ELSEVIER

Repurposing of parenterally administered active substances used to treat pain both systemically and locally

Luigi S. Battaglia [a], Rossella Dorati [b], Francesca Maestrelli [c], Bice Conti [b], Mirko Gabriele [d,e], Lorenzo Di Cesare Mannelli [f], Francesca Selmin [g,*], Donato Cosco [h]

[a] Department of Drug Science and Technology, University of Turin, Turin, Italy
[b] Department of Drug Science, University of Pavia, Pavia, Italy
[c] Department of Chemistry 'Ugo Schiff', University of Florence, Florence, Italy
[d] Patheon Italia SPA, Thermo Fisher Scientific, Ferentino, Italy
[e] President Elect, PDA Italy Chapter
[f] Department of Neuroscience, Psychology, Drug Research and Child Health (NEUROFARBA), Section of Pharmacology and Toxicology, University of Florence, Florence, Italy
[g] Department of Pharmaceutical Science, University of Milan, Milan, Italy
[h] Department of Health Sciences, Magna Græcia University of Catanzaro, Catanzaro, Italy

Pain is a constant in our lives. The efficacy of drug therapy administered by the parenteral route is often limited either by the physicochemical characteristics of the drug itself or its adsorption–distribution–metabolism–excretion (ADME) mechanisms. One promising alternative is the design of innovative drug delivery systems that can improve the pharmacokinetics | (PK) and/or reduce the toxicity of traditionally used drugs. In this review, we discuss several products that have been approved by the main regulatory agencies (i.e., nano- and microsystems, implants, and oil-based solutions), highlighting the newest technologies that govern both locally and systemically the delivery of drugs. Finally, we also discuss the risk assessment of the scale-up process required, given the impact that this approach could have on drug manufacturing.

Teaser: **The management of pain by way of the parenteral route can be improved using complex drug delivery systems (e.g., micro- and nanosystems) which require high-level assessment and shorten the regulatory pathway.**

Keywords: Abridged application; Complex drug delivery system; Extended profiling; Formulation; Market exclusivity; Injection; Risk assessment

* *Corresponding author.* *francesca.selmin@unimi.it* *(Francesca Selmin)*

Luigi Sebastiano Battaglia is Associate Professor at the Department of Drug Science and Technology, University of Turin, Italy, where he obtained a Degree in Pharmacy (2002) and a PhD in Drug Science (2009), and he performed all his academic career, including Research Associate (2006-2012) and Assistant Professor (2012-2020) positions. His main research interests concern drug delivery by means of solid lipid nanoparticles and nanoemulsions, aiming to overcome biological barriers (i.e. blood brain barrier) and to obtain targeted delivery, with a particular focus on protein drugs. He is Editorial Board Member of Pharmaceutics.

Mirko Gabriele – Pharmaceutical Chemistry Degree and PhD in Biomolecular and pharmaceutical Science – is currently Sr Director Sterile Strategy Innovation and Technology in ThermoFisher, leader in the contract development and manufacturing (CDMO) space. With a strong history in R&D, Operations (technology transfer, production, maintenance and validation) and Quality (quality control and analytical method development). His main professional research interest is on sterile and non-sterile drugs manufacturing processes, focusing on their robustness and reproducibility, using state-of-art technology and innovative approaches.

Francesca Selmin - Pharmaceutical Chemistry Degree and PhD in Medicinal Chemistry - is currently Associate Professor in Drug Delivery at the Department of Pharmaceutical Sciences, University of Milan (Italy). The research activities deal with the design and characterization of drug delivery systems intended for parenteral and oromucosal administration. Her research interests also include the study of European regulatory framework on the production, marketing and dispensing of medicinal products. To date, the research activity is documented by about 80 publications on international peer-review journals.

https://doi.org/10.1016/j.drudis.2022.07.006

Please cite this article in press as: L.S. Battaglia et al., Drug Discovery Today (2022), https://doi.org/10.1016/j.drudis.2022.07.006

Introduction

Pain is present in our lives. It is comparable to an alarm that defends us from damage, but which is also a terrible enemy to fight, particularly when persistent. 'Physiological' pain has its origin in normal, functional nervous tissue, including the peripheral and central nervous systems, is of brief duration, and is generally described as acute. Evoked by noxious stimuli, it results from burns or cuts, bee stings, dental work, labor and childbirth, broken bones or surgery. By contrast, 'pathological' pain is a persistent condition arising from articular diseases, fibromyalgia, cancer, and neuropathic and visceral problems, among others. A repeated painful signal can induce a maladaptive response of the nervous system that alters pain perception as well as the efficacy of common analgesics.[1,2] As a part of the chronic pain continuum, the term 'nociplastic pain' was recently proposed to describe the clinical and psychophysical findings related to altered nociceptive functions, in an attempt to join all the aforementioned conditions.[3]

Independently of the characteristics of pain, the Declaration of Montréal (2010) states that 'the access to pain management is a fundamental human right' and an integral component of Universal Health Coverage, a critical objective of the WHO.[4]

Painful and/or inflammatory conditions can be treated with numerous therapeutic agents belonging to different classes, including opioid analgesics, nonsteroidal anti-inflammatory drugs (NSAID), corticosteroids, and antiepileptics, or by using various techniques and administration protocols depending on the patient's need. Indeed, infusions of pharmacological agents into the central neuraxis (e.g., opioid analgesics) can be required to provide good, long-term pain relief, whereas local injections of the drug (e.g., glucocorticoids) into the affected area is a valuable approach for targeting the specific inflamed tissues, thus improving the therapeutic activity and reducing adverse effects.[5] However, the success of these different approaches is often limited either by the physicochemical characteristics of the drug substance itself or its ADME mechanisms.

To overcome these issues, the development of a medicinal product containing a substance never previously used in humans ('first-in-human') is an arduous process that requires a huge investment of money and time with no guarantee of returns. This is because 80% of approved drugs are reported to fail to yield profitable earnings for the companies that developed them.[6] Most of the expenditure can be ascribed to the translation of a medicinal product from preclinical to clinical studies, necessary for demonstrating its efficacy and safety. Hence, approaches that make use of drug candidates with known safety profiles (drug repurposing) can effectively avoid time-consuming, laborious, high-risk, and costly processes. Typically, 'old' drug substances could be sourced from medicinal products (i) approved by regulatory agencies; (ii) undergoing clinical development for a different application; or (iii) that have been abandoned or have failed to demonstrate efficacy during clinical trials (Phase II or III).

To accomplish successful drug repositioning, both maximizing drug interaction at the target site and mitigating or eliminating adverse effects are mandatory. In this regard, the design of a drug delivery system offers unique potential for repurposing applications, by allowing researchers to overcome obstacles of solubility, ADME, and targeting, thus significantly expanding the range of potential novel indications. Benefits arise from the broad range of materials, structures, and physicochemical modifications, all of which can address patient's needs. The development of a new drug product starting from an old active pharmaceutical ingredient (API) brings significant advantages from a regulatory point of view. In most cases, information regarding the efficacy and safety profiles of the drug substance is already available in literature or to the regulatory authorities. This means that the extent of the data to be provided by the applicant for the assessment process is reduced, and drug products can be authorized following an abridged application (Box 1). The nature and extent of such data can vary based on the type of the API (biological or nonbiological), the intrinsic complexity of the drug product, and its therapeutic indications.[7]

Based on these considerations, here we discuss how this idea has been successfully applied to design parenteral drug delivery systems for pain management in different settings (Fig. 1). We review cases of micro- and nanosystems (i.e., liposomes and nanoemulsions) available on the market to highlight the role of drug delivery systems in reducing adverse effects, optimizing PK, or improving patient compliance.

Box 1 Abridged (or hybrid) application

Abridged/hybrid applications (also called hybrid applications) can be used by the applicant if the 'generic' regulatory pathway cannot apply to the drug product, but its benefit/risk balance assessment can be partially derived from those available in literature or products already on the market. This is the case of old drug products reformulated to improve or optimize their therapeutic efficacy. They have the same or similar therapeutic indications as a result of changes to the pharmaceutical form or the administration route or by developing a novel fixed combination. An abridged application can also be used for follow-on (licensed) products with a high-intrinsic complexity for which bioequivalence studies cannot be applied as surrogates of therapeutic equivalence (i.e., conventional generic regulatory pathway).

