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Transdermal delivery of β-blockers

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β-Adrenoceptor blocking drugs (β-blockers) are one of the most frequently used class of cardiovascular drugs that are mainly used in conventional dosage forms., which have their own limitations including hepatic first-pass metabolism, high incidence of adverse effects due to variable absorption profiles, higher frequency of administration and poor patient compliance. Essentially, attempts have been made to develop novel drug delivery systems for β-blockers, including transdermal delivery systems, to circumvent the drawbacks of conventional drug delivery. However, so far none of the β-blocker drugs have been marketed as transdermal delivery systems. Nevertheless, there have been noteworthy research endeavours worldwide at the laboratory level to investigate the skin permeation and to develop transdermal formulations of β-blockers including: propranolol, metoprolol, atenolol, timolol, levobunolol, bupranolol, bopindolol, mepindolol, sotalol, labetolol, pindolol, acebutolol and oxprenolol. Innovative research exploiting penetration-enhancing strategies, such as iontophoresis, electroporation, microneedles and sonophoresis, holds promise for the successful use of these drugs as consumer-friendly transdermal dosage forms in clinical practice. This paper presents an overview of the transdermal research on this important class of drugs.

Keywords: β-blocker, drug delivery, penetration enhancer, transdermal

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1. Introduction

The last 80 years have witnessed the move of transdermal delivery from a promising route of drug administration to a widely accepted clinical reality, with the marketing of an appreciable number of drugs as transdermal delivery systems (TDS). The opening studies on transdermal drug delivery essentially focused on understanding the physiological barrier properties of the skin. In 1924, Rein discovered that the cells on the outermost layer of the skin, the stratum corneum (SC), present a formidable challenge against the inward traffic of many therapeutically active substances [1]. Blank further advanced this idea by illustrating that the removal of the SC led to an increase in water loss from the skin [2] and Scheuplien *et al.* presented the hypothesis that transdermal permeation was regulated by the passive diffusion of molecules through the SC [3]. Michaels and colleagues were successful in determining the diffusion coefficients of some drugs and showed that some possessed significant permeability [4]. This prompted the development of TDS in the 1970s, culminating in the approval of the first patch by the FDA in 1979 for the delivery of scopolamine for the treatment of motion sickness. Subsequently, nitroglycerin patches were approved in 1981 for the management of angina pectoris. A number of TDS for different drugs are now in the market including those for nicotine, clonidine, testosterone, oxybutinin, fentanyl, lidocaine and estradiol [5]. These have a $3 billion-strong market in the US.

β-blockers have been the drugs of choice for many years in the treatment of cardiovascular disorders. These drugs block the β-adrenoceptors in the heart, bronchi, pancreas, liver and peripheral vasculature. Traditionally, they have been used as conventional dosage forms, which have their own limitations (e.g., hepatic first-pass metabolism, a low bioavailability, a high incidence of adverse effects due to variable

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absorption profile, higher frequency of administration and poor patient compliance). The shortcomings of conventional oral delivery can be potentially minimised by novel drug delivery systems including transdermal dosage forms. Although none of the β-blockers are commercially available as TDS, this class of drugs has still attracted the attention of many scientists across the globe. The feasibility of transdermal delivery of drugs such as propranolol (PP), metoprolol (MP), atenolol (AT), timolol (TM), levobunolol (LB), bupranolol (BP), bopindolol (BD), mepindolol (MD), sotalol (ST), labetolol (LT), pindolol (PD), acebutolol, oxprenolol and so on has been explored in-depth. The advances and innovations in the transdermal delivery of β-blockers are discussed in the text and a summary is presented in Table 1.

2. Propranolol

PP is a nonselective prototype β-adrenoceptor blocker drug. It has been the most frequently sought-after drug for the development of transdermal dosage forms because of its near ideal characteristics as a drug candidate for transdermal drug delivery. PP is hydrophilic, highly lipid stable and has a low molecular weight. It undergoes extensive hepatic first-pass metabolism resulting in a poor bioavailability (15 – 23%) from oral formulations [6,7].

Due to its hydrophilic nature [8,9], PP invariably does not permeate in therapeutically effective amounts by passive diffusion. Accordingly, a number of attempts have been made to enhance its permeation using a variety of skin models. Kunta *et al.* [8] investigated the effect of menthol and other terpenes (limonene, linalool and carvacrol) on the percutaneous absorption of hydrochloride salt (PP-HCl) through hairless mouse skin. These authors concluded that alcohol terpenes are very effective in enhancing the transdermal transport of PP-HCl. In the case of linalool, the flux values increase six- to sevenfold at 5 – 10% enhancer concentration, whereas L-menthol provides a significant enhancement in percutaneous absorption at a concentration as low as 1%. Their results are in agreement to those of Zhao and Singh [10] who managed to achieve a significant enhancement in the PP-HCl flux through porcine skin using terpenes (menthone and limonene) in an ethanolic vehicle. This is attributed to a greater partitioning of PP-HCl with the enhancer treatment than the control (without enhancer) treatment. The above study corroborates the extraction of SC lipid by terpenes as the possible mechanism of penetration enhancement. Microscopic barrier perturbation is also supposed to contribute to enhanced PP flux.

In a comparative study [11] on the enhancement of *in vitro* permeation of a hydrophilic (PP) and a lipophilic drug (diazepam or indomethacin), by various putative enhancers such as 1-nonanone, 1-nonalol and 1-decanol, it was found that 1-nonalol and 1-decanol enhance PP flux in significant amounts, whereas the indometacin or diazepam flux is enhanced by 1-nonanone only. A rise in PP flux by terpenes is reported to be comparable to that observed with 1-nonalol [11].

