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Current Pharmaceutical Design on Adhesive Based Transdermal Drug Delivery Systems

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Abstract: Drug-in-adhesive transdermal drug delivery matrix exploits intimate contact of the carrier with stratum corneum, the principal skin barrier to drug transport, to deliver the actives across the skin and into the systemic circulation. The main application challenges of drug-in-adhesive matrix lie in the physicochemical properties of skin varying with age, gender, ethnicity, health and environmental condition of patients. This in turn poses difficulty to design a universal formulation to meet the intended adhesiveness, drug release and drug permeation performances. This review focuses on pressure-sensitive adhesives, and their adhesiveness and drug release/permeation modulation mechanisms as a function of adhesive molecular structure and formulation attributes. It discusses approaches to modulate adhesive tackiness, strength, elasticity, hydrophilicity, molecular suspension capability and swelling capacity, which contribute to the net effect of adhesive on skin bonding, drug release and drug permeation.

Keywords: Drug-in-adhesive, pressure-sensitive adhesive, transdermal drug delivery.

INTRODUCTION

Human skin provides multiple functions and is primarily a physical barrier against the exogenous substances such as xenobiotics. The protective role of the skin is conferred by its multi-layered structure**.** The superficial layer of the skin is known as stratum corneum. It represents the finished product of the differentiation process at the basal layer of epidermis where keratinocytes are formed by cellular mitotic division. Anatomically, the stratum corneum is composed of corneocytes interdispersed within a lipophilic matrix in a "brick and mortar" architecture. It represents the most critical barrier of the skin [1, 2]. The stratum corneum is well known to exhibit selective permeability and allows only relatively lipophilic compounds to diffuse into the lower skin layers. The solute transport is largely mediated via passive diffusion in agreement with the Fick's Law of diffusion [3, 4] and no active transport processes have been identified [5]. Distinctive delivery systems can be designed to attain transdermal or dermal drug transport. The former involves the breaking of skin barrier whereas the latter only exerts a local effect at or near to the skin surfaces.

SKIN ANATOMY

Skin is characterized by an enormous surface area (approximately 2 m^2) with minimal proteolytic activities. It comprises of three distinct layers: i) subcutaneous tissue layer/hypodermis, ii) viable dermal layer and iii) non-viable and viable epidermal layer [6]. The transdermal drug delivery is hindered by the stratum corneum, the uppermost dead layer of epidermis [7]. The stratum corneum is made up of thick 10 to 20 cell layers over most parts of the body [8]. Each cell is presented in the form of a flat, plate-like structure (length = 34-44 μm, width = 25-36 μm, thickness = 0.2-0.5 μm) with a surface area of 750 to 1200 μm^2 arranged in a brick-like layering fashion within a hydrophobic matrix of phospholipids, glycosphingolipid, cholesterol sulfate and neutral lipid. The thickness and density of the stratum corneum may differ from one body site to another. Such differences could dictate the efficiency of transdermal drug delivery. The epidermal permeability is chiefly modulated by the intercellular lipids, arranged in lamellar sheets [9]. It has been observed that the removal of epidermal lipids by means of organic extraction reduces the skin barrier attribute [10, 11].

Broadly, three modes of solute transport have been proposed with respect to transdermal drug delivery:

I. intercellular diffusion through the lipid lamellae.

II. transcellular diffusion through both the keratinocytes and lipid lamellae.

III. diffusion through the hair follicles and sweat ducts.

Generally, it is recognised that the polar solutes permeate the skin mainly through the polar pathway within the hydrated stratum corneum. On the other hand, the non-polar solutes permeate the skin through the lipid matrix of the stratum corneum.

TECHNOLOGICAL ENHANCEMENT OF TRANSDERMAL DRUG DELIVERY

In the past 25 years, numerous new and modified methods have been reported with the aim to overcome the skin barrier and improve the transdermal drug transport. These are divided into two prime categories:

1. Passive technology
2. Active technology

Passive Technology

The passive transdermal drug delivery technology enhances the skin solute transport solely based on the principle of diffusion theory [12]. It gives rise to the development of conventional dosage forms namely creams, pastes, ointments, gels and patch system where the drug is migrated from skin exterior into dermis and systemic circulation along its concentration gradient. Currently, such conventional dosage forms have been redesigned to enhance the

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driving force for drug diffusion (thermodynamic activity) and/or enhance skin permeability for the intended solute. The feasible approaches include the use of permeation enhancers [13], supersaturated drug systems [14], pro-drug approach [15, 16], liposomes and other nanovesicular systems [17-20]. In spite of extensive efforts are devoted, the rate and extent of drug that can be delivered by these methods are still limited by the complex structure and barrier properties of skin.

Active Technology

Active transdermal drug delivery technology operates in accordance with the principle of diffusion aided by various penetration enhancement approaches, namely iontophoresis, electroporation, microporation, laser ablation, radio frequency, thermal, ultrasound and microwave [21-24]. The aforementioned approaches generally involve the application of external energy that acts as a driving force to reduce the barrier attribute of the stratum corneum, and to increase the rate and extent of drug permeation through the skin.