In the European Union (EU), the 'hybrid' procedure is described by Article 10(3) of Directive 2001/83/EC; In the USA, the applicant should follow the 505(b)(2) New Drug Application (NDA). In both cases, the information included in the common technical document (CTD) to support a marketing authorization can be reduced compared with 'first-in-human' products. The quality part related to the API can be reduced, whereas the quality part of the CTD related to the drug product should be fully complete, including all the information regarding the physicochemical and technological characterization of the product and its critical quality attributes based on the intended use and route of administration. Data included in the preclinical and clinical parts of the dossier are reduced, but should be sufficient to allow an evaluation on the part of the regulatory authorities regarding the efficacy and safety profiles of the product based on its features, besides the complexity of the dosage form, and nature of the therapeutic improvement.

Please cite this article in press as: L.S. Battaglia et al., Drug Discovery Today (2022), https://doi.org/10.1016/j.drudis.2022.07.006

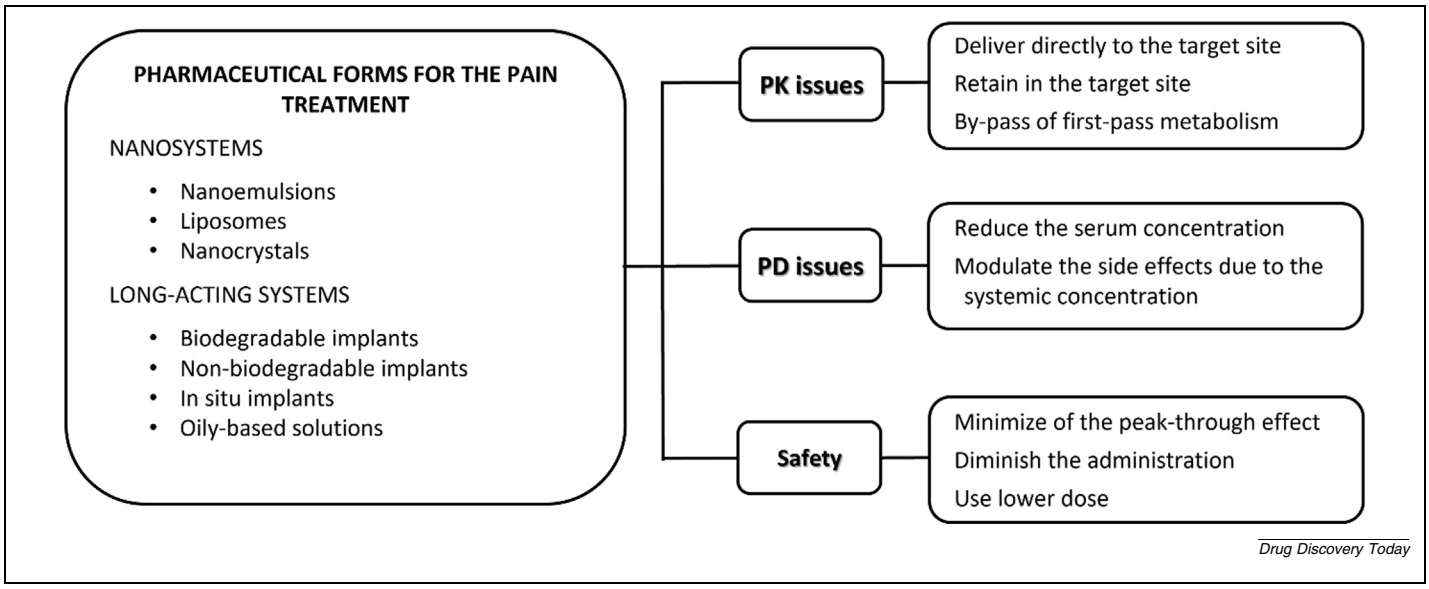

FIGURE 1

Possible relationship between formulations and pharmacokinetics (PK) and/or pharmacodynamics (PD) properties influencing the efficacy and safety of repurposed drugs in pain therapy.

Lipid based-delivery systems

Lipid based-delivery systems offer the opportunity for optimizing a variety of therapeutics owing to their specific therapeutic benefits and versatility of application. Indeed, they are capable of encapsulating small drugs as well as macromolecules, protecting them from chemical degradation, increasing their *in vivo* half-life, enhancing the drug payload, and providing controlled release and targeted delivery, among other things. Two main classes are approved in pain management, namely nanoemulsions and liposomes, as a result of their therapeutic benefits and optimal safety profiles.

Regarding micro- and nanosystems, key points that determine whether clinical translation and commercialization will be successful are related to challenges in cost-effective manufacturing and scale-up, appropriate regulatory guidelines regarding benefit/risk balance assessment, and validated characterization methods. Indeed, developing a scalable and reproducible manufacturing process generally involves multiple and complex steps (e.g., homogenization, centrifugation, extrusion, sterilization, lyophilization, etc.). Considering that these products are administered by parenteral route, the careful selection of materials, solvents, and manufacturing methods is important from the point of view of patient safety. Among them, sterility is mandatory, even if the sterilization process can pose challenges to the stability of nanomedicines. For instance, liposome components are sensitivity to physicochemical alterations: terminal steam sterilization should be avoided because it can cause the degradation of phospholipids into free fatty acids (FFAs), which can cause serious adverse effects. Sterile filtration is not applicable in systems up to 200 nm in size because of possible filter pore clogging, especially if the dispersion medium is viscous.[8] Alternatively, aseptic manufacturing in closed systems equipped with sterile filter barriers have been developed,[8,9] although these require additional process validation data and justification during regulatory submission.[10]

Finally, an understanding of the effect of storage conditions on the stability and biocompatibility of lipid-based drug delivery systems is vital for their translation into clinical practice. Indeed, storage conditions can affect physical stability (e.g., aggregation or coalescence), causing drug leakage or phospholipid degradation (i.e., hydrolysis oxidation).

Liposomes

Opioids are considered 'gold standard' in clinical practice for the treatment of postoperative pain and the WHO has included morphine in its Model List of Essential Medicines (https://list.essentialmeds.org/). Three major classes of opioid receptors (μ, δ, and κ) mediate spinal and supraspinal (particularly μ opioid receptor subtype 1) analgesia. The coupling with inhibitory G proteins allows inhibition of adenylate cyclase with reduced generation of cAMP and other second messengers. Opioids increase the conduction of potassium ions and hyperpolarize target cells, making them less responsive to depolarizing pulses and inhibiting calcium influx. These actions reduce the release of neurotransmitters from neurons and decrease the generation of the postsynaptic impulse; consequently, these drugs are able to counteract nociceptive pain.[11] In particular, epidural opioids are widely used for central neuraxial blockade and postoperative analgesia.[12] Indeed, epidural morphine sulfate has analgesic efficacy and superiority over systemically administered morphine, although pain relief following a single epidural injection lasts less than 24 h. Techniques used to administer and prolong opioid epidural analgesia, such as patient-controlled analgesia pumps, continuous epidural infusion, and frequent reinjection, are expensive and inconvenient.[13] In this scenario, the advent of extended-release epidural morphine (DepoDur™, SkyPharma) greatly improved postsurgical pain control, providing analgesia for up to 48 h with a single dose.[14] This formulation exploits multivesicular liposomes (DepoFoam technology) to prolong drug release over several days after nonvascular administration

Please cite this article in press as: L.S. Battaglia et al., Drug Discovery Today (2022), https://doi.org/10.1016/j.drudis.2022.07.006

(i.e., intrathecal, epidural, subcutaneous, intramuscular, intra-articular, and intraocular). The peculiar features of DepoDur are related to the mean diameter of the systems (~≥20 μm) and to their structure, which is characterized by closely packed non-concentric vesicles containing morphine sulfate (final drug concentration = 10 mg/ml) stabilized by triglycerides acting as space fillers at the intersection points of the phospholipid bilayer.[15,16] DepoDur comprises dioleoyl phosphatidylcholine (DOPC), dipalmitoyl phosphatidylglycerol (DPPG), cholesterol, Tricaprylin, and triolein in a mass ratio of 42:9:33:3:1.[15]

Although opioids can be used alone for postoperative pain, multiple studies have shown that analgesia is more effective when they are combined with local anesthetics.[12] For example, bupivacaine is able to block Na^+ channels and, thus, might also be able to affect the activity of many other channels, including NMDA receptors. NMDA receptors are crucial for the plastic events in the dorsal horn underlying central sensitization; thus, bupivacaine, by inhibiting NMDA currents, is active also against persistent pain.[17] Bupivacaine is administered by way of subcutaneous injections or intravenous infusions; unfortunately, in most cases, a single administration is not sufficient to manage postoperative pain because the drug is rapidly redistributed from the site of administration, limiting its duration of action. Moreover, the use of perineural catheters requires a clinician's specific skills, additional costs, and potential complications for patients.

