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Review Article

Advanced Formulation Design: Improving Drug Therapies for the Management of Severe and Chronic Pain

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Chronic pain is a condition affecting a vast patient population and resulting in billions of dollars in associated health care costs annually. Sufferers from severe chronic pain often requite twenty-four hour drug treatment through intrusive means and/or repeated oral dosing. Although the oral route of administration is most preferred, conventional immediate release oral dosage forms lead to inconvenient and suboptimal drug therapies for the treatment of chronic pain. Effective drug therapies for the management of chronic pain therefore require advanced formulation design to optimize the delivery of potent analgesic agents. Ideally, these advanced delivery systems provide efficacious pain therapy with minimal side effects via a simple and convenient dosing regime. In this article, currently commercialized and developing drug products for pain management are reviewed with respect to dosage form design as well as clinical efficacy. The drug delivery systems reviewed herein represent advanced formulation designs that are substantially improving analgesic drug therapies.

Keywords review; pain management; opioid; morphine; oxycodone; hydromorphone; oxymorphone; fentanyl; gabapentin; ketamine

INTRODUCTION

Physical pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Turk & Okifuji, 2000). Avoiding and seeking relief from pain is a biological impulse indispensable to the survival and proliferation of species. Pain is wholly subjective and often difficult to describe with regard to the nature and the source, and in almost all cases impossible to quantify. Therefore, in a clinical setting, pain must be defined according to the patient's description.

Tens of millions of Americans are partially or totally disabled by pain, and the annual cost of pain to American society is estimated to be in the billions of dollars (Joint Commission on Accreditation of Healthcare Organizations, 2000; Gallagher, 1999). Pain often goes undertreated and is a persistent problem in hospitals, long-term care facilities, and society in general. Therefore, it is essential that the techniques and therapies utilized to diagnose and treat pain continue to improve.

When considering pain and pain therapy it is crucial to distinguish between acute and chronic pain. Acute pain is pain of rapid onset, can be severe, but lasts a relatively short time. Chronic pain is pain that persists for a prolonged period of time beyond the normal healing time for an acute injury. It can also be associated with a chronic disease, or it may be a result of a persistent indefinable cause. Pain is useful for alerting individuals of disease states and potentially harmful situations; however, when it exceeds its biological usefulness, either in severity or duration, it can cause many harmful physiological and emotional effects.

Eliminating the underlying cause is the ideal method for relieving pain; however, this is often not possible, and in these cases management of pain via symptomatic treatment is the only option. Options for treating symptoms of pain include pharmacological treatment, stimulation therapies, and psychological therapies. Of these options, drug treatments are the most common and most effective means of pain relief.

Drugs used in the treatment of pain can generally be classified as nonopioid and opioid agents. Nonopioid agents such as acetaminophen, acetylsalicylic acid, and nonsteroidal anti-inflammatory drugs are preferred over opioids in the treatment of mild pain. The therapeutic outcome with these drugs, however, is insufficient in moderate and severe cases. In these cases, opioid drugs are most often used to assuage pain symptoms.

Opioid drugs are vital in the management of severe and chronic pain. Opioids are commonly used in the treatment of cancer and naturopathic pain, as well as pain resulting from other noncancer disease states. Opioids are administered to patients by various routes, although the American Pain Society has identified the oral route of administration as the most preferred due to comfort, convenience, flexibility, and consistency of blood levels (American Pain Society, 1999). As many

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patients dealing with chronic pain require around-the-clock treatment, typical immediate-release (IR) dosage forms that require multiple daily dosing are highly nonideal. Therefore, the development of extended-release (ER) dosage forms for the delivery of pain management drugs has vastly improved drug therapy for pain management and thereby improved the quality of life for patients suffering form chronic pain. By reducing the frequency of dosing, these ER dosage forms improve patient compliance, reduce the occurrence of breakthrough pain, and allow patients to sleep through the night without suffering from a pain episode. In this article, various advanced drug delivery systems for several of the most prescribed opioids and some emerging pain management drugs are reviewed to illustrate how advanced-formulation design can benefit drug therapy and ultimately improve patient quality of life.

MORPHINE

A complete listing of the commercial products available in the United States for morphine (morphine sulfate) is provided in Table 1. It can be seen in this table that there are a number of branded and generic commercial morphine products of various modes of delivery and drug-release profiles. As this review is focused on advanced-formulation design for the delivery of pain management drugs, the focus of the discussion to follow will be the ER solid oral morphine products. The leading modified release products for morphine are Avinza®, Kadian®, Oramorph®, and MS Contin®. These oral dosage forms provide release of therapeutic levels of morphine sulfate from 12 to 24 hours.

Oramorph® Sustained-Release Tablets

Oramorph® SR is a sustained-release (SR) tablet dosage form that delivers therapeutic levels of morphine sulfate to the patient over a period of 8 to 12 hours. The dosage form is a matrix tablet design, which utilizes the retardant properties of high molecular weight hydroxypropyl methylcellulose (HPMC) to control the rate of dissolution of morphine sulfate and its subsequent release within the digestive tract of the patient. In vivo, when gastrointestinal (GI) fluids penetrate an Oramorph® SR tablet, the HPMC component of the tablet swells, forming a viscous gel layer that impedes the continued inward diffusion of the surrounding fluid as well as the outward diffusion of solubilized drug. As digestive fluids continue to permeate the tablet and the swelling of HPMC propagates inward toward the tablet core, the outer layers begin to erode, providing an additional mechanism for drug release. Therefore, the release of morphine sulfate from the Oramorph® SR tablet follows a general diffusion/erosion release mechanism that results in the SR of morphine sulfate and overall therapeutic efficacy per dose for a period of 8 to 12 hours.

Clinical evaluations of Oramorph® SR tablets have shown that 50% of the absorbed morphine dose reaches the central compartment 1.5 hours following administration, on average (Xanodyne Pharmaceuticals, Inc., 2006). When compared with IR oral morphine products, this absorption time represents a modest increase of approximately one hour. Oramorph® SR administered once every 12 hours exhibits a similar pharmacokinetic profile as conventional IR dosage forms administered every four hours. However, the Oramorph® SR tablet provides less fluctuation between peak and trough plasma levels, which ultimately provides more consistent therapy while reducing morphine related side effects (Xanodyne Pharmaceuticals, Inc., 2006).

MS Contin® and MS Contin XL®

MS Contin® is a controlled-release (CR) morphine sulfate tablet system produced and commercialized by Purdue Pharma. The MS Contin® tablet formulation is based on the Contin™ delivery system, which was first described by Boroda and colleagues in 1973 and later in U.S. Patent No. 3965256 (Boroda, Miller, Leslie, Nicol, & Thomson, 1973; Leslie, 1976). The Contin™ system is based on a dual-control matrix consisting of hydrophilic and hydrophobic polymeric components that act synergistically to retard drug release (Reder, 2001). With MS Contin®, hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC) comprise the hydrophilic swellable polymeric matrix that contains morphine sulfate and is embedded in a hydrophobic, high molecular weight aliphatic alcohol, that is, cetostearyl alcohol (Amabile & Bowman, 2006; Purdue Pharma L.P., 2004a). The system is produced by first blending the active with hydrophilic cellulosic polymers followed by wet granulation with a polar solvent such as water or alcohol. Once this granulated product has been dried and sieved, it is then combined with cetostearyl alcohol that has been melt granulated with a filler excipient such as lactose. The combined granulated masses are then thoroughly blended into a uniform granulated mass and subsequently mixed with tableting aids. This blend is then compressed to produce the final SR tablet dosage form (Leslie, 1976, 1986).

When the MS Contin® tablet comes into contact with GI fluids, the aqueous media penetrates the tablet, causing the HPMC/HEC matrix to swell, forming a viscous gel. The rate of fluid penetration, and hence the swelling of the polymer matrix, is controlled by the hydrophobic aliphatic alcohol component (Gourlay, 1998). The rate of drug release is dependent on the rate of diffusion of the dissolved drug through the hydrated gel layer. As the gelation rate is controlled by the hydrophobic matrix, the overall drug release rate can be controlled by varying the ratio of the hydrophilic gel-forming polymers to the hydrophobic matrix material. Therefore, release of therapeutic levels of morphine can be achieved with this system for a 12 hour dosing interval.

