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REVIEW

Characteristics of Analgesic Patch Formulations

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Abstract: Topical and transdermal formulations are a common means of pharmaceutical drug delivery. If a drug is able to penetrate transcutaneously, the skin is an ideal site for the delivery of medications for both local (topical) and systemic (transdermal) effects. The administration of analgesics through the skin poses several potential advantages to those administered orally including compliance, the ability to deliver a drug to a peripheral target site and more stable and sustained plasma levels. One method of drug delivery is with the use of patch formulations – also known as patch systems. Typically, transdermal patches deliver medications intended to reach the systemic circulation, whereas topical patches are designed to keep medication localized for targeted delivery in proximity to the application site. There are a variety of technologies and materials utilized in patches, as well as penetration and formulation enhancers that ultimately affect the performance, efficacy and safety of the patch system. The degree of adherence to the skin is also of critical importance in drug delivery. Patches that lift up or fall off before the prescribed time period may represent a therapeutic failure and must be replaced, increasing patch utilization and cost to the healthcare system or to the patient. The added risk from accidental exposure makes poor patch adhesion a safety issue as well. A variety of analgesics are currently available as patch formulations including local anesthetics, capsaicin, nonsteroidal anti-inflammatory drugs and opioids. This review will highlight each of those patch delivery systems and introduce newer patch technologies that lend towards improved adhesion and compliance. Understanding the designs, limitations and benefits of patch systems will allow clinicians to select between these therapies when appropriate for their patients.

Keywords: topical, transdermal, lidocaine, capsaicin, patch adhesion

Introduction

Delivery of analgesics via topical and transdermal patch formulations has become increasingly common. Some analgesic patch systems are used to deliver drugs topically through the skin to local tissues while limiting systemic exposure; others are used to deliver drugs transdermally with the medication ultimately entering into the systemic circulation and targeting pain distant from the application site of the patch. Analgesic patches include both prescription and over the counter (OTC) medications including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, lidocaine, capsaicin, and others. Patch systems are used to treat a variety of mild, moderate and even severe pain conditions. Patches can offer local analgesia of the skin before injections or minor surgical procedures as well as relief of minor strains, sprains, contusions, and some neuropathic pain syndromes including postherpetic neuralgia (PHN) and diabetic peripheral neuropathy (DPN).[1–7] Transdermal opioid analgesics have also been shown to be effective for moderate to severe pain syndromes.[8,9]

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A patch system is a combination of both the active pharmaceutical ingredient and its delivery system. When considering patch systems for analgesic therapies, clinicians need to consider the type of pain (eg nociceptive or neuropathic), what/which analgesics are best suited for those targeted pain receptors, and if the choice of medication is suitable for delivery by a patch system. There can be certain benefits of patch systems over the conventional oral route of administration. These can include avoidance of first-pass metabolism and gastrointestinal (GI) issues, limited systemic exposure and others.[10–15]

Different technologies and ingredients are utilized to optimize patch delivery systems. The design of the patch system and its physical characteristics, active pharmaceutical drug, excipients, penetration enhancers and adhesives help determine the ultimate delivery of the analgesic drug to its targets. This review focuses on patch system formulations and critical properties, including adhesion that affects the efficacy, safety, costs and drug delivery of analgesics from these systems. The characteristics that allow the patch system to achieve their therapeutic goals as well as those that limit their usefulness and safety will be covered.

Advantages of Patch Systems

Patch systems offer advantages over other methods of drug delivery. For the purposes of this review, "topical" will refer to the delivery of medications to the local tissues where applied, and "transdermal" will refer to medications delivered through the skin targeting uptake into the systemic circulation. Topical patch systems deliver the drug directly to the targeted tissue while potentially reducing side effects that result from systemic exposure. Transdermal patch systems can provide for the controlled and prolonged delivery of drugs with less fluctuation of circulating drug levels (reduced peaks and troughs) that occur with oral administration.[10,11] Delivery of drugs by patch systems can avoid first-pass metabolism and may help minimize GI side effects.[12–15] Patients generally find that patch systems are convenient to use and thus have the potential to improve compliance over timed or scheduled dosing.[14,15] Patch systems are also suitable for use by patients who are unable to ingest or tolerate oral formulations. Although medicated creams and ointments are available, they are often malodorous, messy to handle and may be cosmetically non-appealing. Patch formulations typically lack these characteristics and have the added benefit of measured and controlled dosing.

