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Review Article

TRANSDERMAL DELIVERY A PRECLINICAL AND CLINICAL PERSPECTIVE OF DRUGS DELIVERED VIA PATCHES

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ABSTRACT

As skin is a readily accessible organ of the body, it acts as the portal of entry for extraneous substances for their effective transdermal delivery. Possessing various advantages, it has the limitation of low permeability of drugs across it, limiting the efficacy of drugs. Therefore, various carrier systems have been developed to enhance the permeation deep into the systemic circulation. The potential of using the intact skin as the portal for drug administration to the human body has been recognized for several decades. With the advent of modern era of pharmaceutical dosage forms, transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Transdermal patches are polymeric formulations which when applied to skin deliver the drug at a predetermined rate across dermis to achieve systemic effects. The number of drugs formulated in the patches has gained tremendous potential to deliver the drug via transdermal route. Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal system. Numerous studies have been conducted to evaluate the potential of patches for efficacious transdermal delivery. The present review focuses on the preclinical and clinical aspects of drug delivery of various therapeutic categories through transdermal patches emphasizing enhanced safety and efficacy via these carriers.

Keyword: Flux, Matrix, Permeation, Patches, Skin, Transdermal.

INTRODUCTION

Transdermal drug delivery system as an effective route for drug delivery offers various advantages over traditional delivery systems involving benefits such as avoiding first pass metabolism, reducing pain, and providing sustained release of drugs. Transdermal drug delivery though offers a non-invasive route of drug administration; its applications are limited due to low permeability across the stratum corneum [1]. Various penetration enhancers like iontophoresis, chemicals, ultrasound, and electroporation have been in use to increase transdermal drug transport. These enhancers act by several mechanisms to enhance the drug delivery. These mechanisms include increase in drug solubility, improving diffusion coefficient or by providing supplementary driving force. Since last twenty five years there have been explosions in the development of new therapeutic agents. Related advancements in drug delivery systems have not only enabled the successful implementation of many of these novel pharmaceuticals, but also permitted the development of new medical treatments with existing drugs. The creation of transdermal delivery systems has been one of the most important of these innovations [2]. Delivery of drugs via transdermal system is gaining prominent importance nowadays across the globe. The main motive behind the development of transdermal system is to enhance the efficiency and safety of drugs being delivered and provide more convenience for the patients. Various researches conducted during the past several years have led to the development of technologies that meet the required criteria for delivering the drug through transdermal route [3]. The application of drug to the skin to treat various ailments is a practice that has been utilized by mankind over the millennium and has included the application of poultices, gels, ointments, creams, and pastes. These applications were primarily intended for a local topical effect. The use of adhesive skin patches to deliver drugs systemically is a relatively new phenomenon. The first adhesive transdermal drug delivery system (TDDS) patch was first approved by the Food and Drug Administration in 1979 (scopolamine patch for motion sickness). Nitroglycerine patches were approved in 1981. This method of delivery became widely recognized when nicotine patches for smoking cessation were introduced in 1991. TDDS offer pharmacological advantages over the oral route and improved patient acceptability and compliance. As such, they have been an important area of pharmaceutical research and development over the last few decades. Conditions for which TDDS are suitable include analgesia, hypertension, hormonal replacement, contraception, angina, motion sickness, Parkinson's disease/restless leg's syndrome, smoking cessation, hypogonadism etc [4]. Today drugs administered through skin patches include scopolamine (for motion sickness), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), and lidocaine to relieve the pain of shingles (herpes zoster). Non medicated patches include thermal and cold patches, weight loss patches, nutrient patches, skin care patches (therapeutic and cosmetic), and aroma patches, and patches that measure sunlight exposure [5]. Transdermal drug delivery systems are topically administered medicaments. In the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. Transdermal patches are flexible pharmaceutical preparation of varying sizes, containing, one or more active ingredients. They are intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers. These devices allow for pharmaceuticals to be delivered across the skin barrier. Theoretically, transdermal patches works in a very simple way. A drug is applied in a relatively high dosage to the inside of patch, which is worn on the skin for an extended period of time. Though a diffusion process, the drug enters the bloodstream directly though the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood; the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow [6]. The present review summarizes various research reports on drugs delivered via transdermal patches across the skin. This review thus, specifically focusing on preclinical and clinical aspects of drugs that have been reported to be delivered via transdermal route.

PRECLINICAL AND CLINICAL ASPECT OF VARIOUS DRUGS

A number of drugs have been reported to be delivered from transdermal patches. Table 1 highlights the few drugs that have been recently reported to be delivered via transdermal patches.

Table 1: Recent research reports on preclinical and clinical studies of drugs delivered via transdermal patches.

S. No.	Therapeutic Agent	Preclinical and clinical studies	Animal used	Inference	Reference
1	Trimetazidine Hydrochloride	*In vivo* skin irritation	Rabbits	No sign of irritation or erythema	[7]
2	Betahistine	*In vitro* skin permeation / *In vivo* patch adhesion	Guinea pigs	Significantly higher flux / patch area remained adhered till 36 hrs.	[8]
3	Lornoxicam	*In-vitro* skin permeation / Skin irritation test / Pharmacodynamics activity	Rats	Highest flux / Non-irritant / Decreased swelling of the injected paw	[9]
4	Pentazocine	Skin irritation / in vivo studies	Rabbits / Rabbits	No noticeable edema, erythema or inflammation / enhanced permeation	[10]
5	Indomethacin	*In vitro* skin permeation / skin irritation	Rats / Rabbits	Sustained drug permeation / No visible erythema or edema	[11]
6	Diltiazem Hydrochloride	In vitro skin permeation / skin irritation	Rat / rabbits	Controlled drug release / no visible erythema or edema	[12]
7	Gentamicin	Skin irritancy test / *In vitro* skin permeation	Rabbits / Rats	No erythema / improved flux	[13]
8	Clonidine hydrochloride	*In Vivo* Studies / Skin Irritation	Rabbits / Rabbits	Enhanced Flux / No skin irritation	[14]
9	Lisinopril	*Ex vivo* permeation / skin irritation	Rat / Cadaver	Improved permeability / No signs of erythema, edema or ulceration	[15]
10	Pioglitazone Hydrochloride	*In vitro*-skin permeation/skin irritation	Goat / Rabbit	Controlled drug release/No erythema or edema	[16]
11	Ibuprofen	*In vitro*-skin permeation/skin irritation	Rats / Rabbit	Enhanced flux/no sign of erythema/edema	[17]
12	Sertraline Hydrochloride	*In vitro*-skin permeation / Modified forced swim test / Tail suspension test	Mice / Mice / Mice	Enhanced permeation/Increased swim behavior/, effective anti-depressant activity/ Increased immobility behavior.	[18]

Numerous preclinical and clinical studies have been conducted to evaluate the safety and efficacy of these transdermal systems in delivering drugs deep into the systemic circulation. A brief outline has been given below emphasizing on preclinical and clinical studies conducted on various drugs delivered via patches for effective transdermal delivery.

Rosiglitazone Maleate

Rosiglitazone Maleate loaded patches were formulated by Damodharan and Roy. Patches were characterized for drug–excipient interaction, scanning electron microscopy (SEM), and thickness, area of the patches, moisture content, moisture uptake, in vitro drug-release study and in vitro permeation study. A modified Keshary–Chien (40-mL capacity diffusion cell) was used for the *in vitro* skin-permeation study. A square section of excised human cadaver skin was used for the study. The skin was stored at -80 °C. The thawed skin was then tied with an adhesive tape so that its dorsal side faced upward. A measured portion of transdermal patch was placed on the skin, keeping the backing membrane facing upward on the donor compartment. The donor compartment containing the skin and the patch was placed on the reservoir compartment of the diffusion cell containing 20% v/v PEG 400 in normal saline. The temperature was maintained at 37 ± 0.5 °C using an air-circulating water jacket. One ml of sample was withdrawn at various time intervals and the absorbance was taken. The mean cumulative amount of drug permeated per square centimeter of skin was plotted against the time. The study was performed by taking various media such as normal saline, phosphate buffer, and 20% PEG 400 in normal saline were used. Of the media, 20% v/v in normal saline provided biphasic characteristics of *in vitro* receptor fluid, which is believed to be one of the best media for studying the *in vitro* skin permeation of a drug. The solubility of rosiglitazone maleate in 20% v/v PEG 400 in normal saline was 14.15 mg of the drug dissolved per ml of the media. This result indicated that 20% v/v PEG 400 in normal saline is suitable for *in vitro* release and skin-permeation studies of the drug. It was depicted by the authors that drug release sharply increased for 5 h to a mean cumulative amount of 1.5 mg/cm^2 from both formulations. The release patterns and rates changed afterward, and the drug released in comparatively slower rates till the study was continued. At 72 h, drug release was about 2 mg/cm^2 of patch for both formulations. The drug present on the patch-matrix surface and near the matrix surface initially released more drugs. However, the duration of the release from the patches might be less because of the increased amount of time required for drug molecules to reach the patch surface through the entanglement of polymeric network of the patch matrix. The *in vitro* skin-permeation study of a drug predicts the drug's *in vivo* skin-permeation performance. The cumulative amount of the drug permeated through skin from each cm2 of patch area was about 500 µg in the first 2.5 h. Then, the skin permeation of the drug slowly increased with a similar permeation pattern until the 50-h point. The faster release of the drug from the patch surface and near to the patch surface in the patch matrix was observed. During the first 10 h, drug permeation was fast, and then it gradually slowed. The slowdown could have resulted from the availability of the drug on the skin surface as depicted in the drug-release data. Furthermore, the patches were evaluated on drug- induced diabetic and normal-control rats. The patches were applied to the animals' backs. The average blood-glucose levels of Group III and IV animals were similar to those in diabetic-control Group II animals. The plain patch without drug did not alter the glucose levels of animals in Group III and Group IV. Orally administered rosiglitazone maleate reduced Group VII diabetic animals' blood-glucose level to 140 mg/dl from 250 mg/dl in 12 h. However, the blood-glucose level rose to 220 mg/dl in 24 h. This rise necessitated the additional dose to be given to maintain the glucose level. Again, it is worth mentioning that the glucose level was not reduced to the level of the control animals (i.e., Group I) upon administering the drug orally or transdermally. This suggests that additional therapy such as insulin analogues may be required because STZ damages islets cells irreversibly. Blood-glucose levels in Group V and Group VI animals were effectively reduced for 48 h to 150 mg/dl, which suggests that the patches controlled blood-glucose levels at least for 48 h in the diabetic rats. Formulation I reduced blood-glucose levels more

