Review Article

Role of Permeation Enhancers in the Treatment of Hypertensive Drugs by Transdermal Drug Delivery Route: A Review

G. Sreeja Sreekumar*
School of Pharmacy, PRIST University, Thanjavur, Tamilnadu- 613403, India.
***Corresponding author's E-mail:** sreeja.s.chinnu@gmail.com

Received: 05-03-2020; **Revised:** 22-05-2020; **Accepted:** 28-05-2020.

ABSTRACT

Transdermal drug delivery systems (TDDS) are a kind of novel type of controlled drug delivery option which is aimed at achieving the controlled application of medication across the skin surface. TDDS are gaining wide popularity in the recent past, for the patients suffering from life style diseases such as hypertension, diabetics, cardiac problems etc. TDDS techniques provide the time controlled delivery of the drug to the human body. Success of the TDDS route depends on the selection of the permeation enhancers which enables the penetration of the drug to the body through the skin. Various modern trends in the selection of permeation enhancers are discussed in the present review.

Keywords: Transdermal drug delivery, Hypertension, Permeation enhancers, Drug delivery, Blood pressure.

INTRODUCTION

Hypertension (HT), which is otherwise referred as high blood pressure (HBP), is caused by the continual increase of the blood pressure in the arteries.[1] This causes an increased force imparted by the blood flow to the heart arterial walls. Hypertension is a long-term medical condition which does not cause any active symptoms. It leads to severe health problems which might leads to heart related problems, stroke and sometimes loss of life also. Hypertension is often associated with lifestyle disorder as it is caused by the inappropriate food habits. [2] Research studies shows that approximately 30 % of the adult global population is victim of hypertension.[2] Obesity is associated with the hypertension risk. Common medication of hypertension includes[3] diuretics such as thiazides, indapamide, chlorthalidone etc, beta-blockers and alpha-blockers, calcium-channel blockers, central agonists, peripheral adrenergic inhibitors, vasodilators, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers etc. Selection of medication is based on individual's medical conditions.

Different types of hypertension

Measurement of blood pressure is expressed as measurement of two numbers: top value known as systolic pressure and bottom value known as diastolic pressure. A value of blood pressure falling within the range 120 to 80 mm Hg is considered within the normal (or healthy) value. The systolic pressure value (120) attributes the pressure imparted by the blood in your arteries during the contraction of your heart muscle and the diastolic pressure value (80) is attributed to the pressure imparted by blood pressure when your heart muscle is between beats. Any value above the stipulated value indicates the hypertensive condition which requires treatment. Table 1 shows the different types of hypertensive disorders.[4] As discussed earlier, the value of blood pressure falling within the range 120 to 80 mm Hg is considered within the normal value. Any value above this value is considered as hypertensive disorder. Generally, the value of blood pressure value ranging from systolic value up to 129 and diastolic value up to 80 is considered as elevated blood pressure value. If the blood pressure systolic value ranging from 130 to 139 Hg and diastolic value ranging from 80 to 89 Hg is considered as stage 1 hypertension. The blood pressure value above 140 systolic pressure and above 90 diastolic pressure is known as stage 2 hypertension. The extremely higher value of blood pressure in which systolic blood pressure value above 180 Hg and diastolic pressure value above 120 Hg is called as hypertensive crisis.

Table 1: Different types of hypertensive disorders.

Condition	Systolic pressure (Hg)		Diastolic pressure (Hg)
Normal	Below 120	and	Below 80
Elevated	120-129	and	Below 80
High blood pressure-stage 1	130-139	or	80-89
High blood pressure-stage 1	140 or higher	or	90 or higher
Hypertensive crisis	Above 180	and or	Above 120

Medication for hypertensive disorders.

Patients having elevated blood pressures are often advised to follow strict diet procedures and it might not require any medication. However, if the blood pressure is above 140 (systolic) and 90 (diastolic) pressures are administered

with various doses of medications. The kind of medication prescribed for each patient depends on the individual's medical condition. The kind of medical treatment aimed at reducing the blood pressure below 130 -80 Hg. Table 2 compares the commonly administered drugs for various hypertensive disorders. [5]

Table 2: Commonly used medicines to treat hypertensive disorders

Medicinal type	Chemical content	Biological action
Thiazide diuretics	chlorthalidone, hydrochlorothiazide etc.	Drug action is on kidneys to eliminate sodium and water
Angiotensin-converting enzyme (ACE) inhibitors.	lisinopril (Zestril), benazepril (Lotensin), captopril (Capoten) etc	Help to relax blood vessels by blocking the formation of a natural chemical that narrows blood vessels.
Angiotensin II receptor blockers (ARBs).	(Atacand), losartan (Cozaar)	Help to relax blood vessels by blocking the action
Calcium channel blockers.	Amlodipine (Norvasc), diltiazem (Cardizem, Tiazac, others)	Help to muscles of your blood vessels.