The current pharmaceutical advancement in active technology is a resultant fruit of research and development in pharmaceutical and biopharmaceutical sciences, bioengineering, computing, chemical engineering, precision engineering and material sciences. Extensive works have been done to manufacture small but powerful devices that can produce the desired clinical responses [23]. The usage of active technology resolves challenges faced by the arrival of biotechnology, where large molecular weight (> 500 Dalton), hydrophilic and gastrointestinal-labile therapeutics, mostly proteins and peptides, are concerned. An effective transdermal drug delivery is deemed to be brought about by combination strategies [24]. The combination of both active and passive technologies is envisaged to enable a synergistic rise in the skin solute transport, with reduced adverse effects particularly by those of active approaches that may be anatomically invasive.

Table **1** summarizes the operational mode of active technology and its risks in application. Further details can be obtained from the recent review that has described extensively about electrical, magnetic, photomechanical and cavitation waves on transdermal drug delivery [24]. Other active technologies that have been used in the early phase of development include modest pressure application [25], skin stretching under tension forces range from 0.01 to 10 mPa [26, 27] and skin abrasion [28-30].

PRESSURE-SENSITIVE ADHESIVE

With reference to passive technology, the latest advancements primarily focus on the new formulation strategies that facilitate drug diffusion through the skin. The supersaturation system has been designed to increase the thermodynamic activity of drugs such as nifedipine and lavendustin derivative, and their skin permeability [79-81]. The permeation enhancers, namely surfactants, fatty acids, terpenes and solvents, have been introduced into the transdermal formulations [82]. The permeation enhancer is also known as sorption promoter or accelerant. It is able to interact with the stratum corneum and induce a temporary, reversible increase in skin permeability for the drug diffusion to take place effectively [83].

To enhance the contact between skin and drug or permeation enhancer, it is ideal if an adhesive is introduced to the transdermal formulation and available particularly at the skin-dosage form interface. Among adhesives, the pressure-sensitive acrylic adhesive has made tremendous strides and is now presented as a sophisticated science. This review intends to discuss pressure-sensitive adhesives and their finished dosage forms for medical application with a special emphasis on transdermal drug delivery.

The pressure-sensitive adhesive refers to adhesive, which in the dry form, is aggressively and permanently tacky at room temperature and firmly adhered to a variety of dissimilar surfaces through mere contact without the need for more than finger or hand pressure. It is a non-metallic material that exerts bonding via the adhesion and cohesion forces [84]. The application of pressure-sensitive adhesive does not involve any phase changes. The pressure-sensitive adhesive begins as a highly viscous and sticky liquid (viscosity in the order of 10^6 poise), and remains in the same form throughout their application life cycle [84]. It technically never crosslink or cure during the process of bonding. The strength of its bond to a surface is dependent upon the pressure with which it is applied. The bond may be broken when the adhesive becomes fluidized under the peeling forces beyond a yield value, or the adhesive crosslinks to form a hard and brittle layer. The natural rubber has long been used as an adhesive. The synthetic butyl rubber and poly(acrylate ester) are now gaining a widespread application [85]. The current commercial products are typically made of a complex mixture. The popular pressure-sensitive adhesives are acrylic acid and its co-polymers, synthetic rubber-like styrene-butadiene and ethylene co-polymers, silicone, polyurethane, polyvinyl ether, and ethylenevinylacetate copolymers. The acrylate-, silicone- and rubber-based pressure-sensitive adhesives are commonly used in the design of transdermal drug delivery system [86]. The typical features of pressure-sensitive adhesives are displayed in Table **2**.

Rubber-Based Pressure-Sensitive Adhesive

Rubber-based pressure-sensitive adhesive comprises of either natural or synthetic rubber, in addition to oils, resins and antioxidants as tackifier and stabiliser respectively. It is reputed as the cheapest pressure-sensitive adhesive among others. The classical examples of rubber-based pressure-sensitive adhesive are styrene-butadiene, polyisobutylene, polyisoprene, polybutadiene, polystyrene-polyisoprene-polystyrene, polystyrene-polybutadiene-polystyrene, polystylene-poly(ethylene/butylene)-polystylene and polystylene-poly(ethylene/propylene)-polystylene [87]. However, the rubber-based pressure-sensitive adhesive is met with low physicochemical stability and is prone to aging. The synthetic rubber pressure-sensitive adhesive such as polyisoprene has a lower cohesive strength and its cost of production is higher than that of natural rubber [88].

Acrylic-Based Pressure-Sensitive Adhesive

Acrylic-based pressure-sensitive adhesive is prepared from acrylate esters, methacrylic acid, acrylamide, methacrylamide, N-alkoxyalkyl or N-alkyl-acrylamides without or with the addition of tackifier (Fig. **1**). It possesses a higher level of physicochemical stability against the heat and light, and superior resistance to oxidation when compared to rubber-based materials [89]. The acrylic-based pressure-sensitive adhesive is optically transparent and characterized by an excellent water proof property [90]. In addition, it is non-irritant to the skin [90].

