of the dosage form thereby decease the size and number of doses. In novel drug delivery system, transdermal formulation or drug delivery through skin is the most interesting dosage form, due to delivery for systemic and delivery by predetermined rate. Delivery of drug from transdermal formulation is more controllable compared conventional dosage form. Transdermal drug delivery may be active or passive type delivery through skin which can provide an alternative route for parenteral application. Delivery of drug from transdermal formulation depend upon the size, amount of drug, excipients composition and application site. Many of the transdermal dosage form are available in the market. Mainly matrix type of the dosage form is available.

37.0/ Sandhu Premjeet (2011), Transdeomal drug delivery system (patches), applications in present scenario (34), this review article is based on the application of transdermal formulation in current time. Even after common dosage form, conventional dosage form have many of the drawbacks like poor bioavailability, hepatic metabolism, GIT disturbance, uneven distribution of drug in blood stream. To avoid problem related to the conventional dosage form, there was a need to develop the novel drug delivery system; which can be improve the patient comfort and safety and efficacy of the dosage form thereby decease the size and number of doses. In novel drug delivery system, transdermal formulation or drug delivery through skin is the most interesting dosage form, due to delivery for systemic and delivery by predetermined rate. Delivery of drug from transdermal formulation is more controllable compared conventional dosage form.
Transdermal drug delivery may be active or passive type delivery through skin which can provide an alternative route for parenteral application. Delivery of drug from transdermal formulation depend upon the size, amount of drug, excipients composition and application site. Many of the transdermal dosage form are available in the market. Mainly matrix type of the dosage form is available.

38.0/ Prodduturi S (2010), Transdermal delivery of fentanyl from matrix and reservoir systems: effect of heat and compromised skin (249), The aim of the present investigation is to evaluate the delivery of fentanyl from matrix and reservoir type of transdermal system and see the effect of heat and compromised skin. Many of the serious adverse effect including patient death were received to USFDA from patient and caregiver due to uneven delivery of fentanyl from patch. Many of the marketed formulations are available to deliver the fentanyl from skin. To get the proper understanding of drug delivery from patch only durogesic and mylan fentanyl transdermal patch was evaluated. Both formulation were evaluated to see the effect of heat and compromised skin. Other than human cadaver skin, additional synthetic membrane were evaluated the delivery of fentanyl from matrix and made the useful model to simulate the human skin. Both formulations deliver the similar amount of fentanyl from dosage form but when applied on intake skin at normal condition but at higher temperature fentanyl deliver the twice amount compared to control room temperature for initial 12 hrs. On compromised skin, fentanyl delivers the higher in matrix formulation compared to reservoir formulation. Delivery of fentanyl from artificial membrane was unpredictable from both of the formulation.

39.0/ Anna M. Wokovich (2011), Evaluating elevated release liner adhesion of a transdermal drug delivery system (TDDS): A study of Daytrana™ methylphenidate transdermal system (105). The aim of the present study is to evaluate the adhesion of release liner with matrix during application. Many of the complaints are submitted from health care provider regarding problem of removal of release liner during application of Daytrana™ Transdermal formulation of methylphenidate. Daytrana™ transdermal formulation is packed in papare pouch and papare pouch is the moisture permeable. The aim of the project is to determine the packaging system of the Daytrana™ create
the difficulty in removal of the release liner during application. Pouch is packed within sealed tray containing desiccant and compared with the pouched patch in open tray. Both pouched was charged into controlled environment condition, 25°C and 60% relative humidity for 30 days and afterwards, release the release liner from patch using 90° at 300mm/min peel speed was performed. Daytrana™ was evaluated for two strengths, 10mg/9h TDDS and the 15mg/9h TDDS in both of the strength open chamber required less force compared to closed chamber for removal of the release liner and other observation was that there were significant difference in force required to remove the liner of old and new lot of the closed chamber but not significant difference in open chamber. Overall conclusion was that, for Daytrana™ storage condition particularly humidity in storage area is effect the product performance.