Purdue Pharma is currently developing a once-daily morphine sulfate product to be marketed under the brand name

TABLE 1
Summary of Commercial Morphine Products Available in the United States

Brands	Dosage Form	Strengths	Manufacturer
Controlled-Release Formulations			
Avinza®	Capsules ER Beads	30 mg (27 mg ER, 3 mg IR) 24 hrs 60 mg (54 mg ER, 6 mg IR) 24 hrs 90 mg (81 mg ER, 9 mg IR) 24 hrs 120 mg (108 mg ER, 12 mg IR) 24 hrs	Ligand
Kadian®	Capsules ER pellets	20 mg/24 hrs 30 mg/24 hrs 50 mg/24 hrs 60 mg/24 hrs 100 mg/24 hrs	Actavis
Oramorph SR®	Tablets ER	15 mg/12 hrs 30 mg/12 hrs 60 mg/12 hrs 100 mg/12 hrs	Xanodyne
MS Contin®	Tablets ER	15 mg/12 hrs 30 mg/12 hrs 60 mg/12 hrs 100 mg/12 hrs 200 mg/12 hrs	Endo Pharms, Ethex, Mallinckrodt Purdue Pharma
Immediate-Release Formulations			
Morphine sulfate oral solution	Solution	10 mg/5 ml 20 mg/5 ml	Roxane
Morphine sulfate concentrate oral solution	Solution	20 mg/ml	Ethex, Mallinckrodt
Roxanol			Xanodyne
Roxanol-T			Xanodyne
Morphine sulfate tablets	Tablets	15 mg 30 mg	Ethex, Roxane
Morphine sulfate tablets	Tablets, soluble	10, 15, 30 mg	Ranbaxy
Injectables			
Morphine sulfate injection	IM, IV, SC	Various concentrations	Hospira, Baxter, AstraZeneca
DepoDur	Injectable liposomal suspension	10, 15, 20 mg/ml	Endo Pharms
Suppositories			
Morphine sulfate suppositories	Suppositories	5, 10, 20, 30 mg	G&W, Paddock Upsher-Smith

MS Contin XL®. The dosage form is a multiparticulate capsule system; however, the details of the ER formulation are not publicly available. In a recent study conducted by Hagen and colleagues (2005), the efficacy, safety, and pharmacokinetics of the MS Contin XL® once-daily formulation were compared with the twice-daily MS Contin® tablet. No difference was observed between the two formulations with respect to morphine absorption, overall pain intensity, analgesic efficacy, or adverse events. However, pain scores were seen to increase during the day with the MS Contin® tablet, but remained stable with the MS Contin XL® capsule. Additionally, greater fluctuations in plasma morphine levels were seen with the twice-daily formulation versus the once-daily formulation, with fluctuation indices of 179.3 ± 41.3% and 93.5 ± 28.8% for these two delivery

systems, respectively. The plasma morphine concentration versus time profile of the two formulations shown in Figure 1 illustrates the substantially more stable profile of the once-daily formulation versus the twice-daily formulation. This more constant profile suggests enhanced therapeutic efficacy of the once-daily formulation as plasma morphine levels remain constant and within the therapeutic window for an extended duration while the twice-daily formulation exhibits substantial fluctuation.

By reducing morphine plasma level fluctuation, not only is pain alleviation improved, but occurrences of morphine-related side effects will also be reduced. The drop in morphine levels near the midpoint of the dosing interval seen with the twice-daily formulation could lead to a pain breakthrough episode resulting in the administration of an additional daily dose. Exceeding the suggested dosing schedule in this way will expedite the onset of morphine tolerance and is another reason the 24-hour MS Contin XL® formulation is preferred over the 12-hour MS Contin® tablet. A majority (68%) of patients participating in the study preferred the once-daily MS Contin XL® formulation to the twice-daily MS Contin® formulation, presumably because of the improved convenience of the dosing schedule (Hagen et al., 2005).

This direct comparison of a twice-daily formulation to an once-daily formulation clearly illustrates the impact of advanced-formulation design when applied to drug therapies for the management of chronic pain. The MS Contin® tablet system provided improved morphine therapy over conventional IR formulations; however, this tablet technology has been proven inferior to the MS Contin XL® capsule. By improving therapeutic efficacy, minimizing side effects, delaying the onset of drug tolerance, and minimizing the dosing regime over both ER formulations and the twice-daily tablet formulation, the MS Contin XL® formulation represents a substantial advancement in the oral delivery of morphine that will improve the quality of life for patients suffering from chronic pain.

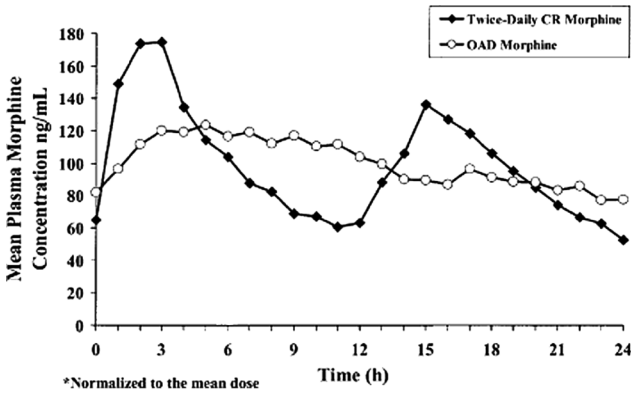

FIGURE 1. Mean plasma morphine concentration time profiles following administration of once-daily (OAD) morphine and twice-daily CR morphine for one week. Plasma concentrations were normalized to a total daily dose of 427 mg. (Reprinted with permission from Hagen et al., 2005.)

Avinza® Extended Release Capsules

Avinza® is an ER morphine sulfate capsule marketed by King Pharmaceuticals, Inc., the composition of which is described by U.S. Patent No. 6066339. Each Avinza® capsule contains both IR and CR morphine sulfate beads (1–2 mm in diameter) in a 9:1 (w/w) ratio with respect to drug content (Ligand Pharmaceuticals, 2003). With this combination of beads, plateau morphine levels are achieved within 30 minutes via the IR portion while the ER beads maintain these blood levels for the 24-hour dosing interval (Amabile & Bowman, 2006). A drug delivery system proprietary to the Elan Corporation known as the spheroidal oral drug absorption system (SODAS®) is the underlying technology employed to produce the ER Avinza® capsule. With this system, the ER beads are produced by first coating sugar spheres with a morphine sulfate/excipient layer followed by an ammoniomethacrylate copolymer coating; i.e., a blend of EUDRAGIT® RL and EUDRAGIT® RS. The IR beads are produced by the same process; however, they do not contain the release-rate controlling ammoniomethacrylate polymer coating. These beads are combined in the aforementioned ratio and filled into hard gelatin capsules to produce the final Avinza® capsule.

Once ingested, the gelatin capsule shell rapidly dissolves, releasing the coated beads to the gastric fluid. As there is no rate-controlling polymer on the IR beads, the drug content of this fraction is rapidly released and absorbed, hence providing an immediate onset of therapeutic action. The ammoniomethacrylate copolymer film coat is insoluble and permeable to GI fluids, acting as a semipermeable membrane that controls the diffusion of aqueous media into, and consequently the drug release out of, the coated beads. Fumaric acid contained in the bead core acts as both an osmotic agent and as a local acidifier to mediate the rate at which the GI fluid permeates the insoluble film and solubilizes the drug. Dissolved morphine then diffuses out of the core through the film at a controlled rate, thereby prolonging in vivo drug release and extending absorption for 24 hours.

At steady state (two to three days after dosing initiation), once-daily Avinza® (60 mg) was determined to be equivalent to six daily doses of 10 mg morphine solution (Ligand Pharmaceuticals, 2003). These results thus indicate a vast improvement with respect to the convenience of managing pain with oral morphine with Avinza® over a conventional IR formulation. In addition to the maintenance of therapeutic morphine levels for 24 hours, plasma levels resulting from once-daily Avinza® capsules remain relatively constant over the dosing interval. Consequently, fluctuations in systemic morphine levels are avoided, and thus morphine-related side effects are minimized.

A steady-state pharmacokinetic (PK) comparison of once daily Avinza® and twice-daily MS Contin® was conducted by Portenoy and colleagues (2002) in patients suffering from moderate to severe pain. Twenty-four–hour steady-state PK profiles were obtained for morphine and its active metabolites with both the Avinza® and MS Contin® formulations. These results are shown in Figure 2.

These results reveal that once-daily Avinza® and twice-daily MS Contin® provided similar bioavailability of morphine and its metabolites; however, Avinza® exhibited 19% lower C_{max}, a 66% greater C_{min}, as well as a 44% lower peak-to-trough fluctuation than the MS Contin® formulation over the 24-hour period. It was also seen that the Avinza® formulation maintained plasma morphine levels of greater than 50% and 75% of the C_{max} value longer than MS Contin®. Overall, once-daily Avinza® reached maximum concentration values faster, maintained elevated morphine plasma levels longer, and demonstrated less morphine plasma level fluctuation than MS Contin®. Hence, the evaluation of Avinza® in comparison to an alternative SR formulation revealed the therapeutic benefit of the once-daily oral morphine product to supplement the advantage of the reduced dosing regime.

