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Review

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Transdermal Delivery of Antihypertensive Agents: A tabular update

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Abstract

Transdermal Drug Delivery System is viable drug delivery platform technology and has a strong market world wide. Transdermal Drug Delivery System is particularly desirable for drugs that need prolonged administration at controlled plasma level that basis make appropriateness to antihypertensive agents for their transdermal development. Controlled zero order absorption, easily termination of drug delivery, easy to administration also support for popularity of transdermal delivery. This paper reviews the work on transdermal studies of antihypertensive agents in the tabular form.

Keywords: Transdermal, Antihypertensive agents.

Introduction

The principal of transdermal drug transport is to deliver drug across epidermis to achieve systemic effect over a prolong period of time. Controlled zero order absorption, simple administration mode, easy termination in case of failed, avoidance of first pass effects, reduction in side effects, sustained drug delivery, and improved patient compliance make the research interest of researchers.

The first patch of scopolamine approved in 1979, and now in the present market there numbers of transdermal patches are available for drug such as scopolamine, nitroglycerin, nicotin, clonidine, fentanyl, estradiol, testosterone, lidocain, and oxbutinin. Limited permeability of human skin is still a fundamental problem limiting its widespread therapeutic use. So it is the very big challenge of creating effective transdermal system because it involves sufficient drug permeability through the stratum corneum.

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Furthermore it is also important to ensure that the drug delivery systems do not irritate the skin, and the drug is not unduly metabolized and delivered according to the desired pharmacokinetics and pharmacodynamics. [1]

The first transdermal drug delivery system was bringing forward before 20 years in the United States. The technology induced remarkable enthusiasm and curiosity in various pharmaceutical companies in the 1980s and 90s. This curiosity diminished by limitations of the existing transdermal technology, and it was found that the numbers of drug candidates suitable for this route was found to be limited.

However thanks to the development of some ground-breaking permeation enhancement techniques interest in Transdermal Delivery such as:

- The prodrug approach
- Chemical Potential Adjustment
- Ionic complex

- Eutectic Systems
- Encapsulting in Liposomes
- High Velocity particles
- Lowering of skin resistance by chemicals
- Microneedle array
- Abrasing the Skin
- Phonophoresis, Sonophoresis
- Electroporation
- Magnetophoresis
- Damaging the Stratum corneum by Laser radiation
- Iontophoresis

More than 20 transdermal patches, containing 13 drug molecules are already available in the market. Clonidine, nicotine and glyceryl nitrate transdermal products are commercially availability. This small group of marketed products is representative of many important pharmacological classes like antianginal (nitroglycerine, isosorbide dinitarte), antihypertensive (Clonidine), antiemetics (Scopolamine), hormones (estradiol, testosterone), urinary antispasmodic (oxybuyrin), local anesthetic (lidocaine) and CNS drugs (fentanil, nicotine). Many others are in pipeline awaiting FDA approval [2]. Some drugs that are being extensively investigated for transdermal use include albuterol, enalapril, dronabinol, ketorlac, alprazolam, cytarabine, atenelol, buprenorphine, selegiline, isosorbide dinitrate and prozasin. A major breakthrough is expected anytime in the form of transdermal insulin.

Introduction of the physical enhancement techniques like iontophoresis combined with the prospect of the programmed delivery has contributed significantly in the growth of transdermal research. Iontophoretic products have already been launched in the US market hailing a new age programmed transdermal drug delivery [3]. Extensive research is going on to develop transdermal delivery systems for a wide range of drugs.

Advantages of transdermal drug delivery [4]

Transdermal Drug Delivery offers several important advantages like:

1. Transdermal medication delivers a steady infusion of a drug over an extended period of time.
2. Adverse effects or therapeutic failures frequently associated with intermittent dosing can be avoided.
3. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption, decomposition due to hepatic “first-pass” effect, formation of metabolites that cause side effects, short half-life necessitating frequent dosing etc.
4. An equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if, for example, the drug is given orally.
5. The simplified medication regimen leads to improved patient compliance and reduced inter- and intra-patient variability
6. Self administration is possible with these systems.
7. The drug input can be terminated at any point of time by removing transdermal patch.
8. Transdermal drug delivery can be used as an alternative delivery system for patients (nauseated or unconscious) who cannot tolerate oral dosage forms.

Limitations of transdermal drug delivery [4]

1. One of the greatest disadvantages of transdermal drug delivery is the possibility that a local irritation may develop at the site of application.
2. The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching, and local edema.
3. Another significant disadvantage of transdermal drug delivery is that the skin’s low permeability which limit the number of drugs that can be delivered in this manner.

