Marketed New Drug Delivery Systems for Opioid Agonists/Antagonists Administration: A Rapid Overview

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Review Article

Abstract

Novel drug delivery systems for controlled-release of opioid agonists as a long time painkillers or opioid antagonists for opium, heroin, and alcohol addiction are under development or in clinical use today. In this article, the field of "new drug delivery systems" is momentarily reviewed from the viewpoint of the marketed opioid agonists/antagonists dosage forms today.

Keywords: Opium; Controlled release; New drug delivery systems

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Introduction

During the past four decades, controlled release systems have impacted virtually every branch of medicine including ophthalmology, pulmonary, pain medicine, endocrinology, cardiology, orthopedics, immunology, neurology, and dentistry.[1] Polymeric nano/microspheres, liposomes, transdermal (TD) patches, and oral controlled-release dosage forms are currently in clinical practice.

Polymeric nano/microparticles can entrap therapeutic agents and release them in a regulated manner through bulk or surface erosion of the particles, diffusion of the drug through the polymer matrix, or swelling followed by diffusion. Alternatively, drug release can be triggered by the environment or other external events such as changes in pH, temperature, or the presence of an analyte such as glucose.[1]

Lipid vesicular systems such as liposomes and niosomes could be used for encapsulation of both hydrophilic and lipophilic compounds.[2] The first Food and Drug Administration (FDA) approved liposomal formulations, doxorubicin nano-liposomes (Doxil™) is administered in patients suffering from ovarian or breast cancer and in human immunodeficiency virus (HIV)-positive patients with Kaposi sarcoma.[3] Ambisome™, another FDA-approved formulation for amphotericin B is used in life treating fungal infections and visceral leishmaniasis and recently was studied for mucormycosis therapy.[4]

TD drug delivery patches were extensively used for transport of different drugs through the most important barrier in the skin, stratum corneum, and delivering the drug in bloodstream for achieving a systemic effect. TD fentanyl is an example of topically used dosage form for pain management in both malignant and non-malignant pains.[5] In a more recently approved TD patch, the anti-Parkinson's disease drug, rotigotine, is applied in developed neurodegenerative patients.[6]

Different technologies were also utilized for slow, extended, controlled, or sustained release of various therapeutic agents using new oral drug delivery systems such as polymeric matrix or gel-forming tablets[7] and oral osmotic pumps.[8] Many of these technologies have been used for extended-release opioid drugs with lower potential of abuse and addiction.

In the present rapid review, the marketed controlled-release dosage forms for opioid agonists/antagonists will be briefly introduced and the rational of design and application this type of formulations will be explained.

New Drug Delivery Systems for Opioid-Related Therapeutics

Naltrexone

This compound is an opioid antagonist with

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maximum affinity for the μ-opioid receptors and has few, if any inherent effects as well its opioid blocking properties. The US FDA approved naltrexone for the treatment of alcohol dependence in 1994. In spite of this permission, the studies of the efficacy of naltrexone for alcohol dependence have yielded variable findings.[9] One reason for the lack of success in alcohol dependence treatment with oral naltrexone is patient's non-compliances.[9] Some studies[10,11] have also shown that only subjects who are highly compliant with naltrexone have greater reductions in alcohol consumption and risk of relapse than subjects treated with placebo. One-way for overcoming this problem is the utilizing of sustained release or depot formulations. Depot injectable dosage form of naltrexone, Vivitrol™ (Figure 1), was approved by FDA on April 13, 2006, for the alcohol dependence treatment in patients who are capable to withdraw from drinking in an outpatient setting and who are not actively drinking at the therapy beginning. Vivitrol recommended dose is 380 mg administered intramuscularly once a month or every 28 days. Other depot parenteral formulations of naltrexone are Depotrex™ and Naltrel™. Vivitrol has demonstrated efficacy at decreasing heavy drinking among alcohol-dependent males and Naltrel helped to promote abstinence and decrease the incidence of relapse in two samples of alcohol-dependent subjects.[12]

Figure 1. Vivitrol™ (naltrexone depot injectable formulation)

Naltrexone affords a blockade against the intoxicating and reinforcing effects of opioid like compounds, which theoretically can result in the extinction of drug-taking behavior. It offers no euphoric effects, and thus, is not abused; nor does it engender physiological dependence.[13] As with the alcohol, the major problem with the oral formulation of naltrexone for heroin or opium dependence is poor compliance (adherence). Long-acting sustained release formulations of naltrexone (injectable or implantable) may assist to develop compliance, and thus, augment the efficacy of abstinence-oriented cure of heroin or opium dependence with naltrexone.[14,15] Vivitrol is administered for the preclusion of relapse to opium dependence, following opioid detoxification.