Analgesic Patch Design

Two patch configuration designs have typically been used when formulating analgesic patches: a reservoir system and a drug-in-adhesive (DIA) patch system (also called "matrix" design).[15–17] The basic design of these patch systems is illustrated in Figure 1. The reservoir system has 4 basic components, a backing layer, the drug reservoir, a rate-controlling membrane, and a drug-in-adhesive layer.[12] The patch system comes with a liner that covers the drug-in-adhesive layer, which is removed before application of the patch on to the skin.[12] The reservoir system is a system designed for extended delivery of the drug. Some of the drugs in the drug-in-adhesive layer would be available immediately upon application of the patch system, while drug in the drug reservoir would only come into contact with the skin after passing through the membrane and diffusing through the drug-in-adhesive layer. This provides a steady delivery of drug at a nearly constant level over an extended period of time.[12] One risk of reservoir patch systems was dose-dumping of a large amount of drug when exposed to certain conditions. Some of the fentanyl patches currently marketed are reservoir patch system.[18] All the other analgesic patches currently marketed are DIA patch systems.

DIA patch systems have two layers, a backing layer (furthest from the skin) and the drug-in-adhesive layer. DIA patch systems also come with a liner that covers the DIA layer and is removed before application (Figure 1). These patch systems are usually thinner, lighter, and more flexible than reservoir designs, which makes for better skin conformability.[12] These improvements help with patient compliance and adherence.[12] They have a lower potential for drug dose-dumping than with reservoir systems. The

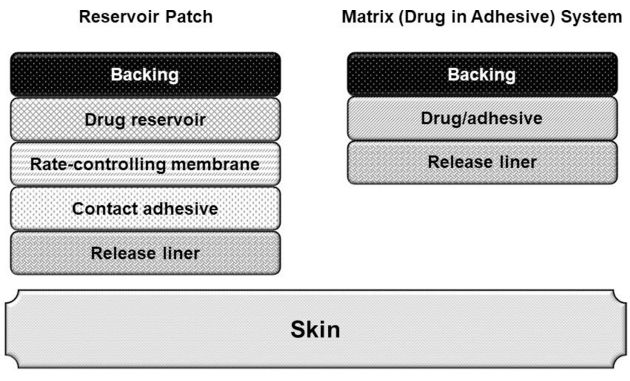

Figure 1 Analgesic patch system designs. Depicted are two patch systems used for analgesic patch systems, the reservoir system and the matrix or drug in adhesive system. Each system comes with a liner that is removed when applied to the skin. The drug-in-adhesive layer in each design is applied directly onto the skin.

thickness of the DIA layer means that some of the drug has to diffuse through the layer before reaching the skin, which can take a variable amount of time depending on the formulation.

The thin and flexible outermost layer of the patch system furthest from the skin is known as the backing layer. It needs to be impermeable to the drug and other ingredients as it keeps the drug and other inactive ingredients within the patch. In some patch systems, the backing material contains a metallic component such as aluminum or titanium dioxide. A safety concern may arise from the presence of these metallic components in the patch for patients undergoing magnetic resonance imaging (MRI) or who may need external defibrillation. Historically, serious thermal injuries (burns) have occurred, resulting in alerts from FDA recommending removal of any patch known or suspected to contain any metal before MRI is performed.[19] Analgesic patch systems covered in the (2009) warning included the diclofenac patch, a lidocaine/tetracaine patch, and an OTC menthol/methyl salicylate patch. The original reservoir fentanyl patch also had metal components in its backing, but prior to the 2009 FDA warning the original fentanyl patch was redesigned from a reservoir system to a DIA system and the backing was changed. Since the warning was issued, other patch systems have changed their backing and (to our knowledge) the lidocaine/tetracaine patch is the only system remaining on the market with warnings about removal prior to MRI.[6]

Drug Delivery with Topical and Transdermal Patch Systems

Skin provides a barrier between the body and the external environment that protects against chemicals, microorganisms, and UV radiation while keeping water and nutrients in. The outermost layer of the epidermis, the stratum corneum, provides the principal barrier function of the skin. The stratum corneum consists of multiple layers of corneocytes packed in a multilamellar lipid matrix.[14,20,21] Skin penetration of the drug is determined by the product solubility and diffusivity in the stratum corneum.[14,20] Drugs that can diffuse through the skin generally are lipophilic and low in molecular weight (<500 Daltons).[12,14] The process of a drug crossing this barrier begins with release of the drug from the adhesive layer of the patch. Diffusion into and through the stratum corneum follows either passively or with the aid of permeation enhancers. Once through the stratum corneum, the drug can partition into the more aqueous environment of the deeper layers of dermis and be taken up into cutaneous circulation, thus entering the systemic circulation.[20] Transdermal patch systems are designed to get drug across the dermis to the capillary/blood vessel layer for absorption into the circulation where it becomes available systemically.[20] Penetration enhancers that interact with the intracellular lipid matrix of the stratum corneum, such as ethanol, oleic acid, and propylene glycol and triacetin are often used in transdermal patch systems to increase penetration of the drug.[22]

With analgesics such as lidocaine, capsaicin and diclofenac, topical patch systems target localized pain at superficial and deep cutaneous, musculoskeletal and neurological sites. If the active ingredient remains mostly in the periphery with limited penetration into the systemic circulation, adverse effects are typically limited as well. For instance, with intravenous use as an antiarrhythmic drug, lidocaine has adverse systemic side effects which may include dizziness, drowsiness, muscle twitches, seizures, respiratory distress, loss of consciousness, and cardiac arrest.[3,4] In contrast, while treating localized pain, topical application with the 5% lidocaine patch yielded mean peak blood lidocaine concentrations approximately 1/10 the concentration needed to treat cardiac arrhythmia and about 1/38 the concentration that produced toxicity.[3,23] Thus, the risk of adverse events related to systemic exposure is usually limited with the use of the topical patch systems.

