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Review Article

TRANSDERMAL PATCHES FOR THE TREATMENT OF ANGINA PECTORIS: AN EFFECTIVE DRUG DELIVERY SYSTEM-A REVIEW

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ABSTRACT

Topical delivery methods have been used since the dawn of time, employed to cure a wide range of ailments and for aesthetic purposes. Transdermal drug delivery has evolved throughout time, with the development of passive and active technologies that have resulted in enhanced distribution, accuracy in drug dosage, and better fulfilment of the requirements of the individual. The search for more powerful pharmaceuticals that can be delivered to the skin through appropriate transdermal technologies will continue to be a focus in the development of drugs for transdermal patches and other forms of delivery. Topical and transdermal distribution has been around for a while, but this review will focus on transdermal patches and how they've evolved. The articles have been searched on different search engines such as Scopus database, Science direct, PubMed, Google scholar, and Bentham science using multiple keywords. An adhesive transdermal patch is applied to the skin and contains medicine that is absorbed into the bloodstream through the skin. It aids in the recovery of an afflicted part of the body. When compared to oral, topical, i. v., and i. m. administration systems, transdermal drug delivery allows a controlled release of the medicine into patients, often by either a porous membrane or by body heat melting small layers of medication embedded in the adhesive. The fundamental drawback of transdermal delivery methods is that the skin is a highly efficient barrier, therefore, only tiny molecules can enter the skin and be administered in this manner.

Keywords: Transdermal patch, Angina pectoris, Solvent-casting method, Nitroglycerin

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INTRODUCTION

The skin is the largest organ in the human body, with an area of 1.5 to 2.0 m^2 in adults. Drugs have been applied to the skin to cure superficial disorders, administer therapies transdermally to control chronic illnesses, and as cosmetics from man's earliest medical records. Salves, ointments, cures, and even patches containing fruit, animal, or mineral extracts were already prevalent in ancient Egypt and Babylonian medicine (around 3000 BC) [1]. Transdermal delivery systems became normal practice once delivery technology was developed to enable precise and repeatable administration through the skin for systemic effects in the third decade of the twentieth century. To evaluate a technology's overall efficacy and appropriateness for systemic treatment, drug blood level–time profiles that are equivalent to or approximated from oral or parenteral delivery are often employed [2]. The drug concentrations in the blood are determined by the amount of medicine delivered into the circulation from the delivery mechanism and the application area. Transdermal transmission is often utilized to obtain therapeutic outcomes deep inside or under the epidermis, such as local anesthetic and anti-inflammatory effects. Topical distribution, on the other hand, tries to treat localized skin issues that are typically severe [3].

This review aims to go through the long history of topical and transdermal distribution, concentrating on the evolution and present usage of transdermal patches for the treatment of angina pectoris. The articles have been searched on different search engines such as Scopus database, Science direct, PubMed, Google scholar, and Bentham science using multiple keywords.

History of transdermal delivery development

Adoption of topical drug delivery (before the 20th century)

Topical treatments consecrated, bandaged, applied, or added to the skin are probably to have been employed from the origin of man, with the procedure being apparent as written documents exist, such as on the clay tablets being used by Sumerians [4-6]. It has been proposed that a liquidized ochre-rich mixture, produced some 100 000 y ago and discovered in Blombos Cave in South Africa, might have been used for decorative and skin defense [7]. Ancient Egyptians used oil (e. g. castor, olive, and sesame), fats (mainly animals), perfumes (e. g. bitter almond, peppermint, and rosemary), and other additives to produce their beauty and dermatological items (unguents, creams, pomades, rouges, powders, and eye and nail paints) [8]. Mineral ingots of copper and lead were used to make kohl, a cream used to color the eyes. Red ochre has been used as a lip or face polish, and a combination of crushed lime and oil has been used as a washing cream [9]. Ancient lead-containing cosmetics have been used both for beauty and, based on moral values, for defense against eye diseases [10]. However, these results may have been real as recent experiments involving incubation of low levels of the lead ion with NO-produced skin cells, which are considered to provide defense against infection. On the negative hand, it might be questioned whether these lead materials were indeed harmful, considering that elevated blood levels of lead have been identified in modern consumers of kohl [10, 11].

The well-known Papyrus Ebers (1550 BC), which described over 800 prescriptions and around 700 medicines, seems to have been the strongest medicinal source in prehistoric times [12]. It includes several recipes for curing skin disorders, including burns, bruises, blisters, and exudation. Other treatments include maintaining the hair, making the hair expand, improving the skin, and embellishing the body. A pollutant (with 35 ingredients) is identified for the vulnerability of the human male. Other therapies include the first transdermal distribution of medicines with systemic symptoms, such as the topical usage of patchouli to expel pain in the head and the product administered to the abdomen of a woman or a man to expel pain induced by tapeworm. The focus on topical therapies in that period is apparent in the painting of an ointment workroom in the Egyptian tomb from 1400 BC [13-17].

