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REVIEW ARTICLE

Opioid-based micro and nanoparticulate formulations: alternative approach on pain management

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ABSTRACT

Context Opioids have been used as the reference treatment on chronic pain. However, they are related to serious adverse effects which affect the patient compliance to treatment, as well as, his quality of life. Particulate formulations have been investigated as an alternative to improve opioid efficacy and safety. **Objective** Summarise the available studies concerning micro and nanoencapsulated opioid formulations discussing their biopharmaceutical characteristics, such as composition, size, *in vitro* release, pharmacokinetic and antinociceptive profile. **Methods** Papers available in 1995–2015 at Medline, Science Direct and Web of Science databases were collected and assessed. Searches were performed using varied combinations of the keywords of this work. **Results** Opioid-loaded particles showed prolonged drug release with maintenance of serum therapeutic concentrations and extended analgesia when compared with the free drugs. The side effects incidences were reduced or maintained the same. **Conclusion** Particulate formulations can significantly increase both potency and safety profiles of opioids.

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Definitions and background

The term opioid was originally stated for defining natural alkaloids extracted from opium, and afterwards extended to their synthetic and semisynthetic derivatives (Bourland, 2011). Currently, there has been a great confusion between the terms opioids and opiates in literature. In this context, Reisfield et al. (2007) have stated the term opiate specifically to substances extracted from poppy seed latex, such as morphine and codeine. The term opioid includes very different chemical substances with some degree of agonist activity on opioid receptors through the nervous system. Thus, opioids include some opiates, semi-synthetic, synthetic derivatives, as well as peptides. Opium is composed of dried latex obtained from the pods of *Papaver somniferum*, commonly known as poppy, which has been cultivated since 3400 BC in ancient Mesopotamia (Trescot et al., 2008b). The use of opium for pain relief is described in ancient Egyptian papyri dated from 1552 BC (Breasted, 2001). Through the years, a plenty of clinical studies evidenced the remarkable analgesic activity of opioid molecules which made them being taken as the gold treatment for chronic pain and severe acute pain (WHO, 2007). Table 1 lists some opioid molecules distributed according to their origin, including opioid peptides.

Despite the confusion in defining chronic pain, the definition provided by the International Association for the Study of Pain (IASP) is considered as an international standard (Doth et al., 2010; VanDenKerkhof et al., 2014). This concept remains the same since 1986 and establishes chronic pain as the pain that persists beyond normal tissue healing time, i.e. 3 months or more (Merskey and Bogduk, 1994).

Previous data has shown chronic pain affecting around 20% of the European population and is more common in women and elderly (Van Hecke et al., 2013). In Germany, a study reported 39.2% of prevalence of chronic pain (Häuser et al., 2013). Johannes et al. (2010) showed that the prevalence in the US reaches about 30.7%. A Canadian study conducted by Schopflocher et al. (2011) reported 18.9% of population suffering from chronic pain. In Hong Kong, this value reached 34% (Fielding and Wong, 2012), while Japan demonstrated 17.5% (Sakakibara et al., 2013).

Chronic pain is also marked by its impact upon public economy. Only in the US, the total costs ranged from $560 to $635 billion in 2010. This value exceeds the annual costs of heart disease ($309 billion), cancer ($243 billion) and diabetes ($188 billion) (Gaskin and Richard, 2012). Europe has an estimated cost of 200 billion Euros a year with chronic pain (Tracey and Bushnell, 2009). These expenses are mainly composed of total health care costs attributable to pain and annual costs of pain associated to decrease on work productivity (Gaskin and Richard, 2012).

The use of opioids as therapy for chronic pain has increased over the past few decades. However, there has been a concern to its analgesic efficacy, since it usually decreases through the course of treatment, despite increasing doses (Ballantyne and Shin, 2008). This pattern is related to development of tolerance to opioid therapy (Dumas and Pollack, 2008). This tolerance is evidenced during long-term treatment with opioids in which neuroadaptation takes places altering the normal function of nervous system homeostasis, desensitising opioid receptors and altering nociceptive signalling (Ballantyne and Shin, 2008; Allouche et al., 2014). This is a result of concomitant complex mechanisms, such as metabolic changes,

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Table 1. Opioids classified according to their origin.

Natural	Semisynthetic	Synthetic	Peptides
Morphine	Diamorphine	Butorphanol	DAMGO[1]
Codeine	Dihydrocodeine	Fentanyl	DALDA[2]
Papaverine	Buprenorphine	Alfentanil	DTLET[3]
Thebaine	Etorphine	Sufentanil	
	Nalbuphine	Methadone	

[1]Synthetic peptide [D-Ala2, N-MePhe4, Gly-ol].
[2]Endogenous peptide [Tyr-D-Arg-Phe-Lys-NH_2].
[3]Synthetic peptide [d-Thr2,Leu5,Thr6].

Table 2. Adverse reactions caused by the use of opioids.

Central	Peripheric
Tolerance	Immunological changes
Physical dependence	Hormonal changes
Sedation	Hyperalgesia
Sleep Disorders	Constipation
	Urinary disorders
	Cardiovascular changes

mediated by enzyme expression modulations and alterations on transporters functions (Dumas and Pollack, 2008).

Further, as described in Table 2, a large spectrum of possible adverse reactions can be developed due to the prolonged use of opioids. The awareness of opioid tolerance and adverse reactions are closely related to a fear of physicians in prescribing opioids for pain management and also to patient non-compliance, which sadly lead to adoption of subtherapeutic schemes (Trescot et al., 2008a; Manchikanti et al., 2010).

Taking into account that several opioids, such as morphine, oxycodone and hydromorphone possess very short half-lives, they commonly require frequent administration leading to inconsistent drug levels and a higher incidence of adverse events. Therefore, the use of extended-release formulations modulate the drug absorption providing constant and more predictable therapeutic drug levels improving the safety of opioid therapy. There is also more efficient coverage of analgesic gaps, even when compared with naturally long-acting opioids, such as methadone (Holt et al., 2007; Wood et al., 2010; Ngwuluka et al., 2013).

