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TRANSDERMAL PATCHES: ADVANCES, FORMULATION AND FUTURE PERSPECTIVES

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ABSTRACT

TDDS (transdermal drug delivery systems) provide an effective method of delivering medication without requiring injections or pills. TDDS do this by delivering the active ingredients of medications directly through your skin into your bloodstream. Because TDDS bypass your gastrointestinal system and the first-pass effect (a metabolism step in the liver), they can improve the bioavailability of medications, they can provide a more consistent zero-order release of the medication, and they can help increase the patient's adherence to the medication regimen. A major physical barrier to delivering medications via TDDS is the stratum corneum (the outermost layer of your skin). The most common way of disabling the stratum corneum is by using specialized patch designs such as drug in adhesive, reservoirs, matrices, or microreservoirs. To help the medication move through the stratum corneum and into the bloodstream, permeation enhancers are often used in conjunction with specialized patch designs. Currently, commercially available TDDS are used for multiple indications—from pain relief to smoking cessation—with new uses emerging for herbal products such as using ginger patches to relieve nausea. When developing and standardizing TDDS; physicochemical, in vitro and in vivo studies should be performed to ensure that all TDDS demonstrate safety, stability and steady-state flux of drug delivery. Future efforts in TDDS will be focused on the development of smart responsive patches, the use of biodegradable materials, microneedle arrays and nanotechnology. Together, these advancements are expected to expand the types of therapeutics delivered via TDDS to include the delivery of macromolecules, biologics, and personalized medicines.

KEYWORDS: Transdermal drug delivery; stratum corneum; permeation enhancement; patch architecture; microneedles; controlled release; bioavailability

1. INTRODUCTION

Transdermal Drug Delivery Systems are medicinally based adhesive formulations designed to deliver active pharmaceutical ingredients (APIs) through the skin in a controlled manner and into the bloodstream.[1]. Unlike traditional oral or parenteral routes, TDDS rules out gastrointestinal degradation and first-pass hepatic metabolism thereby providing greater bioavailability than would be achieved via those methods. This principle of drug delivery occurs in accordance with Fick's first law of diffusion which can be mathematically expressed as; J = K x D x C / h. Where J = the steady state flux; K = the partition coefficient between patch and skin; D = the diffusion (or permeation) coefficient; C = drug concentration gradient; h = length of diffusive path (generally SC thickness of 10 – 20 microns).[2] The earliest example of a product that utilized the TDDS methodology is the scopolamine TDDS (Transderm-Scop), which received FDA approval in 1979 for the prevention of nausea and vomiting associated with motion sickness.[3] Since that time, TDDS products have grown exponentially in terms of usage, with products such as fentanyl matrix patches for chronic pain management introduced in 1990, nicotine reservoir patches for smoking cessation in 1991, and an expanding list of products having been approved with over 30 individual molecules approved by the end of 2026. As of 2020, the global TDDS industry was approximately $7 billion and is projected to expand by between 14% and 15% growth per year; primarily due to the development of combination formulations, integration of nano-delivery systems, and development of-herbal products.[3] The non-invasive, once-daily and multi-day dosing method of application as well as the reversible nature of the dosing (a major advantage of topical drug delivery systems) lead to significant increased patient adherence [1],[9]. To be considered ideal candidates for transdermal drug delivery systems (TDDS), drugs must have very low daily requirements (less than 20 mg), possess plasma half-lives between 10 to 100 hours, have skin-compatible pKa values in the range of 7 to 9, and a molecular weight of less than 500 Da [8]. Two possible permeation enhancers are dimethyl sulfoxide (DMSO) and mentha oil, both of which have been shown to reduce stratum corneum (SC) resistance by fluidising the intercellular lipid matrix, thus providing a two to five times increase in flux without producing clinically significant levels of irritation [3]. This review article is intended to consolidate the state-of-the-art knowledge on the skin anatomy and permeation mechanisms, classifications of patch designs, commercial product specifications, formulation and manufacturing technologies, regulatory evaluation frameworks, and future innovations with TDDS.