A decade and a half years later, Galen (AD 129–199), a Greek practitioner, incorporated medicinal and other excipient compounds

into dosage formulations. He is generally regarded as the 'Father of Pharmacy' and his methods are recognized as 'Galenic Pharmacy.' Galen's Cerate, a cold cream, is certainly his most renowned recipe, with a formulation relatively close to that found nowadays [18]. Medicated plasters (emplastra), which were commonly applied to the skin under particular conditions, can be traced back to ancient China (around 2000 BC) and are the early ancestors of today's transdermal patches (emplastra transcutanea). These earlier plasters commonly included various ingredients of medicinal medicines scattered onto a natural rubber-based adhesive added to a backrest made of cloth or parchment [19]. Nicotine, a new-world transdermal agent, was still in use in plaster (Emplastrum opodeldoch) during the period of Paracelsus (1493–1541). Unlike medicated plasters originating in China, Western-type medicated plasters were much simplified formulas in that they had just one active ingredient. Examples of plasters identified in the United States Pharmacopoeia (USP) nearly 70 y ago included belladonna (used as a local analgesic), mustard (as an important local irritant) and salicylic acid (as a keratolytic agent). The idea that such medicines cross the skin seems to have been applied by Ibn Sina (980–1037 AD), a Persian practitioner better regarded as Avicenna in the Western World. In The Canon of Medicine, he said that topical medications had two spirits or states: gentle and strong. He indicated that as topical drugs are added to the skin, the soft portion would enter the skin while the hard part would not. He further suggested that dermal medications not only have local effects but also impact tissues directly below the skin, including joints (regional effects) as well as effects in distant regions (systemic effects) [20, 21]. One of his topical preparations, acting systematically, concerned cases under which medications should not be taken orally. One of Avicenna's regional remedies was the usage of a plaster-like solution in which sulfur was combined with tar and added to the skin with a sheet of paper used as a backing to hold the formulation in position. This product was used to relieve sciatica, that is, discomfort caused by the compression of the sciatica nerve felt in the spine, hip, and outer side of the body. Such precursors to contemporary transdermal medicines are mercurial ointments (Unguentum Hydrargyri) used in the care of syphilis at the end of the 15th century. One example of these preparations is the Unguentum Hydrargyri Fortius L. (Strong Mercurial Ointment), made of purified mercury, lard and suet [22–24].

In the twentieth century, the emergence of topical products

In 1904, Schwenkenbecker generalized that the skin was relatively permeable to lipid-soluble compounds but not to water or electrolytes [25]. A great variety of toxicity, often in children, was recorded in France at the beginning of the 1900s after topical application of nitrobenzene or aniline dyes in dyed clothing or shoes and further backed the notion of possible systemic absorption of topical items [26–28]. The death resulting from the systemic ingestion of phenol from a vast body surface of a young man after the unintentional spill of a container of phenol over him, underscored the possibly fatal effects of accidental 'overexposure' to drugs added to the skin [29]. However, lethality has been encouraged by the corrosive quality of phenol at higher doses, leading to a significant increase in human skin penetration and the saturation of the Sulphate and glucuronidation routes existing in the body for detoxification [30]. A more recent collection of studies identified the potential for lethal toxicity resulting from exposure to hexachlorophene after topical exposure to kids [31, 32].

At the start of the twentieth century, numerous *in vivo* trials showed chronic absorption following topical administration by measuring drug amounts in skin, urine, and feces [33]. Primary analytical techniques were purely qualitative and compounds were observed in the blood or urine by examining the change in the assessed sample in terms of color, acidity, or density compared to the normal sample [34]. Mercury, one of the first medicinal agents to be discovered and quantified in human excreta, was originally detected in the urine after syphilis infusion using amalgamation processes (i.e. Reinsch test) [35]. After, more precise analytical techniques (e. g. utilizing a measured capillary tube) made it possible to quantify 5 mg of mercury in 1 L of solution [36]. Colorimetric approaches have been widely used. The concentration of p-chloro-m-xylenol (halogenated phenol) in biological materials (i.e. semen, blood, and minced tissue) was measured using the Millon reagent (an aqueous solution of mercury and nitric acid). The filthy red compound that was produced was then removed by ether to provide a transparent yellow solution appropriate for photometric measurements [37]. The absorption of methyl salicylate from different vehicles in 10 male subjects was analyzed through excretion of its salicylate metabolite in the urine using colorimetric titration with ferric alum. Absorption of free iodine by unbroken dog skin was studied through redox titration of iodine excreted in the urine with sodium thiosulphate. The penetration-promoting effect of polyethylene glycol ointment was studied *in vivo* in humans by the determination of the excreted concentration of phenolsulfonphthalein used as tracer dye using a photoelectric colorimeter [38, 39].