Silicone-Based Pressure-Sensitive Adhesive

Silicone-based pressure-sensitive adhesive is prepared mainly from gum and resin. The resin is a resultant product of the reaction of silicic or polysilicic hydrosol with trimethylchlorosilane [91]. The gum used is a high molecular weight linear polysiloxane polymer [91]. Silicone-based pressure-sensitive adhesive is considered to be more supreme than other adhesives due to its consistent bonding with silicone substrates, thermostability even at elevated temperatures over 500°C or over a wide temperature range, and adhesiveness to skin having high to low surface energy [92]. In spite of such excellent features, the silicone-based pressure-sensitive adhesive is however costly, and possesses low initial tack and adhesion that are detrimental to quick bonding [93].

MECHANISTIC ASPECTS OF PRESSURE-SENSITIVE ADHESION

The transdermal drug delivery system that adopts pressure-sensitive adhesive is available in several designs. It is primarily classified as membrane, matrix or monolithic patch, and drug-in-

Table 1. Active transdermal drug delivery technology.

Mode of operation	Drug candidate	Side effect
Iontophoresis		
Electrical current 0.5 mA/cm^2 for minutes or hours [31-33].	Low and high molecular weight drugs [34-40].	Pain or irritation beyond mild erythema is not induced [32]. No irreversible damage to the skin through water electrolysis [41], which if occurs, can manifest pH shift and may induce discomfort as well as reduced drug delivery and stability [36, 42]. Alternating current generates fewer skin burns as a result of polarity reversal [42]. Continuous direct current can be employed in acute medical situations [42]. Pulsed current is preferred in the treatment of chronic illness in order to avoid skin irritation due to frequent electrical stimulation.
Electroporation		
Electrical voltage 50 to 1500 V for microseconds to milliseconds with pulsing interval of a few seconds to a minute [43].	Low and high molecular weight drugs [43-45].	*In vivo* experiments using hairless rats indicate no significant skin irritation using short and long pulses in conjunction with stratum corneum heating [43]. Overall, high voltage skin electroporation is regarded as mild and reversible on the skin tissue [33, 43, 46]. The most common side effect is muscle contraction. The level of sensation such as muscle contraction, itching, tingling, pricking and pain can rise with pulse rate, duration and voltage. The adverse sensation can be minimized through concentrating the electric field on stratum corneum without involving the nerve endings in dermis [33, 43, 46]. Skin pore can be resealed using poloxamer 188 or phosphatidylcholines [47], which selectively partition into low density lipid bilayers and induce tight bilayer packing.
Ultrasound (phonophoresis/sonophoresis)		
Low frequency 20 to 100 kHz, therapeutic frequency 1 to 3 MHz and high frequency 2 to 16 MHz with a pressure between 1 and 5 bar in the order of tens of minutes [32, 48, 49].	Low and high molecular weight drugs [32, 50, 51].	No permanent damage to the skin or underlying tissues [49, 52]. The use of high ultrasound amplitudes may bring discomfort, slight and transient erythema, dermal necrosis or burn [53-55]. The most frequent adverse effects during or after sonophoresis are skin erythema, pain, and tinnitus [52, 56]. In comparison to high frequency sonophoresis, the more permeating low frequency sonophoresis lacks the safety evidences [50].
Radiofrequency		
High frequency (~100 kHz) alternating current.	Low and high molecular weight drugs [57].	-
Laser radiation		
Photomechanical waves in the hundreds of atmospheres (300 to 1000 bar) for nanoseconds (100 ns) to a few microseconds (10 µs) [32, 48, 49].	Low and high molecular weight drugs [48, 58, 59].	A single application of pressure wave gives no observable injury to keratinocytes and only minor erythema is developed with 1 µs pressure wave [48]. Multiple doses of pressure waves may cause cell injury.

(Table 1) Contd….

Mode of operation	Drug candidate	Side effect
Magnetophoresis		
Magnetic field 5 to 300 mT [49, 60, 61].	Low molecular weight drugs [60, 61].	-
Thermal poration/Thermophoresis		
Shorter exposure (< 1s) to higher temperatures (> 100˚C) [62].	Nitroglycerin [63], testosterone, lidocaine, tetracaine [64] and fentanyl [65].	-
Microneedle		
Microneedle of height between 50 and 110μm [66].	Calcein and insulin [66, 67].	Minimal levels of discomfort, skin irritation and erythema/edema are indicated [68].
Needleless injection		
High velocity jet (> 100 m/s) of compressed gas (usually helium) that accelerates through the nozzle of the injector device, carrying with it drug particles from the cartridge it disrupts on its passage into the nozzle [69-71].	Testosterone, lidocaine hydrochloride, insulin and calcitonin [71-74].	-
Suction ablation		
Application of negative pressure or vacuum to isolate epidermis [75].	Morphine [76].	Formation of blister due to the prolonged duration of treatment [77, 78].

Table 2. Typical features of pressure-sensitive adhesive.

