CHAPTER 19

Topical and Systemic Drug Delivery Systems for Targeted Therapy

URS O. HÄFELI and AMIT KALE
Faculty of Pharmaceutical Sciences, The University of British Columbia

Content
19.1 Introduction 476
19.2 Overcoming the epidermal (skin) barrier 477
   19.2.1 Physiology of the skin 478
   19.2.2 Skin conditions affecting permeation of active drugs 479
19.3 Advances in topical and transdermal drug delivery 479
   19.3.1 Iontophoresis 481
   19.3.2 Microneedle-based devices 484
   19.3.3 Skin abrasion 485
   19.3.4 Needleless injection 488
   19.3.5 Ultrasound (sonophoresis or phonophoresis) 489
   19.3.6 Laser radiation 489
   19.3.7 Magnetophoresis 490
   19.3.8 Synergistic effects of combination treatments 490
19.4 Other methods of increasing local drug concentration 492
   19.4.1 Local catheterization 492
   19.4.2 Epidural and intrathecal delivery systems 492
   19.4.3 Magnetic targeting 493
   19.4.4 Slow-release implants based on biodegradable polymers 497
   19.4.5 Lipid-based drug delivery 498
19.5 Oral dosage forms for analgesia 499
   19.5.1 Immediate-onset systems 499
   19.5.2 Slow-release systems 500
19.6 Outlook 502

*Peripheral Receptor Targets for Analgesia: Novel Approaches to Pain Management*, Edited by Brian E. Cairns
Copyright © 2009 John Wiley & Sons, Inc.
19.1 INTRODUCTION

The most effective drugs in the fields of pain management and pain treatment are opioids. As with all highly active drugs, however, their use produces not only the desired effect of pain amelioration but also toxicities and side effects. The side effects include nausea, constipation, and central nervous system (CNS) depression or excitation. CNS depression is more common than excitation and leads to drowsiness, lightheadedness, euphoria or dysphoria, and confusion. The less commonly observed CNS excitation side effects include hyperalgesia (extreme sensitivity to pain), myoclonus (voluntary jerking of muscles), or, in rare cases, seizures. Some less common side effects of opioids are urinary retention, respiratory depression, pruritus, and miosis. Most of these side effects can be managed well, for example, by administering the antiemetic drug metoclopramide for the treatment/prevention of nausea and by using oral laxatives, suppositories, or enemas for the treatment of constipation. Such additional drug interventions for the prevention of side effects would be rendered unnecessary if these side effects could be kept to a minimum, an outcome that is possible when opioids are delivered only to where they are needed.

Although early attempts at targeted drug delivery were described by the Roman scholar Pliny the Elder (23–79 AD) and by the Greek speculative scientist Thales of Miletus (ca. 624–547 BC), it was not until 1900 that drug targeting became a clearly stated concept. In that year, Paul Ehrlich spoke about his “search for the magic bullet” in his Croonian lecture before the Royal Society [1]. He was looking for a cure for syphilis and some 9 years later found it with his synthesis of salvarsan. Salvarsan proved to be amazingly effective because it targeted only the bacterial intruder in patients and spared all other cells. For these two reasons, it quickly became the most prescribed drug ever until the advent of penicillin in the 1940s. Salvarsan demonstrates how packaging of the active component arsenic into the organic arsenical compound arsphenamine can reduce undesired systemic side effects by being specifically targeted toward the syphilis-causing bacteria.

In principle, drug targeting can be achieved by physical or biological means [2,3]. The physical means of drug targeting include the direct application of a drug into the target tissue (the diseased area) via one of the many different methods to be discussed in this chapter. A more indirect application of physical means includes passive drug targeting in which the drug itself, or the drug bound to a nano- or microsized carrier, spontaneously accumulates in areas with leaky vasculature (e.g., tumors) with the help of the enhanced permeability and retention (EPR) effect [4]. The reasons for this accumulation are blood flow and tissue pressures, as well as accumulation of drugs based on abnormal pH values [5] and/or temperatures [6] in the pathological zone. Another more recent physical means of drug delivery is the combination of an active drug with a magnetically responsive carrier, the result of which is then directed, accumulated, and held in the target tissue with the help of externally applied magnetic fields [7]. Overall, the aim of employing physical means in drug targeting is to gain improved control over the fate of the drug.

Biological means of drug targeting refer to the use of drugs with a natural affinity for body tissues, most advantageously for the diseased tissue of interest. Not all drugs have this natural affinity and therefore constructs must be engineered to fill the gap. Most often, the drug is directly connected to specific “vector” molecules or ligands that are able to bind to specific groups in the body and thus accumulate in the target tissue. To date, the most successful biologically targeted drug deliveries have included the use of monoclonal antibodies, peptides, and specific cell receptor ligands [8–13] either on their own or bound to pharmaceutical drug carriers. Such carriers include soluble polymers, microcapsules, microparticles, cells, cell ghosts, liposomes, and micelles [2].

It is important to understand that for both physical and biological drug targeting, simply getting the drug near the site of action may not be sufficient. To guarantee that the drug is able to bind to (pain) receptors or to pass through membranes and reach the target cells (e.g., neurons), cell compartments, or intracellular target molecules, the drug must be first released from the mentioned drug carriers. This release occurs by passive mechanisms, such as desorption or release from within microspheres, by enzymatic mechanisms, such as the chemical cleaving of ester bonds, or by physical effects, such as temperature changes or ultrasound.

The group of drug delivery systems that can be targeted both by physical and biological means is the chemical drug delivery systems which consist of a drug chemically linked to a carrier molecule. In order to be active, the chemical link between drug and carrier molecule must be broken at the time the effect is needed and the active component is then released. This is often done by enzymatic means, taking advantage of abundant esterases present in the human blood and other body compartments. This so-called prodrug therapy [14,15], where a nonactive drug-carrier construct is activated in the body, might also be useful in the area of local pain treatment. It has already been successfully used for the treatment of inflammatory bowel disease with a polymeric poly(anhydride ester) linked to salicylic acid [16].

19.2 OVERCOMING THE EPIDERMAL (SKIN) BARRIER

The skin can be used both as a major target for topical drug delivery (i.e., drug delivery to the skin for skin treatment) and also as an access point for transdermal drug delivery (i.e., drug delivery through the skin, mostly for systemic drug therapy). Conceptually, the skin is the most accessible body organ, can be used for the delivery of highly potent drugs without going through the parenteral route, and has been a major target of the pharmaceutical industry’s developmental efforts in recent years. At the time of this writing, 19 transdermal products are U.S. Food and Drug Administration (FDA)
approved in the United States [17], generating predicted sales of more than $4.5 billion in 2008.

19.2.1 Physiology of the Skin

The skin, which in an adult covers a surface area of about 2 m² and constitutes about 15–20% of the total body weight, is the largest organ of the body and is made up of three layers: the epidermis, the dermis, and the subcutaneous tissue (Figure 19.1). Any drugs that are intended for the deeper skin layers must first penetrate the outermost layer of densely keratinized dead cells in the stratum corneum. Depending on its location on the body, this outermost epidermal layer may be as thin as a few cells, such as on the scalp, or may be thicker than 50 cell layers, such as on the elbow. Especially for water-soluble drugs, this layer is almost impenetrable, provides an excellent barrier function between the inside of our body and the outside world, and is thus crucial in maintaining homeostasis. When using the skin as the drug target, for example, into the living part of the epidermis for vaccination purposes, into the dermis for local anesthetic or systemic drug delivery, or into the fatty subcutaneous tissue for more prolonged drug action, care must be taken to deliver the drugs into the correct skin layer (Figure 19.1) by using the right technique, such as subcutaneous, intradermal, or epidermal injection or any of the specific methods mentioned in the following paragraphs.