effectively (i.e., in Group V animals) compared with Formulation II (i.e., in Group VI animals). Although numerical values did not differ greatly, the differences were persistent and statistically significant. The location of the patch on humans is an important factor because the thickness of skin differs at different locations on the body. Different permeation rates were found at different locations when patch-type formulations of scopolamine hydrobromide were applied behind the ear and on the thigh (24). The steady-state permeation rate of this drug was 10 μg/cm^2/h from the patch applied behind the ear, where average skin thickness is 0.084mm. The permeation rate was 4.7 μg/cm^2/h from the patch applied on the thigh, where average skin thickness is 0.106 mm. Hence, the authors chose to apply the rosiglitazone transdermal patch to the neck region behind the ear. The plasma-drug level was determined using HPLC. Figure 8(a) shows the chromatogram of pure drug and internal standard in solvent. Figure 8(b) represents the chromatogram of blank plasma. Figure 8(c) represents the chromatogram of rosiglitazone and pioglitazone in plasma for a standard sample. Figure 8(d) is a representative chromatogram of rosiglitazone in plasma after 8 h in humans, where pioglitazone was used as an internal standard. Drug release from the experimental patches and subsequent penetration through the skin reached a drug concentration in human plasma of 106.45 ng/ml after 2 h, 258.36 ng/ml after 4 h, 460.08 ng/ml after 8 h, 232.63 ng/ml after 24 h, and 143.24 ng/ml after 48 h. The maximum concentration of the drug (C_{max}) in plasma was 460.08 ng/ml, and this level was reached in 8 h (T_{max}). An important limitation of the present study is that it was conducted only at a few predetermined time points, as permitted by the Institutional Ethics Committee, and based on those time points the C_{max} and T_{max} data were calculated. However, values might have varied if more time points had been considered. Thus, these results depict only the trend of drug skin-permeation patterns in humans, and the C_{max} and T_{max} of the formulations might not be accurate. The variation in drug concentration in the plasma among the volunteers may result from various factors such as variation in skin type and absorption characteristics. The study reveals that rosiglitazone can permeate through human skin and reach the blood circulation for at least 48 h from formulated patches [19].

Galantamine and Rivastigmine

Wouters et al have developed galantamine and rivastigmine transdermal patches for the treatment of Alzheimer's disease. The objective behind this study was to describe the daily practice of oral galantamine and rivastigmine transdermal patch in a real life population of a memory clinic of a suburban teaching hospital in The Netherlands. A randomized open label study in 84 ambulant Alzheimer's patients with at least 6 months follow-up was treated either with oral galantamine (group G) or rivastigmine transdermal patch (group R). Data collection included patients' demographic and disease variables. Adverse events were collected and, in case of interruption of the primary treatment, the alternative treatment was registered. No serious adverse effects were observed by the authors. In group G and group R adverse events occurred in 20 patients (50%) and 18 patients (41%) respectively. No difference occurred in the frequency of nausea or vomiting. In group R more patients possessed dermatological adverse events. In group G and group R medication was stopped in 12 patients (30%) and 14 patients (32%) respectively. However, in comparison to group G after stopping the treatment in group R more patients received a new anti-dementia medication. Despite different forms, the use of galantamine and rivastigmine transdermal patch showed neither difference in the frequency of adverse events neither in the frequency of stopping primary treatment. However, compared to oral galantamine use, rivastigmine transdermal patch resulted in more dermatological adverse events and after stopping rivastigmine transdermal patch, new anti-dementia medication or form was more often started. More research is urgently required [20].

Nicotine

Nicotine based transdermal patches were prepared by George et al for schizophrenic patients have high rates of cigarette smoking. The authors compared the outcomes of two group psychotherapy programs for smoking cessation in patients with schizophrenia or schizoaffective disorder who were also treated with the nicotine transdermal patch and with either atypical or typical antipsychotic medications. Forty-five subjects were randomly assigned to 1) the group therapy program of the American Lung Association (N=17) or 2) a specialized group therapy program for smokers with schizophrenia (N=28) that emphasized motivational enhancement, relapse prevention, social skills training, and psycho education. All subjects were subjected to 10 weeks treatment with the nicotine transdermal patch (21 mg/day) and 10 weekly group therapy sessions and continued to receive their prestudy atypical (N=18) or typical (N=27) antipsychotic medications. Evaluated variables included treatment retention, rate of smoking abstinence, and expired-breath carbon monoxide level. Smoking abstinence rates did not differ in the two group therapy programs. However, atypical antipsychotic agents, in combination with the nicotine transdermal patch, significantly enhanced the rate of smoking cessation (55.6% in the atypical agent group versus 22.2% in the typical group), which was reflected by a significant effect of atypical versus typical agents on carbon monoxide levels. Risperidone and olanzapine were associated with the highest quit rates. It was suggested by the authors that smoking cessation rates with the nicotine transdermal patch are modest in schizophrenia. Specialized group therapy for schizophrenic patients is not significantly different from American Lung Association group therapy in its effect on smoking cessation. Atypical agents may be superior to typical agents in combination with the nicotine transdermal patch for smoking cessation in schizophrenia [21].

Wilson et al have formulated patches enclose in order to the study the effects of sustained delivery of nicotine on behavior, cognition, and physiology of the patients suffering with Alzheimer's disease (AD), a widely investigated treatment strategy for the cognitive deficits in AD is cholinergic stimulation. A double-blind placebo-controlled trial was conducted by taking six patients with probable AD by exposing them to 7, 8, and 7 days of placebo, nicotine, and washout, respectively. Daily sessions evaluating learning, memory, and behavior were conducted. Global cognitive functioning, rest and activity levels, cardiac activity, and blood levels were also measured. Findings included improved learning during the nicotine condition, which persisted throughout washout. Memory, behavior, and global cognition were not significantly affected. It was depicted by the authors that sustained administration of nicotine was safe and effective [22].

Lewis et al have prepared the patches for effective transdermal delivery. Two types of patches i.e. monolayered and bilayered were prepared with respect to the drug layer by solvent-casting technique using sodium alginate containing nicotine. The physical characteristics of the patches were evaluated by standard techniques. The patches were evaluated for drug content and all patches were found to possess uniform drug content. In *in vitro* release of nicotine from transdermal patches, a specially designed rectangular diffusion cell (4´3 cm=12cm^2) was used in the release study. The whole 12 cm^2 patch, along with the backing membrane, was used for the release study. A commercial semi permeable membrane was employed in the study as the permeation barrier. The membrane used was transparent, and regenerated cellulose. The patch was kept on the sigma/dialysis membrane, previously soaked in the buffer solution for 12 h. The membrane along with the patch, was then firmly tied to the diffusion cell, and was immersed in a beaker containing 200 ml of (PBS) pH 7.4. The contents in the beaker were stirred with the help of a magnetic bead, at a constant speed. The release study was carried out for a period of 24 h. An aliquot of samples were withdrawn at regular predetermined intervals. The drug content was analyzed with the help of a spectrophotometer. *In vitro* release studies of transdermal patches showed a biphasic release pattern, with diffusion as the dominating mechanism of drug release for the matrix type, while the membrane-controlled released nicotine, gradually over the 24 h study. A comparison of the release graphs of the two formulations (F_1-F_3 and F_4), showed that the initial release rate is fast for the bilayer film for the first one hour. This could be due to the fact, that 5 mg of nicotine is present in the top layer of the bilayered sodium alginate patch, which is responsible for the fast release of the nicotine from the systems. The nicotine present in the second layer of sodium alginate (35 mg), starts permeating through the pores

created in the upper layer of the sodium alginate patch, by the diffusion of nicotine into the receptor medium. The cross-linking of sodium alginate with calcium chloride to form calcium alginate, retards the release of nicotine. In the system containing ethyl cellulose as the rate controlling membrane, the release rate is controlled from the commencement of study. It was observed by the authors that the release rate is steady throughout the 24 h study, because of the rate controlling membrane. The *in vitro* release data was treated with kinetic equations, such as the first order rate kinetic equation, Higuchi's diffusion equation, and peppas equation, to understand the release kinetics and mechanism of release from the formulated patch. It can be inferred, that the incorporated drug was released by the non-fickian type of diffusion, involving swelling of the polymer matrix, as is evident by the slope values of more than 0.5 for the plots of log amount released, Vs log time. *Ex vivo* release of nicotine was observed from transdermal patches. For this study, rat skin was mounted on the diffusion cell, with the dermal side in contact with receptor medium, and the subcutaneous side facing the donor compartment. The experimental set up was the same as conducted for the *in vitro* study. Similar to the results obtained through commercial dialysis membrane, the permeation of nicotine through the hairless rat skin, was observed to follow first order kinetics throughout the 24 h of skin permeation study. The flux values for permeation through the rat skin was lower, compared to flux values for permeation through the sigma membrane. It was reported, that different trends between skin and membrane permeation rate, was due to the difference of pathways. Solutes primarily permeate through water-filled pores in the artificial membrane. Generally, the pore sizes of the artificial membrane are large, compared to that of skin. Studies have reported that craving for nicotine, however, responded better to higher transdermal nicotine doses. Formulation F3 was selected by the authors for further pharmacokinetic studies. This formulation bears a rate controlling membrane that regulates the release of nicotine to the skin. It showed a flux of 95 µg/cm ^{2}/h, which would deliver about 27 mg of nicotine for 24 h, using the 12 cm ^{2} patch. Thus, it was concluded by the authors that transdermal delivery nicotine is appropriate and effective [23].