Fentanyl

Opioids are the mainstay of the treatment for chronic moderate to severe pain. The availability of TD opioid formulations has provided new treatment choices for long-term pain management in patients suffering from chronic pain.[16]

Fentanyl is a potent synthetic opioid approximately 100 times more powerful than morphine used as a general anesthetic and analgetic (painkiller). It is a potent Schedule II narcotic analgesic recommended for use in the management of unremitting pain not controlled by morphine or other opiate/opioid drugs.[17] Duragesic™ (Figure 2) is the most famous pain relief fentanyl TD patches. TD form of fentanyl in children with cancer pain may demonstrate less side effects in comparison to other opioids, especially constipation.[18]

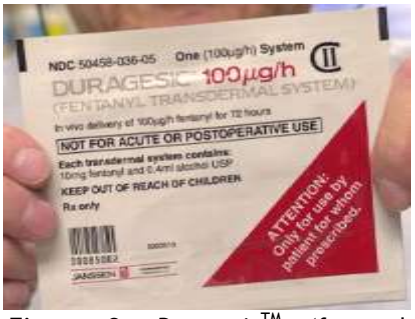

Figure 2. Duragesic™ (fentanyl transdermal system)

Fatal fentanyl intoxication following excessive TD[17,19] or intravenous (IV) misuse of TD formulations[20] have been reported. Due to these reports, on July 15, 2005, the FDA issued a Public Health Advisory warning physicians and users of fentanyl patches that "deaths and overdoses have occurred in patients using both the brand name

product Duragesic and the generic product."[21]

Slatkin et al.[22] reported the high efficacy, well tolerance, and rapid onset of analgesia in opioid-tolerant patients with chronic cancer pain after using fentanyl buccal tablet, a new opioid formulation. Borland et al.[23] also showed that the effective analgesia in children aged 7-15 years presenting to an emergency division with an acute fracture comparing with IV morphine at 0.1 mg/kg. Allan et al.[24] compared the safety and efficacy of TD fentanyl and sustained release morphine in strong-opioid naïve patients with chronic low back pain. The results showed equivalent levels of pain relief, but TD fentanyl was associated with less constipation. They concluded that sustained-release strong opioids could safely be used in strong-opioid native patients.

Ackerman et al.[25] assessed patient-reported utilization patterns of fentanyl TD patch and concluded some patients used the patches in an incorrectly way.

Morphine

Intrathecal drug delivery, using an implantable drug delivery system, can improve pain relief, reduce suffering, and enhance quality of life in patients who do not answer well to conventional therapies such as oral analgesics.[26] One of these drug delivery systems called liposomes has been extensively studies for preparation of sustained-release of therapeutics. Liposomes are the hydrated mixture of cholesterol and natural or synthetic phospholipids which form nano/microparticles through the assembly of amphiphilic bilayer membrane lipids.[27] A specific form of multivesicular liposomes called DepoFoam™ has been used for encapsulation and extended-release of morphine through epidural route.[28] Extended-release epidural morphine (EREM) is available in the market as DepoDur™ for severe chronic pain such as spinal cord tumors (Figure 3). Both the extended-release and enhanced retention of morphine in the epidural space could be achieved due to the large size of the DepoFoam particles (7-40 μm).[29]

Gambling et al.[30] showed that the adverse events with those of epidural opioids (i.e., nausea, vomiting, pruritus, and hypotension) were acceptable and predictable for the single-dose EREM (DepoDur) after lower abdominal surgery. DepoDur provided better and extended post-Cesarean analgesia in comparison with a common epidural morphine with no considerable raise in adverse effects.[31]

Figure 3. DepoDur™ EREM (extended-release epidural morphine)

Opioid extended-release formulations hold a superior desirability for abusers than immediate-release formulations due to their per dose level of the drug.[32] Therefore, the use of opioid formulations intended to deter or prevent product abuse and tampering significantly improves pain management while minimizing opioid abuse.[33,34] A new oral dosage form that combines naltrexone hydrochloride and morphine sulfate in a single capsule (Embeda™) was recently (September 2009) approved by US FDA for the long-term management of moderate to severe pain.[35] The first Embeda consists of extended-release morphine with sequestered naltrexone that is released if the tablet is compromised by chewing or crushing.[36] Morphine pellets have been used in the outer layer of Embeda formulation (Figure 4) while naltrexone has been incorporated in internal core of this formulation. The reason for this formulation use is to prevent abusers from crushing the solid dosage form for intranasal administration or from injecting themselves. If it is crushed, the morphine would blend with the naltrexone, which this compound would competitively antagonize the morphine effects in the body. The inner core containing naltrexone is formulated so that if consumed orally, the core encapsulating the naltrexone would not be digested by the gastrointestinal (GI) tract. The pellets in the capsule are sprinkled over approximately one tablespoon of apple sauce and the whole sauce and pellets will be swallowed (Figure 5). Embeda has been profitably used in the treatment of chronic pain of osteoarthritis of the knee or hip, while the sequestered naltrexone did not interfere with efficacy.[37]