Skin can be both the target of drug delivery and the route of administration for systemic drug delivery through blood circulation. In the first case, topical

19.2.2 Skin Conditions Affecting Permeation of Active Drugs

The percutaneous absorption of a deposition of the active drug applied topically on the skin surface depends on several parameters related to the inherent properties of skin itself. A summary of such factors is shown in Table 19.1.

19.3 ADVANCES IN TOPICAL AND TRANSDERMAL DRUG DELIVERY

Despite major research and development efforts in transdermal drug delivery systems, low stratum corneum permeability still limits the usefulness of topical drug delivery. To overcome this limitation, various strategic methods have been developed to increase permeation of drugs. The goal of further improvements in transdermal drug delivery systems is to increase drug flux into the skin without significantly affecting normal skin barrier function. Current technologies that attempt to increase drug flux into the skin to allow effective therapy from a reasonable sized skin area [18] can be broadly classified into passive and active approaches [19].

The passive delivery approach, sometimes called the chemical approach (Table 19.2), was conventionally based on applying drugs to the skin in ointments, creams, gels, and patches, vehicles that used diffusion as the primary method of releasing the drug. More recent developments in this area aim at enhancing the driving force of drug diffusion (thermodynamic activity) with the help of nanotechnology-based carriers such as nanoemulsions and nanogels. Not only can the vehicle be optimized toward maximized drug diffusion, but it is also possible to alter the permeability of the skin for active drugs with the help of penetration enhancers [20], supersaturated systems [21], hyaluronic acid [22], prodrugs [23–25], liposomes, and other vesicles [26–28].

The amount of drug that can be delivered with passive technologies is not sufficient for many applications because the barrier properties of the skin cannot be fundamentally changed. It is therefore often necessary to resort to the second type of approach, the active delivery approach, which acts via active mechanisms and is sometimes called the physical approach (Table 19.2). This
### TABLE 19.1. Parameters Affecting Percutaneous Absorption of Active Drugs.

<table>
<thead>
<tr>
<th>Biological Factors</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patient</td>
<td>The effect of age is due to the larger surface-to-volume ratio in adults as compared with newborn infants; however, both adults and infants exhibit similar barrier functions of the skin [172,173].</td>
</tr>
<tr>
<td>Body region (site of application)</td>
<td>Composition and barrier properties of the stratum corneum vary at different body sites due to differences in thickness, number of cells, and, sometimes overemphasized, the density of skin appendages [174].</td>
</tr>
<tr>
<td>Moisture state of skin (hydration and occlusion)</td>
<td>Occlusion hydrates the keratin in corneocytes and increases the water content between adjacent intercellular lipid lamellae. For hydrophilic substances, released from an aqueous delivery device, the partition coefficient between the stratum corneum and the vehicle increases up to unity [175].</td>
</tr>
<tr>
<td>Metabolism</td>
<td>The viable epidermis contains several enzyme systems that catalyze processes such as oxidation, reduction, hydrolysis, or conjugation. Therefore, skin metabolism may have an additional impact on the transdermal delivery of drugs [176-178].</td>
</tr>
<tr>
<td>Disease state of skin</td>
<td>In general, psoriasis and other skin diseases facilitate drug delivery through the skin [179].</td>
</tr>
<tr>
<td>Species differences</td>
<td>The difference of skin surface lipids in different species affects the partitioning of active drugs from the vehicle to the stratum corneum [180].</td>
</tr>
</tbody>
</table>

### Physicochemical Properties of Active Drugs and Vehicle

| Partition coefficient of active drug | For more hydrophilic molecules with lower logP < 1, the transcellular route is more predominant, while the intercellular route is predominant exclusively for highly lipophilic molecules with logP > 3. For molecules with intermediate partition coefficient (logP = 1–3), both trans- and intercellular routes occur. |
| Molecular size of active drug | Molecular weight influences the diffusion coefficient. The larger the molecule, the lower the diffusivity. Most conventionally selected transdermal therapeutics have a narrow range of molecular weights, with the smallest being nicotine (162 Da) and the largest being oxybutinin (359 Da). |
| Solubility of active drug and melting point | In general, when similar drugs are compared, then the ones with better water solubility and lower melting point (less crystallinity) have the best permeation. |
| Ionization | The complex nature of the skin does not strictly follow the pH-partition hypothesis, which states that unionized molecules permeate more than ionized ones. Reason: Charged drugs might pass due to higher solubility and might use electrically assisted movement via shunt routes. |
| Drug binding | Depending on permeant (weak acid/base, ionized species, neutral molecule), varying interactions resulting from hydrogen bonding to van der Waals forces have significant to minimal effects on skin flux. |
| Type of formulation | The selection of the type of formulation largely affects percutaneous delivery of active drugs depending on their solubility status in the vehicle, overall charge of vehicle, and structural organization within the delivery system. For example, the transdermal flux of benzotropine in lipophilic carriers is enhanced compared to a hydrophilic vehicle [181]. |

### TABLE 19.2. Strategies to Overcome the Stratum Corneum Barrier Function in order to Deliver Drugs Both Intra- and Transdermally.

<table>
<thead>
<tr>
<th>Strategies to Overcome the Stratum Corneum Barrier</th>
<th>Passive (Chemical) Approach</th>
<th>Active (Physical) Approach</th>
<th>Synergetic Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulations</td>
<td>Removal/bypassing of the stratum corneum</td>
<td>Chemical enhancers</td>
<td>Iontophoresis with Electroporation Ultrasound</td>
</tr>
<tr>
<td>Vehicle systems</td>
<td>Skin abrasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supersaturation</td>
<td>Microneedles</td>
<td></td>
<td>Electroporation</td>
</tr>
<tr>
<td>Ion pairs and complex coacervates</td>
<td>Laser ablation</td>
<td></td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Eutectic systems</td>
<td>Needleless injection</td>
<td></td>
<td>Iontophoresis with Electroporation</td>
</tr>
<tr>
<td>Pharmacogel</td>
<td>Appendageal bypass</td>
<td></td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Vesicles and particles</td>
<td>Electrically assisted methods</td>
<td></td>
<td>Laser ablation</td>
</tr>
<tr>
<td>Microemulsions</td>
<td>Ultrasound/phonophoresis</td>
<td></td>
<td>Electroporation with Ultrasonic</td>
</tr>
<tr>
<td>Prodrugs</td>
<td>Electrophoresis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnetophoresis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modification of the stratum corneum</td>
<td>Local catheterization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical enhancer to increase diffusivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>increase solubility/p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>partitioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidural/intrathecal delivery</td>
<td>Magnetic drug targeting</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Approach has enormously benefited from advances in precision engineering (bioengineering), computing, chemical engineering, and material sciences, all of which have helped to achieve the creation of powerful, miniaturized devices that have the ability to facilitate the generation of a desired therapeutic effect. These device-based techniques, many of them still under development, include iontophoresis, electroporation, microneedles, abrasion, needleless injection, suction, stretching, ultrasound, magnetophoresis, radiofrequency, lasers, photomechanical waves, and temperature control. Some of these techniques and their (potential) application to pain treatment are discussed in the subsequent sections.

### 19.3.1 Iontophoresis

Iontophoresis or iontophoretic delivery involves the application of a low-level electric current, typically <0.5 mA/cm², to enhance the percutaneous delivery of charged therapeutic drugs [29–32]. Iontophoresis uses an electrode of the same polarity as the charge on the drug to drive charged drugs into the body by electrostatic repulsion [33], utilizing the physical phenomenon of "like
charged drugs repel and opposite charges attract.” In the case of the negatively charged drugs, the drug is placed between the negative electrode (cathode) and the skin for its delivery across a biological membrane, while for cationic drugs, the electrode polarities are reversed (Figure 19.2a). In both cases, the electric circuit is completed by the movement of endogenous counter ions within the skin. Generally, high voltages applied for short treatment durations (milliseconds) have been found to be most effective [34–36].

