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REVIEW

Systemic delivery of β-blockers via transdermal route for hypertension

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Abstract Hypertension is the most common cardiovascular disease worldwide. Moreover, management of hypertension requires long-term treatment that may result in poor patient compliance with conventional dosage forms due to greater frequency of drug administration. Although there is availability of a plethora of therapeutically effective antihypertensive molecules, inadequate patient welfare is observed; this arguably presents an opportunity to deliver antihypertensive agents through a different route. Ever since the transdermal drug delivery came into existence, it has offered great advantages including non-invasiveness, prolonged therapeutic effect, reduced side effects, improved bioavailability, better patient compliance and easy termination of drug therapy. Attempts were made to develop the transdermal therapeutic system for various antihypertensive agents, including β-blockers, an important antihypertensive class. β-blockers are potent, highly effective in the management of hypertension and other heart ailments by blocking the effects of normal amounts of adrenaline in the heart and blood vessels. The shortcomings associated with β-blockers such as more frequent dose administration, extensive first pass metabolism and variable bioavailability, make them an ideal candidate for transdermal therapeutic systems. The present article gives a brief view of different β-blockers formulated as transdermal therapeutic system in detail to enhance the bioavailability as well as to improve patient compliance. Constant improvement in this field holds promise for the long-term success in technologically advanced transdermal dosage forms being commercialized sooner rather than later.

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Contents

1. Introduction

The potential of using intact skin as the route of drug administration has been known for several years. The inspiration for using skin for the delivery of drug is obtained from ancient times. In recent times, development of transdermal delivery system started in 1970s, and in 1979, the first transdermal patch of scopolamine was approved by USFDA for the treatment of motion sickness and later on a nitroglycerine patch was marketed for the management of angina pectoris (Ahad et al., 2010). The transdermal therapeutic system (TTS) prevents many of the problems associated with oral and intravenous routes. Major advantages provided by TTS include improved bioavailability, more uniform plasma levels, longer duration of action resulting in less dosing frequency, reduced side effects, and improved therapy due to the maintenance of plasma levels (Ahad et al., 2009; Ahad et al., 2014). Advances in modern technologies are resulting in a larger number of drugs being delivered transdermally including conventional hydrophobic small molecule drugs, hydrophilic drugs and macromolecules. There is no potential limit for the therapeutic area for the development of transdermal systems. A number of TTS for different drugs are now in the market including those for nicotine, clonidine, testosterone, oxybutinin, fentanyl, lidocaine and estradiol. The general acceptability of transdermal products by patients is very high, which is also evident from the increasing market for transdermal products. The transdermal market is estimated to represent today, worldwide, ca. $9.5 billion (Aqil et al., 2006).

Hypertension is usually defined by the presence of a chronic elevation of systemic arterial pressure above a certain threshold value. This is a progressive cardiovascular syndrome arising from complex and interrelated etiologies. Progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidneys, brain, vasculature, and other organs and lead to premature morbidity and death (Giles et al., 2009). Global burden of disease study reported that there were 5.2 million deaths from cardiovascular diseases in economically developed countries and 9.1 million deaths from the same causes in developing countries (Jain and Joshi, 2007). Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals and approximately 7.1 million deaths per year may be attributable to hypertension (Kearney et al., 2005; Chockalingam et al., 2006; Alderman, 2007). Therefore cost effective approaches to optimally control blood pressure are very much needed (Selvam et al., 2010). There are many categories of antihypertensive agents, which lower blood pressure by different means; among the antihypertensive, most important and most widely used are the thiazide diuretics, β-blockers, the ACE inhibitors, calcium channel blockers and angiotensin II receptor antagonists.

In the 1980s and 1990s, β-blockers were listed as preferred first-line antihypertensive drugs along with diuretics in national hypertension guidelines. Subsequent updates of the guidelines favored diuretics as initial therapy and classified all other categories of antihypertensive medications to be alternatives to diuretics (Moser, 1997; Che et al., 2009). Although β-blockers remain alternative first-line drugs in the latest guidelines (Chobanian et al., 2003), they are the preferred antihypertensive agents for patients with cardiac disease. It is well established that β-blockers are effective in treating patients with all grades of hypertension and because these drugs are potentiated by thiazide diuretics, it is general policy to use this combination in most patients with hypertension. Although the β-blockers have many individual side effects, when compared to many other antihypertensive drugs, they are remarkably free of a number of troublesome side effects that have bedeviled the treatment of hypertension for many years. The drowsiness, lethargy, and nasal congestion so common with methyldopa, the interference with sexual function and postural hypotension frequently encountered with the adrenergic neurone blocking drugs, and the serious withdrawal phenomena found with clonidine are not frequent manifestations of β-blocker therapy (O'Brien, 1978).

The shortcomings associated with conventional oral delivery of β-blockers can be potentially minimized by novel drug delivery systems including transdermal dosage forms. However, so far none of the β-blocker drugs have been marketed as transdermal delivery systems. Nevertheless, there have been noteworthy research endeavors worldwide at the laboratory level to investigate the skin permeation and to develop

transdermal formulations of β-blockers including: Propranolol (PP), Atenolol (AT), Metoprolol (MP), Bupranolol (BPL), Labetalol hydrochloride (LHCL), Carvedilol (CVD), Timolol maleate (TM) and Bisoprolol (BSP). Several studies have been investigated to develop transdermal systems of anti hypertensive drugs. Recently, Ahad et al., reviewed details of transdermal research specifically on calcium channel blockers for the management of hypertension (Ahad et al., 2013a), while Güngör and Ozsoy, 2012 and Selvam et al. have done a brief overview on the different antihypertensive drugs delivered via skin in the literature (Selvam et al., 2010; Güngör and Ozsoy, 2012). Antecedently, Aqil et al. reviewed details of the studies focused on the transdermal delivery of β-blockers (Aqil et al., 2006).

This review shows an outline of the transdermal research in the area of β-blockers reported in various pharmaceutical journals. The advances and innovations in the transdermal delivery of β-blockers for the management of hypertension are discussed in the text and a summary is presented in Table 1.

2. Nonselective β-blockers (β1 and β2)

2.1. Propranolol

PP is a nonselective β-adrenergic blocking agent. It inhibits response to adrenergic stimuli by competitively blocking β-adrenergic receptors within the myocardium and within bronchial and vascular smooth muscle. It has been widely used in the treatment of hypertension and many other cardiovascular disorders. PP is subject to an extensive and highly variable hepatic first-pass metabolism following oral administration, with a reported systemic bioavailability of between 23% (Ahad et al., 2011; Rao et al., 2003; Dey et al., 2007). The peak plasma concentrations occur about 1–2 h after an oral dose (80 mg), but vary greatly between individuals. The biological half-life of propranolol is longer than would be anticipated from its plasma half-life of about 3–6 h. It has a logarithm partition coefficient (log*P*) of 3.03 and short elimination half-life of about 3 h (Zhao and singh, 1999), which makes it a suitable candidate to be delivered transdermally at a controlled rate (Aqil et al., 2005; Ahad et al., 2011). The enhancement of hydrochloride salt of PP (PP–HCl) penetration by chemical and physical enhancers across the skin in vitro has been studied (Hori et al., 1991). Recently, Ahad et al., 2011, studied the effectiveness and mechanism(s) of percutaneous absorption of PP–HCl across rat and human cadaver skin using seven novel terpenes with reference to marker terpene 1,8-cineole (Ahad et al., 2011). Terpenes are considered as safe absorption promoters and they have been categorized as generally safe by FDA (Aqil et al., 2007a; Akhtar et al., 2011). Furthermore, they have ability to enhance the cutaneous permeation of lipophilic as well as hydrophilic actives (Hassan et al., 2010; Aqil et al., 2007a,b). Ahad et al., claimed that amongst the terpenes, 1,4-cineole was found to be most effective enhancer for diffusion of PP–HCl through rat skin (ER = 3.07) and human cadaver skin (ER = 2.42) as compared to control. Fourier transform infrared spectroscopy (FTIR) spectra and differential scanning calorimetry (DSC) thermogram of skin treated with aforesaid terpenes indicated that permeation occurred due to the disruption of lipid bilayers. No apparent skin irritation (erythema, edema) was observed on treatment of skin with terpenes, the irritation was higher with the β-citronellene and rose oxide. It was concluded that 1,4-cineole can be successfully used as potential permeation enhancer for PP–HCl (Ahad et al., 2011).