Characteristic pharmacological or physiological endpoints have been used in other early trials as evidence of the incorporation of substances into the systemic circulation [40]. For example, sex hormones have been extensively studied using laboratory animals as subjects. Testosterone or testosterone propionate added as an ointment to the skin of castrated male guinea pigs is readily absorbed as accessory reproductive organs stay functional [41]. Similarly, the application of estrogen to the shaved back skin of ovariectomized female mice utilizing ethanol and/or benzol-containing automobiles has contributed to oestrus [42]. Convulsions have been identified in rodents, rats, and guinea pigs after the external use of extremely harmful strychnine alkaloids [43]. Percutaneous absorption of another alkaloid, eserine, was analyzed using the volume and color of tear secretion in rats in reaction to Ach potentiated by topically applied eserine. This approach has been used as a biochemical endpoint for a variety of ointment bases [44]. One controversial technique used to measure the amount of mercury absorbed after the application of mercurial ointment with various bases was dependent on the amount of mercurial ointment recovered after scratching a given surface of the skin with a pre-weighted shaving blade, i.e. the difference between applied and recovered weight reflected the amount of ointment absorbed by the skin [45, 46].

Advancement of topical drug delivery system with systemic effect

The very first quantitative study on the clinical management of systemic disease through topical treatment seems to be Zondek's job, about 70 y earlier. It has been stated that chloroxylenol, an external disinfectant still present in antiseptic soaps and solutions today (Dettol®; Reckitt Benckiser, Slough, Berkshire, UK), can be useful in the treatment of urogenital infections when applied topically as 30% lanolin ointment. Amusingly, the possible percutaneous ingestion of medications currently present in many of our latest transdermal goods has been shown even earlier through inadvertent toxicity after topical application during manufacture, market usage of products, and in agriculture. For example, nitroglycerin permeation through human skin, now used transdermally to avoid and cure angina, first emerged in the early 1900s as a side effect-'nitroglycerin brain'-a serious headache suffered by people employed in the manufacturing of explosives or otherwise handling nitroglycerin-containing products [47, 48]. Experimentally, 1 and 10% alcoholic nitroglycerin solutions applied topically to the forearm of healthy individuals resulted in prolonged systemic effects (i.e. headaches, increases in BP and pulse rates), with participants gradually displaying an increased susceptibility to headache effects after an average of 38 h [49]. It was not until 1948, though, that nitroglycerin ointment was successfully used to treat Raynaud's disease [50, 51]. This study contributed to the usage of a 2% nitroglycerin ointment (Nitrol®; Kremers Urban Company, Seymour, IN, USA) to treat angina pectoris in the 1950s. A wooden applicator was used to calculate the dosage of nitroglycerin added to the chest [52]. A clinical trial conducted in 1974 showed a continuous prophylactic efficacy of up to 5 h in duration [53]. The ointment was, though, sticky and required to be used many times a day. Concerns persisted over the actual number of drugs used each day. Another example was the systemic side effects of nicotine, a transdermal smoking prevention medication, which became evident during the topical interaction associated with its usage as a topical insecticide [54, 55]. In addition, nicotine absorption among employees processing tobacco leaves in the form of green tobacco disease has been noted.

Percutaneous ingestion of estrogens was found in the 1940s when men employed in stilboestrol plants observed breast enlargement [56, 57]. The US FDA has licensed commercially viable transdermal patches, has been tabulated in table 1 [58].

