Transdermal patches: history, development and pharmacology

Abbreviated title: History of transdermal patches

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Abbreviations:
ADHD (Attention Deficit Hyperactivity Disorder)
CHADD (Controlled Heat-Aided Drug Delivery)
DIA (Drug-In-Adhesive)
EMEA (European Medicine Agency)
FDA (Food and Drug Administration)
HRT (Hormone Replacement Therapy)
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)

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Abstract
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, 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.
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 common practice in the latter third of the 20$^{th}$ century when delivery technology was developed to enable precise and reproducible administration through the skin for systemic effects.

The goal of this paper is to detail the rich history of topical and transdermal delivery that has evolved over thousands of years, focussing 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 oral 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, though 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 1-A) 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 almonds, peppermint and rosemary) and other ingredients to make their cosmetic and dermatological products (unguents, creams, pomades, rouges, powders, eye-paints 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 pain 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 on 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 concentration with skin cells produced nitric oxide (Tapsoba et al., 2010), that 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 tape-worm (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 before 1400 BC (Kremers, 1976).

A millennium and a half later, Galen (129-199 AD), 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 1-B), 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) in 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 (980-1037AD), 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 while 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 systemically 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 the formulation in place. This product was used to treat sciatica, i.e. 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 1-C) (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.

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. Individualised delivery system: nitroglycerin ointment; G. Topical delivery device (Wurster & Kramer’s system); H. First patch system – the reservoir – introduced for scopolamine, nitroglycerin, clonidine and estradiol; I., J., K. Other types of patches – matrix and drug-in-adhesive (e.g. fentanyl and nicotine 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 late 19th century as a phase of “non-belief” in transdermal products

The German Pharmacopoeia 1872, a compilation produced in Latin, listed 28 Emplastrum formulae. These included: adhesive products (e.g., Emplastrum adhaesivum, that contained oleic acid, lead oxide, colophony, Emplastrum adhaesivum anglicum, a hydrophilic formula); products meant to produce systemic effects (e.g., Emplastrum aromaticum that contained peppermint and other aromatic oils targeted for the treatment of the stomach, Emplastrum belladonnae (Figure 1-D), from Atropa belladonna leaves, meant for the treatment of tuberculosis and tumours, Emplastrum opiatum to reduce stomach movement and associated pain, Emplastrum conii containing Conium maculatum (poison hemlock as used by Socrates) that 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® 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 1860-70s (Morgan, 1866; Harrison, 1872).

Development of topical products in the 20th Century

In 1904, Schwenkenbecker generalised 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) emphasised the potential lethal consequences associated with accidental “over-exposure” 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 Elliot, 1917). Later more accurate analytical methods (e.g. using a calibrated capillary tube) enabled the quantitative determination of 5 mg of mercury in 1 litre 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 in an ointment to the skin of castrated male guinea pigs were shown to be readily absorbed since the accessory reproductive organs remained functional (Moore et al., 1938). Similarly, the application of oestrogen to the shaven back skin of ovariectomised 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 acetylcholine 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 on the amount of mercurial ointment recovered after scraping a defined skin surface area with a pre-weighed razor blade, i.e. 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 above, 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 diiodofluorescein (¹³¹I) 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 seventy years ago. He reported that chloroxylenol, an external disinfectant still present in antiseptic soaps and solutions today (Dettol®), could be effective in the treatment of urogenital infections when topically applied as a 30 % lanolin ointment (Figure 1-E) (Zondek, 1942a; Zondek, 1942b). Interestingly, the potential percutaneous absorption of the drugs now found in many of our current transdermal products have 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; Laws, 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 blood pressure...
and pulse rate), with volunteers eventually showing an acquired tolerance to headache effects after an average of 38 hours (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) 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 hours (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; Gehlbach et al., 1975). The percutaneous absorption of estrogens was discovered in the 1940s when men working in stilboestrol plants began lactating (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 1-G) 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 on 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 oral 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” was 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 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 ten drugs thought to have potential for the method (Michaels et al., 1975). Of the drugs studied, scopolamine, nitroglycerin, estradiol 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, oral administration of 0.6 mg 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®), 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 United States soldiers suffering seasickness whilst sailing to Germany and found to be effective within 1 hour 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 hours 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; Shaw et al., 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 on 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 got sick while most of those wearing the scopolamine patch did not (Hoffman, 2008). Controlled trials were then conducted as part of the program for the American Spacelab missions; these demonstrated the efficacy of the transdermal scopolamine system (Graybriel et al., 1976;
Graybriel, 1979; Graybriel et al., 1981). 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®) 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 to placebo and oral 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 oral sustained release capsule dose forms (Maier-Lenz et al., 1980), the plasma levels were dependent on 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 %), used in clinical trials were determined using a ruler to define the length of ointment ribbon ejected from the ointment tube (Figure 1-F) and ranged from 1.3 cm (1/2 inch; 7.5 mg) to 5.1 cm (2 inches; 30 mg), typically applied to 232 cm$^2$ (36 square inches) of skin on the trunk of the body. An additional limitation of semi-solids is the need for frequent dosing, e.g. every 8 hours 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 volatilisation 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 on 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 80’s, 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 learned in clinical studies that nitroglycerin inactivated itself upon sustained delivery, each marketed patch was to be applied once daily with an approximately 12 hours “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 µg.cm$^{-2}$.h$^{-1}$ (preferably in the range 50-150 µg.cm$^{-2}$.h$^{-1}$) greater than the prior art (Gale and Berggren, 1986a). In the US, 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 one 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, 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 blood pressure 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 oral 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 µg.cm⁻².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 oral administration in decreasing blood pressure 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 estradiol for female hormone replacement therapy

Cutaneous application of follicular hormone (follicle-stimulating hormone), oestrone, for amenorrhoea was introduced in 1938 by Zondek (Zondek, 1938). In 1960, 2 g of an ointment containing both radiolabeled estradiol-17β and progesterone were applied to human subjects. Between 16.5 to 44% of the radioactivity appeared in the urine within 72 hours (Goldzieher and Baker, 1960). Estradiol 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 estradiol within a vehicle rich in ethanol, the latter used as a percutaneous absorption enhancer (Campbell and Chandrasekeran, 1983). A microporous polymer film membrane was used to maintain the fluxes of estradiol and ethanol in the vicinity of 0.1 µg.cm⁻².h⁻¹ and 400 µg.cm⁻².h⁻¹, respectively. The sustained plasma levels of estradiol obtained with the device overcame the key peak and trough profile limitation of the then marketed estradiol ointment (Strecker et al., 1979). In 1984, the first transdermal estradiol system reached the US market. Its application resulted in circulating estradiol plasma levels (40-60 pg.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 oral estrogen treatment (i.e. reduction in daily dose required, limited effects on liver function) (Laufer et al., 1983; Powers et al., 1985). Eventually, patches with estradiol 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 the Elestrin® (estradiol 0.06 % in a hydroalcoholic gel base)
packaged as 100 doses each of 0.87 g gel and Divigel® packaged 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 estradiol,
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 to 3.8 µg.cm⁻².h⁻¹
(average, 2 µg.cm⁻².h⁻¹) at 30 °C. A 1986 US patent, disclosing various transdermal system
designs with different sizes (5-100 cm²) for the delivery of the free base of the narcotic
fentanyl, observed that in vitro skin penetration rates of 0.5 to 10 µg.cm⁻².h⁻¹ could be
maintained for at least 12 hours and for up to 7 days (Gale et al., 1986b). The system’s in vivo
delivery of fentanyl citrate and base (and sufentanil citrate and base) through the skin
was demonstrated applying 50 µg of drug in water to the forearm skin of 5 volunteers (6
volunteers for sufentanil) under an occlusive dressing and showing that about 20 % of the
absorbed dose was recovered in urine after 24 hours (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; Roy and Flynn, 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, whilst 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),