Kunta et al., 1997 investigated the effect of menthol, limonene, linalool and carvacrol on the percutaneous absorption of PP–HCl across hairless mouse skin. 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 6 to 7-fold at 5–10% terpene concentration, whereas L-menthol provides a significant enhancement in percutaneous absorption at a concentration as low as 1%.

In another report, Zhao and Singh, investigated the mechanism(s) of percutaneous absorption enhancement of PP–HCl across porcine epidermis by terpenes (e.g. menthone and limonene) in combination with ethanol. Five percent menthone or limonene in combination with ethanol (menthone/ethanol or limonene/ethanol) significantly enhanced the flux of PP–HCl across porcine epidermis in comparison to ethanol (control). The partitioning of PP–HCl to the stratum corneum (SC) from the SC/enhancer system was also significantly greater than the SC/control system. It was observed that the above terpenes showed a decrease in the peak heights and areas for both asymmetric and symmetric C—H stretching absorbance in comparison with the untreated SC, indicating the SC lipids extraction. Thus, an enhancement in the flux of PP–HCl by menthone/ethanol and limonene/ethanol is due to SC lipid extraction, macroscopic barrier perturbation, and improvement in the partitioning of the drug to the SC (Zhao and singh, 1999). Similar mechanism of action was also reported for the terpenes such as (+)-borneol, (+)-camphor, and α-bisabolol (Cui et al., 2011). It was described in the study that each of (+)-borneol, (+)-camphor, and α-bisabolol significantly increased the transdermal flux of PP–HCl through rat skin in comparison to the control. The enhancement mechanism of the terpenes is involved with disruption of the lipid bilayer and increases the PP–HCl partitioning coefficient to the SC (Cui et al., 2011).

In 2005, Amnuaikit et al., developed film formulations of PP–HCl containing menthol, cineole and propylene glycol as enhancers for transdermal use. In vitro skin permeation study presented that cineole was found to be the most promising terpene among the investigated enhancers which provided high skin permeation rates (Amnuaikit et al., 2005).

It is reported in the literature that a variety of chemical permeation enhancers have been shown to increase percutaneous absorption of both hydrophilic and hydrophobic drugs (Williams and Barry, 2004; Hassan et al., 2010). In this regard, a comparative study (Hori et al., 1992) was done for the percutaneous enhancement of a hydrophilic (PP–HCl) and a lipophilic drug (diazepam or indomethacin) by various enhancers such as 1-nonanone, 1-nonalol and 1-decanol. It was found that 1-nonalol and 1-decanol significantly enhance the PP–HCl flux, whereas the indomethacin or diazepam flux is enhanced by 1-nonanone only. A rise in PP–HCl flux by terpenes is reported to be comparable to that observed with 1-nonalol (Hori et al., 1992). The prodrug approach has also been employed to enhance the transdermal delivery of PP (Namdeo and Jain, 2002). An increase in PP–HCl flux as high as 20- and 25-fold can be achieved from two PP prodrugs namely hydrochloride salts of PP stearate and PP palmitate respectively. Transdermal administration of these prodrugs improves the bioavailability of PP–HCl up to 7–8 times over the oral treatment.

Table 1 Research advances in systemic delivery of β-blockers via skin.

β-Blockers	Characteristics	Transdermal research	Refs.
Nonselective β-blockers (β1 and β2)			
PP	MW = 259.34, BCS class = I	Elastic liposomal of PP–HCl provided better transdermal flux and higher entrapment efficiency	Mishra et al. (2007)
	log*P* = 3, $t_{1/2}$ = 4 h	*n*-Alkanes having chain lengths of between 7 and 16 promoted the flux of PP–HCl	Hori et al. (1991)
	Bioavailability = 23%, Well absorbed following oral administration at variable plasma concentrations	ER of 3.07 and 2.42 of PP were obtained when 1,4-cineole was used as penetration enhancer across rat and cadaver skins, respectively	Ahad et al. (2011)
		Permeability of PP was much higher from the hydrogel-based patches (methanol enhancer) than the control patch across the mouse skin	Kunta et al. (1997)
		Menthone (5%) in combination with ethanol significantly increased the flux of PHCL	Zhao and singh (1999)
		α-Bisabolol (5% w/v) increased the partition coefficient of PHCl to the SC	Cui et al. (2011)
		PP transport across hairless mouse skin was improved significantly in the presence of 4% (v/v) *n*-nonane	Hori et al. (1992)
		Developed a novel self-assembled pharmacogel for the enhanced transdermal delivery of PP–HCl	Namdeo and Jain (2002)
		Microdialysis technique was used as a tool for dermatopharmacokinetic studies	Muller et al. (1995)
		PP was delivered iontophoretically in the dermis of healthy human volunteers	Stagni et al. (2000)
		In vivo study in rabbits showed that a sustained therapeutic activity of PP was observed over a period of 24 h after transdermal administration compared to oral administration	Rao et al. (2003)
TM	MW = 432.50, BCS class = I	Water-activated, pH-controlled transdermal patches of TM were found to be well tolerated by the hypertensive patients	Sutinen et al. (2000b)
	log*P* = 1.2, $t_{1/2}$ = 2.5–5 h	*In vivo* study in rabbits showed that iontophoresis in combination with Azone can increase the transdermal delivery of TM	Kanikkannan et al. (2000)
	Bioavailability = 75%	Plasma TM concentrations collected from the left antecubital vein were 2.4–10.7 times greater than those from the right arm and had significant correlations (rs = 0.55–0.76) with the parameters indicating the extent of erythema developed where a patch containing TM was applied.	Kubota et al. (1991)
		Rate of TM release was decreased when the control devices were placed on human cadaver skin	Sutinen et al. (2000a)
		In vivo study in humans indicated that steady-state plasma levels were achieved rapidly by iontophoretic patches	Green (1996)
		Total amount of TM transported up to 24 h was not significantly different among the different species studied	Kanikkannan et al. (2001)
		Transdermal delivery of TM by electroporation through human skin was investigated	Denet and Préat (2003)
		Laurate sugar fatty acid ester with shorter fatty acid chain length and higher HLB value significantly increased the amount of TM liberated from the patch (99%) and its permeation across rat skin (86%)	El-Laithy (2009)
		Lauryl chloride was found to be the most effective penetration enhancer for transdermal delivery of TM	Soni and Dixit (1994)
BPL	MW = 271.78, BCS class = II	Used isopropyl myristate and *N*-methyl-2-pyrrolidone as enhancer and *in vitro* penetration of BPL obtained 3.6 times higher flux compared with that without enhancers	Ogiso et al. (2001)
	log*P* = 2.9, $t_{1/2}$ = 2–4 h,	Hydroxy propyl β-cyclodextrin and partially methylated β-cyclodextrin were used as penetration enhancers for BPL	Babu and Pandit (2004)
	Bioavailability = 10%	Reservoir-type TTS of BPL was developed and penetration enhancers increased the skin permeation of BPL at 4–5 times higher levels than the desired target delivery rate	Babu and Pandit (2005a)
		2-Pyrrolidone and 1-methyl-2-pyrrolidone (5% w/v) increased permeation of BPL by 3.8- and 2.4-fold respectively through the rat skin	Babu and Pandit (2005b)