Property	Acrylic	Rubber	Silicone	Polyurethane	Polyester	Polyether
Tack	Low to high	Typically high	Typically low	Typically Low	Medium to high	Medium
Peel adhesion	Medium to high	Medium to high	Low to medium	Low to medium	Medium to high	Low to medium
Cohesion	Low to high	Medium to high	High	Low to medium	Low to medium	Low to medium
Solvent/chemical resistance	High	Good	Excellent	High	Medium	Excellent
Plasticizer resistance	Low to medium	Generally low	Good	Medium	Medium	Low to medium
Adhesive colour	Clear to straw	Yellow (more with time)	Clear	Clear to straw	Clear	Clear
Cost	Medium	Low	High	High	Medium to high	Medium

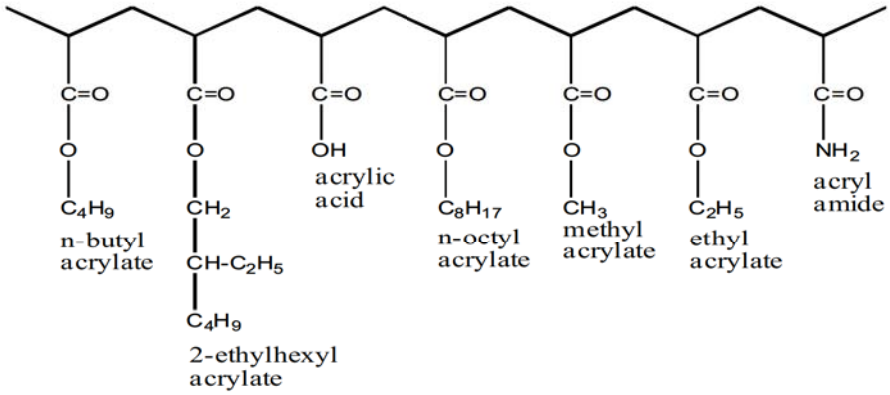

Fig. (1). Typical chains of pressure-sensitive acrylic copolymer.

adhesive patch. The latter consists of a backing layer, a polymeric matrix, an adhesive and a protective liner. An effective amount of therapeutic agent is included within the adhesive layer. The adhesive layer is positioned between a backing membrane layer and a temporary protective liner. The removal of the protective liner exposes the drug-in-adhesive which initiates contact with the surface of a subject.

Many theoretical adhesion models have been proposed, with contradictory and complementary concepts between these models. Examples of adhesion model theories include mechanical theory, electrostatic theory, chemical bonding theory, adsorption or thermodynamic theory, diffusion theory of adhesion, adhesive effect of thin liquid films and theory of weak boundary layers [94, 95]. These theories of adhesion have been empirically investigated and require further experimental evaluation to complete the mechanistic insights in bonding-debonding processes [95-97]. The pressure-sensitive adhesive elicits adhesion which involves bonding and debonding components in tack and peel operations respectively [97, 98]. It also demonstrates cohesion which is deemed necessary against debonding [96-98]. The balance of adhesion and cohesion embodies the pressure-sensitive character of the adhesive in a transdermal drug delivery system. An optimal balance between high tack, peel adhesion, and high cohesion is necessary in most cases. The behaviour of a pressure-sensitive adhesive can be reduced to three fundamental and interconnected physical properties: tack (initial adhesion), adhesion (peel adhesion) and shear strength or resistance (cohesion) [98-101].

Tack (Initial Adhesion)

The tack of a pressure-sensitive adhesive is primarily a measure of the wettability of an adhesive under controlled application conditions, with due regard for its optimum adhesion value [102]. Till now, it is still considered and rated by many as how well it sticks to the finger following slight pressure and short dwell time [102]. The application of a pressure-sensitive adhesive onto a surface may take a small fraction of a second to days or weeks to wet the required area and develop adhesion [102]. Generally, the tack value of a pressure-sensitive adhesive is higher upon adding soft and viscous components to the formulation [102].

Peel Adhesion (Adhesion)

Adhesion is defined as the process in which two bodies are attached to each other through a sum of all intermolecular and electrostatic forces acting across the interface [103]. Alternatively, it can be described as the force or energy required to separate the two bodies, often known as "practical adhesion" or "adherence". In the latter, the process of breaking the already adhesive in contact is examined. A high peel adhesion requires specific tack levels for bonding and cohesion levels to against debonding. The bonding and debonding extents of a pressure-sensitive adhesive are a function of the ratio of elastic-to-viscous components in an adhesive formulation [104-106]. Peel adhesion measures the force required to peel away an adhesive once it has been attached to a surface. Most currently used peel adhesion test methods for transdermal drug delivery system are based on methods developed for industrial tapes [107]. They typically adopt the stainless steel test panel as the substrate, cut sample with an exact width, dwell time of one minute and peel speed of 300 mm/min [108]. The peel adhesion measurement is greatly influenced by the experimental parameters such as dwell time, substrate type (stainless steel, skin or polyolefin), peel angle, peel speed, nature of transdermal drug delivery system backing membrane and adhesive thickness [103].

Shear Strength or Resistance (Cohesion)

In accordance with ASTM definition, cohesion refers to the propensity of a single substance to adhere to itself, the internal attraction of molecules towards each other, the ability to resist partition from the mass, the force holding a single substance together and internal adhesion [109]. The most important means to influence the cohesion of a pressure-sensitive adhesive are tackification and crosslinking. The crosslinking results in rigidity, antagonizing the tackification of an adhesive. The pressure-sensitive adhesive is a viscoelastic material which allows it to respond to both bonding and debonding steps. For permanent adhesive, it should not break under debonding (mainly shear and peel) forces. It must be equipped with a higher level of cohesive or shear strength than the removable adhesive [110, 111].