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
minutes 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 systolic
blood pressure (Rose et al., 1984). A follow-up study showed a reduced craving in 10
cigarette smokers after application of 8 mg 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 minutes, 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 hours (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 males to their female sexual partners were reported, resulting in precocious puberty or pronounced virilisation (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; Campbell et al., 1989a). However, Ahmed et al. (1988) reported high serum dihydrotestosterone levels after scrotal application. 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®) 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; Keith and Snipes, 1981c). 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,
Despite encouraging results in healthy volunteers, neither a transdermal timolol ointment (Vlasses et al., 1985) nor a transdermal timolol patch (Kubota et al., 1993) have 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 oral first pass chemical or enzymatic degradation in the gastrointestinal tract or liver. Transdermal delivery is therefore of particular interest for molecules with limited systemic (oral) 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 on 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 emphasised 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-limiting membrane pioneered in the early 1970s by the entrepreneur Alejandro Zaffaroni through his company Alza. His first commercialised TTS was a scopolamine TTS. Alza championed the view that the coexistence of a reservoir and a rate-limiting membrane in their system was a key requirement to minimise 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 minimised undesired central nervous system adverse events such as drowsiness and confusion (Shaw and Urquhart, 1979). A patent filled in August 1971 (US 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 1-H. 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 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 2-A and B show, 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 on 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. A major limitation in this system is potential for leakage from its sealed liquid reservoir that could eventuate 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 2000’s. Figure 2-C 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 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.

**Figure 2.** Manufacturing process for and potential failures of reservoir patches: A. Form-filling and sealing process. B. Coating and drying process. C. Potential problems arising during patch reservoir manufacturing process.
Early on Alza created an estradiol patch intended to yield a constant flux of estradiol over 4 days, in which the reservoir contained estradiol in an ethanolic solution. However, an unexpected estradiol 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 estradiol 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 estradiol in the reservoir solution was reduced by the formation of estradiol hemihydrates and its crystallising 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 on an intrinsic variability in the transdermal flux of nitroglycerin through human skin in vivo being 46% (based on the variability in the nitroglycerin lost from a transdermal ointment applied to 12 volunteers for 24 hours) 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, one inch 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 mm Hg in systolic blood pressure (Thadani et al., 1986). The variability in maximum tolerated doses of nitroglycerin after intravenous 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 maximise its thermodynamic activity and enhance skin penetration as well as enabling its membrane barrier to partly control the release of fentanyl into the skin (Gale et al., 1986b; Santos 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, that 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, estradiol 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 both overcame the Alza intellectual property ownership in the liquid reservoir/rate-controlling membrane design and most of the limitations detailed herein associated with that design.

**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 ( ).

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 1-I 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 on just how any such 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 which 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 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 to 30 % by weight) (Stricker, 1983). A transdermal tape, where nitroglycerin (25 to 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, 1993b). 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 material. It was realised that the DIA could be loaded onto the patch backing in the same way (Cleary GW personal communication to Roberts MS, 8th World Congress on Clinical Pharmacology and Therapeutics, Brisbane, 1-6 August 2004). The DIA patch design is illustrated in Figure 1-K.

However, whilst 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 characterised 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, characterised 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 to 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 on 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: Transderm-Nitro® 45 %, Nitro-Dur II® 13 %, Minitran® 28 % and Deponit® 87 %.
In conclusion, the design of all transdermal patches is characterised 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 which 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). Whilst 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 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 % 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 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 patch data fall within boundaries derived using a similar single pathway model 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 Figure 4 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.