Micro and nanoparticulate formulation

For several years, the research on development of drug formulations has been focussed on tailoring of delivery systems which are capable of delaying and sustaining the drug release post-administration (Maderuelo, 2011). These kind of formulations, commonly known as modified drug delivery systems, present several advantages when compared to conventional pharmaceutical forms. Their capability of maintaining constant drug blood levels confers to them improved efficacy, reduced toxicity, improved patient compliance and convenience (Lehner et al., 2013). In addition, delayed drug release formulations are usually designed for controlled drug release. Controlled release may be defined as a method which allows controlling time and the site of drug release at a specific rate (Zhang et al., 2013).

Among the controlled drug release systems, colloidal dispersions have been playing a prominent role on pharmaceutical research field. Colloidal dispersions are known as systems composed of particles, in which at least one of their dimensions presents a colloidal size (1–1000 nm), of varied nature, are dispersed in a continuous phase of a different composition. Specific physical characteristics are commonly attributed to colloids, such as light scattering, Brownian particle movement and alteration of colligative properties of solutions. Formerly, colloidal particles ranging from 10 to 1000 nm have been stated as nanoparticles (Huber, 2005; Olivier, 2005). More recently, only particles that possess <100 nm size had been stated as nano- and those ranging from 100 to 900 nm have been assumed as submicron-sized particles (Fraser et al., 2008; Fang et al., 2010).

The small dimension of nanoparticles allows their facilitated passage across biomembranes, increasing significantly drug typical bioavailabilities. In addition, the large surface area of nanoparticles collaborates with the improvement of drug solubility rates into biological fluids (Fröhlich and Roblegg, 2012; Campbell and Hoare, 2014). These special characteristics confer alternative strategies for approaching complex treatments. In this context, varied nanoparticle formulations have been assessed upon clinical trials, as well as, some of them have been approved by Food and Drug Administration (FDA) for commercialisation (Lehner et al., 2013). Besides controlling the release on different sites of the body, these nanoparticle carriers can also protect drug molecules from potential thermal and photo-mediated oxidation reactions, as well as, hydrolysis and other chemical transformations during shelf life.

In this context, microparticulated systems (>1000 nm) also remain as a significant alternative for drug delivery, presenting some advantages when compared to nanoparticles. Microparticles preparation usually demands simpler methods, with easier scale up. The larger structure of microparticles allows loading higher amounts of drug into their matrices, demanding less concentrated doses to reach therapeutic levels during treatment. Further, their smaller surface area leads to a less susceptibility to physicochemical degradations (Kohane, 2007).

It is important to state that the main aspect that runs the choice between micro and nanoformulations is the intended application. The pharmacokinectic profile of micro and nanoparticles differ greatly as a result of significant differences on immune system uptake pathways, affinity to plasmatic proteins, absorption and accumulation rates, as well as, drug release mechanisms (Chakravarthi et al., 2010; Hardy et al., 2013).

Liposomes

Liposomes are vesicles constituted of hydrophobic phospholipid bilayers separated by aqueous compartments that cover one or multiple aqueous cores (Figure 1). Through the years, a large range of different types of liposomes have been developed with respect to lipid composition, number of bilayers, size, charge and preparation methods. Taking into account the presence of compartments with different chemical natures, it is feasible the entrapment of both hydrophilic and hydrophobic drug molecules (Lasic, 1993; New, 1990). The similarity of the lipid bilayers of liposomes with cellular membranes makes them good candidates for studying drug–cell interactions. Furthermore, it allows the delivery of the drug into an intracellular environment. This delivery can also be targeted by use of a wide range of receptor-specific ligands on liposomal membrane leading to drug release on specific tissues or cell types (Allen and Cullis, 2013). These features justify the versatility and popularity of liposomal products.

Considering all these advantages, researches have been carried out focussing on the manufacturing of liposomal opioid formulations. Table 3 reveals a number of works that evaluated the performance of opioid molecules entrapped into liposomes in different experimental models.

Since the 1990s, various works have been published describing the elongation of duration of analgesia, with no significant

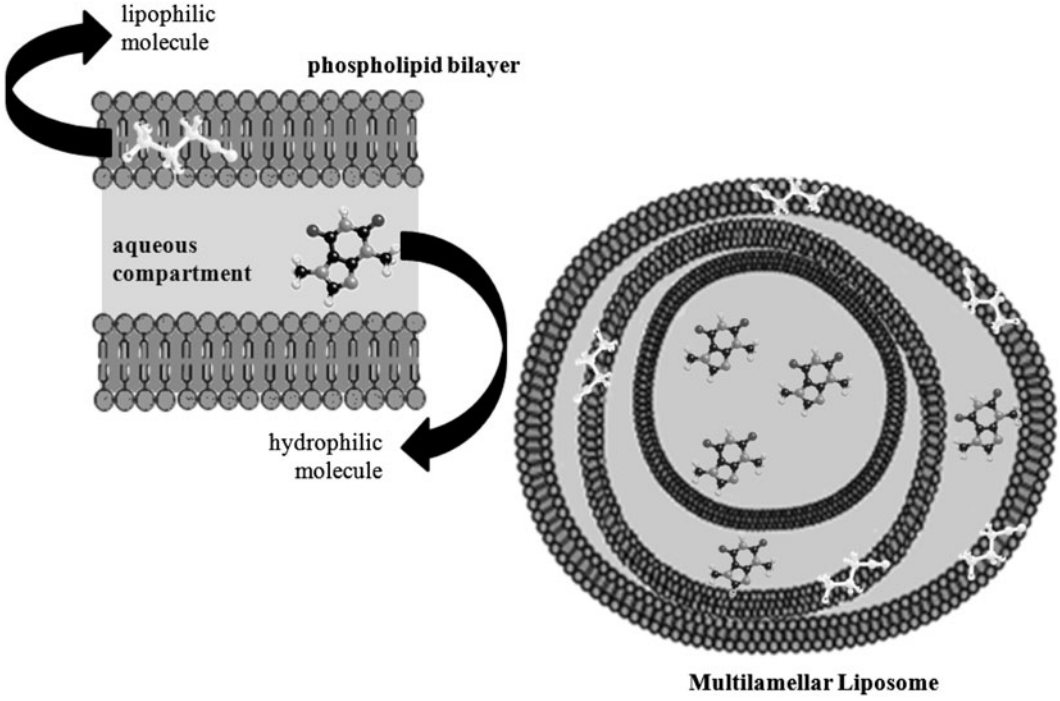

Figure 1. Scheme of lipophilic and hydrophilic molecules entrapped into different compartments of a liposome.

