Reproposing of Active Substances Currently Used to Treat Pain both Systemically and Locally and Administered by Parenteral Routes

Teaser

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

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Abstract

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

Keywords

Abridged application, Complex drug delivery system, extended profiling, formulation, market exclusivity, injection, risk assessment.

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 rises from burns or cuts, bee stings, dental work, labor and childbirth, broken bones or surgery. On the other hand, '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 psycho-physical findings related to altered nociceptive functions, in an attempt to join all the aforementioned conditions [3].

As a matter of fact, 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 World Health Organization [4].

Painful and/or inflammatory conditions can be treated with a large number of active pharmaceutical ingredients (APIs) belonging to different classes, including opioid analgesics, non-steroidal 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, while 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 side effects [5]. But the success of these different approaches is often limited either by the physico-chemical characteristics of the drug substance itself or its adsorption-distribution-metabolism-excretion (ADME) mechanisms.

In order to overcome these issues, the development of a medicinal product containing a substance never before 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 expenditures can be ascribed to the translation of a medicinal product from preclinical to clinical studies, necessary for demonstrating its efficacy and safety according to the current regulatory framework. Hence, approaches that make use of drug candidates having known safety profiles (drug repurposing) can effectively avoid utterly time-consuming, laborious, high-risk and costly processes. Typically, 'old' drug substances could be sourced from medicinal products (a) approved by regulatory agencies; (b) undergoing clinical development for a different application; or (c) those having been abandoned or having failed to demonstrate efficacy during clinical trials (phase II or III). In order to accomplish successful drug repositioning, both maximizing drug interaction at the target site and mitigating or eliminating off-target effects are mandatory. A suitable strategy should involve the *in vivo*

optimization of the drug release profile of a substance in order to achieve the desired bioavailability. 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 physico-chemical modifications all of which can address the therapeutic necessities. The development of a new drug product starting from an old 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, this review discusses how this idea has been successfully applied to design parenteral drug delivery systems for pain management in different settings (**Figure 1**). Cases of micro- and nanosystems (i.e., liposomes and nanoemulsions) currently available on the market are reviewed to point out the role of drug delivery systems in reducing side effects, optimizing pharmacokinetics (PK) or improving patient compliance.

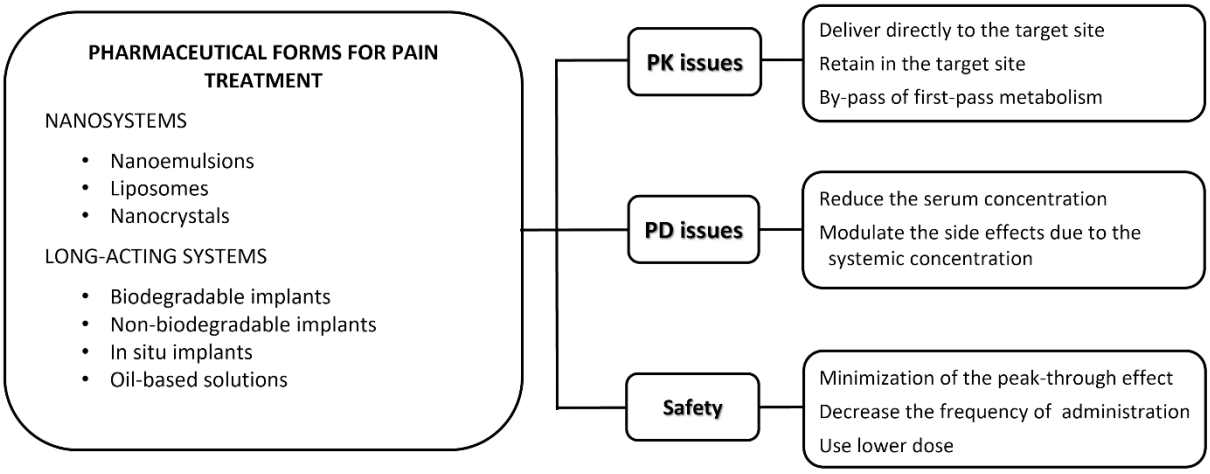

Figure 1 – Possible relationship between formulations and pharmacokinetic (PK) and/or pharmacodynamic (PD) properties influencing efficacy and safety of repurposed drugs in pain therapy.