In addition to the above, sometimes doctors may prescribe certain drugs to treat the adverse situations. These drugs are as Alpha blockers (doxazosin, prazosin), Alpha-beta blockers (carvedilol, labetalol), Beta blockers (acebutolol, atenolol), Aldosterone antagonists (spironolactone (Aldactone) and eplerenone (Inspra), Renin inhibitors (Aliskiren (Tekturna), Vasodilators (hydralazine and minoxidil), Central-acting agents clonidine (Catapres, Kapvay), guanfacine (Intuniv, Tenex) and methyldopa etc.

Transdermal drug delivery route for hypertension treatments

Effectiveness of a particular drug for specific purpose depends on the method of drug delivery route opted. Each type of drug delivery systems are designed to provide effective way to administer the drugs. Various methods of drug delivery routes are opted for different purposes depend on the drug action on the body and type of drug used. Among the various drug administration routes, oral, intrauterine, intra vaginal, implants and injectable routes are most widely used. Transdermal drug delivery systems (TDDS) received tremendous attraction in the recent past, due to its advantages over the conventional drug delivery systems. [6-10] TDDS provides a suitable drug administration option due the advantages such as elimination of first pass metabolism, superior rate of absorption, enhanced compatibility with the patient body, cost-effectiveness, and dosage can be tuned according to the requirement. [8,9] TDDS, involves a non-invasive delivery of medications across the skin surface and the drug delivery is achieved at a predetermined rate across the skin. TDDS provides the controlled and constant administration of the drug. TDDS is a type of modulated or controlled drug delivery systems. Controlled drug delivery systems are designed to achieve the goal crossing the physicochemical barriers such as poor water solubility of drugs, large molecular weight of peptide and protein drugs, and difficulty of controlling drug release kinetics and biological barriers such as distribution of drug delivery systems by the body rather than by formulation properties, limiting delivery to a specific target in the body, during the absorption of the drug to the target organ.

During early 1950s, the drug administration was based on pills or capsules which are loaded with the target drug, which release the drug molecule when contact with the water.[11] However, this type of the drug delivery system lacks the systematic drug delivery. Several chronic diseases conditions such as hypertension, cholesterol, diabetics etc. require systematic and modulated release of drugs for longer duration of time.[11] Later, the enhanced bioavailability of the drug had lead to the extensive use of injectables for drug administration.[12] However, the usage of injectables also found to have several disadvantages in terms of bioavailability, side effects, non-portability etc.[12] Moreover, the chronic diseases such as hypertension, diabetics etc demand a regulated release of drug for prolonged duration of time. In this context, past several decades had witnessed extensive research focussing on developing of a targeted drug delivery systems.[13] This type of drug delivery system aimed at releasing the drug molecule to the target organ. However, these types of drug administration suffer the advantages that the current drug-carrier targets are not effective in finding the exact target. Therefore, this type of drug delivery systems are often limited to its used in cancer treatments where the specific drug administration has been found to be effective through the use of a targeted drug carrier. Moreover, after the absorption of the targeted drug molecule, there is no control over the release of the drug to the body. Modern trends of pharmaceutical research focus on developing drug delivery systems which include administration of optimum drug according to the therapeutic requirement, enhancing effectiveness of treatment with minimum amount of drug, lesser side-effects, modulate the frequency of drug administration, having convenience way of administration etc.

Transdermal drug delivery systems (TDDS) is one of the systems lying under the category of controlled drug delivery, which constitutes of self controlled, distinct dosage forms deliver the drug through the skin at a controlled rate to the systemic circulation [6-10]. TDDS are also known as patches and these patches are applied to the intact skin. The outermost layer of the skin, which consisting of keratinized cells, stratum corneum is considered as the rate limiting barrier in transdermal permeation of most molecules.[6,7] The TDDS patch is used to adhere to skin for the constant delivery of the drug to the body. Structure of TDDS mainly constituted by a polymer matrix, drug constituent, liners, penetration enhancers, pressure-sensitive adhesives, backing