2. Skin Anatomy and Permeation Mechanisms

The area of skin that covers the human body is roughly equal to 1.5 to 2 square meters. Human skin has three main layers: the superficial layer, or epidermis (with a thickness of 50 to 150 micrometers (μm)), the middle layer dermis (with a thickness between 1-4 millimeters (mm)), and the innermost layer: hypodermis (with a thickness between 0.5-30 mm)). [11] The living portion of the epidermis is known as the Stratum Corneum (SC), and it is the thinnest and outermost portion of the epidermis. The SC is approximately 10 to 20 μm thick and consists of 15 to 20 layers of flattened, dead skin cells (i.e., corneocytes or "bricks") that are embedded within a continuous matrix of intercellular lipids (which act as "mortar" for the "bricks") containing ~40% ceramides, 25% cholesterol and 25% free fatty acids. [14] This structure makes the SC the major barrier for transdermal drug delivery, accounting for approximately 90% of the total transcutaneous (i.e., through the skin) diffusional resistance (i.e., via the intercellular lipid route).[3]

2.1 Epidermal Structure

The epidermis is formed by a keratinizing stratified squamous epithelium that rejuvenates approximately every 28-30 days, due to the multiplication of keratinocytes originating from the stratum basale. [4] The epidermis contains five layers (sub-layers) of epithelial cells, which are arranged in the following order from deep to superficial layers: (i) the stratum basale, which consists of melanocytes and Merkel cells attached to hemidesmosomes; (ii) the stratum spinosum (eight to ten layers thick), which contains Langerhans cells that are involved in providing immunity; [12] the stratum granulosum (three to five layers thick), and provides lamellar bodies that release ceramides, cholesterol, and free fatty acids that combine to provide the inter-cellular lipid barrier; [13] stratum lucidum, which is visible only in regionally thickened (palmar and plantar surface) areas of skin; and (v) the stratum corneum, which is maintained at a pH of 4.5-5.5 with approximately 15% water content [14] Skin appendages (i.e. hair follicles and sebaceous glands) function as shunt routes and comprise 5-10% of the overall permeation flux through the skin, and provide the major component of the early lag period before the achievement of steady-state diffusion [15]

2.2 Dermis and Factors Influencing Permeation

The dermis is a layer of connective tissue beneath the epidermis that is highly vascularized, ranging from 1 to 4 mm in thickness, and is made up of 70% Type I collagen, 2% elastin, and various glycosaminoglycans, including hyaluronic acid. [11] The dermal papillae (the part of the dermis that is adjacent to the epidermis) contains capillary loops that allow drugs that are absorbed through the skin (transdermal) to reach the bloodstream, and are also sites of

clearance of absorbed substances after they have crossed the stratum corneum (SC). There are many factors that affect the amount of drug that can be delivered through the skin (transdermal flux), including the following: (1) occlusive dressings will increase the hydration of the SC to above 25%, which causes intercellular lipids to swell and therefore increases the diffusion coefficients for many drugs; (2) an increase of 10°C in temperature approximately doubles transdermal flux, as determined by Arrhenius kinetics; [13] the site of application and the age of the patient have an impact on the permeability of the SC — the SC becomes thinner with age, and is therefore 20% more permeable than that of younger patients, and the abdomen and back are more permeable than the extremities; [16] and (4) chemical penetration enhancers, such as DMSO, oleic acid, and menthol, disrupt the packing of the lipids in the SC, leading to a two- to five-fold increase in drug flux. The inter-subject variability in transdermal flux ranges from 20% to 50%, indicating the need for ex vivo validation using human or animal skin in Franz diffusion cells prior to advancing to clinical use. [7]

3. Classification of Transdermal Patch Architectures

The four primary structural types of transdermal patches, which are classified based on how the drugs will be distributed and released, include: drug-in-adhesive (DIA), reservoir, matrix diffusion, and micro-reservoir systems. [48],[49],[50] Each of the different designs produces a unique pharmacokinetic profile, and to determine which type of patch to use, the drug's physicochemical properties, the desired duration of drug release, and the intended dose must be considered.