Nanosystems: challenges in production

Nanosystems are possibilities for optmizing a variety of novel therapeutic and diagnostic uses owing to their specific therapeutic benefits and versatility of application. Indeed, they are capable of encapsulating small drugs well as macromolecules, protecting them from chemical degradation, increasing the *in vivo* half-life, enhancing the drug payload and providing controlled release and targeted delivery, among other things. Two

main classes of nanosystems are approved in pain management, namely nanoemulsions and liposomes, thanks to their therapeutic benefits and optimal safety profiles. Indeed, this is the key point which determines whether clinical translation and commercialization will be successful or not.

The major factors contributing to the clinical failure of nanomedicines are related to challenges in cost-effective manufacturing and scale-up, appropriate regulatory guidelines regarding benefit/risk balance assessment, validated characterization methods, the instability of nanosystems and the poor understanding of disease heterogeneity in patients. Of course, the first challenge is that of developing a scalable and reproducible manufacturing process which generally involves multiple and complex steps. In the laboratory, the optimization and reproducibility of these steps (e.g., homogenization, centrifugation, extrusion, sterilization, lyophilization, etc.) can be accomplished relatively easily but on a large scale it can prove to be much more difficult. Considering that these products are intended for use by way of the parenteral route, a careful selection of materials, solvents, manufacturing methods, cost-effectiveness and clinical acceptability of the finished product is important from the point of view of patient safety.

Moreover, the sterility assurance level (SAL) has to be guaranteed, but the sterilization process can pose challenges to the stability of nanomedicines. For instance in the case of phospholipids, terminal steam sterilization raises the free fatty acid (FFA) content because it trips their degradation, and since excess FFA content can cause serious adverse effects the USP limits their level (≤0.07 mEq/g oil). So in the presence of heat-labile components, sterile filtration based on the use of 0.22 μm bacteria-free membranes could be used but only for nanocarriers sizing below the nominal porosity of the filters. Alternatively, aseptic manufacturing may be employed, consisting of preparing and filling a product in a sterile environment (class A environment) with sterile raw materials and using sterile equipment, despite the fact that it requires additional process validation data and justification during regulatory submission [8].

In the case of liposomes, due to their sensitivity to physicochemical alterations, sterilization remains a challenge. Since conventional sterilization methods (i.e., heat, ethylene oxide, ultraviolet and gamma irradiations) are unsuitable, the recommended method includes filtration and aseptic manufacturing [9]. And again, filtration is not applicable when the size of the liposomes is >0.2 μm because of possible filter pore clogging, especially if the dispersion medium is viscous [10]. In the case of aseptic production, the maintenance of sterility is quite complex, since several handling steps must be carried out in conventional liposome manufacturing. In order to solve this problem, a few aseptic manufacturing processes of liposomes in closed systems equipped with 0.2 μm sterile filter barriers, have been developed [10,11]

Finally, an understanding of the effect of storage conditions on the stability and biocompatibility of nanocarriers is of paramount importance 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. hydrolisis oxidation).

Liposomes

Opioids are considered “gold standard” in clinical practice for the treatment of postoperative pain and the WHO (World Health Organization) has included morphine in its Model List of Essential Medicines (WHO, 2007). Epidural morphine sulfate has been proven to possess 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 [12]. In this scenario, the advent of extended-release epidural morphine (DepoDur™, SkyPharma) has greatly improved post-surgical pain control, providing analgesia for up to 48 h with a single dose [13]. This system exploits the same DepoFoam technology, based on the use of multivesicular liposomes to promote a prolonged release of the entrapped compounds over a period of several days following non-vascular administration (intrathecal, epidural, subcutaneous, intramuscular, intra-articular and intraocular). It was firstly employed for liposomal cytrabine (DepoCyt™), the first DepoFoam formulation approved for human application, although it was discontinued by Pacira Pharms Inc. in 2017 for unspecified technical problems in the manufacturing process [14]. The peculiar features of DepoDur™ are related to the mean diameter of the systems (≥10 μm) and to their structure which is characterized by closely-packed non-concentric vesicles containing morphine sulphate (final drug concentration=10 mg/ml) stabilized by triglycerides acting as space fillers at the intersection points of the phospholipid bilayer [15,16]. DepoDur™ is made up of dioleoyl phosphatidylcholine (DOPC), dipalmitoyl phosphatidylglycerol (DPPG), cholesterol, tricaprylin and triolein in a mass ratio of 42:9:33:3:1 and the systems are characterized by an average diameter of ~20 μm [15].

