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REVIEW

Transdermal patches: history, development and pharmacology

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Transdermal patches are now widely used as cosmetic, topical and transdermal delivery systems. These patches represent a key outcome from the growth in skin science, technology and expertise developed through trial and error, clinical observation and evidence-based studies that date back to the first existing human records. This review begins with the earliest topical therapies and traces topical delivery to the present-day transdermal patches, describing along the way the initial trials, devices and drug delivery systems that underpin current transdermal patches and their actives. This is followed by consideration of the evolution in the various patch designs and their limitations as well as requirements for actives to be used for transdermal delivery. The properties of and issues associated with the use of currently marketed products, such as variability, safety and regulatory aspects, are then described. The review concludes by examining future prospects for transdermal patches and drug delivery systems, such as the combination of active delivery systems with patches, minimally invasive microneedle patches and cutaneous solutions, including metered-dose systems.

Abbreviations

DIA, drug-in-adhesive; EMEA, European Medicine Agency; FDA, Food and Drug Administration; J&J, Johnson & Johnson; LTS, Lohmann Therapie-Systeme; OTC, over-the-counter; Ph Eur, European Pharmacopoeia; PI, prescribing information; PIB, polyisobutylene; PSA, pressure-sensitive adhesive; TTS, transdermal therapeutic system; USP, United States Pharmacopoeia

Tables of Links

LIGANDS		
Clonidine	Methylphenidate	Oxybutynin
Dihydroergotamine	Methyl salicylate	Rivastigmine
Dimenhydrinate (diphenhydramine)	Naltrexone	Rotigotine
Ephedrine	Nicotine	Scopolamine
Fentanyl	Nitroglycerin	Selegiline
Haloperidol	Sumatriptan	Stilboestrol
Lidocaine	Oestradiol	Sufentanil
		Testosterone

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 (Alexander *et al.*, 2013).

Introduction

The skin is the largest organ in the human body by mass, with an area of between 1.5 and 2.0 m^2 in adults. Drugs have been applied to the skin to treat superficial disorders, for the transdermal administration of therapeutics to manage systemic ailments and as cosmetics, dating back to the oldest existing medical records of man. For instance, the use of salves, ointments, potions and even patches, consisting of plant, animal or mineral extracts, was already popular in ancient Egypt and in Babylonian medicine (around 3000 BC) (Magner, 2005; Geller, 2010). However, the routine use of transdermal delivery systems only became a common practice in the latter third of the 20th century when delivery technology was developed to enable precise and reproducible administration through the skin for systemic effects.

The goal of this review is to detail the rich history of topical and transdermal delivery that has evolved over thousands of years, focusing particularly on the evolution and current use of transdermal patches. The potential efficacy and suitability of this technology for systemic therapy is normally determined by drug blood level–time profiles, which can be compared to or predicted from p.o. or parenteral administration. These drug concentrations in the blood are, in turn, defined by the amount of drug released into the body from the delivery system and the application area. Transdermal delivery is also used to produce clinical effects, such as local anaesthesia and anti-inflammatory activity, deep within or beneath the skin. In contrast, topical delivery seeks to treat superficial, although at times very serious, skin problems through a relatively local action.

History

Early use of topical therapy (pre-20th century)

Topical remedies anointed, bandaged, rubbed or applied to the skin (Figure 1A) are likely to have been used since the origin of man, with the practices becoming evident with the appearance of written records, such as on the clay tablets used by the Sumerians (Kramer, 1963). Indeed, it has been suggested that a liquefied ochre-rich mixture, made some 100 000 years ago and found at the Blombos Cave in South Africa, may have been used for decoration and skin protection (Henshilwood *et al*., 2011). Ancient Egyptians used oil (e.g. castor, olive and sesame), fats (mainly animals), perfumes (e.g. bitter almond, peppermint and rosemary) and other ingredients to make their cosmetic and dermatological products (unguents, creams, pomades, rouges, powders, and eye and nail paints) (Forbes, 1955). The mineral ores of copper (malachite: green) and lead (galena: dark grey) were used to prepare kohl, a paste used to paint the eyes. Red ochre was used as a lip or face paint, and a mixture of powdered lime and oil was used as a cleansing cream (Lucas and Harris, 1962). The ancient lead-based products were applied for both appearance and, based upon religious beliefs, for protection against eye diseases (Tapsoba *et al*., 2010). However, these effects may have been real as recent studies involving incubation of low lead ion concentrations with skin cells produced NO (Tapsoba *et al*., 2010), which is known to provide defence against infection (Coleman, 2001). On the negative side, it could be asked if these lead products also caused toxicity, noting that high blood levels of lead have been reported in modern kohl users (Hallmann, 2009).

The well-known *Papyrus Ebers* (1550 BC), describing more than 800 prescriptions and about 700 drugs, appears to be the best pharmaceutical record from ancient times (LaWall, 1927). It contains many recipes for treating skin conditions, including burns, wounds, blisters and exudation. Other remedies are *to preserve the hair*, *to make the hair grow*, *to improve the skin* and *to beautify the body*. A poultice (with 35 ingredients) is reported for *the weakness of the male member*. Other remedies are the first transdermal delivery of drugs for systemic effects, such as the topical application of frankincense *to expel pain in the head* and a product applied to the belly of a woman or a man *to expel pains caused by tapeworm* (Bryan, 1930; Ebbell, 1937). The emphasis on topical treatments at that time is evident by the portrayal of an ointment workroom in an Egyptian tomb painting from 1400 BC (Kremers, 1976).

A millennium and a half later, Galen (AD 129–199), a Greek physician, introduced the compounding of herbal drugs and other excipients into dosage forms. He is widely considered to be the 'Father of Pharmacy' and his practices are known as 'Galenic pharmacy'. Galen's Cerate (*Cérat de Galien*), a cold cream (Figure 1B), is certainly his most renowned formula with a composition relatively similar to the one used today (Bender and Thom, 1966). Medicated plasters (*emplastra*), which were generally applied to the skin for local conditions, can be traced back to Ancient China (around 2000 BC) and are the early predecessors of today's transdermal patches (*emplastra transcutanea*). These early plasters generally contained multiple ingredients of herbal drugs dispersed into an adhesive natural gum rubber base applied to a backing support made of fabric or paper (Chien, 1987). Nicotine, a new-world transdermal agent, was already being used in a plaster (*Emplastrum opodeldoch*) during the time of Paracelsus (1493–1541) (Aiache, 1984). Unlike the medicated plasters that originated in China, Western-type medicated plasters were much simpler formulations in that they contained only a single active ingredient. Examples of plasters that were listed in the United States Pharmacopoeia (USP) almost 70 years ago included belladonna (used as a local analgesic), mustard (as an effective local irritant) and salicylic acid (as a keratolytic agent) (Pfister, 1997). The concept that certain drugs cross the skin appears to have been applied by Ibn Sina (AD 980–1037), a Persian physician best known as Avicenna within the Western World. In *The Canon of Medicine*, he proposed that topical drugs have two spirits or states: soft and hard. He suggested that when topical products are applied to the skin, the soft part penetrates the skin whereas the hard part does not. He further proposed that dermally applied drugs not only have local effects but also affect tissues immediately beneath the skin including joints (regional effects) as well as effects in remote areas (systemic effects). One of his topical formulations acting systematically was for conditions where drugs could not be taken orally. One of Avicenna's regional therapies was the use of a plaster-like formulation in which sulphur was mixed with tar and applied to the skin with a piece of paper applied as backing to keep

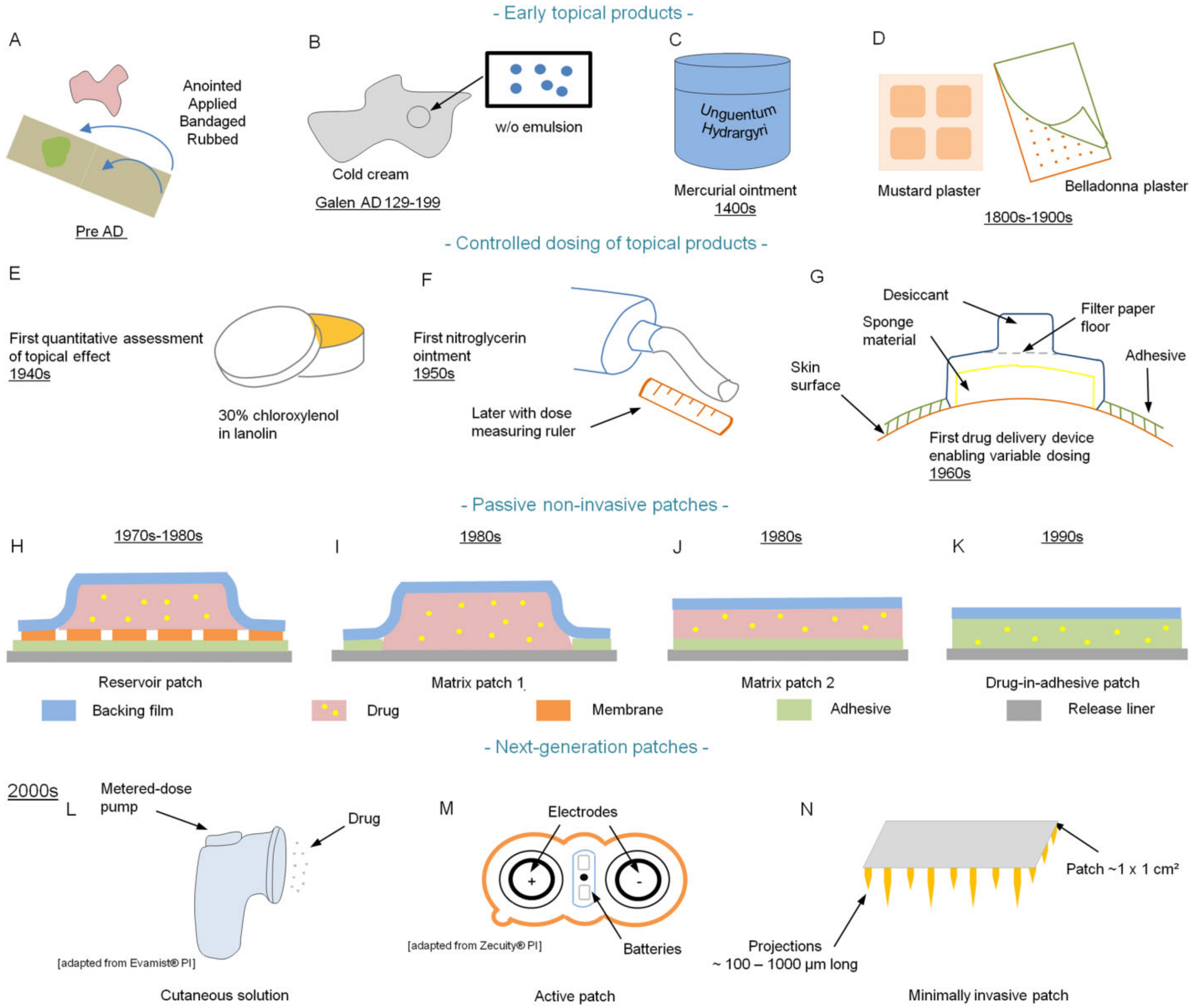

Figure 1

Historical development of patches. Early topical products: (A) products from ancient times; (B) Galen's cold cream; (C) mercurial ointment; (D) mustard and belladonna plasters; controlled dosing of topical products. (E) First quantitative systemic delivery (Zondek's system). (F) Individualized delivery system: nitroglycerin ointment. (G) Topical delivery device (Wurster & Kramer's system). Passive non-invasive patches. (H) First patch system – the reservoir – introduced for scopolamine, nitroglycerin, clonidine and oestradiol. (I, J, K) Other types of patches – matrix and drug-in-adhesive (e.g. fentanyl and nicotine patches). Next-generation patches. (L) Cutaneous solutions (e.g. Patchless Patch®, Evamist®). (M) Active patches (e.g. iontophoresis, Zecuity®). (N) Minimally invasive patches (e.g. microneedles, Nanopatch®).

the formulation in place. This product was used to treat sciatica, that is, pain arising from the compression of the sciatic nerve felt in the back, hip and outer side of the leg (Moghimi *et al.*, 2011). Other forerunners of modern transdermal medications include mercurial ointments (*Unguentum Hydrargyri*) that were used for the treatment of syphilis in the late 15th century (Figure 1C) (Cole *et al.*, 1930). *Unguentum Hydrargyri Fortius L.* (stronger mercurial ointment), made of purified mercury, lard and suet (Castle, 1828; Coxe, 1830; Pereira, 1839), is one example of these preparations.

The late 19th century as a phase of 'non-belief' in transdermal products

The German Pharmacopoeia 1872, a compilation produced in Latin, listed 28 *Emplastra* formulae. These included adhesive products (e.g. *Emplastrum adhaesivum*, which contained oleic acid, lead oxide and colophony, and *Emplastrum adhaesivum anglicum*, a hydrophilic formula); products meant to produce systemic effects [e.g. *Emplastrum aromaticum*, which contained peppermint and other aromatic oils targeted for the treatment of the stomach; *Emplastrum belladonnae*

(Figure 1D), from *Atropa belladonna* leaves, which was meant for the treatment of tuberculosis and tumours; *Emplastrum opiatum*, which was used to reduce stomach movement and associated pain; *Emplastrum conii* containing *Conium maculatum* (poison hemlock, as used by Socrates), which was thought useful for treating tuberculosis and tumours]; and products for topical use (e.g. *Emplastrum hydrargyri* with pure quicksilver for treating topical swellings and infections, *Emplastrum cantharidum ordinarium*, a vesicant, *Emplastrum picis irritans* and *Emplastrum fuscum* for dealing with topical infections). However, many of these disappeared in later formulations so that the German Pharmacopoeia 2 of 1883 had reduced the number of patch monographs to 11 – Leukoplast® [BSN Medical (formely Beiersdorf) Hamburg, Germany], which is still used was invented in 1882. Nevertheless, in 1877, one review still suggested that intact human skin was totally impermeable to all substances (Fleischer, 1877) – even though several cases of systemic poisoning after external application of belladonna (e.g. plaster, liniment and lotion) were reported in the *British Medical Journal* in the 1860–1870s (Morgan, 1866; Harrison, 1872).

Development of topical products in the 20th century

In 1904, Schwenkenbecker generalized that the skin was relatively permeable to lipid-soluble substances but not to water and electrolytes (Schwenkenbecker, 1904). Various cases of poisoning, mostly in children, were reported in the early 1900s in France after topical application of nitrobenzene or aniline dyes in dyed clothing or shoes (The Lancet annotations, 1902; White, 1909; Muehlberger, 1925), and further supported the notion of the potential systemic absorption of topical products. The death arising from the systemic absorption of phenol from a large body surface in a young man after the accidental spillage of a bottle of phenol over himself (Johnstone, 1948) emphasized the potential lethal consequences associated with accidental 'overexposure' to drugs applied to the skin. However, lethality was promoted by the corrosive nature of phenol at higher concentrations, causing a substantial enhancement of human skin penetration (Roberts *et al*., 1977) and the saturation of the sulphate and glucuronidation pathways present in the body for its detoxification (Mellick and Roberts, 1999). A more recent series of reports described the potential lethal toxicity arising from exposure to hexachlorophene after topical application to babies (Martin-Bouyer *et al*., 1982).

In the beginning of the 20th century, various *in vivo* studies demonstrated systemic absorption after topical application by estimating drug levels in blood, urine and faeces (Malkinson and Rothman, 1963). Initial analytical methods were strictly qualitative and substances were detected in the blood or urine by looking at the change in a measured sample with regard to its colour, acidity or density relative to that of a standard sample (Scheuplein and Blank, 1971). Mercury, one of the first therapeutic compounds to be detected and then quantified in human excreta, was initially detected in urine following inunction treatment of syphilis using amalgamation methods (i.e. Reinsch test) (Wile and Elliott, 1917). Later more accurate analytical methods (e.g. using a calibrated capillary tube) enabled the quantitative determination of 5 mg of mercury in 1 L of solution (Cole *et al*., 1926). Colorimetric methods were commonly used. The concentration of *p*-chloro-m-xylenol (a halogenated phenol) in biological materials (i.e. urine, blood and minced tissues) was determined using Millon's reagent (an aqueous solution of mercury and nitric acid). The dirty red compound that was formed was then extracted by ether to give a clear yellow solution suitable for photometric measurements (Zondek *et al*., 1943). The absorption of methyl salicylate from various vehicles in 10 male subjects was studied via excretion in the urine of its salicylate metabolite using a colorimetric titration with ferric alum (Brown and Scott, 1934). The absorption of free iodine, through unbroken dog skin, was investigated by redox titration of the iodine eliminated in the urine with sodium thiosulphate (Nyiri and Jannitti, 1932). The penetration-promoting effect of a polyethylene glycol ointment was investigated *in vivo* in humans by determining the excreted concentration of phenolsulfonphthalein that was used as a tracer dye using a photoelectric colorimeter (Nadkarni *et al*., 1951).