**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: \( \log \text{ maximum delivery rate (µg.cm}^{-2}.\text{h}^{-1}) = 1.6 + \log MW - 0.0086 MW - 0.01 (MP - 25) - 0.219 \log P \) and is based on a regression of maximum transdermal flux (in nanomoles, 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.)
### Table 1: Physicochemical, pharmacokinetic and safety data for currently marketed transdermal drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>MW* (Daltons)</th>
<th>MP (°C)*</th>
<th>Unionised</th>
<th>log P</th>
<th>Smax (mg.mL⁻¹)*</th>
<th>CI (L.h⁻¹) (70kg)</th>
<th>t₁/₂ (h)</th>
<th>Oral F (%)</th>
<th>Target plasma level (ng. mL⁻¹)</th>
<th>Estimated Jₘₐₓ required (µg.h⁻¹)</th>
<th>In vivo Jₘₐₓ (µg.cm⁻².h⁻¹)</th>
<th>Equivalent maximum hourly dose (µg.cm⁻².h⁻¹)</th>
<th>Safety margin= max dose per hour/in vivo Jₘₐₓ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>468</td>
<td>209</td>
<td>3.8</td>
<td>0.047</td>
<td>0.008² (32°C)</td>
<td>77iv, 55im⁷</td>
<td>3iv², 28sd⁴, 19bc⁷, 26dv⁴</td>
<td>51sl⁴, 28bc⁵</td>
<td>&gt; 0.1³</td>
<td>7.7</td>
<td>8.0</td>
<td>3-30</td>
<td>12.5</td>
</tr>
<tr>
<td>Clonidine</td>
<td>230</td>
<td>130</td>
<td>2.7</td>
<td>0.17</td>
<td>13.58³</td>
<td>15³</td>
<td>8-13iv⁴, 12-16sv⁴, 20dv⁴</td>
<td>95³</td>
<td>0.2-2³</td>
<td>24-48</td>
<td>2-37</td>
<td>1.2</td>
<td>0.2, 0.17, 0.14³, 0.12³, 0.42³, 0.18³, 0.63³, 0.2³, 0.09³</td>
</tr>
<tr>
<td>Estradiol</td>
<td>272</td>
<td>173-179</td>
<td>4.2</td>
<td>0.003, 0.003³</td>
<td>600-800³</td>
<td>-1po⁸</td>
<td>5³</td>
<td>0.04-0.06³</td>
<td></td>
<td></td>
<td></td>
<td>4.2</td>
<td>-20</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>296</td>
<td>141-146</td>
<td>4.3</td>
<td>0.039, 0.009²</td>
<td>70po⁸</td>
<td>7.7po⁸, 17d⁸</td>
<td>55³</td>
<td>0.025-0.075³</td>
<td>1.75-5.25</td>
<td>0.07</td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>337</td>
<td>83-84</td>
<td>3.9</td>
<td>0.15, 0.2³</td>
<td>27-75³</td>
<td>3-12iv³, 20-27hd³</td>
<td>500et³</td>
<td>1-3³</td>
<td>27-225</td>
<td>2.4</td>
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<td></td>
<td>100</td>
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<tr>
<td>Granisetron</td>
<td>312</td>
<td>152-154¹</td>
<td>2.6</td>
<td>0.017</td>
<td></td>
<td>33-76³</td>
<td>4-6iv³, 36dv³</td>
<td>60³</td>
<td>3.9 (td mean Cₘₐₓ)³</td>
<td>129-296</td>
<td>2.5</td>
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<tr>
<td>Levonorgestrel</td>
<td>312</td>
<td>235-237</td>
<td>3.8</td>
<td>0.017</td>
<td></td>
<td>5.7po⁹</td>
<td>19.3po³, 28dv³</td>
<td>94³</td>
<td>0.17 (td Cₘₐₓ)³</td>
<td>60-315</td>
<td>88</td>
<td></td>
<td></td>
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<tr>
<td>Methylphenidate</td>
<td>233</td>
<td>74-75,</td>
<td>2.1</td>
<td>1.8</td>
<td></td>
<td>12(d); 21(l)</td>
<td>1.5-5po³, (children)³</td>
<td>22(d); (5(l))</td>
<td>5-15³</td>
<td>385-2310</td>
<td>40³, 31³, 69³, 29²</td>
<td></td>
<td></td>
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<tr>
<td>Nicotine</td>
<td>162</td>
<td>-79, liquid</td>
<td>1.1</td>
<td>62, 1085³</td>
<td>216-327⁰</td>
<td>0.03-0.05po⁸</td>
<td>&lt; 1²</td>
<td>0.02-0.4³</td>
<td>4.32-1308</td>
<td>20³, 30³</td>
<td></td>
<td></td>
<td>833</td>
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<tr>
<td>Nitroglycerin (glyceryl trinitrate)</td>
<td>227</td>
<td>13, liquid</td>
<td>1</td>
<td>0.66, 1.3³</td>
<td></td>
<td>216-327⁰</td>
<td>0.03-0.05po⁸</td>
<td>&lt; 1²</td>
<td>0.02-0.4³</td>
<td>4.32-1308</td>
<td>20³, 30³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norethindrone acetate (norethisterone acetate)</td>
<td>327</td>
<td>110-130, 3.67 (pred)</td>
<td>0.0043</td>
<td>28td³</td>
<td>-</td>
<td>20-6²</td>
<td>34.8po⁸, 6-8sd³</td>
<td>60³</td>
<td>0.5-0.8³</td>
<td>10.3-16.5</td>
<td>0.65</td>
<td></td>
<td></td>
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<tr>
<td>Oxybutynin</td>
<td>358</td>
<td>56-58⁴</td>
<td>4.3</td>
<td>0.0093</td>
<td></td>
<td>10-64¹</td>
<td>2iv⁸, 7-8sd³</td>
<td>6³</td>
<td>0.5-3³</td>
<td>5-192</td>
<td>4.2</td>
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<tr>
<td>Rivastigmine</td>
<td>250</td>
<td>Oil at 25°C⁵</td>
<td>2.3</td>
<td>25</td>
<td></td>
<td>108²</td>
<td>1.3-2po³, 3.4dv³</td>
<td>36³</td>
<td>2.5-20 (td mean Cₘₐₓ)³</td>
<td>270-2160</td>
<td>39</td>
<td></td>
<td></td>
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<tr>
<td>Rotigotine</td>
<td>316</td>
<td>75-77⁵</td>
<td>4.7</td>
<td>0.017</td>
<td></td>
<td>600³</td>
<td>7d³</td>
<td>-</td>
<td>0.4-2³</td>
<td>240-1200</td>
<td>8.3</td>
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<tr>
<td>Scopolamine (hyoscine)</td>
<td>303</td>
<td>55, liquid</td>
<td>0.8</td>
<td>1.8, 75³</td>
<td>65-121³</td>
<td>1-5po³</td>
<td>4-27³</td>
<td>&gt; 0.05³</td>
<td>3.25-6.05</td>
<td>5.6</td>
<td></td>
<td></td>
<td>210³</td>
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<tr>
<td>Selegiline (deprenyl)</td>
<td>187</td>
<td>liquid at 25°C⁹</td>
<td>2.7</td>
<td>0.73</td>
<td></td>
<td>84³</td>
<td>9-15po³, 15-25sd³</td>
<td>4³</td>
<td>2³</td>
<td>168</td>
<td>12.5</td>
<td></td>
<td></td>
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<tr>
<td>Testosterone</td>
<td>288</td>
<td>155</td>
<td>3.6</td>
<td>0.02, 0.02²</td>
<td>41³</td>
<td>0.17-1.7³, 7³</td>
<td>3-10.5³³</td>
<td>123-430.5</td>
<td>13.9</td>
<td></td>
<td></td>
<td>417</td>
<td>-30</td>
</tr>
</tbody>
</table>
Abbreviations: bc, buccal; Cl, total body clearance; d, dextro isomer; F, oral bioavailability; im, intramuscular; iv, intravenous; J_{skin}, skin flux; l, levo isomer; log P, log the octanol-water partition coefficient; MP, melting point of the unionised form; MW, molecular weight; ot, transmucosal; po, per oral; S_{aq}, aqueous solubility of the unionised form; sl, sublingual; t_{1/2}, elimination half-life; td, transdermal.

a Sci Finder Scholar; 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' Still et al., 2003; d' Lowenthal et al., 1988; e' Catapres-TTS® PI; f' Cleary, 1993a; 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' Lowenthal et al., 1988; ae' Catrapres-TTS® PI; af' Cleary, 1993a; ag' Estraderm®; ah' Alora®; ai' Combipatch®; aj' Climara Pro®; ak' Nicoderm CQ®; al' Nicorette®; am' Nicorette® Invisi patch®; an' Habitrol®; ao' Nitro-Dur®; ap' Minitran®.

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 (2014).
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., $C_{ss} = \frac{R_0}{Cl} = \frac{J_{\text{skin}} \times A}{Cl}$), noting also that:

$$J_{\text{skin}} = A \times R_{\text{skin}}$$

where $J_{\text{skin}}$ 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 molecular weight, 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 to 3.8 µg.cm$^{-2}$.h$^{-1}$ (Michaels et al., 1975) through excised human skin, the desired skin flux requires a patch of 25 to 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 5-10 µg.cm$^{-2}$.h$^{-1}$, requiring the use of a patch of 10-20 cm$^2$ (Cleary, 1993a). Accordingly, fentanyl is now widely used in transdermal delivery to manage postoperative 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).

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 on 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 to 100. An exception based on Watkinson’s data appears to be scopolamine (hyoscine). However, in practice, up to 5 mg (0.65 each 8 hours) can be given to adults over 24 hours (Drugs, 2014). As Dorne and Renwick (2005) point out there should be at least a 10-fold safety factor to allow for human variability. Drugs such as estradiol, nitroglycerin, oxybutynin, scopolamine, selegiline and testosterone may be unsuitable for oral delivery because of a high oral first pass effect or a low intrinsic water solubility with that of estradiol, 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) point out, only intravenous 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 oral dosing of the same active.
An example of a drug which 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 on 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 readily available in various oral 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 on a 150 µg.mL$^{-1}$ therapeutic concentration and a skin penetration flux of 20 µg.cm$^{-2}$.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 B2 serum levels at day 21 in 9 male volunteers.

Table 2 summarises the approximately 20 to 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.
Table 2 Commercially available transdermal patches approved by the US FDA.