Iontophoretic drug delivery has many of the same advantages over oral and parenteral drug delivery as does the transdermal route. Specifically, it avoids first-pass effect, prevents variation in the absorption seen with oral administration, controls the rate of drug delivery, has the ability to program the drug delivery profile, and minimizes the local tissue trauma. Because iontophoresis delivers the drug to the target area without systemic exposure, it is appropriate for active drugs with (very) short biological half-lives. It delivers the active

drug directly into the bloodstream with no delay. Once the iontophoretic delivery system is turned off, the drug’s effect rapidly ceases. It thus also gives the physician and patient full control over the dosing regimen, using a simple push button to activate the iontophoretic device (Figure 19.2b).

Iontophoretic delivery is affected by several factors. The first factor is the composition of the formulation and it plays an important role with respect to concentration of the drugs (an increase in concentration has been shown to increase the apparent steady-state flux of a number of drugs) [37,38]. A second factor, the pH of the donor compartment, affects the amount of ionized drug [39]. A third factor is ionic strength and the presence of co-ions (an increase in ionic strength will decrease drug delivery, as extraneous ions compete with the drug ions) [40,41]. A fourth factor is the physicochemical properties of the drugs and includes molecular size and molecular weight (MW) (transport of compounds decreases with an increase in MW under identical conditions) [42,43], charge (the sign of the charge determines the mechanism by which iontophoresis will proceed, e.g., electrophoresis or electrophoresion and electrotaxis), and polarity of drug (generally, the compounds that are hydrophilic are considered ideal candidates for optimum flux) [44]. A fifth factor comprises experimental conditions such as current density (a linear relationship is found between the apparent flux of a number of compounds and the applied current) [45,46], electrode material [47], and some electrical pulse parameters that include waveform, rate, and number [48]. A sixth factor is biological aspects that include variability in and among subjects, skin pH, regional blood flow [49], and skin conditions [50].

Iontophoresis is applied extensively to enhance the skin transport of a wide variety of molecules, such as molecules with different lipophilicity and size (i.e., small molecules, proteins, peptides, oligonucleotides, and even larger biopharmaceuticals) [51–53].

19.3.1.1 Iontophoresis in Pain Research. Iontophoresis is a very useful delivery technique in the area of pain relief as it provides a noninvasive means of systemic administration of a minute amount of highly active drugs [54]. It has been extensively tested in animal studies for the delivery of methadone [55] and hydromorphone [56]. In hairless rat skin, the flux of hydromorphone through the skin could be increased from 72 to 280 μg/cm²/hour simply by adjusting the electric current from 0.1 to 0.5 mA. Control of hydromorphone flux is thus directly proportional to the applied current. In addition, the concentration of the drug in the device is proportional to the hydromorphone flux attained. From these studies, the authors conclude that it is feasible to reach therapeutically effective concentrations of hydromorphone for the management of cancer-related pain via iontophoretic administration.

In clinical trials, sodium salicylate iontophoresis has been shown to be effective in the management of hip pain [57]. Specifically, 20 patients suffering from sickle cell disorders were given conventional physiotherapy and either their regular medication or iontophoretic salicylate. The iontophoresis treatment
group showed statistically significant reduction in pain intensity and improvements in the hip range of motion as compared to the control group.

In 1995, IOMED, Inc. became the first company to receive FDA approval for an iontophoretic delivery system. The system consisted of lidocaine HCl 2% and epinephrine 1:100,000 (Iontocaine® or Numby Stuff) for local dermal anesthesia. This was followed in 2004 by Vyteris (NJ, USA), which received FDA approval for its Lisodette™ topical prefilled/preprogrammed iontophoretic system for the delivery of lidocaine. Lisodette anesthetizes the skin within 10 minutes at a depth sufficient for all anticipated needlestick and dermatological procedures. Both lidocaine and lignocaine, delivered by iontophoresis, have been successfully used to prevent pain from venipuncture [58–60]. Iontophoretically delivered lidocaine was also found to be useful for decreasing the pain caused by cannulation and propofol injection [61–63].

More recently in May 2006, the FDA approved the IONSEYS fentanyl HCl system from ALZA (Johnson & Johnson, NJ, USA), an iontophoretic delivery device for the treatment of postoperative pain (Figure 19.2b). The credit card-sized patch showed comparable pharmacokinetics to intravenous fentanyl infusions and is therapeutically equivalent to the standard regimen of IV morphine, the most commonly used modality for postoperative patient-controlled analgesia (PCA) [64]. The fentanyl HCl system is needle free and contains a fenestrated hydrogel that functions as an anode, a cathode composed of an inert hydrogel, microprocessor, battery, a light-emitting diode, and a drug delivery button [65]. The system is attached to the skin of the upper outer arm or chest with an adhesive backing. When the on-demand button is pressed, an imperceptible current drives the fentanyl from the hydrogel through the epidermis and into the systemic circulation.

Many more iontophoretic systems are under commercial development and include the Phoresor® device (IOMED, Inc.) [66], the Vyteris and E-TRANS devices (ALZA Corp.) [67], Dupel® from Empi, Inc., and Microplor® from Life-Tech International. Integrated iontophoretic patches are available from Travantti Pharma Inc. and IOMED, Inc., are disposable, single-use iontophoretic patches and are useful for the delivery of many charged drugs with very little additional development needed.

### 19.3.2 Microneedle-Based Devices

In 1976, Gerstel was the first to describe microneedles in a U.S. patent [68], but it was not until the early 1990s that microfabrication technology was developed to a level that allowed for the fabrication of microneedle systems. Microneedles are lanceletlike mechanical structures with shaft widths typically between 10 and 500 μm and lengths of 30 μm to several millimeters. They are most often used to provide a pathway to the upper layers of the skin. Solid microneedles are used to abrade or to perforate the stratum corneum (the topmost about 20-μm-thick skin layer; see Figure 19.1) in order to allow topically applied drugs to reach the epidermis or to diffuse from the injection site toward the blood vessels of the dermis. Hollow microneedles additionally allow for penetration of the stratum corneum, with their lumens simultaneously providing rigid conduits for drug injection or sampling of biomolecules from the skin. Because the vast majority of nerve endings are located in the dermis, drug injection into the approximately 100-μm-thick epidermal skin layer (Figure 19.1) is painless [69].

In order to access a wider area of the skin, microneedles have been fabricated in single rows and in two-dimensional arrays. The first array of solid microneedles, the “Utah array” [70], was developed by researchers at the University of Utah and was used to record neural signals. It is currently available through Cyberkinetics, Inc. (Salt Lake City, UT, USA). The first hollow microneedles were developed by Lin et al. in 1993 [71]. Thereafter, rapid advancement in microfabrication technology led to the development of a vast variety of microneedles made primarily from silicon, metal, and more recently, polymers. Arrays of hollow silicon microneedles are already available through NanoPass Technologies Ltd. (Nes Ziona, Israel), while Theratechnologies in Montreal, Canada (supported by ALZA Corp.) is currently clinically testing its growth factor-releasing microneedle technology called Macroflux® [72].

The two main drug delivery mechanisms for the delivery of drugs by microneedles are to either dry-coat the drug on the microprojection array [73], a technique that is primarily used for intracutaneous immunizations, or to inject the drug through a hollow needle from a drug reservoir [72]. A system that is easy to implement is the use of microneedles attached directly to a syringe (Figure 19.3) [74]. A third approach of transcutaneous drug delivery with microneedles is to prepare an array of solid needles that contain the drug in a biodegradable needle matrix material, using a molding process [75]. In this approach, the encapsulated drug is released as soon as the needles start to dissolve, which occurs immediately after they have been inserted into the skin.