4. Many drugs especially drugs with hydrophilic structures permeate the skin too slowly to be of therapeutic benefit.
5. The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.

Selection of drug candidates

Transdermal route of drug administration has certain inherent difficulties that make it unsuitable for large number of drugs. The selection of suitable of candidates is an important step for success of transdermal research. [5]

- Realistically, a transdermal drug delivery system should not cover an area more than 50 Sq.Cms. and hence transdermal drug delivery is suitable only for drugs for which the daily dose is of the order of a few milligrams.
- The effective concentration of the drug should be low, presumably in the nanogram per ml level.
- The half life ($t_{1/2}$) of the drug should be short.
- For drugs having very long biological half-life, the transdermal route may have little extra benefits for the common patients (however this route can be beneficial for the special patients like preterm infants.)
- The active ingredients should not have skin toxicity.
- As the diffusion of drug through polymer as well as skin is dependent on molecular size, the drug of low molecular size is preferred.
- The drug should have a low melting point.
- Drugs, which degrade in the GI tract or/are inactivated by hepatic first-pass effect, are suitable candidates for transdermal delivery.
- Tolerance to the drug must not develop under the near zero-order release profile of transdermal delivery.
- Drugs, which have to administer for a long period of time or which cause adverse effects to non-target tissues can also be formulated for transdermal delivery.

Research trends in transdermal and antihypertensive agents:

The main problem associated with the oral drug delivery include an uneven bio distribution, lack of drug targeting specificity, the necessity of large doses to achieve local concentration and adverse side effects due to such high dose. Since antihypertensives suffer from the disadvantage of extensive first pass metabolism and variable bioavailability, they are considered ideal Transdermal candidates [6].

Various research in this categories so far done are summarised below in tabular form:

S No.	Name of Researcher(s)/ Year	Work Title	Findings
1.	Anroop et al **2009**	Transdermal delivery of atenolol:effect of prodrugs and iontophoresis	They were studied the combined effect of two such techniques, iontophoresis and esterification, on the transdermal delivery of atenolol. Prodrugs significantly enhanced the transdermal flux of atenolol in passive process while in iontophoresis the enhancement ranged from 1.4 to 2.7 fold compared to atenolol. [7]
2.	Vinay Pandit et al **2009**	Formulation & evaluation of transdermal films for the treatment of overactive bladder	That transdermal films are a promising drug delivery system for tolterodine tartarate with more patient compliance in the treatment of overactive bladder. [8]
3.	Omray et al. **2008**	Development of mesoph-asic microreservoir -based transdermal drug delivery system of propranolol	The system was also studied for tensile strength, moisture content, water vapour transmission, drug content,anisotropy & In-vitro drug release studies. [9]

4.	Wahid et al **2008**	Preparation and evaluation of transdermal drug delivery system of etoricoxib using modified chitosan	Drug free polymeric films of chitosan, chemically modified chitosan & blend were prepared and evaluated for various physiochemical characters. [10]
5.	Gajbhiye et al **2008**	Dendrimeric nanoarchitectures mediated transdermal and oral delivery of bioactive	Pulled off ensues from above exploration craft our psyche that the dendrimer can be proficiently utilized in transdermal and oral drug delivery system with immense accomplishment. [11]
6.	Desai et al **2008**	Effect of enhancers on permeation kinetics of captopril for transdermal system	Citral and dimethyl formamide as permeation enhancers showed the best perm-eability as comp-ared to sodium tauroglycolate, sodium laurel sulphate. [12]
7.	Jamakandi et al **2009**	Recent trends in transdermal cardiovascular therapy	This article reviews the research on cardiovascular patches as well as the marketed products. [3]
8.	Sadashivaiah et al **2008**	Design and in vitro evaluation of haloperidol lactate transdermal patches containing ethyl cellulose-povidone as film formers	In this study, different ratios of EC and PVP transdermal haloperidol lactate patches were formulated using 4% hyaluronidase as a permeation enhancer. It can be reasonably concluded that haloperidol lactate can be formulated into transdermal polymeric patches to prolong its release characteristics. [13]
9.	Qureshi et al **2009**	Formulation strategy for low absorption window antihypertensive agent	It could be concluded from R2 value for Higuchi model and K-Peppas model that release followed fickian diffusion mechanism. **[**14]
10.	Ashish et al **2009**	A study of transdermal delivery of Glibenclamide using iontophoresis	In study we conclude that the Permeation rate of drugs across the pigskin can be considerably enhanced by the use of iontophoresis. [15]
11.	Gursharanjit et al **2008**	Screening of vanlafaxine hydrochloride for transdermal delivery: passive diffusion and iontophoresis	In this study researcher group reported Iontophoresis increased the permeation rate at both concentration levels over their passive counterparts, but surprisingly higher steady-state flux was obtained from obtained from lower donor drug load. [16]
12.	Shinde et al **2008**	Development and characterization of transdermal therapeutics system of tramadol hydrochloride.	The present work was designed to develop suitable transdermal matrix patches of tramadol hydrochloride using hydroxy propyl methyl cellulose, Eudragit RL-100 and Eudragit RS-100 with triethyl citrate as a plasticizer and dimethyl sulfoxide as a penetration enhancer The batch containing Eudragit RL-100 : HPMC (8 : 2) showed 79.65% release within 12 h and batch containing Eudragit RL-100 : HPMC (2 : 8) showed only 58.30% release in 12 h. This is because that the Eudragit produce crystallization free patch. [17]