Patch System Attributes

Attributes of specific patch systems affect their product performance. Patch liners, drug layers, backing and adhesive components all play a role in effective drug delivery by the patch.

Adhesion – A Safety, Efficacy, and Quality Attribute of Patch Systems

Whether or not the system adheres to the skin is critical for the efficacy and safety of all topical and transdermal patch systems. The adhesive material must be non-irritating and non-sensitizing to the skin. Three related fundamental attributes of patch adhesion are tack, shear and peel.[16] Tack is the ability of the patch to adhere quickly and with light pressure to all types of skin on initial contact.[16] Manufacturers therefore describe the adhesives in patch systems as “pressure-sensitive adhesives” (PSAs). Patch systems must also exhibit shear adhesion or holding power. The PSA must allow the patch to adhere strongly to

the skin for the prescribed application period while resisting tangential shear stress and environmental factors.[16] Prescription analgesic patch systems have prescribed application times ranging from 30 minutes to 7 days.[6,9] Skin and body movements, along with clothes or other wearables (eg backpack, pocketbook) rubbing the patch, exert shear stress on the patch and can affect its adhesion, as can environmental factors like sweating, moisture, temperature, and bathing. Another attribute of concern is peel adhesion; when the patch is to be removed, it must be readily detachable without trauma to the skin while leaving a minimal amount of residue on the skin.[16] The adhesive material must also be minimally irritating and non-sensitizing to the skin.[16]

There are three common types of PSAs that are used in analgesic patch systems: acrylic-based, silicone-based, and polyisobutylene (PIB)-based. Most patch systems have replaced acrylic- and silicone-based PSAs with polyisobutylene due to their reduced allergenicity.[24]

Adhesion problems can affect efficacy, safety and the cost of patch systems. Poor adhesion leads to a phenomenon known as "patch lift" that results in suboptimal dosing and drug delivery.[16] When patch systems lift or partially detach, the effective area of patch-skin contact is changed, affecting drug absorption in an unpredictable manner.[16] Because the drug is compounded within the adhesive formulation, constant contact over the entire administration period allows for consistent drug delivery throughout the entire application area on the skin. Supplementing with sleeves or adhesive tape to attach patch systems that come loose or even fall off is often suggested by drug manufacturers[5,8,9] and medical personnel, but the effect of this on drug delivery or on skin irritation has not been well studied.[16] Patch systems that fall off before the prescribed time period must be replaced, thereby increasing patch utilization and cost to the healthcare system or to the patient.[16] Poor adhesion can be a safety issue. When patch systems fall off there is the potential for accidental exposure to others, including children or pets. Warnings for this specific safety hazard are included in the prescribing information for numerous patch systems.[3,4,8,9] Patch systems that adhere too well can lead to tearing of the skin and injury when they are removed. This can be a problem specifically with the frail skin of elderly patients. Their skin has lower moisture content and is less elastic.[16] Box 1 lists some problems that can arise from improper adhesion.

Adhesion data is generally unavailable or unpublished for most existing patch systems. Experts and regulatory authorities have called for the inclusion of adhesion studies in Abbreviated New Drug Applications (ANDAs).[16,24] European guidelines for generic patch systems require a demonstration of non-inferior in vivo adhesion performance.[25] FDA is addressing this issue and has issued a Draft Guidance to Industry on Adhesion with Transdermal and Topical Delivery Systems for ANDAs.[26] The draft guidance recommends human in vivo testing of adhesion using a scoring system of 0–4. Patches are applied to skin and adhesion is scored at various time points. A score of 0 equals 90% or greater adhesion (essentially no lifting) over the testing period, score of 1 equals 75–90% adherence, a score of 2 equals 50–75% adherence, a score of 3 equals less than 50% adherence but the patch has not fallen off and a score of 4 is given for detached patches. The scores are measured at various times after the application up to and including the maximum time the patch is to be applied. In these tests, the new patch is to be compared to the existing approved reference patch and the new patch should have adherence at least comparable to the reference patch.[26] To our knowledge, only the most recently approved DIA patch system, the 1.8% lidocaine patch, reports on these adhesion studies in its prescribing information.[4]

Box 1 Problems and Issues Related to Adhesion of Transdermal and Topical Formulations