increment or even reduction of systemic side effects of opioids encapsulated on liposomes when compared to standard formulations (Bernards et al., 1992; Grant et al., 1994; Yaksh et al., 1999). These findings highlight the liposomal carriers as suitable candidates for chronic pain treatment investigation. In a study with a neuropathic pain model in Sprague–Dawley rats, liposomal morphine and oxymorphone prevented hyperalgesia for up to 7 days after one subcutaneous dose (Smith et al., 2003). The slow drug release from liposomes could explain this result. Correlating to this hypothesis, other work performed with rhesus macaques demonstrated the persistence of oxymorphone in serum for over 2 weeks after a single subcutaneous dose of liposomal formulation, whereas the standard oxymorphone concentration decreased rapidly after injection (Krugner-Higby et al., 2009). A similar result was observed for liposomal butorphanol. The plasma free butorphanol concentration usually decays drastically 2 h after IV administration (Groenendaal et al., 2005; Knych et al., 2013). A sustainable release for up to 24 h of butorphanol on Sprague–Dawley rats bloodstream was achieved with a transdermal liposomal formulation (Lim et al., 2008).

Considering the combined degrading effects of the acidic pH of the stomach, bile salts and pancreatic lipases on gastrointestinal tract, the administration of liposomal suspensions by oral via is limited (Shaji and Patole, 2008). Thus, polymer coating has been taken as an alternative. Further, polymer coating is also largely used for prolonging the maintenance of liposomes in blood circulation by avoiding immune system uptake (Watanabe et al., 2012). Concerning to this, a couple of works have studied polymer-coated liposomal opioids, such as PEG for tramadol (He et al., 2010) and Eudragit® S100 for endomorphin-1 (Eskandari et al., 2013). In both works, the coating significantly improved the retard on drug release. Eudragit® S100 coating also improved the passage of liposomal endomorphin-1 across gastric cells. The polymer acted not only as a shell, but also as a permeation enhancer on gastric epithelium.

On the other hand, the coating material can facilitate the interaction with biomembranes. Hoekman et al. (2014) investigated the performance of Arg–Gly–Asp (RGD) peptide-coated liposomes entrapping fentanyl on tail-flick test after nasal administration in Sprague–Dawley rats. The liposomal fentanyl exhibited greater analgesic effect, as well as, reduced drug in the plasma around 20% which leads to less adverse reactions occurrence. It was hypothesised that, due to the integrin-binding properties of the RGD peptide, the liposomes most likely bound to the epithelium after aerosol deposition on nasal tract, creating a local depot effect of fentanyl on nasal and olfactory epithelium.

Taking into account that several opioids, mainly those morphine-like, are typically hydrophilic, they are usually entrapped into multilamellar liposomes in which the varied number of aqueous cores and higher diameter enable higher entrapment efficiency when compared with the unilamellar type. Membrane interaction studies demonstrated that morphine, codeine and other synthetic derivatives were located into aqueous core of DPPC liposomes with large interaction with phosphate groups into inner membrane surface preventing the phospholipid mobility into the membrane making the liposomes rigid (Budai et al., 2003).

Considering the modified release of the encapsulated opioids, dose adjustments are mandatory. A single dose of a liposomal formulation is higher than a single dose of an immediate release drug, however the cumulative dose over the extended time period is similar. Generally, a liposomal opioid is administered at 10 times the parenteral dose for the free drug (Krugner-Higby et al., 2009). Unfortunately, there is still a lack of studies on liposomal opioids, which compromises the comprehensive analysis of the different observed phenomena.

On the other hand, some disadvantages of this carrier must be taken into consideration. Liposomal preparations have a relevant tendency to aggregate leading to drug release, with subsequent degradation and increase of toxic potential (Risselada, 2009). The usual presence of organic solvent residues has been also a concern (Gregoriadis, 2007). Besides, there is difficult in running sterilisation processes of liposomal particles without affecting their integrity (Mehnert and Mader, 2001; Mozafari, 2005).

Table 3. Experimental works with liposomal opioids.

Opioid	Liposome type	Liposomal composition	Particle Diameter	Experimental model/Route of administration	Nature of study	References
Alfentanyl	MLV	DPPC/cholesterol	NP	Sprague–Dawley rats/Intrathecal	Hot-plate and paw-pressure tests	Bernards et al. (1992)
Butorphanol	MLV	Egg yolk PC/cholesterol/polyoxyethylene	500 nm	Sprague- Dawley rats/Transdermic	Permeation tests	Lim et al. (2008)
C10LAA-Endo-1	Eudragit S100 coated LUV	Phospholipon 90H®/Eudragit S100	102 nm	*in vitro*	Sample preparation and characterisation	Eskandari et al. (2013)
Fentanyl	MLV	Phospholipon 90G®/cholesterol	100–1000 nm	Healthy Human/Pulmonary	Pharmacokinetic assessment	Hung et al. (1995)
Fentanyl	Peptide-coated SUV	Arg–Gly–Asp (RGD) peptide/DMPC/DMPG		Sprague–Dawley rats/Nasal	Tail-flick	Hoekman et al. (2014)
Morphine	MLV	DMPC/cholesterol	NP	Swiss-Webster mice/Intraperitoneal	Tail-flick	Grant et al. (1994)
Morphine	MLV	Depofoam®	14.7 μm	Beagle dogs/Epidural	Evaluation of latency time for skin-twitch reflex	Yaksh et al. (1999)
Morphine	LUV	Soybean lecithin	150–200 nm	Sprague–Dawley rats/Subcutaneous	Carrageenan-induced inflammation of the paw	Planas et al. (2000)
Morphine/alfentanil/sufentanil/Fentanyl	MLV	DPPC	NP	Pigs/Epidural	Pharmacokinetic assessment for different compositions	Bethune et al. (2001)
Morphine/oxymorphone	MLV	DOPC/DPPG/cholesterol/triolein	29 μm	Sprague–Dawley rats/Subcutaneous	Evaluation on neuropathic pain	Smith et al. (2003)
Morphine/codeine/*N*-methyl-morphine/*N*-methyl-codeine	SUV	DPPC	32–43 nm	*In vitro*	Membrane interaction studies	Budai et al. (2003)
Oxymorphone	MLV	DPPC/cholesterol	NP	Rhesus Macaques/Intravenous	Pharmacokinetic assessment	Krugner-Higby et al. (2009)
Tramadol	PEG coated MLV	Soy PC/DOPC/DPPG/cholesterol	18–31 μm	*In vitro*	Sample preparation and characterisation	He et al. (2010)