13.	Aqil et al **2008**	Transdermal therapeutic system of enalapril maleate using piperidine as penetration enhancer	The optimized formulation was stable with a tentative shelf life of two years. Significant fall in BP ($p<0.001$) was observed in experimental hypertensive rats which was maintained for 2 days. There was 3 fold improvement in bioavailability with Transdermal system vis-à-vis marketed tablet (AUC(0 to t) : 1253.9 ng.h/ml vs. 422.88 ng.h/ml). These preclinicial studies indicate the feasibility of matrix-type TTS of EM for 2 day management of hypertension. [18]
14.	Gupta et al **2007**	Design and development of a proniosomal transdermal drug delivery system for captopril	It is evident from this study that the promising prolonged delivery system for captopril and has reasonably good stability characteristics. [19]
15.	Sunita et al **2007**	Development of transdermal matrix system of captopril based on cellulose derivative	The transdermal delivery system of Captopril employing different ratios of polymers, ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC) as (3:1) and (2:2) were developed. The *in vitro* skin permeation and *in vitro* dissolution studies showed that Captopril release was more in matrices containing ratio EC : HPMC as 2:2 compared to 3:1. Captopril from matrix containing EC : HPMC ratio 2:2 was able to penetrate through rabbit abdominal skin. The prepared matrices were free from any irritating effect and stable for 3 months. [20]
16.	Trommer et al **2006**	Overcoming the stratum corneum: The modulation of skin permeation	The progress made mainly over the last decade by use of chemical permeation enhancers. [21]
17.	Subal et al **2006**	Transdermal patches: What pharmacists need to know?	Reduced the side effects and sometimes improved the efficacy over other dosage forms. **[**22]
18.	Aqil et al **2005**	In-vivo characterization of monolithic matrix type transdermal drug delivery systems of pinacidil monohydrate: A technical note	a single patch application of pinacidil TDDS (B-4) can effectively control hypertension in rats for two days. The system holds promise for clinical studies. [23]
19.	Heather et al **2005**	Transdermal drug delivery: Penetration enhancement technique	Enhancement effects are associated with toxicity, therefore limiting their clinical application. [24]
20.	Babu et al **2005**	Effect of penetration enhancers on the release and skin permeation of bupranolol from reservoir-type transdermal delivery systems.	After some time by some researches they made a new system for the drug called reservoir. By this system they increase the permeation time 4-5 times more then the desired flux. [25]

21	Anroop et al **2005**	Synthesis and comparative skin permeability of atenolol and propranolol esters.	In this study Researchers had used the prodrug approach, where atenolol esters were prepared to increase its lipophilicity and permeation studies were carried out in isolated porcine skin; promising results were obtained with caproate ester. [26]
22.	Robert Langer **2004**	Transdermal drug delivery: past progress current status, and future prospect	He suggest skin represents a very important route of delivery in that it can provide an destroyed by the liver when taken orally. [1]
23.	Lizzy et al **2004**	Systematic review: Antihypertensive drug therapy in blank patients	Drug differ in their efficacy for reducing blood pressure in blank patients but there is no solid evidence that efficacy for reducing morbidity and mortality outcomes differs once patients achieve the blood pressure goal. [27]
24.	Grafe et al **2004**	Carrier mediated transport of clonidine in human keratinocytes	In the mechanistic study which performed on the human epidermal kiratinocytes cell culture revealed that the clonidine transport is affected due to pH. This experiment shows the transport of clonidine beyond the epidermal layer was affected by the transport of tertiary amine and inhibit by the competition with other amines such as triptamine,diphenhydramine, quinine , guanidine. [28]
25.	Babu et al **2004**	Effect of cyclodextrins on the complexation and transdermal delivery of bupranolol through rat skin	Methylated beta-cyclodextrin used as a enhancer, they shows the good permeation of the drug. [29]
26.	Cho et al **2004**	Enhanced transdermal delivery of atenolol from the ethylene-vinyl acetate matrix.	This study had shown that a matrix system containing ethyl vinyl acetate and polyoxy-ethylene 2-oleyl ether as penetration enhancers releases the drug in a diffusion-controlled manner and is sufficient to cause effective permeation. [30]
27.	Zhioxiong et al **2003**	Novel Transdermal Drug Delivery System with Polyhydroxyalkanoate and Starburst Polyamidoamine Dendrimer	This is the report of the application of PHA and dendrimer to the TDDS. [31]
28.	Mohamed et al **2003**	Matrix type transdermal drug delivery system of metoprolol tartrate: In-vivo characterization	It was concluded that MT could be administered transdermally through the matrix type TDDS developed in our laboratory. The drug remained intact and stable in the TDDS during storage. [32]
29.	Manvi et al **2003**	Formulation of transdermal drug delivery system of ketotifen fumarate	Concluded that films of eudragit L 100; hydroxyl propyl methylcellulose and ethyl cellulose; hydroxypropyl methylcellulose polymeric combinations may be feasible for formulating rate controlled transdermal therapeutic systemof ketotifen fumarate for effective control and prophylaxis of allergic asthma. [33]