A similar study was conducted by Caldwell and colleagues (2002) comparing once-daily Avinza® to twice-daily MS Contin® for treating chronic pain in patients suffering from osteoarthritis. The results of this study reveal that similar analgesic efficacy was achieved with both products; however, Avinza® was found to be more effective in improving quality of sleep. It was demonstrated that the more constant plasma morphine concentrations produced by the Avinza® formulation reduced occurrences of pain breakthrough at night, and thus allowed patients to sleep comfortably without being awakened by a pain episode.

Kadian® Sustained Release Capsules

Kadian® is another brand of ER morphine sulfate capsule, which is marketed by Alpharma Pharmaceuticals. The

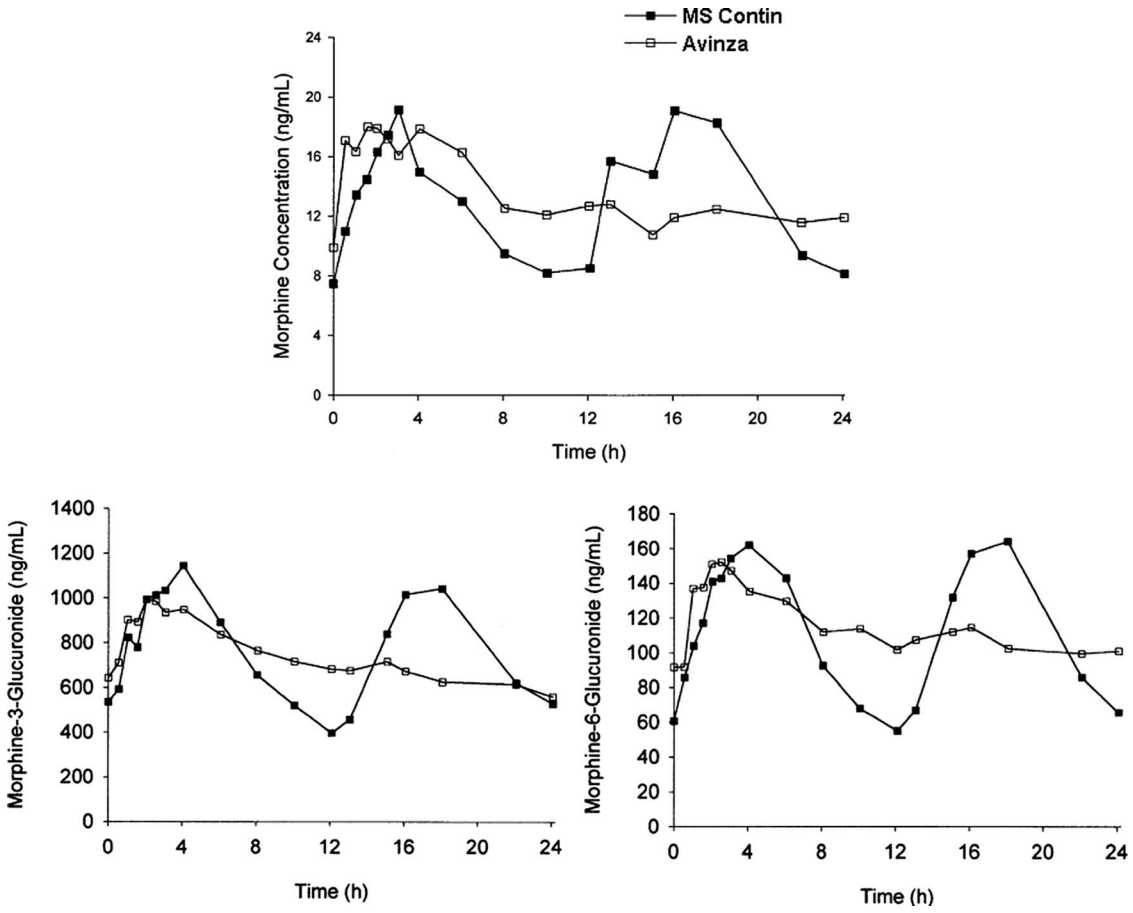

FIGURE 2. Mean morphine plasma concentration time curves obtained after administration of the different forms (n = 12). (Reprinted with permission from Portenoy et al., 2002.)

formulation design of the Kadian® capsule is described in U.S. Patent Nos. 5202128 and 5378474. The Kadian® SR pellet system, like Avinza®, is a multiparticulate dosage form contained inside a hard gelatin capsule. The important distinction between these products is that the Kadian® capsule does not contain a fraction of IR pellets. Rather, the immediate and extended drug release profiles are achieved from the same pellet design. The Kadian® system is based on an insoluble ethylcellulose coating which contains both a pH-independent, readily soluble, pore-forming agent (polyethylene glycol [PEG]) and a pH-dependent pore-forming agent (methacrylic acid copolymer), which is coated onto drug/excipient layered sugar spheres (Alpharma Pharmaceuticals, 2007). Drug release on ingestion begins just after the capsule is swallowed and the hard gelatin shell dissolves, releasing the pellets into the gastric fluid. In the acidic environment of the stomach, only the PEG component of the pore-forming agents contained in the insoluble coat dissolves. This creates pores that allow gastric fluid to enter the pellet to solubilize morphine sulfate contained in the core, which can then diffuse out and become absorbed. Since the methacrylic acid copolymer is insoluble in the acidic gastric environment, the extent of pore formation is limited to the PEG component of the ethylcellulose coat. This allows for controlled diffusion of morphine sulfate at the early stages following ingestion, hence producing an immediate therapeutic effect without compromising the ability of the insoluble film to continue to retard drug release in the more distal regions of the GI tract. As the pellets continue to traverse the GI tract and the pH of the surrounding intestinal fluid increases, the methacrylic acid copolymer begins to dissolve, creating more and larger pores through which drug release can occur. As the porosity of the insoluble film coat increases, the release of morphine sulfate from the diminishing core remains relatively constant, hence providing therapeutic morphine levels over the 24 hour dosing interval.

On average, eight or more hours are required for 50% of an administered dose of morphine sulfate from Kadian® capsules to reach systemic circulation. When compared with an oral morphine solution, which requires only 30 minutes for 50% of the dose to reach systemic circulation, this represents a substantial prolongation of therapeutic action and, consequently, a vast reduction in dosing frequency. At steady state, Kadian® has been shown to produce reduced C_{max} and increased C_{min} values when compared with equivalent doses of oral morphine solution as well as other ER morphine preparations (Alpharma Pharmaceuticals, 2007). Kadian® therefore produces a more constant plasma concentration versus time profile than a multidosing regime, reducing fluctuations in systemic drug levels and minimizing morphine-related side effects.

In a study conducted by Kerr and Tester (2000), Kadian® administered every 24 hours was compared with a twice-daily morphine tablet formulation (MS Contin®) administered every 12 hours for efficacy, tolerability, and patient preference. This study determined that Kadian® provided a similar amount of pain relief with a similar profile of morphine-related adverse effects as MS Contin® despite the reduced dosing frequency. Of the population of patients that were surveyed, 55% preferred Kadian®, 33% preferred MS Contin®, and 13% had no preference. These results thus demonstrated a statistically significant patient preference for the once-daily Kadian® formulation versus the twice-daily MS Contin® formulation, likely resulting from the greater convenience of the dosing schedule.

A retrospective analysis of the long-term use of ER morphine sulfate capsules for the treatment of chronic, nonmalignant pain was recently conducted by examining the charts of 68 patients taking Kadian® capsules (Chao, 2005). The range of daily doses for this patient population was 20 mg to 400 mg with a mean of 82.1 mg. The dosing frequency for a vast majority of the patient population (97.1%) was in accordance with the prescribing information (once or twice daily) and over half of these patients were maintained on a single daily dose of Kadian®. As a result of chronic pain treatment with Kadian® capsules, the mean pain score of this patient population was reduced from a baseline mean of 7.7 to 4.9. Moreover, long-term use of Kadian® did not result in morphine dose escalation or an increase in dosing frequency, which would indicate the development of a morphine tolerance.