MLV – mulilamellar vesicle; LUV – large unilamellar vesicle; SUV – small unilamellar vesicle; 2-aminodecanoic acid (C10) lipoaminoacid-endomorphin-1; Depofoam®: DOPC; DPPG; cholesterol; triolein and tricaprylin; DMPC: dimyristoylphosphatidylcholine; DOPC: dioleoylphosphocholine; DPPC: dipalmitoylphophatidylcholine; DPPG: dipalmitoylphosphoglycerol; DMPG: dimyristoylphosphoglycerol; PC: Phosphatidylcholine; Phospholipon 90G®: 94–102% phosphatidylcholine (granules); Phospholipon 90H®: 90% hydrogenated phosphatidylcholine; NP: Not Provided.

Marketed liposomal opioids

On 18 May 2004, the extended-release epidural morphine (EREM) was first approved by the FDA under the trade name Depodur®. This formulation was designed for management of post-operative pain in many types of surgery, including deep abdominal surgeries, hip and knee replacements, hysterectomies, caesarean sections and other surgical procedures involving pain that can be blocked by epidural administration (Mantripragada, 2003). Depodur® is composed by the opiate morphine sulphate entrapped into micrometric multivesicular liposomes named Depofoam® developed by Pacira Pharmaceuticals Inc. (San Diego, CA), previously known as SkiePharma Pharmaceuticals Inc. (Cambridge, MA). Depofoam® has a singular structure that includes hundreds of enclosed bilayers which form several aqueous pockets where morphine salt is retained, as depicted in Figure 2 (Mantripragada, 2003; Pasero and McCaffery, 2005; Nagle and Gerancher, 2007).

After a Depodur® single injection into the epidural space, a prolonged and sustained release of morphine is provided for up to 48 h by erosion or reorganisation of the lipid membranes. This procedure offers various advantages, such as elimination of multiple injections and an indwelling epidural catheter, continuous pain relief, improved safety, greater convenience for patient and physician and faster patient recovery from surgery (Mantripragada, 2003; Pasero and McCaffery, 2005). However, in some clinical conditions, the EREM can demand supplementation on pain pharmacotherapy and present an analgesic profile comparable to that conventional approach (Gambling et al., 2005; Vanterpool et al., 2010; Sugar et al., 2011). Up to date, Depodur® is the only liposomal opioid commercially available.

Polymer particles

Another carrier system with large application on drug delivery is composed by polymeric particles. The polymeric carriers are able to create amorphous solid dispersions in which the drug can be distributed in the molecular state as a solid solution or solid suspension. This amorphous condition facilitates the solubilisation of the drug into biological fluids, enhancing the biodistribution of hydrophilic as well as poorly water-soluble drugs (Buttini et al., 2012). Furthermore, the availability of a wide range of synthetic, semi-synthetic and natural polymers offers a plethora of possibilities for drug delivery system design, in which is highly important to possess a non-toxic, biocompatible and biodegradable profile (Anderson and Shive, 2012).

Two main types of polymer particles have been used on drug formulation preparations: spheres and capsules. Spheres have a massive matrix in which the entrapped molecule can be distributed in small aggregates, or molecularly distributed, i.e. homogenously dispersed, or either on the sphere surface. Capsules are core-shell systems in which a core of different composition from outer layer is present (Pinto Reis et al., 2006). Figure 3 depicts spheres and capsules with different schemes of distribution of the drug molecules

Polymer particles have important advantages when compared with liposomes. Among them, their superior stability due to their solid nature with low tendency to aggregate confers to polymeric particulate products a larger shelf life. In addition, the relatively easiness with which particle size and surface characteristics of these particles can be modified allows their application for both passive and active drug targeting after parenteral administration (Gelperina, 2005; Mohanraj and Chen, 2006).

Other interesting features make this kind of particulate system the first choice for a series of uses. These includes the ability of

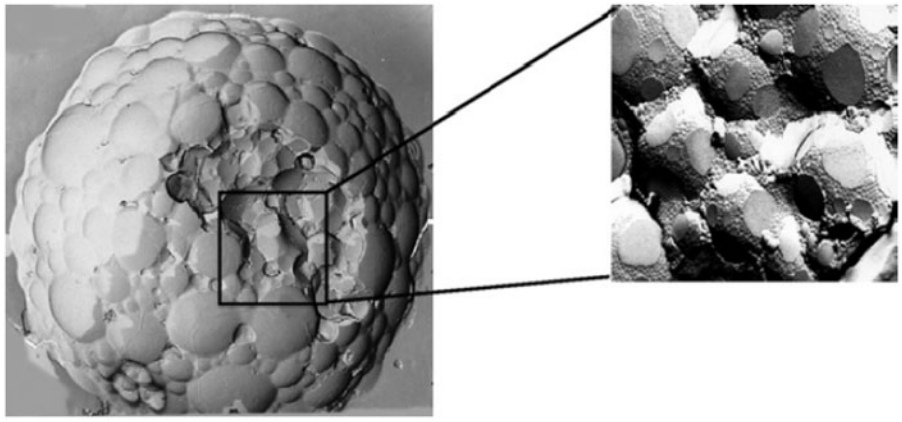

Figure 2. Electron micrograph of freeze-fracture replicas of the multi-vesicular liposome particle (DepoFoam®) carrying morphine sulphate (Nagle and Gerancher, 2007).

