Available online at www.sciencedirect.com
SCIENCE DIRECT
International Journal of Pharmaceutics 317 (2006) 1–6
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Mini review

Microprocessor controlled transdermal drug delivery

J. Anand Subramony [a,*], Ashutosh Sharma [b], J.B. Phipps [a]

[a] *ALZA Corporation, 1900 Charleston Road, Mountain View, CA 94043, United States*
[b] *Vyteris Inc., 13-01 Pollitt Drive, Fair Lawn, NJ 07410, United States*

Received 13 December 2005; received in revised form 20 December 2005; accepted 29 March 2006
Available online 18 April 2006

Abstract

Transdermal drug delivery via iontophoresis is reviewed with special focus on the delivery of lidocaine for local anesthesia and fentanyl for patient controlled acute therapy such as postoperative pain. The role of the microprocessor controller in achieving dosimetry, alternating/reverse polarity, pre-programmed, and sensor-based delivery is highlighted. Unique features such as the use of tactile signaling, telemetry control, and pulsatile waveforms in iontophoretic drug delivery are described briefly.

Keywords: Transdermal; Iontophoresis; Controller; Lidocaine; Fentanyl; Drug delivery

1. Introduction

Transdermal drug delivery introduces therapeutic agents into the body through the skin. Drug transport can either be passive, relying on drug diffusion across the skin, or actively driven by application of an electric field (iontophoresis) (Phipps et al., 2002). Compared to other means of drug delivery, the transdermal route offers a unique combination of advantages: transdermal drug delivery is non-invasive; transdermal drug absorption is not affected by food intake; and transdermally delivered drug is not subject to first-pass metabolism in the liver. In addition, active transdermal drug delivery systems allow precise control of drug dosing and delivery rate through modulation of the electric field used to drive drug transport.

Fig. 1 depicts the movement of ions through the skin during iontophoresis. Under the influence of an electric field, positively charged drug ions from the donor compartment, which is in contact with a positive electrode (anode), migrate into the skin, while biological anions (primarily chloride) travel from the body into the donor reservoir. Simultaneously, anions from the receptor compartment, which is in contact with a negative electrode (cathode), migrate into the skin, while biological cations such as Na^+ and K^+ flow from the body into the receptor, or counter-electrode reservoir. The rate of drug ion transport is generally proportional to the magnitude of applied current. Specifically, the transdermal flux of drug ion, J_d, during iontophoresis is described by the following expression derived from Faraday's law:

$$J_d = \frac{t_d I M_d}{Z_d F}$$

where t_d is the drug transport number, I the current density, M_d the molecular weight of the drug ion, Z_d the charge of the ion, and F is Faraday's constant. The transport number t_d, which expresses the charge carried by drug ion d as a fraction of the total transported charge, is unique for each drug ion and depends on its mobility, charge, and concentration in skin relative to those of the other migrating species. The two drug formulation parameters that most affect the rate of transdermal drug delivery are, therefore: (1) drug content, which influences the drug concentration in the skin, and (2) pH, which influences the charge state and, thus, the solubility of the drug ion as well as the permeability of skin to the drug ion. These formulation parameters, together with the magnitude of the applied current, largely determine the rate of drug delivery from an iontophoretic system.

Inspired by the early experiments and observations of 18th and 19th century scientists such as Etius, Veratti, and Morton (as reviewed by Banga, 1998), the French scientist, Leduc, demonstrated the feasibility of iontophoresis with in vivo studies in rabbits at the beginning of the 20th century (Leduc, 1908). Early clinical applications of iontophoresis focused largely on the inhibition and generation of sweat, which illustrate the

* Corresponding author. Tel.: +1 650 564 2418; fax: +1 650 564 2484.
E-mail address: asubramo@alzus.jnj.com (J.A. Subramony).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.03.053