3.1 Drug-in-Adhesive Systems

The active ingredients of a transdermal delivery system (TDS) can be incorporated into a pressure-sensitive adhesive (PSA) matrix either by single-layer drug-in-adhesive (DIA) patches (i.e., in which the adhesive is the drug reservoir/skin-contact layer) or multilayer DIA patches (where the drug is placed between two or more PSAs) [54],[55] Single-layer DIA patches have first-order drug release kinetics as the concentration of active ingredient in the patch decreases, making them appropriate for uses with low doses of drug (0.5-1 g/patch), thin profiles (<200 μm), and improved patient confidentiality and compliance. Multilayer DIA patches additionally use a rate-controlling membrane to provide zero-order kinetics and reduce local skin irritation through pH compatibility (5.9-7.4). [56],[57] The production of DIA patches can be accomplished using high-speed, roll-to-roll solvent coatings (i.e., knife-over-roll, slot-die) at rates of up to 10 m/min. A key disadvantage of the DIA system is the

potential for drug recrystallization (at higher drug loads), potentially blocking the release channels. [60],[61] Examples of commercial products that utilize this technology are Nicoderm CQ® (nicotine patch) and Catapres-TTS® (clonidine patch).

3.2 Reservoir Systems

A reservoir patch has an enclosed compartment that can contain a liquid, gel or suspension of the drug and this compartment is seaLED between a backing of impermeable polyethylene/aluminium foil and a microporous ethylene-vinyl acetate (EVA - 10-50 µm pore diameter) rate-controlling membrane. [65],[66] Drug release occurs at a zero-order rate, with steady state flux ($J = P \times \Delta C$), which is constant with respect to the amount of drug remaining, because the rate of delivery is controlled by the membrane rather than the concentration of drug. [67] A reservoir patch can accommodate large amounts of drug (up to 1.5 g) and is exemplified by the fentanyl reservoir patch (Duragesic®), which can maintain plasma concentrations of fentanyl that are maintained at 0.3-1.5 ng/mL for 72 hours [74] The major risk of a reservoir patch is dose-dumping due to rupture of the rate-controlling membrane; however, this risk can be minimized by the use of multiple laminate protective layers. Reservoir patch designs are rarely used for compounds that are volatile or poorly stable. [17]

3.3 Matrix Diffusion Systems

The active pharmaceutical ingredient (API) is uniformly distributed within a hydrophilic or hydrophobic polymer matrix using a matrix system. The most common examples would be through using either 5% w/v hydroxypropyl methylcellulose (HPMC K4M) or polyvinyl alcohol (PVA), and as it hydrates and erodes that will allow for drug release in accordance with the Higuchi model as given in the following formula: $Q = \sqrt{(D(2C_0 - C_s)C_s t)}$.[18] These matrix systems are made by solvent casting polymers (ethanol–water systems) at 45–60°C, which has produced flexible films with folding endurance greater than 200 folding cycles, tensile strength (approximately 1.32 N/mm²), moisture content of 1.32–3.96%, and elongation at break (approximately 129%).[5],[7] The three-layer design of the backing, medicated matrix, and adhesive has helped support more simplistic methods of manufacture, which reduces overall costs when compared to reservoir systems. Medium duration wear (24–48 h) is preferred for matrix systems that are typically used in herbal formulations. Examples of this system currently on the market would be Lidoderm® (5% lidocaine matrix) and rivastigmine (Exelon Patch®).[10],[19]

3.4 Micro-Reservoir Systems

Hybridization of reservoir systems and matrix design was achieved through the use of solid polymer matrices containing suspended delivery microspheres, liposomes, or nano-vessicles that had been loaded with drugs, thus allowing drug to be delivered from micro reservoirs. [3],[20] Deformable transethosomes, having a phospholipid to edge activator ratio of 90:10, provide predictably controlled erosion-driven pseudo zero-order release with greater than three times the transdermal flux of traditional matrix systems (12.61 µg/cm²/h); [3] these transethosomes can be manufactured using the emulsion-solvent evaporation process and are favourable for use in developing polyherbal synergistic systems. Micro-reservoirs continue to grow in use for developing oncology product pipelines, vaccine development pipelines, and acne treatment pipelines (Clinical Trial V.) [3],[17]

Table 1. Comparative summary of transdermal patch architectures.