Successful drug delivery through microneedles into human skin has only recently been reported [69] in vivo using methyl nicotinate as a model drug. No standard protocols for microneedle-based transdermal administration of therapeutics have been established yet, although the technique is very promising.

### 19.3.3 Skin Abrasion

The abrasion technique involves either the direct disruption or removal of upper skin layers to facilitate the permeation of topically applied drugs. Some skin abrasion devices are based on techniques used by dermatologists for superficial skin resurfacing, such as microdermabrasion, which is used in the treatment of acne, scars, hyperpigmentation, and other skin blemishes as a skin rejuvenation procedure. **Microdermabrasion** partially ablates and homogenizes the skin layers. Lee et al. found an 8–24 times higher 5-fluorouracil permeation across microdermabrasion-treated skin than across intact skin [76].
In a similar study, microdermabrasion also enhanced the skin delivery of the hydrophilic 5-aminolevulinic acid (ALA), an enhancement of drug uptake that was not seen with the lipophilic drug clobetasol. The same group studied the effect of microdermabrasion on the enhancement of topical vitamin C delivery [77]. The flux and skin deposition of vitamin C across microdermabrasion-treated skin was approximately 20 times higher than across intact skin.

Another abrasion technique, microcisioning, is based on creation of microchannels in the skin through the eroding of the impermeable outer layers with sharp microscopic metal granules (Figure 19.4). It is a rapid and painless procedure and has been used in vivo to deliver lidocaine to the wrist of volunteers, providing complete anesthesia around the site within 3 minutes as compared to the approximately 1.5 hours required for topical application without the microconduit [78]. The authors also concluded that microcisioned microconduits can provide a minimally invasive basis for the delivery of any size molecule, and for the extraction of interstitial fluid and blood samples. Based on this technique, Carlisle Scientific is currently developing a penlike handheld device called the "microcisioner." Another company, MedPharm Ltd (Guildford, UK), has developed a novel dermal abrasion

**FIGURE 19.3.** (a) Scanning electron microscopy image of a sharp microneedle array compared to a 25-gauge steel needle with an outer diameter of 0.53 mm. (b) Close up of one of the microneedles. (c) Potential way of using such a microneedle array connected to a normal syringe. With permission from Sivamani et al. [69].

**FIGURE 19.4.** (a) Microcisioning produces microconduits using sharp, micron-sized, inert crystals carried by an inert gas, directed toward a mask aperture placed against the stratum corneum or the nail. (b) Four in vivo microconduits of 150µm in diameter are shown on the left with abrasive particles present. On the right, the particles have been removed from the microconduits. With permission from BioMed Central [78].
device (D3S) for the delivery of a wide variety of therapeutics ranging from hydrophilic low-molecular-weight compounds to biopharmaceuticals. In vitro data indicate that application of the device can increase the penetration of angiotensin into the skin 100-fold compared to untreated human skin [79]. This device is noninvasive and histological studies on human skin show that the effects on the stratum corneum are reversible and nonirritating.

Microporation is another abrasive technique that utilizes a vaporization process to remove tiny areas of the stratum corneum creating microscopic pores that allow access to the underlying viable epidermis [80]. The vaporization is produced by passing a current, for a short duration (milliseconds), through an array of tiny resistive elements to the skin surface. Microporation creates micropores in the skin surface by physically removing the cells and thus alters the barrier properties of the skin for drugs. Microporation is pain free and nontraumatic as the temperature gradient does not reach the capillary loops or pain-sensing nerves in the upper dermis. Microporation technology is currently most often used to reliably and easily induce skin-directed vaccination. As an example, the reporter gene expression increased 10-fold following application of an adenoviral vector to microporated skin when compared to the same application but to intact skin [80]. Furthermore, 10- to 100-fold increases in cellular and humoral immune responses were observed thereafter.

19.3.4 Needleless Injection

Another pain-free method of administering drugs to the skin is needleless injection. This method circumvents the issues of safety, fear, and pain associated with the use of hypodermic needles. The needleless syringe comprises an elongated tubular nozzle with a rupturable membrane initially closing the passage through the nozzle. Particles of a therapeutic agent to be delivered are dispensed behind the membrane and are then blasted—with high gas pressure sufficient to burst the membrane—into the patient's skin. Different devices are available and include liquid (Ped-O-Jet, Iject, Biojector 2000, Medi-Jector, Intraject) and powder (particle mediated epidermal delivery [PME]) device formerly known as Powderject) systems. The PMED device consists of a helium gas cylinder, drug powder sealed in a cartridge made of plastic membrane, a specially designed convergent-divergent supersonic nozzle, and a silencer to reduce the noise associated with the rupturing of the membrane when particles are fired. The PMED device has been reported to successfully deliver testosterone, lidocaine hydrochloride and macromolecules such as calcitonin and insulin [81–83].

The most advanced application of needleless injection is the needle-free delivery of vaccines using a powder jet. This technique could aid in mass vaccinations by increasing the ease and speed of delivery and by offering improved safety and compliance, decreasing costs, and reducing the pain associated with vaccinations [84]. Brave et al. successfully used needle-free injection for intra-

dermal delivery of multigenic/multisubtype HIV-1 vaccine that resulted in induction of potent cellular and humoral immune responses in patients [85]. Another novel nanoparticle-based DNA vaccine delivery system was also found to enhance immune responses after intradermal injection with the needle-free jet injection device Biojector 2000 [86]. Targeting the antigen-presenting cells in the epidermis with needleless injection thus seems to work well, and even direct intracellular delivery of DNA or protein vaccines for transfection is being attempted to induce gold particle-mediated immunization [87].

19.3.5 Ultrasound (Sonophoresis or Phonophoresis)

Sonophoresis, also called phonophoresis, involves the use of ultrasonic energy to enhance the transdermal delivery of solutes. Although the exact mechanism of sonophoresis is not known, it is thought that drug absorption may involve a disruption of the stratum corneum lipids through a combination of thermal, chemical, and mechanical alterations within the skin tissue, allowing the drug to pass through the skin [18]. The enhancement induced by ultrasound is particularly significant at low frequencies of less than 100kHz [88,89].

The low-frequency ultrasound (LFS) enhances the permeability of the skin to macromolecular drugs via induction of localized transport regions. Several therapeutic macromolecules including insulin [90–92], low-molecular-weight heparin [93], and vaccines [94] have been delivered using LFS in vivo. Clinical trials have been performed with several drugs including lidocaine [95] and cyclosporine [96].

The Sonoprep device (Echo Therapeutics, Franklin, MA, USA) uses low-frequency ultrasound (55kHz) for an average duration of 15 seconds to enhance skin permeability. This battery-operated, handheld device consists of a control unit, ultrasonic horn with control panel, a disposable coupling medium cartridge, and a return electrode [90]. Applied to the delivery of lidocaine, ultrasound seemed to disorder the lipid bilayers and increased lidocaine diffusion and uptake by 3.3-fold. In the absence of ultrasound, lidocaine diffusion in lipid bilayers of the stratum corneum is slowed to a diffusion coefficient of 50 × 10⁻⁹cm²/s by the presence of densely packed and ordered lipid bilayers.