In other early studies, characteristic pharmacological or physiological end points were used as proof of absorption of compounds into the systemic circulation (Gemmell and Morrison, 1957). For instance, sex hormones were widely investigated using experimental animals as subjects. Testosterone or testosterone propionate applied as an ointment to the skin of castrated male guinea pigs was shown to be readily absorbed as the accessory reproductive organs remained functional (Moore *et al*., 1938). Similarly, the application of oestrogen to the shaven back skin of ovariectomized female mice, using vehicles containing ethanol and/or benzol, led to oestrus (Zondek, 1938). The occurrence of convulsions in mice, rats and guinea pigs was observed following external application of the highly toxic strychnine alkaloids (Macht, 1938). The percutaneous absorption of another alkaloid, eserine, was studied using the amount and colour of secretion of tears in rats in response to ACh potentiated by the topically applied eserine. This method was used as a physiological end point for different ointment bases (Hadgraft and Somers, 1954). One questionable method used to determine the amount of mercury absorbed following application of mercurial ointment made with different bases was based upon the amount of mercurial ointment recovered after scraping a defined skin surface area with a pre-weighed razor blade, that is, the difference in applied and recovered weight represented the amount of ointment absorbed by the skin (Wild, 1911; Wild and Roberts, 1926).

The introduction of radioactive trace substances later offered a new approach for studying the systemic absorption through the skin. Unlike the methods described earlier, radioactive tracer methods permitted the detection of small quantities in biological materials. For instance, Hadgraft *et al*. (1956) detected small quantities of radioactivity in the rat blood after the topical application of [^{131}I]diiodofluorescein in five different ointment bases.

Development of topical products with systemic effects

The first quantitative report of clinically managing a systemic condition by topical application appears to be the work of Zondek, now some 70 years ago. He reported that chloroxylenol, an external disinfectant still present in antiseptic soaps and solutions today (Dettol®; Reckitt Benckiser, Slough, Berkshire, UK), could be effective in the treatment of urogenital infections when topically applied as a 30% lanolin ointment (Figure 1E) (Zondek, 1942a,b). Interestingly, the potential percutaneous absorption of the drugs now found in many of our current transdermal products has been demonstrated much earlier through inadvertent toxicity after topical exposure during manufacturing, consumer use of the products and in farming. For instance, nitroglycerin permeation across human skin, now used transdermally to prevent and to treat angina, first came to light in the early 1900s as a side effect – 'nitroglycerin head' – a severe headache experienced by people working in the manufacture of explosives or otherwise handling nitroglycerin-containing materials (Laws, 1898; 1910; Evans, 1912). Experimentally, 1 and 10% alcoholic nitroglycerin solutions applied topically to the forearm of healthy humans led to prolonged systemic effects (i.e. headache, changes in BP and pulse rate), with volunteers eventually showing an acquired tolerance to headache effects after an average of 38 h (Crandall *et al*., 1931). However, it was not until 1948 that a nitroglycerin ointment was successfully applied to treat Raynaud's disease (Fox and Leslie, 1948; Lund, 1948). This work led to a 2% nitroglycerin ointment (Nitrol®; Kremers Urban Company, Seymour, IN, USA) being used to treat angina pectoris in the 1950s. Here, a wooden applicator was used to measure the dose of nitroglycerin applied to the chest (Davis and Wiesel, 1955). A clinical trial published in 1974 demonstrated a sustained prophylactic efficacy lasting for up to 5 h (Reichek *et al*., 1974). However, the ointment was messy and needed to be applied several times a day. Concerns remained about the exact amount of drug being applied each time (No authors listed, 1976). As another example, systemic adverse effects of nicotine, the transdermal smoking cessation drug, became apparent after topical contact associated with its use as a topical insecticide (Wilson, 1930; Faulkner, 1933; Lockhart, 1933). In addition, nicotine absorption was noted among workers harvesting tobacco leaves in the form of green tobacco sickness (Gehlbach *et al*., 1974; 1975). The percutaneous absorption of oestrogens was discovered in the 1940s when men working in stilboestrol plants noticed an enlargement of their breasts (Scarff and Smith, 1942; Fitzsimons, 1944).

The development of adhesive transdermal delivery devices

Dale Wurster's contribution to the early understanding of transdermal delivery is seldom acknowledged (Roberts, 2013). Important components of that work, often associated with transdermal delivery, are the defined delivery system in dose, area, vehicle and device; the quantification of the time course of absorption into urine; and the application of pharmacokinetic principles to quantify the resulting drug delivery kinetics. In Wurster's first set of transdermal studies, his student Sherman Kramer glued a diffusion cell containing a defined dose of salicylate esters to the forearm of his human volunteers and then measured their systemic absorption by the excretion of salicylates in the urine. The extent of absorption could be modified by varying the diffusion area of the cell and by changing the level of skin hydration (Wurster and Kramer, 1961). The primitive diffusion cell designed (Figure 1G) and used in their study appears very much to be the forerunner of cells currently used in transdermal research and could even be considered a first prototype of today's commercial transdermal devices in that the *in vivo* diffusion cell permitted a precise, area-dependent dosing of a topically applied drug (Roberts, 2013). There are now a number of salicylate esters and other non-steroidal anti-inflammatory products on the market for local pain relief. Skin biopsies and microdialysis have been used to show their selective targeting of deeper tissues in preference to the systemic blood supply (Cross *et al*., 1998; Roberts and Cross, 1999). More recently, we have suggested that the dermal vasculature is a major conduit to deeper tissues for highly bound anti-inflammatory drugs based upon our analysis of the available microdialysis data (Dancik *et al*., 2012) and for corticosteroids by biopsy (Anissimov and Roberts, 2011).

Ten years after Kramer's studies, the first patent *using a rate-controlling membrane* to control the rate of transdermal delivery from a bandage for the continuous delivery through the skin of drugs into the systemic circulation was filled by the biochemist and entrepreneur Alejandro Zaffaroni (1923–2014) (Zaffaroni, 1971). In 1972, Beckett *et al*. compared the systemic absorption of ephedrine (and ephedrine analogues) through the skin to that achieved with p.o. administration. They fastened an ephedrine and ethanol solution spread over an adhesive, impervious occlusive tape to a male human subject (Beckett *et al*., 1972). The data obtained with this 'transdermal patch' were subsequently analysed by Riegelman (1974). It was concluded that the 'patch' delivery resulted in an absorption-limited terminal elimination phase (the pharmacokinetic phenomenon referred to as 'flip-flop' kinetics). Accordingly, patches were seen to offer the potential of maintaining sustained steady-state blood levels after topical application, with the levels being varied by manipulating the drug concentration and vehicle components in the patch and/or the area of skin exposed to the patch. The potency of the drug was noted as an important therapeutic determinant given that therapeutic blood levels would have to be achieved (Riegelman, 1974). The next step in this journey to a working transdermal system was to identify transdermal candidates. This step was taken in a pioneering work by Michaels *et al*. in 1975. Using diffusion cells fitted with human cadaver skin membranes, these researchers reported *in vitro* fluxes of a series of 10 drugs thought to have potential for the method (Michaels *et al*., 1975). Of the drugs studied, scopolamine, nitroglycerin, oestradiol and fentanyl have now been developed into marketed transdermal systems. We can now consider the history associated with the patch development of each of these drugs.

Scopolamine (hyoscine) patch for the treatment of motion sickness: the first transdermal patch to reach the market

Powder of *Hyoscyamus* (scopolamine's parent plant) was mentioned as an agent to be topically applied or taken orally for abdominal discomfort in the *Papyrus Ebers*. Scopolamine was first applied topically as an antiperspirant (MacMillan *et al*., 1964). In 1944, p.o. administration of 0.6 mg of scopolamine (hyoscine), tested with other drugs, was used to prevent seasickness in troops. A larger dose (1.2 mg) was shown to be more effective but was also associated with dry mouth (Holling *et al*., 1944). In 1947, dimenhydrinate (Dramamine®; Prestige Brands, Tarrytown, NY, USA), an antihistamine and anticholinergic drug, given experimentally to a woman to treat hives, led to the unexpected disappearance of the car sickness that she had suffered all her life. As a consequence, 100 mg of Dramamine was tested on 389 US soldiers suffering seasickness while sailing to Germany and found to be effective within 1 h in 372 of them (Gay and Carliner, 1949). Scopolamine was later used successfully to prevent airsickness in student navigators (Lilienthal, 1945; Smith, 1946b) but found to be only moderately effective in flexible gunnery students (Smith, 1946a). Unfortunately, scopolamine has a comparatively short elimination half-life of 4.5 h and is therefore expected to only have a short duration of action (Putcha *et al.*, 1989).

The finding that scopolamine had a substantial flux through excised human skin (Michaels *et al.*, 1975) led to a follow-up study in which the mechanism by which scopolamine penetrated the stratum corneum was studied in more depth (Chandrasekaran *et al.*, 1976). This 1970s work culminated in the Alza Corporation developing a transdermal therapeutic system (TTS) for prevention and treatment of motion-induced nausea designed to provide controlled administration of scopolamine through the surface of the skin, such that the system governed drug input kinetics to the systemic circulation (Shaw *et al.*, 1975; 1976). Studies were performed to locate a highly permeable skin site. It was found that the transdermal patch with a Zaffaroni design applied behind the ear worked best. The patch had a drug reservoir and a microporous membrane that could control the delivery of scopolamine (Shaw and Urquhart, 1979). As a result of a redistribution of scopolamine into the contact adhesive lamina, an initial bolus (loading) dose of scopolamine was released upon application of the patch to the skin, enabling therapeutic scopolamine plasma levels to be achieved rapidly (Urquhart *et al.*, 1977; Shaw and Urquhart, 1979). The device was first tested with Alza employees sailing in a large sailboat through a rough stretch of water close to the Golden Gate Bridge known as the ‘potato patch’. Employees wearing the placebo patch were sick, whereas most of those wearing the scopolamine patch did not (Hoffman, 2008). Controlled trials were then conducted as part of the programme for the American Spacelab missions; these demonstrated the efficacy of the transdermal scopolamine system (Graybriel *et al.*, 1976; 1981; Graybriel, 1979). In 1979, a 2.5 cm^2-TTS (which is still one of the smallest patches on the market) programmed to deliver 1.5 mg of scopolamine over 3 days (Transderm Scōp®; Novartis Consumer Health, Parsippany, NJ, USA) was the first transdermal patch to reach the US market. Alza’s scientists later conducted four double-blind clinical trials in healthy men and women with a history of motion sickness to evaluate the efficacy of transdermal scopolamine for the prevention of motion sickness at sea. Transdermal scopolamine not only provided significant protection against motion sickness compared with placebo and p.o. dimenhydrinate but was also associated with minimal side effects (Price *et al.*, 1981).

Nitroglycerin for angina pectoris: from the ointment to the transdermal patches

Until the marketing of the transdermal scopolamine patch, a nitroglycerin ointment was the only transdermal product on the market. Whereas the nitroglycerin ointment led to more sustained serum levels than sublingual and p.o. sustained release capsule dose forms (Maier-Lenz *et al.*, 1980), the plasma levels were dependent upon the surface area to which a given dose of ointment was applied (Sved *et al.*, 1981). However, applying a precise dose to a stratified area is difficult. For example, the dosages of Nitro-Bid® (nitroglycerin ointment USP 2%; Fougera, Melville, NY, USA), used in clinical trials were determined using a ruler to define the length of ointment ribbon ejected from the ointment tube (Figure 1F) and ranged from 1.3 cm (1/2 in.; 7.5 mg) to 5.1 cm (2 in.; 30 mg), typically applied to 232 cm^2 (36 $in.^2$) of skin on the trunk of the body. An additional limitation of semi-solids is the need for frequent dosing, e.g. every 8 h for Nitro-Bid, to achieve the intended therapeutic effect, which is likely to lead to greater patient non-compliance than once daily dosing possible with patches. However, nitroglycerin volatilization appeared not to be an issue (Cossum and Roberts, 1981). In contrast, unintentional transfer through interpersonal contact was a problem, as evidenced by the report of spousal headache after intercourse with a partner who had rubbed a nitroglycerin patch on his penis to treat erectile dysfunction (Talley and Crawley, 1985).

In 1973, Alza Corporation filed an additional US patent based upon its topical rate-controlling membrane medicated adhesive bandage concept for the controlled systemic administration of vasodilators such as nitroglycerin. An embodiment of the patent was that the drug within the reservoir could be mixed with a transporting agent to assist drug delivery (Zaffaroni, 1973). At the beginning of the 1980s, Key Pharmaceuticals and Searle Laboratories disclosed two different nitroglycerin transdermal system designs: a water-soluble polymeric diffusion matrix containing nitroglycerin and a microsealed pad with a polymer matrix containing nitroglycerin within a hydrophobic solvent to enhance nitroglycerin transport and diffusion (Keith and Snipes, 1981a; Sanvordeker *et al.*, 1982). Associated with these patents, three nitroglycerin transdermal patches varying in structure and dosages were introduced onto the US market in 1981 for the prevention and treatment of angina pectoris: Transderm-Nitro® (Ciba Pharmaceuticals Company), Nitro-Dur® (Key Pharmaceuticals) and Nitrodisc® (Searle Laboratories) (Dasta and Geraets, 1982). Since it had been learnt in clinical studies that nitroglycerin inactivated itself upon sustained delivery, each marketed patch was to be applied once daily with an approximately 12 h ‘rest period’ between wear times. A subsequent patent claimed that addition of ethanol as a permeation enhancer to a transdermal nitroglycerin system enabled nitroglycerin skin fluxes of at least 40 $\mu g \cdot cm^{-2} \cdot h^{-1}$ (preferably in the range of 50–150 $\mu g \cdot cm^{-2} \cdot h^{-1}$) greater than the prior art (Gale and Berggren, 1986). In the United States, Key Pharmaceuticals eventually developed a patch in which the drug was contained solely in the adhesive, the first successful commercial patch of this kind and this patch captured the greatest share of the nitroglycerin market. The patch was later marketed as Nitro-Dur II® and described in a US patent (Sablotsky *et al.*, 1993).

Transdermal clonidine for the treatment of hypertension

Clonidine, approved by the US Food and Drug Administration (FDA) in 1984 for up to 1 week transdermal delivery to manage mild-to-moderate hypertension (Sica and Grubbs, 2005), was first applied to facial skin in the form of a shaving lotion, a soap or a cream for its pilomotor effect (Zeile *et al.*, 1965), in which the stimulation of the arrector pili muscle of the skin causes goose bumps so that hairs are raised away from the skin. In the 1960s, the hypotensive effect of clonidine was discovered by accident when a solution of the drug was introduced into the nose of a woman suffering a cold to test the nasal decongestive properties of clonidine. Surprisingly, the woman then fell into a deep sleep until the next day. Controlled tests, run after she woke up, showed a significant drop in BP and heart rate (Stähle, 2000). Transdermal clonidine was developed to reduce drug side effects (mainly drowsiness and dry mouth) and to improve patient compliance (Shaw *et al.*, 1983), which was estimated to be no more than 50% with p.o. hypertensive therapy (Haynes *et al.*, 1978). In 1980, a US patent disclosed a transdermal patch for hypertension therapy. The system contained a gelled mineral oil–polyisobutene–clonidine reservoir and contact adhesive layer with a microporous membrane in-between that controlled the drug release rate (Chandrasekaran *et al.*, 1980). In a subsequent patent, it was claimed that the drug release rate of a clonidine transdermal system could be modulated from 1.6 to 2.4 $\mu g{\cdot}cm^{-2}{\cdot}h^{-1}$ by modifying the polyisobutylene (PIB)/mineral oil ratios in the drug reservoir and in the contact adhesive with and without the presence of colloidal silicon dioxide (Enscore and Gale, 1985). First clinical trials showed that the clonidine transdermal patch was an effective alternative to p.o. administration in decreasing BP in healthy volunteers (Arndts and Arndts, 1984) and in patients with essential hypertension (Popli *et al.*, 1983; Weber *et al.*, 1984). However, clonidine patches have since been associated with a high rate of dermatological adverse reactions (e.g. allergic contract dermatitis), leading sometimes to treatment discontinuation (Boekhorst, 1983; Groth *et al.*, 1983; Holdiness, 1989).