40.0/ Ashish A. Heda (2010), Development and In vitro Evaluation of Betahistine Adhesive-Type Transdermal Delivery System (90), the aim of the [present investigation is to develop and in vitro evaluation of the transdermal formulation of betahistine formulation. Acrylate, silicone and polyisobutylene pressure sensitive adhesive was used to develop the transdermal formulation of the betahistine. Solvent casting method was used to manufacture the transdermal patch. Pressure sensitive adhesive like hydrophilic acrylate, acrylate vinylacetate, acrylic non-curing, styrenic rubber and polyisobutylene rubber adhesive were evaluated for compatibility with drug, miscibility, drug loading, effect on tack and permeation through guinea pig skin. Same properties were evaluated for penetration enhancers. As per stability results, formulation with AVA and HA were stable compared to other formulation. If we increase the drug loading in formulation, significant fall down in tack properties were observed. Permeation of drug from guinea pig skin demonstrated that polymer of HA was deliver the significant amount of drug from formulation compared to AVA. Compared with other penetration enhancers, Oleic acid with 2.0% showed good enhancement and tack properties up to 36 hr compared to other penetration enhancers. Formulation with 2.0% oleic acid with HA showed demonstrated a good potential for further development.
41.0/ Seyed Mojtaba Taghizadeh (2011), A New Liposomal-Drug-in-Adhesive Patch for Transdermal Delivery of Sodium Diclofenac (250). The aim of the present investigation is to evaluate the delivery of diclofenac from matrix and reservoir type of transdermal system and see the effect of heat and compromised skin. Many of the serious adverse effect including patient death were received to USFDA from patient and caregiver due to uneven delivery of diclofenac from patch. Many of the marketed formulations are available to deliver the diclofenac from skin. To get the proper understanding of drug delivery from patch only durogesic and mylan transdermal patch was evaluated. Both formulation were evaluated to see the effect of heat and compromised skin. Other than human cadaver skin, additional synthetic membrane were evaluated the delivery of fentanyl from matrix and made the useful model to simulate the human skin. Both formulations deliver the similar amount of diclofenac from dosage form but when applied on intake skin at normal condition but at higher temperature diclofenac deliver the twice amount compared to control room temperature for initial 12 hrs. On compromised skin, diclofenac delivers the higher in matrix formulation compared to reservoir formulation. Delivery of diclofenac from artificial membrane was unpredictable from both of the formulation.

42.0/ V. G. Jamakandi (2009), Formulation, characterization, and evaluation of matrix-type transdermal patches of a model antihypertensive drug (251), Nicorandil is used as antiaginal drug and this is suitable candidate for transdermal formulation. Transdermal formulation is evaluated for different evaluation parameter. Other than human cadaver skin, additional synthetic membrane were evaluated the delivery of fentanyl from matrix and made the useful model to simulate the human skin. Final formulation is evaluated for the physicochemical properties and in-vitro evaluation for drug delivery. If we increase the drug loading in formulation, significant fall down in tack properties were observed. Permeation of drug from guinea pig skin demostrateted that polymer of HA was deliver the significant amount of drug from formulation compared to AVA. Total six formulations were study for the chemical and physical parameter evaluation. Among all six formulations, 6.0% DMSO formulation with HPMC as a
polymer adhesive formulation showed the maximum drug delivery in in-vitro drug delivery evaluation.

**43.0/ Janardhanan Bagyalakshmi (2008),** *Formulation development and in vitro and in vivo evaluation of membrane-moderated transdermal systems of ampicillin sodium in ethanol: pH 4.7 buffer solvent system (252).* Aim of the present investigation is to develop the transdermal drug delivery system of ampicillin sodium and evaluated for drug delivery and physicochemical properties. The membrane type of transdermal drug delivery system was prepared for delivery of ampicillin for better controllable drug delivery. Hydrophilic and hydrophobic type of polymer adhesive, e.g. HPMC, MC, chitosan, cellulose acetate phthalate and sodium alginate were used for preparation. Transdermal patch was prepared by solvent casting methods. Compared to other type of formulation, SA patch deliver the higher amount of drug compared to other type of the polymer. SA patch content higher amount of the moisture compared to other polymer. Based on in-vivo study, it was concluded that hydrophilic patch deliver the higher amount of ampicillin and it can be a alternative of intravenous administration with minimum adverse effect. Ampicillin sodium can be delivered through the skin by transdermal formulation with help of hydrophilic sodium alginate polymer and HPMC as the control the deliver as a rate controlling membrane. Final formulation can deliver the dose as per requirement and without the irritation and so it can be improve the patient compliance.

**44.0/ Murthy T.E.G.K. (2008),** *Aim of the present investigation is to develop the transdermal formulation of the carvidilol from hydrophilic and hydrophobic polymer (177).* Solvent evaporation method used to prepare the transdermal patch, different combination of polymer such as EC: HPMC, EC: PVP K-30 and EC: Carbopol-934 used to develop transdermal patch. After formulation development, patches were evaluated for film’s uniformity, folding endurance and transparency. Initial optimization did on above parameter and finally six formulations were selected for further evaluation. All six formulations had good physicochemical properties, uniformity, drug content and thickness. Franz type of diffusion cells with hairless rat skin were used to see the
delivery of drug from patch. Based on physicochemical and delivery from patch, two formulation A-3 and A-5 were selected as a best formulation. As per stability information, final two formulations have good stability. Final formulation was evaluated for the different evaluation parameter like, drug release characteristic, thickness, appearance, and drug release and in-vitro permeation. Final formulation follows the zero order kinetic and controlled by diffusion mechanism.