Table 1: The US FDA has licensed commercially viable transdermal patches

Drug (Trade name, year of FDA approval)	Type	Indication	Site of application	Duration of application
Buprenorphine (Butrans®, 2010)	Therapeutic	Chronic pain	Upper outer arm, upper chest, upper back, or the side of the chest	7 d
Clonidine (Catapres-TTS®, 1984)		Hypertension	Upper outer arm or upper chest	
Oestradiol (Estraderm®, 1986)		Female HRT	The trunk of the body including the buttocks and abdomen	3-4 d
Oestradiol (Climara®, 1994)			Lower abdomen or upper quadrant of the buttock	7 d
Oestradiol (Vivelle®, 1994)			The trunk of the body including the abdomen and buttocks	3-4 d
Oestradiol (Alora®, 1996)			Lower abdomen, upper quadrant of the buttock, or the outer aspect of the hip	
Oestradiol (Vivelle-Dot®, 1999)			Lower abdomen	
Oestradiol (Menostar®, 2004)			Lower abdomen	7 d
Oestradiol (Minivelle®, 2012)			Lower abdomen or buttocks	3-4 d
Oestradiol (E)/Norethindrone (NT) (Combipatch®, 1998)			Lower abdomen	
Ethinyl oestradiol (EE)/Norelgestromin (NL) (Ortho Evra®, 2001)		Female contraception	Buttock, abdomen, upper outer arm, or upper torso	7 d
Oestradiol (E)/levonorgestrel (L) (Climara Pro®, 2003)		Female HRT	Lower abdomen	
Fentanyl (Duragesic®, 1990)		Chronic pain	Chest, back, flank, or upper arm	72 h
Granisetron (Sancuso®, 2008)		Chemotherapy-induced nausea and vomiting	Upper outer arm	Up to 7 d
Methylphenidate (Daytrana®, 2006)		ADHD	Hip area, avoiding the waistline	Up to 9 h in a day
Nitroglycerin (Nitro-Dur®, 1995)		Angina pectoris	Chest, shoulder, upper arm, or back (hairless area)	12-14 h
Nitroglycerin (Minitran®, 1996)				
Oxybutynin (Oxytrol®, 2003)		Overactive bladder	Abdomen, buttocks, or hip	3-4 d
Rivastigmine (Exelon®, 2007)		Alzheimer's and Parkinson's disease	Upper/lower back, upper arm, or chest	24 h
Rotigotine[c] (Neupro®, 2007)		Parkinson's disease restless legs syndrome	Abdomen, thigh, hip, flank, shoulder, or upper arm	
Scopolamine (Transderm Scōp®,1981)		Motion sickness	Behind one ear	72 h
Selegiline (Emsam®, 2006)		Major depressive disorder	Upper chest or back, upper thigh or the outer surface of the upper arm	24 h
Testosterone[d] (Androderm®, 1995)		Hypogonadism	Back, abdomen, thighs, or upper arm	
Testosterone[d] (Androderm®, 1995)		Hypogonadism	Back, abdomen, thighs, or upper arm	
Nicotine (Nicoderm CQ®, 1991)[e]	Over The	Smoking cessation	Anywhere on the body, avoiding joints	
Nicotine (Nicorette®)[f]	Counter		To an area on the upper body or upper outer arm that is non-hairy, intact, non-irritated, clean, and dry	16 h
Nicotine (Nicorette® Invisipatch®)[f]			A clean, intact, dry, and hairless skin of the thigh, arm, or chest	
Nicotine (Habitrol®, 1990)[g]			Upper body or the outer part of the arm	24 h
Sumatriptan (Zecuity®, 2013)	Active	Migraine	Upper arm or tight	4 h
Capsaicin (Qutenza®, 2009)	Topical	Neuropathic pain	The most painful areas, excluding the face and scalp	Single 60 min Application of up to four patches
Diclofenac epolamine (Flector®, 2007)		Topical treatment for acute pain	The most painful area	12 h
Lidocaine (Lidoderm®, 1999)		Post-herpetic neuralgia pain	The most painful area, avoiding contact with the eyes	Up to three patches only once for up to 12 h within a 24 h period
Lidocaine (L)/Tetracaine (T) (Synera®, 2005)		Local dermal analgesia	Site of venipuncture, i. v. cannulation or superficial dermatological procedure	20-30 min
Menthol (M)/Methyl salicylate (MS) (Salonpas®, 2008)		Muscles and joints pain	The affected area	Up to 8–12 h
Oestradiol (Evamist®, 2007)[h]	Therapeutic	Menopausal symptoms	The inside of the forearm between the elbow and the wrist	One spray once daily (starting dose)
Testosterone (Axiron®, 2010)[h]		Hypogonadism	The axilla (armpit)	2 pump actions once Daily (starting dose)

The transdermal patch of scopolamine (Hyoscine) to combat motion sickness: first of its kind to reach the market