In summary, these studies comparing ER MS Contin XL®, Avinza®, and Kadian® to conventional IR formulations and twice-daily formulations such as MS Contin® and Oramorph® SR reveal the significant enhancement in managing chronic pain with morphine that is provided through advanced-formulation design. These studies have demonstrated that ER, once-daily oral morphine formulations improve therapeutic efficacy and minimize side effects by reducing fluctuations in morphine plasma levels. Moreover, the reduced dosing schedule improves the convenience of the drug therapy that ultimately enhances patient compliance and provides a greater opportunity for a continuous night of sleep uninterrupted by pain episodes. It is not surprising that with these advantages, the 24-hour ER morphine formulations are preferred by a majority of patients receiving morphine treatments for chronic pain.

Noncommercial ER Morphine Delivery Systems

There are surprisingly few papers in the pharmaceutical literature that demonstrate ER formulations of morphine. One of the few articles describing a SR morphine sulfate delivery system was recently published by Nakamura and colleagues (2006). This study demonstrated the SR of morphine hydrochloride from a multiparticulate delivery system known as the swelling polymer incorporation layer system (SPILA). This system consists of core granules coated first with an intermediate water-soluble polymer layer followed by a second coating with a mixture of carboxyvinyl polymer (CP), a water-insoluble polymer, and a water-soluble polymer. A schematic illustrating the system is shown in Figure 3. This coating system was demonstrated to produce a pH-dependent drug release profile in vitro with slower

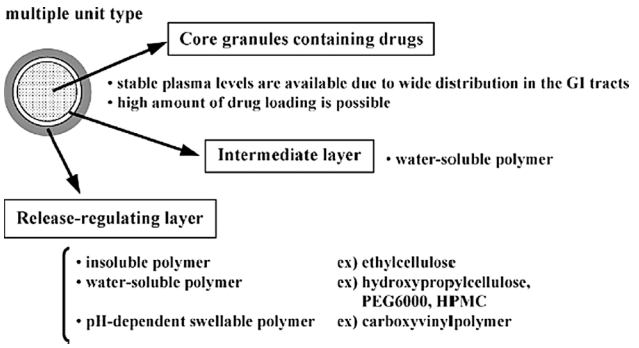

FIGURE 3. Steady-state mean plasma concentration time profiles following administration of once-daily Avinza® and twice-daily MS Contin® in patients with chronic moderate-to-severe pain. Plasma concentrations were normalized to a total daily dose of 100 mg. (Reprinted with permission from Portenoy et al., 2002.)

drug release in acidic pH than in neutral pH. In vivo studies conducted in beagle dogs revealed that the SPILA system provided quantifiable plasma concentrations for up to 24 hours.

A bioadhesive buccal tablet design for CR delivery of morphine was described in a study by Beyssac and colleagues (1998). Milk protein derivatives were utilized as bioadhesive excipients in the tablet formulation to adhere the drug to the buccal mucosa, thereby increasing exposure to the absorption site and improving drug uptake. An in vivo study was conducted with 12 healthy volunteers in which the bioadhesive buccal tablet was compared with morphine sulfate aqueous solution and MS Contin®. The results of this in vivo analysis are shown in Figure 4. From this study, it was seen that the

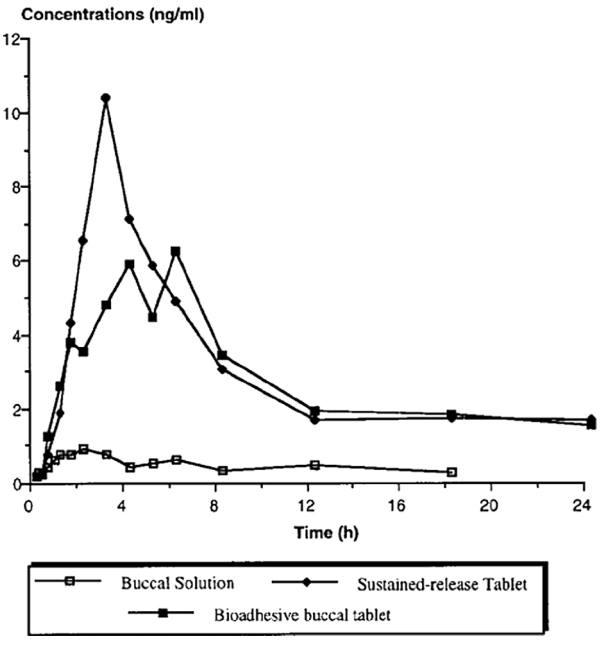

FIGURE 4. Schematic diagram of the SPILA system. (Reprinted with permission from Nakamura, Nara, & Akiyama, 2006.)

buccal tablet provided substantially better morphine absorption than the oral solution and equivalent absorption to the SR tablet (98% of AUC). However, the buccal tablet exhibited a reduced C_{max} and a greater T_{max} values, indicating more consistent absorption than the with the MS Contin® tablet. Thus, this study demonstrated that the buccal cavity is a viable site for morphine absorption.

OXYCODONE

The commercial oxycodone products available in the United States are summarized in Table 2. There are several marketed IR formulations and combination drug products; however, OxyContin® is the only branded ER product.

OxyContin® (oxycodone HCl CR tablets) is a commercial product of Purdue Pharma and is based on the AcroContin™ drug delivery system as first described by U.S. Patent No. 4861598. Like the previously described Contin™ system, the AcroContin™ tablet utilizes a dual-control matrix system to provide extended drug release for a period of up to 12 hours. The AcroContin™ delivery system also contains a higher aliphatic alcohol as the hydrophobic component of the matrix; however, the system differs from the Contin™ system in that an ammoniomethacrylate copolymer is used in place of a hydrophilic cellulosic polymer (Reder, 2001; Amabile & Bowman, 2006; Purdue Pharma L.P., 2004b). With this system, the ammoniomethacrylate polymer forms a barrier to control drug diffusion from drug-containing particles while the hydrophobic aliphatic alcohol matrix controls the rate at which the GI fluids penetrate the tablet. An important benefit to the AcroContin™ system is that it produces a biphasic drug release profile in which approximately 30% to 40% of the dose is released in the first hour, followed by an extended slow absorption phase with a half-life of about 6.2 hours (Amabile & Bowman, 2006). This release profile produces immediate therapeutic plasma levels of oxycodone and extends them for up to 12 hours. The IR phase is achieved by dissolution and diffusion drug from drug-containing particles at the surface of the tablet, while the ER phase arises from the dissolution and diffusion of drug that is entrapped within the matrix. Another benefit of the AcroContin™ system is that the nature of the polymers that make up the hydrophobic matrix allow for pH-independent release and resistance to food effects (Anderson, Fritz, & Muto, 2002; Fukshansky, Are, & Burton, 2005).

The absorption of oxycodone from OxyContin® tablets is in the range of 60% to 87%, with 100% bioavailability as compared with IR oral dosage forms (Purdue Pharma L.P., 2004b). The biphasic release profile of OxyContin® results in $t_{1/2}$ values of oxycodone absorption of 0.6 and 6.9 hours. With respect to IR oral oxycodone formulations ($t_{1/2}$ = 0.4 hrs), this represents a substantial prolongation of oxycodone absorption in a single dose, which allows for a substantially reduced dosing regime, that is, twice-daily versus four times daily (Purdue