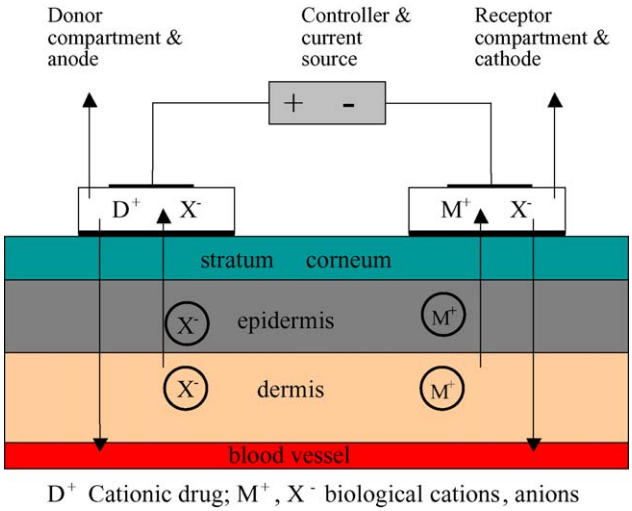

Fig. 1. An iontophoretic drug delivery system comprising donor and receptor compartments along with a current source and controller. D^+: cationic drug; M^+: biological cations; X^-: biological anions.

therapeutic and diagnostic application of iontophoresis. While control of sweating is needed for the treatment of hyperhidrosis (as reviewed by Banga, 1998), generation of sweat is required for the diagnosis of cystic fibrosis (CF). In the 1950s, Gibson and Cooke (1959) used iontophoretic delivery of pilocarpine to induce rapid sweating in order to facilitate diagnosis of cystic fibrosis. Based on this concept, several commercial iontophoretic systems for diagnosis of cystic fibrosis (CF Indicator® (Scandipharm, Birmingham, Alabama), Webster Sweat Inducer (Wescor Inc., Logan, Utah)) have been developed since (Yeung et al., 1984; Fogt et al., 1984). Iontophoresis has also been used to deliver drugs such as lidocaine for local anesthesia, or dexamethasone for the treatment of local inflammation (Banga, 1998). A major advance in the capabilities of iontophoretic systems came with the availability of microprocessors, when, in 1971, Intel Corporation introduced the first commercial microprocessor. Microprocessors allow precise control of drug dosing and delivery profile and provide increased system safety through monitoring of system functions such as current levels and battery voltage. The ability of microprocessor-controlled iontophoretic systems to offer noninvasive and controlled administration of medications to patients has spurred an increased interest in the use of iontophoresis for systemic delivery of drugs, especially those with limited oral bioavailability.

2. Commercial devices for transdermal delivery of drugs via iontophoresis

Currently, commercial devices for transdermal drug delivery are available from Iomed Inc. (Salt Lake City, UT), Empi Corporation (St. Paul, MN), and Travanti Pharma Inc. (St. Paul, MN). These systems are sold without drug and require the physician to add drug solution to a reservoir before treatment. The IontoPatch® (Travanti Pharma Inc.) incorporates the company's wearable electronic disposable drug delivery platform (WEDD®), which is based on a thin, flexible, low-cost battery technology within a single-use, disposable, iontophoretic patch. Vyteris, Inc. (Fair Lawn, NJ) has recently received a New Drug Application (NDA) approval for a prefilled transdermal lidocaine system, which uses a mild electric current to rapidly administer lidocaine cations through the skin for local anesthesia. An NDA for a transdermal iontophoretic system providing systemic drug delivery has also been filed by ALZA Corporation (Mountain View, CA). ALZA's E-TRANS® fentanyl HCl is designed for patient controlled administration of the opioid fentanyl for acute pain management in a medically supervised setting (Viscusi et al., 2004). In addition to these iontophoretic drug delivery systems, a device to extract glucose from the skin via reverse iontophoresis to detect hypoglycemia and hyperglycemia has been developed by Cygnus Inc. (Redwood City, CA) which is currently marketed by Animas Corp. (West Chester, PA).