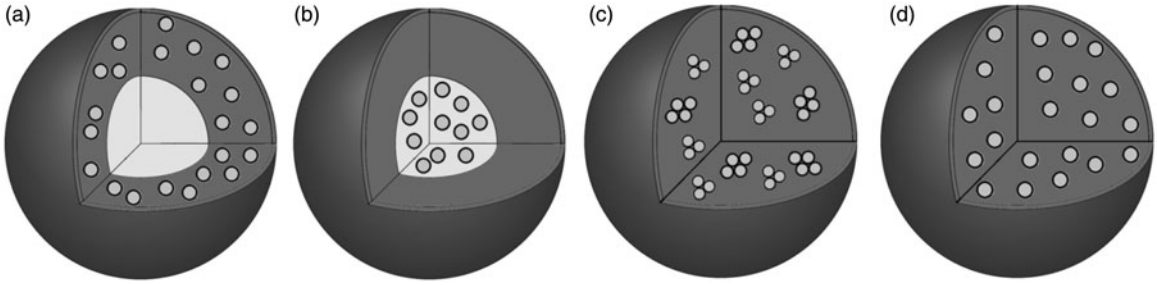

Figure 3. Possible structures of polymeric particles according to the distribution of drug molecules (light grey spheres) in the polymeric matrix (dark grey filling). Capsule structures can contain drug molecules into the shell (light grey filling) (a) or in the core (b). Sphere structures can be constituted by drug aggregates (c) or molecularly dispersed drug (d).

controlling and sustaining the drug release during the particle biodistribution and at the deposition site, altering the whole pharmacokinetic profile of the drug molecule in order to achieve an increased therapeutic efficacy and reduction of side effects. Further, the pattern of release, as well as particle degradation can be readily modulated by the choice of matrix constituents. As liposomes, polymeric particles can target a specific site through attachment of ligands to their surface and this system can be administrated by various routes, including oral, nasal, parenteral, intra-ocular and others (Lehner et al., 2013).

Table 4 shows plenty of experimental studies in which the development of opioid entrapment into polymeric particles has been investigated. Most of the studies have described opioid entrapment in spheres, with an average encapsulation efficiency of 80%.

One of the first works on this matter demonstrated the microencapsulation of tramadol ionically complexed to a sulphonic acid cation-exchange resin. Considering that this complex is unable of establishing a sustainable drug release by itself, the polymer microencapsulation seemed to be an interesting alternative. An ethylcellulose microcapsule wall provided a sustained release of tramadol. The drug release profile was strongly influenced by viscosity of ethylcellulose pre-solution used for spray drying process. Low and middle viscous polymer solution obtained the best results, whereas the high viscosity solution provided coalesced microcapsules with a burst release of drug (Zhang et al., 2000).

In vitro tests also demonstrated a prolonged release of opioids on aqueous media. The use of hydrophobic polymers, such as ethylcellulose, kollidon® SR and PLLA lead to a wide prolonged release of opioid molecules for about 24 h. Considering the use of water-soluble opioids, such as morphine and tramadol, the release can be ruled mainly by polymer swelling, porous diameter on the particle surface or even by polymer degradation rate in the release media (Morales et al., 2004; Arias et al., 2009; Aamir et al., 2011; Chen et al., 2013a). The use of hydrophilic polymers in particle tailoring in general reduces the drug release time due to their solubilisation or hydrolyses upon aqueous media. The use of HPMC in a polymeric blend leads to a total release of tramadol in 12 h (Patel et al., 2011). Chitosan, a hydrophilic and highly swellable polymer, conferred a total release for up to 5 h to the microencapsulated tramadol. The use of crosslinkers modulates the particle porosity reducing the drug release (Harris et al., 2010). The addition of a hydrophilic non-hydrolysable monomer, PEG, on PLLA structure accelerated the morphine release by attraction of H_2O molecules to the particle matrix, acting as 'water pump' favouring the drug dissolution on release media (Chen et al., 2013a).

The production technique is also pivotal for that matter. According to production steps, most opioid molecules can be distributed on the particle surface, leading to a significant burst release in the first minutes of exposure to a release media (Chen et al., 2013a). In addition, the low chemical affinity between the drug and the matrix can favour a phase separation during particle preparation, leading to significant burst release, as demonstrated for morphine-loaded PLLA microparticles in which 50% of the drug was released on the first 4 h (Zhang et al., 2012).

Despite the large number of studies of opioid-loaded polymer particles, there is still a lack of *in vivo* tests performed with these systems, which impairs the interpretation of numerous possible effects of body compartments on the performance of these formulations. In this context, a pharmacokinetic work with thienorphine, a synthetic opioid analogue of buprenorphine produced by Beijing Institute of Pharmacology and Toxicology

Table 4. Experimental works with opioid-entrapped polymer particles.