<table>
<thead>
<tr>
<th>Drug (Trade name, year of FDA approval)</th>
<th>Type</th>
<th>Indication</th>
<th>Patch design</th>
<th>Dose and size of patch - Delivery rate</th>
<th>Site of application</th>
<th>Duration of application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine (Butrans®, 2010)</td>
<td>Therapeutic</td>
<td>Chronic pain</td>
<td>DIA</td>
<td>5 mg in 20.25 (6.25) cm² - 5 µg/h</td>
<td>Upper outer arm, upper chest, upper back or the side of the chest</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.5 mg in 33.65 (7.5) cm² - 7.5 µg/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 mg in 30.60 (12.5) cm² - 10 µg/h</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>15 mg in 42.48 (18.75) cm² - 15 µg/h</td>
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<td></td>
<td></td>
<td></td>
<td>20 mg in 51.84 (25) cm² - 20 µg/h</td>
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<tr>
<td>Clonidine (Catapres-TTS®, 1984)</td>
<td>Therapeutic</td>
<td>Hypertension</td>
<td>Reservoir/Membrane</td>
<td>2.5 mg in 3.5 cm² - 0.1 mg/d</td>
<td>Upper outer arm or upper chest</td>
<td>7 days</td>
</tr>
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<td></td>
<td></td>
<td>5.0 mg in 7.0 cm² - 0.2 mg/d</td>
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<td></td>
<td></td>
<td>7.5 mg in 10.5 cm² - 0.3 mg/d</td>
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<tr>
<td>Estradiol (Estraderm®, 1986)</td>
<td>Therapeutic</td>
<td>Female HRT</td>
<td>Reservoir/Membrane</td>
<td>4 mg in 18 (10) cm² - 0.05 mg/d</td>
<td>Trunk of the body including the buttocks and abdomen</td>
<td>3 to 4 days</td>
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<tr>
<td></td>
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<td></td>
<td>8 mg in 31 (20) cm² - 0.10 mg/d</td>
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<tr>
<td>Estradiol (Climara®, 1994)</td>
<td>Therapeutic</td>
<td>Female HRT</td>
<td>DIA</td>
<td>2 mg in 6.5 cm² - 0.025 mg/d</td>
<td>Lower abdomen or upper quadrant of the buttock</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.85 mg in 9.375 cm² - 0.0375 mg/d</td>
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<td></td>
<td></td>
<td>3.8 mg in 12.5 cm² - 0.05 mg/d</td>
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<td></td>
<td>4.55 mg in 15 cm² - 0.06 mg/d</td>
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<td></td>
<td>5.7 mg in 18.75 cm² - 0.075 mg/d</td>
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<td></td>
<td></td>
<td>7.6 mg in 25 cm² - 0.1 mg/d</td>
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<tr>
<td>Estradiol (Vivelle®, 1994)</td>
<td>Therapeutic</td>
<td>Female HRT</td>
<td>DIA</td>
<td>4.33 mg in 14.5 cm² - 0.05 mg/d</td>
<td>Trunk of the body including abdomen and buttocks</td>
<td>3 to 4 days</td>
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<tr>
<td></td>
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<td></td>
<td>8.66 mg in 29.0 cm² - 0.1 mg/d</td>
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<tr>
<td>Estradiol (Alora®, 1996)</td>
<td>Therapeutic</td>
<td>Female HRT</td>
<td>DIA</td>
<td>0.77 mg in 9 cm² - 0.025 mg/d</td>
<td>Lower abdomen, upper quadrant of the buttock or outer aspect of the hip</td>
<td>3 to 4 days</td>
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<tr>
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<td>1.5 mg in 18 cm² - 0.05 mg/d</td>
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<td></td>
<td>2.3 mg in 27 cm² - 0.075 mg/d</td>
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<td></td>
<td></td>
<td>3.1 mg in 36 cm² - 0.1 mg/d</td>
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<td>Estradiol (Vivelle-Dot®, 1999)</td>
<td>Therapeutic</td>
<td>Female HRT</td>
<td>DIA</td>
<td>0.29 mg in 2.5 cm² - 0.025 mg/d</td>
<td>Lower abdomen</td>
<td>3 to 4 days</td>
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<tr>
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<td></td>
<td>0.585 mg in 3.75 cm² - 0.0375 mg/d</td>
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<td></td>
<td></td>
<td>0.78 mg in 5.0 cm² - 0.05 mg/d</td>
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<td>1.17 mg in 7.5 cm² - 0.075 mg/d</td>
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<td></td>
<td></td>
<td>1.56 mg in 10.0 cm² - 0.1 mg/d</td>
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<tr>
<td>Estradiol (Menostar®, 2004)</td>
<td>Therapeutic</td>
<td>Female HRT</td>
<td>DIA</td>
<td>1 mg in 3.25 cm² - 0.014 mg/d</td>
<td>Lower abdomen</td>
<td>7 days</td>
</tr>
<tr>
<td>Estradiol (Minivelle®, 2012)</td>
<td>Therapeutic</td>
<td>Female HRT</td>
<td>DIA</td>
<td>0.02 mg in 2.48 cm² - 0.0375 mg/d</td>
<td>Lower abdomen or buttocks</td>
<td>3 to 4 days</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>0.83 mg in 3.30 cm² - 0.05 mg/d</td>
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<td></td>
<td></td>
<td>1.24 mg in 4.95 cm² - 0.075 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>1.65 mg in 6.6 cm² - 0.1 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (Trade name, year of FDA approval)</td>
<td>Type</td>
<td>Indication</td>
<td>Patch design</td>
<td>Dose and size of patch - Delivery rate</td>
<td>Site of application</td>
<td>Frequency of application</td>
</tr>
<tr>
<td>----------------------------------------</td>
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</tr>
<tr>
<td>Estradiol (E)/Norethindrone (NT) (CombiPatch®, 1998)</td>
<td>Therapeutic</td>
<td>Female HRT</td>
<td>DIA</td>
<td>0.62 mg E / 2.7 mg NT in 9 cm² 0.05/0.14 mg E/NT per day 0.51 mg E / 4.8 mg NT in 16 cm² 0.05/0.25 mg E/NT per day</td>
<td>Lower abdomen</td>
<td>3 to 4 days</td>
</tr>
<tr>
<td>Ethinyl estradiol (EE)/Norelgestromin (NL) (Ortho Evra®, 2001)</td>
<td>Therapeutic</td>
<td>Female contraception</td>
<td>DIA</td>
<td>0.75 mg EE/ 6.00mg NL in 20 cm² 0.035/0.15 mg EE/NL per day</td>
<td>Buttock, abdomen, upper outer arm or upper torso</td>
<td>7 days</td>
</tr>
<tr>
<td>Estradiol (E)/Levonorgestrel (L) (Climara Pro®, 2003)</td>
<td>Therapeutic</td>
<td>Female HRT</td>
<td>DIA</td>
<td>4.40 mg E/ 1.39 mg L in 22 cm² 0.045/0.015 mg E/L per day</td>
<td>Lower abdomen</td>
<td>7 days</td>
</tr>
<tr>
<td>Fentanyl (Duragesic®, 1990)</td>
<td>Therapeutic</td>
<td>Chronic pain</td>
<td>DIA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.1 mg in 5.25 cm² - 12.5 µg/h 4.2 mg in 10.5 cm² - 25 µg/h 8.4 mg in 21 cm² - 50 µg/h 12.6 mg in 31.5 cm² - 75 µg/h 16.8 mg in 42 cm² - 100 µg/h</td>
<td>Chest, back, flank, or upper arm</td>
<td>72 hours</td>
</tr>
<tr>
<td>Granisetron (Sancuso®, 2008)</td>
<td>Therapeutic</td>
<td>Chemotherapy-induced nausea and vomiting</td>
<td>DIA</td>
<td>34.3 mg in 52 cm² - 3.1 mg/24h</td>
<td>Upper outer arm</td>
<td>Up to 7 days</td>