Therefore, to promote a controlled and prolonged release of an active compound, a DepoFoam-based system was developed. This multivesicular liposomes containing bupivacaine (Exparel®) have a diameter of 24–31 μm and are suspended in a 0.9% sodium chloride solution. The inactive components are cholesterol, 1,2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol), tricaprylin, and 1,2-dierucoylphosphatidylcholine (DEPC). Compared with traditional bupivacaine, which has a duration of less than 10 h, the duration of action of Exparel® typically ranges from 72 to 96 h.[18–20] The medicinal product (Exparel, Pacira Ireland Limited) approved by the US Food and Drug Administration (FDA) in October 2011 is proposed as a single-dose administration directly into the surgical site, to obtain a prolonged postoperative analgesia (bunionectomy, hemorrhoidectomy, and interscalene nerve block).[21,22] In recent years, its off-label use has also been proposed for laparoscopic hysterectomy, femoral and intercostal nerve block, epidural injections, and knee, shoulder, and hip arthroplasties.[23–25] The two formulations (266 mg/20 ml or 133 mg/10 ml as a single vial) received marketing authorization from the European Medicines Agency (EMA) in 2020,[26] as a brachial plexus/femoral nerve block for the treatment of postoperative pain in adults and as a field block for the treatment of somatic postoperative pain from small- to medium- sized surgical wounds in adults.

It was reported that more than 6 million patients in the USA have been treated with bupivacaine liposomes since 2012, and the annual sales of Exparel® reached US$331 million in 2018.[27] The clinical use of this formulation has been shown to decrease the hospitalization time of patients, even though the actual overall reduction resulting from the use of Exparel with respect to other conventional drugs remains under investigation.[28–30]

Nanoemulsions

The clinical experience accumulated over ~40 years of the use of phospholipid stabilized nanoemulsions for parenteral nutrition has led them to be a template for the design of drugs administered via the intravenous (IV) route.[10,31,32]

From a formulation perspective, the selection of the surfactant is crucial for forming and stabilizing because nanoemulsions are thermodynamically unstable, but kinetically stable. Among the possible emulsifying agents accepted by regulatory agencies, egg or soy lecithin are typically used, whereas long-chain triglycerides (LCT) and medium-chain triglycerides (MCT) are first-choice excipients as the inner phase. Given that, within a few minutes after IV administration, nanoemulsions are cleared by lipoprotein lipase (LPL), which hydrolyzes triglycerides into FFAs, the phospholipid content, droplet size, lipid type, and infusion rate are among the factors determining the rate of plasma clearance.[33] Free phospholipids (not involved in the emulsification process) interfere with LPL activity; thus, 20% oil emulsions are cleared faster compared with those containing 10%, because they have proportionally fewer free phospholipids owing to a larger oil content. Moreover, a large total interfacial area, along with reduced droplet size, facilitates LPL activity, although droplets >250 nm are cleared faster, indicating greater involvement of the reticuloendothelial system (RES). In addition, MCTs are cleared more rapidly than LCT, because of more efficient LPL activity, and because their fatty acid metabolism is independent of the mitochondrial carnitine co-transporter.[10] The maximum clearance rate for injectable nanoemulsion is 3.8 g fat/kg/day. Beyond this rate, LPL becomes saturated and the infused triglycerides accumulate in the plasma, leading to major adverse effects, including impairment of RES/immune function (especially for LCT) and of pulmonary hemodynamics, hepatobiliary disorders (steatosis, cholestasis, and gallbladder sludge/stones), pancreatitis and fat-overload syndrome (fever, jaundice, irritability, and spontaneous hemorrhage).[33]

The most outstanding example of a nanoemulsion-based drug delivery system is propofol. In its pure form at room temperature, it is an oil, but it freezes at 19 °C. Given its chemistry, propofol cannot be administered as an aqueous salt because the only ionizable functional group (the hydroxyl group) has a pK_a of 11. The remaining portion of the molecule, the benzene ring and isopropyl side groups, is highly lipophilic. The result is a molecule with poor water miscibility (150 mg/l). Its high lipophilicity (logP = 4.16) means that good propofol miscibility can only be achieved in lipophilic substances or organic solvents.[34] In early human testing, propofol formulated as Cremophor EL micellar solution[35] presented several adverse effects because, apart from severe pain at the injection site, it caused a high incidence of anaphylaxis and peripheral neuropathy. Conversely, development of the propofol soybean oil nanoemulsion formulation (Diprivan®, AstraZeneca) exhibited greater potency, a smaller distribution volume, less first-pass lung sequestration, and decreased time to peak EEG effects.[36–38] Pain reduction following IV administration can be ascribed to the lipid sequestration of propofol from the aqueous phase, which minimizes distribution to vessel walls.[39]

Please cite this article in press as: L.S. Battaglia et al., Drug Discovery Today (2022), https://doi.org/10.1016/j.drudis.2022.07.006

In pain management, nanoemulsions are used for the repurposing of different substances, including anaesthetic,[40] analgesic, and anti-inflammatory agents.[41] Etomidate is a hypnotic agent used in general anesthesia that has a stable hemodynamic profile and causes minimal histamine release, even though pain on injection and myoclonus are the most common adverse effects. The nanoemulsion formulations (Etomidat-Lipuro®, BB Braun) abolish soreness at the injection site, venous irritation, and hemolysis.[42–44]

A similar problem of lipophilicity is presented by diazepam, a benzodiazepine used in preoperative settings for its sedative and muscle-relaxant properties. To avoid pain on injection and thrombophlebitis, an oil-in-water nanoemulsion (Diazemuls®, Pharmacia) can be used[45–47] or diazepam can be added to ready-prepared emulsions.[10]

Nanoemulsions might or might not have a significant impact on the distribution and elimination of loaded drugs, depending on their partitioning. Indeed, low drug lipophilicity (i.e., diazepam) causes a rapid release from the emulsion.[45] By contrast, very lipophilic drugs are subject to metabolism by the liver or RES, with a different tissue biodistribution profile.[10]

Besides proper drug repurposing, nanoemulsions have also been used for the delivery of conventional NSAIDs, but in the form of insoluble cleavable prodrug esters aiming to control nociceptive and inflammatory pain. This can be achieved through the inhibition of cyclo-oxygenase as well as, at least for some molecules of the class, of lipoxygenase and algogenic metabolites; thus, central mechanisms can enhance peripheral signaling.[48] As an example, flurbiprofen, practically insoluble in water, can be intravenously administered as a solution only by using sodium salt, but this formulation causes irritation at the injection site. Nanoemulsions loaded with a prodrug (i.e., flurbiprofen axetil, Lipo-NSAID - Ropion®, Kaken Pharmaceutical) can be administered for postoperative pain or in patients with cancer, without irritation and reaching higher drug concentrations in the bloodstream, with faster analgesic effects and fewer adverse gastrointestinal reactions, compared with conventional formulations.[49]

Similarly, the preparation of a nanoemulsion (Limethason®, GreenCross) using dexamethasone palmitate allows the reduction of drug dosages, with a consequently reduced risk of steroid-inherent adverse effects.[50] Indeed, subsequent to intra-articular injection, this prodrug is gradually hydrolyzed by esterases, exhibiting greater anti-inflammatory activity compared with conventional water-soluble dexamethasone phosphate, primarily because of a more specific distribution in the inflammatory lesion and greater uptake by macrophages.[51,52] This product is particularly useful to treat rheumatoid arthritis, a chronic, autoimmune rheumatic disease that evolves with inflammatory flares associated with inflammation of joint synovial membranes, progressive bone and cartilage destruction, and strong pain. Indeed, local corticosteroid delivery can reduce inflammation, immune cell response, and pain.[53]

Long-acting injectable formulations

In the case of parenteral administration, long-acting implantable or injectable dosage forms (LAIs) extend drug release over a suitable period of time to guarantee a therapeutically relevant concentration either in the bloodstream or locally in a specific tissue/organ (e.g., eye or intra-articular cavity) for days, weeks, or months. Many technologies have been proposed for controlling drug release, including crystal suspensions, emulsions, or implantable or injectable dosage forms, which can be based either on nonbiodegradable and biodegradable polymers or on *in situ* gelling systems.[54] To avoid tissue damage after the extraction procedure at the end of the release period or in the case of harmful events/adverse reactions, biodegradable polymers are generally used [e.g., poly(lactide-co-glycolide) (PLGA)] as they typically undergo complete degradation in biocompatible byproducts. Finally, a device required for injection and/or implantation should be optimized along with the implantation procedure.