Type	Kinetics	Drug Load	Key Polymers	Wear Time	Commercial Example
Drug-in-Adhesive	First-order	Low (0.5 g)	Acrylate/Silicone PSA	24 h	Nicoderm CQ®
Reservoir	Zero-order	High (1.5 g)	EVA membrane + gel	72 h	Duragesic®
Matrix	Higuchi	Medium	HPMC K4M / PVA	24–48 h	Lidoderm®
Micro-reservoir	Pseudo zero	Nano-enhanced	Liposomes in matrix	24–72 h	Investigational

4. Advantages and Limitations of TDDS

4.1 Therapeutic Advantages

Transdermal drug delivery systems (TDDS) provide numerous pharmacokinetic and pharmacodynamic benefits compared with either oral or parenteral routes of administration. For instance, the transdermal delivery of lipophilic drugs increases their bioavailability by 2-5 times compared to when given via the oral route due to bypassing hepatic first-pass metabolism; estradiol's bioavailability increases by approximately five times when delivered transdermally. [30] Additionally, TDDS provide zero-order kinetics within a 24–72-hour time frame, which helps eliminate the peaks and troughs that occur with oral dosing and maintains plasma levels within the therapeutic window, thus decreasing the risk for toxicity. [27],[29] Elderly patients report an approximately 90% compliance rate with transdermal delivery compared to 50% for oral regimens; this is attributed to the ease of use (painless and needle-

free) and the fact that TDDS can be removed at any time to stop drug delivery (whereas implants must be surgically removed). [1],[30] Finally, the elimination of first-pass hepatic degradation from the gastrointestinal system is extremely beneficial for drugs prone to degradation by acid-catalysed hydrolysis and/or significant metabolism in the intestines. [9]

4.2 Limitations and Challenges

The TDDS's biggest obstacle is the SC's permeability limit, which means that the SC can only transfer about 10% of all pharmaceutical compounds through passive transdermal delivery. The TDDS can only deliver pharmaceutical compounds with an MW < 500 Da, log P 1 -3 and a daily dose < 20 mg [33],[34] Approximately 20% of available pharmaceuticals have an MW > 500 Da; therefore, hydrophilic (water-soluble), high-molecular-weight, and ionised compounds are mostly excluded. Therefore, without active enhancement technologies, the TDDS are significantly restricted to fewer drugs. Fell pressure time to reach steady-state plasma concentrations after 2 - 12 hr makes it impossible to use TDDS for acute therapeutic indications requiring rapid onset of action.[33] Approximately 20 - 50% of users have local adverse effects (contact dermatitis, erythema, and/or oedema), due to peel/adhesive materials or chemical enhancers, which contribute to a 5 - 10% dropout rate in clinical studies. [35],[36],[41] In humid and/or tropical climates, adhesion failure occurs in approximately 10 - 30% of the applications, requiring additional dressings. [42],[43] There are wide ranges (20 - 100%) in flux between individuals (due to differences in skin age, hydration, and application site), which also makes dose standardisation difficult. [35] The high cost of research and development (USD $50 - $200 million) per approved patch, and the amount of drug remaining in discarded patches (~20% of total load) that presents an environmental hazard and provides the opportunity for diversion of controlled substances, such as fentanyl, create concerns from regulatory and societal perspectives. [37],[38]

5. Marketed Transdermal Products

By 2026, over thirty FDA transdermal patch approved molecules exist across a broad range of treatment regimens available for use in the market today. [71],[72],[73] The existing products that are available in the market offer a very large clinical utility for TDDS products, and represent the existing gold standard against which new formulations will be judged.

