Recent Trends in Transdermal Cardiovascular Therapy

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Transdermal dosage forms, though a costly alternative to the conventional formulations, are becoming popular because of some unique advantages. Controlled zero-order absorption, simple administration mode and the option of easy removal in case of adverse manifestations make them particularly desirable in cardiovascular therapy. Nitroglycerin and isosorbide dinitrate, the two antiischaemic drugs; and clonidine, an antihypertensive molecule, are being extensively used in the transdermal form. Studies that compared these patches with the established dosage forms had shown that though patches were costlier than conventional prescription products, they reduced the occurrence of hospitalization and diagnostic costs. Currently a number of antihypertensive drugs are being developed for transdermal administration. This article reviews the research on cardiovascular patches as well as the marketed products.

The age-old theory that imparted the status of "dead, impermeable barrier devoid of biological activity" to skin had already been challenged by the development of pioneering transdermal products[1]. But a less than impressive commercial growth in this sector had raised some doubts about the feasibility of this route as an efficient device of drug delivery. The journey of transdermal research had commenced with a lot of enthusiasm, as it heralded the promise of noninvasive cutaneous application[1]. The projected advantages were publicized so much that the target consumers were prepared to accept the products even if they were costlier alternatives to the conventional therapy. This acceptability factor had encouraged researchers and industries alike to take up challenging projects in this particular arena. For the last two decades, it remained an area of vital research interest, and data was generated for almost every available drug[2].

The extensive work of last 25 years has generated around 10 marketed transdermal patches and a large number of patents. Surveys had been undertaken to assess the contribution of these products to medical expenditure and clinical benefits too. It was found that though only two antianginal (nitroglycerin and isosorbide dinitrate) agents and one antihypertensive agent (clonidine) have been available in the transdermal form, they have reduced cardiovascular emergencies significantly. This article is dedicated to the review of transdermal research in the area of cardiovascular agents reported in various pharmaceutical journals.

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Transdermal delivery systems (TDDS) – risks and benefits:

Transdermal systems are ideally suited for diseases that demand chronic treatment. Hypertension, a disease equally prevalent in the developed and the underdeveloped countries, demands chronic treatment. An analysis shows that cardiovascular disease (CVD) was responsible for the highest mortality rate, and mild hypertension may be the humble beginning for the fatal cardiovascular ailments[3]. Hypertensive patients need to be on prolonged medication, and sometimes lifelong therapy is advised. Hence noncompliance of the therapy, especially in cases where dosing frequency is high, is a major problem. Transdermal delivery is considered to be the ideal method which can bypass the difficulties of first-pass metabolism, enable absolute elimination of GIT toxic effects, maintain the steady plasma level of drug for a prolonged period and deliver the drug at predetermined rate without the hazards of specialist care as is required in the intravenous infusion[4]. Since transdermal patches offer a better quality of life, they are more popular than the oral dosage forms[5-6]. Sizeable number of antihypertensives undergo extensive first-pass metabolism,

which too can be avoided by transdermal therapy. Hence cardiovascular agents of both therapeutic and prophylactic usage have been subjected to transdermal investigation.