Diclofenac Diethyl ammonium salt

Arora and Mukherjee have developed matrix-type transdermal patches loaded with diclofenac diethyl amine. The formulations were prepared by solvent evaporation technique by using different ratios of polyvinyl pyrrolidone (PVP) and ethyl cellulose (EC). All the formulations were then subjected to evaluation for moisture content, moisture uptake, flatness, *in vitro* release studies and *in vitro* skin permeation studies. In *in vitro* permeation studies cumulative amount of drug permeated per square centimeter of patches across the skin was plotted against time. From the results obtained, it was depicted by the authors that the permeation profile showed a rectilinear curve in case of a formulation PA5. Zero-order drug-release kinetic was observed. In case of the formulations, PA1 to PA4, the release pattern of drug was found to be apparent zero-order or pseudo first-order kinetics. Initially up to 24 h, the drug released followed zero-order kinetics because the dispersed drug matrix ensured constant concentration. Afterwards, the concentration- dependent release kinetic system modified to a first-order reaction. The process of drug release in transdermal patches is mainly via diffusion and the polymer matrix has a strong influence on the diffusivity as the motion of a small molecule is restricted by the three-dimensional network of polymer chains. So, different in vitro drug release profiles from the different blends of PVP and EC formulations could be attributable to the varied cross linking networks of polymeric chains of the different blends of polymeric transdermal experimental formulations as tortuosity and diffusion pathway varied and they have thereby been reported to vary the release of drug and the duration of diffusion. Moreover, the implication of skin permeation of drug on release-rate profiles of the experimental formulations should not be ignored, because the skin is known to have a substantial role in variation of release kinetic. At an early stage as well as in a steady state of skin permeation, diffusion of drug through appendages (hair follicles, sebaceous and sweat ducts) were considered to be significant and the variation of shunt pathways from one part of skin to the other may even be one of the causes of variation in the release-rate profiles of the experimental formulations. When the release-rate constants were compared among the formulations, almost similar values of rate constants were observed in formulations PA2 to PA4, and PA5 gave the slowest release. It was also clear that the increased amount of EC in the formulations decreased the release rate of diclofenac diethylamine. Based on physicochemical and in vitro release experiments, formulations PA5, PA4, PA3, and PA2 may be chosen for further in vivo studies. The anti-inflammatory activity and sustaining action of the drug-loaded matrix patches were evaluated using the ‘‘carrageenan-induced hind paw edema’’ method in Wistar rats. Young male rats, weighing 120–250 g, were randomly divided into four groups, each containing four rats. The rats were given free access to water and food. The rats were kept under observation for 24 h. The backsides of rats were shaved 12 h before starting the experiments. Patches were applied on the shaved backs of all the animals (except the control group) half an hour before sub plantar injection of carrageenan in the right paws. Paw edema was induced by injecting 0.1 ml of a 1% w/v homogeneous suspension of carrageenan in double-distilled water. The volume of injected paw was measured immediately (0 h) and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 h after injection using an IMCORP plethysmometer. The amount of paw swelling was determined time to time and expressed as percent edema relative to the initial (0 min) hind paw volume.

The mean values of percentages were determined for each time interval. Percent inhibition of edema produced by each patch-treated group was calculated against the respective control group. Experiments were performed with formulations PA4 and PA5 and with Voveran1 gel. The same set of experiments was performed with the formulation PA4 which showed no edema by applying the patch 12 h before sub plantar carrageenan injection in the hind paw. Variable effects of controlling paw edema induced by carrageenan were observed in the formulations PA4 and PA5. The formulation PA4 was found to provide maximum protective effect as compared with PA5 and Voveran1 gel application in the rat paw edema model. Carrageenan-induced rat paw edema has been considered as a useful model for studying the anti-inflammatory effect of drug in rats. As described by the authors, paw edema was induced in rats by injecting 1% w/w carrageenan solution (in double-distilled water) to study the anti-inflammatory effect and sustaining action of diclofenac diethyl amine from the two transdermal patches (PA4 and PA5 formulation) selected based on their physicochemical characteristics and in vitro release profiles. Carrageenan-induced mean percent paw edema was found to increase about 114% as compared with initial paw volume, 12 h after carrageenan injection in the carrageenan control group of animals. Formulation PA4 was very effective in terms of inhibiting carrageenan-induced edema as 100% inhibition, that is, no edema was observed even after 12 h of the carrageenan challenge. However, an application of formulation PA5 produced about 4% mean percentage edema within half an hour after the carrageenan injection and the value became 19.23% 12 h after the carrageenan injected. This may be because of the less percentage of drug release from PA5, which was not enough to control edema effectively for long hours. Approximately 83% inhibition was observed 12.5 h after the application of PA5 formulation. Application of Voveran1 gel half an hour before carrageenan insult showed about 3% mean percent edema value which increased eventually up to 38.28% after 12 h. As in the case of formulation PA4, there was no edema in animals after 12 h of carrageenan challenge. Further study was initiated by applying the formulation 12 h before the carrageenan insult. It was depicted by the authors that there was 100% inhibition of paw edema up to 3 h after carrageenan application and edemas returned and mean percent edema value gradually increased with the duration. t was demonstrated that formulation PA4 (PVP/EC, 1:2) controlled edema effectively for about up to 19 h after its application in the in vivo rat model. Thus, it was concluded by the authors that formulation PA4 has the best effective combination of polymers PVP and EC, among the formulations studied for further development of the transdermal matrix patch type delivery system of diclofenac diethyl amine [24].

Panchaxari et al have developed Diclofenac Diethyl amine (DDEA) encapsulated transdermal patch using the combination of silicone

and acrylic adhesives. Patches were formulated by modified solvent evaporation method. All the optimized patches were characterized for thickness, moisture content, drug uptake, adhesion, dissolution and stability studies. A 7-day skin irritancy test on albino rabbits and an in vivo anti-inflammatory study on Wistar rats by carrageenan induced paw edema method were also conducted by the authors. Ex vivo skin permeation studies were conducted on pig ear skin (75–80 mm). The skin was dermatome to remove dermis. The isolated epidermis (100 µm) was rapidly rinsed with hexane to remove surface lipids and then rinsed with water and used immediately. The *ex vivo* skin permeation was performed by using Franz diffusion cell. Phosphate buffer of pH 7.4 was used as a dissolution medium. The diameter of the donor compartment cell provided an effective area of 3.4 cm^2. The dermatome pig ear skin was mounted between the two compartments of Franz diffusion cell with stratum corneum facing towards the donor compartment. A 3 cm^2 patch was used for the study. The release liner was removed. The patches to be studied were placed in between the donor and the receptor compartment in such a way that the drug releasing surface faced toward the receptor compartment. After securely clamping the donor and receptor compartments together, the elution medium was magnetically stirred for uniform drug distribution at a speed of 60 rpm. The temperature of the whole assembly was maintained at 32 ± 0.5°C by thermostatic arrangements. An aliquot of 0.5 ml was withdrawn at preset time intervals for a period of 24 h and an equivalent volume of fresh buffer was replaced. The samples removed were analysed by HPLC described below. In *ex vivo* skin permeation study, in all the combinational patches, the CDP of combinational patches was higher than that DA patches which contains Acrylic polymer alone. Among all five formulations C_5displayed high CDP value due to its high Silicone content (50% of the total polymer). The 7 day skin irritancy study revealed that the test formulation showed a skin irritation score (erythema and edema) of less than 1. From the draize method of scoring, the control animals showed severe erythema and moderate to slight edema whereas the test animals showed only very slight erythema and no edema on the site of application. Compounds producing scores of 2 or less are considered non-irritant. Hence from the study, we can conclude that formulations are non-irritable to skin and safer for therapeutic use. In *in vivo* anti-inflammatory activity, control group animals, the mean percent increase in edema with respect to initial volume (Group –I) was 114.3 ± 15.0 at the end of 24 h which is because of swelling nature of carrageenan. While in case of test group animals the value is 0.37 ± 0.54 at the end of 24 h indicating that test patches, C_4/OLA, are effective in inhibiting carrageenan induced inflammation. Moreover, the test group animals showed 99.68% inhibition of edema with respect to control after 24 h indicating the efficacy of the formulation during the period. The initial percent increase in edema with respect to initial volume in case of test group half an hour after the carrageenan induction was 0.4 ± 0.54 as opposed to Control group (3.57 ±1.08) indicating that the test patch, C_4/OLA showed action from the first hour without any appreciable lag time. Throughout the study the percent increase in edema value with respect to initial volume for test group remained well below than the control group indicating the sustaining effect of the drug against carrageenan challenge. Thus, it can be concluded by the authors that an ideal combination of adhesives would serve as the best choice, for fabrication of diclofenac diethyl amine loaded patches for sustained deliver with better enhancement in permeation characteristics and robustness [25].