Selective β-1 blockers			
AT	MW = 266.33, BCS class = III log*P* = 0.5, $t_{1/2}$ = 6–7 h, Bioavailability = 50%	Used polyoxyethyene-2-oleyl ester as penetration enhancer for enhanced AT transdermal delivery	Shin and Choi (2003)
		Developed TTS using blends of different polymeric combinations such as HPMC, PVP and carbopol for transdermal delivery AT	Anitha et al. (2011)
		Modified xanthan films were applied as a matrix system for the transdermal delivery of AT	Mundargi et al. (2007a,b)
		Permeation via cadaver skin showed about 27% reduction in the amount of AT as compared to rat abdominal skin	Agrawal and Munjal (2007)
		Developed a matrix-type TTS with different concentrations of hydrophobic polymers like E-RL100 and E-RS100 by the solvent evaporation technique	Baria and Patel (2011)
		Polyoxyethylene 2-oleyl ether showed the best enhancement among others enhancers used such as glycols, fatty acids and non-ionic surfactants	Cho and Shin (2004)
		In vivo study in rabbits showed that bioavailability of AT was increased by 46% from an EVA matrix system	Shin and Choi (2003)
MP	MW = 267.36, BCS class = I log*P* = 1.6, $t_{1/2}$ = 3–7 h, Bioavailability = 50%	Optimized TTS comprising HPMC E50 + EC (3:2), with enhancer DMSO showed 70% drug release after 12 h	Thakare et al. (2012)
		Improved in vitro drug release and skin permeation of monolithic matrix system of MP	Aqil et al. (2003)
		Significant reduction in mean blood pressure was achieved in methyl prednisolone-induced hypertensive rats on treatment with the TTS of MP	Aqil et al. (2004)
		n-Decylmethyl sulfoxide was found to enhance skin permeation rate of MP through the human cadaver skin at a loading dose of 5% (w/w)	Ghosh et al. (1992)
		3-Fold improvement in bioavailability of MP was observed with the TTS	Aqil et al., 2007a,b
		Used Easyjet Plus® (Equibio) electroporating equipment for the permeation enhancement of MP across hairless rat skin	Vanbever et al. (1994)
		Significant enhancement of MP across full thickness hairless rat skin was observed in comparison to diffusion through untreated skin	Vanbever et al. (1996)
BSP	MW = 325.44, BCS class = I log*P* = 2.2, $t_{1/2}$ = 9–12 h, Bioavailability = 80%, Approximately 50% of the dose is metabolized by CYP3A4	BSP-maleate was found the most promising candidate for long-acting transdermal patches among the different ion-pair complexes prepared such as BSP maleate, BSP tartarate, BSP besilate, and BSP fumarate	Song et al. (2012)
		Azone can be used as a good penetration enhancer for BSP	Dinakar et al. (2010)
		Developed a novel TTS containing isosorbide dinitrate with BSP. The bioavailability of 33.6% for isosorbide dinitrate, and 31.3% for BPL was observed on transdermal delivery in rabbits	Zhao et al. (2007)

(*continued on next page*)

Table 1 (*continued*)

Mixed β-blockers (has additional α-blocking activity)			
CVD	MW: 406.47, BCS class = II log*P* = 2.2, $t_{1/2}$ = 7–10 h, Bioavailability = 25–35%, undergoes extensive first pass	In vivo studies concluded that the CVD transdermal patches provided steady-state plasma concentrations with minimal fluctuations and improved bioavailability (71%) in rats	Ubaidulla et al. (2007)
		CVD matrix TTS composed of a 4:1 ratio of HPMC and E-RL100 showed both maximum drug release (12.31 mg) and permeation (2987.67 μg/cm^2) in 24 h across the rat skin	Gannu et al. (2008a)
		The steady-state plasma level and improvement in bioavailability (72%) of CVD in rats was obtained following transdermal application	Kshirsagar et al. (2012)
		Resulted in sustained release of CVD transdermal patches containing glycyrrhizin–chitosan mixture which was able to control the hypertension in DOXA induced hypertensive rats through 28 h	Sapra et al. (2008)
		Black cumin oil (5%) was found the best permeation enhancer amongst several enhancers tested such as tulsi (basil) oil, eucalyptus oil, clove oil, OA and Tween 80	Amin et al. (2008)
		Different matrix-type transdermal patches were formulated to study the effect of polymers on transdermal release	Agrawal and Aggarwal (2010)
		Resulted in sustained release of CVD transdermal patches containing *soybean* extract-chitosan mixture which was able to control the hypertension in DOXA induced hypertensive rats through 24 h	Sapra et al. (2009a)
		Resulted in sustained release of CVD transdermal patches containing *Asparagus racemosus* extract-chitosan mixture which was able to control hypertension in DOXA induced hypertensive rats through 36 h	Sapra et al. (2009b)
		Nanoemulsion consisted of OA: isopropyl myristate (1:1, 6%), Tween 80 (22.5%), Transcutol-P (22.5%), and distilled water showed higher permeation rate of CVD via rat skin	Dixit et al. (2008)
		CVD flux in the presence of camphor, limonene, Transcutol, carvone, Labrasol, and menthol solution (5% w/v), were 9.7, 7.6, 7.6, 6.3, 4.7, and 2.3 times higher, respectively, than that observed with control across porcine skin	Gannu et al. (2008b)
LHCL	MW = 364.87, BCS class = I log*P* = 2.7, $t_{1/2}$ = 6–8 h, Bioavailability = 100%, Almost completely absorbed from the gastrointestinal tract, undergoes significant first pass	Matrix type TTS comprised of LHCL (36%), enhancer DMSO (10–12%) and plasticizer PEG 400 (2.5–7.5%) in methanol-acetone solvent system was developed for transdermal applications	Aqil et al. (2005)
		DMSO (10% v/v) was found to be the most effective enhancer for LHCL via the dermal route	Zafar et al. (2010)
		TTS comprised of E-EPO/E-RL100 and Plasdone S 630 as polymers and LHCL was investigated for the therapy of hypertension	Mittal et al. (2009)

AT: atenolol; BPL: bupranolol; BCS: biopharmaceutical classification system; BPS: bisoprolol; CVD: carvedilol; DMSO: dimethyl sulfoxide; DOXA: deoxycorticosterone acetate; ER: enhancement ratio; E: eudragit; HPMC: hydroxy propyl methyl cellulose; LHCL: labetalol hydrochloride; log*P*: logarithm partition coefficient; MP: metoprolol; MW: molecular weight; OA: oleic acid; PP: propranolol; PVP: polyvinyl pyrolidone; *t*1/2: half-life; TM: timolol maleate; TTS: transdermal therapeutic system.