Among the drugs that can be loaded into LAIs, glucocorticoids are one of the most successful examples. Indeed, the use of glucocorticoids, despite their long history as anti-inflammatory and immunosuppressive drugs, is limited to short-term treatments to relieve inflammation during flare-ups because of their severe side effects.[55] In this context, polymeric implants can take advantage of the specific physiopathology of inflamed tissues and the vascular-enhanced permeability effect to deliver encapsulated molecules to the target tissue through passive diffusion into the affected area. This means that the extended residence time of an implant in the inflamed tissues can improve the anti-inflammatory activity of the loaded drug, while reducing doses and, consequently, adverse effects.

Biodegradable implants

To maximize the efficacy of glucocorticoids while reducing their adverse effects, a local intra-articular injection has been shown to be a valuable approach for targeting synovial inflammation, a typical feature of osteoarthritis, a degenerative joint disease characterized by cartilage breakdown, fibrotic changes to the joint capsule, bony changes, and inflammation of the synovial membrane.[56] Triamcinolone acetonide is widely used for this purpose, although providing relatively short-lived analgesia.[57,58] To avoid the need for multiple injections, a PLGA formulation (Zilretta®, Pacira Bioscience) of triamcinolone acetonide was developed to favor the slow release of the drug into the synovium, prolonging efficacy to over 3 months.[59]

Zilretta® is formulated as microspheres of ~45 mm loaded with small crystals of triamcinolone acetate [nominal drug load of 25% (w/w)].[60] Size control is essential here to assure the compatibility and efficacy, because particles smaller than 6 μm are taken up by synovial macrophages.[61]

Drug release is controlled by nanochannels (500 nm), which permit the flow of fluids into the particle matrix, thus prolonging drug release and slowing PLGA erosion. This slow and homogeneous degradation is favored by the low glycolic acid content (75:25 molar ratio) and by the small sizes of the microspheres.[59] A pivotal Phase III trial showed that Zilretta® significantly reduced knee pain for a full 12 weeks, with some patients experiencing pain relief through week 16. A clinical trial is in progress (NCT04261049[62]) to assess the pre- and post-effects of a single knee injection on physiological measures of pain and disability, physical performance, and physical activity in individuals with

Please cite this article in press as: L.S. Battaglia et al., Drug Discovery Today (2022), https://doi.org/10.1016/j.drudis.2022.07.006

knee osteoarthritis. Thirty-five patients with symptoms were recruited and data were collected before injection (baseline), as well as at 4- (post 1) and 8-week follow-ups (post 2).

Commercial implants ('rods') are also available for the treatment of inflammation in ocular diseases, aiming to overcome ocular barriers and prolong the duration of drug effects. Ozurdex® (Allergan Pharmaceuticals) is an intravitreal rod-shaped implant containing dexamethasone, which is injected via a 22G applicator directly into the vitreous body to treat non-infectious uveitis. In this case, the polymeric matrix (NOVADUR®), comprising two grades of 50:50 PLGA differing in hydrophobicity, provides a gradual release of 700 mg dexamethasone at the target site over 6 months. The rod is obtained by a hot-melt extrusion process, an efficient and accurate method for controlling the consistency and diameter of the filament, which is suitable for placement inside a 22G hypodermic needle.[63,64] Treatment with Ozurdex® was shown to be more effective than sham treatment for reducing inflammation in patients with uveitis, as measured by vitreous haze scoring. In a study involving 229 adults with uveitis, 8 weeks after injection around 47% of patients treated with Ozurdex® (700 mg) achieved a vitreous haze score of zero compared with 36% of patients treated with Ozurdex® (350 mg) and 12% of patients who received the sham treatment.[65]

In situ-forming polymer implants typically comprise a drug, solvent, and biocompatible polymer that controls drug release. Upon injection, the solution forms a solid polymer matrix at the injection site, via phase separation triggered by co-solvent and tissue-for-fluid (non-solvent) exchange. Based on the use of DMSO and a low molecular mass tri(ethylene glycol) poly (orthoester) (Biochronomer™ technology[66]) delivers a fixed-dose combination of bupivacaine with a low dose of meloxicam to produce postsurgical analgesia for up to 72 h after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty (Zynrelef®, Heron Therapeutics). Similarly, Posimir® (Durect Corporation) utilizes bupivacaine impregnated in a viscous carrier to be used for postsurgical analgesia for up to 72 h following arthroscopic subacromial decompression, obtained after administration into the subacromial space under direct arthroscopic visualization. This formulation is based on a nonpolymeric scaffold (i.e., sucrose acetate isobutyrate) in ethanol and benzyl alcohol (SABER®). This material is an extremely hydrophobic viscous liquid that forms a low-viscosity fluid when dissolved in some types of organic solvent. If the solvent is water miscible, it would diffuse out upon contact with the aqueous biological fluids, leaving a highly viscous biodegradable matrix, which can act as a drug depot.[67]

Nonbiodegradable implants

To manage ocular diseases, sustained-release systems made of nonbiodegradable polymers have shown prolonged drug retention at the site of action. Retisert® (Bausch & Lomb) is an implant designed to release fluocinolone acetonide to the posterior segment of the eye. The nominal initial rate of 0.6 μg/day decreases over the first month to a steady state ranging between 0.3 and 0.4 μg/day, which is maintained for approximately 2.5 years. This implant comprises a tablet enclosed in a silicone elastomer cup containing a release orifice and a poly(vinyl alcohol) membrane positioned between the tablet and the orifice; it is indicated in the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.[68]

The Iluvien® implant (Alimera Sciences) is a nonbiodegradable cylindrical polymer tube that measures 3.5 mm in length and 0.37 mm in diameter. Fluocinolone acetonide is incorporated into a poly(vinyl alcohol) matrix within a polyimide tube, which has membrane caps on each end to allow the diffusion of water into the matrix. The drug diffuses through the tube, allowing a consistent and sustained release for up to 3 years.[68] It is a continuous Microdosing™ Delivery System, the device which provides the sustained delivery of 0.59 mg poly(vinyl alcohol) and enables physicians to treat diabetic macular edema (DME) in an effective and consistent manner.[69,70]

Nanocrystal suspensions

Nanocrystal suspensions with sustained release characteristics and suitable administration volumes have been developed to both reduce administration times and improve patient compliance. Indeed, the injection of a steroid decreases inflammation and provides pain relief at a later stage. In clinical application, several types of commercial nanocrystal suspension are available for the treatment of ocular diseases, including Betason L.A® (Caspian Tamin Pharmaceutical Co.; betamethasone acetate), Depo-Medrol/Lidocaine® (Pfizer; methylprednisolone, lidocaine hydrochloride) and Kenalog® (Bristol-Myers Squibb; triamcinolone acetonide).