Moving on to local anesthetics, bupivacaine is administered by way of subcutaneous injection or intravenous infusion; unfortunately, in most cases a single administration is not sufficient to manage post-operative pain as it 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 [17].

Therefore, in order to promote a controlled and prolonged release of an active compound, a DepoFoam-based system was developed. The multivesicular liposomes containing bupivacaine (Bupisomes) are characterized by a mean 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). The commercial formulation (Exparel®, Pacira Ireland Limited) was approved by the FDA in October 2011 and is proposed as a single-dose administration directly into the surgical site, to obtain a prolonged post-operative analgesia (bunionectomy, haemorrhoidectomy, and interscalene nerve block) [18,19]. In recent years it has also been proposed as an off-label formulation for laparoscopic hysterectomy, femoral and intercostal nerve block, epidural injections, and knee, shoulder, and hip arthroplasties [20–22].

It was reported that more than 6 million patients in the United States have been treated with bupivacaine liposomes since 2012, and the annual sales of Exparel reached $331 million in 2018 [23].

The formulation received a marketing authorization by EMA valid throughout Europe on 16 November 2020 under the name of "Exparel liposomal" [24]. Exparel® is available in two formulations (266 mg/20 mL or 133 mg/10 mL as a single vial) as a brachial plexus/femoral nerve block, for the treatment of post-operative pain in adults, and as a field block for the treatment of somatic post-operative pain from small- to medium- sized surgical wounds in adults. Compared to traditional bupivacaine, which has a duration of less than 10 hours, the duration of action of Exparel® typically ranges from 72 to 96 hours [25–27]. The clinical use of this formulation has been shown to decrease the hospitalization time of patients, even though the actual overall reduction due to the use of Exparel® with respect to other conventional drugs is still under investigation [28–30].

Nanoemulsions

The clinical experience accumulated in about 40 years of the use of phospholipid stabilized nanoemulsions for parenteral nutrition has led them to be a template for the design of drug delivery administered by the intravenous route [8,31,32].

Nanoemulsions are nano-sized emulsions with sizes ranging from 10 to 1000 nm. Typical nanoemulsions consist of oil, water and a surfactant. The selection of the surfactant is critical for forming and stabilizing nanoemulsions since they are thermodynamically unstable, but kinetically stable. This means that phase separation of nanoemulsions occurs when given sufficient time. Among the possible emulsifying agents accepted by the regulatory agencies, egg or soy lecithin are typically used as the emulsifier, while long chain triglycerides (LCT) and medium chain triglycerides (MCT) are first-choice excipients as the inner phase. Within a few minutes following IV administration, nanoemulsions are cleared by enzyme lipoprotein lipase (LPL), which hydrolyzes triglycerides into fatty acids. In particular, the phospholipid content, droplet size, lipid type and infusion rate are among the factors which determine the rate of plasma clearance [33]. Free phospholipids (not involved in the emulsificaion process) interfere with LPL activity, so the 20% oil emulsions are cleared faster as compared to 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 reticulo-endothelial system (RES). Also, MCTs are cleared more rapidly than LCTs, due to more efficient LPL activity, and because their fatty-acid metabolism is independent from the mitochondrial carnitine co-transporter [8]. 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 side effects: impairment of RES/immune function (especially for LCTs) and of pulmonary

haemodynamics, hepatobiliary disorders (steatosis, cholestasis and gallbladder sludge/stones), pancreatitis and fat-overload syndrome (fever, jaundice, irritability, spontaneous haemorrhage) [33].