3. Electronic control circuitry in iontophoretic drug delivery

A typical iontophoretic drug delivery system consists of four types of components: electrodes (anode and cathode), reservoirs containing biocompatible electrolytes or drug in suitable formulations, an electrical energy source such as a battery, and an electronic controller. The electronic controller greatly expands the capabilities of the iontophoretic system by allowing regulation of the current output in a preprogrammed or on-demand fashion. Three different types of current output patterns have been used in iontophoretic systems described in the literature: (1) continuous unidirectional current, (2) periodically reversing continuous current, and (3) pulsed unidirectional current. In addition to regulating current output, the electronic control circuitry can also provide feedback about the system operation to the patient or caregiver, allow remote control by telemetry, and extend the system shelf life.

One of the major advantages of iontophoretic drug delivery is the ability to readily and precisely control the drug-delivery profile through modulating the current output. Most commercially available iontophoretic systems apply continuous unidirectional constant current. Electronic controllers are used to keep current output constant by automatically adjusting the applied voltage for intra- and interindividual variations in skin resistance, resulting in a constant drug delivery rate. The simplest current regulator consists of a battery and a resistor connected in series to limit the maximum output current to the patient. More commonly, active current regulators use a field effect transistor (FET) to obtain constant current. An iontophoretic device with electrical dosimetry control has also been described; in this case, the charge and, thus, the total dose delivered to the patient are fixed, while the dose duration or current output may vary from person to person (Tapper, 1989).

In addition to direct-current applications, the use of complex waveforms has been described in the literature. In one system, a polarity-control circuit added between current source and electrodes periodically reverses the direction of current to the electrodes (Lattin and Spevak, 1983), leading to drug delivery from both electrode reservoirs. This strategy can serve to

reduce skin irritation, especially when higher drug doses are being delivered (Tapper, 1993). A storage capacitor and a resistor connected in parallel and connected to the diode in the circuit were used to achieve this periodic reversal of current. By using a timer circuit to communicate between the current source and the polarity-switching circuit, the current can be modulated during the switching process. Periodic interruption of treatment current by a relatively short pulse of current in the opposite direction has been shown to prevent the formation of undesirable vesicles and bulla in the treated skin (Tapper, 1982). An electronic controller capable of automatically imposing the reverse pulse of current at regular intervals is composed of a transformer, diode, and shunt transistor.

Use of pulsed current to drive transdermal drug delivery represents another approach to iontophoresis. Using a microcontroller, pulses are generated at a predetermined frequency and pulse width. The controller also determines the attributes of each pulse segment, such as amplitude and waveform, which can assume sinusoidal, trapezoidal, exponential, or rectangular shape. If the pulse voltage is too small, little or no drug delivery will occur since the current induced will only charge the capacitive elements of the system (electrode and reservoir) and skin (space charge layers at the skin boundaries). Unidirectional dual-segment waveforms have been used to compensate for these capacitive losses (McNichols and Lattin, 1991). The first segment is a constant voltage pulse that rapidly charges the capacitive components of the system and skin, while the second segment is a constant current pulse that promotes net drug ion transfer into the skin. Similarly, an application specific integrated circuit (ASIC) can serve to overcome impedance of body tissues during discontinuous delivery of a therapeutic agent (McNichols et al., 1997).

Drug delivery from most microprocessor-controlled iontophoretic systems is preprogrammed or patient activated. There are only a few examples of sensor-based, closed-loop transdermal delivery devices. One of those is a system that provides feedback control of the drug delivery rate based on a patient's physical activity status, which is detected by a piezoelectric sensor (Lattin et al., 1993). This strategy is similar to the one used in activity-sensing pacemakers.

In addition to controlling the drug delivery rate, the electronic controller can also be used to provide feedback about system operation to the patient and caregiver. Typically, visual or audible signals are used to alert the patient to a condition or event, such as the start or termination of drug delivery, or the need to take corrective action. An electrotransport drug delivery device that can generate and transmit a tactile signal to the patient's skin during operation has also been described (Sorenson et al., 2001). The tactile signal may be generated either electrically or electromechanically with a device such as a piezoelectric element or magnetodynamic element that is placed in contact with the skin.

Storage and display of data associated with the system function can be important features of an iontophoretic system. Lattin and Bernstein (1998) have devised an electrotransport delivery device with circuit elements to count and store the number of patient-initiated activations during treatment of pain. In addition, a microcontroller-based iontophoretic delivery system that uses electrically erasable, programmable, read-only memory (EEPROM) has been proposed (Millot, 2000).