19.3.6 Laser Radiation

The direct and controlled exposure of skin to a laser results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of both lipophilic and hydrophilic drugs [97,98]. Different lasers enhance and control skin permeation differently, as has been demonstrated in vitro with the drug 5-fluorouracil [99]. The authors showed that an erbium-doped yttrium aluminum garnet (Er:YAG) laser partly ablated the stratum
corneum and resulted in an up to 133-fold higher drug uptake than the one measured across intact skin. When a CO₂ laser was used, both stratum corneum ablation and increased temperature effects contributed to an up to 41-fold increase in 5-fluorouracil flux when higher fluencies (7.0 J/cm²) were used. In another study, fluorescein isothiocyanate (FITC)-labeled dextran of increasing MWs (4.4, 19.4, 38.0, and 77.0 kDa) was used as the model macromolecule to investigate the skin permeation in vitro [97]. Dextran of all MWs could be delivered transdermally after laser treatment. It was thought that intercellular pathways played an important role in the delivery of the dextran. The postulated mechanisms of action were the ablation of the stratum corneum layer, photomechanical stress on intercellular regions, and alterations of the morphology and arrangement of corneocytes [97].

A handheld portable laser device has been developed by Norwood Abbey Ltd. (Victoria, Australia), which, in a study involving human volunteers, was found to reduce the onset of action of lidocaine to 3–5 minutes, while 60 minutes was required to attain a similar effect in the control group. The Norwood Abbey system has been approved by the FDA for the administration of topically applied anesthetics.

19.3.7 Magnetophoresis

Another method that might be useful to drive analgesic drugs across the skin is magnetophoresis, the process of moving particles or molecules in a viscous medium under the influence of a magnetic field [100]. Based on work by Murthy, it seems that different diamagnetic molecules, such as benzoic acid [101] and terbutiline [102], can be driven across biological barriers with the help of a magnetic field. Their system consisted of a drug-containing hydroxypropyl methyl cellulose gel, which was made into a film by applying a polystyrene-butylene polymer backing [102]. Control films were additionally made with or without the permeability enhancer isopropyl myristate in the gel. In a diffusion apparatus, placing a 2-mm thick magnet on the film increased the drug release about threefold over a film without the magnet. Adding the permeability enhancer resulted in a drug release similar to the release seen with a magnetic setup, both in terms of release time and amount of drug released. The authors accounted for this magnetophoretic effect by pointing to the diamagnetic properties of the drugs, explaining that these properties tend to cause “the drug escape from the applied magnetic field.” Further studies, however, are needed to confirm these data and to discover the mechanistic reasons for the drug release under the influence of a magnetic field.

19.3.8 Synergistic Effects of Combination Treatments

Many of the above methods can be used in combination with each other (Table 19.2) to further enhance the uptake of drugs through the skin [103]. Although such combined approaches clearly work, the mechanisms behind their synergistic effects are often speculative. Also, the safety of the combined procedures requires additional attention as they could cause extra damage to the skin or could result in added side effects.

Combination approaches based on biological targeting can also be very useful for the treatment or prevention of pain. One recent and very elegant example is the use of QX-314 and capsaicin, which together block pain while permitting normal sensation [104]. This novel effect is based on the charged lidocaine derivative QX-314, which is not able to diffuse across membranes and thus cannot access the neuronal voltage-dependent sodium channels. When another compound, the selective transient receptor potential vanilloid 1 (TRPV1) channel activator capsaicin, was added, the large TRPV1 pores allowed the passage of QX-314, and as a result, pain was blocked. This approach is specific to sensory C-fiber neurons involved in nociception because the TRPV1 channels are restricted to that location (see Chapter 8), and thus no numbness is produced [105,106]. Applications of this combination therapy might include dentistry procedures and many other local interventions. Both drugs could be combined into a patch similar to the capsaicin patches currently used extensively in the treatment of rheumatic ailments.

It should be kept in mind that even the “simple” approach of local drug application to the skin produces not only local but also systemic effects. Systemic effects are mainly the result of transdermal uptake (Figure 19.1) of an often not insignificant percentage of the drug. Ideally, drugs used for systemic therapy should be those that are readily absorbed into the blood stream, whereas drugs used for local treatments should be those that penetrate only into the underlying deep tissue, such as the muscle tissue under viable skin. The contribution of both local and systemic effects has been explored with different nonsteroidal anti-inflammatory drugs (NSAIDs) in vivo by Hijikata et al. [107]. Both direct penetration through the skin to the muscle as well as uptake after systemic circulation has been reported and is shown in Figure 19.5. The extent of how much of the drug stays local or gets absorbed into the

![FIGURE 19.5](image-url)
blood stream depends on how much of the drug in viable skin will be bound to cytosolic components, and on the balance between the unbound fraction in the skin and plasma [19]. If the unbound fraction in the skin is too large and the local effect thus becomes less important, then it might be possible to influence the system and to bind the drugs to carriers that cannot physically leave the application site. Useful carriers for such an approach are, for example, microspheres that will slowly release an encapsulated drug at the site of injection over extended time periods.

19.4 OTHER METHODS OF INCREASING LOCAL DRUG CONCENTRATION

Postoperative pain management has dramatically improved with the advent of PCA delivery. There are, however, still some issues with PCA use including premature discontinuation, resource-intensive setup and maintenance, interruptions in analgesia, and the potential for medication errors. For these reasons, pain control with preemptive analgesia and multimodal therapy has been thought to be more appropriate for some patients. Currently, the most efficient preemptive analgesia methods used in the clinic are local catheterization and epidural/intrathecal injection of therapeutic drugs.

19.4.1 Local Catheterization

Local catheterization that induces peripheral nerve blocks is especially useful in surgery on extremities [108]. Peripheral nerve blocks include perineural catheters, which are normally used for a maximum of 12–16 hours, and portable infusion pumps. The two most successful drugs for this procedure are bupivacaine and ropivacaine [109]. The intense, site-specific analgesia with local anesthetics produces fewer side effects (minimal nausea and vomiting) and leads to faster recovery and discharge, thus reducing overall healthcare costs.

19.4.2 Epidural and Intrathecal Delivery Systems

Postoperative pain management is a serious issue. Postoperative pain can be safely and effectively treated by one-time or intermittently administered bolus doses of epidural morphine and by continuous epidural infusions of opioids/local anesthetics with and without patient-controlled epidural analgesia [108]. Epidural treatments involve the insertion of a catheter into the epidural space, a narrow sleeve-like area that surrounds the spinal cord, or into the intrathecal space, which contains the cerebrospinal fluid and the spinal cord. Pain-relieving drugs are then delivered through the catheter. Epidural and intrathecal analgesia are used when other methods either do not give sufficient pain relief or produce excessive adverse effects. Because the dose of drugs is much smaller than if given through a normal injection or if swallowed as a tablet, the side-effect profile for epidural and intrathecal drug delivery is much better than for these other methods.

Postoperative and postpartum pain usually lasts several days, but the injectable opioids used to treat the pain have only relatively short durations of action. To extend their action, extended-release opioid formulations have been developed. Most recently, effective postoperative analgesia was induced for 48 hours using an extended-release epidural morphine (EREM) injection [110]. EREM consists of a liposomal formulation, in particular a foam with multiple lipid vesicles containing morphine suspended in an aqueous solution. After injection, reorganization of the liposomal membrane leads to extended release of the opioid within the epidural space. Importantly, caution must be exercised with this approach because this is still a systemic drug application with serious respiratory depression as a potential side effect [108].

At the end of 2004, the FDA approved Prialt® (ziconotide intrathecal infusion; see Chapter 5) from Elan Corporation (Dublin, Ireland) for the management of severe chronic pain in patients for whom intrathecal therapy is warranted, and who do not tolerate or are refractory to other treatments, such as systemic analgesics, adjunctive therapies, or intrathecal morphine.

19.4.3 Magnetic Targeting

A more recent physical means of drug delivery involves combining a drug with a magnetically responsive carrier and directing them to, or at least accumulating them in, the target tissue with the help of magnetic fields [7]. Magnetic drug delivery by particulate carriers is a very efficient method of delivering a drug through the bloodstream to a localized disease site. Very high concentrations of chemotherapeutic or radiological agents can be achieved near the target site, for example, a tumor, without any toxic effects to normal surrounding tissue (Figure 19.6).