Issues That Occur with Poor Adhesion of Patch Systems
1. Patches failing to adhere because of sweating, bathing, swimming
2. Body movements and the rubbing of clothing leading to poor adhesion or patches falling off
3. Need for overlay or tape to keep patches adhering leading to unpredictable drug delivery
4. Lack of effectiveness
5. Increased cost that results from increased use of patches that need to be replaced because of non-adherence
6. Adverse Effects • Adverse skin reactions • Abrasion or tearing of skin upon removal
7. Accidental/Incidental Exposure • Opioid patches falling off and being picked up by children or pets, deaths have occurred

Note: Data from these studies.[16,29,39,40]

Delivery of Drugs

How much drug gets delivered onto and into the skin or into the circulation is more important than the concentration of the drug in the patch. Drug delivery can be affected by the thickness of the patch. With a thick DIA layer or a thick reservoir layer, the drug needs to diffuse over

longer distances and only a portion will reach the skin. Thinness of the patch promotes more efficient drug delivery and reduces the potential of patch lifting, detachment and from getting caught on clothing, bedding, or chairs. An example of this is noted with two different, yet bioequivalent lidocaine patch systems. The thicker, original 5% lidocaine hydrogel patch contains 700 mg of lidocaine.[3] In contrast, the recently approved thinner 1.8% lidocaine topical system contains only 36 mg of lidocaine per patch.[4] These two patch systems are identical in size (10 cm × 14 cm) and have been shown to be bioequivalent, delivering the same amount of lidocaine through the skin. The bioavailability of lidocaine from the 1.8% patch is approximately 48% while that from the 5% hydrogel patch is estimated at only 3±2%.[27] The adhesive composition and novel design of the 1.8% patch also allows for a significantly thinner patch (system) (0.8 mm vs.1.71 mm) that is more efficient in delivering lidocaine to the target. In each case, the thickness reported here also included the thickness of the backing layer (both products use nonwoven backing material). The thinness of 1.8% topical lidocaine system along with the malleability of the nonaqueous polymer adhesive allows for a pliable patch that maintains contact with the skin during activity and at contour-challenged areas of the body. These two very different patch systems deliver the same amount of drug, yet one is a 5% patch containing 700 mg of lidocaine while the other is a 1.8% patch containing only 36 mg of lidocaine.[4]

Residual Drug in Patch Systems

Another important property of a patch system is the amount of residual drug left in the patch after use. Patch delivery systems are typically designed to contain more drug product than the patch actually delivers. Marketed patch systems have a residual of 10%−95% of the drug after its intended period of use.[28] This presents a safety issue to the patient as well as to others due to potential unintended exposure. Failure to remove the patch system at the end of the intended use period can lead to an increased dose or prolonged pharmacological effects of the drug on the patient.[28] Used patches are a hazard to children, pets, and caregivers who may be inadvertently exposed to drug from discarded patch systems.[28] In 2012, 32 cases of accidental exposure to fentanyl from patches had been reported in the previous 15 years. Most of the cases involved children under the age of two. Twelve of these cases resulted in deaths and hospitalization was required in an additional 12 cases.[29] The prescribing information on numerous analgesic patch systems contain a warning about preventing accidental exposure in children and that care should be taken in disposing of used patch systems.[3,4,8,9,30] FDA guidance to industry in 2012 recommended that the amount of residual drug be minimized in patch systems to help mitigate this safety issue.[28]

Patches that contain the same drug and are indicated for the same use can differ greatly in the amount of residual drug remaining at the end of the dosing period. As was mentioned above, the 5% lidocaine hydrogel patch contains 700 mg of lidocaine but delivers only 3 ± 2% of the applied dose is absorbed; 95% or more of the drug (at least 665 mg) remains in the patch following use.[3] The 1.8% lidocaine patch, contains only 36 mg of lidocaine, delivering over half to the patient and less than 18 mg (48%), remains as residual. Although these two patches are bioequivalent, as discussed above, they differ in design and biopharmaceutic performance.[3,4] The 5% hydrogel patch was developed in the 1990s prior to FDA issuing guidance recommending minimalization of residual drug.

Approval of Topical and Transdermal Formulations by the Abbreviated New Drug Application or by the 505(b)(2) Pathways

Most prescription analgesic patch systems are available in an original formulation but also in multiple formulations approved through the ANDA (ie generics) or the 505(b)(2) regulatory pathways. A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use.[31] To obtain approval, ANDA topical and transdermal formulations must demonstrate that they are bioequivalent to the reference product. Bioequivalence is usually demonstrated by showing equivalent plasma exposure of the drug over time. As discussed above, adherence to the skin is a problem for some patches; a recent draft Guidance to Industry from FDA requires that patch system ANDAs also need to demonstrate statistically noninferior adhesion performance to the reference patch via in vivo clinical studies.[26] Generic product also typically needs to demonstrate noninferior dermal safety assessed in a repeat-insult patch test (RIPT) to assure the generic product does not present with worse potential for sensitization or irritation.