TABLE 2
Summary of Commercial Oxycodone Products Available in the United States

Brands	Dosage Form	Strengths	Manufacturer
Controlled Release			
OxyContin®	Oral tablets, ER	10, 15, 20, 40, 80 mg	Purdue Pharma
Generic Oxycodone hydrochloride	Oral tablets, ER	10, 20, 40 mg	Endo Pharms, Impax Pharms, Teva
Generic Oxycodone hydrochloride	Oral tablets, ER	80 mg	Global, Teva, Impax labs
Immediate Release			
Roxicodone®	Oral tablet	15, 30 mg	Xanodyne Pharm
Generic Oxycodone hydrochloride	Oral tablet	5–30 mg	Actavis Totowa, KV Pharm, Mallinckrodt
OxyIR®	Oral capsule	5 mg	Purdue Pharma
Generic Oxycodone hydrochloride	Oral capsule	5 mg	Ethex
Various	Oral solution	5 mg/5 ml and 20 mg/ml	Mallinckrodt, aaiPharma, Ethex, Purdue Pharma
Combination Therapies			
	Capsule; oral	500 mg; 5 mg	Ortho McNeil Pharm
Roxilox® Acetaminophen; oxycodone hydrocholoride	Capsule; oral	500 mg; 5 mg	Roxane
Generic Acetaminophen; oxycodone hydrocholoride	Capsule; oral	500 mg; 5 mg	Actavis Totowa, Barr, Duramed Pharms, Endo Pharms, Mallinckrodt, Mutual Pharm, Vintage Pharms, Watson Labs
Roxicet®	Solution; oral	325 mg/5 ml; 5 mg/5 ml	Roxane
Generic Acetaminophen; oxycodone hydrocholoride	Solution; oral	325 mg/5 ml; 5 mg/5 ml	Mallinckrodt
Percocet®	Tablet; oral	650–325 mg; 2.5–10 mg	Endo Pharms
Oxycet®	Tablet; oral	325 mg; 5 mg	Mallinckrodt
Roxicet®Roxicet 5/500®	Tablet; oral	325 mg; 5 mg 500 mg; 5 mg	Roxane
Generic Acetaminophen; oxycodone hydrocholoride	Tablet; oral	325–650 mg; 5–10 mg	Actavis Totowa, Barr, Duramed Pharms, Mallinckrodt, Mikart, Vintage Pharms, Watson Labs
Percodan® Aspirin; oxycodone hydrocholoride; oxycodone terephthalate	Tablet; oral	325 mg; 4.5 mg ;0.38 mg	Endo Pharms
Generic Aspirin; oxycodone hydrocholoride	Tablet; oral	325 mg; 4.8355 mg	Endo Pharms
Generic Aspirin; oxycodone hydrocholoride	Tablet; oral	325 mg; 4.5 mg; 0.38 mg	Mutual Pharm, Watson Labs
Combunox® ibuprofen; oxycodone hydrocholoride	Tablet; oral	400 mg; 5 mg	Forest Labs

Pharma L.P., 2004b). OxyContin® (10 mg) dosed every 12 hours was found to be equivalent to an IR oxycodone formulation (5 mg) dosed every 6 hours with respect to AUC and C_{max} (Purdue Pharma L.P., 2004b). However, less fluctuation was seen in oxycodone plasma levels with the OxyContin® delivery system than with the IR formulation.

In a study conducted by Watson and colleagues (2003), OxyContin® administered every 12 hours was evaluated against placebo for efficacy, safety, and health-related quality of life in patients with diabetic neuropathy suffering from moderate or greater pain for at least three months. This study revealed that OxyContin® significantly reduced mean daily

pain, steady pain, brief pain, skin pain, as well as total pain and disability with respect to placebo. A portion of these results are given in Figure 5. This study therefore demonstrated that twice-daily administration of OxyContin® is a safe and effective means of managing pain associated with diabetic neuropathy and improving the quality of life for patients suffering from this disease.

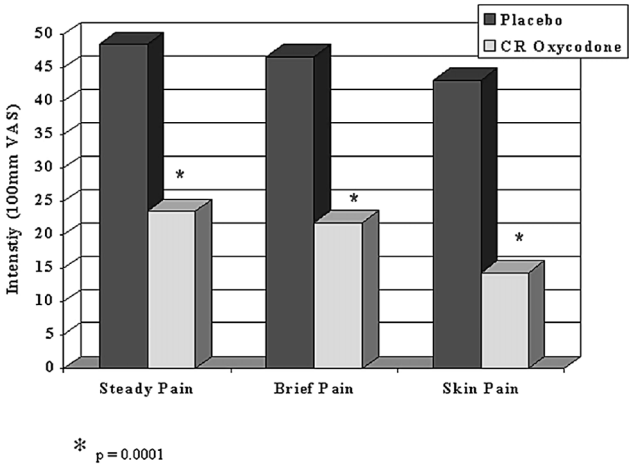

FIGURE 5. Mean steady, brief, and skin pain at the final week of each treatment. (Reprinted with permission from Watson, Moulin, Watt-Watson, Gordon, & Eisenhoffer, 2003.)

HYDROMORPHONE

A summary of hydromorphone products commercialized in the United States is given in Table 3. Palladone™ (hydromorphone ER capsules) is a product of Purdue Pharma and is the only ER hydromorphone product to have been marketed in the United States. However, in July of 2005, Palladone™ was pulled off of the market due to risk of fatality if taken with alcohol (Kaufman, 2005). Although it is no longer a commercial product, the Palladone™ delivery system warrants discussion because it is unique in being one of the few marketed products to utilize hot-melt extrusion processing. The delivery system for Palladone™ is based on a CR melt extrusion technology first described by U.S. Patent No. 5958452, whereby, in a single processing step, hydromorphone HCl is mixed with the hydrophobic carrier materials, the mixture is rendered molten, and the molten material is subsequently forced through a cylindrical die to form thin, noodle-like strands. The strands

TABLE 3
Summary of Commercial Hydromorphone Products Available in the United States

Brands	Dosage Form	Strengths	Manufacturer
Controlled Release			
Palladone™ (Off market)	Capsule, ER; oraL	12, 16, 24, 32 mg	Purdue Pharma LP
Immediate Release			
Dilaudid®	Tablet; oral	8 mg 2 mg 4 mg	Abbott KV Pharm KV Pharm
Generic Hydromorphone hydrochloride	Tablet; oral	8 mg	KV Pharm, Actavis Totowa, Mallinckrodt, Roxane
Dilaudid®	Solution; oral	5mg/5mL	Abbott
Generic Hydromorphone hydrochloride	Solution; oral	5mg/5mL	Roxane
Injectables			
Dilaudid-HP®	Injection	1, 2, 4 mg/ml 10 mg/ml 250 mg/vial (powder for injection)	Baxter, Hospira Abbott Abbott
Generic Hydromorphone hydrochloride	Injection	10mg/ml	Hospira Mayne Pharma USA Watson Labs
Suppositories			
Dilaudid®	Suppositories	3 mg	Abbott
Generic Hydromorphone hydrochloride	Suppositories	3 mg	Paddock

are then pelletized to produce the multiparticulate SR drug delivery system (Oshlack, Chasin, & Huang, 1999). The hydrophobic matrix is composed of ammoniomethacrylate copolymer type B, ethylcellulose, and stearyl alcohol. The combination of these polymers produces a matrix that retards the rate of water permeation into the pellet and hence controls the dissolution of hydromorphone HCl contained within each pellet. Once the drug is dissolved, the matrix again functions as a retardant to control the rate of diffusion of the solubilized drug out of the pellet matrix. The overall effect is the continuous and sustained release of hydromorphone in concentrations that provide therapeutic plasma levels over a period of 24 hours. The 12 mg, 16 mg, 24 mg, and 32 mg capsules are filled with identical pellets using different fill weights to achieve desired strengths (Purdue Pharma L.P., 2004c).

OXYMORPHONE

Opana ER® (oxymorphone hydrochloride) is an ER oxymorphone tablet commercialized by Endo Pharmaceuticals. The delivery system is based on a technology known as TIMERx™, which is a proprietary technology of Penwest Pharmaceuticals and is described in U.S. Patent No. 4994276 (Endo Pharmaceuticals, 2006). The TIMERx™ formulation utilizes a combination of xanthan gum and locust bean gum that in the presence of dextrose forms a hydrogel when in contact with water (Baichwal & Neville, 2002). This polysaccharide layer is compression coated around a drug-containing core. The rate of drug release from the tablet is controlled first by the rate at which water permeates into the tablet through the polysaccharide layer. As the surrounding medium penetrates the tablet, the polysaccharide coat swells to form a viscous gel layer that acts to retard diffusion of the drug from the tablet core into the surrounding medium (Adams & Andieh, 2004; Prommer, 2006). The retardant gel layer acts to control the release of oxymorphone HCl to provide therapeutic plasma levels for a period of up to 12 hours.

An evaluation of Opana ER® in healthy volunteers revealed lower C_{max} values and greater C_{min} values than an equivalent dose of a conventional IR oxymorphone formulation, indicating decreased dose fluctuations (Adams & Andieh, 2004). By reducing dose fluctuations, the Opana ER® formulation maintains oxymorphone plasma concentrations within the therapeutic window for the duration of the dosing interval. This absorption profile results in consistent therapeutic efficacy of the dose with minimal occurrences of harmful side effects. The mean T_{max} value of the Opana ER® formulation was determined to be 3 hours and concentrations at 12 hours were found to only decrease by 30% of the maximum plasma concentration value, thus indicating that the Opana ER® formulation is able to produce therapeutic plasma levels for the entire 12 hour dosing interval.