Betason L.A® is supplied as a dual-acting formulation containing both betamethasone acetate and betamethasone (as disodium phosphate). It has multiple indications for use, such as inflammatory or allergic reactions and rheumatic disorders, and as a palliative treatment for neoplastic disease. Depending on the indications, Betason L.A® is administered via intramuscular, intra-articular, intrabursal, or intradermal injections. In a PK study in healthy human volunteers, Salem *et al.* demonstrated the controlled-release capabilities of this dual-acting suspension upon intramuscular injection.[71] The PK profiles showed that the soluble betamethasone (phosphate ester) had a faster release to achieve a prompter onset of activity and that the prodrug nature of hydrophobic betamethasone (acetate ester) is responsible for the extended-release characteristics of the formulation. A double-blind trial using a betamethasone phosphate/betamethasone acetate suspension for intra-articular injections showed an average duration of ~14 days for pain relief in patients with rheumatoid inflammation.[72]

Depo-Medrol/Lidocaine® is an injectable suspension containing methyl prednisolone acetate combined with lidocaine hydrochloride. It is used to treat inflammatory or rheumatic conditions requiring local glucocorticoid effects. It can be injected weekly via intra/periarticular or intrabursal routes or else directly into the tendon sheath, according to necessity. It is formulated for localized anti-inflammatory or antirheumatic pain management, although, following its intra-articular injection, several cases of anaphylaxis have been reported.[73] In these cases, the allergic reaction could have been caused by sensitivity to the drug itself or the excipients it contains, such as carboxymethylcellulose or, less probably, to the polyethylene glycol.[74] Further investigations are required to understand the origin of such aller-

Please cite this article in press as: L.S. Battaglia et al., Drug Discovery Today (2022), https://doi.org/10.1016/j.drudis.2022.07.006

gic reactions and to guarantee the safe use of Depo-Medrol/Lidocaine®.

Kenalog™ is a microcrystal formulation of the poorly water-soluble triamcinolone acetonide. The latter is a chemical derivative of triamcinolone, the two hydroxyl groups of which are cross-linked by a molecular equivalent of acetone, such as a ketal.[75] This covalent modification renders triamcinolone acetonide more lipophilic and less water soluble compared with triamcinolone (0.043 versus 0.847 mg/ml, respectively). This micronized suspension exhibits an extended duration of pharmacological action. The administration of Kenalog™ was accompanied by retinal toxicity after 14 days, but some studies have demonstrated that this toxicity could be in response to one of its excipients, probably benzyl alcohol.[76,77]

Oil-based formulation

Naldebain® (Taiwanese) is an oil-based formulation containing dinalbuphine sebacate. Dinalbuphine sebacate is a prodrug of nalbuphine, which is a mixed opioid antagonist–agonist, and has a ceiling effect in terms of respiratory depression and a potentially lower risk for addiction and abuse compared with full opioid agonists. The single-dose regimen is administered before surgery and the extended duration of action (i.e., several days) provides an advantage over the need for continuous postsurgical administration of a short-acting opioid. Following injection, dinalbuphine sebacate (pro-drug) is converted into the active moiety, nalbiphine. Naldebain® is available as an injection containing 75 mg/ml of dinalbuphine sebacate and benzyl benzoate dissolved in sesame oil.[78,79]

The clinical efficacy of dinalbuphine sebacate intended for treating acute postsurgical pain was based on a pivotal Phase III study, SDE-2–001. This was a randomized, double-blind, placebo-controlled study aiming to assess the safety and efficacy of a single-dose intramuscular injection of dinalbuphine sebacate for post-hemorrhoidectomy pain management. The primary efficacy variable considered was pain assessment (time-specific pain intensity), which was calculated as the area under the curve (AUC) of the visual analog scale (VAS) pain intensity scores, for 48 h after surgery. The $AUC_{0–48}$ (mean VAS scores of pain intensity) for the dinalbuphine sebacate group showed statistically significant superiority compared with the placebo group in both the modified intent-to-treat (209.93 ± 111.26 versus 253.53 ± 108.49; $P = 0.0052$) and the per-protocol (207.46 ± 112.41 versus 254.9 1 ± 106.17; $P = 0.0039$) populations.[75,80]

High-level assessment of the scale-up and manufacturing processes

According to current pharmaceutical guidelines,[81] any pharmaceutical process should be designed to be capable of reproducible performance. This means that, based on scientific data and experimental studies, each manufacturer should demonstrate that a medicinal product is routinely reproducible with the same level of quality, efficacy, and safety for the patient. This puts a strong focus on the understanding, control, and optimization of the critical manufacturing process parameters (CPPs) during the preliminary phase of development of a new drug and/or formulation. These are defined as process parameters the variability

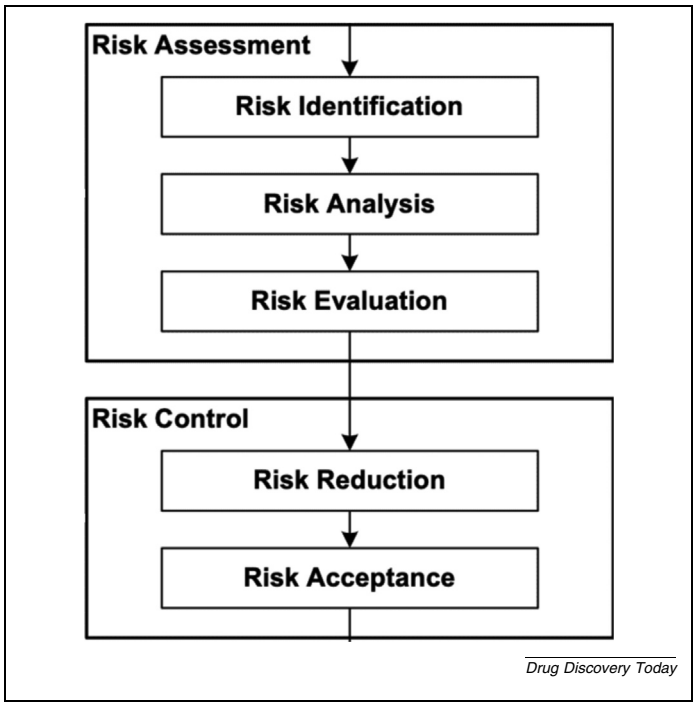

FIGURE 2
Risk assessment flow chart.

of which have an impact on a critical quality attribute (CQA)[81,82] of the product and, therefore, should be monitored or controlled to ensure that the process produces the expected results. Moreover, in line with current regulations, process understanding, and challenges, they must be viewed and treated as a continuous entity, starting in the development laboratory but continuing throughout the life-cycle of the medicine and being a conspicuous part of the registration and industrialization processes. Guidelines and Best Practices documents[82] offer advice and tools for how to put this approach into place, indicating how critical process parameters can be investigated, quantified, and assessed during the scale-up phase and consolidated during the commercial supply process. This focus becomes even more important when the manufacturer must use a complex environment, such as one of those described in this review, suitable for reproposing.

The approach is described in the following steps (Fig. 2): the first stage is the definition of the CPPs, starting from a clear

TABLE 1

Example of process steps and related parameters identified during the first step of the risk assessment.

Process step	Parameter
Compounding	Excipient mixing time
	Excipient mixing speed
	Holding time
	Transfer pressure
	Transfer time
Filtration	Differential filtration pressure
	Filtration time
	Filtration contact time

Please cite this article in press as: L.S. Battaglia et al., Drug Discovery Today (2022), https://doi.org/10.1016/j.drudis.2022.07.006

TABLE 2

Example of FMECA application during the second step of the risk assessment.

Process step	Parameter	Impacted CQAs	Failure mode
Compounding	Excipient mixing time	Compounded solution pH Osmolarity Viscosity Assay Impurity profile	Incorrect mixing parameters could lead to incomplete dissolution of excipients. Their concentrations in the solution will change, impacting chemical characteristics of micro-environment. Moreover, in case of stabilizing excipients, their lower concentration will negatively impact impurity profile of API
Filtration	Filtration differential pressure	Filtered solution sterility Particle size distribution Assay Impurity profile	Differential pressure higher than operative range can create shear stress on API, leading to degradation; moreover, aggregation can occur because of increased pressure
Filtration	Filtration contact time	Filtered solution Assay Impurity profile	Prolonged contact time with components of filtration medium can increase extractable levels. Those foreign chemical entities can then react with excipients or APIs, generating leachables

TABLE 3

Example of the severity, probability, and detection scales used for the third step of the risk assessment.