Krishna and Pandit developed three transdermal formulations containing PP-HCl in a hydrophilic polymer matrix [12]. Two of these carried an ethylene vinyl acetate (EVA) membrane of varying thickness and one did not have the membrane. A high amount of the drug (~ 80%) permeated across excised hair-free rat skin from the one without membrane in 24 h. The other two patches provided variable permeation profiles, with higher values obtained from the one containing the lower thickness of rate-controlling membrane. These authors later developed carboxy methyl cellulose (CMC) sodium-based TDS of PP with 67% permeation achieved in 24 h [13]. Krishna and Pandit also reported mild skin irritation with the application of these patches. Hydroxypropyl methylcellulose matrix-based TDS of PP have also been attempted. Various grades of hydroxypropyl methylcellulose have been used in the preparation of a matrix-dispersion type system of PP, which was evaluated for an *in vitro* dissolution profile using a Cygnus' sandwich patch holder. Almost 100% of the drug was reported to be released from the above system by Verma and Iyer with a good correlation with *in vivo* data (C_{max}, $AUC_{0\text{-}24\ h}$, $AUC_{0\text{-}\infty}$) [14]. The same group prepared TDS of PP using mixed grades of Eudragits (Rohm Pharma) with a good release and permeation profile [15]. Higher plasma values of the AUC, T_{max} and C_{max} are observed than the corresponding values from urinary data. Insignificant differences have been reported in the values of elimination rate constant, $t_{½}$, elimination $t_{½}$ generated from the plasma and from urinary analyses [14-16].

The relative contribution of the device and the membrane in the drug release and permeation of PP from a TDS needs to be mentioned. Iordanskii *et al.* [17] compared the permeability of PP with or without the placement of carbosil membrane between the device and the receptor solution. Although the permeability of the carbosil membrane is higher than human skin, it can still be used to predict the transdermal delivery of candidate drugs [18]. It is impractical to assess the drug release from a hydrophilic matrix into an aqueous receptor fluid because of the inevitable matrix dissolution of the matrix itself; hence, software is used to predict the hypothetical drug release assuming zero membrane thickness, which indicates simulated barrier-free conditions. Release of PP from the hydrophilic matrix across the skin mimetic carbosil membrane marginally depends on the drug diffusion coefficient in the matrix and is totally independent of the diffusion coefficient in the membrane. The drug partition coefficient between the membrane and the matrix seems to have a significant effect when the release from the hydrophilic matrix is faster. The rate-limiting step for the drug release from such matrices is drug transport through the membrane/skin. Water counter flow from the receptor solution through the membrane into the hydrophilic matrix leads to membrane plasticisation and hydration of the matrix, which modifies the drug delivery kinetics. Time-dependent percutaneous penetration enhancement by skin hydration that is achieved by occlusive device application is well documented [19].

Table 1. Research advances in transdermal delivery of β-blockers

β-Blocker	Characteristics	Transdermal research	Ref.
PP	Soluble in water MW: 259.81 g Extensive hepatic first-pass metabolism Oral bioavailability = 15 – 23%, $t_{½}$ = 3 h	Terpenes as penetration enhancers through hairless mouse skin Best results with 10% carvacrol PP flux: control (without enhancer) = 0.135 µg/cm^2/h, with enhancer = 122 µg/cm^2/h	[8]
		Cineole (1% w/w) as enhancer through rat skin PP flux: control = 6.2 µg/cm^2/h, with enhancer = 27.4 µg/cm^2/h	[9]
		5% limonene as penetration enhancer PP flux: control = 0.85 µmol/cm^2/h, with enhancer = 2.80 µmol/cm^2/h	[10]
		Nonalol and decanol as enhancers through hairless mouse skin	[11]
		TDS with EVA (20 µm) rate-controlling membrane Permeation of PP through rat skin ≤ 79.2%	[12]
		Sodium CMC-based TDS of PP Permeation via rat skin ≤ 67%	[13]
		HPMC- and Eudragit-based matrix dispersion type TDS of PP Pharmacokinetics in human volunteers: C_{max} = 388 ng/ml, T_{max} = 5 h, AUC $_{0–36}$ = 430 ng/h/ml	[14,15]
		Illustration of contribution of device and membrane in the release of PP from TDS	[17,18]
		Use of ucecryl polymer-based adhesive for fabrication of TDS of PP	[20]
		Ethyl cellulose and PVP-based films of PP Higher release obtained by increasing the PVP content	[21]
		Permeation of PP is higher from solubilised system in comparison to microemulsion and emulsion	[22]
		Chitosan, a naturally occurring polymer used in formulation of membrane-controlled TDS of PP	[24,27]
		Transdermal application of prodrugs of PP, namely PP stearate hydrochloride and PP palmitate hydrochloride, produce 20- and 25-fold increase in PP flux	[28]
		Effect of drug chirality on skin transport of β-blockers explained by melting temperature-membrane transport concept	[30,31]
MP	β-1 selective adrenergic blocker Very soluble in water MW: 684.82 g Extensive hepatic first-pass metabolism, $t_{½}$ = 4 h	*N*-Decyl methyl sulfoxide as enhancer for transdermal delivery of MP through mouse and human cadaver skins	[37]
		Eudragit-based TDS of MP using menthol as a penetration enhancer, ≤ 90% permeation achieved	[40,41]
		Use of melting temperature-membrane transport technique to compare the permeation characteristics of enantiomers of MP-free base across hairless mouse skin. Permeation of *(R)*- and *(S)*-MP in the presence of L-menthol and (±) linalool increased by 2.4- and 3.6-fold, respectively	[42]
		Use of electroporation technique for enhanced permeation of MP across hairless rat skin	[43]

AT: Atenolol; BD: Bopindolol; BP: Bupranolol; CMC: Carboxy methyl cellulose; DMSO: Dimethyl sulfoxide; EVA: Ethylene vinyl acetate; HPMC: Hydroxypropyl methylcellulose; LB: Levobunolol; LT: Labetolol; NMP: *N*-Methyl-pyrrolidone; MD: Mepindolol; MP: Metoprolol; MW: Molecular weight; OA: Oleic acid; PP: Propranolol; PVP: Poly(vinyl pyrrolidone); $t_{½}$: Half life; TDS: Transdermal delivery system; TM: Timolol.