Skin microdialysis is another technique which permits to measure the kinetics of drug appearance in the dermis under the site of application of drugs in vivo and in humans (Anderson et al., 1991; Groth, 1996; Muller et al., 1995). Thus, skin microdialysis technique was employed to characterize and quantify the dermatopharmacokinetics of iontophoretically delivered PP–HCl in the dermis of healthy human volunteers. Microdialysis probes were inserted in the subject's forearm skin and an iontophoresis device was installed above them. Constant current was applied for two periods of 1 h each separated by a 1 h interval. Dialysate samples were collected every 6 min for 4.4 h and analyzed. It was observed that the skin microdialysis technique was well tolerated and this study demonstrates that intradermal microdialysis is suitable to examine the dermato pharmacokinetics of iontophoretically delivered drugs in the dermis of human subjects. Elimination was well characterized. Quantification of the absorption process by AUC showed a high inter- and intra-subject variability suggesting that more studies are needed to understand whether such variability is due to variation in microdialysis recovery, in iontophoretic delivery, or in dermis clearance (Stagni et al., 2000). In another study, the antihypertensive activity and pharmacokinetic performance of PP–HCl in rabbits following transdermal administration was compared with that of oral administration. In contrast to oral delivery, a sustained therapeutic activity was observed over a period of 24 h after transdermal administration and 5 to 6-fold increase in relative bioavailability of PP–HCl was observed after transdermal administration in comparison to oral administration. This may be due to the avoidance of first pass effect of PP–HCl and the sustained therapeutic activity was due to the controlled release of drug into systemic circulation following transdermal administration (Rao et al., 2003). In 2000, Verma and Iyer also reported slow and controlled release of PP–HCl from polymeric matrix type transdermal films prepared with different grades and ratios of Eudragit (E) (Verma and Iyer, 2000).

In another study, polymeric films containing PP–HCl were formulated using different ratios of ethyl cellulose (EC), polyvinyl pyrrolidone (PVP) by mercury substrate method. It was observed that the release rate of PP–HCl increased linearly with increasing drug concentration and PVP fraction in the film, but was found to be independent of film thickness. The increase in release rate may be due to leaching of hydrophilic fraction of the film former, which resulted in the formation of pores. It was also observed that the release of PP–HCl from the films followed the diffusion-controlled model at low drug concentration. A burst effect was observed initially, however, at high drug loading level, which may be due to rapid dissolution of the surface drug followed by the diffusion of the drug through the polymer network in the film. The transdermal flux values were also added with increase of initial drug concentration in the film, and also with the PVP content. It was suggested that prepared film should be selected for the development of TTS using a suitable adhesive layer and backing membrane for potential therapeutic applications (Rao et al., 2000). In another report, release of PP–HCl from hydroxy propyl methyl cellulose (HPMC) matrices without adhesive coating was found to be fast. Release from these matrices became more regular (reduction of the burst effect) and slow when they are coated with a 12 mm thick Ucecryl layer. Release from different polyisobutylene matrices was found too slow to be suitable as TTS for PP–HCl. Amongst the investigated polymers the best release modulation was obtained from Ucecryl matrices (Guyot and Fawaz, 2000). In another investigation, formulations with the highest proportion of PVP shows faster release of PP–HCl over a day's span whereas increasing the proportion of EC produces a prolonged regimen of sustained drug delivery through the transdermal route for a period of more than a day. It was demonstrated that the fabricated matrix films have the potential to prolong the release of PP–HCl (Dey et al., 2007). The PP–HCl release was regulated by the use of cross-linking agent glutaraldehyde in transdermal membrane prepared by chitosan a natural polymer. Chitosan gel was used as the drug reservoir. The ability of these devices to deliver the drug while supported on rabbit pinna skin was tested by conducting in vitro studies in modified Franz diffusion cells. The drug release profiles showed that the PP–HCl delivery is completely controlled by the devices. The rate of PP–HCl release was found to be dependent on the type of membrane used. It has been proved that natural polymer chitosan can be used successfully for the fabrication of transdermal devices. The drug release can be easily tailored by changing the permeability of the membrane by chemical modifications, like cross-linking or by changing the area of the devices. With the usage of natural polymers such as chitosan for the fabrication of TTS, most of the device-associated adverse skin reactions can be minimized (Thacharodi and Rao, 1995). Rate of PP–HCl release from the pH-controlled, water-activated reservoir devices was also controlled over a 700-fold range by using suitable buffers in the device core (Sutinen et al., 1989, 1990, 2000a).

In another investigation, reservoir-type transdermal enantioselective-controlled delivery system for racemic PP–HCl using a molecularly imprinted polymer composite membrane was examined. The chitosan gel allowed excellent selectivity for delivery of the (*S*)-PP–HCl enantiomer, whilst the more rheologically structured poloxamer gel formulation provided no selective release of (*S*)-PP–HCl. The chitosan gel exhibited high flux and had the ability for enantioselective delivery of (*S*)-PP–HCl across excised rat skin. The reservoir patch for enantiomer-controlled delivery of PP–HCl was therefore fabricated by incorporating the chitosan gel formulation containing racemic PP–HCl into the molecularly imprinted polymer composite membrane laminated backing. These patch devices were shown to exhibit the significant stereoselectivity uptake of PP–HCl. (*S*)-PP–HCl enantiomer plasma concentration profiles for the transdermal patch in the in vivo study were comparable to data for the gel formulations that were applied directly to skin, and containing a single *S*-enantiomer of PP–HCl. The results demonstrate that the transdermal patch based on the molecularly imprinted polymer composite membrane-controlled release system may have potential in the enantioselective-controlled delivery of the *S*-isomer of racemic PP–HCl (Suedee et al., 2008).

Ultradeformable lipid vesicles i.e. elastic liposomes are specially optimized vesicles, which can respond to an external stress by rapid and energetically inexpensive shape transformations. Elastic liposomes differ from conventional niosomes and liposomes by their characteristic fluid membrane with high elasticity (Ahad et al., 2012; Ahad et al., 2013a,b). The elasticity of these vesicles is attributed to the simultaneous presence of different stabilizing (phospholipids) and destabilizing (surfactant) molecules and their tendency to redistribute in bilayers. Such highly deformable vesicles can thus be used to

bring drugs across biological permeability barriers such as the skin. Elastic liposomes were prepared by Mishra et al., 2007 for enhanced PP–HCl transdermal delivery. Elastic liposomes loaded with PP–HCl were prepared by conventional rotary evaporation method. It was observed that the elastic liposome of PP–HCl provides better transdermal flux, higher entrapment efficiency, ability as a self-penetration enhancer and effectiveness of transdermal delivery as compared to traditional liposomes (Mishra et al., 2007). The lower penetration ability that is associated with the use of vesicular carriers such as liposomes and niosomes can be overcome by entrapment of the drugs in the elastic liposomes.

2.2. Timolol

TM is a hydrophilic potent β-adrenoceptor blocking agent that is used to treat hypertension, angina pectoris and myocardial infarction. It possesses a relatively high degree of lipid solubility with a logarithm partition coefficient (log*P*) of 1.2. TM is rapidly absorbed following oral ingestion and metabolized up to 80% in liver with a mean half-life of 2.0–2.5 h and present oral bioavailability of about 75%, thus necessitating frequent administration of doses to maintain therapeutic drug level, hence transdermal delivery could be a potential alternative to oral delivery of TM (Kubota et al., 1991; Kanikkannan et al., 2000, 2001; Sutinen et al., 2000a). In 1994, Soni and Dixit used dimethyl sulfoxide (DMSO), oleic acid (OA) and lauryl chloride to enhance the permeability of TM via human cadaver skin. The authors claimed that lauryl chloride was found to be the most effective enhancer to accentuate transdermal delivery of TM, followed by DMSO and OA (Soni and Dixit, 1994).

Consequently, water-activated, pH-controlled devices were investigated for the transdermal delivery of TM. It was observed that TM release from unbuffered devices was negligible, while there was a pronounced effect of pH-adjusting agents on TM release e.g., TM release from the device was found to be 3150 times greater in presence of a Tris buffer (Sutinen et al., 2000a). In another report (Sutinen et al., 2000b) water-activated, pH-controlled transdermal patches of TM were found to be well tolerated by the subjects, edema raised by the patches was negligible and erythema was confined only to the area where the TM patch was applied. It was also mentioned that the TM–Tris buffer patch was releasing TM faster than the TM–disodium phosphate patch (Sutinen et al., 2000b). It was concluded that by application of water-activated and pH-controlled devices, steady-state plasma concentrations and the duration of patch activity in vivo can be controlled by selecting suitable buffers in the device core.