The 505(b)(2) NDA pathway does not have the "sameness" requirement. For patch systems, the proposed product can differ from the reference patch product in many ways including strength of the active component, salt form of the active component, and new indications. Patch systems approved through this process still must demonstrate comparable pharmacokinetics (and often bioequivalence), adhesion that is noninferior, and noninferior dermal sensitization and irritation. An important point about patch systems approved through the 505(b)(2) pathway is that patch design, composition, and characteristics can differ substantially from the reference patch. This is again exemplified by the 1.8% lidocaine patch which was approved through the 505(b)(2) pathway. The basis of the 505(b)(2) pathway was because of the difference in product strength (1.8% versus 5%). The 1.8% lidocaine patch also differs from the reference product in thickness other attributes as described above, and also has demonstrated superior adhesion. However, these other differentiations in themselves would not necessarily require a 505(b)(2) NDA versus ANDA pathway.[3,4,32]

Topical Analgesic Patch Systems

Analgesics used in prescription topical analgesic patch systems include lidocaine, lidocaine plus tetracaine, lidocaine plus prilocaine, capsaicin, and diclofenac. These systems are designed to deliver the drug locally, minimizing systemic exposure.

Prescription Lidocaine Patch Systems

Lidocaine blocks voltage-gated sodium channels involved in the propagation of action potentials.[33] Lidocaine patch systems target these channels are expressed on A delta and C fibers, some of which are found in or just under the skin. Blockage reduces ectopic discharges thought to underlie certain aspects of persistent pain.[34]

Lidocaine patch systems are indicated for the relief of pain associated with PHN.[3,4] Clinical studies have demonstrated the effectiveness of prescription lidocaine patch systems in PHN.[1,35,36] There are also studies that show that topical lidocaine patch systems may be effective in relieving pain associated with other painful conditions such as diabetic peripheral neuropathy, carpal tunnel syndrome, lower back pain, and osteoarthritis.[27] These findings warrant further study. Lidocaine patches are generally regarded to have limited safety concerns. Application site reactions occur with the most common being skin irritation that is usually mild and transient.[3,4,23,35]

There are seven lidocaine patch systems marketed in the United States, the original 5% lidocaine patch and six others approved through the ANDA and 505(b)(2) pathways (Table 1). All seven are of the DIA design and are indicated for the treatment of pain associated with PHN. Lidocaine patch systems are applied for a 12-hour dosing period followed by a 12-hour off/rest period. A maximum of three patches can be applied at a time and they may be cut into smaller pieces.[3,4]

There are three patch types available (Table 1). The original 5% patch system and four generics have similar compositions, use acrylic-based PSAs, and each contains 700 mg of lidocaine in 14 g of adhesive mix. Another 5% patch differs in that it uses a PBI-based PSA adhesive and contains 140 mg of lidocaine in 2.8 g of adhesive. The remaining patch is a 1.8% lidocaine patch system. All are

Table 1 Characteristics and Composition of Prescription Lidocaine Topical Formulations

Patch	Bioequivalent to Lidoderm Patch	Design	Lidocaine (%)	Lidocaine (mg)	Adhesive Mix (g)	Relative Thickness of DIA Layer*	Adhesive
Lidoderm[3]		DIA	5	700	14	1.0	Acrylic-based hydrogel
ZTlido[4]	Bioequivalent	DIA	1.8	36	2.0	0.14	Polyisobutylene adhesive matrix
Mylan[30]	Bioequivalent	DIA	5	140	2.8	0.20	Polyisobutylene adhesive matrix
Four generics from Teva, Par, Rhodes, and Actavis Pharmaceuticals	Bioequivalent	DIA	5	700	14	1.0	Acrylic-based hydrogel

Notes: *Assumes density of DIA layers are approximately the same, as these patches are all the same size, 10 × 14 cm, the thickness of the DIA layer will be proportional to the amount of adhesive mix is used.

the same size (10 × 14 cm), although the last two patch systems described are considerably thinner than the others (Table 1).

Poor adhesion is a commonly reported issue with lidocaine patch systems; approximately 70% of the concerns about lidocaine patch systems reported to the FDA Adverse Events Reporting System are in regard to poor product adhesion. Other patch system products such as buprenorphine, fentanyl or nicotine patch systems have much lower rates of concerns about adhesion.[37,38] Online consumer complaint threads are filled with comments and reports about poor adhesion of some prescription lidocaine patch systems.[39–41] Adhesion studies, using the human in vivo adhesion testing protocols described above, demonstrate that the 1.8% lidocaine patch has superior adhesion compared to the original reference 5% patch and the 5% lidocaine PBI-based patch.[4,32]

Lidocaine Patch Systems in Combination with Tetracaine or Prilocaine

These patches containing multiple local anesthetics are indicated to provide local dermal analgesia for superficial venous access, injections and superficial dermatological procedures such as excision, electrodesiccation and shave biopsy of skin lesions.[6,42]