In the Papyrus Ebers, powder of Hyoscyamus (scopolamine's parent plant) was reported as a treatment for abdominal pain that could be applied topically or taken orally. Scopolamine was initially used as an antiperspirant on the skin [59]. In 1944, soldiers were given 0.6 mg of scopolamine (hyoscine) orally, along with other medications, to avoid seasickness. While a higher dosage (1.2 mg) was shown to be more successful, it was also linked to dry mouth [60]. Dimenhydrinate (Dramamine®; Prestige Brands, Tarrytown, NY, USA), an antihistamine and anticholinergic medication, was offered to a woman to cure hives in 1947 and resulted in the sudden disappearance of her lifelong car sickness. As a result, 389 US soldiers suffering from seasickness when shipping to Germany were given 100 mg of Dramamine, which was found to be successful in 372 of them within 1 hour [61]. Scopolamine was subsequently shown to be marginally useful in versatile gunnery students but was shown to be ineffective in preventing airsickness in student navigators [62]. Unfortunately, since scopolamine has a very low removal half-life of 4.5 h, it is only supposed to have a brief impact [63].

The discovery that scopolamine had a significant flux across excised human skin prompted follow-up research to investigate the process through which scopolamine entered the stratum corneum. The Alza Corporation developed a transdermal therapeutic system (TTS) for the prevention and treatment of motion-mediated nausea in the 1970s, which provided regulated administration of scopolamine across the skin's surface, allowing the system to monitor medication input kinetics to the systemic circulation [64, 65]. The research aimed to find an extremely permeable skin site. The transdermal patch with a Zaffaroni pattern added behind the ear proved to be the most successful. A medication reservoir and a microporous membrane regulated the delivery of scopolamine in the patch. An initial bolus (loading) dose of scopolamine was issued upon application of the patch to the skin as a consequence of scopolamine redistribution through the contact adhesive lamina, allowing therapeutic scopolamine plasma amounts to be reached quickly [66]. The technology was first put to the test with Alza workers traveling in a huge sailboat through the "potato field," a rugged stretch of water near the Golden Gate Bridge. Employees who wore the placebo patch became ill, while others who wore the scopolamine patch did not. Controlled experiments were later carried out as part of the American Spacelab program, demonstrating the effectiveness of the transdermal scopolamine system [67]. The first transdermal patch to enter the US market was a 2.5 cm^2-TTS (which is now one of the smallest patches on the market) programmed to produce 1.5 mg of scopolamine over three days (Transderm Scōp®; Novartis Consumer Health, Parsippany, NJ, USA) in 1979. The effectiveness of transdermal scopolamine for the treatment of motion sickness at sea was evaluated in four double-blind clinical trials in stable men and women with a history of motion sickness. In comparison to placebo and oral dimenhydrinate, transdermal scopolamine not only offered major motion sickness safety but also had few side effects [68, 69].

From the ointment to the transdermal patches: nitroglycerin for the treatment of angina pectoris

The only transdermal product available before the introduction of the transdermal scopolamine patch was nitroglycerin ointment. The plasma levels of nitroglycerin ointment were based on the surface region on which a specific dose of ointment was added, while sublingual and oral sustained-release capsule dose types contributed to more sustained serum levels [70]. Applying a specific dosage to a stratified environment, on the other hand, is difficult. The dosages of Nitro-Bid® (nitroglycerin ointment USP 2 percent; Fougera, Melville, NY, USA) used in clinical studies, for example, were measured using a ruler to define the length of ointment ribbon expelled from the ointment tube and ranged from 1.3 cm (1/2 in.; 7.5 mg) to 5.1 cm (2 in.; 30 mg), and were usually added to 232 cm^2 (36 Another disadvantage with semi-solids is that they need repeated dosing, such as every 8 h for Nitro-Bid, to produce the desired therapeutic result, which is more likely to contribute to patient non-compliance than the once-daily dosing available for patches [71]. Volatilization of nitroglycerin, on the other hand, did not seem to be a problem. Unintentional transmission through interpersonal touch, on the other hand, was a challenge, as illustrated by a spousal headache following intercourse with a spouse who had rubbed a nitroglycerin patch on his penis to relieve erectile dysfunction [72, 73].

