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RESEARCH: Review

Controlled-release of opioids for improved pain management

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The adequate treatment of pain remains one of the major medical challenges. Morphine and other opioid drugs are most commonly used to counteract moderate to severe pain, but they are also increasingly accessed by patients with chronic non-malignant pain. To achieve long-term analgesia, opioid therapy still represents the standard treatment for chronic pain alleviation. This work presents an overview of current strategies aiming at controlled opioid release. Two important, and intrinsically linked, features are discussed in detail: the used formulations (i.e. polymer systems) and the applied drug administration routes. The different administration routes and their associated advantages and limitations are described. Links between the chemical structure of commonly used opioids and suited administration modes and formulations are made. This review can potentially give insight into new opportunities for adequate relief of chronic pain, a societal burden, by means of alternative (non-)opioid analgesics and may serve as inspiration for future developments in this area.

Introduction

Chronic pain remains a major societal burden that is associated with a decline of normal daily functioning and quality of life. It is defined as pain that lasts longer than three months and which is not in relation with any somatic damage. At least 30% of chronic pain cases evolve from the inadequate treatment of acute postoperative pain [1,2]. To provide sustained analgesia in chronic pain patients, regular administration of drugs is required to ensure that the next dose of an analgesic is given before the effects of the previous dose have dissipated. Unfortunately, despite advances in understanding its etiology and pathophysiology, chronic pain remains inadequately treated to date. In general, the appropriate management of chronic pain [3] aims to improve quality of life and daily function by alleviating not only pain symptoms, but also comorbid conditions.

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This review presents an overview of reported administration routes and polymer systems for the controlled drug delivery of opioids in the management of chronic pain. The remainder of this introduction will focus on the treatment of chronic pain by opioids (Section 'Treatment of chronic pain') and extended-release of opioids for long-term analgesia (Section 'Extended-release of opioids for long term analgesia'). The remainder of this review will provide an overview of the state-of-the-art in controlled opioid release formulations, organized by method of administration, including discussion of the types of polymers to obtain controlled-release (Section 'Routes of administration'). Each of these sections starts with a general reflection on the basic polymer requirements for obtaining sustained release for the different administration routes.

Treatment of chronic pain

The pharmacotherapy of chronic pain includes use of non-opioid analgesics, antidepressants, anticonvulsants, scheduled opioid

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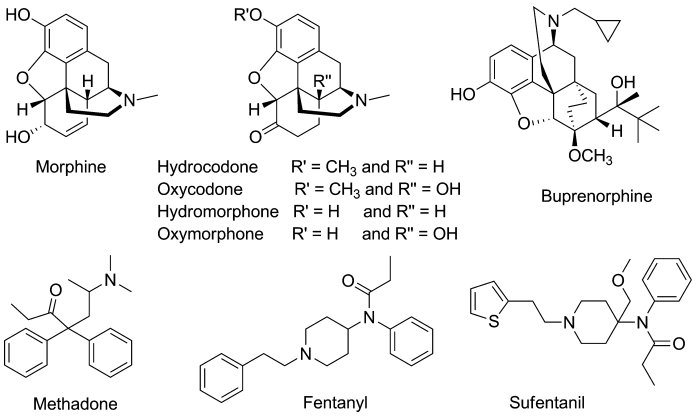

FIGURE 1

Examples of opioid analgesics used for moderate to severe pain treatment.

analgesics, and non-scheduled opioid analgesics. For the treatment of moderate to severe pain, opioid analgesic drugs (see examples in Fig. 1), are most useful [4], and over the past years, opioid drug prescriptions have increased significantly [5–8]. Indeed, around 90% of patients suffering of chronic pain have been treated with opioids [4]. The application of opioid analgesics for chronic pain alleviation is, however, more controversial as opioid therapy generates adverse effects like addiction, abuse, respiratory depression, gastrointestinal effects (constipation), and urologic effects [9]. Opioid use for treating chronic pain may be justified only in patients who have not responded to any other therapy, as long term effects of clinical and excessive use of opioid drugs can affect nearly every organ system of the body.

Clinically, morphine (Fig. 1) remains the most used analgesic drug to date [10]. In addition, hydrocodone, oxycodone, hydromorphone, oxymorphone and buprenorphine are semi-synthetic opioid agonists synthesized from codeine, which present the characteristic phenanthrene-like nucleus [11]. Oxymorphone has a twofold higher potency in comparison to morphine, a characteristic that is often used to make sure that the patient will not develop any breakthrough pain as it can be the case with morphine due to its lower bioavailability. Buprenorphine, a semi-synthetic derivative, is a highly potent (100-fold more active than morphine) partial μ-agonist with a moderate addiction potential. For buprenorphine, there is no contra-indication in case of renal failure or for elderly patients due to its ceiling effect, as no respiratory depression occurs. Its metabolites are not accumulated in the kidneys. Other opioids like methadone, fentanyl and sufentanil are classified as synthetic agonists without the morphinan core included in their structures. Methadone is a highly lipophilic synthetic μ-opioid agonist with a long, but highly variable half-life (from 12 to 120 hours). This particular pharmacokinetic property implies an elevated risk of overdose due to its long duration of action. Fentanyl and sufentanil are lipophilic opioids with a short duration of action, but a much higher potency (100 times and 1000 times, respectively) than morphine. The efficacy can be easily explained by a high lipophilicity, which allows the efficient penetration of the blood brain barrier (BBB). Analogs of fentanyl are widely used in intravenous, epidural and intrathecal continuous infusions, but also in transdermal formulations. Fentanyl has no active metabolites and can safely be used in the case of patients with renal failure. Whereas fentanyl was not successful in recovery of surgically induced immunosuppression, buprenorphine has a more favorable profile, devoid of any intrinsic immunosuppressive activity [12]. Immune responses from all components of the immune system, including both the humoral and cell-mediated components, appear to be suppressed by morphine and other opioid-like substances.

All opioids described above allow pain relief by binding to and activating the μ-opioid receptors in the central nervous central (CNS). Even though the plasmatic drug concentration cannot predict the analgesic effect, it was demonstrated that high doses provide greater analgesia. Effective plasmatic opioid concentration is dependent on many factors such as the opioid drug, the route of administration, the patient and the medical conditions.

Extended-release of opioids for long term analgesia

Prescription opioids are available as short-acting opioid (SAO) and long-acting opioid (LAO) formulations depending on their clinical utility. SAOs have a duration of action from 3 to 6 hours, and they are characterized by a high fluctuation in plasma opioid concentrations. Although they are particularly suitable for the treatment of acute, unstable or intermittent pain, SAOs can also be used around-the-clock, in the case of more persistent or chronic pain, for which a regular administration every 3–6 hours is needed. Indeed, opioids have a high first pass elimination effect in the liver resulting in metabolites, obtained after hydrolysis, oxidation, dealkylation or conjugation of the drug, which undergo renal excretion. Morphine, for example, undergoes a metabolic phase II conjugation process called glucuronidation that makes molecules more hydrophilic to enhance renal excretion, leaving only 30% available to exert a biological effect. The metabolites morphin-3-glucuronide (highly toxic and causes seizure) and morphine-6-glucuronide (potent metabolite with analgesic effects like morphine) are both renally excreted. Therefore, older patients with renal failure are preferentially not treated with long term administration of morphine. As a consequence of this metabolic inactivation, and to provide consistent analgesia, opioid administration requires frequent dosing to maintain effective plasmatic drug levels. Otherwise, blood concentrations of opioids can oscillate, resulting in inconsistent pain relief. To provide such a consistent pain relief, it is necessary to develop proper drug delivery systems that can ensure constant opioid blood levels [13,14].

For the treatment of chronic pain, LAOs are intended for a slow release of opioids and a long duration of action [15–17]. Compared to SAOs, they are dosed less frequently (i.e. one to three times per day) [18]. The beneficial effects of LAOs in chronic pain management, to improve efficacy, quality of life, and reduced toxicity, make them more robust in comparison with the impact of SAOs [19,20].

LAOs formulations use different types of, mostly polymeric, controlled-release delivery systems that have been called extended-release, sustained release, delayed release, prolonged action, long action and slow release. However, there is no specific definition for each term due to the fact they are inconsistently used in literature, for example, by companies that marketed them. The 'extended-release' (ER) profile is characterized by a release profile in which the active molecule released in such a way that blood levels are maintained within the therapeutic window, but below

toxic concentrations, over a period up to 35 hours or even longer (see blue curve in Fig. 2). The therapeutic window includes a concentration range between the minimum therapeutic concentration represented by a gray line and the red line, which represents the start of toxic concentrations; the red dotted line is representative of a minimum concentration beyond which the risk of side effect appearance is increased. These sustained release formulations were designed to deliver a first therapeutic dose, to immediately provide a therapeutic drug plasma concentration, followed by a constant and slow drug release to maintain the therapeutic dose required in the blood.