Opioid	Particle type	Particle composition	Particle diameter	Experimental model/Route of administration	Nature of study	References
Butorphanol	Microspheres	Copolymers (erucic acid/sebacic acid/ carboxyphenoxypropane)	2–10 μm	*in vitro*	Physicochemical characterisation	Chang and Li (2000)
Loperamide	Nanospheres	Copolymer (PLGA-PEG-PLGA)	147–173 nm	ICR mice/Intravenous	Formalin/hot plate test	Chen et al. (2013b)
Loperamide	Nanospheres	Butylcianoacrylate	290 nm	ICR mice/Intravenous	Tail Flick	Alyautdin et al. (1997)
Loperamide	Nanospheres	mPEG-PVA	150 nm	–	Physicochemical characterisation	Dalwadi and Sunderland (2008)
Loperamide	Nanospheres	Poly(butylcyanoacrylate)	223–245 nm	ICR mice/Intravenous	Tail flick	Hekmatara et al. (2009)
Morphiceptin	Nanospheres	Poly(butylcyanoacrylate)	200–300 nm	Swiss mice/Intraperitoneal	Hot plate test	David et al. (2010)
Morphine	Microcomposites	Eudragit L 30D®	100–250 μm	*In vitro*	Physicochemical characterisation	Fernandez-Arevalo et al. (2004)
Morphine	Microspheres	Ethylcellulose	3–5μm	*In vitro*	Physicochemical characterisation	Morales et al. (2004)
Morphine	Microspheres	Mannitol, trehalose, lactose, b-cyclodextrin or HPMC	4.0–14.6 μm	*In vitro*	Physicochemical and biological characterisation	Russo et al. (2006)
Morphine	Microspheres	Ethylcellulose	3–5μm	*In vitro*	Physicochemical characterisation	Morales et al. (2007)
Morphine	Microspheres	Kollidon® SR	10 μm	*In vitro*	Physicochemical characterisation	Arias et al. (2009)
Morphine	Microspheres	PLLA	2.4 μm	*In vitro*	Physicochemical characterisation	Zhang et al. (2012)
Morphine	Microspheres	Copolymer (PLLA-PEG-PLLA)	2–5.7 μm	*In vitro*	Physicochemical characterisation	Chen et al. (2013a)
Naltrexone	Microsphere	PLLA	230–328 μm	*In vitro*	Physicochemical characterisation	Dinarvand et al. (2005)
Tienorphine	Microspheres	PLGA	40 μm	Wistar rats/Subcutaneous	Pharmacokinetic study	Yang and Gao (2010)
Tramadol	Microcapsule	Ethylcellulose/sulphonic acid cation-exchange resin	70–200 μm	*In vitro*	Physicochemical characterisation	Zhang et al. (2000)
Tramadol	Microspheres	Ethylcellulose	181–210 μm	*In vitro*	Physicochemical characterisation	Aamir and Ahmad (2009)
Tramadol	Microspheres	Ethylcellulose	3.3–3.5μm	*In vitro*	Physicochemical characterisation	Morales et al. (2010)
Tramadol	Microspheres	Chitosan-genipin	<10 μm	*In vitro*	Physicochemical characterisation	Harris et al. (2010)
Tramadol	Microcapsules	Ethylcellulose, Eudragit® RS 30D/ Eudragit® RL 30D or Eudragit® RS 12.5/Eudragit® RL 12.5	212–500 μm	*In vitro*	Physicochemical characterisation	Sawicki et al. (2010)
Tramadol	Microspheres	Ethylcellulose	124–156 μm	*In vitro*	Physicochemical characterisation	Aamir et al. (2011)
Tramadol	Microblends	HPMC K-15M/Eudragit® RS100 blend	14.8–19.4 μm	*In vitro*	Physicochemical characterisation	Patel et al. (2011)

Eudragit L® 30D: copolymer (methacrylic acid – ethyl acrylate); Eudragit® RS100: copolymer (ethyl acrylate – methyl methacrylate – methacrylic acid ester); Eudragit® RS 30D and RL 30D: aqueous dispersion of 30% Eudragit® RS 100 and RL 100, respectively; Eudragit® RS 12.5 and RL 12.5: solution (60% isopropyl alcohol/40% acetone) of 12.5% Eudragit® RS 100 and RL 100, respectively; NF HPMC: hydroxypropyl methylcellulose; Kollidon® SR: polyvinyl acetate (8 parts w/w) + polyvinyl pyrrolidone (2 parts w/w); PEG: polyethylene glycol/PLGA: poly(lactic-co-glycolic acid); PLLA: poly-D,L-lactide/PVA: polyvinyl alcohol; mPEG-PVA: monomethoxy-PEG-PVA copolymer.

(China), was performed. After a subcutaneous injection of thienorphine-loaded PLGA microspheres, the drug plasma concentration was maintained at a relatively high level (3–5 ng/mL) for almost 30 days, whereas the free drug formulation had its concentration decreased dramatically just after administration (Yang and Gao, 2010).

The use of nanoparticles can increase the range of applications of drug molecules by improvement of some physical characteristics. Morphiceptin, an opioid agonist peptide, has its analgesia effect upon systemic administration limited by its low diffusion through the blood–brain-barrier (BBB). The morphiceptin encapsulation on poly(butylcyanoacrylate) nanoparticles increased significantly its central analgesia on hot plate model, and increased even more when the particles were coated with polysorbate 80 (David et al., 2010). Similar results were obtained for loperamide, other drug that does not cross the BBB. Loperamide encapsulated into PLGA-PEG-PLGA nanoparticles had their antinociceptive activity on formalin test improved after being coated with polysorbate 80 and poloxamer 188 (Chen et al., 2013b). It has been described in the literature that the surfactant coating of nanoparticles attracts the blood stream apolipoproteins after administration. Considering their similarity to lipoproteins, the apolipoproteins mediate via receptor the nanoparticle endocytosis on brain capillary endothelium. Then, the carried drug can be delivered into the brain improving its efficacy (Kreuter et al., 2002; Wohlfart et al., 2012; Grabrucker et al., 2013; Joseph and Saha, 2013).

An interesting alternative for prolonged opioid release system can be the covalent linking of the drug molecule with particle matrix. In this case, the release mechanism is determined by degradation rate of the particle. The literature describes the production of microparticles containing the complex morphine – Eudragit® 30D for extended release. More recently, the synthesis of a polymer constituted by morphine molecules chemically incorporated into a poly(anhydride-ester) backbone – polymorphine – was studied. *In vivo* results from tail flick test with C57/Bl6 mice showed that polymorphine provides analgesia for 3 days, 20 times the analgesic window of free morphine (Rosario-Meléndez et al., 2012).

Even under so many advantageous evidences, it is important to consider the problems associated to polymer carriers. Considering that the control of drug release demands a large amount of encapsulant species, polymeric particles commonly possess a low loading capacity (Martins et al., 2007; Mehnert and Mader, 2001). The high costs for acquisition of most biodegradable polymer particles excipients are also a remarkable drawback of these systems (Joshi and Muller, 2009).

Marketed polymer particle opiates

Avinza

Avinza® contains once-daily extended-release morphine sulphate capsules filled with polymeric beads which provides a sustained release of the drug maintaining therapeutic plasmatic levels up to 24 h. This formulation uses the proprietary Spheroidal Oral Drug Absorption System (SODAS™) technology to produce the extended release of morphine. The SODAS™ beads are constituted by ammonium-methacrylate copolymers and after oral administration the gastrointestinal fluids penetrates its polymeric net and solubilises the drug content. The resultant solution then diffuses out in a prolonged manner from the beads leading to a prolonged therapeutic effect (KP, 2008).