Alza Corporation registered a new US patent in 1973 focused on its topical rate-controlling membrane medicated adhesive bandage design for the safe systemic administration of vasodilators, including nitroglycerin. The substance in the reservoir may be combined with a transporting agent to help in drug distribution, according to one version of the patent [74]. Key Pharmaceuticals and Searle Laboratories also released nitroglycerin transdermal device prototypes in the early 1980s: a water-soluble polymeric diffusion matrix containing nitroglycerin and a micro-sealed patch with a polymer matrix containing nitroglycerin inside a hydrophobic solvent to facilitate nitroglycerin transfer and diffusion. Three nitroglycerin transdermal patches, Transderm-Nitro® (Ciba Pharmaceuticals Company), Nitro-Dur® (Key Pharmaceuticals), and Nitrodisc® (Key Pharmaceuticals), were launched into the US market in 1981 for the prevention and treatment of angina pectoris and were associated with these patents (Searle Laboratories) [75]. Since it has been discovered in clinical trials that nitroglycerin inactivated itself during prolonged delivery, each branded patch was to be administered once daily with a 12 h 'rest cycle' in between [76]. The addition of ethanol as a permeation enhancer to a transdermal nitroglycerin device, according to a subsequent patent, allowed nitroglycerin skin fluxes of at least 40 $\mu g \cdot cm^{-2} \cdot h^{-1}$ (preferably in the range of 50–150 $\mu g \cdot cm^{-2} \cdot h^{-1}$) above the prior art. In the United States, Key Pharmaceuticals produced the first commercially effective nitroglycerin patch, which included the drug entirely in the adhesive. This patch gained the largest share of the nitroglycerin industry. Nitro-Dur II® was the brand name for the patch, which was later sold and listed in a US patent [77].

Solvent casting method for the preparation of transdermal patch

Solvent-casting is a century-old method of filmmaking. The API is either suspended or dissolved in a solution of polymers, plasticizers, and any additional components dissolved in a volatile solvent such as water or ethanol for medicinal purposes [78]. This substance, referred to as the film dope, is spread out over a continuous roll of release medium, such as plastic-impregnated paper, using traditional solvent-cast film deposition processes [79, 80]. To remove the solvents from the coated medium, they are put through a drying device, such as an oven or a convection chamber. After drying, the film is dying, cut into strips and individually packed in sealed, atmosphere-resistant bags. Because the temperatures necessary to remove the solvents are lower than those required for a hot-melt extrusion method, solvent-casting is excellent for producing films containing heat-sensitive APIs [81, 82]. However, dried solvent-cast films may include small quantities of residual solvents, posing compliance difficulties. Additionally, if any of the solvents being used is flammable, such as ethanol, specific safety equipment and procedures must be utilized to avoid fire and environmental dangers caused by vaporized solvent [83, 84]. Table 2 summarizes the stepwise procedure along with mandatory precautions to be taken during each step [85–88].

Types of excipients used for the formulation of transdermal patch

Matrix and film-forming polymers

Polyethylene glycol: PEG is crosslinking polymer with tris(6-isocyanatohexyl) isocyanurate, with the help of the aurethaneallophante bond, can swell and form gels in phosphate-buffered ethanol or saline. Hence solutes are released in biphasic mode.

Acrylic-acid matrices: Examples: Eudragit S100, Eudragit E100, Eudragit RS PM, Eudragit RL PM, Eudragit Ne 40 D. They are used as matrix-forming agents in the transdermal system and are nonadhesive copolymers of ethyl acrylate and methyl methacrylate.

Cellulose derivatives: Polyvinylpyrrolidone is a water-soluble polymer; when added to water-insoluble films, it produces polymers

such as ethylcellulose, which initiates pore formation and results in leaching out of water-soluble components. Ethylcellulose and Polyvinylpyrrolidone, along with 30% dibutyl phthalate act as a plasticizer.

Hydroxypropyl methylcellulose: It acts as a matrix-forming agent in the transdermal formulation. Clear films of HPMC are formed, and fast drug release is observed due to the bursting effect of polymer while the dissolution study [89, 90].

Table 2: The stepwise procedure of the solvent-casting method and mandatory precautions to be taken

The procedure of film formation by a solvent-casting method	Mandatory precautions during the procedure
Step-I	
Selection of solvent system for producing appropriate solution.	To check the complete solubility of the drug and polymer before starting the procedure. Asure compatibility of drug and polymer in the solvent system.
Step-II	
Preparing suspension or solution out of selected Polymers.	To check the viscosity index of polymeric suspension or solution. Drug and polymers are miscible or not? The mixing temperature should be under control.
Step-III	
The casting of prepared polymeric suspension or solution.	Measures to prevent air entrapment during mixing. Continuous checking for the viscosity of suspension or solution.
Step-IV	
At 40-50°C in hot air, oven-dry the casted polymeric suspension or solution.	The major factor to be considered is maintaining the drying temperature, drying time, and moisture content of the casted polymeric components.
Step-V	
Step 5. Finally, the film is peeled, cut, and packed into desired shape and size as per the requirement.	Suitable packing materials and containers to be selected. Moisture control during packing and within the container.

Rate-controlling membrane polymers

Ethylene-vinyl acetate: Mainly used for preparing the rate-controlling membrane of the patch, as the permeability of the membrane can be altered by changing or altering the vinyl acetate concentration within the polymer.