45.0/ A. Wahid (2008), Preparation and evaluation of transdermal drug delivery system of etoricoxib using modified chitosan (184). The aim of the present study is to develop the transdermal drug delivery system of etoricoxib with hydrophilic modified polymer. In this study chitosan has been modified by chemical reaction with two type of aldehyde e.g. propionaldehyde and acetaldehyde. Drug free chitosan with two different kind of chitosan were evaluated for different type of evaluation parameter. Chemical reaction of chitosan with different aldehyde was confirmed by FTIR investigation. Etoricoxib is finally incorporated in film of chitosan alone and other two type of chemically modified chitosan. Glycerol were used as plasticizer and sodium citrate were used as a cross linker in final formulation. Drug delivery was evaluated with franze type diffusion cell with help of dialysis membrane and rat skin. All formulation were evaluated for different evaluation parameter, bursting strength, swelling index, moisture uptake, thickness uniformity, drug content uniformity, tensile strength, percent elongation at break, percent flatness, water vapor transmission rate and in vitro drug permeation study.

46.0/ Shaila Lewis (2007), Pharmacokinetic evaluation of developed nicotine transdermal system (253), the aim of the present study is to evaluate the pharmacokinetic parameter of already developed transdermal drug delivery system of nicotine. Nicotine is used for withdrawal symptoms of nicotine and has provided the effective assistance to smokers. Nicotine gives the irritation on application on skin so new formulation of nicotine transdermal patch was developed to minimize the side effect of nicotine. Two type of nicotine patch Habitrol™ and Nicoderm® systems were evaluate for comparable study state permeation rate and pharmacokinetic study of two
formulation indicate the nicotine deliver up to 24hrs from patch through study state level. Nicotine transdermal patch was applied to healthy smokers on upper fore arm and evaluate the plasma concentration after single application. Patch was used for application was 12cm² and plasma concentration at maximum level was 14.5 ng/ml for 24 hrs. Two ethnic groups were evaluating for delivery of nicotine from patch. High nicotine drug deliver from transdermal system from Taiwanese smokers compared to American smokers in all three type of formulation. As far as result concert, all three formulations have good usefulness in smoking cessation. Delivery of developed patch and marketed patch had the similar.

47.0/ S. R. Shahi (2007), Effect of enhancers on topical delivery of ketorolac tromethamine studied the effect of various penetrations (254). The aim of the study is to see the effect of enhancers on topical delivery of ketorolac tromethamine. Isopropyl myrisytate, dimethyl sulphoxide, benzyle alcohol and oleic acid are used as a chemical penetration enhancer and menthol oil and eucalyptus oil is used as a natural penetration enhancer. Evaluate the natural penetration enhancer and chemical penetration enhancers for delivery of drug from patch. Rat skin and artificial membrane was used to evaluate the penetration of drug from patch. Delivery of drug from transdermal formulation is more controllable compared conventional dosage form. Transdermal drug delivery may be active or passive type delivery through skin which can provide an alternative route for parenteral application. Delivery of drug from transdermal formulation depend upon the size, amount of drug, excipients composition and application site. DMSO gives highest delivery and benzyl alcohol gives lowest delivery of ketorolac from transdermal patch. Ketorolac tromithamine is suitable candidate for transdermal drug delivery.

48.0/ Vanja K (2006), Pre formulation studies of methotrexate for assessing its suitability for transdermal vesicular drug delivery system (255), The aim of the present investigation is to calculate the solubility of the methotrexate by fedor method and also do the pre-formulation study of methotrexate. Apart from the solubility study, permeability of methotrexate was carried out by Franz type diffusion cell using dialysis
and cellophane membrane as artificial and rat skin and egg shell membrane as rat skin as a biological membrane. Drug delivery of methotrexate indicated that dialysis membrane and egg shell membrane deliver the similar properties of the rat skin compared with cellophane.