The different extended-release drug formulations (*vide infra*) are designed based on the route of administration for which they are developed, but also on the physicochemical, pharmacokinetic and pharmacodynamic properties of the drug. For example, opioids with short half-life such as morphine, oxycodone or hydromorphone are excellent candidates for administration via controlled-release formulations. Ideally, the extended-release drug formulation should release the drug following a zero-order release profile kinetic (blue curve in Fig. 2). Polymeric materials are of utmost importance for the development of such controlled drug release systems [21–25]. To achieve improved drug release profiles and pharmacological responses, new formulations are continuously being designed using polymers as carriers for the drugs. In this way, one can improve the bioavailability of drugs by different factors such as the physicochemical properties of the drug, the dosage, the frequency and the route of administration. A wide variety of drug delivery platforms have been reported based on polymeric carriers that embed or covalently link the active pharmaceutical ingredient. Due to the large diversity of such drugs, the challenge remains in the design of polymers that afford the desired extended-release profile for a specific drug. Furthermore, the type of polymer that can be used is strongly dependent on the mode of administration.

Overall, pain management guidelines advise the use of extended-release (ER) formulations, rather than immediate-release (IR) formulation because they provide sustained analgesia [26,27]. For patients suffering from moderate to severe chronic pain, ER formulations represent a viable option for around-the-clock analgesia, allowing a simpler dosing schedule ('less clock-watching'), but also a more consistent and durable pain relief. An important additional consideration is that slow release formulations can also be utilized to prevent abuse of medically subscribed opioids.

Routes of administration

Opioid analgesics can be administered using a variety of routes (e.g. oral, sublingual and buccal, intranasal, rectal, intravenous, subcutaneous). The route of administration and the formulation of the analgesic are dependent on its pharmacokinetic and pharmacodynamic properties. The availability of more concentrated dosage forms and controlled-release opioid preparations for oral and transdermal opioid formulations are among the most recent innovations in opioid analgesia treatment [28]. However, the wide variety of opioid drug delivery systems for chronic pain management can be confusing, but in some cases there are clear indications to opt for one specific formulation [29]. To determine which drug delivery system is most suited, different parameters need to be considered (e.g. the patient's ability to use a specific

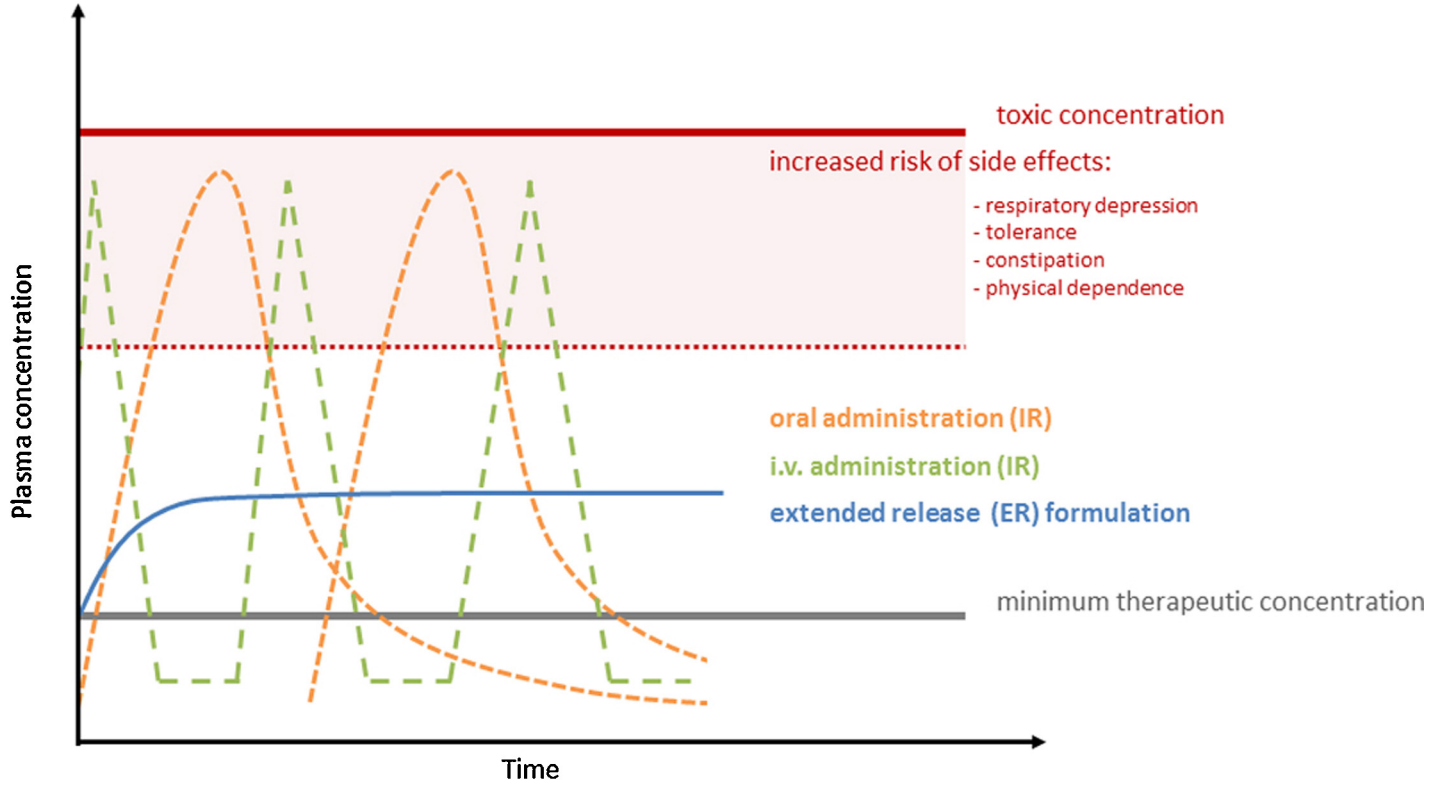

FIGURE 2

Schematic representation of opioid plasma concentrations in function of the administration route (IR: immediate-release and ER: extended-release).

device, the efficiency to deliver acceptable concentrations of opioid, and the potential complications associated to the system). The financial cost of certain formulations and devices is also an important parameter for patients who need to purchase their own medications.

Oral administration

Oral opioid administration is the most common, the easiest and the least invasive delivery system [30]. For patients who are able to take oral medications, this way of administration is the first choice [31]. Indeed, no major complications (except known opioid side effects) are associated with oral administration. The major drawback is based on the biotransformation of opioids in the liver, due to first-pass metabolization of the drug prior to entering the systemic circulation. Consequently, the dose of morphine taken orally, for example, needs to be three times higher than the intravenous or intramuscular dose of morphine. To provide longer-lasting analgesia, several oral formulations are available for slow opioid release (Table 1) [30].

For oral administration it is important to design a drug release formulation to release the drug at the desired place, that is, in the stomach or in the intestines, which depends on the stability and uptake mechanism of the drug. If the drug is unstable at the low pH (1–4) of the stomach, formulations can be coated with an enteric coating, which contains carboxylic acid groups that are protonated and insoluble at the low pH of the stomach, and will dissolve in the higher pH (7–9) range of the intestines. Both water-soluble and water-insoluble polymer excipients and coatings can be used for oral administration leading to controlled drug release by (slow) dissolution of the polymer or by diffusion of the drug through the polymer matrix. Importantly, water-soluble polymers should not contain low molar mass polymer fractions as these lower molar mass chains may be absorbed into the body. Degradability of the polymer is not required for oral administration. It is important to note that even though specific formulations for oral ER are developed, this route of administration remains limited by the formulation's residence time in the gastrointestinal tract, which is commonly 5–10 hours. A very recent development has overcome this limitation based on an elastic polymer formulation that unfolds in the stomach and slowly degrades over the course of several days or potentially weeks [32]. Different polymeric systems are used as a matrix to coat the active drug in long-acting formulations [21]. Opioid ER formulations are available as capsules or tablets in different doses. The difference between each formulation is related to the pharmacokinetics of the delivery system, which determine the dose and the dosing interval. These specific formulations will be discussed in the following paragraphs, organized based on the released opioid (Table 1).