Silicon rubber: It is highly permeable, with very low viscosity observed within the polymer matrix.

Polyurethane: They are condensation products of polyisocyanates and polyols. They are also separated based on synthetic origins, such as polyether polyol known as polyether urethanes and polyester polyol known as polyester urethanes. The main advantage of polyurethane polymer is that the hydrophilic and hydrophobic ratio can be altered to obtain desired permeability of the membrane. Whereas polyether urethanes show high resistance to hydrolysis and on the other hand, polyester urethanes show biodegradability [91, 92].

Polymers as pressure-sensitive adhesives

Polyisobutylene: It is a vinyl polymer, cationic polymerization product of an isobutylene monomer. It is a colorless substance with semisolid elastic nature and shows very less permeability to air and moisture. It is thermally stable and shows a good oxidative property. The molecular weight of this polymer plays an important role, as it changes its physical characteristics. Low molecular weight polymers show less viscosity as compared to high molecular weight polymers.

Polyacrylics: It is a polymerization product of alkyl acrylate ester; it is a polyester-based polymer. They are water-soluble in nature and biodegradable. Polyacrylics at pH 5 are liquid in their state and at pH 7 gels. High molecular weight polyacrylics have good mechanical strength [93–95].

Permeation or penetration enhancers

Alcohols, glycol, and glycerides: Alcohols bring about the disruption of the stratum corneum by extracting biochemicals by hydrophobic alcohols and making tissues permeable for mass transfer. Ex. Alkanols, alkenols, glycols, polyglycols glycerols. Alkanols with low molecular weight have the role of solvent, which increases the solubility of the drug through the stratum corneum matrix. Those penetration enhancers possessing ethylene oxide functional groups have more solubility for the drug. In combination with ethanol, glycerides also show increased permeability.

Surfactants: Surfactants have the potential to solubilize lipids within the layer of the stratum corneum; hence they are used for solubilizing lipophilic drugs. Surfactants are composed of a hydrophilic head and a lipophilic tail having an alkyl and aryl fatty chain. There are many types of surfactants, such as anionic surfactants (eg. sodium lauryl sulfate), and cationic surfactants (eg. cetyltrimethylammonium bromide), and zwitterionic surfactants (eg. dodecyl betaine). It was observed that anionic and cationic surfactants potentially damage the human skin by interacting with intracellular keratin; they both swell the stratum corneum. Whereas sodium lauryl sulfate is highly irritant to the skin and enhances the water loss from transepidermal in humans. Even though with the irritant nature of surfactants, they are used for drug penetration activity across the skin, variations are done in the concentration of surfactant according to formulation and level of penetration to be achieved.

Pyrrolidones: Pyrrolidones are mainly used to create reservoirs of permeant within the skin; these reservoirs are potentially helpful in achieving sustained release action of the permeant from the stratum corneum for a longer period. Pyrrolidones possess a good partition coefficient with the tissues of the stratum corneum. The mechanism by which pyrrolidones act alters the solvent nature stratum corneum [96, 97].

Azone: It was the first molecule specially designed for skin penetration enhancement. Chemically also known as 1-dodecylazacycloheptan-2-one or laurocapran. It is a colorless and odorless liquid, having a melting point of-7℃ Even though oily in nature it is still non-greasy with a smooth feel. It is soluble and compatible with alcohol and propylene glycol and also with most organic solvents. It is highly lipophilic substance with an octanol/water concentration (logP) of 6.2. Azone shows the highest effectivity at the lowest concentration of 0.1-5%, more often employed between 1-3%.

Dimethyl sulfoxide (DMSO): Shreds of evidence obtained from the studies of Fourier transform and Raman spectroscopy show that dimethyl sulfoxide changes the confirmation of keratin present in stratum corneum, from alpha-helical to beta-helical sheet. DMSO and its related compounds also enhance the transdermal permeation for drugs like beta-blockers, papaverine hydrochloride, and ephedrine hydrochloride. 60% v/v or more concentration of DMSO enhances the flux and interacts with lipids present in the stratum corneum.

Alkyl-N, N-distributed amino acetates: Two compounds of this class namely Dodecyl-N, N dimethylaminoacetate, and Dodecyl-2-methyl-2-(N, N-dimethylaminoacetate) are used as penetration enhancers in transdermal drug delivery. These are soluble in organic solvents and

insoluble in water, but solubility is observed in a water-alcohol mixture. Amino acetates show very less irritation toward the skin and this happens due to N, N-dimethyl glycine, an enzyme present within the skin membrane responsible for the biological decomposition of amino acetates. It reacts with stratum corneum keratin to enhance skin permeation; this also increases the hydration efficacy of the skin. As the N, N-dialkyl carbon chain increases, the skin permeation enhancement activity goes on decreasing [98].