Magnetic carriers [111] receive their magnetic responsiveness to a magnetic field from incorporated magnetic materials (magnets, iron, nickel, cobalt) and are normally grouped according to size, starting at 4–6 nm in diameter (ferrofluids, nanospheres) up to 1–100 μm (magnetic microspheres) (Figure 19.7). Often, magnetic liposomes are also included when speaking about magnetic carriers. For biomedical applications, magnetic carriers must be water-based, biocompatible, nontoxic, and nonimmunogenic. Magnets and iron powder were the first magnetic carriers to be used in vivo, as contrast agents in the femoral artery [112,113]. Improved biocompatibility, however, was reached by encapsulating these magnetic components with matrix materials such as chitosan, dextran, poly(lactic acid), or albumin [7].

The only clinical application of magnetic particles currently approved by the FDA is the use of these particles as contrast agents in magnetic resonance imaging (MRI) [114]. There is, however, much ongoing research aimed at using magnetic particles as cancer-treating agents. The different approaches
undergoing testing in cancer therapy include magnetic microspheres loaded with radioactivity or chemotherapeutic drugs; they can also be used directly for magnetic fluid hyperthermia under the influence of an externally applied AC magnetic field [115], as remotely activated drug reservoirs, or for the separation of cancer cells from healthy cells, thus allowing better and side effect-free stem cell transplantation. A good source of information about magnetic carriers, including an extensive bibliography of this field, is available at http://www.magneticmicrosphere.com/.

To date, no pain-relieving drugs have been encapsulated into magnetic particles. The stage is set, however, for this to occur. Nonmagnetic poly(lactide-co-glycolide) (PLGA) microspheres with a release profile appropriate for pain-relieving drugs have been created [116]. These fentanyl-loaded microspheres slowly release the drug in a linear fashion over 2 weeks (Figure 19.8). Making these microspheres magnetic would be a straightforward procedure by adding magnetite to the polymer during the microsphere preparation [117–119]. The magnetic microspheres can then be guided to distinct target tissues or organs. Delivery of the microspheres as a whole to the brain, however, is not possible, as they are not able to cross the blood–brain barrier (BBB). For that purpose, the drug would have to be released and then independently reach the brain.

19.4.3.1 BBB. In terms of drug targeting, the BBB is a formidable obstacle to drug delivery. The BBB is defined in part by its physical structure, the junctions between the capillary endothelial cells, which are unusually tight and

![FIGURE 19.8. Effect of polymer concentration during the microsphere preparation on the fentanyl release pattern from biodegradable poly(lactide-co-glycolide) (PLGA) microspheres. Interestingly, none of the formulations showed a burst effect. With permission from Choi et al. [116].](image)
thus completely prevent paracellular transport. A more important characteristic of the BBB, however, is the fact that it lacks the usual mechanism found in most tissues that allow drugs to be transferred across their capillary walls [120]. In particular, the mechanism of pinocytosis is completely missing. In addition, P-glycoprotein, an efflux membrane pump, actively pumps a wide range of drugs from the brain back into the bloodstream. Uptake of drugs into the brain is thus normally by diffusion and depends on the MW and lipophilicity of the drug. As far as the MW limits, current research has determined that essentially no drug uptake is seen in the brain above 400 Da. Because all opioids fall below this value, they generally cross the BBB well.

In considering drug lipophilicity, the permeability of morphine, codeine (methylmorphine), and heroin (diacetylmorphine) with a calculated logP of 0.24, 1.14, and 1.86, respectively, illustrates well the improved delivery of more hydrophobic drugs into the brain [120]. Codeine has a BBB permeability of about 10 times that of morphine, while that of heroin is another 10 times larger. In addition to lipophilic small molecules, a few small hydrophilic molecules such as hexose, certain amino acids, transferrin, and IGF-II are known to cross the BBB by receptor-mediated drug transport [121].

For the peripheral targeting of analgesic drugs, it is possible to take advantage of the properties of the BBB and to design a drug that reaches the target tissue and spares the brain, thus avoiding any CNS side effects and toxicities. This is best illustrated by considering the drug loperamide, a phenylpiperidine derivative with a chemical structure similar to the opiate receptor agonists diphenoxylate and haloperidol [122]. Loperamide is designed to maintain the antidiarrheal activity of opiate receptor agonists, but has low oral absorption and does not cross the BBB.

There have been reports in the literature that colloids, which are 5- to 200-nm particles suspended in liquid, can pass through the BBB and might thus be useful carriers for drugs that normally cannot reach the brain [123]. In one of the reports, colloidal human serum albumin (HSA) nanoparticles filled with loperamide and conjugated with the same OX26 transferrin antibody induced significant antinociceptive effects in the tail-flick test in ICR (CD-1) mice after intravenous injection, whereas the same system with a control IgG2a antibody yielded only marginal effects [124]. This demonstrates that antibody-coupled nanoparticles are able to transport loperamide across the BBB. In another report, liposomes (which are not technically colloids, but behave similarly) coated with OX26 transferrin antibody and filled with daunorubicin were shown to increase the drug concentration in the brain [125]. In a third report, it was possible to achieve central analgesia, as measured by a hot plate test, when the neuropeptides Leu-enkephalin, dalargin, and the Met-enkephalin ketorophin were adsorbed to the surface of colloidal poly(butylcyanoacrylate) nanoparticles which were coated with polysorbate 80 [126]. Another group similarly showed that poly(butylcyanoacrylate) nanoparticles adsorbing loperamide and polysorbate 80 also induced analgesia, as measured by a tail-flick test [127]. The uptake mechanisms for loperamide and the peptides have yet to be fully explained, but appear to be related to the nonionic detergent, because even a simple mixture of drug and polysorbate showed a rather high brain uptake with some analgesic effect. For the other listed reports, it is not clear how colloids pass through the BBB. They may be internalized in the endothelial cells or might simply adhere to their surface, thus providing a greater concentration gradient to assist in passive diffusion.

19.4.4 Slow-Release Implants Based on Biodegradable Polymers

Biocompatible and biodegradable polymer-based controlled-release implants loaded with pain-relieving drugs (mainly opioids) have shown promising results in pain control, particularly in cancer patients. Such implants are placed subcutaneously, intrathecally, or intraspinally and then slowly release the active drug over an extended time period [128]. One such system, and a first example of a polymer-based device for the delivery of analgesic drugs, is the preparation of implantable rods containing hydromorphone, bupivacaine, or both [129]. In vivo studies conducted in rats showed potent, prolonged analgesia by these implants. Another example demonstrating the use of a polymer-based system consists of the preparation of microspheres from the biodegradable copolymer PLGA encapsulating bupivacaine [130]. After local subcutaneous injection into the plantar hind paw, these microspheres were shown, in the paw pressure test, to prolong analgesia while simultaneously diminishing systemic toxicity. The duration of antinociception increased from 60 to 90 minutes for a dose of 1 mg of plain bupivacaine compared to the same dose encapsulated in microspheres. Longer antinociception of 120 and 180 minutes was possible with microspheres containing 2.5 and 5.0 mg of the drug, respectively. When such doses of plain bupivacaine were used, significant systemic toxicity was induced.