Transdermal oestradiol for female hormone replacement therapy

Cutaneous application of follicular hormone (follicle-stimulating hormone), oestrone, for amenorrhoea was introduced by Zondek (1938). In 1960, 2 g of an ointment containing both radiolabelled oestradiol-17β and progesterone was applied to human subjects. Between 16.5 and 44% of the radioactivity appeared in the urine within 72 h (Goldzieher and Baker, 1960). Oestradiol was first applied transdermally for post-menopausal replacement therapy as a hydroalcoholic gel (Oestrogel®; Benins-Iscovesco) (Holst *et al.*, 1982; Holst, 1983). However, this dosage form was messy and dosage control was difficult. In 1983, a US patent disclosed a bandage to be applied to the skin for administration of oestradiol within a vehicle rich in ethanol, the latter used as a percutaneous absorption enhancer (Campbell and Chandrasekaran, 1983). A microporous polymer film membrane was used to maintain the fluxes of oestradiol and ethanol in the vicinity of 0.1 and 400 $\mu g{\cdot}cm^{-2}{\cdot}h^{-1}$ respectively. The sustained plasma levels of oestradiol obtained with the device overcame the key peak and trough profile limitation of the then marketed oestradiol ointment (Strecker *et al.*, 1979). In 1984, the first transdermal oestradiol system reached the US market. Its application resulted in circulating oestradiol plasma levels (40–60 $pg{\cdot}mL^{-1}$) sufficient to meet the early follicular phase hormone levels (Good *et al.*, 1985). A number of clinical trials demonstrated the efficacy of Alza's transdermal device in reducing hot flushes and showed the advantages of transdermal delivery as compared to conventional p.o. oestrogen treatment (i.e. reduction in daily dose required, limited effects on liver function) (Laufer *et al.*, 1983; Powers *et al.*, 1985). Eventually, patches with oestradiol exclusively in the adhesive were developed and these too assumed strong market positions. Today, an alternative approach is to use metered-dose applicators, exemplified by Elestrin® (oestradiol 0.06% in a hydroalcoholic gel base; Meda Pharmaceuticals, Somerset, NJ, USA) packed as 100 doses each of 0.87 g gel and Divigel® (Orion Corporation Pharm, Turku, Finland) packed as single use gel-filled sachets (0.25, 0.5 and 1.0 g gel-filled foil packets containing 0.25, 0.5 and 1 mg of oestradiol respectively).

Transdermal fentanyl for the treatment of pain

As pointed out by Watkinson (2012), the Alza fentanyl patch, marketed by Johnson & Johnson (J&J) as Duragesic®, has dominated the transdermal market with peak sales of greater than $2 billion in 2004. Michaels *et al.* (1975) showed its potential as a transdermal candidate by reporting maximum fluxes through human thigh skin of 0.8–3.8 $\mu g{\cdot}cm^{-2}{\cdot}h^{-1}$ (average, 2 $\mu g{\cdot}cm^{-2}{\cdot}h^{-1}$) at 30°C. A 1986 US patent, disclosing various transdermal system designs with different sizes (5–100 cm^2) for the delivery of the free base of the narcotic fentanyl, observed that *in vitro* skin penetration rates of 0.5–10 $\mu g{\cdot}cm^{-2}{\cdot}h^{-1}$ could be maintained for at least 12 h and for up to 7 days (Gale *et al.*, 1986). The system's *in vivo* delivery of fentanyl citrate and base (and sufentanil citrate and base) through the skin was demonstrated by applying 50 μg of the drug in water to the forearm skin of five volunteers (six volunteers for sufentanil) under an occlusive dressing, showing that about 20% of the absorbed dose was recovered in urine after 24 h (Sebel *et al.*, 1987). The first clinical studies evaluating Alza's TTS-fentanyl patch, a standard Zaffaroni system with the drug in the pouch of a form-fill-seal design, were conducted in patients in the late 1980s (Duthie *et al.*, 1988; Holley and van Steennis, 1988; Caplan *et al.*, 1989). Further to their studies comparing permeation of fentanyl and sufentanil across human skin *in vitro*, the relationship to their physicochemical properties and their suitability for transdermal delivery (Roy and Flynn, 1989; 1990), Roy *et al.* (1996) showed that optimum flux of fentanyl through human skin from various adhesive patches was achieved when its thermodynamic activity in the patch was maximal. The Alza patch ran into difficulties in 2006 when its patent expired and it was found that fentanyl could leak out of the patch reservoir (Watkinson, 2012). However, while the US FDA approved the Mylan fentanyl matrix [drug-in-adhesive (DIA)] patch, described in a US patent (Miller *et al.*, 2009), in January 2005 and another from Lavipharm in August 2006, J&J had sales of more than $1.2 billion in 2006 and $900 million in 2009, mainly due to J&J's assertive marketing and patent protection (Watkinson, 2012). Interestingly, although Noven received approval for a new generic patch in 2009, its initial application in September 2005 failed because its patch contained much more fentanyl than that in Duragesic. Ultimately, these matrix designs, together with Activis (2007), Watson (2007) and Teva (2008), dominated the market (Watkinson, 2012).

Nicotine patches for smoking cessation aid: first transdermal blockbuster

Nicotine was first used in a transdermal form as a smoking reduction and cessation aid in 1984. One study showed significant levels of nicotine in the saliva between 30 and 90 min after the topical application of 9 mg of nicotine base in a 30% aqueous solution to the volar forearm of a volunteer; there was also an increase in both the pulse and the systolic BP (Rose *et al*., 1984). A follow-up study showed a reduced craving in 10 cigarette smokers after application of 8 mg of nicotine base in a 30% aqueous solution in a polyethylene patch in comparison to an inactive placebo solution (Rose *et al*., 1985). The first German patches containing nicotine proved to be successful in suppressing the urge to smoke in clinical trials in Münster/Germany in 1989 (Buchkremer *et al*., 1989). One of the first US patents dealing with transdermal delivery of nicotine claimed an occlusive transdermal pad to be attached to the skin with a reservoir liquid nicotine base (Etscorn, 1986). In this invention, the delivery of nicotine from the device was controlled with the use of a microporous membrane. Its duration of delivery was on the order of 30–45 min, thus requiring the application of several patches over the course of a day to maintain nicotine plasma levels. A subsequent patent disclosed a monolithic patch with a polyurethane matrix layer that contained between 5 and 50% nicotine. This system was to deliver nicotine through human skin over at least 24 h (Baker and Kochinke, 1989). A later US patent suggested that the concentration of nicotine in the patch reservoir should preferably be at a thermodynamic activity of less than 0.50 (Osborne *et al*., 1991). Between the end of 1991 and early 1992, four nicotine patches with different designs, all obviously approved by the US FDA, reached the US market within a few months. These were Ciba-Geigy/Lohmann Therapie-Systeme (LTS): Habitrol® (matrix); Lederle/Elan: Prostep® (matrix); Marion Merrell Dow/Alza: Nicoderm® (reservoir/membrane); and Warner-Lambert/Cygnus: Nicotrol® (DIA). Collectively, they became a huge commercial success with total sales approaching US $1 billion during their year of introduction. Over a million smokers gave up smoking with the help of nicotine patches (Prausnitz *et al*., 2004). Although transdermal patches had been on the market for around 10 years, it was the arrival of nicotine patches that led to them being widely accepted.

Transdermal testosterone for hypogonadism

Testosterone was initially applied as a cream in order to treat male hypogonadism (Jacobs *et al*., 1975; Klugo and Cerny, 1978; Ben-Galim *et al*., 1980). However, skin-to-skin transfer of testosterone gel from parents to their young children or from male to their female sexual partners was reported, resulting in precocious puberty or pronounced virilization (Delanoe *et al*., 1984; Kunz *et al*., 2004; Busse and Maibach, 2011). The first TTS for administration of testosterone was developed and tested in nine healthy normal men and seven hypogonadal patients (Bals-Pratsch *et al*., 1986). The first systems were developed by Alza Corporation and designed to be applied to the highly permeable scrotal tissue (Testoderm® TTS) (Campbell and Eckenhoff, 1987; Korenman *et al*., 1987; Campbell *et al*., 1988; 1989a). However, Ahmed *et al*. (1988) reported high serum dihydrotestosterone levels after scrotal application and expressed concern about the possible detrimental effects on the prostate. Moreover, the site of application was inconvenient for patients who had to clip their scrotal hair to enable these patches to adhere adequately (Nieschlag, 2006). The next-generation testosterone patch (Androderm®; Watson Laboratories, Inc., Salt Lake City, UT, USA) was therefore designed for application to non-scrotal skin (i.e. the back or the chest) to overcome these difficulties. The naturally low skin penetration rate of testosterone was overcome by raising its concentration to just below saturation and including ethanol or comparable solvent as a skin penetration enhancer (Ebert *et al*., 1992; Meikle *et al*., 1992).

Not all transdermal candidates result in successful, marketed products

In vitro and *in vivo* skin permeation studies showed that ephedrine might be a likely candidate for administration by way of the transdermal route (Beckett *et al*., 1972; Michaels *et al*., 1975). It was thought that the drug could be incorporated in a polymeric transdermal patch for its decongestant effect (Keith and Snipes, 1981d) and for potential anti-asthmatic therapy (Bhalla and Toddywala, 1988). Subsequent *in vitro* drug release studies from a polymeric matrix patch and *in vivo* absorption studies in nine healthy volunteers looked promising (Jain *et al*., 1990). Inventions describing matrix patches containing phenylephrine and phenylpropanolamine were also reported (Keith and Snipes, 1981b,c). A phenylpropanolamine transdermal patch was investigated in a pilot study with three subjects and showed effective plasma levels for appetite suppression (Devane *et al*., 1991). However, none of these transdermal patches reached the market. Nevertheless, the lay press has also reported the use of ephedrine patches as an aid to weigh loss (Real Pharma, 2014). However, since 2004, ephedra-containing dietary supplements have been banned by the FDA due to serious toxicities (FDA, 2004).

Despite encouraging results in healthy volunteers, neither a transdermal timolol ointment (Vlasses *et al*., 1985) nor a transdermal timolol patch (Kubota *et al*., 1993) has received clinical and therefore regulatory acceptance. Captopril, an angiotensin-converting enzyme inhibitor, has also been incorporated into transdermal patches and tested *in vivo* in animal models. However, its physicochemical properties are not favourable for transdermal delivery and the drug is associated with severe skin irritation (Helal and Lane, 2014).

Avoidance of first-pass metabolism and transdermal blood level profile

Administration of therapeutic agents across the skin enables drugs to avoid p.o. first-pass chemical or enzymatic degradation in the gastrointestinal tract or liver. Transdermal delivery is therefore of particular interest for molecules with limited systemic (p.o.) bioavailabilities and short half-lives, providing that the molecule can also be shown not to have a high skin first-pass effect. Examples of molecules with a high skin first pass that are used in topical and transdermal products include testosterone (~60%, *in vitro* mouse skin) (Kao and Hall, 1987); methyl salicylate (>90%, *in vivo* human volunteers) (Cross *et al*., 1998); nitroglycerin (~20%, *in vivo* rhesus monkeys) (Wester and Maibach, 1983) and others (Dancik *et al*., 2010). The zero-order (constant rate of delivery) kinetics of transdermal delivery has been one of the cornerstones in the development of transdermal systems for the treatment, for instance, of neurodegenerative disorders (Poewe *et al.*, 2007; Lefèvre *et al.*, 2008).

Design of patches based upon engineering and pharmacokinetics principles

Reservoir and rate-controlling membrane

The variability in dosing and possible transfer of the active to others with ointment and cream transdermal systems has emphasized the need to have controlled, occluded and safer delivery systems. This has been a major driver in the development of the more sophisticated TTSs that are commonly known as 'transdermal patches'. The first of these systems was a combination of a reservoir containing the active and a rate-controlling membrane pioneered in the early 1970s by the entrepreneur Alejandro Zaffaroni through his company Alza. His first commercialized TTS was a scopolamine TTS. Alza championed the view that the co-existence of a reservoir and a rate-limiting membrane in their system was a key requirement to minimize variability in skin permeability within and between individuals and subsequent drug blood levels. A key premise was that the device, and not the skin, controlled drug input into the bloodstream (Shaw and Theeuwes, 1985). In turn, the precisely controlled delivery into the systemic circulation through intact skin not only attained an adequate therapeutic effect (i.e. to prevent motion sickness) but also minimized undesired CNS adverse events such as drowsiness and confusion (Shaw and Urquhart, 1979). A patent filled in August 1971 (US Patent 3,797,494) described a patch using this concept, which was quite revolutionary in comparison to previously existing transdermal systems (Zaffaroni, 1974). The reservoir/membrane patch design is illustrated in Figure 1H. In this type of patch design (also known as form-fill-seal design), the drug is contained in a compartment and is usually present in the form of a liquid (i.e. solution or suspension) or a gel. This liquid or gel reservoir is separated from a continuous adhesive layer by a permeable membrane that controls the release of the active from the device. Figure 2A and B shows, for the reservoir patch, the process of form-filling-sealing and coating-drying respectively.

An unplanned benefit in this initial patch design is that the drug in the reservoir equilibrates with the adhesive layer so that upon application to the skin, the drug in the adhesive acts as a priming dose of drug that when released can saturate skin binding sites. The advantage of a reservoir/membrane-type patch is that it provides a constant release rate of drug from the system (zero-order kinetics). However, this design also has the disadvantage of requiring a larger patch to achieve its delivery goal as the membrane rate control is increased. One should also mention that the membrane function only applies to the dynamic *in vivo* phase. During storage, drug in a patch will diffuse into and saturate all the membranes of the system as well as the in-line adhesive layer, in this way possibly resulting in overly high initial delivery rates. This phenomenon is a general disadvantage for high-solubility molecules that need some kind of flux moderation.

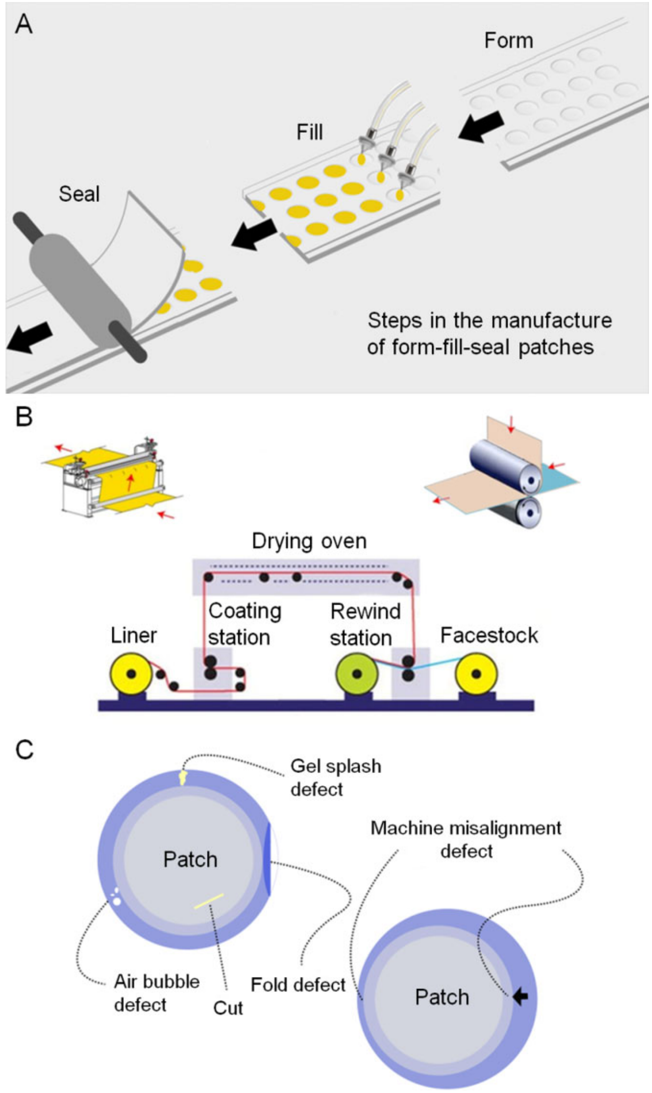

Figure 2

Manufacturing process for and potential failures of reservoir patches: (A) form-filling and sealing process; (B) coating and drying process; and (C) potential problems arising during patch reservoir manufacturing process.