It is reported in the literature that the skin of infants was found to be more permeable to drugs than that of adults and passive diffusion of drugs across the skin of common laboratory animals (e.g. rat, rabbit and mouse) was found to be higher than human skin (Kanikkannan et al., 2001; Wester and Maibach, 1987). It was also mentioned that percutaneous absorption through pig and monkey (squirrel and rhesus) was found to be more closely related to that of human (Kanikkannan et al., 2001; Wester and Maibach, 1987). In this quest, a study was performed to investigate the effect of species variation of the animals (rat, rabbit, mouse, guinea pig and human) on the transdermal iontophoretic transport of TM. Iontophoresis has been demonstrated to be a safe means of delivering peptides and other molecules in a noninvasive and controllable fashion (Kanikkannan et al., 2001; Singh and Singh, 1993; Green, 1996). Further, the amount of drug transported by iontophoresis is proportional to the current applied, it is possible to deliver the drug in a controlled manner using preprogrammed delivery rates (Kanikkannan et al., 2001; Sage, 1993). The author claimed that the iontophoretic transport of TM across the skins obtained from the rats of different age groups was found to be similar. It was suggested that the age of the animal (Wistar rats: 1–8 months) did not appear to influence the transdermal iontophoretic transport of TM (Kanikkannan et al., 2001). In another study, it was observed that the application of skin electroporation strongly promotes the transdermal delivery of TM in vitro compared to passive diffusion and the therapeutic fluxes of TM ($>50\ \mu g/cm^2/h$) through human SC were achieved with the electrical protocols used. It was concluded that the choice of the electrical parameters (voltage, duration and number of pulses) allows a control of the quantity of drug transported through the skin (Denet and Préat, 2003).

In 2009, El-Laithy, prepared a matrix type controlled transdermal patch containing TM and sugar fatty acid ester as penetration enhancer. It was observed that among different acid esters tried, laurate acid ester with shorter fatty acid chain length and higher hydrophilic lipophilic balance value significantly increased the amount of TM released from the patch (99%) and its permeation across rat skin (86%). The total drug permeation and flux values were approximately 5-fold greater compared to acid ester free patch. The developed patch was well tolerated by all the subjects with only moderate skin irritation, which was recovered in 24 h after patch removal. The reports are very promoting and offer an alternative overture to maintain a higher, prolonged and controlled blood level profile of the drug over 18–24 h (El-Laithy, 2009).

2.3. Bupranolol

BPL is a potent nonselective β-blocking agent (Tsukahara et al., 1986). BPL was quickly and completely absorbed from the gut with less than 10% oral bioavailability. Upon oral administration it undergoes an extra-ordinary first-pass metabolism (>90%). It has a log*P* value of 2.9 and is rapidly eliminated with a biological half-life of 1.5–2.0 h. This demands multiple ingestion of a heavy oral dose (100–400 mg/day) in divided doses, which in turn results in undesirable local and systemic side effects (Waller et al., 1982; Wellstein et al., 1986). These properties of BPL make it well suited for TTS development. In previous reports, isopropyl myristate and *N*-methyl-pyrrolidone have been used as absorption promoters for BPL. *N*-methyl-pyrrolidone provides a 3.6-times higher BPL flux than passive diffusion (Ogiso et al., 2001). Isopropyl myristate and *N*-methyl-pyrrolidone enhance the penetration by increasing the solubility of the permeant into SC.

Babu and Pandit, 2004 reported a 3.8- and 4.6-fold enhancement in BPL flux over the control through rat skin by using hydroxy propyl β-cyclodextrin and partially methylated β-cyclodextrin (PMβCD) in 1% aqueous suspension of BPL, cyclodextrins increase the aqueous solubility of the drug and reduce the barrier function of the skin (Babu and Pandit, 2004). The release rate of BPL from HPMC, hydroxy propyl

cellulose (HPC) gel reservoirs was found to be much higher than gel reservoirs of carboxymethyl cellulose, sodium carboxymethyl cellulose and sodium alginate. Permeation rates of the devices containing 5% (w/v) pyrrolidone or 1-methyl-2-pyrrolidone were about 3- and 1.5-fold higher than the control. Pyrrolidone was found to be a better penetration enhancer for BPL than 1-methyl-2-pyrrolidone. The permeation rates of devices containing PMβCD and PMβCD-BPL complex were about 2.5- and 1.4-fold higher than the control. It was suggested that reservoir-type TTS of BPL was developed and penetration enhancers increased the skin permeation of BPL at 4–5 times higher levels than the desired target delivery rate (Babu and Pandit, 2005a). In another study, the effect of different penetration enhancers viz. 2-Pyrrolidone, 1-methyl-2-pyrrolidone, and propylene glycol on the permeation of BPL across the rat skin was investigated. Menthol at different concentrations in isopropanol-water (6:4) mixture was also used as an enhancer wherein BPL at 0.4% w/v was completely solubilized. Skin pretreatment studies were carried out with all the above enhancers to understand their role in the penetration enhancement effect. 2-Pyrrolidone and 1-methyl-2-pyrrolidone at 5% w/v concentrations increased the permeation of BPL by 3.8- and 2.4-fold, respectively, over the control. Propylene glycol at 10% and 30 w/v concentrations increased the flux of BPL by 2.5- and 5.0-fold, respectively, as compared to the control. Menthol at 2% w/v concentration increased the flux of BPL by 3.8-fold and a further increase in menthol concentration significantly decreased the flux of BPL. Overall, pyrrolidones and menthol at low concentrations (5% w/v or less) and propylene glycol at 30% w/v concentration were found to be effective penetration enhancers for the transdermal delivery of BPL (Babu and Pandit, 2005b).