Among parenteral dosage forms related to pain management, nanoemulsions are used for the repurposing of different substances, including anaesthetic [34], analgesic and anti-inflammatory agents [35]. The most outstanding example is propofol, an unique compound compared to the other intravenous anesthetics. In its pure form at room temperature, it is an oil, but it freezes at 19 °C. Due to its chemistry, propofol cannot be administered as an aqueous salt since 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, are highly lipophilic. The result is a molecule with poor water miscibility (150 µg/L). Its high lipophilicity (logP = 4.16) means that good propofol miscibility can only be achieved in lipophilic substances or organic solvents [36]. In early human testing, propofol formulated as Cremophor EL micellar solution [37] presented several adverse effects because, apart from severe pain at the injection site, it caused a high incidence of anaphylaxis and peripheral neuropathy. The development of the propofol soybean oil nanoemulsion formulation (Diprivan®, AstraZeneca), conversely, exhibited greater potency, a smaller distribution volume, less first-pass lung sequestration and decreased time to peak EEG effects [38–40]. Pain reduction following IV administration can be ascribed to the lipid sequestration of the propofol from the aqueous phase, which minimizes distribution to vessel walls [41].

Etomidate is a hypnotic agent used in general anesthesia which has a very stable hemodynamic profile and causes minimal histamine release, even though pain on injection and myoclonus are the most common side 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 was presented by diazepam, a benzodiazepine used in pre-operative settings for its sedative and muscle-relaxant properties. The use of solvents risks causing pain on injection and thrombophlebitis in a high percentage of cases, problems overcome in this case by the implementation of an oil-in-water nanoemulsion (Diazemuls®, Pharmacia) [45–47] or their extemporaneous addition to ready-prepared emulsions [8,33].

It is noteworthy that nanoemulsions may or may 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]. Contrarily, very lipophilic drugs are subject to metabolism by the liver or RES, with a different tissue biodistribution profile [8].

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 pain. 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 pro-drug (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, faster analgesic effects and fewer adverse gastrointestinal reactions, as compared to conventional formulations [48].

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 [49]. Indeed, subsequent to intra-articular injection, this prodrug is gradually hydrolyzed by the blood esterases, exhibiting greater anti-inflammatory activity than conventional water-soluble dexamethasone phosphate, primarily due to a more specific distribution in the inflammatory lesion, and a greater uptake by the macrophages [50,51]. This product is particularly useful in the treatment of rheumatoid arthritis, a chronic, autoimmune rheumatic disease that evolves with inflammatory flares associated with inflammation of the joint synovial membrane, progressive bone and cartilage destruction and strong pain.

Long-acting injectable formulations

In the case of parenteral administration, long-acting implantable or injectable dosage forms (LAI) are chosen to assure the extended release of an API over a period suitable for guaranteeing a therapeutically relevant concentration either in the bloodstream or locally in a specific tissue/organ (e.g., eye, or intra-articular cavity) for weeks, months or years. Many technologies have been proposed for controlling drug release, e.g., crystal suspensions, emulsions, or implantable or injectable dosage forms which can be based either on non-biodegradable and biodegradable polymers or on *in situ* gelling systems [52]. With respect to conventional parenteral formulations, the main advantages of the LAIs include reduced dosage frequency, decreased incidence of side effects, maintenance of stable plasmatic concentrations and better patient compliance [53]. In the case of polymer-based LAIs, they can be easily removed from the administration site either at the end of the release period or in the case of harmful events/adverse reactions. To avoid tissue damage after the extraction procedure, biodegradable polymers are generally used (e.g., poly(lactide-co-glycolide) (PLGA), which typically undergo complete degradation in biocompatible by-products. Finally, a device required for injection and/or implantation should be optimized along with the implantation procedure.

Among the drugs which can be loaded into LAIs, glucocorticoids are one of the most successful examples. Indeed, the use of glucocorticoids, in spite of their long history as anti-inflammatory and immunosuppressive drugs, is limited to short-term treatments to relieve inflammation during flare-ups due to their severe side effects [54]. In this context, polymeric implants can take advantage of the specific physiopathology of inflamed tissues and of the vascular-enhanced permeability effect, in order to address 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, side effects.

Biodegradable implants

In order to maximize the efficacy of glucocorticoids while reducing their side 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 [55]. Triamcinolone acetonide is widely used for this purpose providing, however, relatively short-lasting analgesia [56,57]. In order to avoid the need for multiple injections, a PLGA formulation (Zilretta®, Pacira Bioscience) of triamcinolone acetonide has been developed to favor a slow release of the analgesic into the synovium, prolonging efficacy to over 3 months [58].