Aceclofenac

Transdermal patches in the form of drug-in-adhesive (DIA) patches, containing aceclofenac were formulated by Rhee et al. The effect of formulation factors on the skin permeation of the drug and physical properties of the patch were evaluated using excised rat skins. The optimized patch contained 12 % aceclofenac and 20 % lauryl alcohol in DT-2852 as a pressure-sensitive adhesive. The pharmacokinetic characteristics of the DIA patch were determined after application of the transdermal patches to human volunteers. The calculated relative bioavailability of the aceclofenac DIA patch was 18.2 % compared to oral administration of the drug. The findings of this study suggest that transdermal application of aceclofenac can substitute for oral administration of the drug [26].

Ampicillin sodium

Bagyalakshmi et al have developed membrane-moderated transdermal systems of ampicillin sodium and evaluated them with respect to various in vitro, in vivo parameters, Moisture Content, Moisture Uptake, Swelling Ratio Measurement and skin irritation studies The unilaminate transdermal membrane was prepared by the casting method. In vitro permeation studies were performed by using a modified Franz diffusion cell across a cellulose membrane using phosphate buffer pH 7.4 as the in vitro study fluid in the receptor compartment. The samples were withdrawn (1 ml each time) at different time intervals and an equal amount of phosphate buffer pH 7.4 was replaced each time. The intensities of samples were measured spectrofluorimetrically. The amount of drug permeated per square centimetre at each time interval was calculated and plotted against time. The permeation of ampicillin from volatile vehicles (ethanol/pH 4.7 buffer, 33:67 vol/vol) was examined. The volatile vehicle without polymers (control group) showed a gradual increase in ampicillin permeation, followed by a constant low level of permeation. In the case of patches developed with membrane in ethanol and pH 4.7 buffer, SA exhibited the highest permeation. The patch made with HPMC exhibited the lowest permeation. The release of the drug from CMC and MC was delayed because of their swelling characteristics, and hence their permeation was decreased as ex- pected. Although CAP had greater stability at pH 7.4 than HPMC did, CAP's permeation was not greater than HPMC's because of the rate-controlling membrane made with HPMC. The permeation of the drug was found to be higher from CS than from CMC and MC. The permeation of drug from SA was found to be the highest, which was expected, since the release of the drug from SA was the highest. CS had the lowest release of the drug from the patch, and hence only less amount of the drug was available for permeation and thus permeation was delayed. Permeation of CMC was also delayed since it had maximum swelling ratio, which was expected, as its moisture uptake capacity was the highest and CAP's was the lowest. *In Vivo* study was conducted on healthy male volunteers (weight 55-60 kg; age 25-30 years). All the participants in the study were non- smokers and were not alcoholics. The biochemical examination of the volunteers revealed normal function of the kidney and liver. The nature and purpose of the study were fully explained to the volunteers, and an informed written consent was obtained from each one. None of the volunteers was on drug treatment within the week prior to their participation in the study. An immediate-release capsule dosage form containing 250 mg of ampicillin was chosen as the reference formulation and was administered to volunteers. The transdermal patch was applied to the anterior surface of the forearm near the elbow. The oral administration of the drug as capsule yielded 51.6 µg/ml, whereas the patch yielded 126 µg/ml. The relative bioavailability of the drug from the patch, calculated with respect to the drug administered orally, was 143%. The mean residence time was found to be 6.11 hours. The maximum drug release reaching the systemic circulation is more from a patch containing only 20 mg of the drug from an area of 10 cm2 than from an oral dosage form containing 250 mg of the drug, possibly because, since it is a very hydrophilic drug, it has difficulty crossing the lipophilic membrane of the gut. The excess drug that is ad- ministered to compensate for the loss produces the microbial flora disturbances. The area time curves for the capsule and transdermal patch of ampicillin were 865 and 1236, respectively. Skin Irritation was further conducted and the visual score was found to be 0 (none) on both the erythema scale and the oedema scale. There was no sign of skin irritation. Hence, it can be concluded that hydrophilic ampicillin sodium can be developed as a transdermal delivery system with SA that is an alternative to intravenous administration and has minimal adverse effects [27].

Fexofenadine Hydrochloride

Chaudhary have prepared patches of fexofenadine hydrochloride to treat allergic disorders on long term therapy needs plasma concentration of drug in better manner. This was achieved by formulating the drug in controlled release pattern. Fexofenadine hydrochloride is almost completely absorbed from the gastro-intestinal tract following oral administration, but bioavailability is reported to be only about 45% due to hepatic first-pass metabolism.

The transdermal patches of were prepared by solvent casting method. The prepared fexofenadine hydrochloride patch was evaluated for release pattern using commercially available semi permeable membrane. The membrane and patch were fitted between donor & receptor compartment of self- fabricated modified Franz diffusion cell. The donor compartment was empty & receptor compartment was containing 50 ml of phosphate buffer pH 7.4. The samples were collected at different time intervals for analyzing the drug content in the receptor compartment for release pattern of drug and replaced with equal volume of freshly prepared phosphate buffer pH 7.4. The drug content was analyzed at 259 nm using U.V double beam spectrophotometer. From the study best formulation was selected for further studies. The corresponding value of cumulative percentage drug permeated from the formulations A, B, C, D, E and F after 24 hrs were 78.2%, 69%, 61.2%, 59.4%, 70.2% and 65.3% respectively. From the in vitro skin permeation study it was confirmed that release of formulations A and E after 24 hrs was found to be higher than other formulations (B, C, D and F). The kinetic study data also proved that which follows zero order kinetics for controlled release of drug to maintain drug concentration in better manner. It was concluded that the drug fexofenadine hydrochloride for transdermal therapeutic system of anti-histaminic study shown appropriate release in in-vitro studies. This confirms that the formulation A and F may control the allergic disorder in better manner by achieving drug concentration in steady manner for over a day [28]. Subramanian et al have developed fexofenadine hydrochloride patches for controlled release of drug from matrix type of patch. The patches were formulated by solvent casting method. In-vitro release study. The prepared Fexofenadine patch was evaluated for release pattern using commercially available semi permeable membrane. The membrane and patch were fitted between donor & receptor compartment of self fabricated modified Franz diffusion cell (Jayaprakash S et al). The donor compartment was empty & receptor compartment was containing 50 ml of phosphate buffer pH 7.2. The samples were collected at different time intervals for analyzing the drug content in the receptor compartment for release pattern of drug and replaced with equal volume of freshly prepared phosphate buffer pH 7.2. The drug content was analyzed spectrophotometerically. The formulation F2 shown 94 % of drug release at 15 h & further the release of drug were controlled by incorporating rate controlling membrane of ethyl cellulose 1 % this formulation F7 shown the retardation of release, but release was not completed. Because only 95 % of drug released at the end of 24 h, so rate controlling membrane of ethyl cellulose 0.5 % was incorporated to retard the release and also to release the drug completely from matrix type of Fexofenadine hydrochloride transdermal patch formulation F8 this shown the 94 % of drug release at 23 h. The kinetic study data also proves that which follows zero order kinetics for controlled release of drug to maintain drug concentration in better manner. In *in vivo* study, the formulation F8 was used for in-vivo study on rabbits, rabbits were selected and its hair was removed from dorsal surface with scissor. Animal dose was calculated and the patch size was reduced to 2 cm2 to apply on the rabbit also drug free patch was formulated for control study group. Different group of animals were categorized and the patch was applied at same time to all the groups, but removed at different time intervals. The formulation F8 was studied for in-vivo drug release in rabbit model using remaining drug content formula. In this method, patch was applied and removed at particular time and then analyzed for drug content in U.V spectrophotometer at 220 nm. In-vivo study on rabbit confirms the release of drug fexofenadine hydrochloride in transdermal patch as controlled delivery over 24 h as 99 %. The drug selected of fexofenadine hydrochloride for transdermal therapeutic system of anti-histaminic study shown appropriate release in both in-vitro & in- vivo studies. This confirms that the formulation F8 may control the allergic disorder in better manner by achieving drug concentration in steady manner for over a day [29].

Azasetron

Sun et al have developed a transdermal drug delivery system for azasetron and evaluate the correlation between in vitro and in vivo release. The effects of different adhesives, permeation enhancers, and loadings of azasetron on the penetration of azasetron through rabbit skin were investigated using two-chamber diffusion cells in vitro. For in vivo studies, azasetron pharmacokinetic parameters in Bama miniature pigs were determined according to a non-compartment model method after topical application of transdermal patches and intravenous administration of azasetron injections. The best permeation profile was obtained with the formulation containing DURO-TAK 87-9301 as adhesive, 5% of isopropyl myristate as penetration enhancer, and 5% of azasetron. The optimized patch formulation exhibited sustained release profiles in vivo for 216 h. The in vivo absorption curve in Bama miniature pigs obtained by deconvolution approach using WinNonlin® program was correlated well with the in vitro permeation curve of the azasetron patch. These findings indicated that the developed patch for azasetron was promising for the treatment of delayed chemotherapy-induced nausea and vomiting, and the in vitro skin permeation experiments could be useful to predict the in vivo performance of transdermal azasetron patches [30].