3. Selective β-1 blockers

3.1. Atenolol

AT belongs to the class of β-1 selective adrenoceptor antagonists. It has been used for the treatment of hypertension and stable angina either alone or with other antihypertensive drugs like thiazide diuretics (Salvetti and Ghiadoni, 2006; Lim, 2007). AT is a highly soluble low permeable drug (BCS class 3) with a log$P$ value of 0.5. Due to incomplete intestinal absorption, the systemic bioavailability is about 50–60% in the human (Stoschitzky et al., 1993). The peak plasma concentrations occur about 2–4 h after an oral dose of 50–100 mg. It is reported that in the case of oral administration of AT, it can induce side effects such as diarrhea, nausea, mesenteric arterial thrombosis, ischemic colitis and dry mouth (Vaithiyalingam et al., 2001; Mundargi et al., 2007a). AT is reported to be subjected to extensive hepatic first-pass metabolism following the oral administration and has a short biological half-life of 6–7 h (Singh et al., 2006; Mundargi et al., 2007b). Therefore, to maintain proper blood levels for a long time and to mitigate the adverse effect associated with frequent oral administration of AT, development of TTS of AT is very important (Kim and Shin, 2004; Cho and Shin, 2004). Recently, a TTS containing AT & Glibenclamide was prepared for hypertension associated with diabetes using blends of different polymeric combinations such as HPMC, PVP and carbopol. The prepared formulation showed zero order drug release pattern by diffusion mechanism of the non fickian type. It was concluded that prepared formulation showed prolonged zero order release, reduced frequency of administration, greater therapeutic effect, overcomes the side effects, simplifies the treatment regimen and thus may improve patient compliance (Anitha et al., 2011). In another study, modified xanthan films as a matrix system for transdermal delivery of AT were prepared. All the thin films prepared were slightly opaque, smooth, flexible, and permeable to water vapor, showing their permeability characteristics suitable for transdermal studies. The skin irritation test was done in mice and it was observed that both placebo and drug loaded films produced negligible erythema and edema compared to formalin (standard irritant). The in vitro drug release studies were performed using a Keshary–Chien diffusion cell and the mechanism of drug release was found to be Fickian diffusion (Mundargi et al., 2007b). In 2007, Agrawal and Munjal prepared a matrix type transdermal patches comprising AT and MP-tartrate using 1,8-cineole as the permeation enhancer. The polymers selected were PVP, cellulose acetate phthalate, HPMC and EC. Backing membrane was prepared by wrapping an aluminum foil over the Teflon mold. In vitro permeation studies were performed using rat abdominal skin as the permeating membrane in the Keshary-Chien cell. The maximum release was obtained at 48 h (85% and 44% of AT and MP-tartrate, respectively). The permeation studies via cadaver skin showed about 27% reduction in the amount of drug release compared to the skin permeation study performed on rat abdominal skin. It was observed that the physical appearance of the patches and the effect on ageing showed that the patches need to be stored in properly sealed air tight packing to keep them protected from extremes of moisture that may alter their appearance (Selvam et al., 2010; Agrawal and Munjal, 2007). In another investigation, feasibility of OA for the delivery of AT via rat skin was examined, a matrix-type TTS containing AT and OA using different concentrations of hydrophobic polymers like E-RL100 and E-RS100 was prepared by the solvent evaporation technique. Formulation prepared with E-RL100 polymer containing OA showed good physical stability and produced maximum transdermal flux via rat skin as compared with all other formulations (Baria and Patel, 2011). In another report, OA is reported as the best penetration enhancer for AT amongst a pool of fatty acids including linoleic acid, caprylic acid and lauric acid (Cho and Shin, 2004). It was suggested that OA creates pores on the surface of corneocytes, indicating transcellular permeation of active as the possible mechanism of penetration enhancement (Touitou et al., 2002). Shin et al. used polyoxyethyene-2-oleyl ester and tributyl citrate as a penetration enhancer and plasticiser, respectively, to form an ethylene–vinyl acetate matrix system for an enhanced bioavailability of AT in rabbits (Shin and Choi, 2003). They reported a 46% increase in bioavailability of AT 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. Sustained release and constant blood concentration with minimal fluctuation is possible from the above ethylene–vinyl acetate – AT matrix.

3.2. Metoprolol

MP is a cardio selective β-blocker. It is used in the management of hypertension, angina pectoris, cardiac arrhythmias

and myocardial infarction. It is almost completely absorbed after oral administration, although the systemic bioavailability varies (40% to 50%) widely owing to extensive presystemic metabolism. It is similar to AT in its moderate lipid solubility with log*P* 1.6. The plasma half life is about 4 h, which makes frequent dosing necessary to maintain the therapeutic blood levels of the drug for a long term treatment (Corbo et al., 1990; Bharkatiya et al., 2010). The transdermal route of administration is capable of avoiding the hepatic first pass effect, thus achieving higher systemic bioavailability of drugs.

Recently, matrix type transdermal films of succinate salt of MP were prepared using different polymers such as EC, HPMC (E15, E50) and PVP in varied ratios. All formulations carried DMSO (5%) as penetration enhancer and propylene glycol (30%) as plasticizer in chloroform and ethanol as solvent system. The formulation with a combination of polymers HPMC E50 + EC with DMSO emerged to be the ideal formulation and showed 70% drug release after 12 h (Thakare et al., 2012).

In 2003, Aqil et al., developed a four monolithic matrix system of MP (used in tartrate form), which differed in the ratio of matrix-forming polymers. Formulations MT-1, MT-2, MT-3 and MT-4 were composed of E-RL100 and PVP K-30 with the following ratios: 2:8, 4:6, 6:4 and 8:2, respectively. On the basis of in vitro drug release and skin permeation performance, formulation MT-4 was found to be better than the other three formulations and it was selected as the optimized formulation. It was concluded that MP could be administered transdermally through the matrix type TTS (Aqil et al., 2003).

In another study, Aqil et al., 2004 prepared four MP (used in tartrate form) formulations using E-RL100 and Polyvinyl alcohol (PVA) in different ratios. Formulations M-1, M-2, M-3, and M-4 were composed of E-RL100 and PVA with the following ratios: 2:8, 4:6, 6:4, and 8:2, respectively. All the four formulations carried 10% (*w*/*w*) of MP, 5% (*w*/*w*) of dibutyl phthalate, and 5% (*w*/*w*) of menthol in dichloromethane: isopropyl alcohol (80:20 *v*/*v*). The cumulative amount of drug permeated from the four formulations was 59.72%, 66.52%, 77.36%, and 90.38% respectively. Formulation M-4 was found to be better than the other three formulations and it was selected as the optimized formulation. The formulation was found to be free of any skin irritation as suggested by a skin irritation score of 1.16 (< 2.00) under the Draize score test. Significant reduction in mean blood pressure was achieved in experimental hypertensive rats on treatment with the TTS. The authors concluded that MP developed formulation holds promise to be a viable option for effective and controlled management of hypertension for 48 h (Aqil et al., 2004). Ghosh et al. explored the feasibility of transdermal administration of MP by investigating its permeation across hairless mouse and human cadaver skin using *N*-decyl methy sulfoxide as an enhancer. The authors claimed that 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 (Ghosh et al., 1992).

An open-label, balanced randomized, two-treatment, two-period crossover study was done (Aqil et al., 2007b) to compare the bioavailability of tartrate form of MP from a TTS with that from a conventional marketed tablet in healthy human volunteers. Volunteers were randomized to have a TTS applied to their chest for 48 h or to receive a 100 mg conventional marketed tablet of MP in period I. In period II, the volunteers received the other dosage form. A 3-fold improvement in bioavailability was observed with the TTS form over oral therapy. Plasma MP concentrations drop sharply to therapeutically ineffective concentrations as early as 8 h following oral administration. Finally it was concluded that the developed TTS conforms to the intended objective of two-day management of hypertension with the application of a single patch, avoiding the inconvenience of frequent administration and thus improving patient compliance (Aqil et al., 2007b).

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 actives. Vanbever et al. (1994) used Easyjet Plus® (Equibio) electroporating equipment for the permeation enhancement of MP across hairless rat skin. The authors claimed 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 1 s 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). It was suggested that diffusion factors like pulse voltage, pulse number and pulse duration control the quantity of drug delivered (Vanbever et al., 1996; Prausnitz, 1999).

3.3. Bisoprolol

BSP is a highly selective β1-adrenoceptor antagonist. BSP has a long duration of action, both systolic and diastolic blood pressure are reduced by BSP (by up to about 20%, respectively, in healthy subjects and in patients with mild to moderate essential hypertension) as well as mycocardial oxygen demand (by up to 34%) (Kanikkannan et al., 2001; Costello and Jeske, 1995; Zhao et al., 2007). The absolute bioavailability after a 10 mg oral dose of BSP fumarate is about 80%. Peak plasma concentrations occur within 2–4 h of dosing with 5–20 mg, and mean peak values range from 16 ng/mL at 5 mg to 70 ng/mL at 20 mg. BSP has a biological half life of 10–12 h and oral bioavailability (90%). It has log*P* of 2.3 in *n*-octanol/phosphate buffer system (Leopold et al., 1986). The key to achieve long-acting effects for transdermal patches is to control the drug skin-permeating rate in a moderate range, that is, neither too high and leading to a relatively high blood concentration nor too low to obtain the therapeutic effect. To date, the most common strategies of controlling flux include the use of release controlling membranes and suitable adhesive matrixes. In this aspect, recently a novel simple method of controlling BSP flux by ion-pair was initiated. Different ion-pair complexes including BSP-maleate, BSP-tartarate, BSP-besilate, and BSP-fumarate were prepared and their fluxes through rabbit abdominal skin were determined separately in vitro. It was observed that compared to free BSP, all BSP ion-pair complexes displayed lower and controllable flux. After forming ion-pair complexes, the capability of BSP to penetrate through skin was weakened due to the lowered log*P* and increased molecule weight. It was demonstrated that the flux of BSP could be controlled by ion-pair strategy. Among all

investigated complexes, BSP-maleate was the most promising candidate for long-acting transdermal patches (Song et al., 2012). While in another study, azone was used to enhance transdermal flux of BSP (used as fumarate salt) and about 98.3% BSP release was observed across the transdermal patch prepared using PVP, PVA (Dinakar et al., 2010).