Zilretta® is formulated as microspheres of about 45 μm microns loaded with small crystals of triamcinolone acetate [nominal drug load of 25% (w/w)] [59]. Size control is essential here to assure compatibility and efficacy of this type of drug delivery system, because it is a fact that particles of less than 6 μm are taken up by the synovial macrophages [60].

Drug release is controlled by nano-channels (~ 500 nm) which permit the flow of fluids into the particle matrix, thus prolonging drug release and slowing PLGA erosion. This slowed degradation is favoured by the low glycolic acid content (75:25) and by the small sizes of the microspheres (< 300 μm), which supports a homogeneous PLGA degradation [58]. The pivotal Phase 3 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 [61]) to assess the pre- and post effects of a single Zilretta® knee injection on physiological measures of pain and disability, physical performance, and physical activity in individuals with knee osteoarthritis. Thirty-five symptomatic patients were recruited and all data collected prior to injection (baseline), as well as at 4- (post 1) and 8-week follow-ups (post 2).

Commercial implants ("rods") are currently available also for the treatment of inflammation in ocular diseases, aiming at overcoming ocular barriers and prolonging the duration of the effects of the anti-inflammatory compound in the eye. Ozurdex® (Allergan Pharmaceuticals) is an intravitreal rod-shaped implant containing dexamethasone that is injected via a 22-gauge applicator directly into the vitreous body for the treatment of non-infectious uveitis. In this case the polymeric matrix (NOVADUR®) is constituted by two grades of 50:50 PLGA that differ from each other owing to the end-group substitution (namely acid-free and ester-group), and which provide a gradual release of 700 μg dexamethasone at the target site over a 6 month-period. The rod is obtained by the hot-melt extrusion process, an efficient and accurate method for controlling the consistency and the diameter of the filament, suitable to be placed inside a 22G hypodermic needle [62,63].

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 main study involving 229 adults with uveitis, 8 weeks after injection, around 47% of patients treated with Ozurdex® (700 μg) achieved a vitreous haze score

of zero as compared to 36% of patients treated with Ozurdex® (350 μg) and 12% of patients who received the sham treatment [64].

In situ forming polymer implants are typically made of an API, a solvent and a biocompatible polymer that controls API 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 NMP and PLGA, tri(ethylene glycol) poly(orthoester) (Biochronomer™ technology [65]), Atrigel® delivers a fixed-combination of bupivacaine and meloxicam to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy and total knee arthroplasty (Zynrelef®, Heron Therapeutics). Similarly, Posimir® (Durect Corporation) is a bupivacaine solution to be used for post-surgical analgesia for up to 72 hours following arthroscopic subacromial decompression, obtained after administration into the subacromial space under direct arthroscopic visualization. This formulation is based on a non-polymeric scaffold, i.e., sucrose acetate isobutyrate, in ethanol and benzyl alcohol (SABER®). This material is an extremely hydrophobic viscous liquid, but it forms a low-viscosity fluid when dissolved in some types of organic solvents. If the solvent happens to be water miscible, it would diffuse out upon contact with the aqueous biological fluids present at the site of injection leaving a highly viscous biodegradable matrix which can act as a drug depot for extended *in vivo* drug release [66].

Non-biodegradable implants

In order to manage ocular diseases such as macular edema, sustained-release systems made of non-biodegradable polymers have shown prolonged drug retention at the site of action. Retisert® (Bausch & Lomb) is a sterile implant designed to release fluocinolone acetonide (Fac), locally, 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 consists of a tablet enclosed in a silicone elastomer cup containing a release orifice and a polyvinyl 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 [67]. The Iluvien® implant (Alimera Sciences limited) is a non-biodegradable cylindrical polymer tube that measures 3.5 mm in length and 0.37 mm in diameter. Fac is incorporated into a PVA matrix within a polyimide tube which has membrane caps on each end to allow the diffusion of water into the matrix. The Fac diffuses through the tube, allowing a consistent, sustained release of the medicine with an initial release rate of approximately 0.6 μg/day and continues for up to 3 years [67]. It is a continuous Microdosing™ Delivery System, the device providing the sustained delivery of 0.59 mg Fac, and it enables physicians to treat diabetic macular edema (DME) in an effective, consistent manner [68,69].