49.0/ Saxena M (2006), Formulation and evaluation of transdermal patches of Metaclopramide hydrochloride (256), the aim of the present investigation is to develop and evaluate the transdermal formulation of the metoclopramide HCL. Polyvinyl alcohol and polyvinyl pyrollidone was used as a polymer. Metaclopramide hydrochloride is suitable candidate for transdermal application and it is used in nausea and vomiting. After preparation of the transdermal patch, formulation was evaluated for physicochemical properties like weight variation, thickness, moisture uptake, moisture content and permeation of drug. In vitro drug delivery from patch was evaluated by Franz diffusion a cell and initial bursting was observed during initial period of application and afterward drug was release slowly up to 12 hr. All formulation were put into stability study and stability study indicated that all the formulation was release the drug up to 12hr and also has good physical stability at 40°C and 75% RH for 6 months.

50.0/ Rajagopal K (2005), Designing and Evaluation of Transdermal Patches of Nimesulide (257), The aim of the present study is to develop the transdermal patch of Nimesulide and evaluate as per transdermal formulation. Four different type of polymer used to prepare the transdermal system. Different type of penetration enhancer was used to improve the penetration of nimesulide. Dibutyl phthalate was used as plasticizer. After preparation of the transdermal patch, formulation was evaluated for physicochemical properties like weight variation, thickness, moisture uptake, moisture content and permeation of drug. In vitro drug delivery from patch was evaluated by Franz diffusion a cell and initial bursting was observed during initial period of application and afterward drug was release slowly up to 12 hr. Compared with other formulation, HPMC: PVP formulation deliver the highest amount of drug. Drug followed the zero order release kinetics and Higuchi model for drug delivery from all transdermal formulation of nimesulide.
51.0/ Sadhna Gupta (2005), Effective and controlled transdermal delivery of metoprolol tartarate (258), the aim of the present investigation is to develop the transdermal formulation of metoprolol tartarate and evaluates the patch as per transdermal evaluation parameters. Eudragit and HPMC used as polymer for transdermal patch formulation. After preparation of the transdermal patch, formulation was evaluated for physicochemical properties like weight variation, thickness, moisture uptake, moisture content and permeation of drug. In vitro drug delivery from patch was evaluated by Franz diffusion a cell and initial busting was observed during initial period of application and afterward drug was release slowly up to 12 hr. In the ratio of 40:60 of Eudragit RL and HPMC showed the delivery 87.5µg/h/cm² of metoprolol tartarate for 24 hr. Transdermal patch of metoprolol tartarate deliver the better and constant drug compared to the oral administration.

52.0/ Ramesh Panchangula (2005), Transdermal delivery of naloxone: skin permeation, pharmacokinetic, irritancy and stability studies (259), The aim of the present investigation is to develop the naloxone transdermal patch and evaluate the patch for stability, irritancy, pharmacokinetic and skin permeation studies. Reservoir type of transdermal patch of naloxone was prepared and evaluate. After preparation of the transdermal patch, formulation was evaluated for physicochemical properties like weight variation, thickness, moisture uptake, moisture content and permeation of drug. In vitro drug delivery from patch was evaluated by Franz diffusion a cell and initial busting was observed during initial period of application and afterward drug was release slowly up to 12 hr. Compared to different type of penetration enhancers, oleic acid and propylene glycol have been used to improve the penetration of naloxone. Final formulation was stable, safe and efficacious upon single and multiple applications.

53.0/ Schurad B. (2005), Evaluation of the Transdermal Permeation behavior of Proterguride from Drug in Adhesive Matrix Patches through hairless Mouse Skin (260), The aim of the present study is to develop the transdermal patch of proterguride and evaluate the patch as per evaluation parameters. Transdermal drug in adhesive
matrix type of system was prepared to evaluate the delivery and permeation behavior. After preparation of the transdermal patch, formulation was evaluated for physicochemical properties like weight variation, thickness, moisture uptake, moisture content and permeation of drug. In vitro drug delivery from patch was evaluated by Franz diffusion a cell and initial busting was observed during initial period of application and afterward drug was release slowly up to 12 hr. Compared to different adhesive, Gelva® showed the good physical stability, moderate higher flux and good skin adhesion and it was suitable polymer for proterguride transdermal system.

54.0/ Kanikkannan N. (2004), A Formulation and In Vitro Evaluation of Transdermal Patches of Melatonin (261), The aim of the present investigation is to develop the transdermal drug delivery system of melatonin and evaluate the in vitro drug delivery. Isopropyl myrisytate, dimethyl sulphoxide, benzyle alcohol and oleic acid are used as a chemical penetration enhancer and menthol oil and eucalyptus oil is used as a natural penetration enhancer. Evaluate the natural penetration enhancer and chemical penetration enhancers for delivery of drug from patch. Rat skin and artificial membrane was used to evaluate the penetration of drug from patch. Delivery of drug from transdermal formulation is more controllable compared conventional dosage form. Transdermal drug delivery may be active or passive type delivery through skin which can provide an alternative route for parenteral application. Delivery of drug from transdermal formulation depend upon the size, amount of drug, excipients composition and application site. DMSO gives highest delivery and benzyl alcohol gives lowest delivery of ketorolac from transdermal patch. Ketorolac tromithamine is suitable candidate for transdermal drug delivery.