So far, few investigations have been carried out with the primary objective to evaluate the efficacy and risk factors of TDDS patches in heart patients[7–8]. However, a study using nicotine patch specifically conducted to evaluate the safety of TDDS on heart patients has showed no additional cardiovascular risks[9]. Nicotine is a ganglion stimulant, which increases the heart rate; so the safe result indicates that patches or adjuvants used in the patches as such do not involve any additional risk for the heart patients. However, dose dumping or inadequate release both could be a significant disadvantage for a patch-type dosage form. Major tragedies had occurred because of improper use of fentanyl patches, and FDA has cautioned health care providers against the overdose from transdermal systems[10]. Fentanyl is a potent drug, which is marketed in TDDS form as a pain reliever. Since skin offers high resistance to the absorption of drugs, the patches contain much higher amount of the active ingredient (approximately 20-25 times) than the amount intended to be absorbed. Fentanyl patches carry the black box warning and are advised to be used with utmost caution. Catapres-TTS, the only antihypertensive available as TDDS, comes in three dose levels (0.1 mg, 0.2 mg and 0.3 mg), and the physicians are advised to titrate the dosage according to the individual's therapeutic requirements. While substituting the patch for the oral antihypertensive therapy, a gradual reduction of the oral dose is advised as the antihypertensive effect from the patch might not commence until 2-3 d after initial application. With initial therapy of Catapres-TTS, mild sedation, tiredness and dryness of mouth is usual. Catapres-TTS also caused lowering of heart and pulse rate, and a lowering of heart rate below 56 beats must be avoided for safety. The reports indicate that though the intensity of the side effects is low with the patches, they cannot altogether be avoided and should be used with caution[11].

The marketed patches:

Commercially available transdermal patches are limited in number, but this small group of marketed products represents many important classes: antianginal (nitroglycerin, isosorbide dinitrate), antihypertensive (clonidine), antiemetics (scopolamine), hormones (estrodiol, testosterone), opioids (fentanyl) and anticholinergic (nicotine)[12]. The statistics procured from market survey show that the sales of anaesthetic patches are high, but the patches used to prevent cardiovascular disorders are of higher clinical benefit. Hence we would start the discussion with the analysis of existing cardiovascular patches.

Courtesy transdermal development, nitroglycerin, a drug that had lost its popularity in the 1960s, was reintroduced for clinical use[13]. Unsuitable for gastrointestinal administration owing to its low oral bioavailability (1%), its use was restricted to sublingual and topical form. Absorption of this drug from these forms was low and variable (26-34%), and inadequate understanding of the pharmacology had raised doubts about its clinical efficacy[13]. Until 1970, the only alternative for the sublingual therapy was an intravenous infusion, occasionally used in the intensive care units on patients undergoing treatment for severe chest pain. In 1981, introduction of the transdermal patch opened up the possibilities of its prolonged and continuous use to prevent the unwarranted attacks of angina[14].

Transderm-Nitro patches, one of the first two transdermal systems to be marketed, owed their success to a favourable pharmacodynamic parameter of the drug. Effective at low plasma concentration (1.2-11 ng/ml), a dose in the microgram ranges is sufficient to control the angina[15]**.** Presently there are four manufacturers in the market selling the drug in the transdermal form: (Deponit-Schwarz/Lohmann, Nitrodisc-Searle, NitroDur-Key Pharmaceuticals and Transderm Nitro-Ciba)[1]. On the technological basis too, nitroglycerin delivery systems can be classified into four categories. Transderm-Nitro is a polymer membrane permeation control system, whereas in Deponit the drug is dispersed in adhesive polymer matrix. Nitrodisc carries the drug in micro reservoirs, and NitroDur system uses nonadhesive polymers as the base[1]. An evaluation of these patches have revealed that Transderm-Nitro is better than its two marketed counterparts as it resulted in the highest area under plasma concentration curve and the least coefficient of variation in a comparative study[16]. Yet another study says, though the drug penetrates from the Nitrodisc system at a greater rate, the products are clinically interchangeable[17]. Support for transdermal therapy has also come from another significant clinical study. Patients of unstable angina who could only be sustained by IV nitroglycerin in the intensive care unit responded to transdermal nitroglycerin, which maintained the antiischaemic effects initially achieved with IV nitroglycerin[18]. Though the utility of the transdermal nitroglycerin is yet to be established in the whole spectrum of coronary heart

diseases, it has already improved the quality of life of the ambulant ischemic patients. Special benefits in terms of improvement in haemodynamic abnormalities, reduction in the infarct size and reduction of life-threatening arrhythmias have been noted amongst the users of the products. Finally, the American Heart Association has endorsed the utility of the transdermal form in acute myocardial infarction irrespective of the involvement of left ventricular failure[19]. The proven clinical efficacy and assured market has sustained the research interest on this drug. Work is going on to optimize transdermal therapy by improvising both on formulations as well as techniques.