A major limitation in this system is potential for leakage from its sealed liquid reservoir that could arise from an aberration in the manufacturing of the patch. Uncontrolled drug release from the reservoir and potentially drug overdosing (a dose-dumping effect) could arise, for instance, from an accidental rupture of a backing membrane (Govil, 1988; Peterson *et al.*, 1997). Indeed, recalled lots of the form-fill-seal type of fentanyl patches were apparently associated with this problem and similar problems in the early 2000s. Figure 2C shows some examples of issues that may arise with this patch design. In addition, the use of reservoir solution can also lead to other difficulties. As an example, a design fault in the Estraderm® device, patented by Alza in 1984 (US Patent 4,460,372) (Campbell and Chandrasekaran, 1984) led to an unexpected drug delivery profile despite the presence of a rate-controlling membrane (Paoletti *et al*., 2001). In a system with a 'rate-controlling' membrane, the putative membrane will affect the overall flux of both the drug and the enhancer. Early on, Alza created an oestradiol patch intended to yield a constant flux of oestradiol over 4 days, in which the reservoir contained oestradiol in an ethanolic solution. However, an unexpected oestradiol plasma concentration–time profile was found when the transdermal system was applied to human skin. On day 2, there were higher than expected blood levels, most probably as a result of the back diffusion of moisture from the skin into the patch reservoir reducing the solubility of oestradiol in the reservoir and greatly increasing its thermodynamic activity leading ultimately to the formation of a supersaturated solution and marked skin penetration. However, on day 3, the blood levels significantly fell as the thermodynamic activity of oestradiol in the reservoir solution was reduced by the formation of oestradiol hemihydrates and their crystallizing out of solution.

A key concept Alza advocated to protect their patent was that '. . . each TTS under development or in clinical testing, incorporates a rate-controlling membrane . . .' (Shaw *et al*., 1975). They argued that 'the microporous membrane is chosen to ensure that the delivery rate of scopolamine to the skin surface is much less than the rate at which even the most impermeable skin can absorb the drug. Hence, the system, and not the skin, controls the entry of drug into the systemic circulation. This means that differences in skin permeability among different subjects will be negated; all will receive scopolamine into the circulation at the same rate, predetermined by the system's delivery characteristics' (Shaw and Chandrasekaran, 1978). In support of these assertions, Shaw and Theeuwes (1985) estimated the coefficient of variability in net transdermal flux from a patch through the skin as 25% (=SD.100/mean). This value was based upon an intrinsic variability in the transdermal flux of nitroglycerin through human skin *in vivo* being 46% (based upon the variability in the nitroglycerin lost from a transdermal ointment applied to 12 volunteers for 24 h) and an almost equal resistance to the skin being imposed by the patch in controlling the transdermal flux of nitroglycerin (*in vitro* flux from Transderm-Nitro patch on the skin accounts for 45% of the total resistance when applied to the skin).

However, more important than what is lost from the site of application, as used in these calculations, is the actual systemic plasma nitroglycerin concentration arising from the transdermal products – as these are more reflective of the likely pharmacodynamic effects for the products. The data reported by McAllister *et al*. (1986) for the nitroglycerin concentrations in plasma for 24 male subjects receiving a single application of Transderm-Nitro 50 mg, 1 in. of Nitro-Bid 2% ointment and two other products show a very different nitroglycerin plasma concentration–time profile for the Nitro-Bid ointment versus the other products that show similar profiles. Importantly, the variability in the extent of absorption, as defined by SD.100/mean for $AUC_{0–24}$ (pg·h·mL^{-1}), is comparable: 77.5% for Nitro-Bid ointment and 52% for the Transderm-Nitro patch. An additional source for the higher Nitro-Bid variability is the variation in dose per area applied (Sved *et al*., 1981). The variability in plasma nitroglycerin concentrations of transdermal systems lacking a rate-limiting membrane (Nitrodisc, 43%; Nitro-Dur, 55%) is also similar to that for Transderm-Nitro (McAllister *et al*., 1986), suggesting that this membrane is not essential for controlled transdermal delivery. In reality, pharmacokinetic differences mainly define the variations in plasma concentrations and systemic effects for patches, as can be seen by nitroglycerin patch doses for angina pectoris being normally titrated to give a decrease of 10 mmHg in systolic BP (Thadani *et al*., 1986). The variability in maximum-tolerated doses of nitroglycerin after i.v. infusion, which normally determines the infusion rate in practice, is 64% (Zimrin *et al*., 1988).

A key technology advancement implemented to enable efficacious delivery of certain drugs is the inclusion of a skin penetration enhancer. As an example, in the US Patent 4,588,580 filed by Alza in 1984 for the patch, later named Duragesic, the analgesic fentanyl was formulated in a gel matrix using ethanol as a vehicle to both maximize its thermodynamic activity and enhance skin penetration as well as enable its membrane barrier to partly control the release of fentanyl into the skin (Gale *et al*., 1986; Santus and Baker, 1993). In practice, many adjuvants are included in transdermal formulations to either: (i) increase drug diffusivity in the skin; (ii) increase drug solubility in the skin; and/or (iii) increase the degree of drug saturation in the formulation (Moser *et al*., 2001). Typical adjuvants in patches include ethanol, oleic acid, oleyl oleate, dipropylene glycol and triacetin (Govil *et al*., 1993; Lane, 2013). The most important consideration is the maximal delivery rate through the skin. This is evident in the delivery area for the Mylan matrix fentanyl patches, which came onto the market in the early 2000s, being only slightly smaller than Duragesic patch. In 2011, as a consequence of leakage problems, J&J introduced a matrix patch, in which fentanyl existed in an essentially saturated state in the adhesive.

Matrix patches

Several of Alza's early competitors – Key Pharmaceuticals, Theratech, Cygnus, Noven and LTS – used the matrix concept for nitroglycerin, oestradiol and testosterone to overcome the intellectual property challenges associated with Alza's technology in the 1980s. Collectively and at times individually, these matrix designs became the dominant products within the transdermal market (Figure 3). This market position was achieved because they were not only generally thinner and more flexible and so more comfortable and adhering, but they were also less expensive to manufacture. The matrix design overcame both the Alza intellectual property ownership in the liquid reservoir/rate-controlling membrane design and most of the limitations detailed herein associated with that design.

In general, all patches that do not contain a liquid reservoir may be regarded as matrix patches and these can be applied to the skin by either gluing the backing to the skin adjacent to the matrix or an adhesive on the matrix to the skin (Figure 1I and J). Patches in which drug is mainly incorporated in a polymeric or viscous adhesive (DIA), and discussed later, are also matrix patches. In principle, when a drug is suspended in an internal polymer matrix, in the pouch of a form-fill-seal system or in the adhesive of a patch without a distinct internal reservoir, the delivery can be steady (zero-order), depending upon just how any such

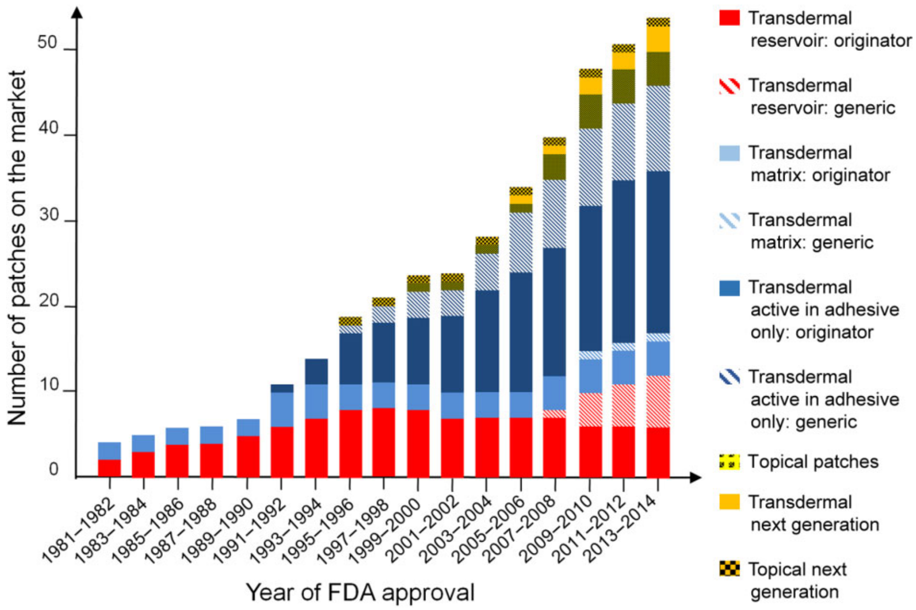

Figure 3

Evolution of commercial topical and transdermal patches – transdermal reservoir: originator, generic; transdermal matrix: originator, generic; transdermal active in adhesive only: originator, generic; topical patches; transdermal next generation; topical next generation.

system is designed. Mylan's fentanyl patch has its drug suspended in the adhesive (approximately 75% is suspended at the outset of patch wear) and it delivers at a constant rate over a multiple day course because as the drug is released from the patch and absorbed, suspended drug dissolves back in the adhesive and compensates for that which is released. The thermodynamic activity of fentanyl is therefore virtually constant over the whole time the Mylan patch is worn.

Active in adhesive patches

The original design of matrix patches was that the matrix was an alternative to the internal reservoir in the reservoir/rate-limiting membrane patch. Later patches, the DIA patches, simply incorporated the drug entirely in the pressure-sensitive adhesive (PSA). This design, which, in principle, is also a matrix patch, constitutes the simplest, state-of-the-art transdermal patch design. The drug is directly included in the adhesive polymer that not only fulfils its adhesion function but also holds the drug and controls its delivery rate (Peterson *et al*., 1997; Tan and Pfister, 1999). A US patent filled in August 1981 (US Patent 4,409,206) described a transdermal release system in which the active (e.g. clonidine, haloperidol, nitroglycerin or dihydroergotamine) was directly incorporated into a skin-compatible polyacrylate adhesive but not in a large amount (0–30% by weight) (Stricker, 1983). A transdermal tape, where nitroglycerin (25–45% by weight) was incorporated into an acrylic adhesive polymer, was later disclosed in a US patent in 1988 (Wick, 1988). In 1993, a US patent describing a DIA design for delivery of fentanyl was disclosed (Cleary and Roy, 1993). It has been suggested that the concept of a DIA patch came from the concept of the bubble jet printer where the ink was printed on the surface of some appropriate materials. It was realized that the DIA could be loaded onto the patch backing in the same way (G.W. Cleary, pers. comm. to M. S. Roberts, 8th World Congress on Clinical Pharmacology and Therapeutics, Brisbane, 1–6 August 2004). The DIA patch design is illustrated in Figure 1K.

However, while the DIA patch appears easier to make than its reservoir/rate-controlling membrane and traditional matrix patch counterparts, the formulation of such a patch is rather challenging (Padula *et al*., 2007). A key outcome from the DIA design are lighter, thinner and more flexible patches that are more comfortable to wear, have better conformity with skin surface variations and a significant improvement in patient acceptability (Hougham *et al*., 1989; Wick *et al*., 1989; Lake and Pinnock, 2000). In 1996, Roy *et al*. evaluated the physicochemical properties of adhesives used in the design of DIA transdermal patches (Roy *et al*., 1996). The effect of various adhesive formulations on transdermal delivery of fentanyl was investigated. Various PSAs (acrylate, silicone-2675, silicone-2920 and PIB) were characterized with respect to fentanyl's solubility, partition coefficient and diffusion coefficient. The fentanyl release profiles from these adhesives and the *in vitro* flux through human cadaver membranes were also evaluated. The silicone-2920 with 2% drug loading, characterized by low drug solubility, a low partition coefficient and a high diffusion coefficient, provided the highest skin flux. Thus, this adhesive appeared to be a promising candidate to design a transdermal patch for the delivery of fentanyl at a therapeutic rate. Interestingly, even though the acrylate adhesive exhibited a relatively higher release rate in water in these studies, its skin flux was considerably lower compared with the silicone-2675 and PIB adhesive formulations. This was seemingly because the acrylate adhesive was a good solvent for fentanyl and the systems in which this adhesive was used were of lower thermodynamic activity relative to the other adhesives.

However, a major disadvantage associated with these patches is that, if the drug is completely in solution, the rate of drug release from the device is dependent upon the drug concentration in the adhesive (first-order kinetics), thus bringing about a decrease in the release rate with wear time (Levin and Maibach, 2008). Hence, a constant rate of delivery could only be achieved if 80% of the amount of drug remained in the patch when the patch was spent and removed or if the drug was in suspension. The early nitroglycerin matrix patches were based upon a high residual content of drug in the patch. Alternatively, like the membrane control for the reservoir patch, the matrix could also provide some resistance to the penetration of drug into the skin, leading to a lower required drug content in the patch. Guy and Hadgraft (1992) estimated that the percentage control exerted by various nitroglycerin patches to the overall penetration of nitroglycerin through the skin was as follows: Transderm-Nitro, 45%: Nitro-Dur II, 13%; Minitran® (3M Drug Delivery Systems, Northridge, CA, USA), 28%; and Deponit® (UCB Pharma, Slough, Berkshire, UK), 87%.

In conclusion, the design of all transdermal patches is characterized by a multi-layered structure with most frequently three or four basic elements: an impermeable backing film, a preparation containing the drug(s) together with the excipient(s), an adhesive responsible for skin adhesion and a protective release liner that is peeled off before applying the patch to the skin. Transdermal patch systems used by the pharmaceutical industry today are mainly reservoir/controlled-release membrane and DIA patches, with the latter becoming the standard in practice (Hopp, 2002).

Drug candidates for transdermal delivery

Not all drugs are suitable for patch delivery. The only drugs that can be used are those that can penetrate the skin, that are sufficiently potent to be active and that meet a clinical need. To date, nearly two dozen molecules have been approved by the regulatory authorities for transdermal administration and have reached the market. The overriding commercial need for any new product is, as Watkinson (2012) puts it, the 'meeting of unmet medical needs' at 'a reasonable cost'.

In principle, the maximal skin penetration flux for a drug is determined by the product of its solubility in the stratum corneum and its diffusivity in the stratum corneum (Kasting *et al.*, 1987; Roberts, 2013). In turn, solubility can be related to melting point (MP), and drug–stratum corneum interactions and diffusivity can be related to molecular weight (MW) or molar volume (Roberts and Cross, 2002). While molecular size can dominate other variables when a wide variety of drugs are used to study percutaneous penetration (Magnusson *et al.*, 2004), the drugs used in topical and transdermal patches have a limited size range. Table 1 shows the properties of the current drugs in transdermal patches. Recently, Wiedersberg and Guy (2014) used some of these properties, a combination of MW and drug–solvent interaction parameters [such as aqueous solubility (S_{aq}) and log octanol–water partition coefficient (log P)], to first estimate the delivery rate of drugs through human skin. They then defined the predicted to actual flux ratios for all marketed drugs. As the average ratio is 5.8 times that expected of 1.0, with a percent coefficient of variation (=SD.100/mean) of 129, the precise prediction of the skin penetration rate for drugs in patches is not straightforward. Wiedersberg and Guy (2014) suggested that higher than expected ratios may arise when penetration enhancers were present in patches, whereas lower ratios arise when the drug concentrations in patches were below saturation. Figure 4 shows a plot of the various drugs now marketed in patches on the Berner–Cooper nomogram (Kydonieus *et al.*, 1999), widely used by the pharmaceutical industry to predict potential candidate drugs for use in transdermal patches. The equation underpinning this nomogram assumes a two-pathway (polar and lipid) model for drug transport through the stratum corneum (Berner and Cooper, 1987). It is apparent from Figure 4 that this nomogram lacks precision in its prediction of the skin penetration rate for the various sized drugs used in patches.

An alternative approach to predicting individual skin penetration fluxes for candidate drugs to be used in patches is to define the physicochemical boundaries within which all candidates in the patch systems should fall. As shown in Figure 4, most, but not all, of the marketed drugs used in patches are above the lower Berner–Cooper boundary of MW = 500, log P = 5 and MP < 250°C. All currently marketed drugs in the patch data fall within boundaries derived using a single pathway model similar to that used by Wiedersberg and Guy (2014) and a larger data set (Magnusson *et al.*, 2004; Milewski and Stinchcomb, 2012) (Figure 4). It is evident from Table 1 that a candidate drug for transdermal patches should normally be moderately lipophilic (log P range from 1 to 5), have a low molecular weight (MW < 500 Da) and a low melting point (MP < 250°C). Implicitly, an upper skin limit is also defined by the risk of local skin reactions.