55.0/ Updesh B. Lade (2011), Design, Formulation and Evaluation of Transdermal Drug Delivery System of Budesonide (237). The aim of the present investigation is to design and formulate and evaluate the budesonide transdermal drug delivery system. As per physicochemical properties, Budesonide is suitable candidate for transdermal drug delivery system. Budaesonide is highly potent steroids. Due to first pass metabolisam and lower systemic availability, Budaesonide is not suitable candidate for
oral drug delivery system. In development, they used Eudragit RL 100, RS, ethyl cellulose and povidone as a polymer with different ration of drug. They used mercury substrate for coating of blend and PEG-400 as a plasticizer. They also evaluate the different penetration enhancers like urea, DMSO on delivery of the budesonide. Final formulations were physically evaluated with regard to drug content, percentage moisture absorption, % elongation thickness, tensile strength, folding endurance and weight variation in dry matrix. Thay also evaluate the skin irritation study. They prepared the patch and evaluate the % of permeation on different moisture contents. As per the investigation, PVP and Eudragit protect the loss of the water from skin, so it’s provided the more occlusion and increase the penetration of drug.

56.0/ Kunal N Patel (2012), Formulation and characterization of drug in adhesive transdermal patches of diclofenac acid (161), The aim of the present investigation is to develop a monolithic matrix type of transdermal drug delivery system containing Diclofenac acid as a model drug and acrylate adhesive as a pressure sensitive adhesive. Transdermal formulation was manufactured by solvent evaporation method by casting technique. Different type of penetration enhancer like Labrasol, oleic acid and triacetin were also used to improve the penetration of the diclofenac acid. Silicone coated polyester film used as liner and polyethylene monolayer film used as a backing film. Final formulations were physically evaluated with regard to drug content, percentage moisture absorption, % elongation thickness, tensile strength, folding endurance and weight variation in dry matrix. Formulation containing 5.0% diclofenac acid with 10.0% triacetin delivered the desired amount of diclofenac from human cadaver skin using Franz diffusion cell. Delivery of the drug from the system followed the zero order kinetic. Final formulation was also stable in all physical parameters. Out of twelve formulations, F3 has shown optimum formulation for delivery and stability. They also conduct stability and irritation study and final formulation was stable in six month and no irritation.

57.0/ Ankur Gupta (2007), Design and Development of a proniosomal Transdermal Drug Delivery System for Captopril (148), the aim of the present study is to develop
and evaluate the captopril gel using pronisomal gel. Pronosomal gel is using the carrier for transdermal drug delivery of the captopril. As per physicochemical properties of captopril, it is the suitable candidate for transdermal drug delivery. Captopril is entrapped encapsulated into different formulation of the pronisomal gel. Pronisomal gel composed of different ratio of cholesterol, sorbitan fatty acid esters, lecithin by coacervation phase separation method. After formation of the captopril gel, formulation was evaluated for drug entrapment, drug release, vesicle count and size of the vesicle. After finalization of the formulation, final formulation was evaluated in stability at different storage condition. Only 66.7-78.7% of captopril was loaded on pronisomal gel encapsulation method. Different formulations of pronisomes gel were characterized by transmission method of electron microscopy. Results indicate that captopril was release from entrapped vesicles and at refrigerator higher drug retention was observed. After all investigation, it will be concluded that pronisomal gel formulation of captopril are providing promising prolonged drug delivery of captopril.

58.0/ G. D. Gupta (2013), Formulation and evaluation of transdermal gel of ketorolac tromethamine along with Neem oil, Tulsi oil and Oleic acid as penetration enhancers (262), The present investigation is related to the transdermal formulation of the ketorolac trimethamine with evaluating the effect of the penetration enhancers like neem oil, tulsi oil and oleic acid. Ketorolac is non-steroidal anti-inflammatory drug and used for the treatment of nociceptive somatic pain. Carbopol 940 and carbopol Ultrez 10NF polymer were used in polymer with three penetration enhancers. Evaluate the delivery of drug with help of three concentrations 2.0%, 3.0% and 4.0% of penetration enhancer and as per the delivery profile, oleic acid is found the best enhancer for tromethamine. After finalization of the formulation polymer, Carbopol 940 and Carbopol Ultrez 10NF is the best polymer used with natural penetration enhancer for preparation of transdermal gel formulation. All formulation was evaluated for the Spreadability, drug content, viscosity, pH, and release of drug from the formulation. All prepared formulation had the good Spreadability, homogeneity and absence of lumps. Compared with other penetration enhancer, oleic acid deliver the higher tromethamine with compared to other penetration enhancers. Drug delivery from
the formulation was evaluated using the Keshary-Chien type diffusion cell. They evaluate the release of tromethamine with respect to the zero order, first order and higuchi release kinetic.