Estradiol and Levonorgestrel

Harrison et al developed adhesive patches of both estradiol and levonorgestrel to deliver the drug through the skin over a 7-day period. Biopharmaceutical in vitro and in vivo studies were conducted by the authors. 3 test patches have been manufactured and observed to deliver estradiol at the same rate, but levonorgestrel was found to be delivered at three different rates. Hairless mouse skin model using Franz diffusion cells was used for the in vitro studies. It was depicted by the authors that the presence of estradiol did not affect the flux of levonorgestrel. The three test products all delivered estradiol at comparable rates was given to the woman showed postmenopausal at steady state (four weeks of once-weekly dosing). Similarly, the levonorgestrel deliveries for the three test products were in the order expected by the authors. By changing the drug loads and patch size in these three test product, target fluxes can be achieved in case of the both drugs. This approach was found to be successful as evident for the penetration experiments in transdermal product development and should provide useful insights for other formulations having to develop complex systems [31].

Galantamine

Park et al investigated galantamine transdermal system which as an alternative route to treat Alzheimer disease patients. In this study adhesive transdermal patch loaded with galantamine was developed and evaluated for in-vitro and in vivo studies. DT – 2510 was used as suitable pressure-sensitive-adhesive and oleic acid was used as an enhancer. Galantamine drug-in-adhesive patches were found to be physicochemically stable for 28 days at 40 °C/75% RH. Sustained effect was obtained on the drug plasma levels for 24 h and high absolute bioavailability of around 80% were observed by the authors. Different pressure-sensitive-adhesive functional groups showed a strong correlation between the skin permeation rate and the area under the curve. The results suggested that the galantamine drug-in-adhesive patches might be an alternative formulation for the treatment of Alzheimer disease with good efficacy and tolerability [32].

Paroxetine Hydrochloride

Patel et al had developed transdermal delivery systems of paroxetine hydrochloride by using solvent casting method. Matrix based patches were prepared by using polymers cellulose acetate butyrate(CAB) and ethyl cellulose (EC) by incorporating polyethylene glycol 200, 400,600, dibutyl phthalate and ethylene glycol as plasticizers. All the formulations were physically evaluated with respect to thickness, moisture content, moisture uptake, and tensile strength, folding endurance, drug content and *in vitro* drug release study. *In-vitro* permeation studies were performed by using Franz diffusion cells. The diffusion medium was phosphate buffer of pH 7.4, which was stirred with Teflon coated magnetic bead (operated by a magnetic stirrer). A treated cellophane membrane was placed between the two chambers. Samples (2 ml) from the receptor compartment were taken at various intervals of time over a period of 8 hours and the concentration of the drug was determined by UV spectrophotometric method using the standard curve at 242nm. Amount of drug diffused at various time intervals was calculated and plotted against time25.The results followed the

release profile of Paroxetine hydrochloride followed mixed zero order and first order kinetics in different formulation. However, the release profile of the optimized formulations indicated that the permeation of the drug from the patches was governed by a diffusion mechanism. These results indicate that the formulation containing the F3 [CAB: EC (1:1) using PEG 600 as plasticizer] has shown optimum release in concentration independent manner.

The In vitro permeation data across treated cellophane membrane showed anomalous diffusion transport and its release mechanism can be said to follows first order kinetics. The cumulative amount of Paroxetine hydrochloride released from different polymeric films was found to be between 7.061 to 8.98 mg in 24hrs using treated cellophane membrane. The formulation no.F3 (CAB: EC PEG 600) have showed optimum release (98.42 %) in 24hrs using treated cellophane membrane. All he formulations showed an optimum release of about 98 % drug mg in 24 hrs. However the release profile of formulation F3 showed the release of the drug in a controlled manner. In the present investigation an attempt has been made to design and develop the formulation of Paroxetine hydrochloride patches using different types of plasticizers by solvent evaporation technique and mercury substrate method. Paroxetine hydrochloride was successfully formulated as controlled release transdermal patches, which prevents the frequency of administration and gives good patient compliance. From the experimental results obtained, F3 formulation can be selected as the best formulation among all the other formulations. The in-vitro drug diffusion study from the formulation was found to be controlled release. All the evaluation parameters obtained from the best formulation were found to be satisfactory. The data obtained from the in-vitro release studies were fitted to zero order kinetic models, from the kinetic data it was found that drug release follows zero order release by diffusion technique from the polymer. Based on the observations, it can be concluded that the attempt of formulation and evaluation of the Paroxetine hydrochloride patches was found to be successful in the release of the drug for an extended period of 24 hrs. Further, in vivo studies have to be performed to correlate with in vitro release data for the development of suitable controlled release patches for Paroxetine hydrochloride [33].

Losartan

Nautiyal and Singh have developed and characterized losartan loaded patches for transdermal delivery. Patches containing different polymers (Cellulose Acetate Phthalate, Ethyl Cellulose, And Hydroxy Propyl Methyl Cellulose) were prepared in methanol/acetone mixture All the patches were characterized for thickness uniformity, weight uniformity, surface pH, swelling studies, drug content, *in vitro* release, effect on aging and skin irritation study. Skin irritation study was conducted by the authors to evaluate the irritation if any was produced by the formulations. The primary skin irritation studies were done using modified draize test. The hair of rabbits were removed by shaving from the dorsal area on both sides 24 h before test, one side of the back of each rabbit i.e. untreated skin area serves as the control for the test. Medicated patch was secured on experimental side using adhesive tape and the non-medicated patch was adhered on the control side of six rabbits. These patches were covered with occlusive covering to approximate the condition of use. The medicated patches were changed after 48 h. and the fresh patches were secured at the same site. However the patches on the control side were not changed. The patches were secured on the back for seven days. After removal of patch after a week each of the areas were examined for any sign of erythema or edema. The primary skin irritation studies of formulation showed that formulation F1 causes slight irritation after 7 days of application (modified draize test). Irritation subsided within few hours after removal of patch. Formulation F2 was not found irritant in primary skin irritation studies. Thus, it was concluded by the authors that the transdermal delivery of losartan via patches was safe and efficacious [34].

Ketorolac

Chandra et al have prepared and characterized transdermal patches of ketorolac. The ketorolac loaded gel formulation was formulated in phosphate-buffered saline (PBS) solution by using hydroxyl propyl methyl cellulose as a gel base. Penetration enhancers were added to the gel base subsequently. Transdermal patches of reservoir type were fabricated by loading ketorolac gel preparation. In vitro skin permeation studies were performed by using excised rat dorsal skin. (Sprague-Dawley) employing modified Keshary - Chien diffusion cell. Phosphate buffer saline pH 5.4, 6.4 and 7.4 were used a permeation medium. Samples were withdrawn periodically and analysed spectophotometrically. From the results obtained, it was depicted by the authors that more permeation of drug was observed at lower pH as compared to at higher pH. Transdermal flux at pH 5.4, 6.4, 7.4 were observed to be 1.24 µg / cm^2 / h, 0.99 µg /cm^2 / h, 0.79 µg / cm^2 / h respectively. Thus, from this study pH 5.4 was optimized as a medium for further studies. Effect of penetration enhancers on permeability of ketorolac was the observed through rat skin. For this purpose, variety of alcohols such as ethanol, n - propanol, iso – propanol, n – butanol and propylene glycol were taken. It was determined by the authors that smaller chain alcohols were found to be more effective in enhancing the permeability of the drug across the rat skin. More permeation coefficient was depicted in case of iso-propyl alcohol and ethanol. Skin irritation studies were also conducted. Effect of eucalyptus oil on permeability from gel based formulation was also evaluated. The formulation containing 10 % oil was selected as optimized formulation. Skin irritation study was also conducted to evaluate the safety of the formulations. In this study, transdermal patch of ketorolac gel was applied onto the dorsal skin of the Wistar rats (220-250 g), which was shaved 24 h before the study. The site of application was occluded with gauze and covered with a non-sensitizing micro porous adhesive tape. After 24 h, the gel was removed and the score of erythema was determined by draize test as follows: 0 - no erythema; 1- mild erythema; 2- moderate erythema; 3-severe erythema. Based on the visual observation score it was suggested by the authors that the formulations were safe to be applied. In case of eucalyptus containing formulations, the score was found to be in between 0 and 2. Though, eucalyptus oil at 15 % w/w showed a small rise in erythema. Anti-inflammatory studies were then conducted by the authors in order to evaluate the anti-inflammatory potential of transdermal patches of ketorolac. This study was performed by carrageenan induced paw inflammation in Wistar rats. It was demonstrated by the authors that Ketorolac patches have tremendous anti-inflammatory potential as compared to the control formulations ($p<0.05$). Thus, it was predicted by the authors that reservoir type transdermal patches consisting of ketorolac gel was found to be a promising carrier in drug delivery [35].