RECENT DEVELOPMENT OF PRESSURE-SENSITIVE ADHESIVE FOR TRANSDERMAL DRUG DELIVERY

The recent development in new adhesives for transdermal drug delivery aims at enhancing the rate of drug transport, achieving a high physicochemical compatibility of adhesives with drugs, permeation enhancers and skin, and having adhesives able to accommodate high drug loads without their adhesive property being negated [112]. It is hoped that the newly designed adhesives can acquire improved skin adhesion and wear duration, smooth texture, have less painful or even painless peel off experiences [113].

The development of new pressure-sensitive adhesives is mediated by two approaches. New polymers are designed and developed into adhesive, beyond the conventional chemistry of polyisobutylene, silicone, and acrylate. These new polymers are hydrophilic materials capable of forming hydrogel [114]. One example is polyurethane [115]. The second approach involves physical or chemical modification of the existing pressure-sensitive adhesive. The physical modification refers to formulation of the basic adhesive with additional functional excipients or adhesives [116]. The chemical modification, on the other hand, exploits grafting tech-

nique to introduce specific functional monomers to the parent pressure-sensitive adhesive polymers [117].

Hydrogel Pressure-Sensitive Adhesive

Conventional pressure-sensitive adhesives such as polyisobutylene, silicone and acrylate are hydrophobic in nature with residual water content as low as 0.1 % [117]. Hydrophilic hydrogel pressure-sensitive adhesive that features high molecular weight polyvinylpyrrolidone and oligomeric polyethylene glycol has an equilibrium water content of 8 to 11% [118]. A hydrogel is defined as a water-swollen but water-insoluble crosslinked polymeric network with rich water content [119]. It is typically compatible with drugs of varying chemical make-ups and able to soften skin thereby leading to effective transdermal drug delivery without the use of permeation enhancer [117, 120].

A two-stage formative mechanism of polyvinylpyrrolidone-polyethylene glycol hydrogel pressure-sensitive adhesive has been recently proposed [121]. Firstly, the hydrogen bonding is formed between the terminal hydroxyl groups of polyethylene glycol with the carbonyl moieties in the repeated units of longer polyvinylpyrrolidone chains. The hydrogen-bonded polyethylene glycol is then crosslinked with the polyvinylpyrrolidone via its flexible interpenetrating chains. The crosslinked complex is gradually dissolved in the presence of excess polyethylene glycol. The resulting hydrogel exhibits an excess free volume, which governs the viscoelasticity, adhesion and diffusivity properties of the adhesive. The adhesive and diffusive properties of the hydrogel polymer are modulated by its viscoelastic property [122].

Hydrophilic Pressure-Sensitive Adhesive

Hydrophilic pressure-sensitive adhesive can be introduced via plasticizing methacrylate copolymers, the film coating agent of oral dosage forms that are characterized by a high glass transition temperature [123, 124]. The methacrylate species can be cationic or anionic copolymers of dimethylaminoethyl methacrylate, methacrylic acid and methacrylic acid esters presented in varying proportions. The acetyl tributyl citrate is used as a plasticizer with succinic acid crosslinking ionically with the amino functional groups of the polymers to impart cohesion strength. The hydrophilic pressure-sensitive adhesive is insoluble in water [123, 125]. Nonetheless, it swells in water and is permeable to water vapour [126]. It can be easily removed from the skin by water flushing though it is reported to be able to withstand short showers for several days pertaining to transdermal drug delivery application [126]. An aqueous solution of such adhesive is prepared by blending the polymers with water-soluble or hydrophilic plasticizers such as polyethylene glycol, glycerin, triethanolamine or triethyl citrate [125]. The aqueous solution formulation is deemed to be able to hydrate the skin, exfoliate hair follicles and provide temporary creation of new aqueous pathways or pores within the stratum corneum for large and hydrophilic drug diffusion [43, 49, 60].

Graft Copolymeric and Enhancer-Tolerant Pressure-Sensitive Adhesive

Hydrophilic pressure-sensitive adhesive can also be prepared through copolymerization of acrylic esters with hydrophilic monomers. A water-absorbing copolymer comprising a carboxylic hydroxyalkylester monomer and a water-soluble macromer, such as an ethoxylated or propoxylated hydroxyalkyl methacrylate has been prepared for use as medical adhesive [127]. A macromer is a macromonomer or a polymer with a polymerizable group at the end of the chain [127]. Copolymerization of acrylic esters with macromers is one of the approaches that may be used to prepare graft copolymeric pressure-sensitive adhesive [127].

Acrylic-based graft polymer can have its adhesion and chemical compatibility properties adjusted through using macromers of specific chemical attributes [128]. The acrylic pressure-sensitive adhesive with a methacrylate-terminated styrene macromer has been prepared and is reported to incur less adhesion build up on skin over time [128]. The pressure-sensitive adhesive that comprises a fatty acid ester enhancer and a polystyrene methacrylate macromer reinforced acrylic polymer has also been prepared [129]. The fatty acid ester is introduced to further promote the compatibility between polymer and macromer.