The second requirement of drugs in a patch is that they are sufficiently potent to be active. This generally means that they have therapeutically attainable plasma concentrations, C_{ss} (Table 1), that are defined by the rate of delivery of a drug from a patch through the skin, R_0, divided by the systemic clearance, Cl (i.e. $C_{ss} = \frac{R_0}{Cl} = \frac{J_{skin} \times A}{Cl}$, noting also that: $R_0 = J_{skin} \times A$, where J_{skin} is the per unit area transdermal drug flux and A is the area of application) (Roberts and Walters, 1998). Indeed, this plasma concentration and the transdermal delivery rate (Figure 4) define the patch area required for therapeutic effect as we now illustrate with a fentanyl patch. Fentanyl, a moderate MW, low melting point and moderate high lipophilicity (MW = 337 Da, MP = 83°C and log P = 3.9) solute, has an average systemic blood plasma clearance in humans of ~50 L·h^{-1} and a therapeutic blood level of ~2 ng·mL^{-1}. Accordingly, assuming a complete skin bioavailability and a maximum flux of 0.8–3.8 μg·cm^{-2}·h^{-1} (Michaels *et al.*, 1975) through excised human skin, the desired skin flux requires a patch of 25–125 cm^2. In reality, the choice of an appropriate skin site and the presence of a skin penetration enhancer can lead to a higher fentanyl skin flux of 5–10 μg·cm^{-2}·h^{-1}, requiring the use of a patch of 10–20 cm^2 (Cleary, 1993). Accordingly, fentanyl is now widely used in transdermal delivery to manage post-operative pain. Similarly, a 50 cm^2 nitroglycerin patch meets its target therapeutic concentration of 1 ng·mL^{-1} and requires a transdermal flux of 20 μg·cm^{-2}·h^{-1} (Naik *et al.*, 2000).

Table 1

Physicochemical, pharmacokinetic and safety data for currently marketed transdermal drugs

Drug	MW[a] (Da)	MP (°C)[a] Unionized	log P[b]	S_{aq} (mg·mL^{-1})[a] Unionized (25°C)	Cl (L·h^{-1}) (70 kg)	$t_{1/2}$ (h)	Oral F (%)	Target plasma level (ng·mL^{-1})	Estimated J_{skin} required (µg·h^{-1})	In vivo J_{skin} (µg·cm^{-2}·h^{-1})[a″]	Equivalent maximum hourly dose (µg·h^{-1})[a‴]	Safety margin = max dose per h/in vivo J_{skin}
Buprenorphine	468	209	3.8	0.047, 0.008[h] (32°C)	77 i.v.[a′], 55 i.m.[b′]	3 i.v.[a′], 28 s.l.[a′], 19 bc[a′], 26 t.d.[b′]	51 s.l.[a′], 28 bc[a′]	>0.1[c′]	7.7	0.8	70.8	~100
Clonidine	230	130	2.7	0.17, 13.58[i]	15[d′]	8–13 i.v.[d′], 12–16 i.v.[e′], 20 t.d.[e′]	95[d′]	0.2–2[d′]	3–30	1.2	12.5	~10
Oestradiol	272	173–179	4.2	0.003, 0.003[j] (30°C), 0.0015 1[k] (25°C)	600–800[f′]	~1 p.o.[g′]	5[h′]	0.04–0.06[i′]	24–48	0.2[b″], 0.17[c″], 0.14[d″], 0.12[e″], 0.42[f″], 0.18[g″], 0.63[h″], 0.23[i″], 0.09[j″]	4.2	~20
Ethinyl oestradiol	296	141–146	4.3	0.039, 0.0092[k] (25°C)	70 p.o.[j′]	7.7 p.o.[j′], 17 t.d.[k′]	55[h′]	0.025–0.075[l′]	1.75–5.25	0.07	0.8	~10
Fentanyl	337	83–84	3.9	0.15, 0.2[j] (30°C), 0.2[l] (25°C)	27–75[m′]	3–12 i.v.[m′], 20–27 t.d.[m′]	50 o.t.[n′]	1–3[o′]	27–225	2.4	100	~40
Granisetron	312	152–154[c]	2.6	0.017	33–76[p′]	4–6 i.v.[p′], 36 t.d.[p′]	60[q′]	3.9 (t.d. mean C_{max})[p′]	129–296	2.5	129	~50
Levonorgestrel	312	235–237	3.8	0.017	5.7 p.o.[j′]	19.3 p.o.[j′], 28 t.d.[r′]	94[h′]	0.17 (t.d. C_{ss})[r′]	1	0.03	–	–
Methylphenidate	233	74–75, liquid	2.1	1.8	12(d); 21(l) (children 30 kg)[s′]	1.5–5 p.o. (children)[s′]	22(d); 5(l)[s′]	5–15[t′]	60–315	88	1250	~15
Nicotine	162	−79, liquid	1.1	62, 1085[i] (30°C)	77[u′]	2 i.v.[u′]	20–45[v′]	5–30[w′]	385–2310	40[k″], 31[l″], 69[m″], 29[n″]	875	~20
Nitroglycerin (glyceryl trinitrate)	227	13, liquid	1	0.66, 1.3[j] (30°C)	216–3270[x′]	0.03–0.05 p.o.[x′]	<1[y′]	0.02–0.4[z′]	4.32–1308	20[o″], 30[p″]	833	~30
Norelgestromin	327	110–130	3.67 (pred)	0.0043	–	28 t.d.[k′]	–	0.6–1.2[l′]	–	0.31	6.25	~20
Norethindrone acetate (norethisterone acetate)	341	161–162	3.2	0.0065	20.6[aa′]	34.8 p.o.[aa′], 6–8 t.d.[ab′]	60[h′]	0.5–0.8[ab′]	10.3–16.5	0.65	10.4	~20
Oxybutynin	358	56–58[d]	4.3	0.0093	10–64[ac′]	2 i.v.[ad′], 7–8 t.d.[ad′]	6[ad′]	0.5–3[ae′]	5–192	4.2	162.5	~40
Rivastigmine	250	Oil at 25°C[e]	2.3	25	108[af′]	1.3–2 p.o.[ag′], 3.4 t.d.[ag′]	36[af′]	2.5–20 (t.d. mean C_{max})[ah′]	270–2160	39	396	~10
Rotigotine	316	75–77[f]	4.7	0.017	600[ai′]	7 t.d.[ai′]	–	0.4–2[aj′]	240–1200	8.3	250	~30
Scopolamine (hyoscine)	303	55, liquid	0.8	1.8, 75[j] (30°C)	65–121[ak′]	1–5 p.o.[ak′]	4–27[ak′]	>0.05[al′]	3.25–6.05	5.6	210[b‴]	~40
Selegiline (deprenyl)	187	Liquid at 25°C[g]	2.7	0.73	84[am′]	9–15 p.o.[an′], 15–25 t.d.[am′]	4[an′]	2[ao′]	168	12.5	500	~40
Testosterone	288	155	3.6	0.02, 0.02[i] (25°C)	41[ap′]	0.17–1.7[aq′]	7[ar′]	3–10.5[aq′]	123–430.5	13.9	417	~30

bc, buccal; *Cl*, total body clearance; d, dextro isomer; *F*, oral bioavailability; i.m., intramuscular; i.v., intravenous; J_{skin}, skin flux; l, levo isomer; log *P*, log octanol–water partition coefficient; MP, melting point of the unionized form; MW, molecular weight; o.t., transmuscosal; p.o., per oral; S_{aq}, aqueous solubility of the unionized form; s.l., sublingual; $t_{1/2}$, elimination half-life; t.d., transdermal.

[a]Sci Finder Scholar, 2014. [b]Chambers Fox, 2014. [c]Gafni *et al.*, 2008. [d]Tang *et al.*, 2008. [e]Chiang *et al.*, 2009. [f]Krivonos and Weisman, 2013. [g]Govil and Weimann, 2006. [h]Roy *et al.*, 1994. [i]Magnusson *et al.*, 2004. [j]Michaels *et al.*, 1975. [k]Shareef *et al.*, 2006. [l]Roy and Flynn, 1988.

[a′]Kuhlman *et al.*, 1996. [b′]Butrans® PI. [c′]Sittl *et al.*, 2003. [d′]Lowenthal *et al.*, 1988. [e′]Catrapres-TTS® PI. [f′]Cleary, 1993. [g′]Estraderm® PI. [h′]Fotherby, 1996. [i′]Good *et al.*, 1985. [j′]Kanarkowski *et al.*, 1988. [k′]Ortho Evra® PI. [l′]Abrams *et al.*, 2002. [m′]Duragesic® PI. [n′]Actiq® PI. [o′]Duthie *et al.*, 1988. [p′]Sancuso® PI. [q′]Kytril® PI. [r′]Climara Pro® PI. [s′]Ritalin LA® PI. [t′]Greenhill *et al.*, 2001. [u′]Benowitz *et al.*, 1982. [v′]Hukkanen *et al.*, 2005. [w′]Bannon *et al.*, 1994. [x′]Bogaert, 1987. [y′]Bauer and Seifert, 2005. [z′]Noonan and Benet, 1986.

[aa′]Singh *et al.*, 1979. [ab′]Combipatch® PI. [ac′]Douchamps *et al.*, 1988. [ad′]Oxytrol® PI. [ae′]Lee *et al.*, 1995. [af′]Exelon® capsules PI. [ag′]Lefèvre *et al.*, 2008. [ah′]Frank *et al.*, 2014. [ai′]Neupro® PI. [aj′]Lauterbach *et al.*, 2002. [ak′]Guay, 2003. [al′]Nachum *et al.*, 2006. [am′]Emsam® PI. [an′]Azzaro *et al.*, 2007. [ao′]Kolli *et al.*, 2010. [ap′]Horton *et al.*, 1965. [aq′]Axiron® PI. [ar′]Tauber *et al.*, 1986.

[a″]*In vivo* J_{skin} is calculated by dividing the labelled dose rate by the patch size (active area). [b″]Estraderm. [c″]Climara®. [d″]Vivelle®. [e″]Alora®. [f″]Vivelle-Dot®. [g″]Menostar®. [h″]Minivelle®. [i″]Combipatch®. [j″]Climara Pro® . [k″]Nicoderm CQ®. [l″]Nicorette®. [m″]Nicorette® Invisi patch®. [n″]Habitrol®. [o″]Nitro-Dur®. [p″]Minitran®.

[a‴]Maximum systemic daily dose (Watkinson, 2012) divided by 24 and multiplied by 1000 to express as µg·h^{-1}. [b‴]Maximum systemic daily dose from Drugs.com (Drugs, 2014).

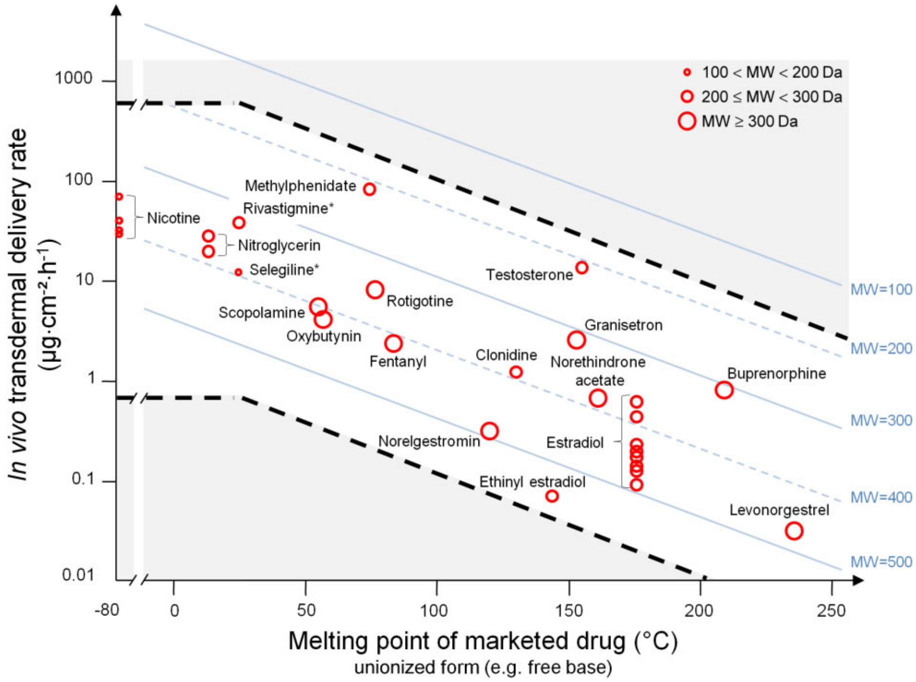

Figure 4

Transdermal delivery rate for currently marketed drugs in patches (log scale) (with symbol size being used to show the actual variation in molecular weight: 100 < MW < 200 Da; 200 ≤ MW < 300 Da; MW ≥ 300 Da) plotted against the active drug melting point (where unknown melting point given by an asterisk is represented as liquid at 25°C) and overlaid on the Berner–Cooper nomogram for a drug with a log *P* of 5 (Kydonieus *et al.*, 1999). Also shown, as dashed black lines, are the estimated upper and lower boundary lines for marketed drug delivery rate from patches as defined by the rates for small (MW = 100), polar (log *P* = 1) and large (MW = 500), lipophilic (log *P* = 5) solutes respectively. [The dashed black lines are calculated from the expression: *log maximum delivery rate* (μg·cm^{-2}·h^{-1}) = 1.6 + log MW − 0.0086 MW − 0.01 (MP − 25) − 0.219 log *P* and is based on a regression of maximum transdermal flux (in nmol, equation 7) versus MP, MW and log *P* for the combined data set of Magnusson *et al.* (2004) (Milewski and Stinchcomb, 2012). The level region in this plot recognises that 25°C is an approximate lower skin surface temperature for patches applied to human skin *in vivo* and at which all drugs with MP < 25°C will be liquid.]

The third driver for transdermal patch systems is a cost-effective safety advantage they may provide over other dosage forms for specific drugs. As discussed earlier, patches have less variability than arbitrarily applied solutions, creams and ointments. Also shown in Table 1 is the estimated maximum hourly systemic exposure based upon the maximum systemic daily dose given by Watkinson (2012). The ratio of this value divided by the *in vivo* patch flux gives a safety ratio for a given transdermal patch and is generally 10–100. An exception based upon Watkinson's data appears to be scopolamine (hyoscine). However, in practice, up to 5 mg (0.65 mg each 8 h) can be given to adults over 24 h (Drugs, 2014). As Dorne and Renwick (2005) pointed out, there should be at least a 10-fold safety factor to allow for human variability. Drugs such as oestradiol, nitroglycerin, oxybutynin, scopolamine, selegiline and testosterone may be unsuitable for p.o. delivery because of a high p.o. first-pass effect or a low intrinsic water solubility with that of oestradiol, norelgestromin, norethindrone acetate and oxybutynin being less than 10 mg·L^{-1} (Table 1). Further, the controlled release that avoids fluctuating blood levels (Figure 5) and the convenience offered by patches make them an ideal delivery system for drugs with short elimination half-lives (Table 1). As Wiedersberg and Guy (2014) pointed out, only i.v. infusion and transdermal patches allow systemic delivery to be stopped at any time, the latter by simply removing the patch.

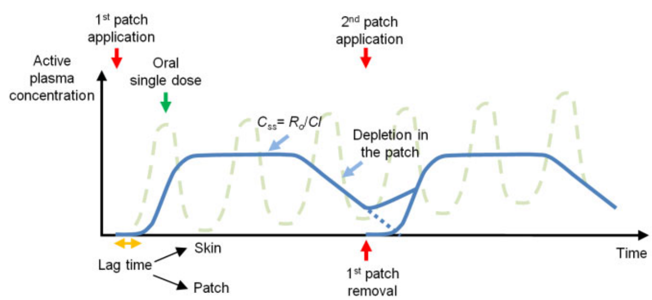

Figure 5

Typical active plasma concentration profile after patch application showing the lag-time, reaching and achieving steady-state, depletion and patch removal as well as the corresponding profile for repeated p.o. dosing of the same active.

An example of a drug that would be unwise to formulate as a patch is paracetamol (MW = 151 Da, MP = 169°C, log *P* = 0.46), with a clearance of about 15 L·h^{-1} (McNeil, 2002), a therapeutic analgesic concentration of 3–5 μg·mL^{-1} (Bacon *et al.*, 2002) and an estimated human skin penetration flux of 0.94 μg·cm^{-2}·h^{-1} (based upon the derived expression in Figure 4). Accordingly, a 6 m^2 paracetamol patch would be needed to be effective. Given that paracetamol is well absorbed and is readily available in various p.o. dosage forms, such a patch is unlikely to be commercially viable. Naik *et al*. (2000) showed that formulating an aspirin patch for use as anti-inflammatory was equally impractical as an area of 22 m^2 would be required based upon a 150 $\mu g \cdot mL^{-1}$ therapeutic concentration and a skin penetration flux of 20 $\mu g \cdot cm^{-2} \cdot h^{-1}$. However, the dose for its antithrombotic effect is about an order of magnitude lower than that of its anti-inflammatory actions. McAdam *et al*. (1996) showed that repeated application of a 50 cm^2 aspirin patch, containing 120 mg of aspirin and limonene as a permeation enhancer, released 33 mg of aspirin daily and led to a 90% suppression of platelet-produced thromboxane B_2 serum levels at day 21 in nine male volunteers.