Ketoprofen

Transdermal patch of ketoprofen, a potent non-steroidal anti-inflammatory drug, was prepared by Wongpayapkul et al using combined acrylate pressure-sensitive adhesives such as Eudragit® NE30D and Eudragit® E100. Propylene glycol (PG), butylene glycol (BG) and oleic acid (OA) were used as additives. The formulations were characterized for adhesive property, *in vitro* release study, *in vitro* permeation study. In Vitro Permeation Studies of Ketoprofen patches were performed on abdominal rat skin (Male Wistar rats). The abdominal skin was excised and the adherent fat and subcutaneous tissue were then removed. The excised skin was rinsed with the normal saline solution and wiped carefully with tissue. The skin was then kept at -40°C until usage. The rat skin was thawed at room temperature and cut into small pieces. The release liner was removed from the patch and the patch was then between donor and receptor compartments. The receptor compartment volume was 12.0 ml. and the effective surface area available for permeation was 0.951 cm2. All studies were performed at 32±1°C and stirred at 600 rpm. Isotonic phosphate buffer, pH 7.4 was used as the receptor medium. The samples were withdrawn (500 µl), at fixed time intervals and the same volume of fresh receptor medium was replaced periodically up to 24 h. The amount of drug permeated through the abdominal rat skin was filtered through 0.45 µm nylon membrane filter and determined using HPLC (High Performance Liquid Chromatography). The chromatographic analysis was carried out with a reverse phase Nucleosil 100–5 C18 column at 40°C and λmax 254 nm. The mobile phase was an acetonitrile/pH 3.5 phosphate buffer mixture (55:45v/v) with a flow rate of 1.0 ml/min. The retention time of KP was 2.73 min. Linearity was demonstrated from 0.6 to 13.0 µg/ml ($r2 > 0.9900$). The cumulative amount of drug permeated per square centimeter at each time interval was

calculated and plotted against time. Each formulation was undergoing permeation study in triplicate. From the repeated measurements of statistical analysis, there were significant differences between the permeation profiles of Ketoprofen (KP) from these formulations. From the ANOVA statistical analysis, followed by Turkey test the flux of KP permeating from the formulation containing oleic acid (OA) or propylene glycol (PG) was significantly higher than the flux of KP permeating from formulation containing butylene glycol (BG) or without additive. In contrast, there was no significant difference among the flux of drug permeating from formulations containing OA and PG. Thus, OA and PG acted as permeation enhancers in this study. It was also observed by the authors that the cumulative amount of KP permeating through rat skin from formulation containing OA or PG after 24 hr. was still very low. This might be due to the size of KP-patches used in this study was only 0.951 cm^2. To improve their potentials, several means will be further investigated: 1) increasing the size of TDDS, 2) increasing the thickness of TDDS, 3) increasing the drug concentration and 4) addition of some chemical permeation enhancers. The correlation between the release rate and the flux or permeation rate of KP was also studied. A good linear correlation (correlation coefficient, r2 = 0.9182) was observed between the release rate and the flux of all the formulations. Though there is a complete difference between the composition of the cellophane membrane and the abdominal rat skin. For this reason, only the release study can be investigated and should represent the permeation study as well. This will be valuable in terms of time- and expense-saving in the further investigations. It was dictated by the authors that KP-transdermal patches containing OA or PG exhibited the higher adhesive property than the formulation containing BG. The release rate and the flux of KP released and permeated from the formulation containing OA or PG was higher than those from the formulation containing BG or the formulation without additives [36].

Glibenclamide

Ali et al have formulated matrix type transdermal therapeutic systems (TTS) of glibenclamide using polymers Eudragit RL 100, ethyl cellulose, PVP K-30, and polyvinyl acetate. Citral was used as the penetration enhancer. The polymeric patches were formulated by varying the ratios of Eudragit RL 100 and PVP K-30. All the formulations were then subjected to evaluation for ex vivo studies, interaction studies, skin irritation studies, accelerated stability analysis, and in vivo studies. To perform ex vivo skin permeation studies, a vertical diffusion cell was used comprising of donor and receiver compartment. The capacity of the receiver cell was 50 ml. Abdomen skin of an albino rat was taken and mounted between two compartments with the stratum corneum facing towards the donor compartment whereas the dermis faced the receptor compartment. 30% (v/v) iso - propanolol in isotonic phosphate buffer, pH 7.4 (IPH) was used as a receptor medium. The receiver fluid was stirred with a magnetic stirrer at a speed of 500 rpm and the assembled apparatus was placed in a hot air oven preset at 37 ± 2°C. The buffer solution was replaced every 30 min to stabilize the skin (21). After applying the transdermal formulation, the samples were withdrawn from the receiver compartment at different time intervals up to 48 h, and an equal volume of permeation medium was added to the receptor compartment to maintain the sink condition. The withdrawn samples were analyzed for drug content. The cumulative percentage of drug permeated through rat skin from the three formulations was found to be 95.3, 98.8, and 99% for formulations A-C, respectively in 48 h. After an initial lag period, permeation was observed to be gradually approaching a constant for the rest of the time, thus illustrating the controlled release behavior of these systems. The graph plotted between cumulative percent drugs permeated versus square root of time was almost linear curves for all three optimized formulations A-C. This suggests that the formulation follows the Higuchi - matrix mechanism of drug release. The result of kinetic analysis of ex vivo data showed a significantly lower coefficient of variation in case of zero order versus first order permeation kinetics except in formulation B in which the difference was not significant. Therefore, it is concluded that the permeation of the drug from the transdermal system followed zero order kinetics. Optimized formulations which have given satisfactory results in *ex vivo* skin permeation studies were subjected to undergone in vivo studies. Initial blood glucose values of all rabbits were determined and the patch was then placed on the back of the rabbit, which was previously cleared of hair with scissors and depilatory, within an area sufficient for application of the transdermal patch (22). Blood glucose level was estimated at different time intervals till 72 h. For these studies, healthy male albino rabbits weighing between 1.5-2 kg were used for better assessment of blood glucose. Rabbits were selected as test animals because the permeability of rabbit skin matches to a great extent that of human skin (23). The blood glucose determinations were carried out in 18 normo - glycemic rabbits in 3 groups containing 6 rabbits each for transdermal therapeutic formulations (A, B and C). For the collection of blood, the hair from the area around the marginal ear vein was cut short with scissors to make the vein clear. After applying xylene, a 26 number disposable needle was used and a prick was given to the marginal ear vein. After discarding the first drop, 20 µl of blood was taken directly into a 20 µl micropipette and put into tubes containing tetrachloric acid, and further analyzed for glucose estimation by the glucose oxidase-peroxidase method. The method involved the use of 4-aminophenazone as a color coupler with sulphonated 2, 4-dichlorophenol for determination of hydrogen peroxide produced from glucose with glucose oxidase. The sensitivity of the method was such that 20 µg of glucose in a final volume of 4 mL gave an optical density of 0.61 at 515 nm with 10-mm cells, which corresponds to a molecular absorption of 22,000. A sufficiently high reduction in blood glucose level was obtained within 2 h for all formulations. The reduced level remained almost constant with a slight rise in blood glucose level on administration of food. These observations were in accordance with the ex vivo release pattern of the drug. Normal glucose levels were restored in approximately 8 h after the removal of the transdermal system. There was insignificant variation ($p > 0.05$) in the blood glucose level when the placebo formulations were applied on the skin of albino rabbits. Only slight variation on administration of food was observed. The possibility of skin irritation arising from the application of the transdermal patches was assessed using a modified score test in rabbits. The intact and abraded rabbit skin was used for this purpose. The patches were placed on four areas, 10 cm apart (two intact and two abraded) on the back of the rabbit. The patches were placed on the rabbit with the help of adhesive to prevent patch removal due to animal movement. The rabbit was placed in an animal holder ensuring minimal movement during the 24 h patch exposure. Upon removal of the patches, the resulting reactions were also recorded after 72 h and the final skin irritation score represents an average of the 24 and 72 h reading. The score for erythema and edema formation (none = 0, very slight = 1, well defined = 2, moderate = 3, severe = 4) were estimated by visual inspection. The study was done in triplicate. On performing the visual score test, the combined average for intact and abraded rabbit skin irritation score for the test formulations was found to be less than one. The compound producing a score of 2 or less at 24 h was considered negative for irritation. Since the test formulation followed the above condition, it was concluded that the patches was free from skin irritation and could be well tolerated during the course of treatment. Thus, on the basis of above ex vivo and in vivo evaluations, it could be concluded that glibenclamide, a potent hypoglycemic drug, could be administered successfully from the matrix type monolithic transdermal patches for controlled and sustained management of non-insulin dependent diabetes mellitus for a period of 48 h. The systems were free of any hazardous skin irritation. Further work needs to be done to establish the therapeutic utility of these systems through long term pharmacokinetic and pharmacodynamic studies on healthy human subjects and patients [37].

Ropinirole Hydrochloride

Bhosale et al have formulated patches of Ropinirole Hydrochloride (HCl), a drug used to treat Parkinson's disease. The patches were prepared by solvent casting method taking combination of Hydroxy Propyl Methyl Cellulose (HPMC) K15 and Eudragit RL100 was used as a polymer to prepare porous matrix in order to control the release of Ropinirole HCl up to 12 hrs. All the patches were subjected to evaluation for appearance, thickness, folding endurance, drug content, percentage of moisture content and percentage of moisture uptake and permeation studies. In vitro skin

permeation studies for all patches were conducted on rat skin using a vertical Franz diffusion cell of diffusion area 1.59 cm^2. The skin was excised and subcutaneous fat was removed. The skin was mounted on the Franz diffusion cell with the stratum corneum facing the donor compartment. The receptor compartment have 7 ml capacity was filled with pH 7.4 phosphate buffer solution (PBS) and temperature was maintained as 32°C. Samples were withdrawn after every 1 hr up to 12 hrs. The collected samples were subjected to UV analysis to determine the drug content. It was depicted by the authors that optimum permeation of drug was observed from formulation F3 among the formulations F1 to F4. Hence, F3 was selected as an optimized formulation to conduct further studies. The permeation enhancers used includes dimethyl sulfoxide (DMSO), ethanol and sodium lauryl sulphate.