Extended-release morphine capsules that use SODAS® (Spheroidal Oral Drug Absorption System) technology [33] are available for sustained drug release over 24 hours (Fig. 3) [34]. This formulation consists of a gelatin capsule that contains both immediate-release (IR) and extended-release (ER) beads of morphine in a ratio of 9:1 (w/w), which allow to reach a therapeutic level of morphine within 30 minutes (IR beads) while maintaining the plasmatic concentration for 24 hours (ER beads). This technology is based on spherical beads with a diameter of 1–2 mm, containing the drug and the excipient (Fig. 3, in gray), coated with a layer of release rate-controlling polymers such as a statistical copolymer of ethyl acrylate, methyl methacrylate and trimethylaminoethyl methacrylate chloride, sold under the tradename Eudragit [35] (Evonik Industries) and also sometimes referred to as an ammonio-methacrylate copolymer (Fig. 3, in blue). The beads are prepared by coating of a sugar/starch core with morphine and fumaric acid as excipient followed by the sustained release polymer coating. This coating is not present for the immediate-release beads. After administration and dissolution of the gelatin capsules, these coated beads are exposed to the gastric fluid and water enters the beads to dissolve the morphine and fumaric acid. The latter is present both as osmotic agent to 'drag' the water into the beads and to control the pH, making the release rate independent of the pH of the GI fluid. Even though the polymer coating layer is insoluble in the GI fluid it controls the morphine release rate by providing a diffusion barrier.

Other sustained release (SR) pellet systems of morphine have been marketed under the brand name Kadian [36] and based on the same SODAS technology. However, the gelatin capsules of Kadian only contain one type of beads that provide both immediate and sustained release [37]. The coating used in this system is formed by an insoluble ethylcellulose layer containing two different pore forming agents, namely polyethylene glycol (PEG with a molar mass of 6000/mol) and a copolymer of ethyl acrylate and methacrylic acid (Eudragit, Evonik Industries, also known as methacrylic acid copolymer (type C)). Once the capsule is administered, the gelatin capsule dissolves and releases the pellets into the GI fluid. In the acidic medium of the stomach only the PEG is dissolved forming small pores into the ethylcellulose layer leading to immediate-release of a small fraction of the morphine. The

TABLE 1

Analgesics, extended-release formulations for oral administration, and delivery systems.

Analgesic	Dosage form	Drug delivery system
Morphine	Capsules ER beads	SODAS
Morphine	Capsules ER pellets	
Morphine	Tablets ER	Contin™
Oxycodone	Tablets ER	AcroContin™
Oxycodone	Capsules ER	DETERx™
Oxycodone	Capsules ER	ORADUR®
Hydromorphone	Capsules ER	
Hydromorphone	Tablets ER	OROS®, Push-Pull™
Oxymorphone	Tablet ER	TIMERx™
Methadone	Tablet ER	
Hydrocodone	Tablet ER	OraGuard™

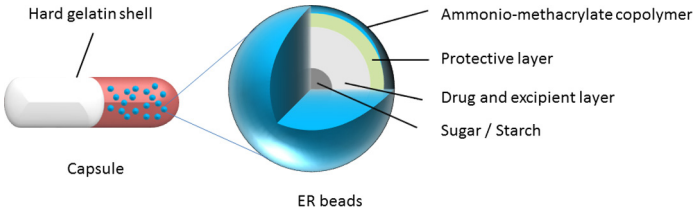

FIGURE 3

Representation of ER capsule using SODAS® technology.

carboxylic acid groups of the ethyl acrylate methacrylic acid copolymer are protonated at this low pH making it insoluble during passage through the GI tract, the pH increases in the intestine leading to the dissolution of the methacrylic acid copolymer resulting in the formation of bigger pores. As such, the drug can continue to diffuse from the beads, providing a constant therapeutic concentration of drug over 24 hours.

In contrast to the previous two sustained release formulation based on rather complex capsules, the Oramorph sustained release formulation [38] is a relatively simple tablet form based on mixing the drug with a hydrophilic polymer excipient, hydroxypropylmethylcellulose [39]. After mixing and compression, the final tablets are obtained. Once the tablet enters the GI tract, the fluid penetrates the tablet, allowing swelling of the polymer, and formation of a viscous gel. The resulting gel network controls the rate of water diffusion into the matrix but also the drug diffusion out of the system. Additionally, a second drug delivery mechanism can occur due to the erosion of the outer part of the matrix. With this device a therapeutic plasmatic concentration can be maintained for a period of 8 to 12 hours. A more advanced controlled-release morphine tablet that is based on the Contin™ delivery system [40] has also been commercialized. Here, the controlled-release process is regulated by the interactions between hydrophilic and hydrophobic polymers to fine-tune the diffusion of the drug and, thus, its release rate. In this formulation, morphine is mixed with a hydrophilic polymer matrix formed by a mixture of hydrophilic hydroxypropylmethylcellulose and hydrophobic hydroxyethylcellulose. The mixture is hydrated with water or alcohol and then fixed with a hydrophobic aliphatic alcohol, for example, cetostearyl alcohol which is a mixture of stearyl alcohol and cetyl alcohol. This hydrophobic component controls the GI liquid penetration rate. The final tablet form is achieved by adding tableting aids after compression of uniform granules. The partition coefficient of morphine between the hydrophilic and the hydrophobic parts controls the drug release from the tablet. Once the tablet comes in contact with the GI liquid, a swelling of the hydrophilic matrix occurs, giving a viscous gel. The kinetics of the drug release are directly linked to the swelling of the hydrophilic polymer matrix, which is controlled by the rate of fluid penetration through the hydrophobic part. Consequently, the general rate of drug release is regulated by variation of the ratio between the hydrophilic and the hydrophobic polymers. Using this system, morphine can be administered as a twice daily formulation.

Oxycodone controlled-release [41] tablets have been designed using the AcroContin™ delivery system [42]. The formulation is based on the same dual polymer matrix as used in Contin™, *vide supra*. This delivery system provides both the immediate and the extended-release of the drug, which cannot be achieved using the Contin™ system alone. Instead of using a neutral hydrophilic polymer, AcroContin™ uses a cationically charged ethyl acrylate, methyl methacrylate trimethylammnoniumethyl methacrylate chloride copolymer to control the drug diffusion. Again the system is fixed with hydrophobic aliphatic alcohols to control the GI liquid penetration rate within the tablet. This formulation shows both immediate and sustained release. The immediate-release comes from the dissolution and the diffusion of the drug that is located at the surface of the tablet. The extended-release is achieved through the same strategy as the Contin™ system, the active component is released from particles embedded into the matrix. This formulation provides a first dose release of 40% over the first hour, followed by an extended-release for up to 12 hours.

Sustained release of oxycodone has also been developed in a more tamper-proof ER formulation, using the DETERx™ technology [43]. Indeed, opioid abuse after prescription has been discouraged through the development of new drug delivery systems [44,45]. The DETERx™ formulation is specifically designed to retain its time-release mechanism even after common methods of tampering (i.e. physical and/or chemical modifications). The formulation consists of small spherical beads containing oxycodone, a fatty acid, and waxy excipients that are charged into a capsule. Embedding the drug in a hydrophobic environment leads to diffusion-controlled slow release. This formulation of oxycodone is unique in that it is an abuse-deterrent formulation designed to allow sprinkle-dosing on food or easy passage through nasogastric and gastrostomy tubes. The intended time-release profile is maintained by either of these two convenient methods of administration [46,47].

Similarly, to facilitate tamper-free drug delivery, another extended-release formulation of oxycodone was developed using the ORADUR® system [48,49]. This technology combines extended-release properties with an improved tamper resistance, limiting potential abusers to self-administer the drug by crushing, snorting, injection or inhalation. The capsule is filled with a high viscosity liquid carrier material and the drug. Herein, this specific formulation the viscous carrier consists of sucrose acetate isobutyrate and a cellulose acetate butyrate as polymeric thickener, to form a hydrophobic viscous fluid that is transformed in a matrix with elastic properties when it is in contact with an aqueous medium (e.g. GI fluid) leading to slow diffusion controlled-release.