laminates, release liner, etc. The liners are used to protect the patch during storage. Polyester film is the most commonly used liner in TDDS. Acrulate or silicone based adhesives are used to adhere the patch to the skin. Release of the drug is controlled by the permeation enhancers (also known as penetration enhancers).[6,7] Various organic molecules such as terpeneoids, solvents like alcohols, surfactants such as sodium lauryl sulphate, pluronic F127 etc are the permeation enhancers.[6-10] Apart from the above, a cellulose or poly propylene silicon rubber based protective film is used to cover the patch from outer environment. Several drugs are commercially offered in the form of transdermal patches. All the drugs may not satisfy the conditions of TDDS criteria. For a drug to be used in TDDS, the drug should have a molecular weight less than 1000 Daltons and should have affinity for both lipophilic and hydrophilic phases and short half life.[8] This review presents the various TDDS drugs used in the treatment of diabetic treatment.

Role of permeation enhancers in transdermal drug delivery systems

TDDS, as discussed, are advantageous compared with other modes of drug administration as it bypassed hepatic first pass metabolism[14]. The rate limiting step for this process is the barrier function of the skin outermost layer, the stratum corneum (SC). Therefore, skin penetration enhancers are widely used for this purpose. Penetration enhancer enhances the permeation of the desired drug (penetrant) through the skin by reducing the impermeability of the skin. Several enzymes and liposomes are widely used as permeation enhancers.

The desirably properties of permeation enhancers are it should be pharmacologically inert by material, non-irritating, nontoxic, non-allergic to skin, compatible with drugs and excipients, odourless, tasteless, colourless, and inexpensive. The solvent properties of the material also are very important in selecting a permeation enhancer. This review article describes the transdermal delivery route by various chemical permeation enhancers. The review also discusses about the use of natural material as permeation enhancer.

Isradipine for enhanced transdermal delivery against hypertension

Isradipine is a kind of calcium channel blocker type of drug used to control hypertension. Isradipine has low bioavailability because it undergoes extensive first pass metabolism. Qadri and co-workers attempted to study the possibility of using isradipine-loaded invasomes as a suitable TDDS.[15] In their work, the authors have prepared by conventional thin layer evaporation technique using Phospholipon 90G, b-citronellene (terpene) and ethanol. The formulation has been characterized in terms of size, size distribution, morphology, entrapment efficiency, and antihypertensive activity. Based on the studies, the optimized formulation obtained was used for pharmacodynamic study.

Studies showed that isradipine has low bioavailability in terms of oral administration.[15] Several research group investigated the possibility of using isradipine for TDDS drug administration because of its unique advantages such as low molecular weight (371.4 Da) and high melting point (168–170 °C). The terminal elimination half-life (about 8 h) is also suitable for using isradipine TDDS.

Angiotensin-converting enzyme inhibitors (ACEIs) for transdermal drug delivery

Angiotensin II receptors also have been implemented for transdermal drug delivery routes.[16] As we discussed earlier, Angiotensin II receptor blockers (ARBs commonly prescribed medications for extreme type of hypertension and most of these drugs have the disadvantage that is undergoes extensive first-pass metabolism, which might reduce its s bioavailability. Therefore, Angiotensin II receptors have a wide scope in utilizing them in TDDS option. One such study is by Ahad *et al.*[16] The authors investigated the possibility of using angiotensin-converting enzyme inhibitors as a TDDS for managing hypertension.

Proniosomal based Transdermal Drug Delivery System

Recently, proniosomal based drug delivery route gained tremendous attraction towards targeted drug delivery[17,18]. Proniosomes are dried form of free flowing granular species gives multi lamellar niosomal dispersion during hydration. Thus, proniosomes utilises a suitable carrier coated with non-ionic surfactants. The advantage of pronisomal based drug delivery route is they are water soluble carrier particles and are coated with a surfactant species which upon hydration forms niosomal dispersion immediately. The proniosomes also facilitates distribution, transportation and storage. Moreover, the surfactants present on proniosomes act as penetration enhancers which can entrap both hydrophilic and lipophilic drugs. The surfactants are biodegradable, non-toxic, also. Because of these unique advantages, several researchers studied the feasibility of proniosmal route option for the drug delivery. Anitha et al. reviewed several such drug options which utilises proniosmal based as drug delivery route. [17] In their findings, the authors concluded that ethosomes are as good as or even better than conventional niosomes. Radha et al. also reviewed on similar context and the authors concluded that proniosomes are ideal candidate for targeted drug delivery route. [18]

Gupta et al. had made a similar attempt to utilize proniosme for trasdermal drug delivery route by considering the advantages of proniosmes. [19] The authors have attempted to study the proniosomal carrier system for captopril for the treatment of hypertension. The drug, captopril was encapsuled in various formulations of proniosomal gel consists of different compositions of ratios of sorbitan fatty acid esters, cholesterol, lecithin. These compositions are prepared by coacervation-phase separation method. The different compositions are then characterized in vitro for size, vesicle count, drug entrapment, drug release profiles and vesicular stability at

different storage conditions. Stability of the compositions were tested for a period of four weeks.