It has been suggested in the literature that drug delivery from an iontophoretic system could be controlled through a remote telemetry link based on a radio frequency, ultrasonic, optical, infrared, or inductively coupled signal (Lattin and Riddle, 1996). In addition, the delivery system could transmit system or patient status data back to the remote control unit through this telemetry link.

Batteries are an integral part of iontophoretic devices. In systems in which the batteries are hard-wired to the controller at the time of manufacture, the shelf-life of the battery could determine the shelf-life of the entire iontophoretic system, making it critical to minimize any current drain from the battery before system use. This can be achieved through a metal oxide semiconductor field effect transistor (MOSFET)-based activation circuit that prevents activation of the current-generating circuit during system storage (McNichols et al., 1994). The activation circuit is electrically connected to the power source and is responsive to the magnitude of the resistance between the electrodes of the delivery system. When the system is applied to the patient, the resistance between the electrodes is greatly reduced and the activation circuit automatically starts drug administration. In addition to enhancing shelf-life, this system design increases patient convenience since no action is required by the patient or caregiver to start the system.

4. Transdermal delivery of lidocaine for local anesthesia

An ideal topical anesthetic for minimizing the pain associated with needlesticks (during cannulation or venipuncture) or pain associated with minor dermal surgical procedures should be easy to apply, safe, and rapidly effective (Lener et al., 1997). Several topical formulations of local anesthetics have been developed, such as a eutectic mixture of local anesthetics cream (EMLA, Astra-Zeneca Pharmaceuticals LP, Wilmington, DE), which contains a combination of lidocaine (2.5%) and prilocaine (2.5%), and a liposomal lidocaine formulation (ELA-Max, Ferndale Laboratories Inc., Ferndale, MI). While both formulations have been shown to be effective in reducing the pain associated with venipuncture and venous cannulation (Eichenfield et al., 2002), EMLA cream requires at least 1 h from application to provide effective anesthesia (EMLA package insert), while ELA-Max requires 30 min (ELA-Max package insert). In addition, many patients still experience significant pain despite the use of these anesthetics (Kleiber et al., 2002).

In small clinical trials, lidocaine iontophoresis has been shown to provide effective dermal anesthesia for needlesticks in 7–15 min (Ashburn et al., 1997; Zempsky et al., 1998; Wallace et al., 2001). The LidoSite™ Topical System (Lidocaine Topical Anesthetic System) (Fig. 2) developed by Vyteris, Inc. (Fair Lawn, NJ) is a small, easy-to-use, iontophoretic lidocaine delivery system composed of a drug-filled patch connected to a controller. The patch is a one-time use disposable drug product, which contains a 5 cm^2 circular drug reservoir (anode) that delivers lidocaine and epinephrine to the skin, and an oval return

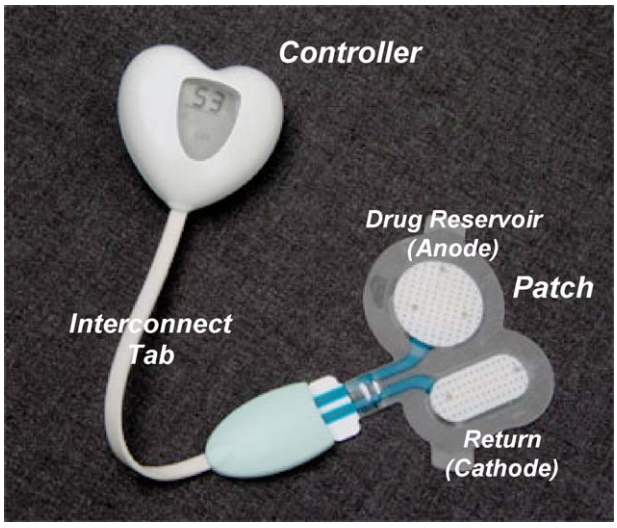

Fig. 2. Vyteris Inc. LidoSite™ topical system.