Comparative pharmacokinetic studies have demonstrated that Avinza® exhibits less peak-to-trough fluctuations in plasma concentration while providing analgesia statistically identical to that produced by MS Contin® (controlled-release morphine sulphate tablet), Oxycontin® (oxycodone HCl controlled-release) and six doses of oral morphine sulphate administered every 4 h. Avinza® improves significantly the quality of sleep. However it causes the same side effects of other opioids: constipation, nausea, vomiting, somnolence and mood swings (Caldwell, 2004; Adams et al., 2006; Rauck et al., 2006). Doses of 30–60 mg/day have been shown to be well tolerated by patients with osteoarthritis who have failed other medications (Caldwell, 2004).

Kadian

The Kadian® extended-release morphine sulphate capsules were firstly approved by FDA in July 1996 for management of moderate to severe pain in cases of a continuous, around-the-clock opioid analgesic is needed for an extended period time. Kadian® capsules are formed by 1.0–1.7 mm diameter granules which are composed of a globular core particle coated with morphine sulphate additionally covered by a mixed polymeric layer. This coat is constituted by three different polymeric layers, comprising an insoluble matrix at pH 1–7.5 range, an enteric polymer insoluble at pH 1–4 and a soluble one at pH6–7.5. This mixed coat provides a gradual delivery of morphine sulphate in different sites of gastrointestinal tract (Jitsu, 2000).

Kadian® pellets are pH-dependent, i.e. the drug release is facilitated in the alkaline environment of intestine, yielding effective plasma morphine concentrations with a relatively small degree of fluctuation for up to 24 h. The bioavailability of Kadian® is not affected by food, so can be administered without regard to meals. The capsules can be administered orally, or can be opened so the pellets contained in the capsules can be sprinkled on apple sauce or administered via gastric feeding tube (Sasaki et al., 2007). The literature has announced that patients with non-adequate management of chronic pain can be successfully switched to Kadian® (AP, 2010).

Since the gastric environment is too aggressive to the liposomal structure, the only available liposomal opioid in market is designed for parenteral administration. This limitation associated to the risk of particle agglomeration during administration offers a market opportunity for polymer-based products. In this context the two commercially available polymer particulate opioid products grab a significant part of the pharmaceutical market since they have been designed for oral administration. Table 5 summarises a panel of all commercially available particulate opioid formulations. The narrow range of products reveals the lack of investment by pharma industry field on these formulations. It can be linked to the fact that there is still a lack of clinical data proving a significant improvement of opioid therapeutic response and safety profile when associated to these drug delivery systems.

Solid lipid-based particles

The efforts for discovering alternatives to overcome the limitations of conventional particulate systems resulted on the development of solid lipid nanoparticles, typically named as SLN. First introduced in 1991, SLN are colloidal particles composed by lipids which are solids

Table 5. Commercially available particulate opioid-based products.

Products	Opioid	Particle nature
Depodur®	Morphine sulphate	Multivesicular liposomes (Depofoam®)
Avinza®	Morphine sulphate	Polymer capsules
Kadian®	Morphine sulphate	Polymer capsules

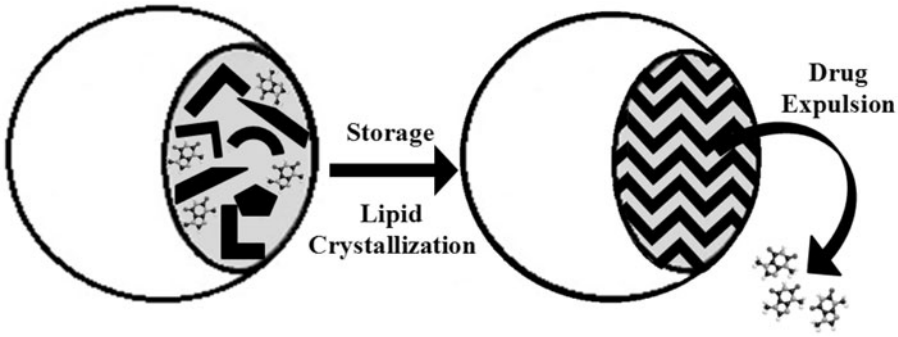

Figure 4. Drug expulsion phenomenon from SLN after crystallization. Under storage, the solid lipid structure of SLN migrates to a less stable and non-organised matrix to a stable and very organised and tight crystal lattice forcing the expulsion of the drug molecule due to the loss of available space.

at room temperature, including triglycerides, partial glycerides, fatty acids, steroids and waxes (Müller, 1991). The drug incorporated into SLN is released on a prolonged way and the drug concentration can be sustained on blood stream (Müller et al., 2000; Mehnert and Mader, 2001; Kamble et al., 2010). SLN has a broad acceptance owed to the physiological nature of its lipid constituents, preventing acute and chronic toxicity. This is ratified by the Generally Recognised as Safe (GRAS) status conferred by FDA (Mehnert and Mader, 2001; Rahman et al., 2010). In addition, the SLN's solid state favours less complicated sterilisation techniques and higher particle physical stability by avoiding of aggregation, resulting in a larger shelf-life, when compared to liposomal or microemulsion formulations.

Briefly, SLN preparation can be conducted by two main pathways: (i) melting of constitutive lipids and drug solubilisation/dispersion into molten lipid mass and after some extrusion process the obtained drops are solidified by cooling or (ii) lipid and drugs are dissolved into organic solvent for emulsion preparation in water dispersant media kept under stirring for solvent evaporation and obtainment of solid particles (Sailaja et al., 2011). Concerning these processes, the chemical affinity between the drug molecule and the lipid matrix is highly important to obtain a large payload. Therefore, commonly lipid-soluble drugs show high entrapment ratios, whereas hydrophilic molecules are hardly incorporated into these particles.

Another important issue related to this is the expulsion of the drug molecule from SLN matrix. During storage, the crystalline lipid structures migrate to more stable polymorphic forms, i.e. from α-form to β'-form and subsequently to β-form. In this process, the hydrocarbon chain packing increase enormously with consequent reduction of imperfections in the lipid lattice (Takechi et al., 2007; Da Silva et al., 2009; Souto and Müller, 2010). As depicted in Figure 4, this physical transition of lipids to highly crystalline state into SLN matrix lead to expulsion of mainly hydrophilic drugs (Pietkiewicz et al., 2006). Considering that mixtures of lipids containing fatty acids of different chain length form less perfect crystals with many imperfections, its use on SLN preparation offers more space to accommodate guest molecules, preventing expulsion of drugs.