Table 1. Research advances in transdermal delivery of β-blockers (continued)

β-Blocker	Characteristics	Transdermal research	Ref.
AT	β-1 selective adrenergic blocker Soluble in water MW: 266.34 g Systemic bioavailability = 50 – 60%	Alcohol and decanol as absorption promoters AT flux increased by alcohol (four times) and decanol (six to eight times)	[50]
		Fatty acids and their esters as enhancers for AT Best enhancers: OA and polyoxyethylene-2-oelyl ester	[51]
		Effect of plasticiser on the release rate of AT from drug–polymer matrix	[55]
		Formulation of EVA–AT matrix for enhanced bioavailability of AT in rabbits using polyoxyethyene-2-oleyl ester and tributyl citrate as penetration enhancer and plasticiser, respectively	[56]
		Good correlation found between steady-state flux of AT with inverse of melting point Poor correlation of drug permeation with partition coefficient, molecular weight and solubility	[57]
TM	Potent noncardioselective β-blocker Freely soluble in water MW: 432.49 g Extensively metabolised in liver Elimination $t_{½}$ = 2 – 2.6 h	DMSO, OA and lauryl chloride used as penetration enhancers for TM; effectiveness of above enhancers for permeation of TM through human cadaver skin: lauryl chloride > DMSO > OA	[61]
		TDS of free base of TM using five different rate-controlling membranes Maximum permeation achieved with Celgard 2400 membrane (Celanese Corporation)	[62]
		Hydrophilic drug reservoirs (sodium CMC and carbopol) present greater TM flux than hydrophobic vehicles (aerosil and plastibase)	[63]
		Iontophoresis as the physical enhancement technique TM flux increases exponentially across microporous membrane on application of current	[64-68]
		Factors affecting iontophoretic delivery of TM explained	[72-75]
		Electroporation provides a fivefold increase in TM flux over passive diffusion	[76,77]
		Ion-activated, pH-controlled disodium phosphate and Tris buffer patches of TM, two- to threefold improvement in oral bioavailability	[78,79]
LB	Potent β-blocker Soluble in water MW: 327.85 g $t_{½}$ = 4 – 6 h	Matrix-type transdermal device fabricated using a plastic cup Both the device and the skin control the LB permeation	[87]
BP	Nonselective β-blocker, MW: 308.2 g Sparingly soluble Hepatic first-pass metabolism (> 90%) $t_{½}$ = 1.2 h	Isopropyl myristate, NMP and pyrrolidone used as absorption promoters for BP NMP provides a 3.6-times higher BP flux than passive diffusion without enhancers, pyrrolidone is twice as effective as NMP Cyclodextrins: hydroxy propyl β-cyclodextrin and partially methylated β-cyclodextrin gave a 3.8- and 4.6-fold enhancement in BP flux over the control through rat skin from 1% aqueous suspension of BP	[90,91, 93]
BD	Nonselective β-blocker MW: 484.5 g Soluble in water $t_{½}$ = 50 min Oral bioavailability = 70%	Clinical trials on TDS of BD to study the pharmacokinetics of BD in healthy human volunteers	[97]

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Table 1. Research advances in transdermal delivery of β-blockers (continued)

β-Blocker	Characteristics	Transdermal research	Ref.
MD	Nonselective β-blocker MW: 262.36 g Sparingly soluble in water Oral bioavailability = 80% $t_{½}$ = 4 h	Double-blind, placebo-controlled, crossover trial showing attenuation of isoprenaline-induced inodilatory responses (increase in mean heart rate, systolic blood pressure, reduction in diastolic blood pressure and so on) by transdermal MD therapy	[98]
		Significant reduction in BP of hypertensive patients by 20-mg transdermal MD treatment	[99, 100]
		Less skin irritation reported with MD patch than PP patch	[101]
LT	Nonselective β-blocker Soluble in water MW: 364.87 g Hepatic first-pass metabolism (60 – 75%) Plasma $t_{½}$ ~ 3.5 h	Eudargit RL 100, Eudragit RS 100 and PVP K-30 as the film-forming polymers for preparation of matrix type TDS of LT with PEG 400 as the plasticiser and DMSO as the penetration enhancer, > 90% drug release from the TDS, therapeutically effective in experimental hypertensive rats	[105]
Miscellaneous		Effect of iontophoresis on the transdermal delivery of five β-blockers of varying lipophilicity (PP, AT, pindolol, acebutolol and oxprenolol) Increase in lipophilicity leads to higher skin absorption but decreased transfer rate to cutaneous vein	[106]
		Combined effect of electroporation and iontophoresis on transdermal delivery of TM and AT through human stratum corneum using a three-compartment diffusion cell. Iontophoretic transport of TM is decreased by electroporation	[108]
		Pretreatment with ion channel modulator drugs, such as nifedipine and verapamil, prior to skin-irritating drugs such as nadolol can suppress the contact hypersensitivity reactions	[109]
		A sensitisation protocol for the development of hypoallergenic TDS is presented Sensitisation is achieved by the application of drugs such as albuterol, chlorphenamine, clonidine or nadolol to shaven dorsal mice skin for 5 days in a hydroxy ethyl cellulose vehicle Contact sensitisation measured by ear-swelling response to application of 1% drug in vehicle	[110]

AT: Atenolol; BD: Bopindolol; BP: Bupranolol; CMC: Carboxy methyl cellulose; DMSO: Dimethyl sulfoxide; EVA: Ethylene vinyl acetate; HPMC: Hydroxypropyl methylcellulose; LB: Levobunolol; LT: Labetolol; NMP: *N*-Methyl-pyrrolidone; MD: Mepindolol; MP: Metoprolol; MW: Molecular weight; OA: Oleic acid; PP: Propranolol; PVP: Poly(vinyl pyrrolidone); $t_{½}$: Half life; TDS: Transdermal delivery system; TM: Timolol.

Ucecryl polymer-based adhesive is arguably ideal for fabrication of adhesive matrix-type TDS for the most optimum controlled release of PP [20]. The burst-release phenomenon (initial quick release) seems to be minimised by this approach. The film thickness also affects the release profile of the film. The drug flux can be accelerated by the addition of propylene glycol, which is believed to form hydrophilic micropores in the adhesive film.