The lidocaine/tetracaine topical patch contains 70 mg of lidocaine and 70 mg of tetracaine. It is applied for short times, 20–30 minutes, before removal and starting the procedure. This patch system is reported to contain metal in the backing material and must be removed before the patient undergoes an MRI.[6]

A patch with similar indications and uses containing 25 mg prilocaine and 25 mg lidocaine is available is many countries outside of the USA. The patch is applied for 1–5 hours, depending upon the depth of analgesia desired. This patch has no warnings about removal before undergoing an MRI.[42]

Topical Capsaicin Patch System

Capsaicin is a phytochemical derived from hot chili peppers native to the Americas.[43] It causes persistent activation of transient receptor potential vanilloid 1 (TRPV1) receptor, a calcium channel expressed in polymodal nociceptive fibers, mainly the C and A delta fibers.[43,44] Activation of these channels leads to massive influx of Ca^{2+} ions which triggers Ca-dependent proteases causing cytoskeletal breakdown, microtubule depolymerization, inhibition of electron-chain transport and mitochondrial dysfunction in these nerve fibers.[43,44] This causes a loss of cellular integrity and "defunctionalization" of nociceptor fibers. The nerve fibers retract and this results in a highly localized loss of nerve fibers in the epidermis and dermis.[44,45] Capsaicin lasts for a long-time, weeks, in skin.[43,44] When it disappears, nerve regeneration takes weeks; thus, the effect on loss of nerves in skin lasts for an extended period of many weeks.[43]

Capsaicin is available by prescription as an 8% patch that is indicated for the management of neuropathic pain associated with PHN in the USA and for broad neuropathic indication including DPN in Europe.[7] The sponsor has recently filed for approval for the treatment of DPN in the US. This filing was mainly based upon a Phase III trial in patients with DPN.[2] Data from a meta-analysis suggested that this high-dose topical capsaicin patch was effective for the treatment of both PHN and HIV-associated neuropathy compared to a low-dose control patch.[46]

The patch systems are of a DIA design, 14 × 20 cm, and contain 179 mg of capsaicin and it uses a silicone-based PSA.[7] The capsaicin patch is applied to the skin for a short time (1 hr) in a clinical setting, and can yield long-term pain relief. If the pain returns and requires treatment, reapplication can be repeated every 3 months.[7] Requirements for the patch are good adhesion for 1 hr with minimal residue left behind after removal as capsaicin is a major skin irritant. It is recommended that the treatment area be pretreated with a topical anesthetic before the application of the patch.[7] Common adverse events (AEs) occur at the application site and include erythema, pain, edema, and pruritus, with 75–96% of patients having application-site reactions. These application site effects are usually transient and resolve in 1–3 days.[43]

Diclofenac Topical Patch

Diclofenac is a NSAID. It is available in multiple formulations including a patch system. The patch contains 1.3% diclofenac with a DIA design (180 mg of diclofenac in 14 g of an acrylate-based adhesive).[5] The patch is similar in size to the lidocaine systems, 10 × 14 cm. The diclofenac patch is indicated in the US for treatment of acute pain due to minor strains, sprains, and contusions in adults and pediatric patients 6 years and older. The patch instructions are to apply the topical system every 12 hours to the most painful area (twice a day).[5]

A recent meta-analysis of the efficacy and safety of topical NSAIDs for osteoarthritis found that diclofenac

patch systems were safe and effective.[47] Furthermore, this international review noted that the most effective topical NSAID for relief of pain associated with osteoarthritis was the diclofenac patch. Serious gastrointestinal and renal adverse events were not associated with the topical diclofenac patch systems in the reviewed trials.[47] As a reminder, one of the major advantages of topical patch systems is that they can minimize systemic exposure and therefore AEs including the risk of gastrointestinal side effects of NSAIDs. The diclofenac patch is not indicated for the pain secondary to osteoarthritis, and further studies could clarify its usefulness for treating this condition.

Over-the-Counter Analgesic Transdermal and Topical Formulations

Active ingredients in OTC analgesic patch systems include lidocaine, capsaicin, methyl salicylate and menthol. Similar to prescription agents, patch characteristics, design, adhesion and backing material will affect the performance and safety of OTC patch systems. The use of these OTC patch systems in pain management has recently been reviewed.[13] Many OTC patch systems lack PK or efficacy data and are not indicated for pain syndromes like neuropathic pain.[13,27] OTC preparations usually have not been subject to the same rigorous clinical trials that are required for approved prescription products.[13,27] In fact, FDA revisited the underlying regulations that allow external analgesics to be commercialized without an NDA approval in 2003, and formally designated topical patches, plasters, and poultices as Category III (safety and efficacy unknown). FDA stated that in order for these dosage forms to be generally recognized as safe and effective, further data would be required including: concentration of the drug ingredient(s); extent of percutaneous absorption under occlusion; the length of contact time that it is safe to leave the product on the skin; how often the plaster or poultice needs to be changed for optimal use; the frequency of application that is considered safe and effective; whether or not directions and a warning are necessary regarding checking the area at specified intervals for erythema to prevent blistering; the age groups for whom poultices and plasters are recommended for safe use; and the adequacy of labeling of currently marketed analgesic OTC patch products.[48,49] FDA has raised issues over certain OTC analgesic patch systems that are on the market without approved market applications (ie, NDA or ANDA), as unapproved products with unsubstantiated therapeutic claims can put patients and consumers at risk.