Scale	Risk classification	Associated value
Severity		
No impact on quality attribute of product on patient health	Negligible	1
Moderate impact on quality attribute of product on patient health	Moderate	2
High impact on quality attribute of product on patient health	Critical	3
Probability		
Highly improbable that negative event will happen	Negligible	1
Some possibility that negative event will happen	Moderate	2
Very high probability that negative event will happen	Critical	3
Detection		
Highly probable or certain that negative event will be detected by control system in place	Negligible	1
Some possibility that negative event will be detected by control system in place	Moderate	2
Highly improbable that negative event will be detected by control system in place	Critical	3

TABLE 4

Example of a Risk Priority Number Grid used during the fourth step of the risk assessment.

RNP	Risk definition	Action needed
RNP > 12	Very high risk	Challenge parameter during development with QbD or comparable scientifically sound approach
3 < RNP < 12	Moderate risk	Appropriate justification or modeling studies are needed before moving to scale-up, clinical/registration, or commercial process phase
RNP < 3	Low risk	Further parameter investigation is not considered necessary because it holds constant during scale-up, clinical/registration or commercial process phase

understanding of the chemistry of the API together with the formulation. As soon as the CPPs have been defined, the second stage is the analysis of how they can affect the CQAs, posing a risk for the efficiency, safety, and quality profile of the product. The third stage is the quantification of those risks, which then makes possible the fourth step, during which mitigating actions with appropriate levels of commitment, and priorities are defined and executed.

With the aim of offering a concrete example of this risk management approach, these four steps are further illustrated here below, together with examples of their application.

First stage: through a deep technical review of the process flowchart carried out by a pool of experts belonging to several different sectors (i.e., R&D, quality, engineering, production, and analytic), each process unit operation and equipment train parameter is listed and characterized based on normal operating parameters (NORs), process acceptance ranges (PARs), and edge of failure (EOF) (Table 1).

Second stage: via a Failure Mode, Effects and Criticality Analysis (FMECA) or similar tool [80], an assessment of risk of impact on CQA, based on experimental data, scientific literature, or the team (Table 2) carries out documented evidence coming from similar manufacturing processes.

Please cite this article in press as: L.S. Battaglia et al., Drug Discovery Today (2022), https://doi.org/10.1016/j.drudis.2022.07.006

TABLE 5

Example of mitigation action plan identified to reduce risks.[a]

Process step	Parameter	CQAs impacted	Failure mode	S	P	D	RPN	Mitigating action
Compounding	Excipient mixing time	Compounded solution pH, osmolarity, viscosity assay, impurity profile	Incorrect mixing parameters could lead to incomplete dissolution of excipients. Their concentrations in the solution will not be uniform, impacting chemical characteristics of the environment. Moreover, in the of stabilizing excipients, zones of lower concentration will negatively impact impurity profile of APIs	3	2	2	12	Mixing challenges carried out during development and scale-up setting appropriate equipment operative range. Classification performance should be successfully completed before moving to GMP manufacturing
Filtration	Filtration differential pressure	Filtered solution sterility, particle size distribution assay, impurity profile	Differential pressure higher than that of operative range can create shear stress on API molecules, leading to degradation phenomena and aggregation	3	3	3	27	Filter validation and filter challenge during development phase with selected filtration media and effective filtration area (EFA)

[a] Abbreviations: D, detection; P, probability; RPN, Risk Priority Number; S, severity.
[b] Yellow shading: moderate RPN; red shading critical RPN.

Third step: each identified risk is then quantified (Table 3) based on severity, probability, and detection. Severity (S) of the risk considers the potential impact on a patient's health; Probability (P) is defined as the frequency of occurrence of the event considering the experience acquired during the process development; and Detection (D) is the probability of detecting the events if they occur, based on the control system in place.

Fourth step: the severity, probability, and detection of each risk are mathematically combined to calculate the Risk Priority Number (RPN) and are prioritized using an appropriate matrix grid. Scientifically sound (TR-65 PDA[83]) mitigation actions are then taken for risk mitigation (Tables 4 and 5).

The current approach shows how to properly set the basis of a sound, reproducible manufacturing process, which guarantees the quality, safety, and efficacy of a medicine. Regular application of this approach during the product life-cycle also offers an excellent tool for change management, identifying optimization or additional controls to be implemented to increase the robustness of the supply chain, as laid down by current regulations.

Concluding remarks

A search through the available literature shows that drug delivery technology is a suitable tool for repurposing active substances currently in clinical use and administered by parenteral routes for treating pain, both systemic and local. The various cited examples that can be found on the market relate to different drug delivery systems, such as micro- and nanosystems (i.e., liposomes and nanoemulsions), together with long-acting formulations, such as biodegradable and nonbiodegradable polymer implants, *in situ*-forming implants, and oil-based solutions. The common advantage of all these types of drug delivery system is better patient compliance, this being a major driving force behind their design.

Nanoemulsions have been shown to be extremely advantageous in overcoming drawbacks arising from drug substance properties, such as in the propofol formulation. LAI, such as crystal suspensions, implantable or injectable dosage forms, based either on biodegradable or nonbiodegradable polymers or *in situ*-gelling systems, allow the reduction of the dosing frequency, decrease adverse effects, and maintain stable plasmatic concentrations.

Moreover, some drug delivery systems, such as polymeric implants, can take advantage of the specific physiopathology of inflamed tissues and of the enhanced vascular permeability effect to address encapsulated molecules to the target site.

As highlighted in this review, the aim of repurposing active substances that are already in use can be both economic and time saving, even to the point of allowing the exploitation of abridged registration procedures. However, repurposing a formulation study using drug delivery systems faces the challenge of developing a scalable and reproducible manufacturing process. This must be developed according to current pharmaceutical guidelines and on a risk-assessment basis, which must be followed starting from the first product design steps. The main challenges are the multiple and complex steps involved in a manufacturing process, and the concerns arising from materials such as polymers and solvents involved in the formulation.

In a future innovation regarding manufacturing processes, it could be advantageous to overcome certain manufacturing-step challenges, such as lyophilization and sterilization processes.

Acknowledgments

The authors are grateful to Lynn Whitted for her language revision of this article.

Declaration of interest

None declared by authors.

Please cite this article in press as: L.S. Battaglia et al., Drug Discovery Today (2022), https://doi.org/10.1016/j.drudis.2022.07.006