Nanocrystal suspensions

Nanocrystal suspensions with sustained release characteristics and suitable administration volumes have been developed both to reduce administration times and to 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 suspensions are currently available for the treatment of ocular diseases, including Betason L.A® (Caspian Tamin Pharmaceutical Co.; betamethasone acetate), Depo-Medrol/Lidocaine® (Pfizer Limited; Methylprednisolone, Lidocaine Hydrochloride) and Kenalog® (Bristol-Myers Squibb Pharmaceuticals Unlimited Company; triamcinolone acetonide).

Betason L.A® is a LAI suspension containing betamethasone, an anti-inflammatory corticosteroid agent. It is supplied as a dual-acting formulation containing betamethasone acetate and betamethasone (as disodium phosphate). It has multiple indications for use such as inflammatory or allergic reactions, rheumatic disorders and as a palliative treatment for neoplastic diseases. Depending on the indications, Betason L.A® is administered by means of intra-muscular, 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 intra-muscular injection [70]. The PK profiles demonstrated that the soluble betamethasone (phosphate ester) has a faster release to achieve a prompter onset of activity as well as the prodrug nature of hydrophobic betamethasone (acetate ester) which 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 about 14 days for pain relief in patients suffering from rheumatoid inflammation [71].

Depo-Medrol/Lidocaine® is an injectable suspension containing methyl prednisolone acetate combined with lidocaine hydrochloride. Depo-Medrol/Lidocaine® is used for treating 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 [72]. In these cases the allergic reaction could be caused by sensitivity to the drug itself or the excipients it contains such as carboxymethylcellulose or, less probably, to the polyethylene glycol [73]. Further investigations are required to understand the origin of such allergic 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 [74]. This covalent modification makes triamcinolone acetonide more lipophilic and less water-soluble than triamcinolone (0.043 vs 0.847 mg/mL). It has been shown that the micronized suspension of triamcinolone acetonide exhibits an extended duration of pharmacological action in the body. The administration of Kenalog® was accompanied by retinal toxicity after 14 days, but some

studies have demonstrated that this Kenalog®-related retinal toxicity could be due to one of its excipients, probably benzyl alcohol [75,76].

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 as compared to full opioid agonists. The single-dose regimen is to be administered prior to surgery and the extended duration of action (i.e., several days) provides an advantage over the need for the continuous post-surgical administration of a short-acting opioid. Following injection, the dinalbuphine sebacate (prodrug) 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 [77,78].

The clinical efficacy of dinalbuphine sebacate intended for treating acute postsurgical pain was based on one 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 hours after surgery. The AUC_{0-48} (mean VAS scores of pain intensity) for the dinalbuphine sebacate group showed statistically significant superiority as compared to the placebo group in both the modified intent-to-treat (209.93 ± 111.26 vs 253.53 ± 108.49; p=0.0052) and the per-protocol (207.46 ± 112.41 vs 254.91 ± 106.17; p=0.0039) populations [74,79].

High Level assessment on the scale-up and manufacturing processes

According to current pharmaceutical guidelines [80], 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 of which have an impact on a critical quality attribute (CQA) [80, 81] 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 thing, starting in the development laboratory but continuing along the lifecycle of the medicine and being a

conspicuous part of the registration and industrialization processes. Guidelines and Best Practices Documents [82] offer advice and tools on 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 employ a complex environment, such as one of those described in this review, suitable for re-proposing.

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

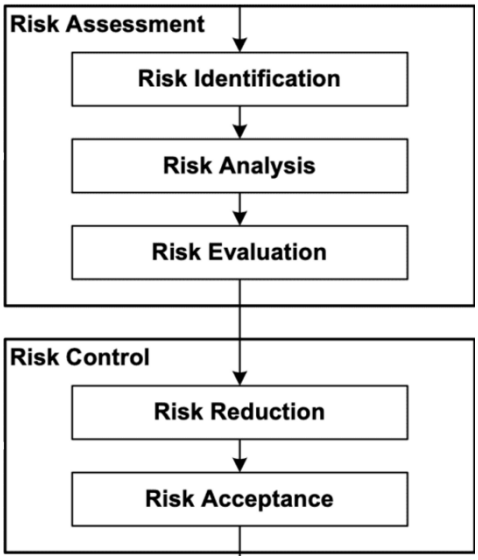

Figure 2 Risk Assessment process flow chart.