Increasing the drug concentration and poly(vinyl pyrrolidone) (PVP) content in ethyl cellulose-PVP based medicated films of PP leads to a higher flux value. PVP causes leaching of the hydrophilic portion of the matrix, leading to the formation of pores in the matrix texture, which triggers a higher drug release [21]. In a study on the comparison of permeation of PP across an artificial double-layer membrane (composed of a barrier foil and a lipid barrier) from various dispersed systems including emulsion, microemulsion and solubilised system, Ktistis *et al.* [22] discovered that PP permeation is more due to the solublised system than from microemulsion or emulsion. Increasing the concentration of surfactant (e.g., polysorbate 80) increases the permeability coefficient of PP from the dispersed system. A high permeability rate of PP can be achieved from reverse micelle-based microemulsion [23].

Synthetic polymers used as rate-controlling membranes, matrix formers and adhesives often pose as critical skin irritation hazards. These can be largely overcome with the use of natural polymers. Chitosan, a naturally occurring polycationic polysaccharide polymer, can be used in the formulation of device (membrane)-controlled TDS of PP [24]. Chitosan is a non-toxic, non-irritant and biocompatible polymer [25,26]. A near zero-order drug release can be achieved using a chitosan rate-controlling membrane and a chitosan PP-drug reservoir. Adhesive sealing is the preferred technique instead of conventional heat sealing, which is a difficult proposition for these biopolymeric polymers. Crosslinking of chitosan membranes with glutaraldehyde reduces the drug release, which is inversely proportional to the degree of crosslinking. Chitosan hydrogels

provide more transcutaneous permeation of PP than a corresponding aqueous solution of the commercial drug. This is attributed to the interaction of hydrogel with the SC, thus increasing the solubility of the drug in the skin. The transdermal gel shows a superior permeation of PP than the liquid solution due to an increase in drug solubility [27]. Increasing the quantity of crosslinker and decreasing the crosslinker acyl chain length in the gel leads to an enhanced PP permeability.

The prodrug approach has also been employed to enhance the transdermal delivery of β-blockers. An increase in PP-HCL flux as high as 20- and 25-fold can be achieved from two PP prodrugs: PP stearate HCl and PP palmitate HCl, respectively [28]. Transdermal administration of these prodrugs improves the bioavailability of PP-HCl up to seven to eight times over the oral treatment, with skin irritation scores within the permissible limits specified by the Code of Federal Regulations. In view of the reports of concentration-dependent skin irritation by parent compounds [29], the prodrug approach can be used to withstand cutaneous irritation in the transdermal delivery of β-blockers.

The role of drug chirality on the skin transport of β-blockers can be explained by the melting temperature-membrane transport (MTMT) concept [30,31]. This predicts a significant difference in skin transport rates when there are large differences in melting temperatures between the pure enantiomers and the racemate. A difference of 21°C between the racemate and the enantiomers of PP was detected by Touitou *et al.* using the MTMT model [30]. This group also predicted a ratio of 3.2 for enantiomer/racemic fluxes through the skin, which was confirmed by experiments using Testskin™ (Organogenesis Inc.; 335 versus 108 μg/cm^2/h) and human cadaver skin (149 versus 45 μg/cm^2/h). Accordingly, enantiomers of PP are perceived to be better candidates for transdermal delivery in comparison to the racemate.

Transdermal delivery leads to a significant improvement in the bioavailability of PP. Studies have shown five- to sixfold increments in the relative bioavailability of PP in rabbits following the administration of TDS [32,33]. Rabbit pinna skin is a good simulation model for human skin [34]. Oral delivery presents low T_{max} and high C_{max} values due to the rapid absorption of the drug from the gastrointestinal tract. Transdermal treatment on the other hand, results in prolonged T_{max} and low C_{max} values due to the barrier properties of the skin, which entails early accumulation of the drug in the skin, followed by a sustained and controlled release into the systemic circulation. Higher mean residence time values are observed after TDS treatment due to continuous replenishment of the drug into the systemic circulation.

3. Metoprolol

MP is a β-1 selective adrenergic blocker and is widely accepted as a first-choice drug in the treatment of mild-to-moderate hypertension and stable angina [32] and is also useful in postinfarction patients. Because of the nonselective β-blocker properties of PP, this drug needs to be used with caution in asthmatic and diabetic patients. As β-blockers such as MP are cardioselective, they are safe for use in patients with these conditions. However, MP is subjected to extensive hepatic first-pass metabolism, resulting in a low oral bioavailability [35,36]. It also has a short biological half-life ($t_{½}$) of ~ 4 h, which necessitates frequent dosing. To overcome this shortcoming, a number of attempts have been made for the development of transdermal dosage forms.

Ghosh *et al.* explored the feasibility of transdermal administration of MP by investigating its permeation across hairless mouse and human cadaver skin [37]. These authors also studied the effect of *N*-decyl methy sulfoxide as an enhancer. According to this group, MP permeated through the mouse and human cadaver skin in therapeutically effective amounts from a polyacrylate patch bearing *N*-decyl methy sulfoxide as an enhancer (5% w/w) with no significant lag time. Remarkable similarities in the absorption of the active pharmaceutical ingredients (APIs) through the hairless mouse and human cadaver skin have been documented [38]. These findings are contradictory to other reports, which suggest a significant difference in the permeabilities of the APIs across the skin of these two species [39].

The transdermal route can be used for the safe and effective delivery of MP for 2 days [40,41]. A matrix-based TDS of MP can deliver ≤ 90% of the drug across albino rat skin with the incorporation of menthol as a penetration enhancer [41]. The system is claimed to be free from any skin irritation and stable enough for a shelf life of 2 years. The TDS reverts blood pressure values to normotensive levels in the experimental hypertensive rats. The Eudragit RL 100 fraction of the matrix has a major influence on the release of MP from the device as the release is found to be exponential to the amount of Eudragit RL 100 that is present in the drug–polymer matrix. Initially, rapid release is observed from this matrix-type TDS due to the rapid dissolution of the surface drug, which later reaches constant values.