Essential Oils, Terpenes, and Terpenoids: Terpenes and terpenoids are the class of volatile oil. These are classified based on the repeated number of isoprene units (C_5H_8). The mechanism by which terpenes act, by altering the solvent nature of the stratum corneum layer easily allows the drug to penetrate tissues. According to the investigation carried out by Cornwell *et al.,* it is found that 12 sesquiterpenes are meaningful in penetration of 5-fluorouracil in human skin (*in vivo*). Essential oils such as eucalyptus, chenopodium, and ylang-ylang are helpful in the skin permeation activity of 5-fluorouracil in humans. Results obtained from FT-IR and partition coefficient studies it is revealed that eugenol has lipid extraction from the stratum corneum hence increasing the permeability coefficient of the drug through the stratum corneum. Eugenol belongs to a class of allylbenzene compounds. Sources from where eugenol can be obtained are clove oil, nutmeg, cinnamon, and bay leaf. It is an extraction product obtained from these natural sources, clear to the pale yellow color of an oily liquid. It has solubility in an organic solvent but is slightly soluble in water. Eugenol has the potential to reduce pain and numbing sensation; hence used in various transdermal preparations. Methanol has increased penetration activity along with limonene and terpenes hence used in various transdermal preparations to enhance drug penetration. It is extracted from flowering tops of *Mentha piperita*. Menthol naturally occurs as (-)-menthol. A sesquiterpenes alcohol is obtained from natural sources of essential oils, such as lemongrass, tuberose, balsam, tolu, neroli, citronella, and cyclamen. The drug penetration activity order is quit comparable: Farnesol>Carvone>Nerodilol>Menthone>Limonenoxide. It is the best candidate used in many transdermal formulations [99, 100].

Backing laminate

Backing laminates are the support systems for transdermal patches. They provide backing support for the whole formulation system. As they play an important role in adhering to the whole formulation on its surface till the delivery of the drug. They must be compatible with the whole transdermal formulation and be chemically resistant. The selection of such polymers is important for backing laminate which will not cause drug, additives, and excipients to leach out when comes in contact for a longer period. The rate of moisture vapor transmission should be very low and have good oxygen transmission. Backing laminate material should have qualities like flexibility, elasticity, and good tensile strength. For Example, Plastic films of polyethylene, polyvinyl, polyester aluminum vapor coated layer, heat seal layer [101, 102].

Release liner

It is considered as a part of the primary packaging for the formulation instead, it is not at all a part of the dosage form. It is a covering for the patch during storage and is to be removed just before the application of the patch. Release liners are in direct contact with drug delivery systems so it is mandatory to be compatible with all components of the formulation. Practically it is observed that cross-linking occurs between the adhesive layer and release liner; hence the force required to separate the liner will be quite more. They are manufactured from non-occlusive i.e. paper fabric or occlusive i.e. polyethylene and polyvinylchloride. Coating material for release liners can be made from Teflon or silicon. They prevent the migration of drugs into the adhesive layer, which results in drug loss and contamination during storage [103–106, 107-109].

CONCLUSION

From the dawn of time, topical delivery systems have been used to treat a variety of illnesses and as cosmetics. Over time, a definition of viable medication candidates for the transdermal delivery has emerged, along with the advancement of passive and active technologies that have resulted in improved delivery, accuracy in drug dosing, and better meeting of personal needs. Seeking enough potent drugs that can reach the skin with suitable transdermal technologies remains a priority in the further advancement of drugs in transdermal patches and related distribution types. Meeting clinical and aesthetic demands that cannot be adequately addressed cost-effectively by other routes of supply is a major challenge. There are several benefits to administering a medicine systemically via the skin, including a steady blood plasma concentration of the drug, fewer adverse effects, and more patient compliance with the drug regimen employed for therapy. The skin has recently been deemed the safest route for the administration of drugs since it allows for a continuous flow of medication into the bloodstream. The data elaborated in the present review can be utilized to formulate transdermal patches containing different novel drugs for the treatment of various diseases.

AVAILABILITY OF DATA AND MATERIALS

Authors can confirm that all relevant data are included in the article and materials are available on request from the authors.

LIST OF ABBREVIATIONS

USP: United States Pharmacopoeia, TTS: Transdermal therapeutic system, Late I_{Na}: Late sodium current, MVA: Microvascular angina

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CONFLICT OF INTERESTS

The authors have declared that there is no conflict of interest exists.

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