Liposomes as mediators

The major difficulty associated with the TDDS is the low permeability of some of hte drugs through the skin barrier, which limits its use in TDDS. In this scenario, liposomes have been utilized as mediators for the transport of drug in TDDS route.[20] Mishra et al. studied the liposome mediated release of propranolol hydrochloride for the treatment of hypertension.[20] The various studies performed revealed the efficiency of liposome as the mediator the transport of proranol hydrochloride. In this aspect, in vitro flux, enhancement ratio (ER), release pattern of the drug etc. were calculated for TDDS. Similarly, the in vivo study conducted on male albino rats was used as a measure of performance of elastic liposomal, liposomal, and plain drug solution. The permeation of the proranol hydrochloride across the skin was monitored by confocal laser scanning microscopy studies. The study confirmed the efficacy of the liposomal formulation for transdermal delivery of propranolol hydrochloride with higher entrapment efficiency.

Nitrendipine is a anti-hypertension drug which is widely used. It suffers the disadvantage in terms of high first pass metabolism and low bioavailability. Gaur et al studied the role of similar nanoliposomes for the delivery of another hypertensive drug, nitrendipine. [21] Their study targets at investigating the role of nanoliposome for the targeted delivery of nitrendipine nanoliposome. The vesicles used for the study were prepared from phosphatidylcholine, cholesterol and dicetyl phosphate using thin lipid film hydration method. The synthesized nanoliposomes were characterized at various size distribution, entrapment efficiency of the drug and in vitro drug release profile. Results of the study revealed that the synthesized nanoliposomal composition exhibited maximum drug permeation with flux 0.622 µg/cm2 and distribution parameter 7.177 cm^2/hr. Therefore, the study concluded that liposome has suitable desirable features which facilitates the drug delivery which minimizes the wastage of drug and its maximum utilization.

Permeation enhancement using Non-Ionic Surfactant

An excellent study by Jain et al. investigated the role of non ionic surfactants in the release of the hypertensive drug, carvediolol[22]. The nonionic surfactants such as Tween 80 and Span 80 were introduced in the films to enhance the drug permeation rate through skin of guinea pig. The drug formulations were prepared with different non-ionic surfactants and different polymers such as HPMC-E5, ERL 100 etc. The authors investigated the role of surface pH, Drug content uniformity, in-vitro permeation studies, skin irritation studies etc. The studies concluded that non-ionic surfactants can be effectively used as a mediator for the transport of hypertensive drugs across the skin.

Role of natural material as permeation enhancers

Several natural materials also have been reported for use as permeation enhancers.[23,24] The advantage of natural materials is that they are non-toxic and less allergic towards skin as compared with the chemical based permeation enhancers. In addition, these materials are easily available and are superior in terms of its compatibility with drug. Natural oils are widely used in cosmetics and in several medicines.

Diltiazem HCl (DH) is a calcium channel blocker type drug used in hypertension. Patel *et al.*[16] studied the role of the natural oils such as linseed oil, pumpkin seed oil, jojoba oil and tea-tree oil evaluated for permeation enhancement activity of the drug Diltiazem HCl across wistar rat skin. The study pointed out towards the fact that natural oils are inexpensive candidates of permeation enhancers for the TDDS route of drug delivery for the patients suffering from hypertension. Similarly, Sharma et al.[17] also studied on similar background for the use of aloe vera as permeation enhancer for the delivery of candesartan cilexetil for the treatment of hypertension.

Conclusion and scope of further studies

The present review reported the importance of permeation enhancers for the delivery of drug through transdermal drug delivery route. The reports from various research groups showed that various liposomal enzyme based transdermal drug permeation enhancers are superior in terms of its several advantages such as low first pass metabolism, high biological availability etc. Natural permeation enhancers also have been reported and showed the advantage such as low irritation to skin, cost effective etc.

The review covering at bringing novel trends in drug delivery route in transdermal route by bringing more insights in terms of permeation enhancers. However, more extensive understanding on such studies are required to understand the exact permeation mechanism and drug-enhancer compatibility. Several natural drug permeation enhancers also have to be explored which might provide several advantages in use of such materials in patients suffering from chronic hypertension.