The first hydromorphone ER formulation (under the brand name Palladone™) was based on a biphasic drug release, combining both IR and ER over 24 hours [39]. The formulation used a controlled-release melt extrusion technology. The drug is blended with a hydrophobic matrix composed of a copolymer of ethyl acrylate, methyl methacrylate and trimethylammoniumethyl methacrylate chloride, stearyl alcohol and ethylcellulose. The matrix controls both the rate of water permeation within the pellet and the diffusion of the drug from each pellet. The therapeutic concentration in the blood is sustained over 24 hours. Unfortunately, the consumption of alcohol was found not to be compatible with such capsules. It results in the disruption of the system, releasing a fatal dose of hydromorphone. Due to the high risk of overdose, the food drug administration decided to block all marketing and sales.

Nonetheless, another hydromorphone ER tablet form has successfully been developed [50,51]. This formulation uses the osmotic extended-release oral delivery system (OROS®) Push-Pull™ technology [52]. It is the only available ER form of this analgesic (Fig. 4) [53]. The OROS® system is suitable for poorly water soluble compounds. The OROS® Push-Pull™ technology consists of a drug layer consisting of the drug, polyethylene glycol and polyvinylpyrrollidone and an osmotic push layer consisting of polyethylene glycol, sodium chloride and hydroxypropylcellulose that is coated by a semipermeable shell membrane consisting of

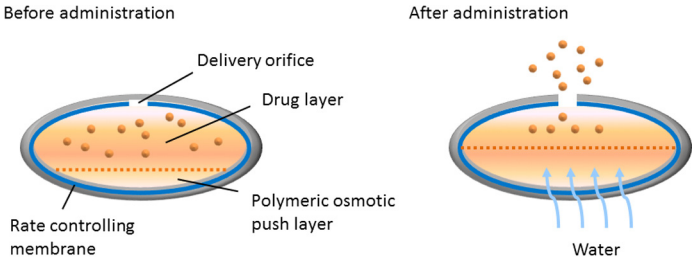

FIGURE 4

Illustration of OROS® Push-Pull™ drug delivery tablet.

cellulose acetate and polyethylene glycol [54]. Once in the GI tract, the fluid flows through the membrane at a controlled rate, allowing the push layer to expand and eject the suspended drug from the drug layer out of the tablet through the delivery orifice. This formulation provides a sustained release over 24 hours [53].

Interestingly, extended-release oxymorphone tablets were developed based on a delivery system called TIMERx™ [55]. This technology is based on a hydrophilic natural polymer based matrix that consists of xanthan gum, locust bean gum and dextrose. These polysaccharides form a coat layer around the drug core. This layer regulates the rate of drug release by controlling the GI fluid permeation into the tablet and the solubilization/diffusion of the drug through the tablet. Contact of the hydrophilic layer with water forms a viscous gel that controls the release of the drug from the tablet, as previously discussed for the Contin™ technology. TIMERx™ drug delivery provides sustained analgesia for 12 hours (Fig. 5) [39].

Hydrocodone ER formulations were developed for the first time as a single-agent drug using the OraGuard™ drug delivery technology [56]. The OraGuard™ tamper deterrent and alcohol resistant platform was designed to protect drugs against mechanical crushing and prevent dose dumping when the drug is taken with alcohol [57]. Hydrocodone is comminuted with a high polymer load and coated with a polymeric membrane that controls the drug release even when the tablet is crushed. This formulation is still in clinical trials (Phase III) and no details on the polymers used have been disclosed [58].

Liquid formulations are also available for patients such as children or elderly patients. The introduction of biocompatible polymers [59–61] is an alternative for the design and the production of modified release formulations. Among adequate polymeric materials used for drug microencapsulation, significant efforts have been devoted to the development of hydrophobic ethyl cellulose as the drug carrier. It has been widely used in liquid oral pharmaceutical formulations, and is generally regarded as a nontoxic, nonirritant, safe and stable material. For example, ethyl

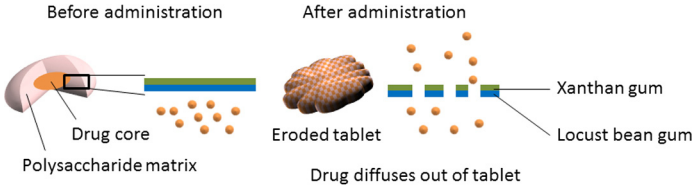

FIGURE 5

Structure and mechanism of the TIMERx™ drug delivery tablet.

cellulose pseudolatex particles are able to encapsulate morphine [62] and used for the development of a stable final pharmaceutical form with diffusion-controlled slow release. Using 1% of carbopol as the thickener in the suspension's final formula, 81% of the initial dose of morphine is released over 8 hours [63].

Oral controlled-release opioid formulations enhance a better pain relief due to the extended therapeutic blood concentration and the improvement in dosing intervals. A reduction of blood drug level fluctuation decreases the appearance of adverse effects (Fig. 1). The differences between all oral ER opioid drugs are the cost, the formulation, including the drug release system, and the excipients. Actually, no data support the higher efficacy of one drug compared to another one. Selection of the first treatment relies mainly on the clinician, who usually prescribes one preferred drug. This preference is sometimes in function of past opioid responses of the patient. Taking into consideration all the parameters such as pain tolerance, drug metabolism and the management of side effects, all treatments have specific benefits and drawbacks.

Transdermal administration

Patches

Transdermal drug delivery systems are an interesting alternative to oral delivery technologies because they offer several advantages over other existing analgesic administration methods [64]. Indeed, this strategy is non-invasive, simple, safe and effective for pain management [65]. Additionally, compared to other parenteral routes, practical drawbacks related to the use of needles and the required venous access, are avoided. Similar to other parenteral routes, transdermal drug delivery also by-passes first-pass hepatic metabolism and circumvents gastrointestinal tract-to-blood passage, common to the use of oral analgesics. In addition, it can also provide release profiles during long periods of time, providing an improvement in patient compliance.

The major challenge for transdermal delivery is the limited number of molecules that can be formulated for this type of administration, as passive diffusion of the drug through the stratum corneum is required [66]. These analgesics have to present certain characteristics, which include a low molecular weight (less than 500 Da), appropriate partition coefficients and a high potency (i.e. with low dosage, typically less than milligram doses per day) [67]. Delivery of hydrophilic drugs using transdermal delivery is difficult and has not been exploited to date for opiates. There are also some general considerations for designing polymer based transdermal patches. These polymers should not be water-soluble to avoid dissolution and potential interactions with the skin. Furthermore, they need to be soft and tacky to have good adherence and contact with the skin. This means that the polymer should have a low glass transition temperature, at least below body temperature, but preferably even lower to facilitate sufficient chain mobility for diffusion of the drugs.

Transdermal delivery systems are, according to the penetration mechanism through the skin, subcategorized in three generations, only two of which were used in opioid applications. The first generation of systems gave way to many of today's patches by judicious selection of drugs that can cross the skin at therapeutic concentrations by passive transport. The second generation was developed to increase the skin permeability of small-molecule

delivery using alternative driving forces for the transport (using for example the iontophoretic transdermal system, *vide infra*), while the third generation enabled the delivery of small-molecules, macromolecules, virus-based and vaccines through the skin's stratum corneum by more invasive systems (such as microneedles and microdermabrasion) [64].

Transdermal delivery systems were applied to the management of chronic pain. Among all molecules which are available to treat chronic pain, only two (fentanyl and buprenorphine) have been used in this type of system due to their high potency, high lipophilicity and low molecular weight. Indeed, due to the very fast metabolization of fentanyl by enzymes in the small intestine and the liver, transdermal delivery technologies are highly suited to provide fast and efficient pain relief.

First generation: reservoir and matrix patches

Fentanyl is a suitable analgesic for transdermal administration thanks to its physicochemical characteristics. It has a low molecular weight (286 Da), high lipophilicity (LogP = 717), and optimal skin flux (around 1000 times higher than morphine) [66].

Different transdermal fentanyl delivery systems [68], patches that contain a drug reservoir or a drug-infused matrix, rely on skin penetration by passive diffusion (Fig. 6).