59.0/ Amir Mehdizadeh (2004), Design and in vitro evaluation of new drug-in-adhesive formulation of fentanyl transdermal patches (74), the aim of the present investigation is to develop the transdermal patch of fentanyl and in-vitro evaluation of fentanyl patch. Evaluate the different type of transdermal patch of fentanyl. Drug in adhesive matrix and reservoir type of patch was evaluated for comparative drug delivery. Full factorial design was applied to develop the transdermal patch of fentanyl and result appeared that release of fentanyl followed the Higuchi model or square root of time model of diffusion. After investigation of drug release from patch, 3.3mg required to deliver from each 10 cm$^2$ patch. Total amount of fentanyl in matrix and reservoir patch was respectively 5.0 and 2.5mg. Also compared to different adhesive type, acrylate adhesive gives the good adhesion with required delivery of fentanyl.

60.0/ Murthy S N (2004), Clinical pharmacokinetic and pharmacodynamics evaluation of transdermal drug delivery systems of salbutamol sulfate (263), The aim of the present study is to develop the transdermal patch of salbutamol sulfate and evaluate the patch for clinical pharmacokinetic and pharmacodynamics properties. Transdermal patch containing 5mg/patch of drug salbutamol sulfate and deliver the 100µg/h of salbutamol sulfate and evaluate the pharmacodynamics and pharmacokinetic study on asthmatic patient. Final formulations were physically evaluated with regard to drug content, percentage moisture absorption, % elongation thickness, tensile strength, folding endurance and weight variation in dry matrix. As per study linear correlation was observed between in-vitro diffusion and AUC of cumulative of serum concentration. 2.87± 0.1 ng/ml steady state serum concentration was obtained dafter application period of 4.67 ±1.03 hr.

61.0/ Nidhi Uppal (2013), Development and evaluation of transdermal drug delivery system of captopril (264), the aim of the present investigation is to develop
the transdermal formulation of captopril and evaluate as per transdermal evaluation parameters. Eudragit RL 100 and RS 100 polymers were used to develop the captopril patch by solvent evaporation method. Captopril is suitable candidate for transdermal drug delivery, as per physicochemical properties. Different ratio of Eudragit RL100 and RS100 were evaluated by release profile of captopril from patch. Different physicochemical parameter was evaluated like moisture loss, moisture content, folding endurance, thickness, flatness and tensile strength. All formulations also evaluated for the different transdermal parameter like thickness, drug content, uniformity, flatness etc. and all formulations were acceptable results. Captopril formulations were evaluated for the drug delivery through artifiial membrane using Franz type of diffusion cell. Amount of eudragit RL 100 was responsible for the increase in drug delivery compared to RS100 and RS 100 polymer was responsible for the prolonged delivery of captopril from patch up to 24 hrs. As per investigation, captopril is suitable candidate for transdermal drug delivery system.

62.0/ Venkatachalam V.V (2012), Formulation and physicochemical evaluation of indomethacin transdermal patches (265), the aim of the present investigation is to develop the indomethacin transdermal patch and evaluate the patch as per the evaluation parameters. Indomethacin is use for the non-steroidal anti-inflammatory disease for several decades. In the present study different formulation of indomethacin with different type of hydrophilic and hydrophobic polymer were used to manufacture the patch in alone or in combination. Hydroxyl propyl methyl cellulose (HPMC), polyvinyl pyrolidine was used as a polymer and drug diffusion were evaluated by 1.0% w/v of ethyl cellulose membrane through Franz type of diffusion cell. 20.0% dibutyl phthalate were used as a plasticizer in patch. Ethanol was used in all formulation as a casting solvent to prepare the transdermal patch. All formulations also evaluated for the different transdermal parameter like thickness, drug content, uniformity, flatness etc. and all formulations were acceptable results. After evaluation of the different parameter, HPMC, EC and PVP is suitable candidate for patch formulation with DBT as a
plasticizer. Final formulation was produced with smooth flexible with good tensile strength, drug delivery and percentage of elongation with drug uniformity.