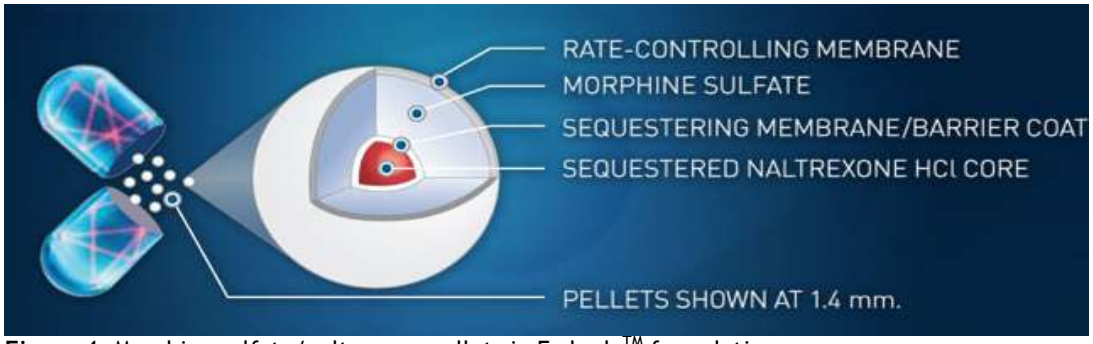

Figure 4. Morphine sulfate/naltrexone pellets in Embeda™ formulation

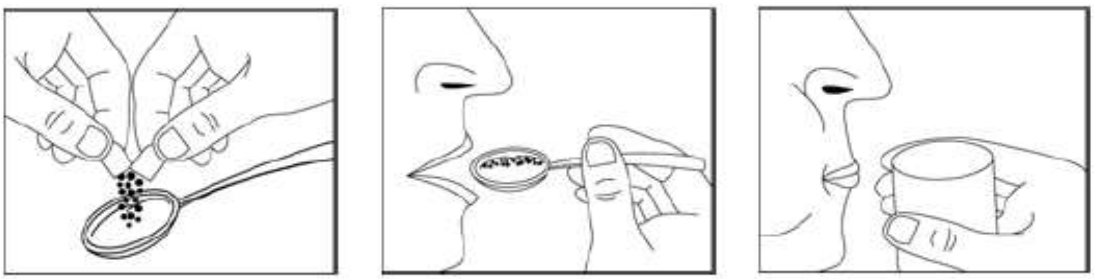

Figure 5. Embeda™ [morphine sulfate/naltrexone hydrochloride (HCl)] capsule administration steps

However, severe adverse events were reported in a 39-year-old woman with a history of chronic pain who chewed her first Embeda dose before swallowing.[35] Approximately 10-20 minutes later, the patient experienced nausea and generalized body aches, followed by four episodes of emesis.

MS Contin™, another morphine sustained release tablet, is administered for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (Figure 6).[38]

Figure 6. MS Contin™ (controlled-release morphine sulfate tablets)

Oxycodone

Oxycodone, a narcotic pain reliever used to treat moderate to severe pain, is available as twice-a-day controlled-release tablets (OxyContin™) for the management of moderate to severe, chronic low back pain.[39] This formulation was thought to have much lower abuse potential than immediate-release oxycodone because of its slow-release properties addiction.[40] However, beginning in 2000, widespread reports of OxyContin abuse surfaced.

Acurox™ contains an aversive agent (niacin) that causes unpleasant effects when injected, inhaled, or taken orally in high doses.[34] Remoxy™ is an oral, long-acting oxycodone gelatin capsule under development with pain therapeutics, to which have been licensed exclusive, worldwide, development and commercialization rights under a development and license agreement entered into in December 2002. Remoxy is formulated with ORADUR® technology.[41]

Oxymorphone

This therapeutic agent is a Schedule II controlled semi-synthetic opioid analgesic which was approved by the FDA in 2006 for the treatment of moderate to severe chronic pain. At present, it is available as an extended-release formulation, Opana ER™ (Endo Pharmaceuticals). This formulation contains xanthan and locust bean

gum which after swallowing become a tight, thick gel, and slowly releases the drug. In a 12-week, double-blind, randomized, placebo-controlled trial in opioid-experienced patients with chronic, moderate to severe low back pain, Opana ER showed efficacious, long-term analgesic effect and was generally well-tolerated.[42]

Naloxone (NLX)

NLX is a non-specific, competitive opioid antagonist and is used to reverse opioid-induced central nervous system and respiratory depression. NLX shows a short biological half-life (64 minutes), following its IV administration.[43]