The MTMT technique has also been employed to compare the permeation characteristics of individual enantiomers of MP-free base using hairless mouse skin with and without chiral permeation enhancers L-menthol and (±)-linalool [42]. In the absence of enhancers, the permeation profiles of *(R)*-and *(S)*-MP from donor solutions containing either *(RS)*-MP or pure enantiomers were found to be comparable; however, in the presence of enhancers L-menthol and (±)-linalool, the flux values were increased by 2.4- to 3.0-fold, respectively. The permeation profiles of *(R)*- and *(S)*-MP from donor solutions containing *(RS)*-MP were comparable. However, when donor vehicles contain pure enantiomers, the permeation enhancing effect of L-menthol on *(S)*-MP was significantly higher by 25% than on *(R)*-MP. Furthermore, in the presence of L-menthol, the flux of *(S)*-MP from donor solution containing pure *(S)*-MP was 35% higher than the flux of *(RS)*-MP from racemate. The study clearly proves that the *(S)*-enantiomer of MP is a better transdermal candidate than the *(R)*-enantiomer and the racemate.

One of the most recent techniques in transdermal drug delivery is electroporation. This is a reversible phenomenon in which a lipid bilayer that is exposed to high-intensity electric field pulses is temporarily modified by the creation of transient pores, thus allowing the enhanced permeation of APIs. Vanbever *et al.* [43] used Easyjet Plus® (Equibio) electroporating equipment for the permeation enhancement of MP across hairless rat skin. The results showed an achievement of a significant enhancement of MP across full thickness hairless rat skin in comparison to diffusion through untreated skin. An increase in the number of twin pulses (300 V for 3 ms, followed after 1s by 100 V for 620 ms) raises drug transport. Single pulse (100 V, 620 ms) is found to be as effective as twin-pulse application (2200, 1100 or 300 V for 3 ms; followed after 1 s by 100 V for 620 ms). Diffusion factors such as pulse voltage, pulse number and pulse duration govern the quantity of drug delivered [44,45]. The technique causes no apparent skin irritation or systemic toxicity, although occasional mild and reversible erythema and oedema have been reported [46-48].

A 90-fold increase in the bioavailability of MP by transdermal administration over oral treatment (30.07 versus 3.48%) has been reported by Ghosh *et al.* [49]. This group also concluded that a lower transdermal dose (16 mg) is sufficient to produce a therapeutic blood level of MP as compared with oral dose (150 mg). In addition, transdermal treatment of MP provides a better safety profile in relation to systemic side effects such as headaches, impotence, tiredness, insomnia and gastric disturbances.

4. Atenolol

As with MP, AT also belongs to the class β-1 selective adrenoceptor antagonists. On oral administration, it can induce side effects such as nausea, diarrhoea and ischaemic colitis. Transdermal delivery of AT has been explored to overcome the above adverse effects. Passive diffusion of AT fails to achieve the target flux commensurate to therapeutic plasma concentration. However, skin permeation of AT is significantly enhanced using alcohol (fourfold) and 5% decanolic solution (six to eight times) as penetration enhancers [50]. The target steady-state flux that is necessary to attain therapeutic plasma concentration is achievable using the above enhancers. Amongst the fatty acids, oleic acid is reported to be the best penetration enhancer for AT amongst a pool of fatty acids including linoleic acid, caprylic acid and lauric acid [51]. Polyoxyethylene-2-oleyl ester, a derivative of oleic acid with a double bond, is an even better enhancer for AT. Oleic acid and its derivatives function by partitioning into the SC lipids and disrupting the structure and lipid fluidity of the SC [52,53]. A recent study suggests that oleic acid decreases the density and increases the shape factor of the Langerhans cells in the epidermis, which could cause immunosuppression as a result. Moreover, oleic acid also creates pores on the surface of corneocytes, indicating transcellular permeation of API as the possible mechanism of penetration enhancement [54]. The effect of plasticiser on the release rate of AT from drug–polymer matrix is also documented [55]. Amongst citrate and phthalate plasticisers, tributyl citrate yields a maximum drug release from the matrix with 1.5-fold enhancement in AT flux over the control. An increase in temperature and the loading dose results in a higher drug release due to a reduction in activation energy.

With heed to the above studies, Shin *et al.* used polyoxyethyene-2-oleyl ester and tributyl citrate as a penetration enhancer and plasticiser, respectively, to form an EVA–AT matrix for an enhanced bioavailability of AT in rabbits [56]. They reported a 46% increase in bioavailability in the enhancer group over the control group (with no enhancer). An insignificant increase in the C_{max} in the enhancer group was observed, although T_{max} decreased significantly in the enhancer group. Again, there was an insignificant difference between the enhancer and control groups in relation to the $t_{½}$ and mean residence time; however, $t_{½}$ and the mean residence time were significantly increased with the transdermal treatment when compared with intravenous administration. Sustained release and constant blood concentration with minimal fluctuation is possible from the above EVA–AT matrix. The latter can potentially be used for development of a TDS.

Studies on the correlation of skin permeability with physicochemical parameters using five antihypertensive drugs (including AT) indicate a good correlation of steady-state flux with inverse of melting point [57]. A poor correlation of drug permeation is found with partition coefficient, molecular weight and solubility. However, skin permeability and solubility profiles present an interesting trend. The initial permeation rates of poorly water-soluble drugs were higher than steady-state flux, whereas moderately water-soluble drugs such as AT showed more or less similar permeation throughout the study. The trend is completely reversed in the case of highly water-soluble drugs such as diltiazem. These observations indicate that the drug derivatives of low melting points and good aqueous solubility are good candidates for transdermal delivery.

Gel-based transdermal delivery of AT was investigated by Demou *et al.* [58]. The amount of AT released from the gel was inversely proportional to the polymer concentration in the gel. Higher amounts of AT were released from Klucel gels than methocel and carbopol gels. The amount of AT that permeated increased with a rise in the drug concentration up to the point of saturation solubility. Elsewhere, it is reported that on increasing the concentration of AT in donor cells, there is a decrease in permeability coefficient and an increase in flux across mouse and guinea-pig skins [59].