Polymeric graft moiety may be attached to the acrylic polymer backbone by post-polymerization reaction of a polymeric moiety with the suitable grafting sites on the polymer backbone. Polymers with a wide range of solubility parameters such as polyisobutylene, polyethylene oxide, polyvinyl acetate, polyvinyl pyrrolidone and polysaccharide are grafted to the acrylic polymer [129-131]. These graft polymers are reported to have a better compatibility with the skin penetration enhancers. There is no noticeable physicochemical interaction between them, thereby rendering their interaction with skin unimpeded [132].

An electron beam crosslinked acrylic pressure-sensitive adhesive has been similarly reported to be tolerant of alcohol-based permeation enhancers [128-129]. The monomer composition of this adhesive is primarily comprised of iso-octyl acrylate and acrylic acid [129-131]. Silicone graft copolymers have been prepared for transdermal drug delivery application. As a pressure-sensitive adhesive, the polyethylene oxide-grafted silicones improve skin permeability towards hydrophilic drugs [133].

Many specific polymers or pressure-sensitive adhesive formulations have been claimed in the patent literature for their ability to enhance the delivery of specific drugs. A copolymer containing 2-ethylhexyl acrylate and vinyl pyrrolidone is reported to have the advantage of maintaining a relatively high concentration of estradiol in the transdermal drug delivery matrix without the estradiol undergoing crystallization [133].

Physical Blend

Adhesive based on simple blending of conventional pressure-sensitive adhesive with other polymers or excipients has been reported to impart benefits to the transdermal drug delivery system. A blend of silicone-based pressure-sensitive adhesive with polyvinylpyrrolidone has been found to prevent the crystallization of several drugs [134]. The inclusion of monoglyceride into an acrylic-based pressure-sensitive adhesive is known to improve the adhesion of transdermal dosage form to the skin and the release of isosorbide dinitrate [135]. This adhesive composition is claimed not to cause pain and damage to the stratum corneum when it is peeled off [136, 137]. The addition of clay has been indicated to improve the cohesiveness of pressure-sensitive adhesive in transdermal formulations without reducing the rate of drug delivery [137-140].

Table **3** highlights recent examples of pressure-sensitive adhesives and their applications in transdermal drug delivery.

CURRENT CHALLENGES IN PRESSURE-SENSITIVE ADHESIVE TECHNOLOGY

Three main categories of challenges are faced by the pressure-sensitive adhesive technology with respect to drug-in-adhesive transdermal system: 1. Drug solubility in adhesive, 2. Drug-adhesive/adhesive dispersion and 3. Drug-adhesive interaction.

Drug Solubility in Adhesive

It is found that the solubility of the same drug molecules is practically low in adhesives of different chemical classes. A drug, which is characterized by a low solubility value in polyisobutylens, shows only slightly higher solubility in an acrylic mass [141]. The poor adhesive solubility of drug may be overcome through using co-solvents to formulate the mixture of drug and adhesive [142]. In the case of non-volatile solvents employed, high molecular weight adhesives with a high shear resistance may be used to keep up the

Table 3. Recent examples of pressure-sensitive adhesives and their applications in transdermal drug delivery.