Hydromorphone

Hydromorphone is a potent semi-synthetic opioid which is commonly used in the hospital setting, mostly IV because its bioavailability orally, rectally, and intranasally is very low. Osmotic extended-release oral delivery system (OROS™) of hydromorphone (Exalgo, Mallinckrodt) was approved by FDA, in 2010, for the treatment of moderate-to-severe pain in patients who are opioid-tolerant and who need around-the-clock analgesia.[33] Following OROS oral administration, an osmotic material absorbs water from GI tract and the drug pushes out through a laser formed or punched orifice on tablet surface in a controlled manner (Figure 7).[44] OROS technology allows hydromorphone to be released at a constant rate over a period of 24 hours. OROS hydromorphone was successfully used once-daily in patients with chronic low back pain[45] and chronic, moderate to severe osteoarthritis pain.[46]

Buprenorphine

Buprenorphine is a partial opioid agonist at the μ-opioid receptors and partial antagonist at the κ-opioid receptors. This double action makes buprenorphine helpful as an analgesic while also providing some abuse deterrence. To augment the level of abuse prevention, NLX was combined with buprenorphine in a 1:4 ratio (Suboxone™) to deter diversion and IV misuse and may be suitable for unsupervised administration.[33] Suboxone is available as both a sublingual tablet and a sublingual film.

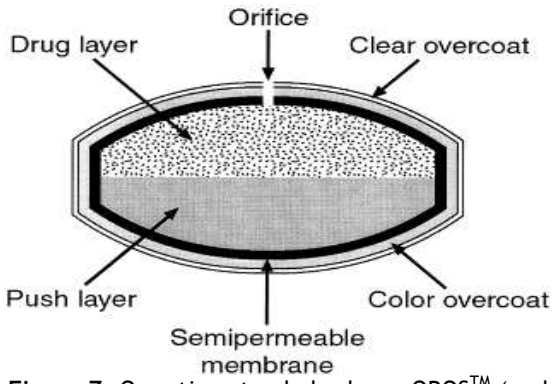

Figure 7. Osmotic extended-release OROS™ (oral delivery system)

A new TD formulation of buprenorphine has been entered in market for long duration of pain control (Figure 8).[47]

Conclusion

Opium-derived substances have strong pain-killing or analgesic effects with high potential of abuse, dependency and other side effects such as constipation and pulmonary distress. For better delivery and effectiveness of these compounds, reducing side effects, demising the abuse potential and achieving a sustained-release effect, vast researches have been done to formulate novel drug delivery systems. However, among these investigated formulations, some FDA approved dosage forms are present in the market, and this brief review explained the superiority of them in comparison to traditional dosage forms.

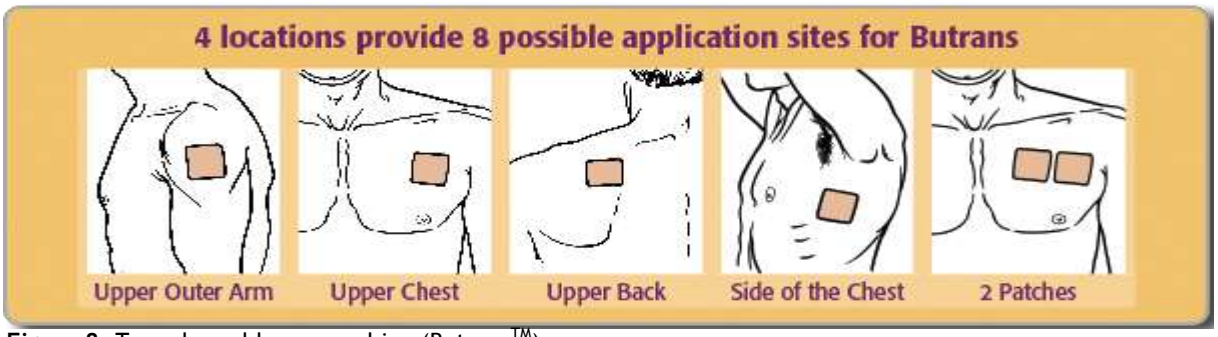

Figure 8. Transdermal buprenorphine (Butrans™)

Conflict of Interests

The Authors have no conflict of interest.

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None.

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سامانه‌های جدید دارورسانی موجود در بازار دارویی برای تجویز آگونیست/ آنتاگونیست‌های مخدر: یک مرور گذرا

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مقاله مروری

چکیده

امروزه سامانه‌های جدید دارورسانی برای رهایش کنترل شده آگونیست‌های مخدر به عنوان ضد دردهای طولانی اثر یا برای آنتاگونیست‌های مخدر در اعتیاد به تریاک، هروئین و الکل مورد استفاده قرار گرفته‌اند و یا در دست توسعه یا کاربرد بالینی می‌باشند. در این مطالعه، سامانه‌های جدید دارورسانی به طور مختصر و از منظر اشکال دارویی آگونیست/ آنتاگونیست موجود در بازار دارویی مورد بررسی قرار گرفت.

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