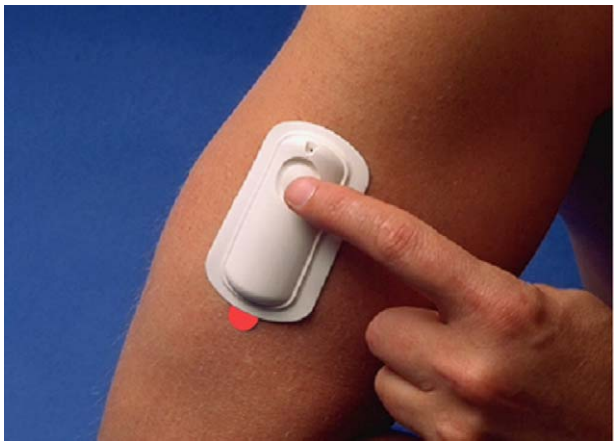

Fig. 3. An iontophoretic patch applied to the upper arm of a patient is initiated for drug delivery using the controller button.

reservoir (cathode) containing electrolytes. The portable controller, which is the more expensive component of the system, can be reused approximately 100 times before it is rendered unusable. It contains a non-replaceable battery that provides up to hundred 10 min applications of direct current at 1.77 mA, and uses discrete analog circuitry to control the delivery of current to the patch. An embedded microprocessor is primarily intended to monitor the current application during controller operation and to control the system indicators. To accomplish these tasks, the microprocessor is programmed to run as a time source. Delivery is initiated by pressing the "ON" button, which allows the device to detect skin at the patch site. Once started, the profile proceeds through three stages of ramp up, constant current delivery, and ramp down.

The controller incorporates both visual and audio indicators to inform the user about the system status. A green light-emitting diode (LED) is used to indicate normal conditions, while activation of a yellow LED alerts the user to an abnormal condition. The controller also has an internal beeper that sounds at the end of every delivery or self-check function. A liquid crystal display (LCD) shows the number of patches used with a given controller.

The LidoSite™ Topical System has been shown to be safe and effective in Phase III clinical studies conducted in more than 600 patients. Vyteris received NDA approval, to commercialze this system in 2004, from the Center for Drug Evaluation and Research (CDER) branch of the US FDA. The controller associated with this system is a medical device covered by a 510(k) premarket approval application and was approved separately by the Center for Devices and Radiological Health (CDRH) branch of the US FDA.

5. Transdermal delivery of fentanyl for patient-controlled analgesia

Specialized devices, such as IV pumps for patient-controlled analgesia (PCA), were introduced more than 20 years ago. Over the past decade, PCA has become a standard of care in many hospitals for management of postoperative and other acute pain. The clinical experience with PCA demonstrates its safety and efficacy in improving pain control for patients, as documented in a large body of literature (as reviewed by Woodhouse and Mather, 1997).

Recently, a patient-controlled transdermal system (PCTS) that uses electrotransport for on-demand delivery of the opioid analgesic fentanyl has been developed as a safe, noninvasive, and convenient alternative to conventional IV PCA. Figs. 3 and 4 show a photograph and an exploded view, respectively, of the E-TRANS® fentanyl HCl system, which is presently being reviewed by the FDA. Fentanyl was selected for use in the PCTS because it is a potent analgesic with proven skin compatibility (DURAGESIC® Fentanyl Transdermal System, Janssen Pharmaceutica Products, L.P., Titusville, NJ 08560) that is commercially available as a salt and has good solubility and stability in water.

When activated by the patient, the preprogrammed, disposable E-TRANS® fentanyl HCl system delivers up to 80 doses of 40 μg fentanyl in a 24-h period. Based on the results of pharmacokinetic studies in human subjects (Fig. 5) (Gupta et al., 1998; Gupta et al., 1999), a current of 170 μA was selected to deliver each 40 μg dose over 10 min. The maximal number of 80 doses per system was shown to be sufficient to allow the majority of patients to achieve safe and effective analgesia. A 24-h treatment period was chosen to be consistent with the normal hospital rhythms for patient evaluation and treatment orders, as well as for patient convenience. If analgesia is required for more than 24 h, a new system can be applied to a different skin site.