Pressure-sensitive adhesive	Remarks	Reference
Blends of DUROTAK 387-2287 and DURO-TAK 87-2852	Thin, flexible, smooth, and uniform patches of buflomedil hydrochloride can be formulated into adhesive matrix transdermal system suitably using Duro-Tak 387-2287 and Duro-Tak 87-2852 PSAs without using any gelling/stiffening agent.	[158]
DUROTAK 387-2287 and DUROTAK 87-2852	The feasibility of formulating transdermal drug delivery systems to deliver salbutamol sulphate as a part of asthma management is evaluated.	[159]
Durotak 87-2852	Effective monolithic drug-in-adhesive patch for *K. parviflora* extract delivery.	[160]
Blends of DUROTAK 387-2287 and DURO-TAK 87-2852	The optimized transdermal patches composed of eserine and 2-PAM are stable for 6 months at 40°C/75% relative humidity.	[153]
Blends of DUROTAK 387-2516 and DURO-TAK 87-2852	Sustained delivery of the developed patch avoids the risk of contracting an excessively high blood concentration of drug and its related toxicity.	[161]
Acrylic adhesive having functional groups such as carboxylic acid and hydroxyl moieties (trade name: 87-2074) and a non-functional acrylic adhesive (trade name: 87-900A)	A monolithic drug-in-adhesive patch containing meloxicam provides a higher efficacy than piroxicam-patch in adjuvant arthritis model.	[162]
DURO-TAK® adhesives 87-2852, 87-2677 and 87-4098	In contrast to oral delivery, a sustained activity is observed for indapamide over a period of 48 h following transdermal administration using an adhesive based system.	[163]
Duro-Tak adhesives	The 24 h mean steady-state drug concentrations for patches without enhancer, with *l*-menthol and (E)-2-isopropyl-5-methylcyclohexyl octadec-9-enoate as enhancers are in good agreement with the *in vitro* data.	[113]
DURO-TAK adhesives 87-2677 (chemical composition: acrylate), 87-4098 (chemical composition: acrylate-vinylacetate) and 87-9301 (chemical composition: acrylate)	The plasma level of S-amlodipine following transdermal application can be maintained for 72 h. The transdermal application of S-amlodipine in a drug-in-adhesive transdermal patch may be used for the treatment of hypertension.	[164]
Duro-Tak 2525	Oral administration of benztropine is often limited because of its many dose-related side effects. In this study, benztropine is formulated into drug-in adhesive patches in an attempt to overcome such problems.	[145]
Polyacrylate pressure sensitive adhesive	Huperzine A patches exhibit good controlled-release properties *in vivo*, maintaining a relatively constant serum drug concentration within 3.5 days after wearing, and are suitable for twice-weekly application.	[165]
Acrylic resin composition	A patient-friendly, convenient, and multi-day dosing transdermal patches incorporating isosorbide dinitrate with bisoprolol can be promising for the prevention and treatment of hypertension.	[166]
Blends of DUROTAK 387-2516 and DURO-TAK 87-2852	Combination of Duro-Tak 387-2516 and Duro-Tak 87-2852 at a volume ratio of 4: 5 is suitable for developing a pressure-sensitive adhesive matrix-type transdermal system for administering nefopam.	[167]
Acrylic adhesive	Incorporation of vehicles into the acrylic adhesive matrix significantly enhances the permeation rate and shortens the lag time of tacrine permeation.	[148]
MA-38 medical grade acrylic adhesive	*In vivo* studies demonstrate that the prodrugs of naltrexone are the most promising drug candidates for transdermal delivery by means of adhesive technology.	[168]
Acrylic adhesive DURO-TAK 387-2287/87-287	Adhesive patch system containing physostigmine and procyclidine, especially in combination with atropine and HI-6, can be a choice for the quality survival from nerve-agent poisoning.	[169]
Acrylate copolymer (Gelva-737) Silicone-2920 and 2675 polyisobutylene solutions (Vistanex LM-MS, Vistanex MML-100)	Acrylic pressure-sensitive adhesive shows the best adhesion and drug release properties.	[170]

(Table 3) Contd….

Pressure-sensitive adhesive	Remarks	Reference
Polystyrene-polybutadiene- polystyrene, acrylic and silicone pressure-sensitive adhesive solutions	Physostigmine is characterized by the highest permeability from silicone adhesive matrix, followed by polyisobutylene, styrene-isoprene-styrene, acrylic, and styrene-butadiene-styrene matrices.	[149]
Acrylic, silicone and polyisobutylene adhesives	Compared to the acrylic adhesives, the polyisobutylene adhesive gives rise to slower drug release rates, while the silicone adhesive provides slightly faster release rates.	[171]
Acrylate copolymer of 2-ethylhexyl acrylate and acrylic acid	The fabricated formulations give transparent systems with good film properties and a higher skin drug permeation profile than that of the marketed system.	[172]
MDX-4-421 (a silicone)	The rate of timolol release decreases when the devices are placed on human cadaver skin, and thus, the skin partly controls the rate and extent of timolol delivery into the systemic circulation *in vivo*.	[173]
Cariflex TR-1107	The plasma concentration and the analgesic effect of dihydroetorphine can be modulated by topical application of the analgesic using pressure-sensitive adhesive tape in the hairless rat.	[174]
Acrylic adhesive and polyisobutylene solutions (Vistanex LM-MH, Vistanex MML-100)	The permeation rate of tacrine is higher with acrylic adhesives containing hydroxyl functional group or none than with polyisobutylene adhesive matrix.	[144]
Urecryl MC 808	Reduction of burst release effect in transdermal matrix coated with a 12 μm thick Urecryl layer.	[175]

cohesion strength of the adhesive without being affected by the solvent [143].

Drug-Adhesive/Adhesive Dispersion

A dispersion system of drug and adhesive is necessary with respect to the need to sustain transdermal drug delivery, maintain the physicochemical stability of drug embedded in the adhesive and/or modulate the adhesion and cohesion strengths of the adhesive [144]. Owing to the high viscosity attribute of adhesive, a homogeneous dispersion is difficult to attain [143]. This is exacerbated by the tendency of the adhesive to emulsify when it is exposed to perspiration thus leading to phase separation between ingredients employed in a transdermal drug delivery system [144]. As such, the dispersion system of an adhesive is largely achieved through the introduction of solvent and/or use of low-melting point hot-melt adhesives that eases the mixing operation via heating and lowering the mixture viscosity [145].

Drug-Adhesive Interaction

The transdermal flux of a drug from a drug-in-adhesive system is strongly governed by the strength and extent of drug-adhesive interaction. The flux of tacrine saturated in acrylic-based pressure-sensitive adhesive is almost double of that in polyisobutylene matrix [145]. Using acrylic-based pressure-sensitive adhesive functionalized with carboxylic acid moiety, almost no drug permeation through skin is however observed from matrix loaded with drug content lower than 8 %w/w [146]. This is ascribed to interaction between the amine group of tacrine and the carboxylic acid moiety of acrylic-based adhesive. Similarly, the transdermal patch of nitrogen-containing benztropine formulated in acrylic-based pressure-sensitive adhesive with carboxylic acid functional group does not show any skin permeation [146]. Under such circumstances, the amine-compatible silicone-based adhesive can be used as an alternative since no interaction is elicited between the silanol group of adhesive and the amine group of drug [147].