References

[1] C.J. Woolf, Central sensitization: implications for the diagnosis and treatment of pain, Pain 152 (3 Suppl) (2011) S2–S15.
[2] C.J. Woolf, M.B. Max, Mechanism-based pain diagnosis: issues for analgesic drug development, Anesthesiology 95 (2001) 241–249.
[3] M.A. Fitzcharles, S.P. Cohen, D.J. Clauw, G. Littlejohn, C. Usui, W. Häuser, Nociplastic pain: towards an understanding of prevalent pain conditions, Lancet 397 (2021) 2098–2110.
[4] F. Brennan, D. Lohman, L. Gwyther, Access to pain management as a human right, Am J Public Health 109 (2019) 61–65.
[5] P. Maudens, O. Jordan, E. Allémann, Recent advances in intra-articular drug delivery systems for osteoarthritis therapy, Drug Discov Today 23 (2018) 1761–1775.
[6] J.A. DiMasi, L. Feldman, A. Seckler, A. Wilson, Trends in risks associated with new drug development: success rates for investigational drugs, Clin Pharmacol Ther 87 (2010) 272–277.
[7] P. Minghetti, U.M. Musazzi, A. Casiraghi, P. Rocco, Old active ingredients in new medicinal products: is the regulatory path coherent with patients' expectations?, Drug Discov Today 25 (2020) 1337–1347.
[8] R. Araki, T. Matsuzaki, A. Nakamura, D. Nakatani, S. Sanada, H.Y. Fu, et al., Development of a novel one-step production system for injectable liposomes under GMP, Pharm Dev Technol 23 (2018) 602–607.
[9] A. Wagner, K. Vorauer-Uhl, Liposome technology for industrial purposes, J Drug Deliv 2011 (2011) 591325.
[10] K. Hippalgaonkar, S. Majumdar, V. Kansara, Injectable lipid emulsions—advancements, opportunities and challenges, AAPS PharmSciTech 11 (2010) 1526–1540.
[11] C. Ghelardini, M.L. Di Cesare, E. Bianchi, The pharmacological basis of opioids, Clin Cases Miner Bone Metabol 12 (2015) 219–221.
[12] N. Youssef, D. Orlov, T. Alie, M. Chong, J. Cheng, L. Thabane, et al., What epidural opioid results in the best analgesia outcomes and fewest side effects after surgery? A meta-analysis of randomized controlled trials, Anesth Analg 119 (2014) 965–977.
[13] M. Vercauteren, K. Vereecken, M. La Malfa, H. Coppejans, H. Adriaensen, Cost-effectiveness of analgesia after Caesarean section. A comparison of intrathecal morphine and epidural PCA, Acta Anaesthesiol Scand 46 (2002) 85–89.
[14] D. Gambling, T. Hughes, G. Martin, W. Horton, G. Manvelian, for the Single-Dose ESG. A comparison of Depodur™, a novel, single-dose extended-release epidural morphine, with standard epidural morphine for pain relief after lower abdominal surgery, Anesth Analg 100 (2005) 1065–1074.
[15] D.E. Large, R.G. Abdelmessih, E.A. Fink, D.T. Auguste, Liposome composition in drug delivery design, synthesis, characterization, and clinical application, Adv Drug Deliv Rev 176 (2021) 113851.
[16] S. Mantripragada, A lipid based depot (DepoFoam® technology) for sustained release drug delivery, Prog Lipid Res 41 (2002) 392–406.
[17] R.R. Ji, C.J. Woolf, Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain, Neurobiol Disase 8 (2001) 1–10.
[18] J. Portillo, N. Kamar, S. Melibary, E. Quevedo, S. Bergese, Safety of liposome extended-release bupivacaine for postoperative pain control, Front Pharmacol 5 (2014) 90.
[19] Y.C.I. Tong, A.D. Kaye, R.D. Urman, Liposomal bupivacaine and clinical outcomes, Best Pract Res Clin Anaesthesiol 28 (2014) 15–27.
[20] B.M. Ilfeld, J.C. Eisenach, R.A. Gabriel, Clinical effectiveness of liposomal bupivacaine administered by infiltration or peripheral nerve block to treat postoperative pain: a narrative review, Anesthesiology 134 (2021) 283–344.
[21] A.D. Kaye, C. Armstead-Williams, F. Hyatali, K.S. Cox, R.J. Kaye, L.K. Eng, et al., Exparel for postoperative pain management: a comprehensive review, Curr Pain Headache Rep 24 (2020) 73.
[22] S.L. Orebaugh, A. Dewasurendra, Has the future arrived? Liposomal bupivacaine versus perineural catheters and additives for interscalene brachial plexus block, Curr Opin Anesthesiol 33 (2020) 704–709.
[23] J.L. Hutchins, R. Kesha, F. Blanco, T. Dunn, R. Hochhalter, Ultrasound guided subcostal transversus abdominis plane (TAP) infiltration with liposomal bupivacaine for patients undergoing robotic assisted hysterectomy: a prospective randomized controlled study, Gynecol Oncol 138 (2015) 609–613.
[24] C.V. Asche, S. Dagenais, A. Kang, J. Ren, B.T. Maurer, Impact of liposomal bupivacaine on opioid use, hospital length of stay, discharge status, and hospitalization costs in patients undergoing total hip arthroplasty, J Med Econ 22 (2019) 1253–1260.
[25] B.C. Jacob, S.K. Peasah, A.O. Shogbon, E.R. Perlow, Postoperative pain management with liposomal bupivacaine in patients undergoing orthopedic knee and hip arthroplasty at a community hospital, Hosp Pharm 52 (2017) 367–373.
[26] Exparel EPAR - Product information https://www.ema.europa.eu/en/documents/product-information/exparel-liposomal-epar-product-information_en.pdf.
[27] B. Lu, Q. Ma, J. Zhang, R. Liu, Z. Yue, C. Xu, et al., Preparation and characterization of bupivacaine multivesicular liposome: a QbD study about the effects of formulation and process on critical quality attributes, Int J Pharm 598 (2021) 120335.
[28] J.J. Cherian, A. Muzaffar, J.W. Barrington, R.D. Elmallah, M. Chughtai, J.B. Mistry, et al., Liposomal bupivacaine in total knee arthroplasty for better postoperative analgesic outcome and economic benefits, J Knee Surg 29 (2016) 180–187.
[29] H.-C. Dinges, T. Wiesmann, B. Otremba, H. Wulf, L.H. Eberhart, A.-K. Schubert, The analgesic efficacy of liposomal bupivacaine compared with bupivacaine hydrochloride for the prevention of postoperative pain: a systematic review and meta-analysis with trial sequential analysis, Reg Anesthesia Pain Med 46 (2021) 490–498.
[30] Y.D. Ji, J.A. Harris, L.E. Gibson, S.K. McKinley, R. Phitayakorn, The efficacy of liposomal bupivacaine for opioid and pain reduction: a systematic review of randomized clinical trials, J Surg Res 264 (2021) 510–533.
[31] J. Fast, S. Mecozzi, Nanoemulsions for intravenous drug delivery, in: M. Mozafari (Ed.), Nanoengineered biomaterials for advanced drug delivery, Amsterdam; Elsevier, 2009, pp. 461–489.
[32] M. Stawny, R. Olijarczyk, E. Jaroszkiewicz, A. Jelińska, Pharmaceutical point of view on parenteral nutrition, Sci World J 2013 (2013) 415310.
[33] J.M. Mirtallo, J.F. Dasta, K.C. Kleinschmidt, J. Varon, State of the art review: intravenous fat emulsions: current applications, safety profile, and clinical implications, Ann Pharmacother 44 (2010) 688–700.
[34] M.T. Baker, M. Naguib, Propofol: the challenges of formulation, Anesthesiology 103 (2005) 860–876.
[35] S. Dutta, Y. Matsumoto, W.F. Ebling, Propofol pharmacokinetics and pharmacodynamics assessed from a cremophor EL formulation, J Pharm Sci 86 (1997) 967–969.
[36] L.P. Briggs, R.S. Clarke, J. Watkins, An adverse reaction to the administration of disoprofol (Diprivan), Anaesthesia 37 (1982) 1099–1101.
[37] J.B. Glen, S.C. Hunter, Pharmacology of an emulsion formulation of ICI 35 868, Br J Anaesth 56 (1984) 617–626.
[38] D.V. Rutter, M. Morgan, J. Lumley, R. Owen, ICI 35868 (Diprivan): a new intravenous induction agent, Anaesthesia 35 (1980) 1188–1192.
[39] M. Buys, P.A. Scheepers, A.I. Levin, Lipid emulsion therapy: non-nutritive uses of lipid emulsions in anaesthesia and intensive care, South Afric J Anaesth Analg 21 (2015) 124–130.
[40] S. Benita, Submicron Emulsions in Drug Targeting and Delivery, CRC Press, 1998.
[41] C.H. Tan, M.K. Onsiong, Pain on injection of propofol, Anaesthesia 53 (1998) 468–476.
[42] M. Mayer, A. Doenicke, A.E. Nebauer, L. Hepting, Propofol und Etomidat®Lipuro zur Einleitung einer Allgemeinanästhesie, Der Anaesthesist 45 (1996) 1082–1084.
[43] P. Altmayer, U. Grundmann, M. Ziehmer, R. Larsen, Comparative effectiveness and tolerance study of a new galenic etomidate formula, Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie 28 (1993) 415–419.
[44] B. Vanacker, A. Wiebalck, H. Van Aken, L. Sermeus, R. Bouillon, A. Amery, Quality of induction and adrenocortical function. A clinical comparison of Etomidate-Lipuro and Hypnomidate, Anaesthesist 42 (1993) 81–89.
[45] O. Von Dardel, C. Mebius, T. Mossberg, B. Svensson, Fat emulsion as a vechicle for diazepam. A study of 9492 patients, Br J Anaesth 55 (1983) 41–47.
[46] D. Selander, I. Curelaru, T. Stekansson, Local discomfort and thrombophlebitis following intravenous injection of diazepam, Acta Anaesthesiol Scand 25 (1981) 516–518.
[47] M.A.K. Mattila, M.L. Rossi, M.K. Ruoppi, M. Korhonen, H.M. Larni, S. Kortelainen, Reduction of venous sequelae of i.v. diazepam with a fat emulsion as solvent, Br J Anaesth 53 (1981) 1265–1268.
[48] J.N. Cashman, The mechanisms of action of NSAIDs in analgesia, Drugs 52 (Suppl. 5) (1996) 13–23.
[49] O. Ohmukai, Lipo-NSAID preparation, Adv Drug Deliv Rev 20 (1996) 203–207.