In addition to the fundamental electronic design parameters of dose current, dose duration, and number of doses allowed per system, other important safety and patient feedback features are included in the system design. For example, to reduce the likelihood of inadvertent dose activation during normal handling and use, the dose initiation button is recessed, and a double push within 3 s is required to start delivery.

Since the E-TRANS® fentanyl HCl system is fully integrated and preprogrammed, no additional assembly or programming by

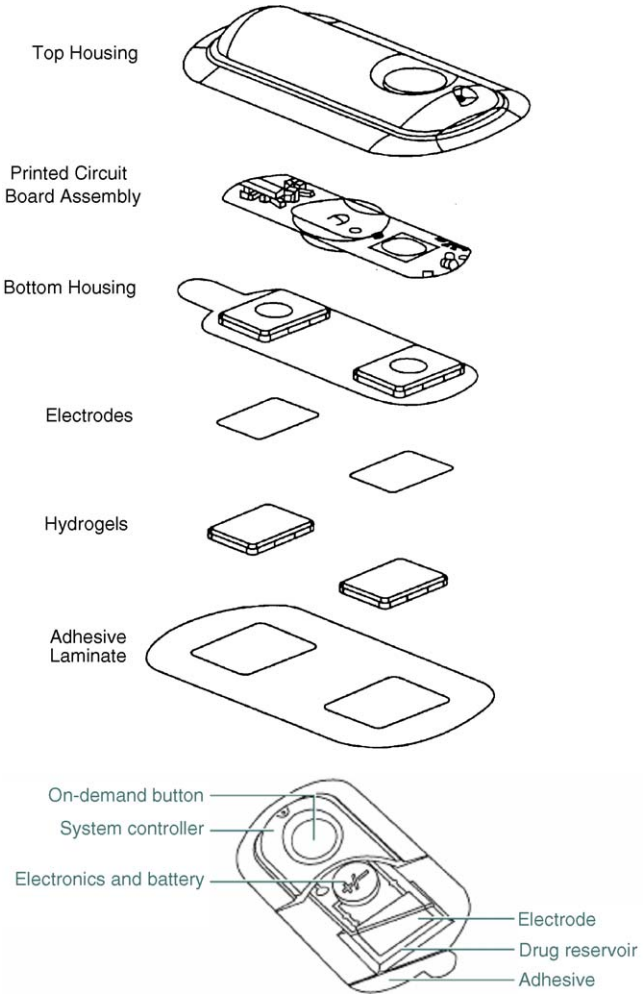

Fig. 4. Internal view of an iontophoretic drug delivery system showing major components: top housing, printed circuit board assembly that forms the controller, a bottom housing containing reservoirs for placement of electrodes and hydrogels, and an adhesive laminate (reproduced from international patent publication number WO 96/39222).

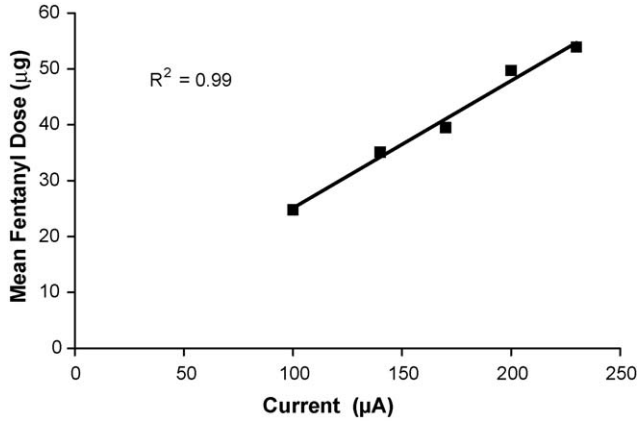

Fig. 5. Plot showing the mean fentanyl dose versus the amount of applied current.

the user is required. This is particularly important in light of the numerous reports of programming errors with IV PCA pumps. The size, shape, and materials of the system allow it to conform to the upper arm and the chest, allowing the patient comfortable, unrestricted movement during wear. Electromagnetic emissions from the system are very low and unlikely to affect the proper operation of electronic devices typically encountered in a medically supervised setting.