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, 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**).

Table 1

Example of process steps and related parameters identified during the *first step* of 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

Second stage. By means of an FMECA (Failure Mode, Effects and Criticality Analysis) or similar tool [81] an assessment of risk of impact on CQA, based on experimental data, scientific literature or documented evidence coming from similar manufacturing processes is carried out by the team (**Table 2**).

Table 2 Example of FMECA application in the *second step*

Process step	**Parameter**	**Impacted CQAs**	**Failure mode**
Compounding	excipient mixing time	compounded solution pH	Incorrect mixing parameters could lead to an incomplete dissolution of excipients. Their concentrations in the solution will change, impacting the chemical characteristics of the micro-environment. Moreover, in the case of stabilizing excipients, their lower concentration will negatively impact the impurity profile of the API.
		osmolarity	
		viscosity	
		assay	
		impurity profile	
Filtration	filtration differential pressure	filtered solution sterility	A differential pressure higher than the operative range can create shear stress on the API leading to degradation; moreover, aggregation can occur due to the increased pressure.
		particle size distribution	
		assay	
		impurity profile	
Filtration	filtration contact time	filtered solution	Prolonged contact time with the components of the filtration medium can increase the extractable levels. Those foreign chemical entities can then react with the excipients or the API generating leachables.
		assay	
		impurity profile	

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.

Table 3. Example of severity, probability and detection scale used for the *third step*

Severity	**Risk Classification**	**Associated value**

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

Fourth Step. The severity, probability and detection of each risk are mathematically combined (S × P × D) to calculate the Risk Priority Number (RPN) and using an appropriate matrix grid, prioritized. Scientifically sound [TR-65 PDA] mitigation actions are then taken for risk mitigation (**Table 4-5**).

Table 4 Example of Risk Priority Number Grid used during the fourth step

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 the 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

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 lifecycle 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.

Table 5. Example of mitigation action plan identified to reduce risks

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 an incomplete dissolution of the excipients. Their concentrations in the solution will not be uniform, impacting the chemical characteristics of the environment. Moreover, in the case of stabilizing excipients, zones of lower concentration will negatively impact the impurity profile of active ingredients	3	2	2	12	Mixing challenges carried out during development and scale-up setting the 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	A differential pressure higher than that of the operative range can create shear stress on the active ingredient molecules leading to degradation phenomena, as well as aggregation	3	3	3	27	Filter validation and filter challenge during development phase with the selected filtration media and effective filtration area (EFA)

Conclusions

A search through the available literature shows that drug delivery technology is a suitable tool for reproposing 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 non-biodegradable polymer implants, *in situ* forming implants and oil-based solutions. The common advantage of all the types of drug delivery systems that are herein introduced and discussed 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. Long-acting parenteral formulations, such as crystal suspensions, implantable or injectable dosage forms based either on biodegradable or non-biodegradable polymers or *in situ* gelling systems, allow the reduction of the dosing frequency, decrease side 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 in order to address encapsulated molecules to the target site.

As highlighted in the review, the aim of reproposing 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, reproposing 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 that must be followed starting from the first product design steps. The main challenges are the multiple and complex steps involved in a DDS manufacturing process, and the concerns arising from materials such as polymers and solvents involved in DDS formulation.

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

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Box 1- Abridged (or hybrid) application

Abridged/hybrid applications (also called hybrid application) can be used by the applicant if the "generic" regulatory pathway cannot apply to the drug product, but its benefit/risk balance assessment may be partially derived from those available in literature or products already on the market. It is the case of old drug products reformulated to improve or optimize their therapeutic efficacy with the same or similar therapeutic indications by changing the pharmaceutical form, 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 the bioequivalence studies cannot be applied as surrogates of therapeutic equivalence (i.e., conventional generic regulatory pathway).

In the EU, the "hybrid" procedure was described by Article 10(3) of Directive 2001/83/EC; In the US, 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 may be reduced compared with first-in-human products. The quality part related to the active pharmaceutical ingredient (API) can be reduced, whereas the quality part of 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.

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