There are many other examples of how polymeric implants have been used for the controlled release of fentanyl and hydromorphone. One research group showed that a single dose of intrathecal fentanyl in poly(DL-lactide) (PLA) composites produced less respiratory depression than the same dose of plain fentanyl [131]. This improved toxicity profile was due to a slow drug release from the implant. Another group prepared an ethylene vinyl acetate (EVA) copolymer disk, measuring 1.05 cm in diameter and 0.27 cm in height, which contained 50% hydromorphone by weight and was coated with poly(methyl methacrylate) [132]. This implant produced a sustained release of the drug over 4 weeks. A third group produced implants from an interpenetrating network of two biocompatible polymers, the biodegradable polyester poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) and the synthetic, nonbiodegradable poly(2-hydroxyethyl methacrylate) (PHEMA) [133]. Fentanyl was released slowly over 2 days after placing the implant in the right paw of a rat.

These examples provide only a glimpse into the enormous area of polymer-based drug delivery. For fuller information, we point the reader to recent
books and reviews in the field of polymeric drug delivery systems. They encompass nanoparticles appropriate for intravascular application [134], microspheres that might be more appropriately used as depots for slow release of drugs after intramuscular or subcutaneous injection [135], polymeric films [136–138], woven or electrospun mats [139], and implants of many other shapes and sizes [140–142]. By choosing the appropriate polymer and device geometry, it is possible to adjust the drug release curve (pharmacokinetics) from zero-order release to any required shape and also from hours to days, weeks, or months for the duration of the release [6,143].

19.4.5 Lipid-Based Drug Delivery

Liposomal drug carriers constitute important vehicles for the topical delivery of pain-relieving drugs. Liposomes are phospholipid vesicles sized between 40 and several thousand micrometers. They can contain hydrophilic drugs in the aqueous core or lipophilic drugs in the phospholipid bilayer. Many liposomal formulation subtypes such as elastic liposomes, lipospheres, liposomal spray gels, transfersomes, and niosomes have shown potential to deliver a variety of analgesic drugs including anesthetics [144], anti-inflammatories [145,146], and analgesics [147]. Phospholipids, the major ingredient used to formulate liposomal systems, easily integrate with skin lipids and provide the desired hydration conditions to enhance drug penetration and localization at the site of action (i.e., in the skin layers of the target area). Liposomal bilayers fuse with multilamellar intercellular lipid layers of the stratum corneum and alter the phase transition properties of stratum corneum lipids. The enhanced permeation of liposomal incorporated drugs is thus the result of an altered physicochemical state of the skin.

The first liposomes filled with analgesic drugs were transfersomes containing 7% lidocaine or 4% tetracaine and were found to be effective for the noninvasive treatment of local pain with direct, topical drug application [148]. In Sprague Dawley rats, these dermally applied analgesic transfersomes increased the heat stimulus reaction time to greater than 70 seconds, compared to a typical reaction time of 30 seconds. The same liposome preparation was also shown to be effective in patients when tested by the pinprick method [148]. Thereafter, different companies produced similar commercially available liposomal products that include a liposomal lidocaine 4% cream (Maxilene, RGR Pharma) and a liposomal diclofenac and also a ketoprofen spray (MIKA Pharma GmbH).

Liposomal preparations are also useful in an injectable or inhalable form. As an example for the injectable form, bupivacaine lipospheres have been prepared as a parenteral sustained-release system for postoperative pain management [149]. Another type of bupivacaine-loaded liposomes was used epidurally and reached extended, complete analgesia for 11 hours in a patient suffering from pain associated with lung cancer [150]. The bupivacaine-loaded liposomes did not induce a motor blockade, although it was seen in control patients who received the free drug. Similarly, liposomal alfentanil given intrathecally to rats provided improved spinal antinociception while eliminating supraspinally mediated side effects completely [151]. An example for an inhalable fentanyl delivery system is the mixture of free and liposome-encapsulated fentanyl, which provided both rapid pain relief and extended action [152]. Specifically, the fentanyl plasma concentrations were 56% and 140% greater at 8 and 24 hours after the simple and noninvasive aerosol administration compared with the concentrations after intravenous administration.

It may be possible to make lipid-based drug delivery more specific by adding or conjugating targeting molecules to the surface of the liposomes. To date, no attempts toward this goal have been made in pain treatment but liposomes with covalently bound antibodies, so-called immunoliposomes, are well-known in the world of anticancer drug delivery [153].

19.5 ORAL DOSAGE FORMS FOR ANALGESIA

According to a report by Global Industry Analysts, Inc., the world’s largest market research company, the major driving forces behind the expanding analgesics market are the aging population and the rising therapeutic benefits of drugs. Together, these factors are expected to produce a growth in demand for pain relief medications that is predicted to reach $35.5 billion by 2015. Interestingly, despite the availability of numerous analgesic products, the choice of simple over-the-counter (OTC) analgesic compounds is limited to only a handful for adults (acetaminophen or paracetamol, acetylsalicylic acid, and ibuprofen) and for children (acetaminophen or paracetamol and ibuprofen).

Most OTC and certain physician-prescribed products for pain relief are intended to immediately release the active drug after oral ingestion and thus result in rapid onset of action. Such products need to be taken frequently if the pain persists. The inconvenience associated with frequent dosing could be overcome through the use of slow-release products. Also, modified-release products have become a mainstay for the treatment of moderate to severe chronic pain. Due to the decreased dosing frequency, these products allow patients to focus on their daily activities and to get uninterrupted nights of sleep.

19.5.1 Immediate-Onset Systems

Rapid-onset pain treatment is needed for the treatment of breakthrough pain. It typically takes 0.5–2.0 hours after swallowing a tablet for an effect to manifest because the tablet must pass through the stomach to the intestines before it can be absorbed into the blood. A faster and safe way to achieve quick oral action is for the drug to be absorbed through the relatively permeable buccal mucosa. This mucosa is robust, has a rich blood supply, and is particularly well
suited for the delivery of drugs that undergo significant first-pass effect in the intestines and in the liver.

The successful buccal delivery of a potent opioid is best illustrated by the fentanyl buccal tablets. The OraVescent® (Cephalon Inc., Frazer, PA, USA) drug delivery technology used in these compressed buccal tablets contains a pH-altering excipient, sodium carbonate, which provides an alkaline environment for converting the ionized fentanyl into an un-ionized, maximally absorbable form of fentanyl. Almost complete drug absorption is achieved within 15 minutes after application [154], making the buccal tablet ideal for the management of breakthrough pain in opioid-tolerant cancer patients. Buccal delivery has the faster pharmacokinetics when compared to fentanyl tablets [155]. In addition, the buccal dosage form bypasses the extensive intestinal metabolism of fentanyl and thus reaches a relative bioavailability of 50% as compared to only 30% for the tablet form [154].

19.5.2 Slow-Release Systems

Many orally ingested drugs have been formulated into extended-release tablets for the treatment of persistent pain. They typically release the active drug over 8-12 hours. Worldwide, the highest-selling such product in the pain market is OxyContin®, with the active ingredient oxycodone. In 2007, OxyContin was sold in the United States for US$1.047 billion and was thus the thirty-third best-selling drug. The following paragraphs describe the top analgesic slow-release systems on the market.

Avinza® extended-release capsules (Elan Corporation) contain morphine sulfate in both immediate- and extended-release beads that measure 1-2 mm in diameter [156]. The immediate-release component (about 10% of the total dose) helps to achieve plateau morphine concentrations within 30 minutes, and the extended-release component then maintains these plasma concentrations throughout the 24-hour dosing interval. Avinza uses SODAS®, the “Spheroidal Oral Drug Absorption System,” to produce the extended-release component of the product (Figure 19.9). A sugar/starch sphere is first coated with a drug/excipient layer and then with an ammonio-methacrylate copolymer coating. The spheres are packed into a hard gelatin capsule shell that immediately dissolves after oral administration. The permeability of the ammonio-methacrylate copolymer coating becomes the rate-limiting step for the entry of gastrointestinal fluid through the polymer coating into the morphine sulfate layer. In addition to controlling the liquid flow, it is also important to control the pH of the drug environment independent of the gastrointestinal environment in order to maintain solubility and dissolution speed constant. Fumaric acid, an osmotic agent and a local pH modifier within the drug/excipient layer, plays this crucial stabilizing role in the release process of the drug.