The combination therapy of nitrate and selective β-adrenoceptor antagonist has shown benefits for the treatment of hypertension and heart disease than either drug alone. In this aspect, the blood pressure lowering effect and pharmacokinetics of a novel transdermal patch incorporating isosorbide dinitrate with BSP were investigated (Zhao et al., 2007). The in vitro transdermal penetration of both isosorbide dinitrate and BSP from the patches showed a zero-order process. After transdermal administration at single dose or multiple doses, the synergistic blood pressure lowering effect was confirmed in spontaneously hypertensive rats. The effect of each patch lasts for 3 days, and increased with the total dose of two drugs, showing a dose dependant manner. After transdermal administration in rabbits, C_{max} of both drugs was significantly reduced while the areas under the plasma concentration–time curve, and mean residence times were evidently increased and extended, respectively. As a patient-friendly, convenient, and multi-day dosing therapeutic system, the transdermal patches incorporating isosorbide dinitrate and BSP could be promising for the prevention and treatment of hypertension (Zhao et al., 2007).

4. Mixed β-blockers (has additional α-blocking activity)

4.1. Carvedilol

CVD is a non-selective β-blocker. It blocks β-1 and β-2 adrenergic receptors as well as the α-1 adrenergic receptors. It is the most widely prescribed drug in the long term treatment of hypertension. It is clinically indicated not only in the management of hypertension, but for myocardial infarction and congestive heart failure too. CVD is rapidly absorbed following oral administration, despite being well-absorbed, its oral bioavailability in human is about 20%, due to a significant degree of first-pass metabolism. CVD has a low molecular weight (406.5), a favorable log*P* (4.115), with a short plasma half-life of 6 h (Chakraborty et al., 2009; Wen et al., 2010; Singh et al., 2013). Long term therapy of hypertension by CVD oral administration may result in poor patient compliance because of low oral bioavailability in humans, leading to increased frequency of administration (Morgan, 1994; Hokama et al., 1999; Singh et al., 2013). Thus, CVD was found to be a good drug candidate for developing a transdermal system because of its physicochemical profile.

Ubaidulla et al., 2007 developed a matrix-type TTS containing CVD with different ratios of hydrophilic and hydrophobic polymeric combinations such as (a) EC and PVP, and (b) E-RL100 and E-RS100 by the solvent evaporation technique. The bioavailability studies in rats indicated that the CVD transdermal patches provided steady-state plasma concentrations with minimal fluctuations and improved bioavailability in comparison with oral administration. The antihypertensive activity of the patches in comparison with that of oral CVD revealed that the patches significantly controlled the hypertension in methyl prednisolone acetate-induced hypertensive rats (Ubaidulla et al., 2007). Monolithic matrix-type TTS for CVD were prepared using a film casting technique involving different ratios and combination of HPMC, HPC, E-RS100 and E-RL100 as matrix-forming polymers. All formulations carried 8% v/w of d-limonene as a penetration enhancer and 20% v/w of dibutyl phthalate as a plasticizer. Formulation F5 (4:1 ratio of HPMC, E-RL100) showed both maximum drug release (12.31 mg) and permeation (2987.67 μg/cm^2) in 24 h, which differed significantly among all the formulations. Formulation F5 showed maximum flux (32.80 μg/h/cm^2), which meets the flux requirements, and differed significantly among all the formulations. A shelf life of 2 years was predicted for the prepared TTS. The authors claimed that, monolithic matrix-type CVD-TTS could be prepared having both the required flux and suitable mechanical properties by using aforesaid polymer (Gannu et al., 2008a).

Recently, matrix-type transdermal patch of CVD was developed using different ratios of polymer combinations by solvent evaporation technique. It was observed that the molded patch followed Higuchi kinetics release pattern and the mechanism of release was found to be diffusion mediated. The pharmacokinetic studies of optimized transdermal CVD patches on rats revealed improved bioavailability of 72% in comparison to oral administration with steady-state plasma concentration. In addition optimized patch shows transdermal flux of 30.08 μg/cm^2/h which was more as compared to plain CVD, further pharmacodynamic activity of the optimized transdermal CVD patch showed significant controlled hypertension as compared to the control group (Kshirsagar et al., 2012). In another study, the patches containing glycyrrhizin–chitosan mixture was also found to be able to control hypertension in experimental hypertensive rats (Sapra et al., 2008). In this study, the influence of glycyrrhizin and chitosan on the permeation of CVD via rat epidermis was evaluated. The permeation of CVD across excised rat epidermis was found significantly higher when glycyrrhizin, chitosan, or glycyrrhizin–chitosan mixture was used as a donor vehicle as compared to propylene glycol:ethanol (7:3) mixture. In addition, developed patches containing glycyrrhizin–chitosan mixture showed sustained release of CVD, which was able to control the hypertension in experimental hypertensive rats. Rat epidermis microconstituents determination exhibit maximum extraction of cholesterol, sphingosine, and triglycerides after treatment with glycyrrhizin–chitosan mixture. Further, increase in intercellular space, disordered lipid structure and corneocyte detachment as observed in scanning electron microscopy (SEM) and transmission electron microscopy (TEM) suggests great potential of glycyrrhizin for use as a transdermal permeation enhancer (Sapra et al., 2008), while extraction of lipids from SC as well as loosening of hydrogen bonds between ceramides as the mechanism of enhancement of CVD by black cumin oil was reported elsewhere (Amin et al., 2008).

In another report, a significant improvement in the bioavailability of CVD was observed with the transdermal patches over oral tablets. In this study, the bioavailability of two drugs viz. CVD and hydrochlorothiazide from a TTS with conventional immediate release oral tablets in healthy volunteers was observed. The developed TTS produced therapeutically effective plasma concentrations of the CVD and hydrochlorothiazide up to a range of 60–72 h. In conclusion, the developed TTS conforms to the aim of at least 2 day management of stage II hypertension with the application of a

single transdermal patch and hence improving patient compliance (Agrawal and Aggarwal, 2010).

Sapra et al., 2009a, investigated the effect of soybean extract and chitosan in facilitating the permeation of CVD across the rat epidermis. The antihypertensive activity of the patches in comparison to that after oral administration of CVD was studied in deoxycorticosterone acetate-induced hypertensive rats. The in vitro permeation of CVD across rat epidermis increased and was maximum with a combination of soybean extract and chitosan. Furthermore, the application of patches containing soybean extract and chitosan mixture resulted in sustained release of CVD, which was able to control the blood pressure in hypertensive rats through 24 h (Sapra et al., 2009a). In another report, the effect of *Asparagus racemosus* extract and chitosan in facilitating the permeation of CVD across rat epidermis was also observed by Sapra et al., 2009b. It was observed that the permeation of CVD via rat epidermis was significantly higher when *Asparagus racemosus* and chitosan alone or their admixture was used as donor vehicle as compared to the propylene glycol/ethanol (7:3) mixture. In addition, the application of patches comprising *Asparagus racemosus* extract and chitosan mixture was able to control the blood pressure in experimental hypertensive rats over 36 h (Sapra et al., 2009b).