To overcome this disadvantage, a hybrid lipid particle was created – the nanostructured lipid carriers (NLC). These particles are constituted by a blend of solid and liquid lipids (oils), generating a less organised matrix what facilitates the accommodation of the drug molecule on the particle matrix. Thus, NLC generally present a larger payload ratio than SLN and also no drug expulsion is evidenced during solidifying step of the preparation process, or upon storage (Pardeike et al., 2009; Severino et al., 2012).

The NLC can be classified into three categories according to the structure of their matrix: (i) imperfect type, (ii) multiple types and (iii) amorphous or structureless type. The imperfect type NLC is composed of a minimum amount of liquid lipid with solid saturated and unsaturated lipids of varied chain lengths. In this type, the lipid crystallisation is still an issue, but in tighter rate than that for SLN. The multiple type NLC is composed of a higher concentration of liquid lipids which forms liquid oil nanocompartments in the matrix. Typically the higher oil concentration is associated with faster drug release. The amorphous type NLC is composed by special lipids that remain amorphous upon solid state, such as hydroxyoctacosanylhydroxystearate and isopropyl-myristate. Thus, there is a lack of crystalline structures on the NLC avoiding the drug expulsion (Müller et al., 2002; Puri et al., 2010).

SLN/NLC and opioids

Table 6 shows the few works concerning the entrapment of opioid molecules into SLN/NLC available in literature. There is no marketed product composed by opioid drugs encapsulated in SLN or NLC.

In order to improve the water solubility of drug molecules, a common strategy is to convert them into salts. Therefore, the opioids are commonly commercialised in salt form. However, considering the general low payload of hydrophilic compounds into SLN, convert opioid salts into their free bases can be an interesting strategy for improving their lipid-solubility, leading to higher entrapment rates. In this context, Küchler et al. (2010) studied the incorporation of morphine free base, converted from morphine hydrochloride, in which 100% entrapment efficiency into SLN was obtained. On a hot plate test, after intrathecal administration of morphine-loaded SLN to Sprague–Dawley rats, Ji et al. (2008) collected interesting results. They observed an equivalent analgesia efficacy to free morphine formulation, as well as obtained a significant prolongation of analgesia without an increase in the incidence of adverse reactions.

The evaluation of buprenorphine hydrochloride and its methylated prodrugs encapsulated into SLN and NLC demonstrated a higher entrapment rate for the prodrugs, due to their higher lipophilicity. On tail-flick test, after a subcutaneous injection on Sprague–Dawley rats, the buprenorphine-loaded SLN maintained the maximum latency of 12s for 8 h, while those for NLC was 4 h and for aqueous control was 3 h. Among the prodrugs, the buprenorphine-propionate-loaded NLC showed to be the most potent formulation with the maintenance of 100% antinociception for 10 h. This outcome is related to *in vitro* drug release data. As the other formulations presented an extremely slow release of the drug/prodrug molecules, it may have led to a under-therapeutic plasma concentrations on experimental models (Wang et al., 2009a, 2009b).

Table 6. Experimental works with opioid encapsulation into solid lipid-based nanoparticles.

Opioid	Particle type	Particle composition	Particle diameter	Experimental model/ route of administration	Nature of study	References
Morphine	SLN	Glyceryl behenate, poloxamer 188	180 nm	*In vitro*	Wound healing models	Küchler et al. (2010)
Morphine	SLN	NP	NP	Sprague–Dawley rats/intrathecal	Hot plate test	Ji et al. (2008)
Buprenorphine/prodrugs (buprenorphine propionate, valerate, enanthate)	SLN	Cetyl palmitate, myverol, pluronic F127®	180 nm	Sprague–Dawley rats/subcutaneous	Cold ethanol tail-flick test	Wang et al. (2009a)
	NLC	Cetyl palmitate, linseed oil, myverol, pluronic F127®	189–204 nm			
Buprenorphine/prodrugs (buprenorphine propionate, valerate, enanthate)	SLN	Precirol, myverol (or Phospholipon 80H®), pluronic F68®	286–302 nm	*In vitro*	Physicochemical characterisation	Wang et al. (2009b)
	NLC	Precirol, squalene, myverol, pluronic F68	227 nm			
C10LAA-Endo-1	Eudragit® S100-coated SLN	Phospholipon 90H®, cetyl palmitate, arlacel®	86 nm	*In vitro*	Sample preparation and characterisation	Eskandari et al. (2013)

Arlacel 1689®: (mixture of sorbitan oleate and polyglyceryl-3-polyricinoleate); DSPE-PEG: distearoylphosphatidylethanolamine with covalently linked polyethylene glycol; Forestall®: soyethyl morpholinium ethosulfate; Myverol®: palmitic acid monoglycerides; Phospholipon 90H®: hydrogenated soybean phosphatidylcholine 90%; Phospholipon 80H®: hydrogenated soybean phosphatidylcholine 80%; Pluronic F127®: polyethylene-polypropylene glycol block copolymer; Pluronic F68®: polyoxyethylene-polyoxypropylene block copolymer; NP: Not Provided.

Conclusion

The comprehension of the importance involved on development of opioid-based controlled release formulations for treatment of chronic pain is already a reality. However, other options on drug delivery must be exploited intending the achievement of more efficient, safer and innovative products. The literature has demonstrated that the association of opioids to particulate systems not only provides a sustained and controlled drug delivery, as well as a superior or equivalent analgesia profile to the free counterparts and reduced side effect occurrence. The maintenance of predictable therapeutic plasma concentration, as well as a reduced drug plasma exposure was crucial for reducing adverse reaction events. The use of various molecules as surface ligands facilitated the interaction of micro and nanoparticles with biomembranes and enhanced opioid absorption, maintaining the prolonged distribution. SLN and NLC seem to be an interesting alternative for future studies, taking into account its large range of advantages and the lack of studies on association with opioids. These studies have not been still enough to warm up the production of new products containing particulate opioids by pharmaceutical industry area. More clinical studies data can help to shift this scenario.

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Declaration of interest

The authors declare that they have no conflict of interest.

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