KADIAN® sustained-release capsules (Alpharma, Bridgewater, NJ, USA) contain morphine sulfate in polymer-coated, sustained-release pellets without an immediate-release component [157]. The extended-release pellets of Avinza and KADIAN share a similar general structure, but KADIAN’s coating consists of an insoluble ethyl cellulose base along with polyethylene glycol (PEG) and a methacrylic acid copolymer. Though PEG and methacrylic acid copolymer are both water soluble, the water solubility of the methacrylic acid copolymer is pH dependent and increases with increasing pH. The PEG component dissolves immediately after ingestion in the stomach. As the pellets later enter and move through the intestines, the pH of the gastrointestinal (GI) environment continues to increase, and the methacrylic acid copolymer begins to dissolve and release more drug.

Oramorph® sustained-release tablets (Xanodyne Pharmaceuticals Inc., Newport, KY, USA) contain morphine sulfate in a simple matrix system instead of a polymer-coated reservoir. This design allows for easy tablet pressing after uniform blending of the drug with the hydrophilic polymer hydroxypropyl methylcellulose. After oral administration, the tablet becomes hydrated, and the cellulose matrix swells and forms a viscous gel layer. The gel layer controls both the diffusion of water into the system and the diffusion of drug out of the system. Although Oramorph controls the drug release well, patient studies have shown that the side effects are significantly larger than, for example, in transdermal fentanyl [158].

MS Contin® controlled-release tablets from Purdue Pharma L.P. (Stamford, CT, USA) contain morphine sulfate in a polymer matrix made of the hydrophilic polymer hydroxypropyl methylcellulose and the hydrophobic polymer hydroxyethyl cellulose. The drug is blended with the hydrophilic polymer,
suitably hydrated with a polar solvent, and fixed with a higher aliphatic alcohol [159]. The release of drug from the tablet is controlled by the partition coefficients of the active ingredient with the hydrophilic and hydrophobic components of the formulation [160].

**OxyContin controlled-release tablets** (Purdue Pharma L.P.) contain oxycodone HCl that is released with a biphasic release profile. Upon dissolution of the hydrophilic ammonio-methacrylate copolymer coating, 30–40% of the drug is immediately released [161]. This causes the formation of channels in the tablet matrix [162], which in turn enhances solubility of the entrapped drug and makes it slowly diffuse through the formed channels of the matrix. The release of oxycodone is pH independent, permitting a uniform release throughout the GI tract.

Extended-release systems with opioids are not without problems, as Purdue Pharma L.P. learned in 2005. They had developed Palladone™ extended-release capsules, which contained hydromorphone HCl in an around-the-clock (ATC) matrix pellet formulation that provided a biphasic release of hydromorphone. Consuming ethanol while taking Palladone disrupted the modified-release mechanism of the product. Peak blood concentrations increased approximately six times with the consumption of 8 oz of a 40% (80 proof) ethanol solution and approximately two times with the consumption of 8 oz of a 4% ethanol solution [163, 164]. In July 2005, the FDA advised Purdue Pharma L.P. that the risk of alcohol interaction could not be adequately managed with warnings alone. At the request of the FDA [165], Purdue suspended all marketing and sales of Palladone.

There are many more slow-release systems under development for the slow release of oral hydromorphone (ALZA Corp.), oral oxymorphone (Endo Pharmaceuticals), or a combination of oxycodone and morphine (QRxPharma). All are based on pharmaceutical technologies similar to those described above.

A different approach to extending the action of pain drugs, which does not involve the use of highly developed slow-release technology, is the chemical modification of the drug. Morphine, for example, has been glucuronated, making it into a longer-acting drug with fewer side effects (less sedation and less respiratory depression) [166]. The glucuronated morphine, however, had a slower onset of action.

### 19.6 Outlook

The search for newer and better analgesic delivery systems and formulations is changing the face of pain management [108]. Many such systems are described in this chapter. One of the relatively mature systems is the iontophoretic patch that allows for patient-controlled drug release through the skin. Other less-mature systems include microneedles and laser ablation. They are appropriate for analgesics that are less skin penetrating, because they can temporarily breach the stratum corneum. For some of these delivery approaches, pain-specific FDA-approved systems already exist, such as in the case of the IONSYS fentanyl iontophoretic patch. For others, the companies are providing the platform technology that can then be adapted for many different drugs. One such case is the microslicer, an instrument that will prepare the skin for elevated drug penetration. The drug to be used can be freely chosen and must be applied in suitable concentration and form.

In order to be accepted in both the healthcare system and in the marketplace, a new drug delivery device must be able to deliver sufficient drug doses to the target area and must be shown to be superior to existing conventional medicines in terms of ease of use, onset of drug action, side effects, length of action, and cost. Advantages and potential new side effects must be carefully compared and the risks calculated.

Many side effects of even the newer systems, such as transdermal systems, would be reduced if the drug could be kept away from the brain, and/or delivered in a targeted way. Drug targeting can be accomplished using organ- or tissue-specific drug delivery systems (e.g., by magnetic targeting), site-specific systems (e.g., by placing biodegradable implants or drug-releasing microspheres in a site), or process-specific systems (e.g., release of the drug from heat-sensitive liposomes in the aching tissue by inflammation-induced small temperature differences).

In the not too distant future, much more directed interventions may be possible, including the enrollment of the help of nanorobots like those described with immense imagination by Robert Freitas [167]. Such nanorobots might be made to behave like bacteria with flagella, or fibroblasts, and could be used to repair clogged vessels, remove cancer or other cells, or perhaps even take up unwanted molecules (e.g., pain-inducing molecules) or release specific substances. It may also be possible to directly drugs on the microscopic level, not only to major organs but also to distinct organelles, such as the lysosomes, mitochondria, or chromosomes. Initial attempts to target intracellular organelles are ongoing, and success stories are beginning to appear. One example from the field of radiation oncology is directing the radiolabeled antibody trastuzumab to HER2-positive breast tumor cells [168]. Once taken up into the cells, a 13-mer peptide covalently bound to the antibody takes over and directs the construct into the nucleus, where the Auger electrons from the also attached radioisotope 111In are close enough to the DNA to both arrest synthesis and repair and kill the cell [168].

More precise targeting of drugs could lead to an increase in the number of drugs available for pain treatment. Many of the highly effective drugs developed by the pharmaceutical industry are currently too toxic to be used. Packaging them into the newly developed drug delivery systems could change their toxicity profile and allow for their reevaluation in clinical trials.

The search for newer and better analgesic delivery systems also increasingly involves the application of the principles of multimodal therapy [108]. Modern medicine, and especially the field of cancer therapy, profits immensely from combination approaches in general. Sometimes, a drug or treatment alone is
sufficient to eradicate cancer, but more often it is necessary to combine two or more treatment approaches to be successful. This might also prove true for analgesic drug delivery. Initial steps in this direction are currently being made. Specifically, drugs with immediate onset of action are being combined with ones that work over longer time periods (i.e., slow-release drugs). The combination of different drugs and drug delivery techniques might expand the benefits that each drug brings and might minimize the side effects of each. To rationally develop and test multimodal therapies, it would be beneficial to engage experts from many different fields, including pharmaceutics, chemistry, pharmacology, and medicine, in all stages of the development process.

REFERENCES


PERIPHERAL RECEPTOR TARGETS FOR ANALGESIA
NOVEL APPROACHES TO PAIN MANAGEMENT

Edited by
Brian E. Cairns, RPh, ACPR, PhD
Faculty of Pharmaceutical Sciences
The University of British Columbia