</tr>
<tr>
<td>Methylphenidate (Daytrana®, 2006)</td>
<td>Therapeutic</td>
<td>ADHD</td>
<td>DIA</td>
<td>27.5 mg in 12.5 cm² - 1.1 mg/h 41.3 mg in 18.75 cm² - 1.6 mg/h 55 mg in 25 cm² - 2.2 mg/h 82.5 mg in 37.5 cm² - 3.3 mg/h</td>
<td>Hip area, avoiding the waistline</td>
<td>Up to 9 hours in a day</td>
</tr>
<tr>
<td>Nitroglycerin (Nitro-Dur®, 1995)</td>
<td>Therapeutic</td>
<td>Angina pectoris</td>
<td>DIA</td>
<td>20 mg in 5 cm² - 0.1 mg/h 40 mg in 10 cm² - 0.2 mg/h 60 mg in 15 cm² - 0.3 mg/h 80 mg in 20 cm² - 0.4 mg/h 120 mg in 30 cm² - 0.6 mg/h 160 mg in 40 cm² - 0.8 mg/h</td>
<td>Chest, shoulder, upper arm, or back (hairless area)</td>
<td>12 to 14 hours</td>
</tr>
<tr>
<td>Nitroglycerin (Minitran®, 1996)</td>
<td>Therapeutic</td>
<td>Angina pectoris</td>
<td>DIA</td>
<td>9 mg in 3.3 cm² - 0.1 mg/h 18 mg in 6.7 cm² - 0.2 mg/h 36 mg in 13.3 cm² - 0.4 mg/h 54 mg in 20.0 cm² - 0.6 mg/h</td>
<td>Chest, shoulder, upper arm or back (hairless area)</td>
<td>12 to 14 hours</td>
</tr>
<tr>
<td>Drug (Trade name, year of FDA approval)</td>
<td>Type</td>
<td>Indication</td>
<td>Patch design</td>
<td>Dose and size of patch - Delivery rate</td>
<td>Site of application</td>
<td>Frequency of application</td>
</tr>
<tr>
<td>----------------------------------------</td>
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</tr>
<tr>
<td>Oxybutynin (Oxytrol®, 2003)</td>
<td>Therapeutic</td>
<td>Overactive bladder</td>
<td>DIA</td>
<td>36 mg in 39 cm² - 3.9 mg/d</td>
<td>Abdomen, buttocks or hip</td>
<td>3 to 4 days</td>
</tr>
<tr>
<td>Rivastigmine (Exelon®, 2007)</td>
<td>Therapeutic</td>
<td>Alzheimer’s and Parkinson’s disease</td>
<td>Matrix</td>
<td>9 mg in 5 cm² - 4.6 mg/24h 18 mg in 10 cm² - 9.5 mg/24h 27 mg in 15 cm² - 13.3 mg/24h</td>
<td>Upper/lower back, upper arm, or chest</td>
<td>24 hours</td>
</tr>
<tr>
<td>Roligotine (Neupro®, 2007)</td>
<td>Therapeutic</td>
<td>Parkinson’s disease Restless legs syndrome</td>
<td>DIA</td>
<td>2.25 mg in 5 cm² - 1 mg/24h (<em>) 4.5 mg in 10 cm² - 2 mg/24h 6.75 mg in 15 cm² - 3 mg/24h (</em>) 9 mg in 20 cm² - 4 mg/24h 13.5 mg in 30 cm² - 6 mg/24h 18 mg in 40 cm² - 8 mg/24h (*)</td>
<td>Abdomen, thigh, hip, flank, shoulder or upper arm</td>
<td>24 hours</td>
</tr>
<tr>
<td>Scopolamine (Transderm Scōp®, 1981)</td>
<td>Therapeutic</td>
<td>Motion sickness</td>
<td>Reservoir/Membrane</td>
<td>1.5 mg in 2.5 cm² - 1.0 mg/3d</td>
<td>Behind one ear</td>
<td>72 hours</td>
</tr>
<tr>
<td>Selegiline (Emsam®, 2006)</td>
<td>Therapeutic</td>
<td>Major depressive disorder</td>
<td>DIA</td>
<td>20 mg in 20 cm² - 6 mg/24h 30 mg in 30 cm² - 9 mg/24h 40 mg in 40 cm² - 12 mg/24h</td>
<td>Upper chest or back, upper thigh or the outer surface of the upper arm</td>
<td>24 hours</td>
</tr>
<tr>
<td>Testosterone (Androderm®, 1995)</td>
<td>Therapeutic</td>
<td>Hypogonadism</td>
<td>Reservoir/Membrane</td>
<td>9.7 mg in 32 cm² (6) - 2 mg/d (#) 12.2 mg in 37 cm² (7.5) - 2.5 mg/d 19.5 mg in 39 cm² (12) - 4 mg/d (#) 24.3 mg in 44 cm² (15) - 5 mg/d</td>
<td>Back, abdomen, thighs, or upper arm</td>
<td>24 hours</td>
</tr>
<tr>
<td>Nicotine (Nicoderm CQ®, 1991)²</td>
<td>OTC</td>
<td>Smoking cessation</td>
<td>Reservoir/Membrane</td>
<td>36 mg in 7 cm² - 7 mg/24h 75 mg in 15 cm² - 14 mg/24h 114 mg in 22 cm² - 21 mg/24h</td>
<td>Anywhere on the body, avoiding joints</td>
<td>24 hours</td>
</tr>
<tr>
<td>Nicotine (Nicorette®)³</td>
<td>OTC</td>
<td>Smoking cessation</td>
<td>Matrix</td>
<td>8.3 mg in 10 cm² - 5 mg/16h 16.6 mg in 20 cm² - 10 mg/16h 24.9 mg in 30 cm² - 15 mg/16h</td>
<td>To an area on the upper body or upper outer arm that is non-hairy, intact, non-irritated, clean and dry</td>
<td>16 hours</td>
</tr>
<tr>
<td>Nicotine (Nicorette® Invisipatch®)³</td>
<td>OTC</td>
<td>Smoking cessation</td>
<td>Matrix</td>
<td>15.75 mg in 9 cm² - 10 mg/16h 23.62 mg in 13.5 cm² - 15 mg/16h 39.7 mg in 22.5 cm² - 25 mg/16h</td>
<td>A clean, intact, dry and hairless skin of the thigh, arm or chest</td>
<td>16 hours</td>
</tr>
<tr>
<td>Nicotine (Habitrol®, 1990)³</td>
<td>OTC</td>
<td>Smoking cessation</td>
<td>Matrix</td>
<td>17.5 mg in 10 cm² - 7 mg/24h 35 mg in 20 cm² - 14 mg/24h 52.5 mg in 30 cm² - 21 mg/24h</td>
<td>Upper body or the outer part of the arm</td>
<td>24 hours</td>
</tr>
<tr>
<td>Drug (Trade name, year of FDA approval)</td>
<td>Type</td>
<td>Indication</td>
<td>Patch type</td>
<td>Dose and size of patch - Delivery rate</td>
<td>Site of application</td>
<td>Frequency of application</td>
</tr>
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</tr>
<tr>
<td>Sumatriptan (Zecuity®, 2013)</td>
<td>Active</td>
<td>Migraine</td>
<td>Iontophoretic system</td>
<td>36 mg in 7 cm² - 6.5 mg/4h</td>
<td>Upper arm or tight</td>
<td>4 hours</td>
</tr>
<tr>
<td>Capsaicin (Qutenza®, 2009)</td>
<td>Topical</td>
<td>Neuropathic pain</td>
<td>DIA</td>
<td>179 mg in 280 cm²</td>
<td>The most painful areas, excluding face and scalp</td>
<td>Single 60-minute application of up to four patches</td>
</tr>
<tr>
<td>Diclofenac epolamine (Flector®, 2007)</td>
<td>Topical</td>
<td>Topical treatment acute pain</td>
<td>DIA</td>
<td>180 mg in 140 cm²</td>
<td>The most painful area</td>
<td>12 hours</td>
</tr>
<tr>
<td>Lidocaine (Lidoderm®, 1999)</td>
<td>Topical</td>
<td>Post-herpetic neuralgia pain</td>
<td>DIA</td>
<td>700 mg in 140 cm²</td>
<td>The most painful area, avoiding the contact with the eyes</td>
<td>Up to three patches only once for up to 12 hours within a 24-hour period</td>
</tr>
<tr>
<td>Lidocaine (L)/ Tetracaine (T) (Synera®, 2005)</td>
<td>Topical</td>
<td>Local dermal analgesia</td>
<td>Eutectic mixture - CHADD® technology</td>
<td>70 mg L/ 70 mg T in 50 cm² - 1.7/1.6 mg L/T per 30 min</td>
<td>Site of venipuncture, intravenous cannulation or superficial dermatological procedure</td>
<td>20-30 minutes</td>
</tr>
<tr>
<td>Menthol (M)/ Methyl salicylate (MS) (Salonpas®, 2008)</td>
<td>Topical</td>
<td>Muscles and joints pain</td>
<td>DIA</td>
<td>3 % M/ 10 % MS in 70 cm²</td>
<td>The affected area</td>
<td>Up to 8-12 hours</td>
</tr>
<tr>
<td>Estradiol (Evamist®, 2007)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Therapeutic</td>
<td>Menopausal symptoms</td>
<td>Cutaneous solution</td>
<td>1.53 mg per spray (90 µL)</td>
<td>The inside of the forearm between the elbow and the wrist</td>
<td>One spray once daily (starting dose)</td>
</tr>
<tr>
<td>Testosterone (Axiron®, 2010)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Therapeutic</td>
<td>Hypogonadism</td>
<td>Cutaneous solution</td>
<td>30 mg per pump actuation</td>
<td>The axilla (armpit)</td>
<td>2 pump actions once daily (starting dose)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Size of patch reported corresponds to the active surface except for Butrans®, Estraderm® and Androderm® patches where both active and overall surface are reported.