30.	Sheree et al **2003**	Transdermal penetration of vasoconstrictors-present understanding and assessment of the human epidermal flux and retention of free bases and ion-pair	Epidermal retention of VCs and SA did not correspond to their molar ratio on application and confirmed that following partitioning into the stratum corneum, ion-pair separate and penetration is vasoconstrictor-transdermal-percutaneous absorption-epidermal retention. [34]
31.	Panigrahi et al **2002**	Formulation and evaluation of pseudolatex transdermal drug delivery system of terbutaline sulphate	The resulted medicated patches were of average thickness (95-155 mium), and content uniformity of the drug varied from 94.5 to 99.1 percent. [35]
32.	Krishnaiah et al **2002**	Effect of solvent system on the In-Vitro permeability of nicardipin hydrochloride through excised rat epidermis	The use of binary solvent system, ethanol and the ratio of 70:30 v/v, is an effective vehiclefor the development of a transdermal therapeutic system for nicardipin hydrochloride. [36]
33.	Namdeo et al **2002**	Liquid crystalline pharmacogel based enhanced transdermal delivery of propranolol hydrochloride	The self maded pharmacogel used in the synthesis of prodrugs propranolol palmitate hydrochloride and propranolol stearate hydrochloride and carried out that the enhancement rate increase inflammatory reaction freely done. The lameller liquid crystals which present in the gel they get the high chemical potency and show the surety of drug is given by the precutaneous route successfully. [37]
34.	Stamatialis et al **2002**	Controlled transport of timolol maleate through artificial membranes under passive and iontophoretic conditions	Timolol is also used in the iontophoretic delivery. The iontophoretic study mainly used for the artificial membranes which have various pore sizes. In such studies timolol showes the high permeability for microporous membrane, which resistant then the skin. [38]
35.	Moroi et al **2001**	The Pharmacological Basis Of Therapeutics	The timolol (beta-blocker) is normally used in the treatment of glaucoma but it belongs to the antihypertensive drugs category. [39]
36.	Lennart et al **1999**	Randomised trial of old & new antihypertensive drugs in elderly patients: Cardiovascular mortality & morbidity the Swedish trial in old patients with Hypertention	The frequency of congestive heart failure was significantly lower in the ACE inhibitors group than in the calcium antagonists group. [40]
37	Kirjavainen et al **1999** Kobayashi et al **2000** Hirvonen et al **1998** Stott et al **2001** Amnuaikit et al **2005**	Skin permeation of propranolol from polymeric film containing terpene enhancers for transdermal use	Some other antihypertensive agents have hydrophilic-lipophilic nature and they created highly expectation. There are the various studies have been done on these drugs. These can be used as model drugs for transdermal development. [41-45]