63.0/ Francesco Cilurzo (2011), Design and Characterization of an Adhesive Matrix Based on a Poly (Ethyl Acrylate, Methyl Methacrylate) (2), the aim of the present investigation is too prepared and evaluate the adhesive matrix. Main problem of hydrogel formulation when matrix made up of poly (ethyl acrylate, methyl methacrylate) (Eudragit® NE 40D, PMM) is adhesive matrix shrinkage during coating and drying of blend on release liner. To resolve the issue of shrinkage they used two methods, one is freeze dried and then dissolves in organic solvent and other one is to addition of commercial PMM latex as a plasticizer like triacetine and tributyl citrate and additives like anti-shrinkage agents. As per there research some of the active ingredients also work as a anti-shrinkage agents like potassium diclofenac and nicotine. Prepared transdermal patches were evaluated for peel, tack and shear study for in-vitro adhesion evaluation. Interaction study of plasticizer was evaluated by FTIR-AIR spectroscopy. They also evaluated drug delivery from skin by help of the Franz diffusion cell. Based on drug delivery PMM latex can be used in the transdermal drug development patches.

64.0/ Updesh B. Lade (2011), Design, Formulation and Evaluation of Transdermal Drug Delivery System of Budesonide (239). The aim of the present investigation is to design and formulate and evaluate the budesonide transdermal drug delivery system. As per physicochemical properties, Budesonide is suitable candidate for transdermal drug delivery system. Budaesonide is highly potent steroids. Due to first pass metabolisam and lower systemic availability, Budaesonide is not suitable candidate for oral drug delivery system. In development, they used Eudragit RL 100, RS, ethyl cellulose and povidone as a polymer with different ration of drug. They used mercury substrate for coating of blend and PEG-400 as a plasticizer. They also evaluate the different penetration enhancers like urea, DMSO on delivery of the budesonide. Final formulations were physically evaluated with regard to drug content, percentage moisture absorption, % elongation thickness, tensile strength, folding endurance and weight variation in dry matrix. Thay also evaluate the skin irritation study. They prepared the
patch and evaluate the % of permeation on different moisture contents. As per the investigation, PVP and Eudragit protect the loss of the water from skin, so it’s provided the more occlusion and increase the penetration of drug.

64.0/ Rajesh Sreedharan Nair (2009), Matrix type transdermal patches of captopril: Ex vivo permeation studies through excised rat skin (266). The aim of the present investigation is to develop the transdermal formulation of the captopril antihypertensive drug and evaluate the drug delivery from rate excised skin. Captopril is suitable candidate for transdermal drug delivery system due to some of the physicochemical properties of drug e.g. short elimination half-life, first pass metabolism, interaction with food and higher oxidation rate in stomach. So to improve the bioavailability and reduce the side effect associated to captopril oral drug delivery, transdermal drug delivery of captopril needs to be developed. Captopril transdermal formulation was prepared with different type of polymer and penetration enhancers’ combination. Total eight formulations were prepared by solvent casting method. Hydroxypropyl methylcellulose (HPMC) and polyethylene glycol with menthol and Aloe Vera as a penetration enhancer were used. FTIR results were showed the compatibility of different excipients with captopril drug. Considered formulations were evaluated for irritation on rat skin and it was showed that no significant or noticeable irritation or any other type of skin reaction observed during study. All formulations also evaluated for the different transdermal parameter like thickness, drug content, uniformity, flatness etc. and all formulations were acceptable results. Ex-vivo drug delivery were evaluated by rat skin through Franz type of diffusion cell and result showed that F6 formulation demonstrated higher permeation for 24 hr. with good stability. The F6 formulation was considered as an ideal formulation for captopril transdermal patch.

65.0/ Oya Kerimolu (2013), Matrix type transdermal therapeutic system containing captopril: formulation optimization, in vitro and ex vivo characterization (267), the aim of the present investigation is to develop and evaluate the transdermal formulation of the captopril. Captopril transdermal patch to be developed by artificial and pH in depended polymer e.g. Eudragit RL100 and RS 100. All prepared formulation were
evaluated for the thickness, uniformity of captopril, content of captopril, appearance, in vitro release from patch and diffusion profiles of developed formulation. Drug diffusion studies conducted through different type of rate limiting membrane with different pore size, thickness, and type of hydrophilic and hydrophobic and also through human cadaver skin from Franz type of diffusion cell. Different type of rate limiting membrane behaving in different manner, delivery of captopril from different membrane was different; it was depended upon the pore size and hydrophilic characteristic of membrane. Transdermal drug delivery system of captopril was developed successfully and delivers the required amount of the captopril from patch. Out of total formulation, formulation no 15 and 16 considered as a best formulation as far as delivery and physical characteristic with stability. According to delivery profile and stability of captopril transdermal formulation, captopril is suitable candidate for further development of transdermal formulation.