<sup>b</sup> Prior 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.

<sup>c</sup> 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 (*).

<sup>d</sup> 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.

<sup>e</sup> Nicoderm CQ® in US, Nicotinell® in the UK and Nicabate® in Australia.

<sup>f</sup> Nicorette® is not FDA approved and available in UK.

<sup>g</sup> Habitrol® in US and Canada, Nicotinell® in the UK.

<sup>h</sup> Evamist® and Axiron® are cutaneous solutions using the Patchless Patch® delivery method developed by Acrux Ltd.

Data source: FDA Orange Book (2014) and products’ PI.
These include (generic name, reference trade name, generic trade name(s)): clonidine, Catapres-TTS® (Boehringer Ingelheim), Clonidine Transdermal System (Aveva, Barr, Mylan Technologies and Watson Labs); estradiol, Climara® (Bayer Healthcare), Estradiol Transdermal System (Mylan Technologies); ethinyl estradiol/ norelgestromin, Ortho-Evra® (Janssen Pharms), Xulane® (Mylan Technologies); fentanyl, Duragesic (Janssen Pharms), Fentanyl Transdermal System (Aveva, Laviphar Labs, Mallinckrodt, Mylan Technologies, Par Pharm and Watson Labs); nitroglycerin, Nitro-Dur® (Merck), Nitroglycerin Transdermal System (Hercon Pharm, Kremers Urban Pharms 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 ($C_{\text{max}}$, $T_{\text{max}}$, $p < 0.001$; $\text{AUC}$, $p < 0.05$) (Gupta et al., 1995). The higher dose of nicotine delivered from the Nicoderm® patch, in particular during the first 8 hours 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 were applied to the upper back for 24 hours. Later patch designs were for 16 and 21 hours so that patients were not exposed to nicotine during their sleep. Fant et al. (2000) conducted a crossover study of 3 nicotine transdermal patches (a 15 mg/ 16 h patch (Nicorette® UK) and two brands 21 mg/ 24 h patches (Nicoderm® (NiQuitin® UK) and Habitrol® (Nicotinell® UK) and showed significant differences in the pharmacokinetic profiles between the two 21 mg patches and the 15 mg patch ($\text{AUC}_{0-24h}$ and $C_{\text{max}}$, $p < 0.05$). 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® UK) 21 mg/ 24 h patch and a newly UK available, Nicorette® 25 mg/ 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 on single and multiple dose randomised 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 Matrifene® in Europe) to the original reservoir Duragesic® formulation in an open-label, randomised, 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 on 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 cm² 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 of estradiol uptake. Gorsline et al. (1992) later showed that bioequivalent ($\text{AUC}_{0-\infty}$, $\text{AUC}_{0-t}$, $\text{T}_{\text{max}}$) plasma nicotine concentrations were achieved irrespective of the application site on the upper body (upper back, upper outer arm, upper chest) from Nicoderm® $14 \text{ mg/24 h}$. Yu et al. (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 the three different skin sites ($\text{AUC}_{0-27}$, $\text{C}_{\text{max}}$ parameters not significantly different). Further, the plasma concentrations of norelgestromin and ethinylestradiol 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 ($\text{AUC}_{0-\infty}$ and $\text{AUC}_{0-\text{last}}$) after the application of Exelon® $8.5 \text{ mg/24 h}$ 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 ($\text{AUC}_{0-168}$ and $\text{AUC}_{0-\text{last}}$) from an estradiol patch (Climara® $0.1 \text{ mg/24 h}$) 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 estradiol levels required for the relief of menopausal symptoms (Taggart et al., 2000). Finally, the systemic exposure of nicotine from Nicorette® $15 \text{ mg/16 h}$ applied to the upper arm was higher compared to the abdomen but equivalent to the back (Sobue et al., 2005). Practically, transdermal systems should not be applied to the waistline since 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) point out that many commonly used 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 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, while 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 other hand, even the clonidine patch, with a noticeable degree of sensitisation (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 characterised 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 of 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; FDA, 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 hospitalisations (FDA, 2012a; FDA, 2012c). 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 et al., 2009).

The US FDA, in a Drug Safety Communication, has recently alerted the public that certain over-the-counter (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 lead to local warmth 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 a magnetic resonance imaging scan (Ball and Smith, 2008; Durand et al., 2012). Skin burns have been reported at the patch site in several patients wearing an aluminised transdermal system during these types of procedures (Hong et
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, randomised 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 ($C_{\text{max}}$ 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 an *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).

Crystallisation is a particular problem that may arise from supersaturated systems that are thermodynamically unstable and where drug may potentially crystallise out during storage. Crystallisation 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 estradiol crystals could be generated in the presence of ambient humidity for any marketed estradiol 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 crystallisation can have on a patch formulation (Chaudhuri, 2008; Waters, 2013). Low molecular weight surfactants (e.g. Cremophor®), copolymers 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 crystallisation 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 Apparatus 6/Ph Eur 2.9.4.3) and the Reciprocating Holder Method (USP Apparatus 7/Ph Eur 2.9.4.2.) (Aggarwal and Dhawan, 2009). The Organization for Economic Cooperation and Development and the European Medicine Agency (EMEA) provide 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 pressure-sensitive adhesive 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: $C_{\text{max}}, T_{\text{max}}, AUC_{0-\infty}$ and $AUC_{0-\text{last}}$ (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 on 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; Maibach and Farahmand, 2009b; 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 utilisation rate and residual amount of drug after use in various marketed patches, in addition to fentanyl discussed earlier, are summarised in Table 3. Transdermal patches retain up to 95 % of the initial total amount of drug after the intended wearing period (e.g. estradiol 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 %.
Table 3 Drug utilisation rate and residual amount of drug after use of recently approved, fentanyl and nicotine transdermal patches.