Research trends:

Since barrier properties of intact skin vary widely among and within the species, reproducibility in drug flux is a major challenge for transdermal dosage forms. Permeation enhancers are mainly used to overcome this high resistance and increase the flux to clinically beneficial levels[20]. An experimental system reported by Varshney *et al.*[21] makes use of Aerosol-OT (AOT), an ionic moiety of the surfactant docusate sodium, to enhance the permeation of nitroglycerin. Here the drug is encapsulated in reservoirs with surfactants arranged in normal and reverse micellar pattern. The authors have shown that 5% weight of AOT in water, arranged in normal micellar pattern, can increase the permeability of nitroglycerin 12.3-fold[21]. Comparable enhancement and slightly better skin compatibility were found in reverse micellar patterns where the AOT was contained in isopropyl myristate.

Because of the rate-controlling effect of stratum corneum, the attainment of much-desirable zero-order drug delivery was relatively easy through skin, but it was not free of disadvantages. Prolonged exposure to a steady concentration of a drug could make the body immune to its beneficial therapeutic effects by inducing tolerance[22]. So attempts were made to develop systems that would release variable amount of drugs at different time intervals, and the technique of enhancer depletion was attempted.

Recently with the advent of iontophoresis, systems with active release control have become a reality. Systems combining electronic circuits and special formulation techniques (discontinuous distribution of nitroglycerin in the reservoir) have been developed to monitor the drug release during emergency or at the volition of the patient[23]. The drug reservoir with its discontinuous layers of nitroglycerin generates pulsed release that is controlled by the production of hydrogen gas activated by a magnetic switch. The trend shows that the development of technology rather than the system will be the focus of transdermal delivery of nitroglycerin in the upcoming years.

Antiischaemics:

The other organic nitrate that has been marketed already in the transdermal form is isosorbide dinitrate. As skin is preferentially permeable to the lipid molecule, the fully nitrated lipophilic polyols are acceptable to skin. Bioavailability of isosorbide dinitrate when administered by conventional routes varies significantly. The drug has a short half-life (0.8±0.4 h), demanding frequent administration, and the prescribed dosage regimen is 2.5-10 mg every 2 to 3 h. From transdermal route, a flux of 4.01 mg/h is necessary to achieve the level of clinical efficiency of maintenance therapy[24]. However, in 1984 a Japanese company "Toa Eiyo" had launched frandol tape in the market, containing the drug in adhesive polymer dispersion. The frandol tape, a once-daily transdermal patch, had reduced the inconvenience of frequent administration and gained wider acceptance. In 1999, another group attempted to develop a membrane-controlled transdermal system of isosorbide dinitrate using carbomer gel as the drug reservoir. Here ethylene vinyl acetate copolymers and polyethylene membranes were used as rate-controlling devices. The release rate achieved using the polyethylene rate controller mimicked the commercial product and was close to the target flux and was thought to be promising for commercial development[24]. However, the drug is not free from cutaneous metabolism. It was found that while penetrating the skin layer, isosorbide dinitrate gets converted to isosorbide-2-mononitrate and isosorbide-5-mononitrate, indicating a possibility of structural change during the permeation[25]. Some workers have used the sophisticated electron beam irradiation technique to synthesize matrix system of the drug[26]. It was found that a particular irradiation dose of 50 kGy is successful in delivering the drug at a higher rate than the marketed product, opening the possibility of improved patch compared to the commercially available one[27].