66.0/ Amir Mehdizadeh (2004), Design and in vitro evaluation of new drug-in-adhesive formulation of fentanyl transdermal patches (74), the aim of the present investigation is to develop the transdermal patch of fentanyl and in-vitro evaluation of fentanyl patch. Evaluate the different type of transdermal patch of fentanyl. Drug in adhesive matrix and reservoir type of patch was evaluated for comparative drug delivery. Full factorial design was applied to develop the transdermal patch of fentanyl and result appeared that release of fentanyl followed the Higuchi model or square root of time model of diffusion. After investigation of drug release from patch, 3.3mg required to deliver from each 10 cm$^2$ patch. Total amount of fentanyl in matrix and reservoir patch was respectively 5.0 and 2.5mg. Also compared to different adhesive type, acrylate adhesive gives the good adhesion with required delivery of fentanyl.

67.0/ G. D. Gupta (2013), Formulation and evaluation of transdermal gel of ketorolac tromethamine along with Neem oil, Tulsi oil and Oleic acid as penetration enhancers (262), The present investigation is related to the transdermal formulation of the ketorolac trimethamine with evaluating the effect of the penetration enhancers like neem oil, tulsi oil and oleic acid. Keturolac is non-steroidal anti-
inflammatory drug and used for the treatment of nociceptive somatic pain. Carbopol 940 and carbopol Ultrez 10NF polymer were used in polymer with three penetration enhancers. Evaluate the delivery of drug with help of three concentrations 2.0%, 3.0% and 4.0% of penetration enhancer and as per the delivery profile, oleic acid is found the best enhancer for tromethamine. After finalization of the formulation polymer, Carbopol 940 and Carbopol Ultrez 10NF is the best polymer used with natural penetration enhancer for preparation of transdermal gel formulation. All formulation was evaluated for the Spreadability, drug content, viscosity, pH, and release of drug from the formulation. All prepared formulation had the good Spreadability, homogeneity and absence of lumps. Compared with other penetration enhancer, oleic acid deliver the higher tromethamine with compared to other penetration enhancers. Drug delivery from the formulation was evaluated using the Keshary-Chien type diffusion cell. They evaluate the release of tromethamine with respect to the zero order, first order and higuchi release kinetic.

68.0/ Nuntakan Suwanpidokkul (2004), Transdermal Delivery of Zidovudine (AZT): The Effects of Vehicles, Enhancers, and Polymer Membranes on Permeation across Cadaver Pig Skin, *AAPS PharmSciTech 2004; 5 (3)*. The determination of this investigation was to examine the properties of vehicles, penetration enhancers, and artificial membranes of polymer on 3'-azido-3'- deoxythymidine (AZT) penetration crossways of cadaver skin of pig. Four double vehicles (combination of isopropyl alcohol/water, ethanol/water, ethanol/isopropyl myristate and polyethylene glycol 400/water) were verified for AZT solubility and penetrability across the skin of pig; ethanol/IPM in the ratio of 50/50 v/v verified the highest skin flux (185.23 µg/cm²/h) of zidovudine. Following, the accumulation of different concentrations of diverse penetration enhancers (N-methyl- 2-pyrrolidone, oleic acid, and lauric acid to diverse ratios volume of ethanol/IPM was examined for their influence on zidovudine solubility and penetrability crossways of pig cadaver skin. The use of 2 mixtures (ethanol/IPM in 20:80 and 10% N-methyl- 2-pyrrolidone and 30:70 of ethanol/IPM, and 10% N-methyl-2-pyrrolidone caused in increased zidovudine solubility (42.6 and 56.27 mg/mL) and also more zidovudine flux values (284.92 and 460.34 µg/cm²/h) without considerable
variations in lag times (6.25 and 7.49 hours) when associated with formulations by only ethanol: IPM at 20: 80 and 30:70 volume ratios deprived of addition of the penetration enhancer \(N\)-methyl-2-pyrrolidone. Finally, zidovudine penetration crossways to pig cadaver skin protected with a microporous polyethylene artificial membrane were examined. The addition of the polyethylene artificial membrane to the cadaver pig skin decreases the flux values of zidovudine to approx. 50% of that seen with pig skin alone. However, the zidovudine flux value reached with ethanol: IPM 30: 70, 10\% \(N\)-methyl-2-pyrrolidone was around 215\(\mu\)g/cm\(^2\)/h. The results got from this research work will be really helpful in the advancement of a zidovudine transdermal drug delivery system.