The highly crosslinked acrylic-based adhesive without a functional group gives rise to a higher skin permeation rate to isosorbide dinitrate than acrylic-based adhesive containing the carboxylic acid functional group [147]. The crosslinked structure of an adhesive appears to affect the drug flux to a smaller extent than the chemical interaction between drug and adhesive. In other studies, the highly crosslinked enhancer-compatible acrylic-based adhesive nevertheless, reduces the permeation of tulobuterol, estradiol and norethindrone acetate [148]. In a study with physostigmine, the highest drug flux is attained with the use of the grafted acrylic-based adhesive followed by those with hydroxyl functional group, without functional group and enhancer-compatible samples [149, 150]. The chemical interaction between drug and adhesive, and the physical hindrance introduced by the crosslinked structure of an adhesive are barrier to drug release from matrix to skin thereby reducing the transdermal drug flux. Further, the drug-adhesive interaction can dictate the solubility of drug in adhesive, its thermodynamic activity and skin permeation propensity [150]. The empirical investigation on drug-adhesive compatibility for transdermal drug delivery is imperative from the structure-activity relationship viewpoint.

FUTURE PERSPECTIVES

The transdermal drug delivery is advantageous as the drug can be transported into the systemic circulation with no substantial first-pass metabolism [151]. A uniform drug dose can be administered over a prolonged duration [151]. Its application onto skin is easy and can be withdrawn at times of adverse effects are developed. More than 30 transdermal drug delivery projects are now subjected to clinical review, for the management of sexual dysfunction, Parkinson, depression and Alzheimer diseases [152]. A number of drugs such as nitroglycerine, nicotine, estradiol, scopolamine, clonidine, testosterone, fentanyl, norethindrone acetate and lidocaine have been made available commercially in the form of transdermal dosage forms (Table **4**). Among all, the adhesive technology including that of pressure-sensitive adhesive receives a widespread application and is met with a high probability of success. The late findings on drug-in-pressure-sensitive adhesive highlight that a combinational prophylactic transdermal patch made of eserine and pralidoxime is able to provide therapeutic plasma levels of both drugs for three days in a rabbit model [153-157].

With respect to pressure-sensitive adhesive technology, issues associated with drug solubility in adhesive, drug-adhesive or adhesives dispersion and drug-adhesive interaction must be resolved

Table 4. Family of commercial transdermal systems [121].

Product name	Active ingredient	Duration of action	Enhancer	Type
Alora®	17β-estradiol	4 days	Sorbitan monooleate	Adhesive matrix
Climara®	17β-estradiol	7 days	Fatty acid esters	Adhesive matrix
Deponit®	Nitroglycerin	12-14 h	Propylene glycol	Adhesive matrix
FemPatch®	17β-estradiol	7 days	monolaurate	Adhesive matrix
Habitrol®	Nicotine	1 day	None	Adhesive matrix
Minitran®	Nitroglycerin	12-14 h	Fatty acid esters	Adhesive matrix
Nitrodur®	Nitroglycerin	12-14 h	None	Adhesive matrix
Testoderm®	Testosterone	1 day	None	Adhesive matrix
Menorest®	71β-estradiol	3-4 days	Oleic acid, propylene glycol,	Adhesive matrix
Nicotrol®	Nicotine	16 h	None	Adhesive matrix
Androderm®	Testosterone	24 h	Ethanol, glyceryl monooleate, methyl laureate, glycerin	Adhesive matrix
Prostep®	Nicotine	24 h	None	Adhesive matrix
Nitrodisc®	Nitroglycerin	24 h	Polyethylene glycol, isopropyl palmitate	Adhesive matrix
Catapres TTS®	Clonidine	7 days	None	Rate-control membrane
Durageslic®	Fentanyl	3 days	Ethanol	Rate-control membrane
Estraderm®	17β-estradiol	3 days	Ethanol	Rate-control membrane
Nicoderm®	Nicotine	24 h	None	Rate-control membrane
Transderm-Nitro®	Nitroglycerin	12-14 h	None	Rate-control membrane
TransdermScop®	Scopolamine	3 days	None	Rate-control membrane

through the development of structure-activity relationship of drugs and adhesives in order to entail an accurate control of drug release and permeation from drug-in-adhesive system or the similars. The inability of pressure-sensitive adhesive to adhere to the skin under strenuous exercise or humid condition must be addressed [122]. The possibility of pressure-sensitive adhesive to induce skin trauma and irritation upon removal shall be weighed against the benefit of continuous application for days [152]. The design of pressure-sensitive adhesive-based transdermal drug delivery system that can deliver large drug doses, large molecular drugs, biologically or physicochemically labile therapeutics requires further scientific research [121]. In all efforts to perfect the pressure-sensitive adhesive technology, the modification must not compromise its adhesion and cohesion strengths, increase its toxicity, and reduce its flexibility to carry a wide range of drugs, permeation enhancers or other functional excipients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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