Transdermal Analgesic Patch Systems

Transdermal analgesic patch systems are those that deliver medication through the skin to reach the systemic circulation. All of the analgesic transdermal systems available in the US contain opioids, either fentanyl or buprenorphine. All are indicated for the management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.[8,9]

The transdermal opioid patch systems provide for some advantages over oral dosing including the avoidance of first-pass metabolism, and potentially less gastrointestinal side effects. These patch systems are designed for long-term drug delivery that provides near-constant plasma levels of the opioids. This should provide sustained pain relief while avoiding the peaks and valleys of circulating drug and of pain relief that can happen with oral dosing. Every 3- or 7-day application reduces the frequency of dosing and may improve patient compliance over every 8- or 12-hour dosing with oral preparations. The use of the transdermal patch systems may also have compliance advantages over oral opioids in patients with difficulty swallowing or with vomiting problems.[11] Compared with oral morphine products, transdermal fentanyl may also be a preferred agent for patients with renal impairment.[11]

There are three approaches used in opioid patch systems that provide for long-term continual delivery of the drug. The first formulation developed was the reservoir system where a rate-controlling membrane keeps the delivery constant. A major problem with this system was manufacturing defects that occurred resulting in leakage from the sealed liquid reservoir that contains the opioid. These defects could lead to uncontrolled drug release (drug-dumping).[12] Specific lots of fentanyl patches with reservoirs were recalled in the early 2000s because of this problem.[12] Recently in 2019, the approval of two long-standing ANDAs for fentanyl patches with reservoir designs was withdrawn when FDA became aware of

> new information related to problems with the manufacturing, design, and quality control of fentanyl transdermal systems with a liquid reservoir design, leading to potential leakage, unintended opioid exposure, and potentially life-threatening adverse events.[50]

Another patch formulation approach is DIA patches that contain an excess of the drug with slow delivery where only a small fraction of the drug is delivered each day. After a dosing period of 3–7 days, greater than 80% residual drug remains in the patch. The third method is also of the DIA design but it uses drug in suspension. These systems typically have 75% of the drug in the DIA layer undissolved, but in suspension, the rest of the drug is in a saturated solution surrounding the suspended drug. As the drug in solution leaves the patch and enters the skin, the drug in suspension dissolves keeping the concentration of dissolved drug in the DIA layer constant and the delivery of the drug constant. The drug in suspension DIA patches has much lower % residue remaining after use than the DIA patches with excess drug and slow delivery.[12]

Fentanyl Transdermal Patch Systems

Fentanyl is a potent, lipophilic opioid with a low molecular weight that is readily able to penetrate the epidermis and enter systemic circulation – making it ideal for delivery via a transdermal patch system.[11] The first fentanyl patch (Duragesic™) developed in the early 1990s was of the reservoir design. It was replaced in 2009 with a DIA system patch.[8] Numerous other fentanyl patch systems have been developed some of the reservoir design, but most are of the drug in suspension DIA design. To our knowledge, there is at least one reservoir design patch remains on the market in the US.[18] Fentanyl patch systems come in a variety of strengths ranging from 12 µg/hr to 100 µg/hr. The patch systems provide for prolonged and steady delivery of the drug and are designed to help maintain a near-constant plasma concentration for the recommended application time of 2–3 days.[8]

There are safety issues that may arise from patch systems designed for constant and steady delivery of the drug. Some of these safety issues are the result of the large amount of opioid that is contained in the patch. Heating the patch will accelerate the delivery of the drug and overdose deaths have been reported.[8] Patients should be advised to avoid wearing the patch in hot tubs, saunas or hot baths, and avoid external sources of heat including heating pads, electric blankets and heated water beds. There may also be a danger for patients with high fevers or whose body temperature may rise with strenuous exertion. It is advised that these patients be closely monitoring and reduce the dose if necessary. Because of the residual fentanyl in the used patches, careful disposal is important [discussed earlier].[8]

When initiating therapy with a fentanyl patch, the skin under the patch absorbs fentanyl, and a depot in the upper layers of the skin is formed. Fentanyl then enters systemic circulation from this skin depot.[8,17] It takes 24–72 hours for steady state to be achieved. It is advised that patients should be monitored closely for respiratory depression, especially within the first few days of initiating therapy as serum concentrations from the initial patch peak.[8]