Table 2 summarizes the approximately 20–25 drugs or drug combinations that are now available as transdermal products and have appeared since the approval of the first transdermal patch for treatment of motion sickness more than 30 years ago. Most of these drugs are for prescription use only, with many being available as generic patches following patent expirations.

These include [generic name, reference trade name, generic trade name(s)]: clonidine, Catapres-TTS® (Boehringer Ingelheim, Ingelheim am Rhein, Germany), Clonidine Transdermal System [Aveva (Miramar, FL, USA), Barr Pharm Labs Div Teva (Montvale, NJ, USA), Mylan Technologies (Albans City, VT, USA) and Watson Labs (Dublin, Ireland)]; oestradiol, Climara® (Bayer Healthcare, Montville, NJ, USA), Estradiol Transdermal System (Mylan Technologies); ethinyl oestradiol/norelgestromin, Ortho-Evra® (Janssen Pharms, Titusville, NJ, USA), Xulane® (Mylan Technologies); fentanyl, Duragesic (Janssen Pharms), Fentanyl Transdermal System [Aveva, Lavipharm Labs (Hightstown, NJ, USA), Mallinckrodt (Hazelwood, MO, USA), Mylan Technologies, Par Pharm (Woodcliff Lake, NJ, USA) and Watson Labs]; nitroglycerin, Nitro-Dur® (Merck, Whitehouse Station, NJ, USA), Nitroglycerin Transdermal System [Hercon Pharm (Emigsville, PA, USA), Kremers Urban Pharms (Princeton, NJ, USA) and Mylan Technologies]; oxybutynin, Oxytrol® (Watson Labs), Oxybutynin Transdermal System (Barr Pharm Labs Div Teva). The corresponding transdermal patches for Japan were first developed by the Nitto Denko Corporation in the 1970s and include isosorbide dinitrate (Frandol® Tape-S) for angina pectoris, tulobuterol (Hokunalin® Tape) for asthma (Tamura *et al*., 2012) and bisoprolol patch (Bisono® Tape) for treating hypertension (Nitto, 2013). Table 2 also lists examples of patches applied to the skin for topical effects. The main active agents used are capsaicin, various diclofenac ion pairs and lidocaine.

In general, the bioequivalence of patch formulations of the same drug can be undertaken using either *ex vivo* human epidermal penetration studies or by assessment of the plasma drug concentration profiles. These are not always equivalent as shown by the similar skin penetration profiles for the nicotine products, Nicoderm and Habitrol (Ho and Chien, 1993), but significantly different nicotine plasma concentrations after 5 days multiple dosing (C_{max}, T_{max}, $P < 0.001$; AUC, $P < 0.05$) (Gupta *et al*., 1995). The higher dose of nicotine delivered from the Nicoderm patch, particularly during the first 8 h after application, was attributed to the presence of nicotine in Nicoderm adhesive layer acting as a priming dose (Gupta *et al*., 1995). In these studies, 21 mg of nicotine was applied to the upper back for 24 h. Later patch designs were for 16 and 21 h so that patients were not exposed to nicotine during their sleep. Fant *et al*. (2000) conducted a crossover study of three nicotine transdermal patches (a 15 mg per 16 h patch (Nicorette®, Maidenhead, UK) and two brands 21 mg per 24 h patches [Nicoderm (NiQuitin®; GlaxoSmithKline Consumer Healthcare, Brentford, UK)] and Habitrol (Nicotinell®; Novartis Consumer Health, Horsham, UK) and showed significant differences in the pharmacokinetic profiles between the two 21 mg patches and the 15 mg patch ($AUC_{0–24\,h}$ and C_{max}; $P < 0.05$). This study showed an unexpected peak-like delivery of nicotine from the reservoir/matrix patch arising from nicotine equilibrating in the adhesive layer during the storage of the patch. DeVeaugh-Geiss *et al*. (2010) also showed significant differences in the single-dose pharmacokinetic profiles of two nicotine transdermal patches, the Nicoderm (NiQuitin) 21 mg per 24 h patch and a newly UK available, Nicorette 25 mg per 16 h patch. A limitation in these studies was the lack of any apparent clinical efficacy or adverse profile comparisons.

A number of comparative bioequivalence studies have also been conducted with nitroglycerin (discussed earlier) and with fentanyl. Sathyan *et al*. (2005) suggested that the Duragesic DIA and reservoir fentanyl patches were bioequivalent, based upon single and multiple dose randomized controlled trials. However, Fiset *et al*. (1995) attributed an observed greater variability in absorption rate and fentanyl concentration for the matrix transdermal fentanyl patch developed by Cygnus compared with Alza's reservoir fentanyl patch to the absence of rate-controlling membrane. More recently, Marier *et al*. (2007) showed bioequivalence between a novel matrix formulation of fentanyl with a rate-controlling membrane (developed by Nycomed and known as Matrifen® in Europe) to the original reservoir Duragesic formulation in an open-label, randomized, fully replicated, four-way crossover study in healthy male subjects over a 72 h single patch application.

Variability, safety and regulatory issues for patches

Site of application

It has been well established that human skin penetration fluxes are highly dependent upon the site of application (Feldmann and Maibach, 1967; Scheuplein and Blank, 1971; Roberts *et al*., 1982; Roberts and Walters, 1998). However, some parts of the body (trunk and upper arm) appear to have similar fluxes, enabling patches to be interchangeably placed at those sites and to achieve similar plasma concentrations. For instance, MacGregor *et al*. (1985) showed that plasma concentrations obtained after the application of a 3.5 cm^2 clonidine patch (Catapres-TTS) on chest and arm were not significantly different over the recommended wear time. Schenkel *et al*. (1986) also showed that Estraderm could be applied to different sites of the trunk and to the upper arm without significant differences in the oestradiol uptake. Gorsline *et al*. (1992) later showed that bioequivalent ($AUC_{0–t}$, $AUC_{0–\infty}$ and T_{max}) plasma were achieved irrespective of the application site on the upper body (upper back, upper outer arm, upper chest) from Nicoderm 14 mg per 24 h. Yu *et al*.

Table 2

Commercially available transdermal patches approved by the US FDA

Drug (Trade name, year of FDA approval)	Type	Indication	Patch design	Dose and size of patch – Delivery rate	Site of application	Duration of application
Buprenorphine (Butrans®, 2010)	Therapeutic	Chronic pain	DIA	5 mg in 20.25 (6.25)[a] cm^2 – 5 µg·h^{-1} 7.5 mg in 33.65 (7.5) cm^2 – 7.5 µg·h^{-1} 10 mg in 30.60 (12.5) cm^2 – 10 µg·h^{-1} 15 mg in 42.48 (18.75) cm^2 – 15 µg·h^{-1} 20 mg in 51.84 (25) cm^2 – 20 µg·h^{-1}	Upper outer arm, upper chest, upper back or the side of the chest	7 days
Clonidine (Catapres-TTS®, 1984)	Therapeutic	Hypertension	Reservoir/ Membrane	2.5 mg in 3.5 cm^2 – 0.1 mg·day^{-1} 5.0 mg in 7.0 cm^2 – 0.2 mg·day^{-1} 7.5 mg in 10.5 cm^2 – 0.3 mg·day^{-1}	Upper outer arm or upper chest	7 days
Oestradiol (Estraderm®, 1986)	Therapeutic	Female HRT	Reservoir/ Membrane	4 mg in 18 (10) cm^2 – 0.05 mg·day^{-1} 8 mg in 31 (20) cm^2 – 0.10 mg·day^{-1}	Trunk of the body including the buttocks and abdomen	3–4 days
Oestradiol (Climara®, 1994)	Therapeutic	Female HRT	DIA	2 mg in 6.5 cm^2 – 0.025 mg·day^{-1} 2.85 mg in 9.375 cm^2 – 0.0375 mg·day^{-1} 3.8 mg in 12.5 cm^2 – 0.05 mg·day^{-1} 4.55 mg in 15 cm^2 – 0.06 mg·day^{-1} 5.7 mg in 18.75 cm^2 – 0.075 mg·day^{-1} 7.6 mg in 25 cm^2 – 0.1 mg·day^{-1}	Lower abdomen or upper quadrant of the buttock	7 days
Oestradiol (Vivelle®, 1994)	Therapeutic	Female HRT	DIA	4.33 mg in 14.5 cm^2 – 0.05 mg·day^{-1} 8.66 mg in 29.0 cm^2 – 0.1 mg·day^{-1}	Trunk of the body including abdomen and buttocks	3–4 days
Oestradiol (Alora®, 1996)	Therapeutic	Female HRT	DIA	0.77 mg in 9 cm^2 – 0.025 mg·day^{-1} 1.5 mg in 18 cm^2 – 0.05 mg·day^{-1} 2.3 mg in 27 cm^2 – 0.075 mg·day^{-1} 3.1 mg in 36 cm^2 – 0.1 mg·day^{-1}	Lower abdomen, upper quadrant of the buttock or outer aspect of the hip	3–4 days
Oestradiol (Vivelle-Dot®, 1999)	Therapeutic	Female HRT	DIA	0.39 mg in 2.5 cm^2 – 0.025 mg·day^{-1} 0.585 mg in 3.75 cm^2 – 0.0375 mg·day^{-1} 0.78 mg in 5.0 cm^2 – 0.05 mg·day^{-1} 1.17 mg in 7.5 cm^2 – 0.075 mg·day^{-1} 1.56 mg in 10.0 cm^2 – 0.1 mg·day^{-1}	Lower abdomen	3–4 days
Oestradiol (Menostar®, 2004)	Therapeutic	Female HRT	DIA	1 mg in 3.25 cm^2 – 0.014 mg·day^{-1}	Lower abdomen	7 days
Oestradiol (Minivelle®, 2012)	Therapeutic	Female HRT	DIA	0.62 mg in 2.48 cm^2 – 0.0375 mg·day^{-1} 0.83 mg in 3.30 cm^2 – 0.05 mg·day^{-1} 1.24 mg in 4.95 cm^2 – 0.075 mg·day^{-1} 1.65 mg in 6.6 cm^2 – 0.1 mg·day^{-1}	Lower abdomen or buttocks	3–4 days
Oestradiol (E)/Norethindrone (NT) (Combipatch®, 1998)	Therapeutic	Female HRT	DIA	0.62 mg E/2.7 mg NT in 9 cm^2 – 0.05/0.14 mg E/NT per day 0.51 mg E/4.8 mg NT in 16 cm^2 – 0.05/0.25 mg E/NT per day	Lower abdomen	3–4 days
Ethinyl oestradiol (EE)/Norelgestromin (NL) (Ortho Evra®, 2001)	Therapeutic	Female contraception	DIA	0.75 mg EE/6.00 mg NL in 20 cm^2 – 0.035/0.15 mg EE/NL per day	Buttock, abdomen, upper outer arm or upper torso	7 days
Oestradiol (E)/Levonorgestrel (L) (Climara Pro®, 2003)	Therapeutic	Female HRT	DIA	4.40 mg E/1.39 mg L in 22 cm^2 – 0.045/0.015 mg E/L per day	Lower abdomen	7 days
Fentanyl (Duragesic®, 1990)	Therapeutic	Chronic pain	DIA[b]	2.1 mg in 5.25 cm^2 – 12.5 µg·h^{-1} 4.2 mg in 10.5 cm^2 – 25 µg·h^{-1} 8.4 mg in 21 cm^2 – 50 µg·h^{-1} 12.6 mg in 31.5 cm^2 – 75 µg·h^{-1} 16.8 mg in 42 cm^2 – 100 µg·h^{-1}	Chest, back, flank or upper arm	72 h
Granisetron (Sancuso®, 2008)	Therapeutic	Chemotherapy-induced nausea and vomiting	DIA	34.3 mg in 52 cm^2 – 3.1 mg per 24 h	Upper outer arm	Up to 7 days
Methylphenidate (Daytrana®, 2006)	Therapeutic	ADHD	DIA	27.5 mg in 12.5 cm^2 – 1.1 mg·h^{-1} 41.3 mg in 18.75 cm^2 – 1.6 mg·h^{-1} 55 mg in 25 cm^2 – 2.2 mg·h^{-1} 82.5 mg in 37.5 cm^2 – 3.3 mg·h^{-1}	Hip area, avoiding the waistline	Up to 9 h in a day
Nitroglycerin (Nitro-Dur®, 1995)	Therapeutic	Angina pectoris	DIA	20 mg in 5 cm^2 – 0.1 mg·h^{-1} 40 mg in 10 cm^2 – 0.2 mg·h^{-1} 60 mg in 15 cm^2 – 0.3 mg·h^{-1} 80 mg in 20 cm^2 – 0.4 mg·h^{-1} 120 mg in 30 cm^2 – 0.6 mg·h^{-1} 160 mg in 40 cm^2 – 0.8 mg·h^{-1}	Chest, shoulder, upper arm or back (hairless area)	12–14 h
Nitroglycerin (Minitran®, 1996)	Therapeutic	Angina pectoris	DIA	9 mg in 3.3 cm^2 – 0.1 mg·h^{-1} 18 mg in 6.7 cm^2 – 0.2 mg·h^{-1} 36 mg in 13.3 cm^2 – 0.4 mg·h^{-1} 54 mg in 20.0 cm^2 – 0.6 mg·h^{-1}	Chest, shoulder, upper arm or back (hairless area)	12–14 h

Table 2

Continued

Drug (Trade name, year of FDA approval)	Type	Indication	Patch design	Dose and size of patch – Delivery rate	Site of application	Duration of application
Oxybutynin (Oxytrol®, 2003)	Therapeutic	Overactive bladder	DIA	36 mg in 39 cm^2 – 3.9 $mg{\cdot}day^{-1}$	Abdomen, buttocks or hip	3–4 days
Rivastigmine (Exelon®, 2007)	Therapeutic	Alzheimer's and Parkinson's disease	Matrix	9 mg in 5 cm^2 – 4.6 mg per 24 h 18 mg in 10 cm^2 – 9.5 mg per 24 h 27 mg in 15 cm^2 – 13.3 mg per 24 h	Upper/lower back, upper arm or chest	24 h
Rotigotine[c] (Neupro®, 2007)	Therapeutic	Parkinson's disease Restless legs syndrome	DIA	2.25 mg in 5 cm^2 – 1 mg per 24 h (*) 4.5 mg in 10 cm^2 – 2 mg per 24 h 6.75 mg in 15 cm^2 – 3 mg per 24 h (*) 9 mg in 20 cm^2 – 4 mg per 24 h 13.5 mg in 30 cm^2 – 6 mg per 24 h 18 mg in 40 cm^2 – 8 mg per 24 h (*)	Abdomen, thigh, hip, flank, shoulder or upper arm	24 h
Scopolamine (Transderm Scōp®,1981)	Therapeutic	Motion sickness	Reservoir/Membrane	1.5 mg in 2.5 cm^2 – 1.0 mg per 3 days	Behind one ear	72 h
Selegiline (Emsam®, 2006)	Therapeutic	Major depressive disorder	DIA	20 mg in 20 cm^2 – 6 mg per 24 h 30 mg in 30 cm^2 – 9 mg per 24 h 40 mg in 40 cm^2 – 12 mg per 24 h	Upper chest or back, upper thigh or the outer surface of the upper arm	24 h
Testosterone[d] (Androderm®, 1995)	Therapeutic	Hypogonadism	Reservoir/Membrane	9.7 mg in 32 cm^2 (6) – 2 $mg{\cdot}day^{-1}$ (#) *12.2 mg in 37 cm^2 (7.5) – 2.5 $mg{\cdot}day^{-1}$* 19.5 mg in 39 cm^2 – (12) 4 $mg{\cdot}day^{-1}$ (#) *24.3 mg in 44 cm^2 – (15) 5 $mg{\cdot}day^{-1}$*	Back, abdomen, thighs or upper arm	24 h
Nicotine (Nicoderm CQ®, 1991)[e]	OTC	Smoking cessation	Reservoir/Membrane	36 mg in 7 cm^2 – 7 mg per 24 h 75 mg in 15 cm^2 – 14 mg per 24 h 114 mg in 22 cm^2 – 21 mg per 24 h	Anywhere on the body, avoiding joints	24 h
Nicotine (Nicorette®)[f]	OTC	Smoking cessation	Matrix	8.3 mg in 10 cm^2 – 5 mg per 16 h 16.6 mg in 20 cm^2 – 10 mg per 16 h 24.9 mg in 30 cm^2 – 15 mg per 16 h	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]	OTC	Smoking cessation	Matrix	15.75 mg in 9 cm^2 – 10 mg per 16 h 23.62 mg in 13.5 cm^2 – 15 mg per 16 h 39.7 mg in 22.5 cm^2 – 25 mg per 16 h	A clean, intact, dry and hairless skin of the thigh, arm or chest	16 h
Nicotine (Habitrol®, 1990)[g]	OTC	Smoking cessation	Matrix	17.5 mg in 10 cm^2 – 7 mg per 24 h 35 mg in 20 cm^2 – 14 mg per 24 h 52.5 mg in 30 cm^2 – 21 mg per 24 h	Upper body or the outer part of the arm	24 h
Sumatriptan (Zecuity®, 2013)	Active	Migraine	Iontophoretic system	36 mg in 7 cm^2 – 6.5 mg per 4 h	Upper arm or tight	4 h
Capsaicin (Qutenza®, 2009)	Topical	Neuropathic pain	DIA	179 mg in 280 cm^2 – *No information on delivery rate*	The most painful areas, excluding face and scalp	Single 60 min application of up to four patches
Diclofenac epolamine (Flector®, 2007)	Topical	Topical treatment acute pain	DIA	180 mg in 140 cm^2 *No information on delivery rate*	The most painful area	12 h
Lidocaine (Lidoderm®, 1999)	Topical	Post-herpetic neuralgia pain	DIA	700 mg in 140 cm^2 21 $mg{\cdot}12\ h^{-1}$	The most painful area, avoiding the 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)	Topical	Local dermal analgesia	Eutectic mixture – CHADD® technology	70 mg L per 70 mg T in 50 cm^2 – 1.7/1.6 mg L/T per 30 min	Site of venipuncture, i.v. cannulation or superficial dermatological procedure	20–30 min
Menthol (M)/Methyl salicylate (MS) (Salonpas®, 2008)	Topical	Muscles and joints pain	DIA	3% M/10% MS in 70 cm^2	The affected area	Up to 8–12 h
Oestradiol (Evamist®, 2007)[h]	Therapeutic	Menopausal symptoms	Cutaneous solution	1.53 mg per spray (90 µL)	The inside of the forearm between the elbow and the wrist	One spray once daily (starting dose)
Testosterone (Axiron®, 2010)[h]	Therapeutic	Hypogonadism	Cutaneous solution	30 mg per pump actuation	The axilla (armpit)	2 pump actions once daily (starting dose)