From in vitro studies various factors such as in vitro flux (Jss) and permeability coefficient (K_p) were then determined. In this study DMSO was proved to be most efficient as a penetration enhancer than ethanol and SLS. It was also observed that optimum release of drug was there when the proportion of Eudragit RL 100 was greater than HPMC K15. Since both these factors influenced the permeation pattern of drug release, various formulations (F8-F14) were then designed using different concentrations of DMSO and polymer mixtures. All the formulations were evaluated for various permeation parameters. The steady state flux achieved from formulation containing DMSO was highest (194 µg / cm^2 / h) as compared to ethanol (170 µg / cm^2 / h) and SLS (178 µg / cm^2 / h). Highest permeation coefficient was achieved using DMSO in formulation. The evaluation results revealed that flux of F5 was highest than other formulations and rate of passage of drug through membrane was highest as well, as indicated by its Permeability coefficient value. Flux and permeability coefficient values were found to be highest for formulation containing DMSO among all permeation enhancer tested. This could be explained by the fact that DMSO is a powerful dipolar aprotic solvent which forms an association complex through dipole-dipole interactions and through hydrogen bonding interactions which are stronger than those formed between water molecules. Skin penetration enhancement produced by DMSO involves changes in protein structure and may also be related to alterations in stratum corneum lipid organization besides any increased drug partitioning effects. Since barrier capacity of the skin is due to integrity of stratum corneum, increase in permeation of a drug is obvious when DMSO is used as a penetration enhancer. Since maximum permeation was observed from F14, this formulation was selected for skin irritation study. In skin irritation study, the albino Wistar rats were housed in polypropylene cages, with free access to standard laboratory diet and water. The dorsal abdominal skin of rats was shaved 24 h before study. Transdermal patch (F14) was applied and side of application was occluded with gauze and covered with a non - sensitizing micro porous tapes. A 0.8 %v/v aqueous solution of formalin was applied as standard skin irritant. The formulation was removed after 24 h and score of erythema was recorded and compared with standard. Score of erythema was read and recorded as: Score 0 for no erythema; Score 1 for Mild erythema (barely perceptible- light pink); Score 2 for Moderate erythema (dark pink); Score3 for Severe erythema (Extreme redness). No erythema was found within 12 hr after application of optimized transdermal patch (F14) when compared with standard irritant. Thus this formulation was suitable for transdermal application. Thus, it was revealed by the authors that the combination of polymers can be successfully manipulated to attain desired efficacy of Ropinirole HCl with minimum fluctuations in plasma levels [38].

Glimepiride

Pachisia and Agrawal have prepared and evaluated transdermal patches of glimepiride. A novel matrix controlled transdermal systems of anti-diabetic drug glimepiride were prepared by using natural polymer chitosan for the extended and controlled delivery of the drug. All the preparation were then evaluated for thickness, physical appearance, uniformity of weight, assay. Optimization of the system was done using in vitro drug permeation studies through rat skin. Skin irritation tests and pharmacokinetic evaluations were also carried out in healthy rats. To conduct permeation studies across rat abdominal skin, rat dorsal skin was excised. Hair and underlying tissues were removed with a sharp scissors. Skin was washed thoroughly with distilled water and normal saline. It was soaked in the normal saline overnight and washed several times before use. The skin was then cut into appropriate size and mounted between the compartments of the diffusion cell with stratum corneum facing the donor compartment. It was left overnight on the receptor fluid for stabilization and optimization. The matrix formulation to be tested was cut into 1cm^2 patch (n = 3) and was placed over the optimized skin. It was then covered with aluminium foil as the occlusive backing. The donor compartment was clamped over it with the help of springs, making sure that there were no air bubbles in the receptor chamber. Samples of 3ml were withdrawn at predetermined time intervals up to 48 hrs. Fresh receptor fluid was added to the receiver compartment to maintain a constant volume. The filtered samples were then analyzed spectrophotometerically. Linearity was demonstrated from 2 to 22 µg / ml (r^2 > 0.999). Formulation P1, P2, P3 and P4 released a total of 26.7%, 27.9%, 33.3% and 23.2% of drug in 48 hrs respectively. Formulation P5 released 50% at 18th hr and a total of 71.4% in 48 hrs. Formulation P6 released 50% and 80% at 8th and 30th hr respectively and a total of 93.6% in 48 hrs. P6 gave maximum flux rate of 10.465 ± 0.261mcg/cm2. Thus P6 was selected as the optimized formulation. A comparison of r^2 values was made in order to assess the nature of release profile of the formulations. The respective r^2 values for formulation P1 - P6 were found to be 0.8025, 0.7967, 0.8792, 0.842, 0.8891 and 0.855 respectively for zero order plot; 0.9768, 0.9746, 0.9816, 0.9699, 0.9882 and 0.9755 respectively for Higuchi plot and 0.9175, 0.9421, 0.9178, 0.9528, 0.9454 and 0.9643 respectively for first order plot. High r^2 values with Higuchi plots shows that the drug release follows a linear Higuchi classic diffusion equation. To conduct in vivo studies, male wistar rats were used weighing 250 – 400 gm. The optimized patch was evaluated for in vivo studies in healthy rats. Two groups containing 6 rats each (weighing 250-400g) were selected. After overnight fast, following treatments were given to each group. Group A: Oral suspension of glimepiride in 2%w/v gum acacia (4mg/day). Group B: Glimepiride patch (17 cm2) was applied. Hairs were removed with the help of sharp scissors prior to the day of study. The appropriate size of the patch was cut and placed on the skin; it was then covered with occlusive covering using adhesive tape to approximate the conditions of use. The pharmacokinetic profile of the drug released was studied by collecting 0.3ml of blood samples from tail vein at pre- determined time intervals and were centrifuged at 4000 rpm, 0 – 4°C for 30 minutes to separate the plasma. These samples were kept at –20°C until analysis. Plasma samples were analyzed by an earlier reported HPTLC (High Performance Thin Layer Chromatography). Different pharmacokinetic parameters were calculated from the resulting data from HPTLC analysis. For oral suspension group and transdermal patch group, mean C_{max} was found to be 15130.91 and 7225.59 ng / ml respectively. T_{max} was found to be 4 and 24 hrs respectively. For oral suspension AUC for first 24hrs was found to be 73600 ng hr/ml and for total of 48 hrs was found to be 198727 ng hr/ml. Relative bioavailability of patch in comparison to oral suspension was calculated to be 146.03%. Unpaired t-test was applied between mean Cmax of glimepiride in rat plasma. An extremely significant P-value of less than 0.001 was obtained. Pharmacokinetic parameters clearly indicated that glimepiride was absorbed slowly, but continuously. Although the increase in drug concentration was slower but it was sustained in effective levels for a prolonged time period. The increase in plasma half-life of glimepiride with patch indicated that the drug remained in the body for a prolonged period of time when administered via novel drug delivery system and thus, will be able to exert a sustained action. The significantly lesser elimination constants of glimepiride obtained with the patch formulation further support the sustained release of the drug from the optimized formulations. Although Cmax was significantly less with transdermal devices, AUC (Area Under Curve) values were significantly higher compared with the suspension treated group, which could be due to maintenance of drug concentration within the pharmacologically effective range for a longer period of time with controlled release delivery systems. The significantly higher AUC values observed with the patch formulation also indicate increased bioavailability of the drug as compared to

oral suspension administration. The optimized transdermal formulation was evaluated for skin irritation studies on 24 healthy rats. The hairs of the dorsal portion were removed physically with the help of sharp surgical scissors and the skin was washed properly one day prior to use. Rats were divided into four groups (six rats in each group). Group I was a normal, No treatment was given. Group II included blank group treated with blank patch (without drug). Group III was a medicated group treated with medicated patch (with drug). Group IV was Formalin group, containing 0.8%v/v aq. solution of Formalin was applied as a standard irritant. The patches were removed after each 48 hr and the area examined for any signs of skin sensitivity or irritation and the fresh patches were secured at the same site at 2nd, 4th, 6th day.

All the respective treatments were continued till 7 days and finally application sites were monitored visually and graded according to the visual scoring scale. No signs of erythema and edema were observed in case of patch group. Formalin treated group was kept as a positive control which showed maximum erythema and edema. A significant difference ($P<0.01$) was observed between the patch and the formalin treated group. Pharmacodynamic evaluation was also done by the authors in diabetic rats. Male Wistar rats weighing 200 – 300g were fasted for 30 hrs and later rendered diabetic by injecting streptozotocin 50 mg/kg, via intra peritoneal route. Blood glucose was measured after 24 hrs and animals with blood glucose levels >250 mg/dl were selected. Selected diabetic rats were divided into two groups (six rats in each group) and fasted overnight. Water was available ad libitum. Rat dose of glimepiride was reported to be 10mg/kg. Group I consisted of oral suspension: suspended in 2%w/v gum acacia. (glimepiride: 10 mg/kg, per oral). Group II: Patch: 17cm2 patch was applied containing mg glimepiride. Blood was withdrawn periodically from tail vein at specific time intervals and blood glucose levels were measured using Accutrend® Alpha glucometer. In all the cases each animal served as its own control and the hypoglycemic response was calculated by taking the difference in glucose levels at the 0 hr and subsequent hours. The results of hypoglycemic activities of transdermal patch were compared with oral suspension of glimepiride (10 mg/kg) in diabetic rats. The initial hypoglycemic effect observed at 2nd hr after treatment was 36.67 % and 20.22 % reduction in blood glucose levels for oral suspension and patch respectively. A maximum hypoglycemic effect of 39.53% for suspension was observed at 8th hr, which remained stable up to 12th hr and decreased thereafter. For transdermal patch, maximum hypoglycemic effect of 38.06 % was observed at 12th hr, which remained stable up to 48 hrs. At 24th hr hypoglycemic effect was 10.61% and 36.41% for suspension and patch respectively. In case of patch, the hypoglycemic response was gradual but sustained for prolonged time period. This non-rapid and prolonged hypoglycemic response could be due to sustained and controlled release rate of drug from the formulation. The higher initial hypoglycemic effect with oral suspension also shows that the severe hypoglycemia associated with the oral administration of glimepiride can be overcome by a transdermal system. Thus it can be clearly seen, that the controlled release from transdermal formulations offered a significantly better control of blood sugar when compared with the conventional release oral suspension. The results of this investigation suggested that transdermal patch provided much better maintenance of therapeutic levels of drug in blood and for a prolonged period of time as well. Also, it provided an easy and efficient method of formulating matrix type transdermal systems using natural polymer chitosan. The non-irritant nature of the patches also revealed the advantage of using the natural mucoadhesive polymer. Consequently this technology can be explored for other anti- diabetic molecules as well so as to achieve better control over the disease [39].