Several studies have been conducted demonstrating the efficacy of Opana ER® for managing chronic pain. One such study evaluated the treatment of osteoarthritis patients with differing doses of Opana ER® (Endo Pharmaceuticals, 2003). The results of this study revealed that 40-mg and 50-mg doses produced marked improvements in the conditions of the patients, that is, pain, stiffness, and physical function with respect to placebo (Endo Pharmaceuticals, 2003). In another study, cancer patients suffering from chronic pain were given twice daily doses of Opana ER® in the range of 80 mg to 140 mg (Slatkin, Frailey, & Ma, 2003). Ninety percent of patients that completed the year-long study rated Opana ER® as either excellent, very good, or good at relieving pain (Slatkin et al., 2003). These studies thus demonstrated the efficacy of oxymorphone for relieving pain as well as the ability of the TIMERx™ delivery system to extend the dosing interval to 12 hours. Hence, Opana ER® is another analgesic product that illustrates how the application of advanced-formulation design can improve drug therapies for pain management.

FENTANYL

Fentanyl is a potent opioid analgesic which is primarily indicated for the treatment of breakthrough pain episodes. An effective delivery system for fentanyl should promote rapid and extensive absorption of the drug to provide fast and effective relief of breakthrough pain. Fentanyl is highly metabolized by CYP 3A4 enzymes in the small intestine and in the liver, and therefore traditional oral delivery systems that rely on drug absorption through GI membranes result in reduced and highly variable bioavailability (Labroo, Paine, Thummel, & Kharasch, 1997; Streisand et al., 1998). It is for this reason that oral SR delivery strategies, like those discussed previously in this article, are not viable for the delivery of fentanyl. Therefore, transdermal, inhalation, and buccal delivery systems are preferred, since by these routes of administration first pass metabolism is avoided, providing improved bioavailability and reduced fluctuation in systemic absorption. Table 4 summarizes the commercial products currently available in the United States for fentanyl and fentanyl citrate. In addition to these commercial fentanyl dosage forms, products currently in development which employ advanced-formulation systems to improve the efficacy of fentanyl will also be discussed.

Duragesic® ER Transdermal Film

Duragesic® is a transdermal delivery system that provides continuous systemic delivery of fentanyl over 72 hours for the management of breakthrough pain (Janssen L.P., 2003). The delivery system comprises a protective liner and four functional layers. Beginning at the outer protective backing and moving toward the adhesive surface, the layers are as follows: (a) a backing layer of polyester film; (b) a drug reservoir of fentanyl and alcohol USP gelled with hydroxyethyl cellulose; (c) an ethylene-vinyl acetate (EVAC) copolymer membrane that controls the rate of fentanyl delivery to the skin; and (c) a

TABLE 4
Summary of Commercial Oxymorphone Products Available in the United States

Brands	Dosage Form	Strengths	Manufacturer
Controlled Release			
Opana ER®	Oral tablets, ER	5, 10, 20, 40 mg	Endo Pharms
Immediate Release			
Opana®	Oral tablet	5, 10 mg	Endo Pharms
Injectables			
Numorphan®	Injectable, injection	1.0, 1.5 mg/ml	Endo Pharms
Suppositories			
Numorphan®	Suppository, rectal	5.0 mg	Endo Pharms

fentanyl containing silicone adhesive (Janssen L.P., 2003). It is important to note that care must be taken when handling and applying the patch, as damage to the EVAC membrane will substantially affect its permeability, thus compromising the ER properties of the system. A schematic illustration of the delivery system is shown in Figure 6.

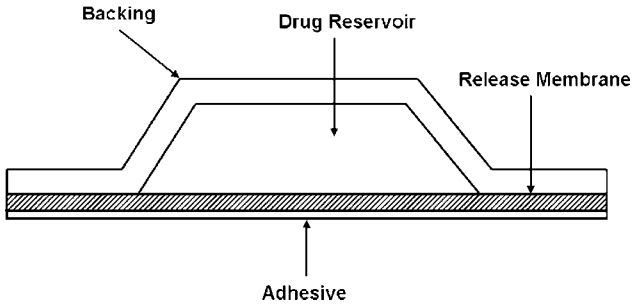

FIGURE 6. Diagram of the Duragesic® transdermal system.

The elevated concentration of fentanyl in the patch reservoir with respect to the skin provides the concentration gradient that drives the diffusion of fentanyl through the EVAC membrane. The rate of diffusion of fentanyl from the reservoir into the skin is controlled by the properties of the EVAC membrane. Duragesic® patches are available at varying nominal flux values—that is, 12.5, 25, 50, and 100 μg/hr—that allow for accurate control of systemic fentanyl levels such that the dose can be titrated to meet individual patient needs. Following application of the Duragesic® patch, fentanyl begins to concentrate in the upper layers of the skin in proportion to the nominal flux. Once the epidermis becomes concentrated with fentanyl, the drug begins to diffuse from the outer skin layers to reach systemic circulation. Maximum systemic fentanyl

TABLE 5
Summary of Commercial Fentanyl Products Available in the United States

Brands	Dosage Form	Strengths	Manufacturer
Controlled Release			
Duragesic®	Transdermal film, ER	12.5, 25, 50, 75, 100 μgm/hr	Alza
Generic Fentanyl	Transdermal film, ER	25, 50, 75, 100 μgm/hr	Lavipharm Labs, Mylan Technologies
Immediate Release			
Fentora®	Tablet, buccal	EQ 0.1, 0.2, 0.4, 0.6, 0.8 mg base	Cephalon
Generic Fentanyl	Oral troche/lozenge	EQ 0.1, 0.2, 0.3, 0.4 mg base	Cephalon
Actiq® (sugar-free)	Troche/lozenge; transmucosal	EQ 0.2, 0.4, 0.6, 0.8, 1.2, 1.6 mg base	Cephalon
Injectables			
Generic Fentanyl citrate	Injectable, injection	EQ 0.05 mg base/ml	Abbott, Hospira, Watson Lab
Generic Fentanyl citrate preservative free	Injectable, injection	EQ 0.05 mg base/ml	Baxter Healthcare, Hospira, Marsam Pharms LLC
Generic sublimaze preservative free	Injectable, injection	EQ 0.05 mg base/ml	Akorn Mfg
Other Transdermal			
Ionsys®	Iontophoresis, transdermal	10.8 μgm	Alza

concentrations are typically achieved in 12 to 24 hours and remain reasonably constant over the 72 hour application period. An evaluation conducted by Clark and colleagues (2004) suggests that the DRUAGESIC® system was superior to SR oral morphine for the treatment of cancer pain and non-cancer-related chronic pain.

Actiq® Lollipop

The Actiq® (oral transmucosal fentanyl citrate) lollipop delivery system incorporates fentanyl citrate into a candy matrix primarily composed of hydrated dextrates, which is formed around a handle. The lollipop design allows the patient to rotate the dosage form in their mouth to promote absorption and to allow for removal if signs of excessive opioid effects occur during administration (Mystakidou, Katsouda, Parpa, Vlahos, & Tsiatas, 2006; Cephalon Inc., 2006). As the candy matrix erodes, the drug is released in the oral cavity and ideally absorbed through the oral mucosa. However, a major limitation to this dosage form is that a substantial portion of the administered drug is not absorbed through the buccal mucosa, but rather is swallowed. Therefore, the lollipop dosage form is a nonideal method of delivery for fentanyl citrate since the swallowed portion of the administered drug will be highly metabolized in the GI tract and the liver, resulting in reduced bioavailability (Zhang, Zhang, & Streisand, 2002).

Fentora® Buccal Tablets

The Fentora® system is formulated as round, flat-faced tablets with beveled edges that are designed to be administered to, and held in, the buccal cavity for sufficient time to allow for complete disintegration of the tablet (Cephalon Inc., 2006). Fentora® is based on the OraVescent® technology developed by Cima Labs Inc., which was first described in U.S. Patent No. 6974590. This system utilizes sodium carbonate and sodium bicarbonate along with citric acid to generate an effervescent reaction that allows for rapid disintegration of the tablet and enhances drug absorption in the buccal cavity (Eichman & Robinson, 1998). The OraVescent® system produces a dynamic pH environment where the pH fluctuates by approximately two units following administration, ideally with the pKa of the drug at the midpoint of the pH fluctuation range (Pather et al., 2001). The liberation of CO_2 from the effervescent reaction results in an initial decrease in pH of the saliva as carbonic acid forms from a reaction of CO_2 with water. Since fentanyl is a weak base, it is more soluble in acidic media, and hence the decrease in pH facilitates the dissolution of the drug. As CO_2 comes out of solution and enters the air space or the surrounding tissues, the pH of the surrounding saliva increases. When the pH increase exceeds the pKa of the drug, the ionized drug in solution will become more neutral, thus causing the drug to become more permeable. Therefore, the overall result of this dynamic pH system is to initially promote drug dissolution by decreasing pH, followed quickly by an increase in pH which converts the ionized drug to a more permeable neutrally charged form. Additional pH modifying agents can be formulated to modulate this pH fluctuation to occur within the desired range. Clinical studies comparing fentanyl absorption to an unenhanced buccal tablet and another commercial product, Actiq®, demonstrate that the OraVescent® system provides enhanced absorption and bioavailability of the drug (Pather et al., 2001).