[a](*x*) Size of patch reported corresponds to the active surface except for Butrans, Estraderm and Androderm patches where both active and overall surface are reported. [b]Prior to July 2009, a reservoir/membrane patch design was on the market . Following numerous reports of deaths and life-threatening side effects due to a serious design defect of the reservoir patch (risk of drug leakage from the patches), the company moved to a DIA patch design. [c]In 2008, the product has been withdrawn from the US market due to the formation of rotigotine crystals in the patches and in 2012 Neupro was re-approved by the FDA with three new strengths (*). [d]In 2011, the two patch strengths available on the market were discontinued and replaced by two new smaller size and lower-dose patches (#) but not as a result of any safety or efficacy concerns. [e]Nicoderm CQ in the United States, NiQuitin® in the UK and Nicabate® in Australia. [f]Nicorette is not FDA approved and available in the UK. [g]Habitrol in the United States and Canada, Nicotinell® in the UK. [h]Evamist and Axiron are cutaneous solutions using the Patchless Patch® delivery method developed by Acrux Ltd. Data source: FDA (2014) and products' PI.
ADHD, attention deficit hyperactivity disorder; CHADD, controlled heat-aided drug delivery; HRT, hormone replacement therapy.

(1997) showed that a testosterone transdermal system (D-Trans testosterone gel system®) could be applied interchangeably to the skin of the upper buttocks, upper arms or upper back, giving similar drug plasma concentrations at three different skin sites ($AUC_{0–27}$, C_{max} parameters not significantly different). Further, the plasma concentrations of norelgestromin and ethinyl oestradiol after application of the contraceptive patch Ortho Evra® remained within the reference ranges during the wear-period after application on abdomen, buttock, arm and torso (Abrams *et al*., 2002). However, Lefèvre *et al*. (2007) showed a higher plasma exposure of rivastigmine ($AUC_{0–\infty}$ and $AUC_{0–last}$) after the application of Exelon® 8.5 mg per 24 h patch to the upper back, chest or upper arm rather than on the thigh and abdomen. Similarly, Taggart *et al*. (2000) showed that the extent of drug absorption ($AUC_{0–168}$ and $AUC_{0–last}$) from an oestradiol patch (Climara 0.1 mg per 24 h) application on buttock was significantly higher than when applied to the abdomen. However, the observed plasma drug concentrations for both sites were consistent with physiological oestradiol levels required for the relief of menopausal symptoms (Taggart *et al*., 2000). Finally, the systemic exposure of nicotine from Nicorette 15 mg per 16 h applied to the upper arm was higher compared with the abdomen but equivalent to the back (Sobue *et al*., 2005). Practically, transdermal systems should not be applied to the waistline as tight clothing may rub or remove the patch.

Safety

As discussed earlier, the safety ratio for the systemic percutaneous absorption of drugs presently marketed in patches relative to the maximum dose for that drug is usually at least 10 or more (Table 1). However, these safety ratios mainly relate to adult skin. Liebelt and Shannon (1993) pointed out that many commonly used over-the-counter (OTC) topical medications, including those containing methyl salicylate, camphor, topical imidazolines and benzocaine, can cause serious toxicity in children when ingested in small doses. Further, whereas the barrier function in full-term infants is fully developed, that in premature infants is incomplete (Fluhr *et al*., 2010; Delgado-Charro and Guy, 2014). Accordingly, transdermal administration has been used to deliver theophylline and caffeine in the premature infant, for whom dosing by conventional routes of administration can be difficult (Barrett and Rutter, 1994). However, this impaired skin barrier function in neonates also puts them more at risk (Kalia *et al*., 1998; Delgado-Charro and Guy, 2014) so that any unplanned percutaneous absorption in neonates is potentially hazardous (Rutter, 1987).

Transdermal patches have an additional drawback relative to other dosage forms and that is the potential for their ingredients, including both the active drug and the excipients, to induce adverse skin reactions, especially when the dosage form has prolonged contact with the skin for a long period of time. There are typically two types of skin reactions with patches: irritant contact dermatitis, which is the most common adverse effect associated with transdermal patch systems, and allergic contact dermatitis, which is infrequent (Ale *et al*., 2009). Most of the cutaneous adverse reactions reported in the literature with transdermal drug delivery systems have been induced by the drug itself, whereas the components of the patch (e.g. adhesive materials and chemical enhancers) have caused skin side effects to a lesser extent. Although generally mild and transient, these reactions can result in the discontinuation of the treatment by the patients (Murphy and Carmichael, 2000; Singh and Maibach, 2002). On the contrary, even the clonidine patch, with a noticeable degree of sensitization (Hogan and Maibach, 1990), is still well accepted and performs well in many patients.

Fentanyl patches have been a continual source for safety concerns. Duragesic was the first fentanyl patch to reach the market in 1990 and was characterized by a drug reservoir containing fentanyl and ethanol combined within a gel (Prodduturi *et al*., 2009).

Manufacturing defects (i.e. seal and membrane defects) with the possibility of dangerous drug leakage during use have led to patches being recalled in 2004 and 2008; as such leakage may expose patients to a potentially fatal overdose. The Duragesic leakage problem was addressed by a redesign of this patch to a DIA design in 2009 (Prodduturi *et al*., 2010). However, Oliveira *et al*. (2012) concluded that the possibility of fentanyl intoxication from the reservoir leakage of a commercially available fentanyl transdermal patch was unlikely to be toxic.

Fentanyl may also lead to patient issues as a result of the illicit use of fentanyl from these patches or after swallowing fentanyl patches. The US FDA issued Public Health Advisories in 2005 and 2007 to raise public awareness of the safe use of fentanyl patches and the dangers of accidental exposure (FDA, 2005; 2007) after receiving reports of death and life-threatening side effects in patients using brand name Duragesic and the generic product due to an inappropriate use (e.g. multiple patch application) (Edinboro *et al*., 1997). Table 3 describes the initial amount of fentanyl on supply and the anticipated residual amount of fentanyl in a patch at the end of an application period. Of particular concern is the risk of fatal exposure for young children who have swallowed or left fentanyl patches on their skin (Teske *et al*., 2007). As a consequence, the US FDA has reinforced education of patients and caregivers for a proper disposal of fentanyl patches after the reports of 26 cases of paediatric accidental exposure to fentanyl over the past 15 years, including 10 deaths and 12 hospitalizations (FDA, 2012a,c). The illicit use of fentanyl by recreational users is also of concern as fentanyl is 100 times more potent than morphine (Arvanitis and Satonik, 2002; Lilleng *et al*., 2004). Recreational users have extracted fentanyl from patches for subsequent injection (Firestone *et al*., 2009) and placed the patches into their mouth so that fentanyl can be absorbed through buccal mucosa (Nelson and Schwaner, 2009).

The US FDA, in a Drug Safety Communication, has recently alerted the public that certain OTC topical muscle and joint pain relievers may cause burns (FDA, 2012b), especially for OTC topical patches containing menthol as the single active ingredient at 3% or more and methyl salicylate combinations above 10%. Concerns have also been reported for capsaicin, which normally leads to local warmth or coolness but no burns.

The presence of metals (e.g. aluminium) in the backing layer of certain transdermal patches such as Catapres-TTS, Habitrol, Nicotine CQ®, Neupro® and Transderm Scōp can pose safety concerns for patients undergoing an MRI scan

Table 3

Drug utilization rate and residual amount of drug after use of recently approved, fentanyl and nicotine transdermal patches

Drug (Trade name, year of FDA approval)	Patch design	Dose and size of patch – Delivery rate	Drug utilization rate (%)[a]	Residual amount of drug in the patch (mg)[b]	Patch area activity (%·cm^{-2})[c]
Methylphenidate (Daytrana®, 2006)	DIA	27.5 mg in 12.5 cm^2 – 1.1 mg·h^{-1}	36	17.6	2.9
		41.3 mg in 18.75 cm^2 – 1.6 mg·h^{-1}	34.9	26.9	1.9
		55 mg in 25 cm^2 – 2.2 mg·h^{-1}	36	35.2	1.4
		82.5 mg in 37.5 cm^2 – 3.3 mg·h^{-1}	36	52.8	1
Selegiline (Emsam®, 2006)	DIA	20 mg in 20 cm^2 – 6 mg per 24 h	30	14	1.5
		30 mg in 30 cm^2 – 9 mg per 24 h	30	21	1
		40 mg in 40 cm^2 – 12 mg per 24 h	30	28	0.75
Rivastigmine (Exelon®, 2007)	Matrix	9 mg in 5 cm^2 – 4.6 mg per 24 h	51.1	4.4	10.2
		18 mg in 10 cm^2 – 9.5 mg per 24 h	52.8	8.5	5.3
		27 mg in 15 cm^2 – 13.3 mg per 24 h	49.3	13.7	3.3
Rotigotine (Neupro®, 2007)	DIA	2.25 mg in 5 cm^2 – 1 mg per 24 h	44.4	1.25	8.9
		4.5 mg in 10 cm^2 – 2 mg per 24 h	44.4	2.5	4.4
		6.75 mg in 15 cm^2 – 3 mg per 24 h	44.4	3.75	3
		9 mg in 20 cm^2 – 4 mg per 24 h	44.4	5	2.2
		13.5 mg in 30 cm^2 – 6 mg per 24 h	44.4	7.5	1.5
		18 mg in 40 cm^2 – 8 mg per 24 h	44.4	10	1.1
Granisetron (Sancuso®, 2008)	DIA	34.3 mg in 52 cm^2 – 3.1 mg per 24 h	63.3	12.6	1.2
Buprenorphine (Butrans®, 2010)	DIA	5 mg in 6.25 cm^2 – 5 µg·h^{-1}	16.8	4.26	2.7
		7.5 mg in 7.5 cm^2 – 7.5 µg·h^{-1}	16.8	6.24	2.2
		10 mg in 12.5 cm^2 – 10 µg·h^{-1}	16.8	8.32	1.3
		15 mg in 18.75 cm^2 – 15 µg·h^{-1}	16.8	12.48	0.9
		20 mg in 25 cm^2 – 20 µg·h^{-1}	16.8	16.64	0.7
Oestradiol (Minivelle®, 2012)	DIA	0.62 mg in 2.48 cm^2 – 0.0375 mg·day^{-1}	21.17	0.49	8.5
		0.83 mg in 3.30 cm^2 – 0.05 mg·day^{-1}	21.1	0.66	6.4
		1.24 mg in 4.95 cm^2 – 0.075 mg·day^{-1}	21.17	0.98	4.3
		1.65 mg in 6.6 cm^2 – 0.1 mg·day^{-1}	21.21	1.3	3.2
Fentanyl (Duragesic®, 1990) *discontinued*	Reservoir/ Membrane	1.25 mg in 5 cm^2 – 12.5 µg·h^{-1}	72	0.35	14.4
		2.5 mg in 10 cm^2 – 25 µg·h^{-1}	72	0.7	7.2
		5 mg in 20 cm^2 – 50 µg·h^{-1}	72	1.4	3.6
		7.5 mg in 30 cm^2 – 75 µg·h^{-1}	72	2.1	2.4
		10 mg in 40 cm^2 – 100 µg·h^{-1}	72	2.8	1.8
Fentanyl (Mylan FTS, 2005)	DIA	1.28 mg in 3.13 cm^2 – 12.5 µg·h^{-1}	70.3	0.38	22.5
		2.55 mg in 6.25 cm^2 – 25 µg·h^{-1}	70.6	0.75	11.3
		5.10 mg in 12.5 cm^2 – 50 µg·h^{-1}	70.6	1.5	5.6
		7.65 mg in 18.75 cm^2 – 75 µg·h^{-1}	70.6	2.25	3.8
		10.20 mg in 25 cm^2 – 100 µg·h^{-1}	70.6	3	2.8
Fentanyl (Lavipharm Labs FTS, 2006)	DIA	1.375 mg in 5 cm^2 – 12 µg·h^{-1}	62.8	0.51	12.6
		2.75 mg in 10 cm^2 – 25 µg·h^{-1}	65.4	0.95	6.5
		5.5 mg in 20 cm^2 – 50 µg·h^{-1}	65.4	1.9	3.3
		8.25 mg in 30 cm^2 – 75 µg·h^{-1}	65.4	2.85	2.2
		11.0 mg in 40 cm^2 – 100 µg·h^{-1}	65.4	3.8	1.6
Fentanyl (Par Pharm FTS, 2007)	Reservoir/Membrane	2.5 mg in 10 cm^2 – 25 µg·h^{-1}	72	0.7	7.2
		5 mg in 20 cm^2 – 50 µg·h^{-1}	72	1.4	3.6
		7.5 mg in 30 cm^2 – 75 µg·h^{-1}	72	2.1	2.4
		10 mg in 40 cm^2 – 100 µg·h^{-1}	72	2.8	1.8
Fentanyl (Watson FTS, 2007)	Reservoir/Membrane	2.5 mg in 10 cm^2 – 25 µg·h^{-1}	72	0.7	7.2
		5 mg in 20 cm^2 – 50 µg·h^{-1}	72	1.4	3.6
		7.5 mg in 30 cm^2 – 75 µg·h^{-1}	72	2.1	2.4
		10 mg in 40 cm^2 – 100 µg·h^{-1}	72	2.8	1.8