The fentanyl-containing reservoir patch represented the first opioid transdermal delivery system available in this form and proved effective and convenient for providing pain relief. This delivery system contains a reservoir of fentanyl with a sufficient dose for a three day treatment [69]. It consists of a backing layer, formed by a polyester film that protects the patch from the environment, a liquid drug reservoir with dehydrated alcohol gelled with hydroxyethylcellulose, a membrane, constituted of an ethylene-vinyl acetate copolymer, which controls the rate of release of fentanyl from the reservoir, and a silicone adhesive layer to adhere the patch to the skin surface. The fentanyl release occurs from the reservoir, at constant rate until the reservoir is emptied. The rate of fentanyl diffusion across the skin layers is determined by the properties of the ethylene-vinyl acetate copolymer membrane. The addition of alcohol (0.1 mL/10 cm^2) into the formulation also helps to increase the permeability of fentanyl through the skin. After the initial application of the fentanyl transdermal system, the skin gradually absorbs fentanyl, resulting in an increase of plasma concentrations. A maximum dose that remains relatively constant is achieved in 12–24 hours, with only some small fluctuations, and an efficacy over 72-hour [70]. After patch removal, fentanyl serum concentrations decline gradually, dropping to 50% in approximately 20–27 hours. The bioavailability of

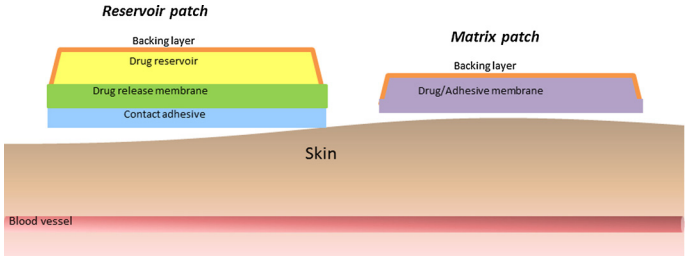

FIGURE 6

Schematic representation of reservoir and matrix patches; adapted from [65].

transdermally administered fentanyl has been calculated to be approximately 90% [71]. This percentage depends on the skin permeability and the body clearance of each patient. The reservoir patch presented a risk of drug leakage (incidental or intentional by cutting), and this was clearly considered as an important concern.

To address this concern about the reservoir system, a second transdermal patch generation was developed. Herein, the drug is directly dissolved into the matrix, a semi-solid formulation of a polyacrylate adhesive. Fentanyl matrix patches with a lower drug load were found to be superior to and as safe as established standard oral and transdermal opioid treatments [72]. Afterwards, a second type of matrix patch was developed. In such systems the drug is dispersed in a semi-solid formulation within the adhesive itself. The matrix is constituted by fentanyl-containing dipropylene glycol droplets dispersed in a silicone matrix formulation. This formulation modifies both the drug release profile by extending it, and the drug loading which can be reduced by 35–50%, compared to other matrix patches. The rate-controlling membrane ensures that fentanyl concentrations are maintained at a constant level throughout a 72-hour application of the patch. It was shown that the two fentanyl transdermal delivery systems (reservoir and matrix patches), described before, have equivalent properties in terms of tolerability and bioavailability of the drug [70].

The fentanyl patches present limited side effects that can, generally, be easily treated. The most important adverse effects reported are dermatological reactions, such as skin occlusion or local irritation [69]. A rotation of skin sites can prevent these mild side effects. For patients suffering of chronic pain, transdermal delivery systems are well tolerated due to the administration of stable opioid doses. Some sort of 'breakthrough' pain coverage is still advised by, for example, an immediate-release oral dose of morphine.

Buprenorphine is also available as a matrix patch. It provides consistent blood drug concentration over a 7-days dosing interval [73]. A comparison between transdermal fentanyl and transdermal buprenorphine patches was reported, showing the equal efficacy [74]. The best treatment seems to switch between the two opioid formulations to increase tolerance and acceptability by suppressing side effects.

Iontophoretic transdermal system (ITS)

The first generation of patches (*vide supra*) functions through passive transdermal diffusion, eventually resulting in a slow absorption of the drug from the skin depot. One drawback of this approach consists of the prolonged action after removal of the patch.

To provide a more precise control over the delivery of the analgesic drug, an alternative system that improves the permeation of the drug through the stratum corneum by using an active transport was developed. The iontophoresis patch technology was designed for the management of moderate to severe pain in a clinical setting (Fig. 7) [75,76].

The iontophoretic system is based on a low intensity electric current that drives the active transport of analgesic drugs through the skin and into the systemic circulation. This device uses the skin to complete the circuit between the anode and the cathode, allowing transport of ionized active molecules present in a reservoir. More precisely, the driving force for the displacement of ionized molecules, is based on the electrostatic-repulsion of similar charges. Drug delivery by an iontophoretic system is

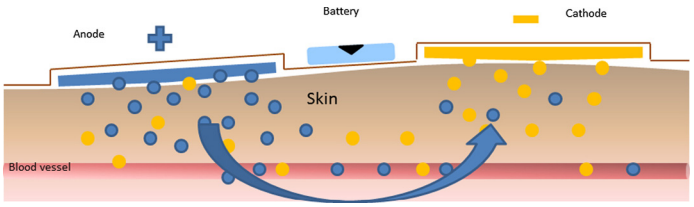

FIGURE 7

Iontophoresis patch technology adapted from [77]. The system is composed of a plastic top containing the battery and electronics, the plastic bottom contains two hydrogel reservoirs and a skin adhesive. The hydrogel located at the anode contains the opioid (blue dots). The other hydrogel, located at the cathode, contains only pharmacologically inactive compounds (yellow dots).

however influenced by several parameters including the skin surface which is in contact with the electrode, the current intensity as well as the duration, but also the chemical properties of the molecule. Generally, the best efficiency of this delivery system is obtained for lipophilic compounds with a low molecular weight and positive charge [75]. As a consequence, the number of opioids that can be used for this delivery system is limited [66]. Nonetheless, fentanyl is suitable for iontophoretic transdermal delivery, reaching blood drug concentrations comparable to those obtained by intravenous infusion [78,79]. In contrast, morphine is not ideal for use in iontophoretic patches [80,81], due to its low lipophilicity that prevents skin penetration. The general requirements for the polymer are similar as described for the first generation patches.

The iontophoresis patch is a patient-controlled analgesia (PCA) system. Patients could self-administer analgesic doses by pressing one button depending on their need for pain relief. For example in the case of fentanyl, a pre-programmed dose delivers 40 μg of drug over 10 min, with a maximum of six doses per hour. This type of administration offers several advantages compare to passive transdermal systems, such as an increase of opioid absorption rate, a rapid decrease in plasmatic concentrations and a more precise control of dosages.

Several limitations inherent to this transdermal drug delivery system need to be noted as well. First, the impossibility to modify the delivered dose during the treatment can become problematic in case of patients with considerable opioid needs for a suitable pain relief. The other limitation is associated to the patient-controlled analgesia (PCA) concept, wherein patient involvement is crucial. The patient needs to be a suitable candidate for pain self-management, since he/she needs to be able to follow the instructions for operating the system. Finally, the most significant drawback of this technology consists however of the associated price which has limited its broad applicability. Iontophoretic transdermal system marked an evolution in pain management system with an improvement in terms of safety and convenience, as compared with existing patient controlled-analgesia, through the use of a pre-programmed and disposable drug delivery systems [82].

Topical administration

Topical opioid treatments give access to local analgesia with attenuated or eliminated systemic adverse effects. Results from case studies and pilot clinical studies on local morphine treatment for painful skin ulcers, however, have not shown to be fully convincing with respect to efficacy and tolerability [83–85]. A major drawback is the required repeated replacement of the wound dressing, which is very painful for the patient and bears a risk of destroying any regenerated epithelia. Therefore, the interval of the changes should be extended as much as possible and new formulations were still needed.

Various studies dealing with local applications of opioids for the treatment of painful skin ulcers have been reported [86]. Most of them show an analgesic effect post administration without side effects that are normally observed after systemic administration. Indeed, the potential advantages of such a delivery system include the possibility to optimize opioid concentration at the site of pain and decreased systemic opioid levels. For topical formulations, a morphine solution is generally mixed with a hydrogel containing 2.3% carboxymethylcellulose polymer with 20% propylene glycol, but other formulations have been used as well [85,87–89]. Unfortunately, this gel-based morphine formulation does not adhere very well to a moist wound surface.