Fentanyl is readily absorbed following administration of the Fentora® tablet to the buccal cavity with an average T_{max} of approximately 45 minutes (Cephalon Inc., 2006). An absolute bioavailability of 65% is achieved with the buccal tablet, with 50% of the administered dose being absorbed from the buccal mucosa. The remainder of the administered dose is swallowed, resulting in delayed and incomplete absorption.

A study conducted by Darwish and colleagues (2007) evaluated the pharmacokinetic profiles of the Fentora® tablet when delivered transmucosally (between gum and cheek) as well as when delivered orally (swallowed) versus the Actiq® lollipop formulation. The results of this study demonstrate that the most rapid absorption of fentanyl occurred with the Fentora® tablet delivered transmucosally exhibiting a t_{max} value of 47 minutes versus the swallowed Fentora® tablet and the Actiq® lollipop, which both exhibited t_{max} values of approximately 90 minutes (Darwish, Kirby, Robertson, Tracewell, & Jiang, 2007). The absolute bioavailability of the transmucosally delivered Fentora® tablet was also found to be greater than that of the swallowed tablet and the Actiq® lollipop with values of 65%, 31%, and 47%, respectively (Darwish et al, 2007). Additionally, the study revealed that a 30% smaller dose of transmucosal Fentora® would produce similar systemic fentanyl levels to that of the Actiq® formulation (Darwish et al, 2007). The primary difference between these two formulations, which resulted in the discrepancy between their absorption characteristics, was determined to be the extent of transmucosal absorption. With the transmucosal Fentora® tablet, 48% of the administered dose was absorbed through the oral mucosa as compared with 22% with the Actiq® formulation. Hence, a substantially greater portion of the Actiq® dose was swallowed, resulting in prolongation of absorption and more extensive drug metabolism.

Rapinyl™ Sublingual Tablet

Rapinyl™ is a mucoadhesive sublingual tablet that was developed by Orexo AB (Uppsala, Sweden) to enhance the bioavailability of fentanyl citrate. Although not currently available in the United States, Endo Pharmaceuticals. recently announced that the company has licensed the rights from Orexo AB to develop and market the sublingual fentanyl product in North America (Newbould, 2004). The design of the Rapinyl™ sublingual tablet system was recently presented by Bredenberg and colleagues (2003). The foundation of this design is what is known as ordered or interactive

mixtures, which are formed when fine particles of drug are attached to coarse excipient (mannitol) carrier particles by dry mixing for 48 to 72 hours (Westeberg & Nyström, 1991). After the ordered mixtures are formed, Kollidon CL and silicified microcrystalline cellulose are added to the mixture by blending for 30 minutes. This powder blend is then mixed with magnesium stearate for two minutes and subsequently compressed into tablets. With this design, the tablet disintegrates rapidly in the mouth of the patient to release the ordered units consisting of drug and the bioadhesive (Kollidon CL) adhered to the surface of the coarse carrier (mannitol). These units then adhere to the sublingual mucosa where the coarse carrier begins to dissolve along with the drug, thus targeting drug absorption to the site of adhesion (i.e., the oral mucosa). With this system, the authors demonstrated immediate dissolution of drug in vitro and rapid absorption in vivo without a secondary plasma concentration peak that would indicate absorption in the intestine due to swallowed drug (Westeberg & Nyström, 1991). These results indicate that the bioadhesive component of the formulation prevented fentanyl from being swallowed by promoting retention in the oral mucosa and, additionally, the ordered units allowed for rapid drug dissolution. Thus, these two aspects of the formulation design act synergistically to facilitate drug absorption.

Fentanyl Pulmonary Delivery Forms

The same properties of fentanyl which make it an excellent candidate for transdermal delivery, namely its low molecular weight and high lipid solubility (Jeal & Benfield, 1997), also make it an excellent drug candidate for pulmonary delivery. It has been reported that fentanyl and other opioid products are manufactured in a variety of noninvasive dosage forms; however, none of these currently marketed forms have onset of actions comparable to intravenous (iv) dosing (Farr & Otulana, 2006). To address this problem a new generation of pulmonary delivery systems are being developed for fentanyl.

At the academic level, several studies have been conducted to elucidate the pharmacokinetics and optimal mode of pulmonary delivery for fentanyl. During the early nineties, two studies were published which demonstrate that therapeutically effective levels of fentanyl could be achieved by pulmonary delivery; these studies also show significantly lower blood levels than those achieved by iv administration (Higgins, Asbury, & Brodie, 1991; Worsley, MacLeod, Brodie, Asbury, & Clark, 1990). In a subsequent study by Mather and colleagues (1998), aerosolized fentanyl was delivered in 100-µg to 300-µg doses using a SmartMist™ breath-actuated microprocessor controlled metered dose inhaler and compared with iv injection (Mather et al., 1998). Their work showed that the pulmonary formulation achieved similar pharmacokinetic profiles to the iv formulation with greater than 50% delivered within five minutes, approximately 100% time-averaged bioavailability, and no significant difference in side effects between the two formulations. Additional formulation techniques, such as lipid-based pulmonary formulations, also offer the potential for SR products (Hung, Whynot, Varvel, & Shafer, 1995). In a recent study by Zeppetella (2000) evaluating the effectiveness of pulmonary administration on pain reduction, it was shown that pulmonary delivery of fentanyl was effective and well tolerated (Zeppetella, 2000). These studies indicate the significant promise of pulmonary fentanyl delivery in pain management therapy, as well as the importance of formulation and delivery device design in achieving an effective therapy.

Several companies are currently in clinical trials to evaluate the potential of pulmonary fentanyl delivery. The two most promising products, both currently at the phase II trial stage, are the Fentanyl Taifun® by LAB International and the Fentanyl AeroLEF™ by YM Biosciences, Inc. These products seek to combine the therapeutic effect of traditional fentanyl iv formulations with the convenience of pulmonary delivery for improved patient compliance.

Fentanyl Taifun®

The Taifun® inhaler is a second generation dry powder inhaler that has been approved in Europe for the delivery of salbutamol. The device utilizes a vortex desegregation chamber, desiccant capsule–based humidity controlled reservoir system, and novel wet suspension surface–treated carrier formulation to provide effective delivery. The device can carry up to 200 doses of medication and is operated by activating the loading mechanism to fill the dosing reservoir, inhaling to draw the dose through the vortex chamber where the drug is separated from the carrier for delivery to the lungs. Several recent studies have shown the device to function independently of patient respiration (Pitcairn, Lankinen, Seppälä, & Newman, 2000) and provide more efficient lung deposition than other currently marketed devices (Newman, 1998, 2003). The respiration-independent delivery and efficient lung deposition make the Taifun® an excellent delivery system for fentanyl.

LAB International recently conducted a multicenter, randomized, double-blind, placebo-controlled, parallel group phase IIA clinical trial of the Fentanyl Taifun® with 122 cancer patients. In company published press releases of the study results, the system demonstrated a rapid patient response with significant relief achieved in 7.8 to 11.6 minutes, approaching onset of action times observed for iv formulations. Doses of 100 µg and 400 µg showed statistically significant differences compared with placebo and the sum of pain intensity differences were also significantly better than placebo; however, results using 200 µg were not statistically different from placebo. Results of a second open-label, dose-titration phase IIB clinical trial were also recently published by LAB International. These results demonstrate successful titration of

24 patients to doses ranging from 100 μg to 400 μg with significant pain relief in 95% of the episodes treated and mean onset of action times of approximately seven minutes. Continued development of this system is currently underway, with an extension of the phase IIB trial already in progress and planning for a phase III clinical trial ongoing. These results show that the Fentanyl Taifun® system can efficiently deliver low doses of fentanyl at therapeutically effective levels and provide onset of action comparable to iv formulations.

Fentanyl AeroLEF™

The design properties of the Fentany AeroLEF™ will allow patients to achieve longer acting and more effective pain relief. The system utilizes a formulation of free and liposome-encapsulated fentanyl delivered by nebulizer to provide rapid and ER. Furthermore, the rapid onset of action coupled with the variable dosing control provided by the nebulizer also allows for patient-controlled dosing to achieve the desired pain relief.