5. Timolol

TM is a potent noncardioselective β-adrenoceptor blocking agent that is used to treat hypertension, angina pectoris and myocardial infarction. Transdermal delivery of TM is a valid option as it is extensively metabolised in the liver and its elimination $t_{½}$ is 2 – 2.6 h [60]. However, because of its hydrophilic

nature, TM is not likely to permeate at the desired (therapeutic) concentration through the skin. Penetration-enhancing strategies may have to be employed to achieve the target flux.

Soni *et al.* [61] used dimethylsulfoxide, oleic acid and lauryl chloride to promote the permeability of TM through human cadaver skin. Lauryl chloride is considered to be the most effective enhancer for TM, followed by dimethylsulfoxide and oleic acid. TM (used in maleate salt form) as used in the above study may not yield therapeutically effective concentration because of its predominantly hydrophilic nature. The free base of TM is comparatively more lipophilic (partition coefficient P; 1.72 versus 0.45). It is accepted that substances with higher P values are so lipid soluble that they tend to remain dissolved in the SC and do not diffuse well into the water-rich dermal layer. The free base of TM was used to formulate a TDS by O'Neill *et al.* [62]. They used five different rate-controlling membranes, namely: Celgard 2400, Celgard 2402, Celgard 2412 (Celanese Corporation), EVA and Silastic® (Dow Corning). Celgard membranes are composed of microporous polypropylene with the 2400 grade having a thickness of 2.5×10^{-2} mm and provides the best permeation rate amongst the five membranes. EVA seems to be most resistant to drug permeation. Hydrophilic drug reservoirs such as sodium CMC and carbopol present a greater AT flux than the hydrophobic vehicles such as aerosil and plastibase. An adhesive matrix-type system of TM can deliver therapeutic plasma level (4 ng/ml) 4 h after the patch application, which could be maintained for ≤ 32 h even when the patch is removed after 24 h [63].

Iontophoresis (the application of direct constant current) can also be employed for enhanced permeation of TM, as it is a charged drug [64]. By using an electrode of the same polarity as the charge of the drug, the drug is driven across the skin by electrostatic repulsion. Bulk-fluid flow or volume flow occurs in the same direction as the flow of counter ions; this phenomenon is called electro-osmosis. The simultaneous reduction of counter ions and pH leads to the enhanced iontophoretic flux of TM [65]. Two kinds of membranes (dense and mesoporous) can be used to simulate the skin barrier for transdermal iontophoresis of TM [66]. The mesoporous membrane is comparatively more permeable than the dense membrane. The permeability of TM through the mesoporous membrane with or without current application is comparable. In contrast, microporous membrane exponentially increases the transdermal ingress of TM by significant amounts following current application. When the mesoporous membrane is applied, the SC mainly controls the TM delivery, whereas when microporous membrane is used, the SC and the membrane contribute to controlling drug delivery [67].

The age of the animal does not affect iontophoretic transport of TM across rat skin [68]. It is accepted that compared with humans, transdermal absorption is higher in laboratory animals such as rat, rabbit and mouse. Close simulation is observed in the dermal permeation of pigs, monkeys and humans [69]. The composition of SC lipids varies between rodents and humans [70]. In one study on the comparison of passive diffusion through hairless mouse, hairless rat, guinea-pig, dog, pig and human skin samples, it was revealed that hairless mouse skin was the most permeable [71]. Iontophoretic treatment, however, produces the maximum TM flux in human skin [68] and the lowest in rabbit skin. Iontophoresis for 2 h followed by passive diffusion for up to 24 h minimises the interspecies variation in transdermal flux of TM. Other factors that affect the iontophoretic delivery of TM are the thickness of the skin, differential binding of the drug to the skin, variation in metabolic activity of the skin and the number of hair follicles in different animal species [72-75].

Application of a high-voltage electric field (electroporation) has been reported to enhance the dermal transport of hydrophilic molecules, neutral or highly charged compounds and macromolecules with a molecular weight of 40 kDa [76]. An increase in TM flux as high as fivefold has been observed as compared with passive diffusion [77] when electrodes were positioned 4 mm from the SC. The flux remains comparable with passive diffusion when electrodes are placed at a distance of 20 mm.

Definite improvements in bioavailability were observed with transdermal versus oral therapy. Transdermal bioavailability of TM from ion-activated, pH-controlled disodium phosphate and Tris buffer patches is reported to be 80 and 116%, respectively [78], as compared with oral bioavailability of 48% [79]. The skin irritation from the above two patches is reported to be mild, which was completely reversed in 50% of the patient population within 24 h. Intersubject variability in bioavailability of ≤ 65% was observed by many investigators [80-82]. In water-activated, pH-controlled devices, as water enters the device, the buffer that is present in the drug reservoir (between two silicon membranes) adjusts the pH, and then controls the drug release through the silicon membranes. The release of TM across human cadaver skin from Tris buffer devices is reduced by ≤ 70% and the lag time is lengthened by ≤ 40 h [83]. *In vitro* skin permeation may overestimate the barrier properties of the skin and may not be a true reflection of the extent of drug absorption *in vivo* [84]. Skin irritation and occlusion *in vivo* could provoke more drug absorption than *in vitro* simulations. Moreover, the contact between the skin and the device may not be as good *in vitro* as *in vivo*. Buffers significantly increase the release rate; Tris buffer increases the TM flux by 3150-times compared with an unbuffered device [84], and a positive correlation is found between the pH of the drug reservoir and release rate. Even duration of the action can be controlled with the pH-mediated devices.