5.1 Pain Management

The fentanyl transdermal delivery system (Duragesic®; Janssen), releases 12–100 µg/h of fentanyl over 72 h through a polyethylene terephthalate/EVA rate controlling membrane, with steady state plasma concentration of 0.3–1.5 ng/mL reached after 12–24 h, with significantly

less fluctuation between peak and trough than oral opioid regimens. [74],[75] The buprenorphine transdermal delivery device (Butrans®; Transtec®), releases 5–20 µg/h through an acrylic-adhesive matrix over 7 days, with approximately 15% bioavailability and peak concentration at 48–72 hours: a pivotal phase III trial of 1,024 subjects, showed that 48% of patients receiving buprenorphine demonstrated at least a 30% reduction in their pain compared to 36% in patients receiving placebo. [72] The lidocaine 5% patch (Lidoderm®) delivers 700 mg of lidocaine over 140 cm^2 of skin for 12 h/day for use in post-herpetic neuralgia, with plasma levels of lidocaine reaching <200 ng/mL and reports of >30% decrease in pain compared to control. [76] The capsaicin patch 8% (Qutenza®) is used to relieve of neuropathic pain up to 12 weeks after a single 30–60-minute application due to TRPV1 receptor desensitization and requires pre-application with topical anesthetic. [79]

5.2 Nicotine Replacement, Hormones, and Cardiovascular Patches

Nicotine replacement crutches (NicoDerm CQ®; Nicorette® InvisiPatch®) make use of ethylene-vinyl acetate copolymer matrix technology in a step-down regimen (21 to 14 to 7 mg/24 h) to achieve bioavailability of 70% to 90%. Quit rates for these crutches are double compared with the placebo (20% to 25% vs. about 10%) when used for an 8- to 12-week program. [80],[81],[82] Estradiol transdermal delivery systems (Climara®, Vivelle-Dot®) deliver estradiol in the form of a matrix patch containing 0.025 to 0.1 mg of estradiol with an application period of 7 days resulting in pharmacokinetically similar serum concentrations of estradiol compared with those achieved by administering fluids at the physiological range and result in a reduction of vasomotor symptoms in clinical trials by approximately 75%. Climara Pro® contains levonorgestrel in addition to estradiol to achieve endometrial protection. .[71] The contraceptive patch (Ortho Evra®) releases ethinyl estradiol (0.75 mg) and norelgestromin (6 mg) from a 20 cm2 patch applied weekly, with a Pearl Index of 1.2%. Nitroglycerin patches (Nitro-Dur®) are used for prophylaxis to prevent angina during exercise by delivering 0.1 to 0.8 mg per hour for 12 to 14 hours. A patch-free interval is required to avoid the development of tolerance to nitrates. Clonidine transdermal delivery (Catapres-TTS®) is utilized for the weekly treatment of hypertension with a dosage of 0.1 to 0.3 mg/day via a matrix patch system.[75]

Table 2. Selected FDA-approved transdermal drug delivery products.

Product	Active Ingredient	Dose Range	Wear Time	Area (cm^2)	Indication
Duragesic®	Fentanyl	12–100 µg/h	72 h	10–42	Chronic pain [74]
Butrans®	Buprenorphine	5–20 µg/h	7 days	5–15	Moderate pain [72]
Lidoderm®	Lidocaine 5%	700 mg/patch	12 h	140	Neuralgia [76]
Qutenza®	Capsaicin 8%	972 mg	60 min	280	Neuropathic pain [79]
NicoDerm CQ®	Nicotine	7–21 mg	24 h	22	Smoking cessation [80]
Climara®	Estradiol	0.025–0.1 mg/d	7 days	6.5–25	Menopause [71]
Nitro-Dur®	Nitroglycerin	0.1–0.8 mg/h	12–14 h	10–40	Angina [75]
Exelon Patch®	Rivastigmine	4.6–13.3 mg/24h	24 h	5–10	Dementia [71]
Neupro®	Rotigotine	2–8 mg/24h	24 h	5–20	Parkinson's [71]
Transderm-Scop®	Scopolamine	1.5 mg	72 h	2.5	Motion sickness [71]

6. Formulation and Manufacturing Technologies

In order to meet their intended profile for flux, adhesion and stability, TDDS formulations depend on the careful choice of all components, including the backing, matrix, rate-controlling membrane (often), PSA and release liner. The ideally suited drug candidate for a TDDS formulation will have a log P in the range of 1 – 4, a molecular weight of < 500 Da and a daily dosing requirement of 10 - 40 mg. The research shows that permeation follows the equation J = KDC/h, where K = partition coefficient, D = diffusion coefficient and C = concentration gradient.[84]