To improve adhesion, a novel topical preparation of morphine was formulated using poloxamer 407 (P407), a thermoreversible gel also known as Pluronic (F127) [90]. The temperature-controlled self-assembly of poloxamer into micellar structures can yield hydrogels at sufficiently high polymer concentrations [91]. Poloxamer 407 is a triblock copolymer consisting, by weight, of approximately 70% polyethylene oxide as outer blocks and 30% polypropylene oxide as middle block with an average total molecular weight of 12.5 kDa. P407 gels show adequate bioadhesive properties. The formulation of 0.5% (w/w) morphine–HCl in a 22% (w/w) P407 hydrogel was developed [90]. The observed release follows zero-order kinetics and is controlled by drug diffusion from the gel matrix. Morphine–HCl was released at a rate of 150 μg/cm^2/h. These results are in favor of the use of P407 gel as a topical sustained release formulation for the treatment of painful ulcers [92], although absorption of these relatively low molar mass polymers may be a concern.

Parenteral administration

Due to limitations in bioavailability and the formulation challenges associated with some of these pharmaceuticals, parenteral drug delivery is an administration route of paramount importance. This includes intravenous, subcutaneous and intramuscular injection. Indeed, parenteral administration of opioids is needed in patients with gastrointestinal tract disorders, when the opioid need is high or in cases where toxicities associated with intermittent dosing schedules emerge. Morphine sulfate is the most commonly used parenteral opioid and it can be administered as a bolus or continuous infusion. Continuous parenteral administration of opioids is usually cumbersome and expensive, it needs availability of vascular or subcutaneous catheters, infusion pumps, and it requires trained nursing and pharmacy personnel.

Subcutaneous administration route

Subcutaneous administration of opioids can be highly useful for patients that do not have indwelling intravenous access and require parenteral opioid administration [93]. Here, the infusion rates of fluid that can be administrated have been found to be around two to four milliliters per hours (without generation of pain at the administration site), which represents the limiting factor [94]. The main advantage in favor of subcutaneous over

intravenous analgesic administration is that there is no need for vascular access. Indeed, the administration sites can easily be changed and problems associated with indwelling intravenous catheters are avoided. For local treatments, parenteral administration of drugs is often associated with poor retention of the pharmaceutical product at the site of delivery. In case of systemic delivery, short half-lives can be problematic. To compensate for these drawbacks, parenteral drug administration is typically done at high concentrations or at high dosing frequencies. However, high concentrations of the drug can result in adverse side effects.

To increase the efficacy of parenteral administration one can make use of delivery vehicles. In this method, the administered drug is encapsulated within a material that releases the therapeutic agent in a controlled manner that optimizes the dosage for a specified period of time. Hence, polymer implants can be used. Advances in polymer chemistry have resulted in the development of polymeric delivery devices that reliably release therapeutic compounds in a controlled and continuous fashion. In this way a highly biocompatible, non-biodegradable, polymeric device which releases hydromorphone at a constant rate over four weeks was developed. This device could improve compliance, minimize the risks of drug diversion, and provide a low cost alternative for patients with pain who could benefit from chronic parenteral opioid infusion [95]. In this formulation hydromorphone is embedded in a controlled-release matrix, namely an ethylene-vinyl acetate (EVA) copolymer. In the study reported by Lesser et al., the implant had a cylindrical geometry and measured approximately 0.27 cm in height and 1.05 cm in diameter. Variations in the thickness and diameter of these devices, as well as in the number of devices implanted, provides flexibility in the amount of hydromorphone released per hour, the duration of hydromorphone release, and the magnitude of plasma hydromorphone levels. To avoid the potentially deadly 'burst effect' with this type of devices, a poly(methyl methacrylate) coating has been used. Placing an uncoated cylindrical channel through the center of the coated polymer limits the available surface area for drug release, and allows hydromorphone to be released with near zero-order kinetics for approximately 4 weeks in preclinical *in vitro* and *in vivo* models. These implants could substantially reduce the need for pumps, storage or refrigeration, frequent medical or nursing evaluations and multiple daily opioid doses.

There are several potential disadvantages linked to the use of these opioid delivery devices. Placement and removal of these polymer disks requires a minor surgical procedure. They are inserted through a small skin incision and advanced into the subcutaneous tissues. It should be mentioned that this may be avoided by developing thin tubular implants with a diameter up to 2 mm that can be simply injected as is done for the contraceptive implant Implanon™. These implanted hydromorphone polymers were developed to meet stable dosing needs of patients in pain. Acute exacerbations in pain intensity will require supplemental oral or parenteral opioids. Finally, this polymeric drug delivery system may not be appropriate for patients requiring high doses of parenterally administered opioids. As noted above, the dose of hydromorphone delivered per hour can be modified by changing the height of the implant and more than one polymer implant can be placed subcutaneously, as was tested in rabbits to increase the delivery rate and dosing even further.

Clinically, subcutaneous administration of opioids is not preferred for patients with very high opioid requirements, who may be best served with another method of opioid delivery or a combination of methods to provide adequate analgesia.

Continuous infusion

The subcutaneous administration of analgesics is often used in combination with a pump-based PCA system. This provides a better control over analgesia by the patient, as compared to the continuous infusion system alone. The subcutaneous administration of hydromorphone using a PCA system gives a bioavailability of around 80% [96]. Steady-state plasma hydromorphone concentrations were reached within 24 hours in a study performed by Moulin and coworkers. When compared to the intravenous route, subcutaneous PCA administrations avoid the need for vascular access, and present the possibility to easily change the administration site. Alternatively, the analgesic drug can be bound to an ionic polymer such as hyaluronic acid or poly-γ-glutamic acid. The polymer can be anionic, and the drug cationic, or vice versa. The polymer-drug matrix can be injected either subcutaneously, intramuscularly or intraperitoneally. The matrix is degraded over time via the enzymatic machinery of the body, thereby releasing the drug [97].

Intravenous route

The intravenous administration is prescribed for patients whose pain relief cannot be controlled by less invasive systems. For patients who need opioid infusion for pain control, nursing support is required, which generates serious costs. Depending on the frequency and duration of the treatment, different devices can be used, such as a Port-a-Cath® or other types of indwelling central or peripheral catheters [98]. Any indwelling intravenous catheter can become a source of infection. Many opioids are commercially available at various concentrations for intravenous solutions, such as morphine, hydromorphone, fentanyl and sufentanil. Due to the above mentioned drawbacks, intravenous administration is only used in extreme cases, when more common routes are not appropriate, for example in advanced cancer, or in palliative care.

Perispinal route

The majority of patients, who suffer of chronic pain, can be adequately treated by opioid administration using one of the many systems discussed above. However, in some cases the pain relief remains troublesome despite large administered opioid doses. Patients can for example suffer from unmanageable adverse effects such as nausea or oversedation. As last resort, opioids can be administered as local anesthetics using the perispinal route [99,100]. Perispinal opioid administration involves the direct application of a small opioid dose close to the spinal opioid receptors. The main advantage of this administration system is the suppression of undesirable effects by decrease of the total opioid dose.

This way of administration requires the implantation of a permanent catheter, associated to an external infusion pump, into the epidural or intrathecal space [101]. Different perispinal approaches including intrathecal injection, continuous intrathecal infusion, epidural bolus, and continuous epidural infusion are available for opioid drug delivery [98].

The choice between epidural versus intrathecal application or external versus implantable pumps to deliver the opioid is based on several factors such as the type and pain location, the duration of treatment, the patient preference, etc. The opioid dose required for epidural administration is around 10 times superior to intrathecal administration [102]. Intrathecal opioid delivery allows higher opioid dose administration due to a focused opioid application at the receptor site, generating decreased drug-related adverse effects. Regarding treatment duration, a therapy exceeding 6 months requires the placement of an intrathecal catheter to limit refills of the pump.

Different types of side effects are associated to perispinal opioid delivery. The surgical and procedural complications include bleeding and/or infections [103]. Some complications can originate from a system malfunctioning, including kinking, obstruction, disconnection, tearing or migration of the catheter, all of which can have an influence on the rate of opioid delivery. Finally, pharmacological side effects such as overdoses can be avoided by means of precise formulation. Generally, except constipation which is the most common adverse effect encountered in opioid treatment, perispinal opioid administration does not generate any supplementary side effects for patients who are already tolerant to opioids.

Clearly, this route of administration needs nursing care and a clinical environment, making this delivery system highly expensive.

Conclusions and perspectives

Chronic pain therapy is a complex pathology with extensive consequences for the patient and society. The main challenge with chronic pain therapy is the need for a multidisciplinary and multipharmaceutical approach, which makes advances in daily treatment difficult to optimize and follow up. Integration in chronic pain schemes of newer drugs such as glutamate antagonists, vanilloid receptor agonists, acetylcholine and norepinephrine modulators, adenosine receptor agonists, anti-inflammatory drugs will be as important as the administration routes of these drugs.