REFERENCES

1. https://www.medicalnewstoday.com/articles/150109.php
2. Nicoll R, Henein M Y, Hypertension and lifestyle modification: how useful are the guidelines, British Journal of General Practice, 60, 2010, 879-880
3. https://www.medicalnewstoday.com/articles/150109.php#management-and-treatment
4. https://www.healthline.com/health/high-blood-pressure-hypertension/blood-pressure-reading-explained
5. https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/diagnosis-treatment/drc-20373417

6. Benson HA. Transdermal drug delivery: penetration enhancement techniques, Current drug delivery, 2, 2005, 23-33.
7. Henry S, McAllister DV, Allen MG, Prausnitz MR, Microfabricated microneedles: a novel approach to transdermal drug delivery, Journal of pharmaceutical sciences, 87, 1998, 922-5.
8. Prausnitz MR, Mitragotri S, Langer R, Current status and future potential of transdermal drug delivery, Nature reviews Drug discovery,3, 2004, 115-24.
9. Barry BW, Novel mechanisms and devices to enable successful transdermal drug delivery, European journal of pharmaceutical sciences, 14, 2001, 101-14.
10. Naik A, Kalia YN, Guy RH, Transdermal drug delivery: overcoming the skin's barrier function, Pharmaceutical science & technology today, 3, 2000, 318-26.
11. Park K, Controlled drug delivery systems: past forward and future back, Journal of Controlled Release, 190, 3-8.
12. Tibbitt MW, Dahlman JE, Langer R. Emerging frontiers in drug delivery. Journal of the American Chemical Society. 2016 Jan 27;138(3):704-17.
13. Rosen H, Abribat T, The rise and rise of drug delivery, Nature Reviews Drug Discovery, 4, 2005, 381-5.
14. Prausnitz MR, Langer R, Transdermal drug delivery, Nature Biotechnology, 26, 2008, 1261–1268.
15. Qadri GR, Ahad A, Aqil M, Imam SS, Ali A, Invasomes of isradipine for enhanced transdermal delivery against hypertension: formulation, characterization, and in vivo pharmacodynamic study, Artificial cells, nanomedicine, and biotechnology, 45, 2017, 139-45.
16. Ahad A, Al-Mohizea AM, Al-Jenoobi FI, Aqil M, Transdermal delivery of angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs) and others for management of hypertension, Drug delivery, 23, 2016, 579-90.
17. Anitha P, Ramkanth S, Sankari KU, Alagusundaram M, Gnanapraksah K, Devi PD, Prasanna RI, Ethosomes-A noninvasive vesicular carrier for transdermal drug delivery, Int. J. Rev. Life. Sci.1, 2011, 17-24.
18. Radha GV, Rani TS, Sarvani B, A review on proniosomal drug delivery system for targeted drug action, Journal of basic and clinical pharmacy, 4, 2013, 42-48.
19. Gupta A, Prajapati SK, Balamurugan M, Singh M, Bhatia D, Design and development of a proniosomal transdermal drug delivery system for captopril, Tropical journal of pharmaceutical research, 6, 2007687-93.
20. Mishra D, Garg M, Dubey V, Jain S, Jain NK, Elastic liposomes mediated transdermal deliveryof an anti-hypertensive agent: propranolol hydrochloride, Journal of pharmaceutical sciences, 96, 2007, 145-55.
21. Kumar Gaur P, Mishra S, Kumar Sharma K, Sadish Kumar S, Puri D, Yasir M, Development of Nitrendipine Nanoliposome for Transdermal Drug Delivery: Preparation, Characterization and Permeation Studies, Drug Delivery Letters, 7, 2017, 48-53.
22. Jain Neha, Kori ML, Jain AK, Permeability Enhancement of Carvediolol Using Non-IonicSurfactant and Different Polymers through Transdermal Film, World Journal of Medical Sciences, 14, 2017, 62-68.
23. Patel JK, Jani RK, Enhancing Effect of Natural Oils as Permeation Enhancer for Transdermal Delivery of Diltiazem Hydrochloride Through Wistar Rat Skin, Skin, 6, 2016,15-20.
24. Sharma K, Skin permeation of Candesartan Cilexetil from transdermal patch containing Aloe Vera gel as penetration enhancer, Asian Journal of Pharmaceutics 10, 2016, 1-14.

Source of Support: Nil, **Conflict of Interest:** None.