6.1 Solvent Casting (Laboratory and Pilot Scale)

Currently, solvent casting (which is the most common laboratory scale method) is used to fabricate patch matrices. In laboratory-scale patch fabrication, hydrophilic polymers (e.g., PVA (Mw 89 - 98 kDa), HPMC K4M (4,000 cP)), are swollen in aqueous media at 80°C, and then mixed with PVP K30, plasticisers (glycerol, PEG 400 (15% - 25% w/w), and drug dissolved in ethanol. Once mixed, the viscous mixture is cast onto tiles of polyester liner (wet thickness of ~ 0.5 mm), then dried at 45 °C - 60 °C for 24 - 48 hours resulting in flexible

smooth films. Channels for QC testing are typically within ±5% of the average weight, a flux of 15 - 60 µg/cm²/h, moisture content of 2 - 8%, and a folding endurance > 300 cycles.[84],[85] In general, Box-Behnken experimental design is used extensively for optimising both polymer ratios and drying conditions simultaneously.

6.2 Hot-Melt Extrusion (Industrial Scale)

The most common method for creating TranSDDS (solvent free) is hot-melt extrusion (HME). The typical throughput of this process is 50 to 200 kg/hour. [86],[87],[88] The process consists of co-extruding drug and polymer (Eudragit RS PO, EVA 28% VA) mixtures using a twin screw extruder (L/D 40:1; Temp range: 120°C - 160°C; speed of 100 RPM) through a die gap of 0.2 mm, which is then calendered onto an appropriate release liner (i.e. parchment paper). Residual solvent content is less than 50 ppm and the amorphous dispersion resulted from HME increases the apparent solubility of an amorphous drug in a polymer matrix by up to 100 times. At no time during the HME process was the torque ever greater than 10 Nm, to avoid overheating and destroying the active ingredient. For reservoir-type patches, gel reservoirs (0.5 to 2 ml/pouch) are introduced using a continuous rotary fill-seal operation and then placed between the membrane and the backing strip via longitudinal ultrasonic welding and transverse thermal sealing.

6.3 Microneedle Fabrication

Microneedle arrays with 100 - 500 needles per cm2 and heights ranging from 250 - 1000 µm have the ability to bypass the stratum corneum (SC) of the skin and allow for transdermal delivery of macromolecule/molecule substrates.[92] Solid microneedles are manufactured through a process called deep reactive ion etching (DRIE Bosch Process) on a silicon substrate and then by polydimethylsiloxane (PDMS) replica moulding. Dissolvable microneedle patches are made with PVA/Sucrose (30% w/v) solutions with drug loaded nanoparticles that have been centrifuged at 5000g for 30 minutes and dried at a controlled low humidity at 25 degrees Celsius for 48 hours. Several high-resolution additive manufacturing platforms including digital light processing (DLP/SLA at 25 µm resolution), fused deposition modelling (FDM with 0.2 mm nozzle), and two-photon polymerisation (TPP, sub µm resolution) are enabling the creation of customisable microneedle geometries in order to provide personalised dosing. [86],[88]

6.4 Permeation Enhancers and Polymer Selection

Chemical permeation enhancers have an effect of reducing SC resistance by disrupting lipid packing, increasing intercellular fluidity, and/or altering drug partitioning. Terpenes such as menthol (5%) have an enhancement ratio (ER = 4), and fatty acids such as oleic acid (10%),

pyrrolidones (e.g., N-methyl-2-pyrrolidone, NMP,5%). There are also co-solvents such as Transcutol + Labrasol (0.1% ER = 10).[92],[93] Matrix polymers are selected according to their desired hydrophilicity for example HPMC, sodium alginate, pectin for hydrophilic swelling matrices or ethylcellulose (EC, 5–50 cP) and Eudragit NE30D for hydrophobic sustained release matrices and EVA (18–40 VA) with Saranex® as rate controlling membranes. Quality by design (QbD) frameworks along with Process Analytical Technology (PAT) tools such as Near Infrared (NIR) Spectroscopy for content uniformity and Raman Spectroscopy for polymorphic monitoring are used at the commercial level to ensure uniformity from batch to batch in terms of material quality.[95]