Adequate pain relief can significantly improve the quality of life of these patients and attenuate this societal burden. Chronic pain management guidelines recommend the use of long-acting, extended-release analgesics because they provide prolonged, and more consistent plasma concentrations of drug compared with short-acting compounds. But before exposing patients to an extended-release formulation of opioids, they must fulfill certain criteria. The most important of all is that the patients must be opioid tolerant; meaning that they must consume more than 60 mg of morphine (or an equivalent) per day for more than seven days.

To manage chronic pain, several opioid delivery systems are available. Selection of the most efficient, cost-effective and user-friendly method needs careful consideration. This means that the patient's ability to use a specific type of delivery system, the efficiency of the system, the potential complications associated, and the cost must be regarded.

Oral administration of opioids is efficient and acceptable for most of patients suffering of chronic pain. Indeed, a large set of oral opioid drug formulations is available. Obviously, the main advantage is the ease of administration. Additionally, various polymer systems have been applied successfully resulting in sustained release providing longer and gradual pain relief. The major disadvantage for oral therapy is the first-pass effect and the organ-dependent metabolism, resulting in the necessity of higher dosage forms compared to other types of administration. Minor and less frequent disadvantages occur in patients with dysphagia or neurological impaired persons that cannot swallow.

Alternatively, the transdermal route is useful for highly lipophilic opioid such as fentanyl and buprenorphine, whereby the drug is formulated into a polymer reservoir coated with an adhesive polymer or the drug can directly be formulated with the adhesive polymer. Fentanyl and buprenorphine are equally effective, but the latter drug is less addictive. Transdermal patches have a medium risk for adverse effects and are even approved in children older than 2 years. No mg/kg dosing is however used as over- and under-dosing can occur due to age-related and developmental changes in pharmacokinetics. Transdermal formulations are often preferred by patients compared to oral controlled-release options [104]. The advantages of transdermal therapy in elderly people include a non-invasive long term administration mode that is independent from intestinal absorption and circumvents first-pass effects. A slow attainment of the peak-plasma concentration also results in improved therapy compliance. Some disadvantages include skin irritation and the limitation of the drug types that can be used with this formulation. The dose is also limited by 240 mg/h, without any possibility for dose adjustments outside the hospital. The second generation of transdermal administration, the iontophoretic delivery system, has a better control of dosage, gives a rapid absorption rate and allows fast clearance. It is important to note that the associated cost of this technique represented a major drawback for its broad applicability.

Even though topical opioid therapy is not fully established, it can give analgesia without common opioid side effects. By applying the drug locally, the total opioid dose can be reduced. The only drawback is related to the repeated replacement of wound dressing, as the regeneration of epithelia can be damaged. The intravenous opioid administration system is useful for patients whose pain cannot be controlled by less invasive ways. The intravenous opioid infusions can be administered by continuous infusion, or using a patient-controlled analgesic device. The delivery can be accomplished by central venous access, vein puncture or implantation of a Port-a-Cath® in the subclavian vein during surgery. The latter is commonly used in cases of chemotherapy. The major disadvantages are the risk of infection, the cost and the need of educated personnel, limiting the patient's freedom. Finally, for a limited number of patients, for who adequate analgesia by systemic administration fails, because of side effects like nausea, sedation and constipation, spinal or epidural dosing via catheters needs to be considered. The dose is directly injected at the spinal cord, giving a better analgesia and a reduction of side effects, which allow a decrease of the total opioid dose. Because this mode of administration is invasive and accompanied by a significant risk of infection, it is restricted to the palliative care.

In the future polymer implants can also be employed in pain therapy. The cylindrical geometry and variations in thickness and diameter can change the rate of release and total dosing. It is reliable, controlled, gives a better compliance, and there is less need for a pump or a daily intake of drugs. The disadvantage is that

it requires a minor surgical intervention, which may be overcome in the future by developing thin tubular implants that can be directly injected. Such a device might present a possible burst-release effect of the drug, with a risk to lose the implant in the body due to migration. For the latter, it should be noted that on-demand drug delivery systems have already been developed and may be applied for opioid delivery in future developments [105–107].

In the field of drug delivery, nanotechnology aims to formulate therapeutic agents in biocompatible nanocarriers (roughly 10 to 200 nanometer size range), such as nanoparticles [108], nanocapsules, micelles and liposomes, nanotubes and dendrimers. The major advantage of these formulations is their extended blood circulation time, in combination with enhanced cellular uptake especially by non-healthy, cancerous, tissue, also known as the enhance permeation and retention effect [109]. Furthermore, functionalization of the nanocarriers with targeting ligands allows direct drug delivery to the site of action, improving the bioavailability of the drug [110]. In this way, these nanosystems help to prevent the possible undesired exposure of the drug to off-target tissues. Although nanotechnology for drug delivery is extensively used for therapeutics in cancer and inflammation applications, in the literature only few examples have already been reported for opioid administration. One example consists of an extended-release morphine suspension, that uses DepoFoam® technology [111]. It is a single dose liposomal formulation of morphine, which is administered by epidural injection [112]. This formulation is applied following important surgery, it decreases the need of repeated systemically administered analgesics, and provides an efficient pain relief for up to 48 hours after injection. This technology disperses lipid-based particles that form multivesicular liposomes containing multiple internal aqueous chambers [113]. The drug is encapsulated in the water-filled particles affording a milk-like solution ready to be injected. This example of a 'nanotherapeutic' exemplifies further innovations based on nanotechnologies [114].

Clearly, if a new technology could arise that realizes a stable continuous opioid release system that lasts longer than the state-of-the-art 72 hour patches; it would represent a tremendous advancement in chronic pain therapy. It could improve the patient's quality of life and compliance by a less timely bound intake of drugs. Continued research remains of paramount important to tune the optimized administration format for each patient with chronic pain.