<table>
<thead>
<tr>
<th>Drug (Trade name, year of FDA approval)</th>
<th>Patch design</th>
<th>Dose and size of patch - Delivery rate</th>
<th>Drug utilisation rate (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Residual amount of drug in the patch (mg)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Patch area activity (%/cm²&lt;sup&gt;c&lt;/sup&gt;)</th>
</tr>
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<tbody>
<tr>
<td>Methylphenidate (Daytrana®, 2006)</td>
<td>DIA</td>
<td>27.5 mg in 12.5 cm² - 1.1 mg/h</td>
<td>36</td>
<td>17.6</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41.3 mg in 18.75 cm² - 1.6 mg/h</td>
<td>34.9</td>
<td>26.9</td>
<td>1.9</td>
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<tr>
<td></td>
<td></td>
<td>55 mg in 25 cm² - 2.2 mg/h</td>
<td>36</td>
<td>35.2</td>
<td>1.4</td>
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<tr>
<td></td>
<td></td>
<td>82.5 mg in 37.5 cm² - 3.3 mg/h</td>
<td>36</td>
<td>52.8</td>
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<td>Selegiline (Emsam®, 2006)</td>
<td>DIA</td>
<td>20 mg in 20 cm² - 6 mg/24h</td>
<td>30</td>
<td>14</td>
<td>1.5</td>
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<tr>
<td></td>
<td></td>
<td>30 mg in 30 cm² - 9 mg/24h</td>
<td>30</td>
<td>21</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>40 mg in 40 cm² - 12 mg/24h</td>
<td>30</td>
<td>28</td>
<td>0.75</td>
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<tr>
<td>Rivastigmine (Exelon®, 2007)</td>
<td>Matrix</td>
<td>9 mg in 5 cm² - 4.6 mg/24h</td>
<td>51.1</td>
<td>4.4</td>
<td>10.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 mg in 10 cm² - 9.5 mg/24h</td>
<td>52.8</td>
<td>8.5</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27 mg in 15 cm² - 13.3 mg/24h</td>
<td>49.3</td>
<td>13.7</td>
<td>3.3</td>
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<tr>
<td></td>
<td></td>
<td>4.5 mg in 10 cm² - 2 mg/24h</td>
<td>44.4</td>
<td>2.5</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.25 mg in 5 cm² - 1 mg/24h (*)</td>
<td>44.4</td>
<td>1.25</td>
<td>8.9</td>
</tr>
<tr>
<td>Rotigotine (Neupro®, 2007)</td>
<td>DIA</td>
<td>9 mg in 20 cm² - 4 mg/24h</td>
<td>44.4</td>
<td>5</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 mg in 40 cm² - 8 mg/24h (*)</td>
<td>44.4</td>
<td>10</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.5 mg in 30 cm² - 6 mg/24h (*)</td>
<td>44.4</td>
<td>7.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Granisetron (Sancuso®, 2008)</td>
<td>DIA</td>
<td>34.3 mg in 52 cm² - 3.1 mg/24h</td>
<td>63.3</td>
<td>12.6</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg in 6.25 cm² - 5 µg/h</td>
<td>16.8</td>
<td>4.26</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.5 mg in 7.5 cm² - 7.5 µg/h</td>
<td>16.8</td>
<td>6.24</td>
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<tr>
<td>Buprenorphine (Butrans®, 2010)</td>
<td>DIA</td>
<td>10 mg in 12.5 cm² - 10 µg/h</td>
<td>16.8</td>
<td>8.32</td>
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<td></td>
<td></td>
<td>15 mg in 18.75 cm² - 15 µg/h</td>
<td>16.8</td>
<td>12.48</td>
<td>0.9</td>
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<tr>
<td></td>
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<td>20 mg in 25 cm² - 20 µg/h</td>
<td>16.8</td>
<td>16.64</td>
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<tr>
<td>Estradiol (Minivelle®, 2012)</td>
<td>DIA</td>
<td>0.62 mg in 2.48 cm² - 0.0375 mg/d</td>
<td>21.17</td>
<td>0.49</td>
<td>8.5</td>
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<td></td>
<td></td>
<td>0.83 mg in 3.30 cm² - 0.05 mg/d</td>
<td>21.1</td>
<td>0.66</td>
<td>6.4</td>
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<tr>
<td></td>
<td></td>
<td>1.24 mg in 4.95 cm² - 0.075 mg/d</td>
<td>21.17</td>
<td>0.98</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.65 mg in 6.6 cm² - 0.1 mg/d</td>
<td>21.21</td>
<td>1.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Drug</td>
<td>(Trade or generic name, year of FDA approval)</td>
<td>Patch design</td>
<td>Dose and size of patch - Delivery rate</td>
<td>Drug utilisation rate (%)</td>
<td>Residual amount of drug in the patch (mg)</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>--------------</td>
<td>----------------------------------------</td>
<td>--------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Duragesic®, 1990 discontinued</td>
<td>Reservoir/</td>
<td>1.25 mg in 5 cm² - 12.5 µg/h</td>
<td>72</td>
<td>0.35</td>
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<tr>
<td></td>
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<td>Membrane</td>
<td>2.5 mg in 10 cm² - 25 µg/h</td>
<td>72</td>
<td>0.7</td>
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<tr>
<td></td>
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<td></td>
<td>5 mg in 20 cm² - 50 µg/h</td>
<td>72</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.5 mg in 30 cm² - 75 µg/h</td>
<td>72</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mg in 40 cm² - 100 µg/h</td>
<td>72</td>
<td>2.8</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1.28 mg in 3.13 cm² - 12.5 µg/h</td>
<td>70.3</td>
<td>0.38</td>
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<td></td>
<td>2.55 mg in 6.25 cm² - 25 µg/h</td>
<td>70.6</td>
<td>0.75</td>
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<tr>
<td></td>
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<td>DIA</td>
<td>5.10 mg in 12.5 cm² - 50 µg/h</td>
<td>70.6</td>
<td>1.5</td>
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<tr>
<td></td>
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<td></td>
<td>7.65 mg in 18.75 cm² - 75 µg/h</td>
<td>70.6</td>
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<td>10.20 mg in 25 cm² - 100 µg/h</td>
<td>70.6</td>
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<td>Fentanyl</td>
<td>Mylan FTS, 2005</td>
<td>DIA</td>
<td>1.375 mg in 5 cm² - 12 µg/h</td>
<td>62.8</td>
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<td>2.75 mg in 10 cm² - 25 µg/h</td>
<td>65.4</td>
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<td></td>
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<td></td>
<td>5.5 mg in 20 cm² - 50 µg/h</td>
<td>65.4</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8.25 mg in 30 cm² - 75 µg/h</td>
<td>65.4</td>
<td>2.85</td>
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<td></td>
<td></td>
<td></td>
<td>11.0 mg in 40 cm² - 100 µg/h</td>
<td>65.4</td>
<td>3.8</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Lavipharm Labs FTS, 2006</td>
<td>DIA</td>
<td>2.5 mg in 10 cm² - 25 µg/h</td>
<td>72</td>
<td>0.7</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>5 mg in 20 cm² - 50 µg/h</td>
<td>72</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.5 mg in 30 cm² - 75 µg/h</td>
<td>72</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mg in 40 cm² - 100 µg/h</td>
<td>72</td>
<td>2.8</td>
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<tr>
<td>Fentanyl</td>
<td>Par Pharm FTS, 2007</td>
<td>Reservoir/</td>
<td>2.76 mg in 10.7 cm² - 25 µg/h</td>
<td>65.2</td>
<td>0.96</td>
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<tr>
<td></td>
<td></td>
<td>Membrane</td>
<td>5.52 mg in 21.4 cm² - 50 µg/h</td>
<td>65.2</td>
<td>1.92</td>
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<td>8.28 mg in 32.1 cm² - 75 µg/h</td>
<td>65.2</td>
<td>2.88</td>
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<td>11.04 mg in 42.8 cm² - 100 µg/h</td>
<td>65.2</td>
<td>3.84</td>
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<td>DIA</td>
<td>2.1 mg in 5.25 cm² - 12.5 µg/h</td>
<td>42.9</td>
<td>1.2</td>
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<td>4.2 mg in 10.5 cm² - 25 µg/h</td>
<td>42.9</td>
<td>2.4</td>
</tr>
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<td></td>
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<td></td>
<td>8.4 mg in 21 cm² - 50 µg/h</td>
<td>42.9</td>
<td>4.8</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>12.6 mg in 31.5 cm² - 75 µg/h</td>
<td>42.9</td>
<td>7.2</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>16.8 mg in 42 cm² - 100 µg/h</td>
<td>42.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Watson FTS, 2007</td>
<td>Reservoir/</td>
<td>2.55 mg in 19 cm² - 25 µg/h</td>
<td>70.6</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Membrane</td>
<td>5.10 mg in 38 cm² - 50 µg/h</td>
<td>70.6</td>
<td>1.5</td>
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<td></td>
<td></td>
<td></td>
<td>7.65 mg in 57 cm² - 75 µg/h</td>
<td>70.6</td>
<td>2.25</td>
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<tr>
<td></td>
<td></td>
<td>DIA</td>
<td>10.20 mg in 76 cm² - 100 µg/h</td>
<td>70.6</td>
<td>3</td>
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<tr>
<td>Fentanyl</td>
<td>Aveva FTS, 2008</td>
<td>Reservoir/</td>
<td>2.75 mg in 7.8 cm² - 25 µg/h</td>
<td>65.5</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Membrane</td>
<td>5.50 mg in 15.6 cm² - 50 µg/h</td>
<td>65.5</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DIA</td>
<td>8.25 mg in 23.4 cm² - 75 µg/h</td>
<td>65.5</td>
<td>2.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11.0 mg in 31.2 cm² - 100 µg/h</td>
<td>65.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Drug (Trade name, year of FDA approval)</td>
<td>Patch design</td>
<td>Dose and size of patch - Delivery rate</td>
<td>Drug utilization rate (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Residual amount of drug in the patch (mg)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Patch area activity (%/cm&lt;sup&gt;2&lt;/sup&gt;)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
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<td>-------------</td>
<td>---------------------------------------</td>
<td>--------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Nicotine (Nicoderm CQ®, 1991)</td>
<td>Reservoir/Matrix</td>
<td>36 mg in 7 cm&lt;sup&gt;2&lt;/sup&gt; - 7 mg/24h</td>
<td>19.4</td>
<td>29</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75 mg in 15 cm&lt;sup&gt;2&lt;/sup&gt; - 14 mg/24h</td>
<td>18.7</td>
<td>61</td>
<td>1.2</td>
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<td></td>
<td></td>
<td>114 mg in 22 cm&lt;sup&gt;2&lt;/sup&gt; - 21 mg/24h</td>
<td>18.4</td>
<td>93</td>
<td>0.8</td>
</tr>
<tr>
<td>Nicotine (Habitrol®, 1991)</td>
<td>Matrix</td>
<td>17.5 mg in 10 cm&lt;sup&gt;2&lt;/sup&gt; - 7 mg/24h</td>
<td>40</td>
<td>10.5</td>
<td>4</td>
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<tr>
<td></td>
<td></td>
<td>35 mg in 20 cm&lt;sup&gt;2&lt;/sup&gt; - 14 mg/24h</td>
<td>40</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>52.5 mg in 30 cm&lt;sup&gt;2&lt;/sup&gt; - 21 mg/24h</td>
<td>40</td>
<td>31.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Nicotine (Prostep®, 1992) discontinued</td>
<td>Matrix</td>
<td>15 mg in 24 (3.5) cm&lt;sup&gt;2&lt;/sup&gt; - 11 mg/24h</td>
<td>73.3</td>
<td>4</td>
<td>20.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg in 32 (7) cm&lt;sup&gt;2&lt;/sup&gt; - 22 mg/24h</td>
<td>73.3</td>
<td>8</td>
<td>10.5</td>
</tr>
<tr>
<td>Nicotine (Nicotrol®, 1992) discontinued</td>
<td>DIA</td>
<td>8.3 mg in 10 cm&lt;sup&gt;2&lt;/sup&gt; - 5 mg/16h</td>
<td>60.2</td>
<td>3.3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.6 mg in 20 cm&lt;sup&gt;2&lt;/sup&gt; - 10 mg/16h</td>
<td>60.2</td>
<td>6.6</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24.9 mg in 30 cm&lt;sup&gt;2&lt;/sup&gt; - 15 mg/16h</td>
<td>60.2</td>
<td>9.9</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Drug utilisation rate (%) = (delivery rate x duration of application) / drug content.