6. Levobunolol

LB is a potent β-blocker that is used in the treatment of cardiovascular morbidity. It has a short $t_{½}$ of 4 – 6 h and is effective at a very low plasma concentration of 16 µg/ml [35,36]. LB is effective in hypertensive patients who are resistant to PP [85] and is

50-times more potent than L-PP [86]. The feasibility of transdermal delivery of LB was explored by Ghosh *et al.* [87]. This study group incorporated the drug in a matrix transdermal disk that was fabricated by using a plastic cup and studied its drug release and permeation behaviour. They found that both the device and the skin control the steady-state skin permeation of LB. Furthermore, this group observed that increasing the loading dose by > 5% gives more drug release with no significant change in the permeation rate. Optimum results are obtained for LB flux with the application of medium duration square-wave type pulses.

7. Bupranolol

BP is a potent nonselective β-blocker with a chlorine substituent in the molecule. Peak plasma concentrations of BP are observed within 1.2 h after oral treatment [88]. The $t_{½}$ is 1.2 h and is subject to extensive first-pass hepatic metabolism (> 90%) after oral administration [89]. These attributes make BP a good candidate for transdermal drug delivery. Isopropyl myristate and *N*-methyl-pyrrolidone (NMP) have been used as absorption promoters for BP. NMP provides a 3.6-times higher BP flux than passive diffusion without enhancers [90]. Isopropyl myristate and NMP enhance the penetration by increasing the solubility of the permeant in SC. Maximum enhancement *in vivo* is observed when D-limonene is used as the enhancer. However, predicted steady-state plasma concentration values could not be obtained *in vivo*, although the plasma concentration was consistently higher than the therapeutically effective plasma concentration of the drug [90]. Pyrrolidone has been used as an enhancer for BP in the development of reservoir-type TDS [91]. Pyrrolidone is reported to be twice as effective as an enhancer for BP than NMP (enhancement ratio 3.0 versus 1.5). A higher release is attainable with the use of nonionic gelling agents in the formulation. BP, being a cationic drug, is released in a much smaller amount when anionic polymers (e.g., sodium CMC, sodium alginate) are used as gelling agents, as the amine groups of the drug interact with the carbonyl groups of the anionic polymer resulting in retarded drug release from the anionic gel matrix. This phenomenon has been observed with the use of anionic polymers as gelling agents in the gel formulation of other cationic drugs including TM [62], AT [58] and PP [92].

Cyclodextrins have also found their use as potential sorption promoters for APIs, including β-blockers. Babu and Pandit reported a 3.8- and 4.6-fold enhancement in BP flux over the control through rat skin by using hydroxy propyl β-cyclodextrin and partially methylated β-cyclodextrin in 1% aqueous suspension of BP [93]. Cyclodextrins increase the aqueous solubility of the drug and reduce the barrier function of the skin [93-95]. Administration of BP 30 mg in TDS yields a steady-state therapeutic plasma concentration for 24 h in human volunteers [88]. The TDS also produces appreciable β-blockade, with significant reduction in exercise-induced tachycardia by isoprenaline bolus injection.

8. Bopindolol

BD is a noncardioselective β-blocker that has some intrinsic sympathomimetic activity. It is used in the management of hypertension and angina pectoris in doses of 0.5 – 4 mg p.o. [96]. TDS of BD are under clinical investigation. Two separate controlled clinical trials were conducted by Drewe *et al.* to study the pharmacokinetics and pharmacodynamics of a TDS of BD in healthy human volunteers [97] . In study I, BD absorption from a 14-mg patch occurred over a whole 7-day treatment period, whereas in study II, a linear pharmacokinetic behaviour but a nonlinear pharmacokinetic/pharmacodynamic relationship was established for the TDS over a dose range of 7 – 21 mg. The peak effects of reduction in exercise-induced tachycardia by TDS and the intravenous injection were comparable, although the effect with TDS was prolonged. The TDS showed a good topical and systemic tolerability over the exposure period.

9. Mepindolol

MD, the methyl analogue of PD, is a noncardioselective β-blocker that is reported to possess intrinsic sympathomimetic activity. MD is used in the management of hypertension and angina pectoris in doses of 2.5 – 10 mg/day [96]. Few studies have been conducted on the transdermal delivery of MD. In one report on a double-blind, placebo-controlled, crossover trial, De Mey *et al.* [98] demonstrated the attenuation of inodilatory responses to isoprenaline (increase in mean heart rate, systolic blood pressure, estimated stroke volume and reduction in diastolic blood pressure, shortening of all systolic time intervals and so on) by transdermally administered MD, at the end of a 1-week treatment.

A significant reduction in blood pressure of hypertensive patients (160/96 to 137/84 mmHg) by transdermal β-blocker therapy (MD 20 mg) in 10 patients was reported by Spieker *et al.* [99,100]. The TDS was applied every 24 h. All of the 10 patients showed a good blood pressure response after 1 week of therapy; in 9 patients who completed the 3-week study, additional lowering of blood pressure occurred. One patient withdrew from the study because of skin irritation. A placebo-controlled study indicated the effectiveness of decreasing the glyceryl trinitrite consumption and angina attacks and improved the exercise tolerance. Transdermal MD is also reported to be more effective than transdermal glyceryl trinitrite or placebo [96].

In a placebo-controlled trial on healthy human volunteers, De Mey *et al.* observed that an acute and repeatedly applied MD patch is well tolerated, whereas the PP patch caused skin irritation, itching and lesions in subjects [96]. Acute and repeated 24-h application of the PP patch caused only small and clinically insignificant changes in heart rate and blood pressure. Acute application of the MD patch induced mild reduction in blood pressure and heart rate responses to isoprenaline intravenous infusion. It was also found that isoprenaline responses are nearly negated after 1 week repeated

24-h application of the MD patch, in a stable fashion for a prolonged time. The plasma levels rised, slowly reaching a maximum at 24 h and achieved a steady-state after 7 days of the patch application [101,102]. Lower plasma concentrations were observed on transdermal treatment as compared with oral therapy.