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References

[1] E. Aasvang, H. Kehlet, Pain 3 (1986) S1.
[2] P.J. Siddall, M.J. Cousins, Anesth. Analg. 99 (2) (2004) 510.
[3] P. Sarzi-Puttini, et al. Clin. Drug Invest. 32 (1) (2012) 21.
[4] A.M. Trescot, et al. Pain Physician 9 (1) (2006) 1.
[5] Y. Olsen, et al. J. Pain 7 (4) (2006) 225.
[6] M.D. Sullivan, et al. Pain 138 (2) (2008) 440.
[7] D. Boudreau, et al. Pharmacoepidemiol. Drug Saf. 18 (12) (2009) 1166.
[8] J.C. Ballantyne, N.S. Shin, Clin. J. Pain 24 (6) (2008) 469.
[9] R. Chou, et al. Ann. Intern. Med. 162 (4) (2015) 276.
[10] R.K. Portenoy, et al. J. Pain Symptom Manag. 23 (4) (2002) 292.
[11] G.R. Hanson, Remington: The Science and Practice of Pharmacy, vol. 2, 1995, . p. 1196.
[12] P. Sacerdote, Palliat. Med. 20 (8 Suppl) (2006) 9.
[13] G.K. Gourlay, Clin. Pharmacokinet. 35 (3) (1998) 173.
[14] B. Mesgarpour, et al. Eur. J. Pain 18 (5) (2014) 605.
[15] P. Sloan, N. Babul, Expert Opin. Drug Deliv. 3 (4) (2006) 489.
[16] P. Sloan, Expert Opin. Drug Deliv. 11 (2) (2013) 155.
[17] P. Sloan, M. Davis, J. Opioid Manag. 10 (6) (2014) 3.
[18] B.H. McCarberg, R.L. Barkin, Am. J. Ther. 8 (3) (2001) 181.
[19] R.L. Rauck, Pain Pract. 9 (2009) 468.
[20] C.E. Argoff, D.I. Silvershein, Mayo Clinic Proceedings, vol. 84, Elsevier, 2009. p. 602.
[21] K.E. Uhrich, et al. Chem. Rev. 99 (11) (1999) 3181.
[22] L. Griffith, Acta Mater. 48 (1) (2000) 263.
[23] M.C. Branco, J.P. Schneider, Acta Biomater. 5 (3) (2009) 817.
[24] G. Vilar, et al. Curr. Drug Deliv. 9 (4) (2012) 367.
[25] K. Park, J. Control, Release 190 (2014) 3.
[26] B. Nicholson, Drugs 63 (1) (2003) 17.
[27] J. Hariharan, et al. J. Gen. Intern. Med. 22 (4) (2007) 485.
[28] M.J. Brennan, J. Multidiscip. Healthc. 6 (2013) 265.
[29] G. Varrassi, et al. Eur. J. Pain Suppl. 3 (2) (2009) 77.
[30] C.M. Amabile, B.J. Bowman, Ann. Pharmacother. 40 (7–8) (2006) 1327.
[31] A. Jacox, et al. N. Engl. J. Med. 330 (9) (1994) 651.
[32] S. Zhang, et al. Nat. Mater. 14 (10) (2015) 1065.
[33] https://pharmaceuticalresearch.wordpress.com/2012/07/05/sodas-spheroidal-oral-drug-absorption-system/.
[34] K. Wilkinson, Clin. J. Oncol. Nurs. 7 (4) (2003).
[35] V.K. Nikam, et al. Pharmacology 1 (1) (2011) 152.
[36] http://maynepharma.com/australian-products/specialty-brands/kapanol-/-kadian-capsules-.
[37] E.L. Ross, K. Hahn, Int. J. Clin. Pract. 62 (3) (2008) 471.
[38] Oramorph SR (morphine sulfate) sustained release tablets [package insert], Xanodyne Pharmaceticals, Inc., Newport, KY, 2006.
[39] D.A. Miller, et al. Drug Dev. Ind. Pharm. 34 (2) (2008) 117.
[40] R.F. Reder, Eur. J. Pain 5 (2001) 109.
[41] D.G. Rischitelli, S.H. Karbowicz, Pharmacotherapy 22 (2002) 898.
[42] http://www.purduepharma.com/healthcare-professionals/products/oxycontin/.
[43] http://www.collegiumpharma.com/technology-platform/overview.
[44] N. Katz, et al. Am. J. Drug Alcohol Abuse 37 (4) (2011) 205.
[45] M. Romach, et al. Drug Alcohol Depend. 130 (1) (2013) 13.
[46] E.A. Kopecky, et al. J. Opioid Manag. 10 (4) (2013) 233.
[47] A.B. Fleming, et al. Pain Pract. (2015).
[48] M. Zamloot, et al. J. Appl. Res. 10 (3) (2010) 89.
[49] J.R. Havens, et al. Drug Alcohol Depend. 139 (2014) 9.
[50] N. Carter, G. Keating, CNS Drugs 24 (4) (2010) 337.
[51] S. Gupta, G. Sathyan, J. Pain Symptom Manag. 33 (2 Suppl.) (2007) S19.
[52] http://www.alza.com/alza/oros.
[53] G. Sathyan, et al. Curr. Med. Res. Opin. 24 (1) (2007) 297.
[54] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021217s000MedR.pdf.
[55] J.N. Staniforth, A.R. Baichwal, Expert Opin. Drug Deliv. 2 (3) (2005) 587.
[56] M. Darwish, et al. Clin. Ther. 37 (2) (2015) 390.
[57] http://www.drug-dev.com/Main/Back-Issues/OraGuardTM-A-TamperingDeterrent-AlcoholResistant-E-517.aspx.
[58] https://clinicaltrials.gov/show/NCT01223365.
[59] X. Guo, et al. Chem. Eng. J. 131 (1) (2007) 195.
[60] V.R. Babu, et al. Carbohydr. Polym. 69 (2) (2007) 241.
[61] Q. Wang, et al. Carbohydr. Polym. 69 (2) (2007) 336.
[62] M. Morales, et al. J. Control. Release 95 (1) (2004) 75.
[63] M. Morales, et al. Mol. Pham. 8 (2) (2011) 629.
[64] M.R. Prausnitz, R. Langer, Nat. Biotechnol. 26 (11) (2008) 1261.
[65] S. Bajaj, et al. Contin. Educ. Anaesth. Crit. Care Pain 11 (2) (2011) 39.
[66] S. Grond, et al. Clin. Pharmacokinet. 38 (1) (2000) 59.
[67] M.R. Prausnitz, et al. Nat. Rev. Drug Discov. 3 (2) (2004) 115.
[68] M.E. Lane, Eur. J. Pharm. Biopharm. 84 (3) (2013) 449.
[69] K. Calis, et al. Clin. Pharm. 11 (1) (1992) 22.
[70] J.F. Marier, et al. J. Clin. Pharmacol. 46 (6) (2006) 642.
[71] J. Varvel, et al. Anesthesiology 70 (6) (1989) 928.
[72] H.G. Kress, et al. J. Pain Symptom Manag. 36 (3) (2008) 268.
[73] R.P. Kapil, et al. J. Pain Symptom Manag. 46 (1) (2013) 65.

[74] F. Mitra, et al. Pain Med. 14 (1) (2013) 75.
[75] Y.N. Kalia, et al. Adv. Drug Deliv. Rev. 56 (5) (2004) 619.
[76] N. Dixit, et al. Curr. Drug Deliv. 4 (1) (2007) 1.
[77] J. Goldstein, et al. Headache 52 (9) (2012) 1402.
[78] M. Ashburn, et al. Anesthesiology 82 (5) (1995) 1146.
[79] G. Sathyan, et al. Clin. Pharmacokinet. 44 (1) (2005) 7.
[80] R. Stephen, et al. Artif. Organs 18 (6) (1994) 461.
[81] M.A. Ashburn, et al. J. Pain Symptom Manag. 7 (1) (1992) 27.
[82] I. Power, Br. J. Anaesth. 98 (1) (2007) 4.
[83] P. Flock, J. Pain Symptom Manag. 25 (6) (2003) 547.
[84] G. Zeppetella, et al. J. Pain Symptom Manag. 25 (6) (2003) 555.
[85] G. Zeppetella, et al. Palliat. Med. 19 (2) (2005) 131.
[86] B. LeBon, et al. J. Pain Symptom Manag. 37 (5) (2009) 913.
[87] R.K. Twillman, et al. J. Pain Symptom Manag. 17 (4) (1999) 288.
[88] P. Farley, J. Pharm, Pharmacology 63 (6) (2011) 747.
[89] M.D. Ribeiro, et al. J. Pain Symptom Manag. 27 (5) (2004) 434.
[90] M.M. Jansen, et al. Int. J. Pharm. 452 (1) (2013) 266.
[91] G. Dumortier, et al. Pharm. Res. 23 (12) (2006) 2709.
[92] S. Heilmann, et al. Int. J. Pharm. 444 (1) (2013) 96.
[93] P. Storey, et al. J. Pain Symptom Manag. 5 (1) (1990) 33.
[94] E. Bruera, et al. Cancer Treat. Rep. 71 (10) (1987) 953.
[95] G.J. Lesser, et al. Pain 65 (2) (1996) 265.
[96] D. Moulin, et al. Lancet 337 (8739) (1991) 465.
[97] A. Prescott, et al., Extended release analgesic for pain control, Patents (2005).
[98] R.A. Stevens, S.M. Ghazi, Cancer Control 7 (2) (2000) 132.
[99] S.J. Hassenbusch, et al. J. Pain Symptom Manag. 10 (7) (1995) 527.
[100] B.M. Bujedo, et al. J. Opioid Manag. 8 (3) (2012) 177.
[101] F.M. Brand, et al. Croat. Med. J. 48 (1) (2007) 22.
[102] E.S. Krames, J. Pain Symptom Manag. 8 (1) (1993) 36.
[103] S. Du Pen, et al. Anesthesiology 73 (5) (1990) 905.
[104] S. Ahmedzai, et al. J. Pain Symptom Manag. 13 (5) (1997) 254.
[105] J.H. Prescott, et al. Nat. Biotechnol. 24 (4) (2006) 437.
[106] K.C. Wood, et al. Proc. Natl. Acad. Sci. U.S.A. 105 (7) (2008) 2280.
[107] J.T.F. Keurentjes, et al. Angew. Chem. Int. Ed. 48 (52) (2009) 9867.
[108] R. Singh, J.W. Lillard, Exp. Mol. Pathol. 86 (3) (2009) 215.
[109] H. Maeda, et al. J. Control. Release 65 (1–2) (2000) 271.
[110] S. Parveen, et al. Nanomedicine 8 (2) (2012) 147.
[111] S. Mantripragada, Prog. Lipid Res. 41 (5) (2002) 392.
[112] http://www.pacira.com/products/depodur.php.
[113] M.S. Angst, D.R. Drover, Clin. Pharmacokinet. 45 (12) (2006) 1153.
[114] A. Hafner, et al. Int. J. Nanomed. 9 (2014) 1005.