<sup>b</sup> Residual amount (mg) = drug content – drug utilisation.

<sup>c</sup> Patch area activity (%/cm<sup>2</sup>) = drug utilisation 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).

For instance, Rivastigmine transdermal patch (Exelon®) dosage strength 4.6 mg/24h, application time 24h, patch size (active surface) 5 cm<sup>2</sup>, overall amount of drug substance incorporated into the patch 9 mg.

Drug utilisation = 4.6 mg; drug utilisation rate = 4.6 / 9 ≈ 50 %; residual amount = 9 – 4.6 = 4.4 mg; patch area activity = 50 / 5 = 10 %/cm<sup>2</sup>.

When the patch has to be apply twice weekly (every 3-4 days), t = 3.5 days is considered for calculation.
Future prospects of transdermal patches and transdermal drug delivery systems

In 2013, four drugs (estradiol, 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 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 semisolid products for topical and transdermal delivery. Watkinson (2012) points 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 estradiol 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® (estradiol) (Figure 1-L) 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 Fontocaine® from Lomed, 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 intradermal powder injector Zingo® that was approved in 2008, withdrawn in 2008 and re-launched in September 2014 (Marathon Pharmaceuticals, 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 (Li et al., 2013; Watkinson, 2012). Its safety features are now being revamped by Incline Therapeutics ( $43 million Series A funding) to be launched in the US in 2014-16 (The Medicines Company, 2012; Watkinson, 2012). Much hope therefore rests with, Zecuity® (NuPathé) (Figure 1-M), which uses iontophoresis to actively deliver sumatriptan through the skin to manage the migraine-related nausea and vomiting that can limit oral 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 1-N) required a 2-order lower dose of antigen to be delivered to the skin to achieve antibody responses comparable to conventional intramuscular 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 ten 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 ADHD. However, whilst 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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References


Castle T (1828). Lexicon Pharmaceuticum: or a pharmaceutical dictionary, comprehending the Pharmacopoeias of London, Edinburgh, and Dublin, with a variety of other use. 2nd edn. E. Cox & Son: London.


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Coxe JR (1830). The American dispensatory, containing the natural, chemical, pharmaceutical and medical history of the different substances employed in medicine, together with the operations of pharmacy. 8th edn. Carey & Lea: Philadelphia.


Faulkner JM (1933). Nicotine poisoning by absorption through the skin. JAMA 100: 1164-1165.

FDA (2004). FDA acts to remove ephedra-containing dietary supplements from market.


FDA (2007). FDA Public Health Advisory: important information for the safe use of fentanyl transdermal system (patch).


FDA (2009b). Topical testosterone gel products (marketed as AndroGel 1% and Testim 1%): secondary exposure of children to topical testosterone products.


FDA (2012a). Fentanyl patch can be deadly to children.


FDA (2012c). FDA reminds the public about the potential for life-threatening harm from accidental exposure to fentanyl transdermal systems (“patches”).

FDA Orange Book (2014).


Macht DI (1938). The absorption of drugs and poisons through the skin and mucous membranes. JAMA 110: 409-414.


Paoletti AM, Pilia I, Nannipieri F, Bigini C, Melis GB (2001). Comparison of pharmacokinetic profiles of a 17β-estradiol gel 0.6 mg/g (Gelestra) with a transdermal delivery system (Estraderm TTS 50) in postmenopausal women at steady state. Maturitas 40: 203-209.

Pereira J (1839). The elements of materia medica; comprehending the natural history, preparation, properties, composition, effects, and uses of medicines. Longman, Orme, Brown, Green, and Longmans: London.


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