7. Evaluation and Testing of Transdermal Drug Delivery Systems

The FDA, EMA, and USP are requesting a complete evaluation of a TDDS prior market approval to verify the physicochemical characteristics for in vitro performance and in vivo bioequivalence. [100-101] The evaluation process includes 3 steps: physicochemical characterisation, in vitro performance/testing and in vivo/clinical pharmacokinetics evaluation. [98-103]

7.1 Physicochemical characterisation

Physically assessing TDDS will include a visual examination (looking at colour, clarity, bubbles, and delamination), measuring the dimensions or thickness (±5 µm of thickness and surface area), and weight checking (n=10 with an acceptable standard deviation of less than 5%).[104-106] To assess drug content uniformity, HPLC or UV-spectrophotometry are used to measure the amount found in each of the pooled patches that were dissolved separately and re-measured in an appropriate solvent. The amount accepted will be between 90% to 110% to of the labelled amount.[110] Any residual solvent from the casting process will be evaluated by a headspace gas chromatograph, and moisture content will be determined using a Karl Fisher titration (with the targeted level being between 2%-8% of the TDDS, as excess moisture will affect both the adhesion of the TDDS and the stability of the drug).[111-115] Mechanical and adhesive properties (i.e. 180° peel strength of greater than 1 N/cm, loop tack number, probe tack number, shear holding power and elasticity) will be important to ensure that patients can wear the TDDS across flexible parts of their body without delaminating.[115-116]

7.2 In Vitro Drug Release and Ex Vivo Permeation

The testing of drug release in the laboratory uses modified Franz-type diffusion cells and standard paddle-over-disk dissolution testing equipment. The diffusion cells are used at a

constant skin temperature (32°C) with phosphate buffer solution at pH 7.4 as the receptor fluid for 24-48 hours, with sampling done at set time intervals over this period. [104],[108] Cumulative drug release is then plotted versus time and fitted to the zero-order, first-order or Higuchi kinetic models in order to describe drug release mechanisms. [97],[108] All regulatory agencies require that drug release methods should be able to discriminate between formulations and predict their in vivo performance. .[113], [112] Ex vivo diffusion studies are performed using either excised human cadaver skin or full thickness animal skin mounted vertically in Franz-type diffusion cells at a constant skin temperature (32°C) and using cumulative diffusion versus time linear regression analysis to determine steady-state diffusion, diffusion coefficient and lag time. [97],[108] Alternatively, Synthetic membranes (e.g StratM™) can be used for screening and QC. Finally, the reproducibility of drug release will depend on the correct validation and adjustment of the Franz testing system (membrane surface area, stirring speed, and temperature). [103]

7.3 In Vivo Pharmacokinetics and Bioequivalence

Pharmacokinetics of Drug in the Body and Comparisons Between Developed and Generic Drugs For example, the pharmacokinetics of a drug after application (Cmax, Tmax, AUC, and ss concentration) are determined in either healthy volunteers or patients with in vitro–in vivo correlations (IVIVC) resulting from in vitro release/permeation studies performed on the transdermal drug delivery system (TDDS). Development of IVIVC's (especially Level A) allow for mathematical linking between release/permeation profiles from the in vitro testing to those obtained postvehicle administration to assess bioequivalence before commercialisation and post approval changes. IVPT is also used as an indicator for bioequivalence of generic TDDS by both FDA and EMA as long as sufficient IVIVC has been developed. When there is not sufficient IVPT for assessment of bioequivalence, then bioequivalence is established by performing crossover pharmacokinetic studies with Cmax and AUC results required to be within 90% confidence of the 80% to 125% limits. Tolerability of the TDDS is assessed by scoring local skin irritations (erythema, oedema, or itching) as well as monitoring for any systemic adverse effects while the TDDS is being worn. Stability studies conducted under ICH conditions (25°C/60% RH for long-term; 40°C/75% RH for accelerated; for a minimum of 6 months) should demonstrate that the content of drug, rate of release, adhesion, and permeation profiles of drug will remain within defined limits throughout the labelled shelf life.[105],[113]