Verapamil, a phenyl alkyl derivative used in hypertension, angina and supraventricular arrhythmias, has drawn the attention of transdermal researchers[28,29]. As the free base is more lipophilic than the hydrochloride salt, skin permeability studies are usually conducted in the free base form. Studies of *in vitro* permeation showed

promising results[30]. *In vivo* studies conducted in rats using absorption promoter azone also reported significant enhancement in permeation for the drug[31]. Another *in vivo* study that delivered the drug from matrix system of Eudragit and HPMC to rabbits had reported successful maintenance of steady and adequate plasma levels up to 24 h of administration[32]. One study aimed at assessing the pharmacokinetic profile of transdermal verapamil using human males as subjects had reported that both steady state plasma concentration and area under the plasma concentration curve for total verapamil concentration were proportional to the surface area of the delivery system[33]. Amongst the other dihydropyridines of antianginal efficacy, amlodipine has been studied for transdermal permeation. Systems have been formulated for this drug using penetration enhancers sodium lauryl sulphate and propylene glycol, etc. But *in vitro* studies indicated a flux value inadequate for clinical use[34].

Nifedipine, a drug of proven efficacy in the treatment of angina and hypertension both, has been dealt with caution. The drug suffers from the disadvantage of photosensitivity, and prolonged processing usually interferes with its stability[35]. Till the early '90s, nifedipine research was focused on the development of oral sustained release dosage forms[36]. Recently some attempts have been undertaken to develop transdermal systems for this difficult drug, and studies have revealed interesting results. Though the measured physicochemical properties showed favourable permeation potentials, the drug showed very poor skin permeability. Wide ranges of penetration enhancers, like sodium lauryl sulphate, propylene glycol, etc., have failed to improve the permeability to an acceptable level[37]. The actual permeation data obtained on this drug seems to defy all the empirical guidelines and shows no correlation between the drug solubility and steady state flux[38].

Antihypertensives:

Another group of cardiovascular agents that had generated excitement amongst the transdermal scientists is antihypertensives, specifically the ß-adrenergic receptor antagonists. These drugs have multiple utilities and are administered in hypertension; ischaemic heart diseases, including certain types of arrhythmias. Since antihypertensives suffer from the disadvantage of extensive first-pass metabolism and variable bioavailability, they were considered ideal transdermal candidates[39].

Clonidine was the first antihypertensive agent to be launched in the transdermal form. Since then the patch (Catapres-TTS) has been evaluated for clinical efficacy – alone and in combinations with diuretics[40]. Clonidine, an α_2 adrenergic agonist, is effective in low doses but was used with caution because of its centrally acting nature. Serious side effects like sedation and xerostomia along with dry nasal mucosa and parotid swelling occur in at least 50% of patients, leading to the discontinuation of therapy when administered orally[41]. However, transdermal patches were rated better in comparison to the conventional dosage forms. Studies involving large populations were carried out in which transdermal form was found to be better tolerated, requiring no discontinuation of therapy[42]. One detailed study based on the retrospective analysis of the Medicaid claims in two American states, Florida and South Carolina, had shown that though the prescription expenditure of the patients using the patch was significantly higher, it saved them from hospitalization and diagnostic costs and reduced the overall health expenditure.

A mechanistic study performed on human epidermal keratinocytes cell culture revealed that the transport of clonidine is affected by pH. The experiment indicated that clonidine transport beyond the epidermal layer was affected by tertiary amine transport system and could be inhibited by competition with other amines like tryptamine, diphenhydramine, quinine and guanidine[43]. Clonidine is widely used now in the transdermal form, and the industries are in competition to evolve better systems. Bupranolol, a drug with extensive first-pass metabolism (90%), had generated interest from the early days of transdermal research. High expectations were generated as pharmacodynamic studies carried out with adhesive transdermal patches of the drug showed effectiveness comparable to that of bupranolol infusions in rabbits[44]. The experimental patch applied to a wider area in human volunteers showed that bupranolol penetrated in sufficient amounts to have pronounced pharmacological effects against isoprenaline-challenged tachycardia[45]. Recently a study using partially methylated β-cyclodextrin as enhancer had reported good permeation of the drug[46]. Later the same researchers have developed a reservoir-type system for the drug, from which the permeation rate achieved was 4 to 5 times more than the desired flux[47].