38	Kobayashi et al 1998	Relationship between the skin permeation movement of propranolol and skin inflammatory reactions.	The permeability is evaluated by the initial studies. That is show drug induces inflammatory reactions. [46]
39	Chesnoy et al **1998**	Strctural parameters involved in the permeation of propanolol HCL by iontophoresis and enhancers	Changes in the electrical and structural properties of the stratum cornium after incorporation of enhansers. [47]
40.	Pao-Chu Wu et al **1996**	In vitro percutaneous absorption of captopril through excised rabbit skin	The pH dependency in skin permeability of zwitterionic drug may reflect the permselective property of the skin dependent on the lipophilicty. [48]
41	Ganga et al **1996**	Effect of azone on the iontophoretic transdermal delivery of metoprolol tartrate through human epidermal in vitro	It was found that both during passive and iontophoresis, azone caused increased transport of the drug through the human epidermis and transport was increased 130-fold during iontophoresis compared to passive flux. [49]
42	Thacharodi et al **1996**	Collagen-chitosan composite membranes controlled transdermal delivery of nifedipine and propranolol hydrochloride	Some authors made the rate controlling device with the help of collagen membrane and reports the good regulation of drug and controlled release. [50]
43	Thacharodi et al **1995**	Development and *in vitro* evaluation of chitosan-based transdermal drug delivery systems for the controlled delivery of propranolol hydrochloride	Regular work helps in the development of a suitable delivery system of propanolol. Various trials of the polymers (artificial or natural) were continuo which helps in the development of reservoir and have rate controlling property. There was developed a gel type reservoir with the help of natural polymer “chistone”. Rate-controlling membranes of varying permeability obtained by controlled cross-linking with gluteraldehyde were also developed using propranolol as model drug. [51]
44	Christine et al **1992**	Iontrophoretically enhanced transdermal delivery of an ACE inhibitor in induced hypertensive rabbits: Preliminary report	Both modes of constant-current iontophoresis of captopril offer a safe and efficacy between the two forms of enhanced delivery. [52]
45	Sclar et al **1991**	Utility of a transdermal delivery system for antihypertensive therapy. Part 1	The transdermal patches have better rate then the other conventional dosage form. This study involving large populations were carried out in which transdermal dosage form shows better effect according to the therapy. [53]

46	Naline et al **1990**	Comparative Beta-adernoceptor blocking effects of propanolol, bisoprolol, atenolol, acebutolol, and diacetolol on the human isolated bronchus	It was concluded that:(1) Atenolol & bisoprolol were the least potent drugs at bronchial level in therapeutic plasma concentration, (2) That test performedon the human isolated bronchus might be a useful screening procedur for new drugs with potential activity on the airways. [54]
47	Banga et al **1988**	Iontophoretic delivery of drugs: fundamentals, development and biomedical applications	This article is intended to review old as well as very recent literature on the technique, methodology, clinical findings, influencing factors, relevant electronics and other related aspects of iontophoretic drug delivery, and to provide the readers a comprehensive overview of the state-of-art of this potential new area of biomedical research. [55]
48	ONeill et al **1988**	Development and evaluation using hairless mouse skin of a transdermal timolol product	Maleate ester inhance the gastrointestinal solubility so that conventional system carried the drug in this form. The free base timolol is used in skin permeation studies and which system used in this study that is free from base, shows and maintained the adequate zero-order plasma profile. [56]
49	Weiss et al **1987**	Transdermal Controlled Systemic Medication	Clonidine is mostly used in the transdermal form because by this form drug avoid first pass metabolism. High expectation were as pharmacodynamic studies carried out with adhesive transdermal patches of the drug showed effectiveness comparable to that of bupranolol infusion in rabbits. [57]
50	Nicholls et al **1986**	Comparision of transdermal nitrate and isosorbide dinitrate in chronic stable angina	It is suggested that the dose of TN may have been inadequate to demonstrate such an effect and further studies using a higher dose schedule will be required. [58]
51	Wellstien et al **1986**	Transdermal delivery of bupranolol: pharmacodynamics and beta-adrenoceptor occupancy	The experimental patch applied to a wider area in human volunieer showed that bupranolol penetrated in sufficient amounts to have pronouncd pharmacological effects against isoprenaline-challenged tachycardia. [59]
52	Weber et al **1984**	Clinical experience with rate-con- trolled delivery of antihypertensive therapy by a transdermal system	The first antihypertensive agent which comes in the form of transdermal patch was clonidine. The transdermal patch first only evaluated and study for clinical efficacy then with the combination of diuretic agents. [60]

Conclusion

Transdermal drug delivery system offer superior uniformity of drug concentrations in plasma throughout their duration of use. This results in reduced side effects and, sometimes, improved efficacy over other dosage forms, by the results of these advantages transdermal drug delivery system has been become research interest of various pharmaceutical industries. But there is limitation in Transdermal drug deliver have a limited drug candidates due to permeability problems. However thanks to the development of some ground-breaking permeation enhancement techniques, researchers are able to deliver drugs having poor permeability. Iontophoresis, Sonopphoresis, use of electron beam radiation etc, contributed significantly in the growth of transdermal research and making hope to develop successful Transdermal system even for poor candidates.

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