The electronic heart of the PCTS consists of a printed circuit board assembly (PCBA). The PCBA contains a single lithium coin cell and an application-specific integrated circuit (IC) that controls all system operations, including timing, output current and voltage levels, error detection, and dose counting.

When the system button is pressed twice, the IC starts a 10 min dose delivery period. A 24-h timer is also initiated after completion of the first dose, and the number of doses activated is tallied. The IC monitors output current continuously and adjusts the applied voltage to compensate for changes in skin resistance so as to maintain a constant current of 170 μA. The IC also monitors battery voltage, clock oscillator function, and the output current and voltage, and will terminate system function if these parameters are outside of normal operating ranges.

An LED and audio transducer provide feedback to the caregiver and patient. The LED illuminates, and the audio transducer beeps when the system is activated to signal dose initiation. After a dose is completed, the LED turns off. The system then automatically indicates the approximate number of doses (in blocks of five) completed by displaying a sequence of LED pulses. This level of estimation reduces the counting time required of the caregiver, while providing a good estimate of the number of doses delivered.

In clinical studies conducted among postoperative patients (Brown et al., 1998) E-TRANS® fentanyl HCl was shown to be significantly more efficacious than placebo in providing pain control, based on withdrawal from the study due to inadequate analgesia after the first 3 h of treatment and mean pain intensity as primary efficacy variables. The patients were randomized postoperatively in a 3:1 ratio to receive E-TRANS® fentanyl ($n = 77$) or placebo systems ($n = 25$). Significantly fewer patients receiving E-TRANS® fentanyl than placebo withdrew from the study because of inadequate pain control (7.9% versus 40.9%, $p = 0.0001$). Compared to placebo, patients using E-TRANS® fentanyl also reported significantly lower mean pain intensity as measured on a 100 mm visual analog scale (20.6 mm versus 37.3 mm, respectively, $p = 0.0006$) at the last observation. Patient and investigator global assessments indicated that successful pain control was achieved significantly more often with E-TRANS® fentanyl than with placebo (89.6% versus 59.1%, $p = 0.0008$). Significant respiratory depression was not observed in any patient. Adverse events were consistent with the patients' postoperative status and use of opioid analgesia. The most common treatment-related adverse event was mild erythema at the application site. The efficacy and safety of E-TRANS® fentanyl HCl system was also compared with that of standard IV morphine PCA in prospective, randomized controlled, parallel group trials and the patient assessments have been reported (Viscusi et al., 2004).

6. Conclusions and future directions

A new generation of transdermal drug delivery systems based on iontophoresis or active electrotransport is in the late stages of development and promises to enhance the treatment of local and systemic medical conditions. The incorporation of microprocessors into these systems has been an important advancement to ensure safe and efficacious administration of potent drugs. In addition, these systems are capable of monitoring, recording, and displaying critical system functions to the caregiver and patient. While still unrealized, the closed-loop use of information from biophysical or biochemical sensors to achieve individualized therapies, will likely drive future innovation in this field.

References

Ashburn, M., Love, G., Gaylord, B., Gautheier, M., Kessler, K., 1997. Iontophoretic administration of 2% lidocaine HCL and 1:100,000 epinephrine in man. Clin. J. Pain 13, 1322–1326.

Banga, A.K., 1998. Electrically Assisted Transdermal and Topical Drug Delivery. Taylor & Francis, Bristol, PA.

Brown, C.R., Moodie, J.E., Bisley, E.J., 1998. Safety and efficacy of Transfenta in the treatment of postoperative pain. In: Proceeding of the 17th Annual Scientific Meeting of the American Pain Society, p. 192 (Abstract #886).

Eichenfield, L.F., Funk, A., Fallon-Friedlander, S., Cunningham, B.B., 2002. A clinical study to evaluate the efficacy of ELA-Max (4% liposomal lidocaine) as compared with eutectic mixture of local anesthetics cream for pain reduction of venipuncture in children. Pediatrics 109, 1093–1099.