Table 3

Continued

Drug (Trade name, year of FDA approval)	Patch design	Dose and size of patch – Delivery rate	Drug utilization rate (%)[a]	Residual amount of drug in the patch (mg)[b]	Patch area activity ($\%\cdot cm^{-2}$)[c]
Fentanyl (Aveva FTS, 2008)	DIA	2.76 mg in 10.7 cm^2 – 25 $\mu g\cdot h^{-1}$	65.2	0.96	6.1
		5.52 mg in 21.4 cm^2 – 50 $\mu g\cdot h^{-1}$	65.2	1.92	3
		8.28 mg in 32.1 cm^2 – 75 $\mu g\cdot h^{-1}$	65.2	2.88	2
		11.04 mg in 42.8 cm^2 – 100 $\mu g\cdot h^{-1}$	65.2	3.84	1.5
Fentanyl (Duragesic®, 2009)	DIA	2.1 mg in 5.25 cm^2 – 12.5 $\mu g\cdot h^{-1}$	42.9	1.2	8.2
		4.2 mg in 10.5 cm^2 – 25 $\mu g\cdot h^{-1}$	42.9	2.4	4.1
		8.4 mg in 21 cm^2 – 50 $\mu g\cdot h^{-1}$	42.9	4.8	2
		12.6 mg in 31.5 cm^2 – 75 $\mu g\cdot h^{-1}$	42.9	7.2	1.4
		16.8 mg in 42 cm^2 – 100 $\mu g\cdot h$	42.9	9.6	1
Fentanyl (Noven TTS, 2009) *discontinued*	DIA	2.55 mg in 19 cm^2 – 25 $\mu g\cdot h^{-1}$	70.6	0.75	3.7
		5.10 mg in 38 cm^2 – 50 $\mu g\cdot h^{-1}$	70.6	1.5	1.9
		7.65 mg in 57 cm^2 – 75 $\mu g\cdot h^{-1}$	70.6	2.25	1.2
		10.20 mg in 76 cm^2 – 100 $\mu g\cdot h^{-1}$	70.6	3	0.9
Fentanyl (Mallinckrodt FTS, 2011)	Reservoir/Membrane	2.75 mg in 7.8 cm^2 – 25 $\mu g\cdot h^{-1}$	65.5	0.95	8.4
		5.50 mg in 15.6 cm^2 – 50 $\mu g\cdot h^{-1}$	65.5	1.9	4.2
		8.25 mg in 23.4 cm^2 – 75 $\mu g\cdot h^{-1}$	65.5	2.85	2.8
		11.0 mg in 31.2 cm^2 – 100 $\mu g\cdot h^{-1}$	65.5	3.8	2.1
Nicotine (Nicoderm CQ®, 1991)	Reservoir/Matrix	36 mg in 7 cm^2 – 7 mg per 24 h	19.4	29	2.8
		75 mg in 15 cm^2 – 14 mg per 24 h	18.7	61	1.2
		114 mg in 22 cm^2 – 21 mg per 24 h	18.4	93	0.8
Nicotine (Habitrol®, 1991)	Matrix	17.5 mg in 10 cm^2 – 7 mg per 24 h	40	10.5	4
		35 mg in 20 cm^2 – 14 mg per 24 h	40	21	2
		52.5 mg in 30 cm^2 – 21 mg per 24 h	40	31.5	1.3
Nicotine (Prostep®, 1992) *discontinued*	Matrix	15 mg in 24 (3.5) cm^2 – 11 mg per 24 h	73.3	4	20.9
		30 mg in 32 (7) cm^2 – 22 mg per 24 h	73.3	8	10.5
Nicotine (Nicotrol®, 1992) *discontinued*	DIA	8.3 mg in 10 cm^2 – 5 mg per 16 h	60.2	3.3	6
		16.6 mg in 20 cm^2 – 10 mg per 16 h	60.2	6.6	3
		24.9 mg in 30 cm^2 – 15 mg per 16 h	60.2	9.9	2

For instance, the rivastigmine transdermal patch (Exelon) dosage strength 4.6 mg per 24 h, application time 24 h, patch size (active surface) 5 cm^2, overall amount of drug substance incorporated into the patch 9 mg. Drug utilization = 4.6 mg; drug utilization rate = 4.6/9 ≈ 50%; residual amount = 9 – 4.6 = 4.4 mg; patch area activity = 50/5 ≈ 10%$\cdot cm^{-2}$. When the patch has to be applied twice weekly (every 3–4 days), t = 3.5 days is considered for calculation.
[a]Drug utilization rate (%) = (delivery rate × duration of application)/drug content. [b]Residual amount (mg) = drug content – drug utilization. [c]Patch area activity ($\%\cdot cm^{-2}$) = drug utilization rate/patch size – 'it is a measure of the formulation's intrinsic capability to release drug substance from the patch *in vivo* and as such a surrogate measurement of thermodynamic activity' (EMEA, 2012).

(Ball and Smith, 2008; Durand *et al.*, 2012). Skin burns have been reported at the patch site in several patients wearing an aluminized transdermal system during these types of procedures (Hong *et al.*, 2010). Consequently, safe practice recommendations have been issued and the temporary removal of the transdermal system before such procedures may be the safest approach (FDA, 2009a; Kanal *et al.*, 2013). Nowadays, most patches contain no conducting metal surfaces.

The prescribing information (PI) of recently approved transdermal patches, such as Butrans®, Exelon and Neupro, warns patients to avoid exposing the application site and surrounding area to direct external heat sources (e.g. heating pads, electric blankets, sunbathing, heat or tanning lamps, saunas, hot tubs or hot baths and heated water beds) while wearing the patch. In theory, fever could also result in an increase in plasma drug concentration due to temperature-dependent increases in drug release from the transdermal patch. In an open, randomized crossover study with 12 healthy smokers, Vanakoski *et al.* (1996) showed that a sauna significantly increased the amount of nicotine absorbed (P < 0.01) and transiently increased plasma drug concentration (C_{max} and $AUC_{0–1}$ significantly higher in the sauna session, P < 0.01) from nicotine transdermal patches (Nicorette) without adverse symptoms. Fentanyl overdoses have been described in case reports in which a fentanyl patch was covered by a warming blanket (Frolich *et al.*, 2001) or a heating pad (Rose *et al.*, 1993).

Regulatory

Three types of studies are normally used to evaluate a finished transdermal patch product: product quality tests, *in vitro* drug product performance tests and *in vivo* drug product performance test. The product quality attributes typically include description (visual examination of the patch), identification, assay (content of drug product), impurities, dosage form uniformity, residual solvent levels, cold flow property (adhesive migration out of the edge of the patch during storage or when the patch is applied to the patient), polymorphism and microbial limits. Other quality attributes may be product-specific such as water content (for hydroalcoholic reservoir patches), particle size (when the drug substance is suspended in the patch), crystal formation test (when a patch contains dissolved drug substance) and leak test (for liquid reservoir patch) (Van Buskirk *et al.*, 2012; USP, 2014a).

Crystallization is a particular problem that may arise from supersaturated systems that are thermodynamically unstable and where drug may potentially crystallize out during storage. Crystallization was first observed with scopolamine patches in the late 1980s when the previously liquid base showed up instantly as crystalline hydrates (Campbell *et al.*, 1989b). Later, more stable but less soluble and permeable polymorphic semi-hydrate oestradiol crystals could be generated in the presence of ambient humidity for any marketed oestradiol patch (Horstmann *et al.*, 1998; Muller and Horstmann, 1999). The formation of 'snowflake' crystals in rotigotine transdermal patches led to the withdrawal of the product from some markets, underlining the severe impact that crystallization can have on a patch formulation (Chaudhuri, 2008; Waters, 2013). Low MW surfactants (e.g. Cremophor®), co-polymers of methacrylic (e.g. Eudragit®) (Kotiyan and Vavia, 2001; Cilurzo *et al.*, 2005) and polyvinylpyrrolidone (Jain and Banga, 2012) are now often included in patches as crystallization inhibitors.

In vitro drug product performance usually involves three tests: *in vitro* drug release, *in vitro* skin permeation studies and *in vitro* adhesive tests. *In vitro* drug release tests evaluate the rate and the extent of release of drug from a transdermal patch as described in both European Pharmacopoeia (Ph Eur) and USP, including the paddle over disk method (USP Apparatus 5/Ph Eur 2.9.4.1), the rotating cylinder method (USP Appartus 6/Ph Eur 2.9.4.3) and the reciprocating holder method (USP Apparatus 7) (USP, 2014b; Ph Eur, 2015). The Organization for Economic Cooperation and Development and the European Medicine Agency (EMEA) provides guidance documents on the performance of *in vitro* permeation studies to evaluate the rate of transport (Organization for Economic Cooperation and Development, 2004; EMEA, 2012). Four tests are generally used to evaluate *in vitro* adhesive properties: the liner release test (force required to remove the liner from the adhesive prior to application of the patch, to determine the feasibility of removal by the patient), the probe tack test (ability of the adhesive to adhere to the surface with minimal contact pressure), the peel adhesion test (force required to peel away an adhesive after it has been attached to the substrate) and the shear test (static or dynamic) (the internal or cohesive strength of the adhesive) (Venkatraman and Gale, 1998; Mausar, 2011; Banerjee *et al.*, 2014). Stainless steel remains the preferred substrate used for *in vitro* testing as it represents an acceptable alternative to human skin, which usually poses ethical issues, restricted availability (Cilurzo *et al.*, 2012) and high variability. An ideal PSA used as part of a transdermal patch, (i) allows easy removal of the (properly selected) protective liner of the patch before use; (ii) has an initial affinity for human skin; (iii) adheres properly to human skin upon application; (iv) remains in place on the skin surface during the whole labelled wear-period; and (v) permits easy and clean removal of the patch after the period of use (Mausar, 2011; Van Buskirk *et al.*, 2012).

In vivo drug product performance pharmacokinetic and *in vivo* adhesive performances are usually conducted in parallel. Clinical studies should determine the pharmacokinetic parameters – C_{max}, T_{max}, $AUC_{0-\infty}$ and AUC_{0-last} (EMEA, 2012) – and the percentage of the patch area that remains attached to the skin throughout the proposed period of use should be assessed with an expectation of a mean adherence greater than 90% (Minghetti *et al.*, 2004; EMEA, 2012). In principle, the most probable pharmacokinetic parameters for a new active in a patch can be estimated from a predicted delivery rate of the drug from patches as defined in Figure 4 and the drug pharmacokinetics *in vivo*. However, as shown in the recent correspondence on attempts to estimate steady-state transdermal patch structure–activity relationships based upon observed drug plasma concentrations, care is required in (i) the choice of physicochemical values, such as aqueous solubility, in calculations, regression models; (ii) identification of the role of rate-controlling membranes and/or enhancer effects, prediction of clearance and dose duration; and (iii) last but not least, consistency of units (Maibach and Farahmand, 2009a,b; Kissel and Bunge, 2010).

Another key regulatory aspect is the amount of unused drug left in the patch when it is removed from the skin, as defined by the FDA's guidance in August 2011 on Residual Drug in Transdermal and Related Drug Delivery Systems (FDA, 2011). The drug utilization rate and residual amount of drug after use in various marketed patches, in addition to fentanyl discussed earlier, are summarized in Table 3. Transdermal patches retain up to 95% of the initial total amount of drug after the intended wearing period (e.g. oestradiol patches). Alza's nicotine (membrane/reservoir) patch delivers only 18% of the nicotine contained, whereas LTS's construction delivers 40% and the PIB formula of Cygnus even reached 60%.

Future prospects of transdermal patches and transdermal drug delivery systems

In 2013, four drugs (oestradiol, fentanyl, nicotine and testosterone) accounted for around 50% of all transdermal clinical trials (463) listed on ClinicalTrials.gov (Watkinson, 2013). Of all the drugs contained in marketed transdermal patches, rotigotine is the only active compound that was originally developed to be administered via the transdermal route (McAfee *et al.*, 2014). We began this review with a discussion of the original solution and semi-solid products for topical and transdermal delivery. Watkinson (2012) pointed out that there are at least nine non-occlusive passive transdermal products, including the 1988 approved Nitro-Bid nitroglycerin ointment (Fougera) delivering about 7.5 mg per dose and contrasting with the 0.2% nitroglycerin ointment used for anal fissures, a range of oestradiol products (Estrasorb®, Estragel®, Elestrin, Divigel and Evamist®, approved in 2003, 2004, 2006, 2007 and 2007, respectively) and oxybutynin (Gelnique®, approved in 2009). In addition, the bulk of the

$2.15 billion testosterone market at the end of 2013 were cutaneous solutions (including gels), consisting of Androgel® ~ 66% (approved in 2000), Axiron® ~ 12.6% (approved in 2010), Testim® gel ~12.6% (approved in 2002) and Fortesta® gel ~5.6% (approved in 2010) with the patch, Androderm, at ~3.2% (Acrux Ltd, 2014). Importantly, two testosterone replacement gels, Androgel and Testim, now carry FDA's strongest black-box warning for secondary exposure in children to application sites, left over gel and unwashed linen (FDA, 2009b). In this context, it is of note that two systems, developed by Acrux Ltd., use a 'no-touch' metered-dose pump technology: Evamist (oestradiol) (Figure 1L) and Axiron (testosterone) (Perumal *et al.*, 2013).

Today, there is a move towards 'active' transdermal delivery systems that use non- and minimally invasive technologies, such as iontophoresis, microneedles, electroporation and sonophoresis, to enhance drug delivery across the skin as well as challenging drug candidates, such as actives that have a low penetration flux and low potency (Naik *et al.*, 2000; Gratieri *et al.*, 2013). The development of active patches has however been associated with much false hope with initial commercial success being hampered by commercial, technical and consumer issues (Watkinson, 2012). This history is probably best illustrated by the mixed success so far in achieving painless local anaesthesia with lidocaine. One of the first FDA-approved topical (local) iontophoretic patch system, Iontocaine® from Iomed (Salt Lake City, UT, USA), was approved in 1995 and discontinued in 2005. This was followed by ultrasound Sonoprep® and iontophoretic LidoSite® both approved in 2004 but discontinued in 2007 and 2008, respectively, and then by the i.d. powder injector Zingo® that was approved in 2008, withdrawn in 2008 and re-launched in September 2014 (Marathon Pharmaceuticals News, 2014). The failed iontophoretic GlucoWatch Biographer® is the only non-invasive glucose monitor to have been approved by the FDA (Wiedersberg and Guy, 2014). The only success story appears to be Synera® (Zars Pharma, now Nuvo Research), a heat-activated topical lidocaine/tetracaine patch, approved in 2005 and still on the market (Synera, 2014). Transdermal systems also face challenges as illustrated by the transdermal iontophoretic patch, Ionsys®, approved in 2006 for the systemic delivery of fentanyl for fast relief of post-operative pain. Ionsys was initially suspended by the EMEA in November 2008 due to patch corrosion, which could potentially lead to self-activation of the system and a potential overdose (Watkinson, 2012; Li *et al.*, 2013). Its safety features are now being revamped by Incline Therapeutics ($43 million Series A funding) to be launched in the United States in 2014–2016 (The Medicines Company, 2012; Watkinson, 2012). Much hope therefore rests with Zecuity® (NuPathe, now Teva) (Figure 1M), which uses iontophoresis to actively deliver sumatriptan through the skin to manage the migraine-related nausea and vomiting that can limit p.o. dosing (Goldstein *et al.*, 2012; Smith *et al.*, 2012).

The most recent 'hype' for a drug delivery system is the use of microneedles with the main focus being on single-dose vaccine delivery (Quinn *et al.*, 2014). For instance, the Nanopatch® (Figure 1N) required a second-order lower dose of antigen to be delivered to the skin to achieve antibody responses comparable to conventional i.m. injection (Fernando *et al.*, 2010). The use of microneedles for long-term treatment has also been recently investigated for the treatment of opiate and alcohol dependence with naltrexone, an opioid antagonist (Wermeling *et al.*, 2008). A parathyroid hormone (1–34)-coated microneedle patch, developed by Zosano Pharma (formerly, Macroflux® Alza Corporation) for the treatment of osteoporosis, has been shown to be efficacious in a Phase II clinical trial (Daddona *et al.*, 2011). A key question asked by Wiedersberg and Guy (2014), concluding a review on these technologies, is: 'where is the obvious unmet medical need that microneedles (or indeed any of the poration approaches) can address better, more reliably and safer than a conventional needle-and syringe?'.

Finally, transdermal delivery systems, particularly transdermal patches, are increasingly being used in the paediatric population. A range of transdermal patches (i.e. about 10 drugs) have been used in children and some have been specifically developed for paediatric use, as illustrated by the methylphenidate patch for the treatment of attention deficit hyperactivity disorder. However, while transdermal delivery can be regarded as a convenient non-invasive method of drug delivery for term infants and older children requiring smaller doses than adults, formulation challenges remain for premature neonates with an immature skin barrier (Delgado-Charro and Guy, 2014).

Conclusions

Topical delivery systems have been used for various ailments and as cosmetics since the arrival of man. Over time, there has been a definition of suitable drug candidates for transdermal delivery and the associated development of technologies, both passive and active, that has led to delivery enhancement, precision in drug dosing and a better meeting of individual needs. A focus in the further development of drugs in transdermal patches and associated delivery forms remains the finding of sufficiently potent drugs that can penetrate the skin with an appropriate transdermal technology. A key challenge is to meet clinical and cosmetic needs, which cannot be appropriately met in a cost-effective manner through other routes of delivery.

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Conflict of interest

The authors disclose no potential conflicts of interest.

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