Similar to other patch systems, adhesion for the fentanyl patch can be an issue. With an application period lasting days, holding power of these patches is very important in order to maintain constant delivery of medication. Poor adhesion of fentanyl patches that mimicked end-of-dosage failure and prompted early patch replacements in hospitalized cancer patients has been reported.[51]

Buprenorphine Transdermal Patch

Buprenorphine is a partial mu opioid agonist that may have advantages over traditional pure mu opioids.[52] It is lipophilic in nature and of low molecular weight. It can readily cross the epidermis and enter systemic circulation when it is applied topically. The buprenorphine transdermal patch system uses a polyacrylate-based adhesive and is of the DIA design.[9] It is applied for 7 days and available in 5 dosage strengths ranging from 5 to 20 µg/hr. Higher dose formulations are available outside of the US, but clinical trials noted a corrected QT interval (QTc) prolongation at 40 µg/hour doses (given as 2 × 20 µg/hour systems).[9]

The buprenorphine patch system uses the DIA design that has a large amount of drug in the DIA layer and only delivers a small amount each day. For instance, the 5 µg/hr patch contains 5 mg of buprenorphine and after 7 days, 4.26 mg residual remains in the patch. Only 0.74 mg is delivered over 7 days, an average of about 0.106 mg/day, or about 2%/day. Approximately 85% remains as residue in the used patch.

The adhesive holding power is critical for a patch that has a 7-day application period. The buprenorphine patch system contains similar warnings to the fentanyl patch systems that included accelerated release of drug when exposed to external heat sources and precautions about proper disposal of the used patches.[9] Like with the fentanyl patches, when initiating therapy, peak concentrations of buprenorphine are not achieved for 24–72 hours and

patients should be monitored for respiratory depression during this period.[9]

Potential Future Analgesic Patch Formulations

As discussed, the ability of medications to traverse the skin is a rate-limiting step in the effectiveness of topical and transdermal products. A variety of "hi-tech" patch technologies have been employed to increase skin permeability and enhance drug delivery. These include the use of micron-sized needle systems, micro electric current iontophoresis and electroporation systems, micro nanotechnology devices and even spray-film aerosol patch formulations. Although we look forward to the development of these technologies, as none of these systems are currently employed in marketed analgesic patch formulations, a more detailed assessment is outside of the scope of this review.[52–55]

Conclusions

Analgesic patch systems, both topical and transdermal, are an effective option for treating a variety of pain syndromes and have advantages for drug delivery. Topical and transdermal systems provide benefits over oral dosing and can control drug release for prolonged delivery of analgesic medications. Topical patches are designed to keep medication localized for targeted delivery and can reduce side effects from systemic exposure. Transdermal patches deliver medication systemically and can provide more uniform plasma drug levels compared to oral administration, potentially improving compliance while bypassing first-pass metabolism and minimizing GI side effects.

Design is important in patch system creation, and characteristics and attributes of patch delivery systems affect the delivery, efficacy, and safety of the analgesic. Adhesion, though initial tack, withstanding shear, and on peeling, is a critical attribute of these systems, which also impacts compliance, cost, efficacy and safety. Patch lift can result in suboptimal drug delivery.

The amount of analgesic delivered is more important than the concentration of drug in the patch. Patch delivery systems, after use, have a residual of 10–95% of drug originally in the system. Patches that are bioequivalent may deliver the same amount of drug, but can differ substantially in design, adhesive used, and properties such as the amount of drug in the patch and the amount of residue.

Topical analgesic patch systems deliver lidocaine, lidocaine plus tetracaine, capsaicin, or diclofenac. Lidocaine patch systems, which come in a variety of bioequivalent formulations, are indicated for PHN pain, but there is evidence of providing benefit in other neuropathic pain conditions. Capsaicin patches are indicated for the management of PHN neuropathic pain in the US and recently filed for approval for treatment of diabetic peripheral neuropathy. Treatment is repeated every 3 months in a clinic setting under medical supervision. Diclofenac topical patches are available in topical formulations and could potentially minimize the systemic side effects associated with oral NSAIDs.

Fentanyl or buprenorphine transdermal analgesic patch systems in the US are designed to provide steady delivery with nearly constant plasma concentrations for several days. Buprenorphine transdermal patches are applied for 7 days and have multiple dose options available, although QTc prolongation has been seen at 40 µg/hr and higher. Exposure to heat has been a concern for transdermal medication patch systems, resulting in accelerated delivery and serious adverse events including deaths.

Analgesic patch systems are an effective option for treating a variety of pain syndromes. Attributes of these patch systems, that derive from their design and composition, affect the delivery of drug, and their efficacy and safety.

Abbreviations

AE, adverse events; ANDA, abbreviated new drug application; DIA, drug in adhesive; DPN, diabetic peripheral neuropathy; GI, gastrointestinal; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; OTC, over-the-counter; PSA, pressure-sensitive adhesive; PHN, postherpetic neuralgia; QTc, corrected QT interval.

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