Several clinical trials have recently been conducted that demonstrate the effectiveness of the AeroLEF™ system in reducing pain and extending the duration of action. Hung and colleagues (2004) recently published results from a phase IB study comparing 1500-μg doses of AeroLEF™ to 200-μg doses of fentanyl iv administered to six healthy volunteers, and showed that the AeroLEF™ formulation provided improved duration of action ($C_f \geq 0.5$ ng/ml, AeroLEF™ = 3.78 ± 1.92 hr, fentanyl iv = 0.86 ± 0.39 hr). This study also showed comparable C_{max} (1.46 ± 0.83 ng/ml vs. 1.76 ± 1.19 ng/ml) and T_{max} (0.39 ± 0.32 hr vs. 0.1 ± 0.03 hr) for AeroLEF™ formulations compared with iv formulations. Results from a recently completed self-administered, single-dose, phase IIA study of postsurgical patients using AeroLEF™ published by YM Bioscience show that 95% of the patients achieved clinically significant analgesic effects and that patients also reported improved duration of action. A randomized, double-blind, placebo-controlled, phase IIB study was also recently conducted to evaluate the safety and efficacy of multiple doses of AeroLEF™ for management of pain in postsurgical patients. Top-line study results published by YM Bioscience showed that the AeroLEF™ system produced statistically significant improvements in the patients' pain intensity and pain relief scores compared with placebo; however, a complete statistical analysis of all secondary end points was not available for this trial at the time this article was written.

Summary of Pulmonary Fentanyl Delivery

Pulmonary delivery of opioids, particularly fentanyl, show great promise in alleviating pain by improving patient compliance through noninvasive delivery and rapid onset of action. Furthermore, these products demonstrate the importance of formulation and delivery device for effective pain management treatment by pulmonary administration. By carefully developing these systems, significant improvements in pain management therapy can be achieved.

GABAPENTIN

Although the primary indication for gabapentin is anticonvulsant, it has also been indicated for use in the management of pain associated with postherpetic neuralgia and diabetic neuropathy, as well as in the treatment of chronic neurogenic pain and restless legs syndrome (Garcia-Borreguero, Larrosa, & de la Llave, 2002; Parke-Davis, 2002; Rose, 2002; Tremont-Lukats, Megeff, & Backonja, 2000). Neurontin® IR oral tablets and capsules are the only branded solid oral dosage forms currently on the market in the United States, as shown in Table 6. Several generic forms of these IR gabapentin tablets and capsules are also available. The current gabapentin oral therapy requires patients to take the medication three to four times daily. Many pharmaceutical companies are developing ER

TABLE 6
Summary of Commercial Gabapentin Products Available in the United States

Brands	Dosage Form	Strengths	Manufacturer
Neurontin®	Oral capsule	100, 300, 400 mg	Pfizer Pharms
Generic Gabapentin	Oral capsule	100, 300, 400 mg	Actavis Elizabeth, Apotex Inc., Ivax Pharms, Mutual Pharm, Ranboxy, Sandoz, Sun Pharm Inds. Ltd., Teva Pharms
Neurontin®	Oral solution	250 mg/5 ml	Parke Davis
Neurontin®	Oral tablet	600, 800 mg	Pfizer Pharms
Generic Gabapentin	Oral tablet	600, 800 mg	Actavis Elizabeth, Glenmark Pharms, Ranboxy, Sandoz, Sun Pharm Inds. Ltd., Teva Pharms
Generic Gabapentin	Oral tablet	100, 300, 400, 600, 800 mg	Apotex Inc., Ivax Pharms

forms of gabapentin that would reduce the daily dosing requirements to improve the convenience of the dosage regime and the therapeutic efficacy. One such dosage form, Gabapentin GR™, is currently being developed by Depomed, Inc., and is claimed to reduce dosing frequency and side effects (Depomed acquines exclusive rights to Gabapentin GR, 2003). Gabapentin GR® is based on Depomed's proprietary drug delivery system known as AcuForm™, which is described in U.S. Patent No. 6723340. The Acuform™ drug delivery technology is a gastroretentive tablet system that allows standard-sized tablets to be retained in the stomach for six to eight hours after administration, thereby extending the duration for which the drug is delivered to the small intestine (Berner & Cowles, 2006). The basis for the tablet formulation is a combination of polyethylene oxide and hydroxypropyl methylcellulose that forms a solid monolithic matrix with drug dispersed therein. The matrix swells upon contact with gastric fluid to a sufficient size to allow the dosage form to be retained by the stomach. The drug then diffuses from the swollen matrix in a controlled and sustained manner to provide therapeutic levels of gabapentin for extended time periods, thus allowing for reduced frequency of administration (Gusler, Berner, Chau, & Padua, 2004).

XenoPort, Inc., is currently developing a prodrug form of gabapentin (XP13512) that is rapidly converted to gabapentin following absorption from the GI tract as well as a SR formulation thereof (Fulda & Wetter, 2005). It is believed that this prodrug form of gabapentin will enhance the suboptimal and variable absorption of gabapentin from the GI tract by targeting high-capacity nutrient transporter mechanisms expressed throughout the length of the intestines (Gallop, Cundy, Zhou, Yao, & Xiang, 2004). Moreover, the SR formulation of the prodrug was shown in clinical trials to produce higher blood levels for extended durations than equivalent doses of gabapentin, thus indicating the potential of this product to reduce dosing frequency and overall pain therapy with gabapentin.

KETAMINE

Ketamine is an N-metyl-D-aspartate (NMDA) receptor antagonist that has been used as a general anesthetic and as a short-acting analgesic since the early 1970s (Csoka et al., 2005; Schmidt, Sandler, & Katz, 1999). Although ketamine has been utilized in clinical practice for over 30 years, little formal research has been conducted to determine the effectiveness of ketamine for chronic pain management (Hocking & Cousins, 2003). The lack of research into the use of ketamine for the management of pain may be a reflection of the perceived adverse risk-to-benefit ratio, as the drug is well known to cause psychotomimetic side effects and cardiovascular stimulation (Schmidt et al., 1999; Hoscking & Cousins, 2003; Finlay, 1999). The uncertainty regarding the use of ketamine for chronic pain therapy and the lack of adequate clinical studies to determine the analgesic effects of ketamine when administered by oral, rectal, or intranasal means is reflected by the lack of marketed commercial products, particularly solid dosage forms. As seen in Table 7, the only currently marketed products for ketamine are parenteral systems. However, it is becoming more apparent that there is a distinction between the use of high-dose ketamine as an anesthetic agent and low-dose ketamine for analgesic effects with regard to the therapeutic effect versus adverse side effects. This has spurred interest in ketamine as a pain management agent, as well as research into the development of less invasive ketamine products (Schmidt et al. 1999).

TABLE 7
Summary of Commercial Ketamine Products Available in the United States

Brands	Dosage Form	Strengths	Manufacturer
Ketalar®	Injectable, injection	EQ 10, 50, 100 mg base/ml	Parkedale
Generic Ketamine hydrochloride	Injectable, injection	EQ 50, 100 mg base/ml	Bedford, Bioniche (Canada), Hospira

Ketamine undergoes extensive first-pass metabolism, leading to an oral bioavailability of 17% (Clements, Nimmo, & Grant, 1982). It is for this reason that the development of ketamine products has focused primarily on transdermal and transmucosal delivery systems that avoid first-pass metabolism similar to those discussed previously for the delivery of fentanyl. Several recent U.S. patents and patent applications have described dosage form designs for buccal and transdermal delivery systems for ketamine. Although there are no current marketed products, the U.S. patent literature seems to suggest that several companies are actively developing advanced, noninvasive delivery systems for ketamine indicated for the management of chronic pain.

CONCLUSION

The commercial products and developing formulations presented in this article illustrate how the application of advanced-formulation design and innovative drug delivery systems are dramatically improving drug therapies for the treatment of severe and chronic pain. In addition to improving long-used drug treatments, advanced drug delivery systems are enabling the use of alternative analgesic molecules for pain therapy. The delivery systems reviewed in this article demonstrate that advanced-formulation design can be applied to analgesic drugs to reduce dosing schedules for improved convenience of around-the-clock pain therapy, provide more consistent plasma

levels for continuous pain relief with reduced side effects, facilitate normal sleep cycles, enhance drug absorption, and accelerate the onset of therapeutic action. It is through these improvements that advanced drug delivery systems have revolutionized drug therapies used to treat chronic and severe pain and ultimately improved the quality of life for patients that rely on daily pain medication.

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