Please cite this article in press as: L.S. Battaglia et al., Drug Discovery Today (2022), https://doi.org/10.1016/j.drudis.2022.07.006

[50] A.D. Sezer (Ed.), Application of nanotechnology in drug delivery, IntechOpen, London, 2014.
[51] K. Yokoyama, H. Okamoto, M. Watanabe, T. Suyama, Y. Mizushima, Development of a corticosteroid incorporated in lipid microspheres (liposteroid), Drugs Exp Clin Res 11 (9) (1985) 611–620.
[52] K. Yokoyama, M. Watanabe, Limethason as a lipid microsphere preparation: an overview, Adv Drug Deliv Rev 20 (1996) 195–201.
[53] L.D. Kumar, R. Karthik, N. Gayathri, T. Sivasudha, Advancement in contemporary diagnostic and therapeutic approaches for rheumatoid arthritis, Biomed Pharmacother 79 (2016) 52–61.
[54] F. Selmin, U.M. Musazzi, G. Magri, P. Rocco, F. Cilurzo, P. Minghetti, Regulatory aspects and quality controls of polymer-based parenteral long-acting drug products: the challenge of approving copies, Drug Discov Today 25 (2020) 321–329.
[55] J.F. Ferreira, A.A. Ahmed Mohamed, P. Emery, Glucocorticoids and rheumatoid arthritis, Rheum Dis Clin N A 42 (2016) 33–46.
[56] J. Samuels, S. Krasnokutsky, S.B. Abramson, Osteoarthritis: a tale of three tissues, Bullet NYU Hosp Joint Dis 66 (2008) 244–250.
[57] A. Kumar, V. Dhir, S. Sharma, A. Sharma, S. Singh, Efficacy of methylprednisolone acetate versus triamcinolone acetonide intra-articular knee injection in patients with chronic inflammatory arthritis: a 24-week randomized controlled trial, Clin Ther 39 (2017) 150–158.
[58] N. Bellamy, J. Campbell, V. Welch, T.L. Gee, R. Bourne, G.A. Wells, Intraarticular corticosteroid for treatment of osteoarthritis of the knee, Cochrane Database Syst Rev 2006 (2006) CD005328.
[59] J. Paik, S.T. Duggan, S.J. Keam, Triamcinolone acetonide extended-release: a review in osteoarthritis pain of the knee, Drugs 79 (2019) 455–462.
[60] G. Spenlehauer, M. Vert, J.P. Benoit, A. Boddaert, *In vitro* and *In vivo* degradation of poly(D, L lactide/glycolide) type microspheres made by solvent evaporation method, Biomaterials 10 (1989) 557–563.
[61] N. Gerwin, C. Hops, A. Lucke, Intraarticular drug delivery in osteoarthritis, Adv Drug Deliv Rev 58 (2006) 226–242.
[62] https://clinicaltrials.gov/ct2/show/NCT04261049.
[63] N. Haghjou, M. Soheilian, M.J. Abdekhodaie, Sustained release intraocular drug delivery devices for treatment of uveitis, J Ophthal Vis Res 6 (2011) 317–329.
[64] C.A. Arcinue, O.M. Cerón, C.S. Foster, A comparison between the fluocinolone acetonide (Retisert) and dexamethasone (Ozurdex) intravitreal implants in uveitis, J Ocul Pharmacol Ther 29 (2013) 501–507.
[65] Effect of Zilretta Injection https://clinicaltrials.gov/ct2/show/NCT04261049.
[66] J. Heller, J. Barr, Biochronomer™ technology, Exp Opin Drug Deliv 2 (2005) 169–183.
[67] A. Tipton, Sucrose acetate isobutyrate (SAIB) for parenteral delivery, Modified-release drug delivery technologyCRC Press, Boca Raton, 2002, pp. 1–10.
[68] G. Soubrane, F. Behar-Cohen, Fluocinolone acetonide (ILUVIEN®) micro-implant for chronic diabetic macular edema, J Français d'Ophtal 38 (2015) 159–167.
[69] Y.Y. Syed, Fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien®): a review in diabetic macular edema, Drugs 77 (2017) 575–583.
[70] I.I. Salem, N.M. Najib, Pharmacokinetics of betamethasone after single-dose intramuscular administration of betamethasone phosphate and betamethasone acetate to healthy subjects, Clin Ther 34 (2012) 214–220.
[71] G. Husby, E. Kåss, K.-L. Spongsveen, Comparative double-blind trial of intra-articular injections of two long-acting forms of betamethasone, Scand J Rheumatol 4 (1975) 118–120.
[72] A. Borderé, A. Stockman, B. Boone, A.S. Franki, M.J. Coppens, H. Lapeere, et al., A case of anaphylaxis caused by macrogol 3350 after injection of a corticosteroid, Contact Dermatitis 67 (2012) 376–378.
[73] D.E. Moran, M.R. Moynagh, M. Alzanki, V.O. Chan, S.J. Eustace, Anaphylaxis at image-guided epidural pain block secondary to corticosteroid compound, Skeletal Radiol 41 (2012) 1317–1318.
[74] C.I. Nkanga, A. Fisch, M. Rad-Malekshahi, M.D. Romic, B. Kittel, T. Ullrich, et al., Clinically established biodegradable long acting injectables: an industry perspective, Adv Drug Deliv Rev 167 (2020) 19–46.
[75] Y. Lang, E. Zemel, B. Miller, I.D.O. Perlman, Retinal toxicity of intravitreal Kenalog in albino rabbits, Retina 27 (2007) 778–788.
[76] A.H. Fong, C.K. Chan, Presumed sterile endophthalmitis afer intravitreal triamcinolone (Kenalog)-more common and less benign than we thought?, Asia-Pacific J Ophthal 6 (2017) 45–49.
[77] C.-J. Li, M.-Y. Ku, C.-Y. Lu, Y.-E. Tien, W.H. Chern, J.-D. Huang, *In vitro* and *in vivo* release of dinalbuphine sebacate extended release formulation: effect of the oil ratio on drug release, Int J Pharm 531 (2017) 306–312.
[78] Y.E. Tien, W.C. Huang, H.Y. Kuo, L. Tai, Y.S. Uang, W.H. Chern, et al., Pharmacokinetics of dinalbuphine sebacate and nalbuphine in human after intramuscular injection of dinalbuphine sebacate in an extended-release formulation, Biopharm Drug Dispos 38 (2017) 494–497.
[79] C.Y. Yeh, S.W. Jao, J.S. Chen, C.W. Fan, H.H. Chen, P.S. Hsieh, et al., Sebacoyl dinalbuphine ester extended-release injection for long-acting analgesia: a multicenter, randomized, double-blind, and placebo-controlled study in hemorrhoidectomy patients, Clin J Pain 33 (2017) 429–434.
[80] International Council for Harmonization, Guideline Q8(R2) on Pharmaceutical Development, EMA, Amsterdam, 2009.
[81] International Council for Harmonization, Guideline Q9 on quality risk management, EMA, Amsterdam, 2006.
[82] D.R.K. Westphalen, J. Brodrick, Guidance for industry – process validation: general principles and practices, Silver Spring, FDA, 2011.
[83] PDA Technical Report No. 65 Revised 2022 (TR 65) Technology Transfer. ISBN Number: 9781945584336.

Please cite this article in press as: L.S. Battaglia et al., Drug Discovery Today (2022), https://doi.org/10.1016/j.drudis.2022.07.006