PATENTS REPORTED ON TRANSDERMAL DRUG DELIVERY

In the past few years transdermal delivery has gained a lot on interest on the field of research. It has now become a patented technology as number of patents has been reported on drug delivery via this route. Table 2 give a brief review on various patents filed and published on transdermal drug delivery.

Table 2 Patents on Transdermal Drug Delivery.

Patent Publication Number	Filing Date	Inference	Reference
CA 2089468 A1	Feb 2, 1993	Involves a process for preparing ultrasonically sealed transdermal drug delivery system.	[40]
CN 103096882 A	Apr 27, 2011	Transdermal system containing donepezil or a pharmaceutically acceptable salt as an active ingredient; and an acrylate-rubber hybrid as an adhesive.	[41]
EP 0737052 B1	Dec 9, 1994	Transdermal system enclosed within a patch consisting of an occlusive covering. Enhancing skin hydration and drug absorption	[42]
EP 0848608 B1	Sept 6, 1996	Methods are provided for manufacturing transdermal system containing supersaturated drug reservoir, increasing the drug flux.	[43]
EP 1307231 A2	Jul 10, 2001	This invention provides a transdermal system for analgesic, antipyretic and anti-inflammatory drugs in combination with tetra glycol and water.	[44]
EP 1383692 B1	Apr 23, 2002	This enclosed a device and a method to stabilize a drug for transdermal delivery. By providing a child resistant packaging to prevent or control degradation.	[45]
EP 2068847 A1	Sep 20, 2007	Involves a composition and method for transdermal delivery.	[46]
EP 2190292 A1	Aug 28, 2008	Specifies a transdermal device consisting of a backing layer, adhesive layer and a release liner coated with a UV-cured highly cross-linked silicone and its method of preparation.	[47]
US 8246976 B2	Oct 7, 2005	A pressure-sensitive adhesive composition for transdermal delivery.	[48]
US 8252321 B2	Oct 31, 2007	An automated, programmable transdermal system to provide pulsed doses of medications, pharmaceuticals, hormones, neuropeptides, anorexigens, pro-drugs, stimulants, plant extracts, botanicals, nutraceuticals, cosmeceuticals, phytochemicals, phytonutrients, enzymes, antioxidants, essential oils, fatty acids, minerals, vitamins, amino acids, coenzymes, or other physiological active ingredient or precursor	[49]
US 8386027 B2	Apr 25, 2008	Included devices, systems, kits and methods for increasing the permeability across the skin.	[50]
US 8404277 B2	Jun 5, 2008	Matrix based transdermal system including capsaicin or a capsaicin derivative as an active component and used for treating neuropathy, pain, and inflammation and a preparation method is provided.	[51]

US 8467868 B1	Apr 26, 2006	A method for transdermal delivery of drugs and other small molecules is described.	[52]
US 8591941 B2	Aug 4, 2011	Transdermal system for the application of one or more active agents contained in one or more polymeric and/or adhesive carrier layers, proximate to a non-drug containing polymeric backing layer.	[53]
US 8632802 B2	Sep 9, 2011	A transdermal system with controlled rate of drug delivery, onset and profiles of at least one active agent by selectively manipulating the monomeric make up of an acrylic-based polymer.	[54]
US 20120321673 A1	Jun 20, 2011	Transdermal system comprising of steroids such as clobetasol propionate, betamethasone dipropionate, amcinonide, or loteprednol etabonate. Also comprises of a pressure-sensitive adhesive layer. Effective for the treatment of disease of the eyelid, like chalazion, blepharitis or meibomian gland dysfunction.	[55]
US 20130137951 A1	Jan 22, 2013	Devices, systems, kits and methods for increasing the skin's permeability controlled by measured skin electrical parameters.	[56]
WO 1994008655 A3	Oct 13, 1993	Specifies a transdermal system that utilizes ultrasonic energy to release a stored drug through the skin forcibly.	[57]
WO 1995017866 A1	Dec 9, 1994	In this transdermal system, rate of drug release is controlled by the encapsulation material. Drug penetration is driven by the resulting concentration gradient.	[58]
WO 1995030411 A1	May 9, 1995	Includes a transdermal system prepared by using polyelectrolyte gel matrix with the maximum ionic concentration based on IPNs (interpenetrating networks). Loading amount is maximized due to increase of ionic functional group in polyelectrolyte gel matrix. Rate of drug release is controlled	[59]
WO 1997010812 A2	Sept 6, 1996	Methods are provided for manufacturing transdermal system containing supersaturated drug reservoirs so that high drug flux can be achieved.	[60]
WO 2001048761 A1	Dec 27, 1999	An automated trans-dermal robotics treatment and a system to provide provide multi-modal therapies. The movement of a robotic arm (10) is pre-programmed to apply and deliver drug to the skin.	[61]
WO 2001087276 A1	May 15, 2001	This invention is related to a hydrogel composition for transdermal delivery containing acrylate polymers like acrylic acid polymer etc which can enable both hydrophilic and lipophilic permeation enhancers to be applicable in the hydrogel composition in order to effectively control skin penetration of drugs.	[62]
WO 2002045701 A2	Dec 5, 2001	This invention relates to compositions and methods for making transdermal system capable to achieve zero-order kinetics over a period of time in excess of 24 hours and at least 72 hours It comprises a pharmaceutically acceptable active agent carrier and a rosin ester which provides a crystal inhibiting and drug stabilizing effect.	[63]
WO 2003047554 A1	Oct 18, 2002	This invention is characterized by using transdermal system as a substitute for the oral or injection dosage form to directly act on the local nervous system through the skin.	[64]
WO 2003066130 A3	Feb 7, 2003	Transdermal delivery employing drug formulated with chaperone moiety to increase the drug transport.	[65]
WO 2003066130 A3	Oct 7, 2005	A transdermal system for the topical application of one or more active agents contained in one or more polymeric and/or adhesive carrier layers, proximate to a non-drug containing polymeric backing layer.	[66]
WO 2007040938 A1	Sept 12, 2006	Systems, devices, and methods for transdermal delivery of one or more therapeutic active agents to a biological interface. The system includes an active electrode assembly, a counter electrode assembly, and a plurality of functionalized microneedles.	[67]
WO 2007041314 A3	Sept 27, 2006	An iontophoretic drug delivery system is provided for transdermal drug delivery. It consists of an active ingredient reservoir. The one or more active agent reservoirs are loadable with a vehicle for transporting, delivering, encapsulating, and/or carrying the one or more active agents.	[68]
WO 2008030497 A3	Sept 5, 2007	An iontophoresis device for transdermal delivery of one or more therapeutic active agents to a biological interface having an active electrode assembly, a counter electrode assembly, and an inductor electrically coupled to the active and the counter electrode assemblies.	[69]
WO 2008106220 A1	Feb 28, 2008	Systems and methods for transdermal delivery employing controlled heat. The system of the present invention can deliver ketoprofen in an amount sufficient to produce a mean blood plasma concentration of ketoprofen in a human subject at least 45 ng/ml within four hours after initial application of the system.	[70]
WO 2009145801 A1	Oct 8, 2008	A ketotifen transdermal delivery system is provided. It includes a support layer and a plaster layer provided on the support, wherein the plaster layer contains ketotifen freebase. Also provided are	[71]

		methods of using the system.	
WO 2012092165 A1	Dec 23, 2011	Described transdermal administration of levonorgestrel, comprising polymer matrix and levonorgestrel acetate. Methods of making and using such systems also are described.	[72]
WO 2012177626 A1	Jun 19, 2012	A transdermal drug delivery system consisting of a steroid as an active agent such as clobetasol propionate, betamethasone dipropionate, amcinonide, or loteprednol etabonate. It also comprises a pressure-sensitive adhesive layer and a support, wherein the steroid is present in the pressure-sensitive adhesive layer.	[73]

CONCLUSION

The creation of transdermal delivery systems has been one of the most important of all the innovations, offering a number of advantages over the oral route. Transdermal patches have been observed as a potential carrier for the delivery of number of drugs transdermally. The preclinical and clinical studies confirmed that patches are promising carriers for enhancing the permeation of drugs deep into the systemic circulation and is effective and safe in the treatment of numerous diseases.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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