Dixit et al., 2008 prepared the nanoemulsion system for increasing the solubility and the in vitro transdermal delivery of CVD. Transdermal permeation of CVD through the rat skin was determined using the Keshary–Chien diffusion cell. Authors claimed that there was a significant increase in the steady state flux and permeability coefficient in nanoemulsion formulations as compared to the control. The highest value of these permeability parameters was obtained in optimized formulation B3 (CVD (0.5% w/w), OA (6% w/w): isopropyl myristate (1:1), Tween 80 (22.5% w/w), Transcutol-P (22.5% w/w) and distilled water. It was suggested that the prepared formulation was found to be devoid of any skin irritation potential.

Consequently, in 2010, Rizwan et al. prepared nanoemulsion or enhanced transdermal delivery of CVD. It was observed that prepared nanoemulsions showed a high skin permeation rate (92.251–161.53 μg/cm^2/h), good enhancement ratio (ER) of 3.5–6.2 and high permeability coefficient in comparison to control. The optimised nanoemulsion formulation consisted of 0.25% w/w CVD, 12.5% w/w Miglyol 810®, 50% w/w Acconon CC6®/CO-20® (1:1) and water. The above formulation had the smallest mean globule size of 9.28 nm. The authors claimed that superior transdermal flux of CVD may be due to nano range size of oil globules that lead to intimate contact with the skin layer. It was suggested that the developed nanoemulsion system is a promising vehicle for the transdermal delivery of CVD (Rizwan et al., 2010).

In another report, the effect of vehicles (labrasol, transcutol, polyethylene glycol 400, propylene glycol, ethanol, OA, and isopropyl myristate) and selected penetration enhancers such as limonene, carvone, camphor, menthol, transcutol, and labrasol at 5% w/v concentrations was investigated on the in vitro permeation of CVD from saturated solutions across porcine skin. Phosphate buffered saline (pH 7.4) containing 40% v/v polyethylene glycol 400 was served as the control. It was observed that the transdermal flux of CVD from transcutol, labrasol, polyethylene glycol 400, ethanol, and OA was 10.5, 8.6, 4.2, 2.9, and 1.5 times higher, respectively, than that of the control. The flux obtained using transcutol was significantly higher than the flux obtained using the other vehicles. Solutions containing camphor (5% w/v) showed maximum permeation in 24 h with a flux of 3.19 μg/cm^2/h, which was significantly different than the flux obtained using other permeation enhancers. The flux of CVD from the solutions containing 5% w/v camphor, limonene, transcutol, carvone, labrasol, and menthol were 9.7, 7.6, 7.6, 6.3, 4.7, and 2.3 times higher, respectively, than the control. The authors claimed that transcutol, labrasol, and polyethylene glycol 400 may be used as potential vehicles and camphor, limonene, and transcutol at a 5% w/v level as penetration enhancers can be used for enhanced transdermal delivery of CVD (Gannu et al., 2008b).

4.2. Labetalol

LHCL is a nonselective blocker of adrenergic receptors. It binds competitively with both α- and β-receptors. It is slightly soluble in water and is well absorbed from the gastrointestinal tract. LHCL is rapidly absorbed following an oral dose but undergoes extensive first pass metabolism, resulting in only 25% oral bioavailability (MacCarthy and Bloomfield, 1983). The drug is eliminated rapidly, so repeated daily administration is required to maintain effective plasma levels. The half-life of LHCL is approximately 4–6 h. It has a low molecular weight (364.9) and favorable log*P* (1.89), with no reported skin irritation history. All these factors suggest that LHCL is an ideal drug candidate for the development of a TTS (Zafar et al., 2010). However, fewer reports were found in the literature on the transdermal delivery of this drug. In 2005, Aqil et al., used E-RL100, E-RS100 and PVP K-30 as the film-forming polymers for the preparation of matrix-type TTS of LHCL along with polyethylene glycol-400 as the plasticizer and DMSO as the penetration enhancer (Aqil et al., 2005). The authors claimed a high release >90% of LHCL from the TTS, which is therapeutically effective in experimental hypertensive rats. In another report, Zafar et al., 2010 investigated the effect of different penetration enhancers namely turpentine oil, dimethyl formamide, menthol, DMSO, pine oil, and 2-pyrollidone for LHCL transdermal delivery. Amongst the investigated enhancers, DMSO (10% v/v) was found to be the most effective enhancer for LHCL. It was observed that on increasing the concentration of drug and enhancer in the donor cell the permeability coefficient of LHCL was also accentuated. It was concluded that LHCL could be delivered via the dermal route with the use of 10% DMSO as the penetration enhancer (Zafar et al., 2010). The effect of basil oil, a volatile oil containing alcoholic terpenes, as a potential penetration enhancer for improved skin permeation of LHCL with reference to camphor, geraniol, thymol, and clove oil was also studied (Jain et al., 2008). In vitro permeation of LHCL in vehicle per se and in the presence of 5% w/v enhancer was investigated by performing in vitro rat abdominal skin permeation studies using a side-by-side glass diffusion cell. Among all enhancers, basil oil produced the maximum enhancement (ER = 46.52) over neat vehicle. Activation energies for LHCL permeation in water, vehicle per se and in the presence of 5% w/v basil oil were found to be 23.16, 18.71, and 10.98 kcal/mol, respectively. Lowering of activation energy in the presence of basil oil suggests the creation of new polar pathways in the skin for enhanced permeation of LHCL. It was concluded that basil oil was found to be a promising transdermal permeation

enhancer for improved LHCL transdermal drug delivery. In another report, a matrix type TTS containing combinations of E-EPO/E-RL100 and Plasdone S630 as polymers was investigated for enhanced transdermal delivery of LHCL (Mittal et al., 2009). The optimized formulation was also assessed for its pharmacokinetic, pharmacodynamic, skin irritation potential, and stability studies. The authors claimed 92.43% and 76.24% drug release and permeation respectively in 48 h from the optimized patch formulation. The developed optimized patch showed sustained action and was seemingly free of skin irritation potential as suggested by the skin Draize score test. It was reported that the above transdermal system holds promise for improved bioavailability and better management of hypertension on a long term basis.

5. Conclusion

Hypertension is an important predictor of cardiovascular disease, cerebrovascular accidents and death. The prevalence of cardiovascular diseases and hypertension is rapidly increasing in developing countries. There are many categories of antihypertensives, amongst which β-blockers are a very important class. Most β-blockers exhibit low bio availability due to hepatic first-pass metabolism following oral administration. They are required to be taken more than once a day due to their short half-lives. For this reason, their administration more than once a day with the conventional oral dosage forms, such as tablets and capsules, results in poor patient compliance. Also, fluctuations in the plasma drug concentrations are observed over the dosing intervals. There is a need to improve drug delivery devices for β-blockers because of the quantum of their utilization and short comings associated with their conventional dosage forms. Transdermal drug delivery systems are one of the most rapidly advancing areas of novel drug delivery, which are designed to deliver a therapeutically effective amount of drug across a patient's skin. In addition, transdermal delivery provides many advantages like avoidance of the first-pass effect, sustained therapeutic action and improved patient compliance (Ahad et al., 2014). As we can see from this review article, a brief overview of the different β-blockers revealed that, delivering through the transdermal route improves bioavailability as well as improves patient compliance by many fold. Further work is needed to allow the β-blockers for transdermal systems and refine it in order to attain suitable clinical levels in patients.

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