Amongst the other antihypertensives, propranolol, a drug with desirable hydrophilic-lipophilic balance, has created high expectations. Enormous data has been generated for this drug as it is also used as a model molecule for mechanistic studies and system development[48-52]. However, initial studies carried out to evaluate

permeability showed that the drug induces inflammatory reactions[53]. A self-assembled pharmacogel using synthesized prodrugs propranolol palmitate hydrochloride and propranolol stearate hydrochloride was found to increase the enhancement rate and was also free of inflammatory reactions. The gel containing the lamellar liquid crystals could achieve high chemical potential and showed the promise of successful percutaneous delivery of the drug[54].

Simultaneously work is going on to develop a suitable delivery system for propranolol. Trials have been undertaken with various natural and artificial polymers to develop reservoirs and rate-controlling membranes. There are reports on the development of gel-type reservoirs using natural polymer chitosan. Rate-controlling membranes of varying permeability obtained by controlled cross-linking with gluteraldehyde were also developed using propranolol as model drug[55]. Same authors have developed systems using collagen membrane as a rate-controlling device and reported successful regulation of drug release[56]. However, there is a recent claim that systems developed with commercially available ucecryl polymer can deliver the drug most effectively[57].

The ß-blocker timolol belongs to the category of antihypertensives but is widely used for treatment of glaucoma[58]. Conventional systems carry the drug in the form of maleate ester because it enhances the gastrointestinal solubility. However, skin permeation studies conducted on this drug used the free base timolol, and systems developed with the free base form showed the promise of maintaining an adequate zero-order plasma profile[59]. In the recent past, timolol has been assessed for iontophoretic delivery too. As electrical resistance changes widely in the natural skin, iontophoretic studies usually use artificial membranes of various pore sizes. In such a study, timolol maleate showed high and adequate permeability through such a microporous membrane, which had resistance comparable to that of the skin[60].

Atenolol, a hydrophilic drug, with a relatively high effective concentration was less investigated compared to other β-blockers. Limited data available on the permeation studies shows that permeation increases in presence of chemical enhancers[61]. Recent study had shown that a matrix system containing ethyl vinyl acetate and polyoxyethylene 2-oleyl ether as penetration enhancers releases the drug in a diffusion-controlled manner and is sufficient to cause effective permeation[62]. One of our studies had used the prodrug approach, where atenolol esters were prepared to increase its lipophilicity and permeation studies were carried out in isolated porcine skin; promising results were obtained with caproate ester[63].

Metoprolol reduces the blood pressure by reduction of cardiac output via slowing of the heart rate and finds substantial use in antihypertensive therapy. The basic drug with a pK_a value of 9.5 and moderately high molecular weight has been investigated both by passive diffusion and iontophoresis[64,65].

Significant enhancement of permeation (130-fold) was observed in one study where the permeation enhancer azone was used along with iontophoretic technique[66]. A bioavailability study carried out on hairless rats had shown much superior systemic bioavailability of the drug from adhesive transdermal patches as compared to the conventional oral forms[65]. Work has also been reported on the development of transdermal metoprolol system in which a composite release pattern adequate to supply the therapeutic need has been claimed by the researchers[67]. Intrinsic permeability data was also generated for some new drugs nimodipine, nicardipine, etc., using various animal skins[68-69].

CONCLUSIONS

The advanced state of research and the plethora of patent applications filed for transdermal systems clearly indicate the renewed interest of pharmaceutical industry in the transdermal field. To include the drugs of poor skin permeability into the transdermal arena, painstaking efforts are being invested to obtain drug derivatives of favourable physicochemical properties.

Simultaneously to combat the permeability problems associated with skin, a band of researchers have started exploring the sophisticated techniques of permeation enhancement. The use of electron beam radiation in the development of transdermal systems has opened up newer channels. There is hope that the drugs that have been written off as poor candidates would be developed into successful transdermal systems in the near future.

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