10. Sotalol

ST is an adrenergic β-receptor blocking agent that also has class III antiarrhythmic properties. ST has about one-third the β-blocking potency of PP. It is devoid of intrinsic sympathomimetic activity, is not cardioselective and also lacks membrane-stabilising properties. Oral doses of 400 – 600 mg/day may be used in the treatment of both hypertension and angina [36]. In patients with angina, exercise tolerance is increased due to a reduction in total myocardial oxygen consumption. ST is completely absorbed after oral administration and has an absolute bioavailability of 100%. First-pass hepatic metabolism and metabolic degradation is negligible. These pharmacokinetic properties of ST indicate that delivery of ST by transdermal route may not be the best option.

Occasional reports are found in the literature on percutaneous absorption of ST. In a comparative pharmacokinetic study of five β-blockers, ST permeation was the maximum in comparison to other β-blockers [103]. The skin irritation index of β-blockers can be minimised by the use of liposomal formulation of the base rather than the base by itself. Osmotic pressure and ion exchange make a significant contribution to the flux enhancement of ST by the diffusion potential. This was postulated by Hirvonen *et al.* based on their study on the transdermal transfer of ST across human skin by varying the sodium chloride concentration in the donor and receiver compartments [104].

11. Labetolol

LT is a nonselective blocker of adrenergic receptors. It binds competitively with both α- and β-receptors and inhibits the progression of cardiovascular disorders. LT is rapidly absorbed following oral administration. Peak plasma concentrations are achieved 20 – 60 min after 100 mg oral dose. The plasma half-life is ~ 3.5 h [36]; hence, frequent dosing is necessary in the case of conventional formulations, which invariably leads to poor patient compliance. It also undergoes extensive hepatic first-pass metabolism (60 – 75%), leading to a poor bioavailability on oral administration. These factors suggest that LT is a good drug candidate for transdermal delivery. However, only one report was found in the literature on the transdermal delivery of this drug [105]. Eudargit RL 100, Eudragit RS 100 and PVP K-30 have been used as the film-forming polymers for the preparation of matrix-type TDS of LT along with PEG 400 as the plasticiser and dimethylsulfoxide as the penetration enhancer. A high release > 90% has been reported from the TDS, which is therapeutically effective in experimental hypertensive rats.

12. Other β-blockers

Few studies have been carried out on the comparative assessment of skin permeation of a variety of β-blockers using various techniques.

A comparative study on the effect of iontophoresis on the transdermal movement of five β-blockers of varying lipophilicity (including PP, AT, PD, acebutolol and oxprenolol) [106] suggests that an increase in lipophilicity leads to a higher skin absorption, but a decreased transfer rate to the cutaneous vein. PD is absorbed in higher amounts systemically despite its hydrophilic nature because of its higher transfer rate from the skin to the cutaneous vein. Iontophoresis increases the cutaneous concentration of most β-blockers and the constant values are obtained within 30 min [106]. Systemic concentrations of these drugs, however, take longer to reach the steady-state due to a decreased transfer rate to the cutaneous vein. Electromigration seems to be the dominant mechanism in drug iontophoresis. In the presence of background electrolyte, PP iontophoretic delivery increases nonlinearly with the concentration [107].

Denet *et al.* investigated the combined effect of electroporation and iontophoresis on transdermal traffic of TM and AT through human SC using a three-compartment diffusion cell [108]. Iontophoretic transport of TM is decreased by electroporation as a high accumulation of the lipophilic cation TM in the SC results in the attenuation of electro-osmosis. Lipophilicity and positive charges seem to affect the electro-transport of drugs. Hence, the physicochemical properties of the drug, as well as the electrical parameters, need to be given consideration when using combinatorial electroporation and iontophoretic approaches for the transdermal influx of candidate drugs.

Adverse skin reactions are a major obstacle in transdermal delivery of drugs. However, pretreatment with ion channel modulator drugs, such as nifedipine and verapamil, prior to sensitising drug, such as nadolol, can suppress the contact hypersensitivity reactions. Therefore, these ion channel modulators can be effectively used for the safe transdermal delivery of the drug with marked skin-irritation potential [109]. A sensitisation protocol for the development of hypoallergenic TDS is presented by Kalish *et al.* [110]. Sensitisation is achieved by the application of drugs such as albuterol, chlorphenamine, clonidine or nadolol to the shaven dorsal mice skin for 5 days in a hydroxy ethyl cellulose vehicle. Contact sensitisation can be measured by ear swelling in response to the application of 1% of the drug in the vehicle. Control mice that were treated with vehicle alone did not show swelling response. Supplementation of mice with vitamin A as well as the application of the drug on the dorsal side enhances the ear-swelling response. Permeability of the dorsal skin to nadolol is twice

that of ventral skin, which reflects the difference in the level of sensitisation at these surfaces.

Other β-blockers such as bisoprolol, betaxolol, bucindolol, bunitrolol, bufetolol, celiprolol, carvedilol, carazolol, carteolol, esmolol, metipranolol, nevibolol and penbutolol are yet to be investigated for transdermal drug delivery.

13. Expert opinion and conclusion

β-blockers are a very important class of cardiovascular drugs as they are considered to be the drugs of choice for many modern lifestyle disorders such as hypertension, angina pectoris, cardiac arrhythmia and myocardial infarction. There is an inevitable need for improved drug delivery devices for these drugs because of the quantum of their usage and limitations of conventional dosage forms. Transdermal delivery of β-blockers has been investigated by many researchers for the improvement in bioavailability, minimisation of adverse effects and enhanced patient compliance to ensure improved management of cardiovascular disorders. Despite a full range of transdermal approaches that have been employed, including passive diffusion, chemical enhancers, iontophoresis and electroporation (with successful permeation in amounts commensurate to therapeutically effective plasma concentrations across a variety of skin models), no representative of this important class of drugs has been able to be introduced into the pharmaceutical market as a TDS for clinical use. There is scope of transdermal delivery of β-blockers other than those discussed above, including esmolol, carvedilol, nevibolol, bisoprolol, carteolol, bucindolol, bunitrolol and so on, depending on their physicochemical properties. Future research may harness microneedles and sonophoresis, the two most recent and promising techniques for enhanced percutaneous absorption of β-blockers. Sustained innovative research in this area holds promise for the long-term success in technologically advanced transdermal dosage forms being commercialised sooner rather than later.

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