8. Future Perspectives

The Transition of TDDS from Passive to Smart, Personalized, and Patient-Centred TDDS: This transition is a result of the convergence of several technological pathways, which are defining future TDDS. [86],[116],[117],[118]

8.1 Smart and Stimuli-Responsive Systems

Closed-loop feedback TDDS are created through the integration of a biosensor and a drug releasing matrix, to adjust drug delivery based upon a physiological response or signal [119],[120] An example of this is a glucose-responsive insulin patch that releases additional insulin when blood glucose levels rise, but automatically reduces the release of insulin as blood glucose levels return to the normal range, thereby mimicking the normal function of the pancreas. [121] Similar designs are being studied for use in developing analgesic, pain-responsive TDDS, where drug release would be controlled based upon cytokines or temperature, and for developing antimicrobial patches to treat chronic wounds by determining the release of the drugs based upon changes in pH or enzyme activity. Most of these TDDS use electrochemical or optical biosensors).[117],[120] Most of these TDDS use electrochemical or optical biosensors). In addition, these TDDS incorporate stimulus-responsive hydrogels that can be worn in a home-use format, making them appealing for chronic disease management. [116],[118]

8.2 Microneedle-Based and Physical Enhancement Approaches

Microneedle patches continue providing innovative new ways of delivering medications and remain among the most advanced technologies in clinical use today. These devices are able to mechanically penetrate the stratum corneum with minimal trauma and without pain to the patient using the microneedle array design. [117],[119] Dissolving microneedle (MN) arrays made from biodegradable polymer materials are able to deliver medications slowly to the patient over hours or days as they dissolve within the interstitial fluid; various MN designs (hollow type or those that form hydrogels) will allow for the programmable and long-acting delivery of medications using a reservoir. [122],[66] MN patches are currently being developed for the delivery of vaccines and hormones or peptides, management of chronic diseases, and targeted oncological therapies. The complementary role of physically enhancing drug delivery (using techniques such as iontophoresis, sonophoresis, and laser/electroporation) for poorly permeable or large macromolecular active pharmaceutical ingredients (APIs) will continue to increase due to the combination of methods providing a greater amplification of flux (typically 5-10 times greater) than using only the passive delivery method. [91],[117]

9. CONCLUSION

Over the last 40 years, transdermal drug delivery systems have changed from basic reservoir-type patches to more modern and complex multi-functional platforms. The stratum corneum (SC) still remains the primary physiological barrier that limits the passive transdermal delivery of most drugs. However, advances in chemical enhancement techniques, nanotechnology, and physical perturbation techniques (particularly with the use of dissolving and hollow microneedles) are steadily opening the possibilities for drug delivery via TDDS beyond small molecules but also biologics and macromolecules.[117],[119]. The four main types of currently approved patch types (DIA, reservoir, matrix, and micro-reservoir) can be used to meet the many dosages needed for drug delivery. Currently, the matrix system is the preferred system for most types of herbal formulations that are being developed in both clinical and non-clinical trials due to their stability, cost and mechanical properties.[5],[7],[18] There are currently a considerable variety of products approved by both the FDA and the EMA for the treatment of pain, addiction to nicotine, hormonal replacements, and cardiovascular diseases using transdermal delivery systems establishing large capacity for drug delivery using TDDS. However, all of these products have been evaluated with specific testing prescribed by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), as well as the United States Pharmacopeia (USP) in regards to physicochemical characteristics (characterising), release rate studies with the use of Franz cells (in vitro), permeation studies (in vitro) and in vivo pharmacokinetic studies to ensure a uniform quality, safety and bioequivalence for all of these products.[71],[100],[101] The combination of smart responsive systems, biodegradable scaffolds, nanotechnology-enabled systems and wearable closed-loop systems will serve as a foundation of next generation phase II TDDS; thus, helping to form the foundation of future patient-centric and personalised pharmacotherapy with a projected global market of $30 billion by 2030.[3],[116],[118]

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