Fogt, E.J., Norenberg, M.S., Untereker, D.F., Coury, A.J., 1984. Fluid absorbent quantitative test device, US patent 4,444,193.

Gibson, L.E., Cooke, R.E., 1959. A test for the concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. Pediatrics 23, 54–549.

Gupta, S.K., Southam, M., Sathyan, G., Klausner, M., 1998. Effect of current density on pharmacokinetics following continuous or intermittent input from a fentanyl electrotransport system. J. Pharm. Sci 87, 976–981.

Gupta, S.K., Sathyan, G., Phipps, J.B., Klausner, M., Southam, M., 1999. Reproducible fentanyl doses delivered intermittently at different time intervals from an electrotransport system. J. Pharm. Sci 88, 835–841.

Kleiber, C., Sorenson, M., Whiteside, K., Gronstal, B.A., Tannous, R., 2002. Topical anesthetics for intravenous insertion in children: a randomized equivalency study. Pediatrics 110, 758–761.

Lattin, G.A., Spevak, R., 1983. US Patent, 4,406,658.

Lattin, G.A., Padmanabhan, R., Grace, M.J., Sorenson, P.D., Phipps, J. B., McNichols, L.A., 1993. US Patent 5,213,568.

Lattin, G.A., Riddle, T.A., 1996. US Patent 5,551,953.

Lattin, G.A., Bernstein, K.J., 1998. US Patent 5,843,014.

Leduc, S., 1908. Electric Ions and Their Use in Medicine. Rebman Ltd., Liverpool, UK.

Lener, E.V., Bucalo, B.D., Kist, D.A., Moy, R.L., 1997. Topical anesthetic agents in dermatologic surgery. Dermatol. Surg. 23, 673–683.

McNichols, L.A., Lattin, G.A., 1991. US Patent 5,047,007.

McNichols, L.A., Bradzinski, J.D., Hayden, G.K., 1994. US Patent 5,314,502.

McNichols, L.A., Bradzinski, J.D., Haak, R. P., 1997. US Patent 5,697,896.

Millot, P., 2000. US Patent 6,167,302.

Phipps, J.B., Scott, E.R., Gyory, J.R., Padmanabhan, R.V., 2002. Iontophoresis. In: Swarbrick, J., Boylan, J.C. (Eds.), Encyclopedia of Pharmaceutical Technology, 2nd ed. Marcel Dekker Inc., New York, pp. 1573–1587.

Sorenson, P.D., Lattin, G. A., Nichols, L.A., 2001. US Patent 6,175 763.

Tapper, R., 1982. US Patent 4,340,047.

Tapper, R., 1989. US Patent 4,822,334.

Tapper, R., 1993. US Patent 5,224,927.

Viscusi, E.R., Reynolds, L., Chung, F., Atkinson, L.E., Khanna, S., 2004. Patient-controlled transdermal fentanyl hydrochloride vs. intravenous morphine pump for postoperative pain: a randomized controlled trial. JAMA 291, 1333–1341.

Wallace, M.S., Ridgeway, B., Jun, E., Shulteis, G., Rabussay, D., Zhang, L., 2001. Topical delivery of lidocaine in healthy volunteers by electroporation, electroincorporation, or iontophoresis: an evaluation of skin anesthesia. Reg. Anesth. Pain Med 26, 229–238.

Woodhouse, A., Mather, L.E., 1997. Patient-controlled analgesia (PCA) for postoperative pain relief: what have we learned and where do we go from here? Analgesia 3, 1–14.

Yeung, W.H., Palmer, J., Schidlow, D., Bye, M.R., Huang, N.N., 1984. Evaluation of a paper-patch test for sweat chloride determination. Clin. Pediatr. 23, 603–607.

Zempsky, W.T., Anand, K.S., Sullivan, K.M., Fraser, D., Cucina, K., 1998. Lidocaine iontophoresis for topical anesthesia prior to intravenous line placement in children. J. Pediatr. 32, 1061–1063.